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(54) Title: SUBSTITUTED BENZANILIDES AS MODULATORS OF THE CCR5 RECEPTOR

(57) 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.

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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 are not only key regulators of the immune response to infectious agents but are believed critical for the initiation and maintenance of the inflammatory reaction in a variety of chronic diseases. Increased numbers or enhanced activation state of T cells, especially CD4+ T cells, have been demonstrated in the synovium of individuals with rheumatoid arthritis (M.J. Elliott and R. N. Maini, Int. Arch. Allergy Immunol. 104: 112-1125, 1994), in the bronchial mucosa of asthmatics (C.J. Corrigan and A.B. Kay, Immunol. Today 13:501-506, 1992), in the lesions of multiple sclerosis (R. Martin and H. F. McFarland, Crit. Rev. Clin. Lab. Sci. 32: 121-182, 1995), in psoriatic lesions (J.L. Jones, J. Berth-Jone, A. Fletcher and P.E. Hutchinson, J. Pathol. 174: 77-82, 1994) and in the fatty streaks of atherosclerosis (R. Ross, Annu. Rev. Physiol. 57: 791-804, 1995).

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. Baggiolini, 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 late after antigen activation of T-cells (T.J. Schall, J. Jongstra, B.J. Dyer, J. Jorgensen, et al., J. Immunol. 141:1018-1025, 1988), however, RANTES has been shown to be synthesized and secreted by a diverse group of cells that include epithelial and endothelial cells (C. Stellato, L.A. Beck, G.A. Gorgone, D. Proud, et al., J. Immunol. 155: 410-418, 1995; and A. Marfaing-Koka, O. Devergne, G. Gorgone, A. Portier, et al., J. Immunol. 154: 1870-1878, 1994), synovial fibroblasts (P. Rathanaswami, M. Hachicha, M. Sadick, T.J. Schall, et al., J. Biol. Chem. 268: 5834-5839, 1993) and dermal fibroblasts (M. Sticherling, M. Kupper, F. Koltrowitz, E. Bornscheuer, et al., (J. Invest. Dermatol. 105: 585-591, 1995), mesangial cells (G. Wolf, S. Aberle, F. Thaiss, et al., Kidney Int. 44: 795-804, 1994) and platelets (Y. Koameyoshi, A. Dorschner, A.I. Mallet, E. Christophers, et al., J. Exp. Med. 176: 587-592, 1992). In these cells, RANTES mRNA is rapidly upregulated in response to IL-1 or TNF•. Although RANTES mRNA is not usually detected in normal tissues (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-1995), increased mRNA or protein has been found in diseases characterized by a mononuclear infiltrate. For example, RANTES mRNA was visualized using *in situ* hybridization in renal allografts undergoing rejection (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995; and K.C. Nadeau, H. Azuma and N.I. Tilney, Proc. Natl. Acad. USA 92: 8729-8733, 1995) in the skin of atopic dermatitis patients after exposure to antigen (S. Ying, L. Taborda-Barata, Q. Meng, M. Humbert, et al., J. Exp. Med. 181: 2153-2159, 1995), and in endothelial cells of coronary arteries undergoing accelerated atherosclerosis after cardiac transplant (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995). Further, increased immunoreactive protein for RANTES has been detected in bronchoalveolar lavage fluid (R. Alam, J. York, M. Boyers, et al., Am. J. Resp. Crit. Care Med. 149: A951, 1994) and sputum from asthmatic individuals (C.M. Gelder, P.S. Thomas, D.H. Yates, I.M. Adcock, et al., Thorax 50: 1033-1037, 1995).

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.

A subset of compounds included in formula (I) have been reported to have 5-HT receptor activity (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; international application publication number WO 95/30675 published 16 November 1995; international application publication number WO 95/17401 published 29 June 1995; international application publication number WO 96/31508 published 10 October 1996; international application publication number WO 97/10824 published 27 March 1997; international application publication number WO 96/11934 published 25 April 1996; international application publication number WO 96/19477 published 27 June 1996; international application publication number WO 97/17350 published 15 May 1997; international application publication number WO 97/34900 published 25 September 1997; international application publication number WO 97/34901 published 25 September 1997; international application publication number WO 97/35862 published 2 October 1997; international application publication number WO 97/19070 published 29 May 1997; international application publication number WO 95/32967 published 7 December 1995; international application publication number WO 97/07120 published 27 February 1997; U.S. Patent 3,931,195, issued Jan. 6, 1976; and U.S. Patent 4,000,143, issued Dec. 28, 1976). In addition, WO

99/01127, published January 14, 1999, discloses substituted benzanilides useful for modulating CCR5-mediated diseases.

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 and or prophylaxis 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.

In addition, the present invention is directed to a method of preventing or treating CCR5-mediated diseases in a mammal, preferably a human, by administering to the mammal an effective amount of a CCR5 receptor ligand, or a pharmaceutically acceptable salt or solvate thereof.

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 modulate chemokine receptor activity and thereby 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 know 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 benzanilides 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 or solvate 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.

Compounds of formula (I) for use herein as CCR5 modulators include the 5-HT ligands as described in international application publication number WO 95/15954, published 15 June 1995, (U.S.S.N. 08/652,581, filed June 7, 1996); international application publication number WO 95/17398, published 29 June 1995, (U.S.S.N. 08/663,291, filed June 21, 1996); international application publication

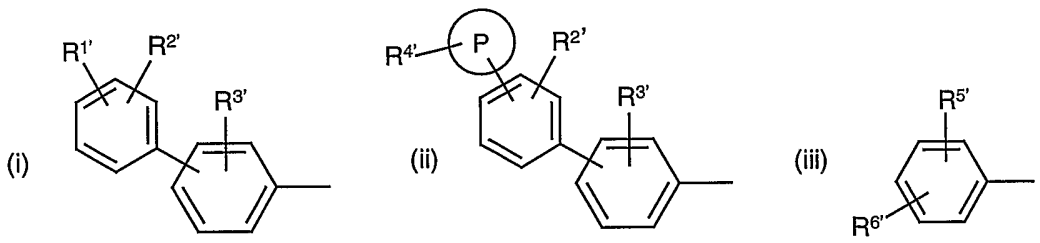
number WO 95/26328, published 5 October 1995, (USSN 08/718,481, filed Sept. 26, 1996); international application publication number WO 96/06079, published 29 February 1996, (USSN 08/793,428, filed Feb. 21, 1997); GB 2276161 published 21 September 1994, and GB 2276165 published 21 September 1994; international application publication number WO 95/30675, published 16 November 1995, (USSN 08/737,147); international application publication number WO 95/17401, published 29 June 1995 (USSN 08/663,290, filed June 21, 1996); international application publication number WO 96/31508, published 10 October 1996 (USSN 08/930,848, filed Oct. 7, 1997); international application publication number WO 97/10824, published 27 March 1997 (USSN 09/043,346); international application publication number WO 96/11934, published 25 April 1996, (USSN 08/817,619); international application publication number WO 96/19477, published 27 June 1996 (USSN 08/849,932); international application publication number WO 97/17350, published 15 May 1997 (USSN 09/068,382, filed May 8, 1998); international application publication number WO 97/34900, published 25 September 1997 (Attorney Docket No. P31419); international application publication number WO 97/34901, published 25 September 1997 (Attorney Docket No. P31418); international application publication number WO 97/35862, published 2 October 1997 (Attorney Docket No. P31426); international application publication number WO 97/19070, published 29 May 1997 (USSN 09/077,263); international application publication number WO 95/32967, published 7 December 1995 (USSN 08/737,660); international application publication number WO 97/07120, published 27 February 1997 (USSN 09/011,338, filed Feb. 11, 1998); U.S. Patent 3,931,195, issued Jan. 6, 1976; and U.S. Patent 4,000,143, issued Dec. 28, 1976. Each of these references is incorporated herein in their entirety.

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:

Ar—A—E Formula (I)

wherein Ar represents 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 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, $(CH_2)_aNR^{7'}R^{8'}$, $(CH_2)_aNR^{7'}COR^{9'}$, $(CH_2)_aNR^{7'}CO_2R^{10'}$, $(CH_2)_aNR^{7'}SO_2R^{11'}$, $(CH_2)_aCONR^{12'}R^{13'}$, hydroxy$C_{1-6}$alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), $(CH_2)_aCO_2C_{1-6}$alkyl, $(CH_2)_bOC(O)R^{14'}$, $CR^{15'}=NOR^{16'}$, $CNR^{15'}=NOR^{16'}$, $COR^{17'}$, $CONR^{12'}R^{13'}$, $CONR^{12'}(CH_2)_cOC_{1-4}$alkyl, $CONR^{12'}(CH_2)_aCO_2R^{18'}$, $CONHNR^{19'}R^{20'}$, $CONR^{12'}SO_2R^{21'}$, $CO_2R^{22'}$, cyano, trifluoromethyl, $NR^{7'}R^{8'}$, $NR^{7'}COR^{9'}$, $NR^{23'}CO(CH_2)_aNR^{23'}R^{24'}$, $NR^{23'}CONR^{23'}R^{24'}$, $NR^{7'}CO_2R^{10'}$, $NR^{7'}SO_2R^{11'}$, $N=CNR^{23'}NR^{23'}R^{24'}$, nitro, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, $OC(O)NR^{25'}R^{26'}$, $SR^{27'}$, $SOR^{28'}$, $SO_2R^{28'}$, $SO_2NR^{25'}R^{26'}$ or halogen;

$R^{3'}$ and $R^{4'}$ are 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, $CONR^{29'}R^{30'}$, $CO_2R^{31'}$, cyano, aryl, trifluoromethyl, $NR^{29'}R^{30'}$, nitro, hydroxy, C_{1-6}alkoxy, acyloxy, or halogen;

$R^{5'}$ 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}alkynyl, $(CH_2)_dOR^{32'}$, $(CH_2)_dCOR^{33'}$, $(CH_2)_dCR^{34'}=NOR^{35'}$, $CONR^{36'}R^{37'}$, $CO_2R^{38'}$, 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_{1-6} 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;

$R^{22'}$ is hydrogen or C_{1-6}alkyl optionally substituted with one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or $NR^{7'}R^{8'}$;

$R^{23'}$ and $R^{24'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{25'}$ and $R^{26'}$ are independently hydrogen or C_{1-6}alkyl, 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_{1-6}alkyl;

$R^{28'}$ is C_{1-6}alkyl;

$R^{29'}$, $R^{30'}$ and $R^{31'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{32'}$ 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 $CO_2R^{45'}$, 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_2H, CO_2C_{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;

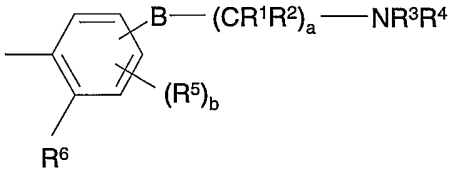
c' is 1, 2 or 3;

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_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

E represents a group (a):



(a);

wherein:

B is oxygen, C≡C, $S(O)_c$, $CR^7=CR^8$, 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, 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, $OCOR^{12}$, $NHCOCF_3$, $NHSO_2R^{13}$, $NHCO_2R^{14}$, or $NHCOC_{0-6}$alkyl wherein the alkyl of $NHCOC_{0-6}$alkyl is optionally substituted by OH;

R^5 is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{15}R^{16}$, CO_2R^{17}, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$ or halogen;

R^6 is hydrogen, C_{1-6}alkyl, aryl, trifluoromethyl, hydroxy, C_{1-6}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_{1-6}alkyl;

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

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

a is 1, 2, 3, or 4;

b is 1 or 2;

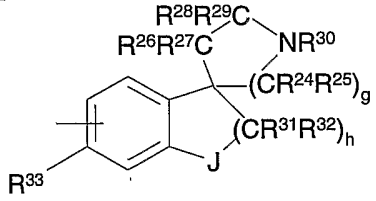
c and d are independently 0, 1 or 2;

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_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

alternatively, E represents a group (b):



(b);

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

R^{30} is hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl;

R^{33} is hydrogen, C_{1-6}alkyl, trifluoromethyl, hydroxy or halogen, or R^{33} and $R^{30'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N;

J is oxygen, $CR^{36}R^{37}$, or NR^{38}, or J is a group $S(O)_k$;

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

g is 1, 2 or 3;

h is 1, 2 or 3;

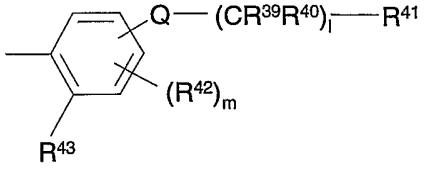
i is 2, 3, or 4;

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 $CONR^{46'}$, NHCO, -$NHCH_2$, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

alternatively, E represents a group (c):



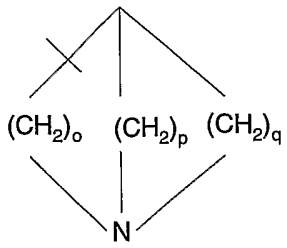
(c);

wherein:

Q is oxygen, $S(O)_n$, $CR^{44}=CR^{45}$, $CR^{44}R^{45}$, or Q is NR^{46};

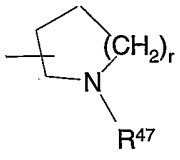
R^{39} and R^{40} are independently hydrogen or C_{1-6}alkyl;

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



(d)

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



(e)

R^{42} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{48}R^{49}$, CO_2R^{50}, trifluoromethyl, $NHCO_2R^{51}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_sR^{52}$, $SO_2NR^{53}R^{54}$, 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 C_{1-6}alkyl;

R^{47} is hydrogen, C_{1-6}alkyl, or C_{3-7} cycloalkyl;

R^{51} and R^{52} are independently C_{1-6}alkyl;

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;

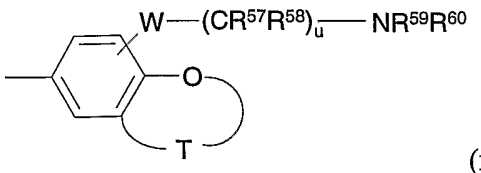
r is 0,1, 2, or 3;

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 CH_2NH,

alternatively, E represents a group (f):



(f);

wherein:

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, 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, $OCOR^{63}$, $NHCOCF_3$, $NHSO_2R^{64}$, $NHCO_2R^{65}$, or $NHCOC_{0-6}$alkyl wherein the alkyl of $NHCOC_{0-6}$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;

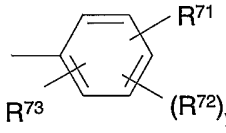
v is 2 or 3;

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_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

alternatively, E represents a group (g):



(g);

wherein:

R^{71} is a 5- to 7-membered saturated or partially saturated heterocyclic ring containing a 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;

R^{72} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{74}R^{75}$, CO_2R^{76}, trifluoromethyl, $NHCO_2R^{77}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_zR^{78}$, $SO_2NR^{79}R^{80}$, 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;

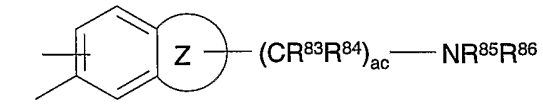
z is 0, 1, or 2;

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 $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

alternatively, E represents a group (h):



(h);

wherein:

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, 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, $OCOR^{92}$, $NHCOCF_3$, $NHSO_2R^{93}$, $NHCO_2R^{94}$, or $NHCOC_{0-6}$alkyl wherein the alkyl of $NHCOC_{0-6}$alkyl is optionally substituted by 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 $(CR^{95}R^{96})_{ad}$ 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_{1-6}alkyl;

R^{93} and R^{94} are independently C_{1-6}alkyl;

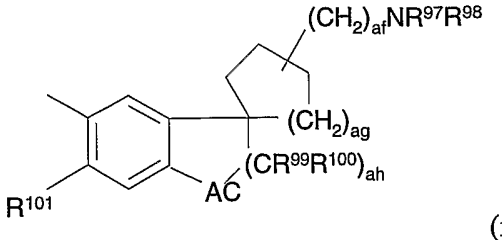
ac is 0 to 4;

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 $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

alternatively, E represents a group (i):



(i);

wherein:

R^{97} and R^{98} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, 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, $CONR^{102}R^{103}$, $NR^{104}R^{105}$, hydroxy, $OCOR^{106}$, $NHCOCF_3$, $NHSO_2R^{107}$, $NHCO_2R^{108}$, or $NHCOC_{0-6}$alkyl wherein the alkyl of $NHCOC_{0-6}$alkyl is optionally substituted by OH;

R^{99} and R^{100} are independently hydrogen or C_{1-6}alkyl;

R^{101} is hydrogen or C_{1-6}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_{1-6}alkyl;

R^{107} and R^{108} are independently C_{1-6}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.

For compounds of formula (I) various embodiments are as follows. It will be understood that the basic nitrogen in moiety E may be optionally quaternized with C_{1-6}alkyl 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 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, $(CH_2)_aNR^{7'}R^{8'}$,

$(CH_2)_a$-$NR^{7'}COR^{9'}$, $(CH_2)_a$-$NR^{7'}CO_2R^{10'}$, $(CH_2)_a$-$NR^{7'}SO_2R^{11'}$, $(CH_2)_a$-$CONR^{12'}R^{13'}$, hydroxyC_{1-6}alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), $(CH_2)_a$-CO_2C_{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, $CONR^{12'}(CH_2)_a$-$CO_2R^{18'}$, $CONHNR^{19'}R^{20'}$, $CONR^{12'}SO_2R^{21'}$, $CO_2R^{22'}$, cyano, trifluoromethyl, $NR^{7'}R^{8'}$, $NR^{7'}COR^{9'}$, $NR^{23'}CO(CH_2)_a$-$NR^{23'}R^{24'}$, $NR^{23'}CONR^{23'}R^{24'}$, $NR^{7'}CO_2R^{10'}$, $NR^{7'}SO_2R^{11'}$, N=$CNR^{23'}NR^{23'}R^{24'}$, nitro, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, $OC(O)NR^{25'}R^{26'}$, $SR^{27'}$, $SOR^{28'}$, $SO_2R^{28'}$, $SO_2NR^{25'}R^{26'}$ or halogen.

Preferably, $R^{1'}$ and $R^{2'}$ are independently one or more of hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, $COR^{17'}$, $CONR^{12'}R^{13'}$, $CO_2R^{22'}$, cyano, trifluoromethyl, $NR^{7'}R^{8'}$, $NR^{7'}COR^{9'}$, $NR^{23'}CONR^{23'}R^{24'}$, $NR^{7'}SO_2R^{11'}$, nitro, hydroxy, C_{1-6}alkoxy, $SO_2R^{28'}$, $SO_2NR^{25'}R^{26'}$, or halogen.

Suitably, $R^{3'}$ and $R^{4'}$ are 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, $CONR^{29'}R^{30'}$, $CO_2R^{31'}$, cyano, aryl, trifluoromethyl, $NR^{29'}R^{30'}$, nitro, hydroxy, C_{1-6}alkoxy, acyloxy, or halogen.

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

Suitably, $R^{6'}$ 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}alkynyl, $(CH_2)_d$-$OR^{32'}$, $(CH_2)_d$-$COR^{33'}$, $(CH_2)_d$-$CR^{34'}$=$NOR^{35'}$, $CONR^{36'}R^{37'}$, $CO_2R^{38'}$, hydroxy, $O(CH_2)_e$-$R^{39'}$, $NR^{36'}R^{37'}$, $SR^{40'}$, $SO_2NR^{41'}R^{42'}$ or halogen; or, $R^{5'}$ and $R^{6'}$ form a fused benzo ring optionally substituted with C_{1-6} alkyl, C_{1-6}alkoxy or halogen.

Suitably, $R^{7'}$ 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.

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

Suitably, $R^{10'}$ is C_{1-6}alkyl.

Suitably, $R^{11'}$ is C_{1-6}alkyl or phenyl.

Suitably, $R^{12'}$ 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.

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

Suitably, $R^{15'}$ and $R^{16'}$ are independently hydrogen or C_{1-6}alkyl.

Suitably, $R^{17'}$ is hydrogen or C_{1-6}alkyl.

Suitably, $R^{18'}$ is hydrogen or C_{1-6}alkyl.

Suitably, $R^{19'}$ and $R^{20'}$ are independently hydrogen or C_{1-6}alkyl.

Suitably, $R^{21'}$ is hydrogen or C_{1-6}alkyl.

Suitably, $R^{22'}$ is hydrogen or C_{1-6}alkyl optionally substituted with one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or $NR^{7'}R^{8'}$.

Suitably, $R^{23'}$ and $R^{24'}$ are independently hydrogen or C_{1-6}alkyl.

Suitably, $R^{25'}$ and $R^{26'}$ are independently hydrogen or C_{1-6}alkyl, 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.

Suitably, $R^{27'}$ is hydrogen or C_{1-6}alkyl.

Suitably, $R^{28'}$ is C_{1-6}alkyl.

Suitably, $R^{29'}$, $R^{30'}$ and $R^{31'}$ are independently hydrogen or C_{1-6}alkyl.

Suitably, $R^{32'}$ is C_{1-6}alkyl, hydroxyC_{1-6}alkyl, or C_{1-4}alkanoyl.

Suitably, $R^{33'}$ is hydrogen or C_{1-6}alkyl.

Suitably, $R^{34'}$ is hydrogen or C_{1-6}alkyl.

Suitably, $R^{35'}$ is hydrogen or C_{1-6}alkyl.

Suitably, $R^{36'}$ 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 $CO_2R^{45'}$, wherein $R^{44'}$ and $R^{45'}$ are independently hydrogen or C_{1-6}alkyl.

Suitably, $R^{38'}$ is hydrogen or C_{1-6}alkyl.

Suitably, $R^{39'}$ is C_{1-6}alkoxy, CO_2H, CO_2C_{1-6}alkyl or $CONR^{36'}R^{37'}$.

Suitably, $R^{40'}$ is C_{1-6}alkyl.

Suitably, $R^{41'}$ and $R^{42'}$ are independently hydrogen or C_{1-6}alkyl.

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 thienyl, furyl, pyrrolyl, triazolyl, diazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, 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 $R^{4'}$. Preferably, P is 1,2,4-oxadiazol-3-yl wherein $R^{4'}$ is 5-methyl, or tetrazol-5-yl.

Suitably, a' is 1, 2, 3 or 4.

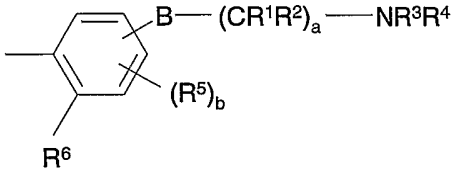
Suitably, b' is 0, 1, 2 or 3.

Suitably, c' is 1, 2 or 3.

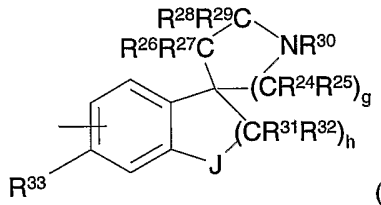
Suitably, d' is 0, 1, 2, 3, 4, 5, or 6. and

Suitably, e' is 1, 2, 3, 4, 5 or 6.

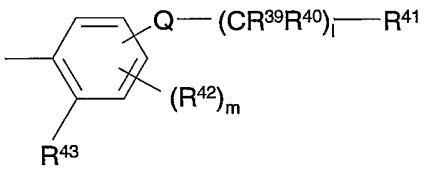
Suitably, when Ar is (i), (ii), or (iii), substituent E is selected from the following groups:



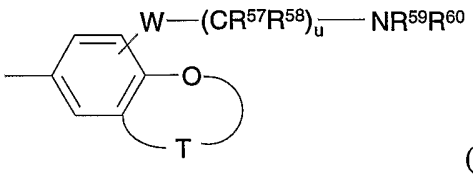
(a);



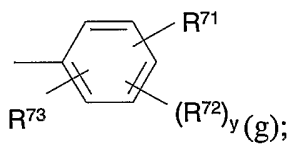
(b);



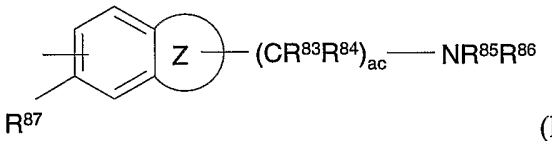
(c);



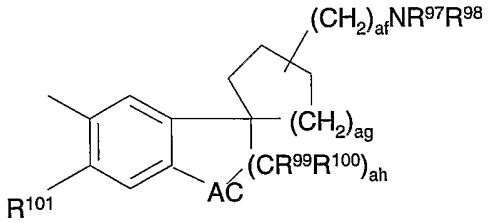
(f)



(g);

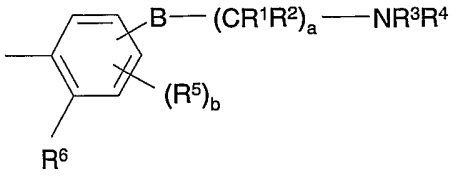


(h); and



(i).

Suitably, when Ar is (i), (ii) or (iii), and A is $CONR^{46'}$, NHCO, $-NHCH_2$, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl, E suitably represents a group (a):



(a).

B is suitably oxygen, C≡C, $S(O)_c$, $CR^7=CR^8$, or CR^7R^8, or B is NR^9. B is preferably CR^7R^8, or oxygen.

R^1 and R^2 are suitably independently hydrogen or C_{1-6}alkyl. Preferably, R^1 and R^2 are hydrogen. Alternatively, $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OH)CR^1R^2$ or $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$. Preferably, when $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OH)CR^1R^2$ or $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$, R^1 and R^2 are hydrogen.

R^3 and R^4 are suitably independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, 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, $OCOR^{12}$, $NHCOCF_3$, $NHSO_2R^{13}$, $NHCO_2R^{14}$, or $NHCOC_{0-6}$alkyl wherein the alkyl of $NHCOC_{0-6}$alkyl is optionally substituted by OH. Preferably R^3 and R^4 are both C_{1-6}alkyl, 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, $B\text{-}(CR^1R^2)_a\text{-}NR^3R^4$ 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_{1-6}alkyl, aryl, CN, $CONR^{15}R^{16}$, CO_2R^{17}, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$, or halogen. R^5 is preferably C_{1-6}alkoxy, SC_{1-6}alkyl 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 $(CR^{22}R^{23})_f\text{-}G$ where G is oxygen, sulfur, or $CR^{22}=CR^{23}$, $CR^{22}=N$, $=CR^{22}O$, $=CR^{22}S$, or $=CR^{22}\text{-}NR^{23}$. 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.

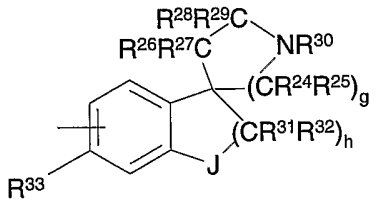
b is suitably 1 or 2. Preferably, b is 1.

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_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl, E suitably represents 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, or C_{3-7}cycloalkyl. Preferably, R^{30} is C_{1-6}alkyl or C_{3-7}cycloalkyl.

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 $(CR^{34}R^{35})_j$ -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.

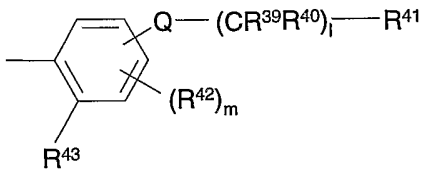
h is suitably 1, 2, or 3. Preferably, h is 1.

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_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl, E suitably represents a group (c):

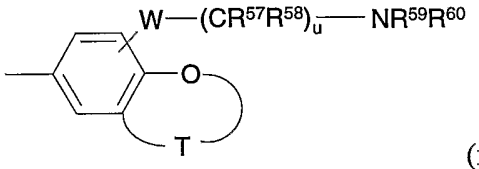


(c).

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_{1-6}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_{1-6}alkyl; suitably, R^{42} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{48}R^{49}$, CO_2R^{50}, trifluoromethyl, $NHCO_2R^{51}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_sR^{52}$, $SO_2NR^{53}R^{54}$, or halogen, wherein R^{48}, R^{49}, R^{50}, R^{53}, and R^{54} are hydrogen or C_{1-6}alkyl, and R^{51} and R^{52} are C_{1-6}alkyl; suitably, R^{43} is hydrogen or R^{43} together with $R^{46'}$ forms a group R where R is $CR^{55}=CR^{56}$, $CR^{55}=CR^{56}CR^{55}R^{56}$, or $(CR^{55}R^{56})t$ wherein R^{55} and R^{56} are independently hydrogen or C_{1-6}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_{1-6}alkyl, or C_{3-7} cycloalkyl; 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.

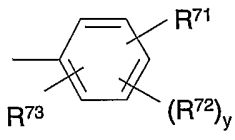
Alternatively, when Ar is (i), (ii) or (iii), and A is CONH, NHCO, or CH_2NH, E suitably represents a group (f):



(f).

Suitably, R^{57} and R^{58} are independently hydrogen or C_{1-6}alkyl; suitably R^{59} and R^{60} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, 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, $OCOR^{63}$, $NHCOCF_3$, $NHSO_2R^{64}$, $NHCO_2R^{65}$ or $NHCOC_{0-6}$alkyl wherein the alkyl of $NHCOC_{0-6}$alkyl is optionally substituted by OH, and wherein R^{61}, R^{62}, and R^{63} are independently hydrogen or C_{1-6}alkyl, and R^{64} and R^{65} are independently C_{1-6}alkyl; suitably, T is $-(CR^{66}R^{67})_v-$ or $-O(CR^{66}R^{67})_w-$, wherein R^{66} and R^{67} are independently hydrogen or C_{1-6}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 NR^{68}, wherein R^{68} is hydrogen or C_{1-6}alkyl, or W is $CR^{69}=CR^{70}$, C=C, or $CR^{69}R^{70}$, wherein R^{69} and R^{70} are independently hydrogen or C_{1-6}alkyl; and suitably, u is an integer from 1-4.

Alternatively, when Ar is (i), (ii) or (iii), and A is $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl, E suitably represents a group (g):



(g).

Suitably, R^{71} is an optionally substituted 5- to 7-membered saturated or partially saturated heterocyclic ring containing a nitrogen atom and optionally a further one or two heteroatoms selected from nitrogen, oxygen or sulfur, or R^{71} 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 C_{1-6}alkyl, and substituted on nitrogen with hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl. 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, R^{71} is an optionally substituted 5- or 6-membered saturated or partially saturated heterocyclic ring containing a nitrogen atom and is substituted on nitrogen with C_{1-6}alkyl or C_{3-7}cycloalkyl.

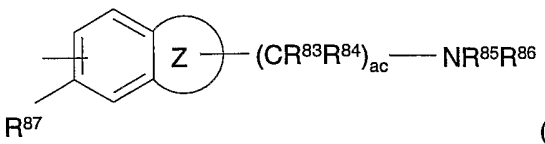
R^{71} is preferably located meta to A, ortho to R^{72} and para to R^{73}, and R^{72} is located para to A.

Suitably, R^{72} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{74}R^{75}$, CO_2R^{76}, trifluoromethyl, $NHCO_2R^{77}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_zR^{78}$, $SO_2NR^{79}R^{80}$, or halogen wherein R^{74}, R^{75}, R^{76}, R^{79} and R^{80} are independently hydrogen or C_{1-6}alkyl, R^{77} and R^{78} are C_{1-6}alkyl, and z is 0, 1, or 2. R^{72} is preferably C_{1-6}alkoxy, SC_{1-6}alkyl or halogen.

Suitably, R^{73} is hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy or halogen, or R^{73} and $R^{46'}$ taken together from a group -X- where X is $(CR^{81}R^{82})_{aa}$, wherein aa is 2, 3 or 4, and R^{81} and R^{82} are independently hydrogen or C_{1-6}alkyl, or X is $(CR^{81}R^{82})_{ab}$-Y, wherein ab is 0, 1, 2 or 3, and Y is oxygen, sulfur or $CR^{81}=CR^{82}$ wherein R^{81} and R^{82} are independently hydrogen or C_{1-6}alkyl. Preferably, R^{73} is hydrogen.

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

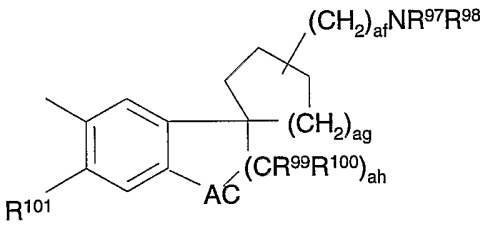
Alternatively, when Ar is (i), (ii) or (iii), and A is $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl, E suitably represents a group (h):



(h).

Suitably, R^{87} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or halogen, or R^{87} together with $R^{46'}$ form a group -AA-, wherein AA is $(CR^{95}R^{88})_{ad}$, wherein ad is 1, 2 or 3, and R^{95} and R^{88} are independently hydrogen or C_{1-6}alkyl, or AA is $(CR^{95}CR^{96})_{ae}$-AB, wherein ae is 0, 1 or 2, and AB is oxygen, sulfur, $CR^{95}=CR^{96}$, $CR^{95}=N$, $CR^{95}NR^{96}$ or N=N wherein R^{95} and R^{96} are independently hydrogen or C_{1-6}alkyl; suitably, R^{83} and R^{84} are independently hydrogen or C_{1-6}alkyl; suitably, R^{85} and R^{86} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, 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, $OCOR^{92}$, $NHCOCF_3$, $NHSO_2R^{93}$, $NHCO_2R^{94}$, or $NHCOC_{0-6}$alkyl wherein the alkyl of the $NHCOC_{0-6}$alkyl is optionally substituted by OH, and wherein R^{88}, R^{89}, R^{90}, R^{91} and R^{92} are independently hydrogen or C_{1-6}alkyl, and R^{93} and R^{94} are independently C_{1-6}alkyl; 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 $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl, E suitably represents a group (i):



(i).

Suitably, R^{101} is hydrogen or C_{1-6}alkyl or R^{101} and $R^{46'}$ together form a group -AD- wherein AD is $(CR^{109}R^{110})_{ai}$ wherein ai is 2, 3 or 4 or AD is $(CR^{109}R^{110})_{aj}$-AE wherein aj is 0, 1, 2 or 3 and AE is oxygen, sulfur or $CR^{109}=CR^{110}$, and R^{109} and R^{110} are independently hydrogen or C_{1-6}alkyl; suitably, R^{97} and R^{98} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, 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, $CONR^{102}R^{103}$, $NR^{104}R^{105}$, hydroxy, $OCOR^{106}$, $NHCOCF_3$, $NHSO_2R^{107}$, $NHCO_2R^{108}$, or $NHCOC_{0-6}$alkyl wherein the alkyl of $NHCOC_{0-6}$alkyl is optionally substituted by OH, and wherein R^{102}, R^{103}, R^{104}, R^{105} and R^{106} are independently hydrogen or C_{1-6}alkyl, and R^{107}

and R^{108} are independently C1-6alkyl; suitably, R^{99} and R^{100} are independently hydrogen or C_{1-6}alkyl; suitably, AC is oxygen, $CR^{111}R^{112}$ or NR^{113} wherein R^{111}, R^{112} and R^{113} are independently hydrogen or C_{1-6}alkyl 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 $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen.

More preferably, A is $CONR^{46'}$ or NHCO, wherein $R^{46'}$ is hydrogen.

Most preferably, A is $CONR^{46'}$, wherein $R^{46'}$ is hydrogen.

Preferably, when Ar is (i), (ii), or (iii), E represents group (a), (b), or (g).

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

Most preferably, when Ar is (i) or (ii), E represents group (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, $R^{1'}$ and $R^{2'}$ are independently one or more of hydrogen, methyl, hydroxymethyl, acetyl, carbamoyl, ethoxycarbonyl, cyano, trifluoromethyl, amino, methylamino, butylamino, dimethylamino, acetamido, uriedo, (dimethylamino)carbonylamino, methanesulfonamido, nitro, hydroxy, methoxy, ethoxy, isopropoxy, methanesulfonyl, sulfamoyl, chloro or fluoro.

More preferably, when E is group (a), A is attached to group (a) meta to B-$(CR^1R^2)_a$-NR^3R^4 and para to $(R^5)_b$, wherein B is oxygen or CR^7R^8, R^1 and R^2 are hydrogen, R^5 is methoxy, methylthio or iodo, R^3 and R^4 are independently C_{3-6}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_{1-6}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.

Most preferably, when E is group (a), A is attached to group (a) meta to B-$(CR^1R^2)_a$-NR^3R^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.

More preferably, 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_{3-6}alkyl, 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, 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 isopropyl, g is 2 and h is 1.

More preferably, 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_{3-6}alkyl or C_{3-7}cycloalkyl, R^{72} is methoxy, methylthio or iodo, y is 1, and R^{73} is hydrogen..

Most preferably, when E is group (g), A is attached to group (g) meta to R^{71} and para to R^{72} wherein R^{71} is piperidin-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, or pyrrolidin-3-yl substituted on nitrogen with isopropyl, 3-pentyl, cyclopropyl, or cyclopentyl, R^{72} is methoxy, y is 1, and R^{73} is hydrogen.

A particularly effective subgenus of compounds of formula (I) is wherein: Ar is (i) or (ii), E is group (g), and A is $CONR^{46'}$ and $R^{46'}$ is hydrogen, and further wherein, A is attached to group (g) meta to R^{71} and para to R^{72}, and wherein R^{71} is piperidin-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, or pyrrolidin-3-yl substituted on nitrogen with isopropyl, 3-pentyl, cyclopropyl, or cyclopentyl, R^{72} is methoxy, y is 1, and R^{73} is hydrogen.

The term "acyloxy" is used herein at all occurrences to mean a moiety –O-C(O)-R, wherein R is hydrogen or C_{1-6}alkyl as defined below.

The term " C_{1-4}alkanoyl " is used herein at all occurrences to mean a -C(O)C_{1-4}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-butenyl, 2-butenyl, 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 "C_{1-6}alkoxyC_{1-6}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 "C_{1-4}alkoxyalkyl" is used herein at all occurrences to mean a C_{1-4}alkoxy group as defined above bonded to an alkyl group as defined below, including, but not limited to, -CH_2-CH_2-O-CH_2-CH_2-CH_3 and the like.

The term "C_{1-6}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 C_{1-6}alkyl. 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, thienyl, pyridyl, and the like.

The term "hydroxyC_{1-6}alkoxy" 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-CH_2-CH(OH)CH_3 and the like.

The terms "hydroxyC_{1-6}alkyl" and "hydroxyalkyl" are used herein interchangeably to mean an hydroxyl group bonded to a C_{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, wholly or partially saturated, 5-10-membered ring system (unless the cyclic ring system is otherwise limited) wherein the ring system contains one to 3 heteroatoms selected from oxygen, sulfur, or nitrogen, which ring system may be optionally substituted with C_{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, 1,2,3,4-tetrahydroquinoline, 1,2,3,6-tetrahydropyridine, and hexahydroazepine, which may be optionally substituted by C_{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_a or NR_aR_b moiety, wherein R_a and R_b are, independently, hydrogen or C_1 to C_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_{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:

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

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

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

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

3',5'-Dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

4-Cyclohexyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide;

2',6'-Dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

4-Iodo-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide;

4-Bromo-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide;

N-[3-[1,2,3,6-Tetrahydro-1-(1-methylethyl)-4-pyridinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-(1-Methylethyl)-3-pyrrolidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclopropyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

3'-[4-(1H-Tetrazol-5-yl)]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

4'-[4-(1H-Tetrazol-5-yl)]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

2',5'-Dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3',5'-Dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

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

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

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

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

3'-[4-[[(Dimethylamino)carbonyl]amino]]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

2'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Methyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-[4-(1H-Tetrazol-5-yl)]-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclohexyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

3'-Ethoxycarbonyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Isopropoxy-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Cyano-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Dimethyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Acetamido-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Acetyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

3'-Methanesulfonamido-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Di(methoxycarbonyl)-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Sulfamoyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Uriedo-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Carbamoyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-(4-Piperidinyl)-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide; and

3'-Uriedo-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide.

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

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

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

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

3',5'-Dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

4-Cyclohexyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide;

2',6'-Dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

4-Iodo-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide;

4-Bromo-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide;

N-[3-[1,2,3,6-Tetrahydro-1-(1-methylethyl)-4-pyridinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-(1-Methylethyl)-3-pyrrolidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclopropyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

3'-[4-(1H-Tetrazol-5-yl)]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

2',5'-Dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3',5'-Dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

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

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

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

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

3'-[4-[[(Dimethylamino)carbonyl]amino]]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

2'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Methyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-[4-(1H-Tetrazol-5-yl)]-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclohexyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

3'-Ethoxycarbonyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Isopropoxy-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Cyano-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Dimethyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Acetamido-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Acetyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

3'-Methanesulfonamido-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Di(methoxycarbonyl)-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Sulfamoyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Uriedo-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Carbamoyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-(4-Piperidinyl)-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide; and

3'-Uriedo-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide.

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

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

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

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

3',5'-Dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

2',6'-Dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

3'-[4-(1H-Tetrazol-5-yl)]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

2',5'-Dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3',5'-Dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

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

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

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

2'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Methyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

3'-Ethoxycarbonyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Isopropoxy-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Cyano-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Dimethyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Acetamido-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Acetyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

3'-Methanesulfonamido-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Di(methoxycarbonyl)-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide; and

3'-Uriedo-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide.

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 blood stream. 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 (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 silicaceous 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.

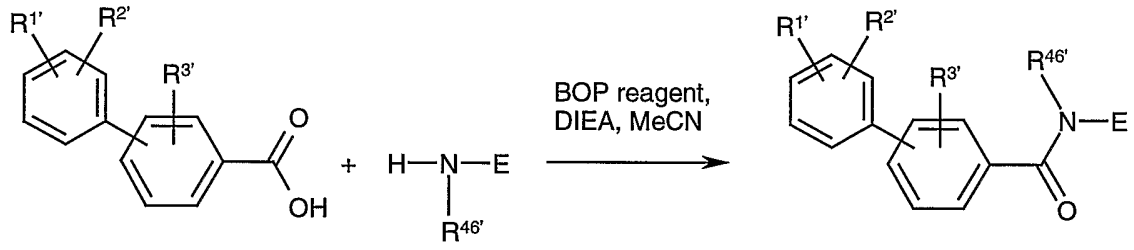
Methods of Preparation

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 $NR^{46'}$ 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-yloxytris(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).

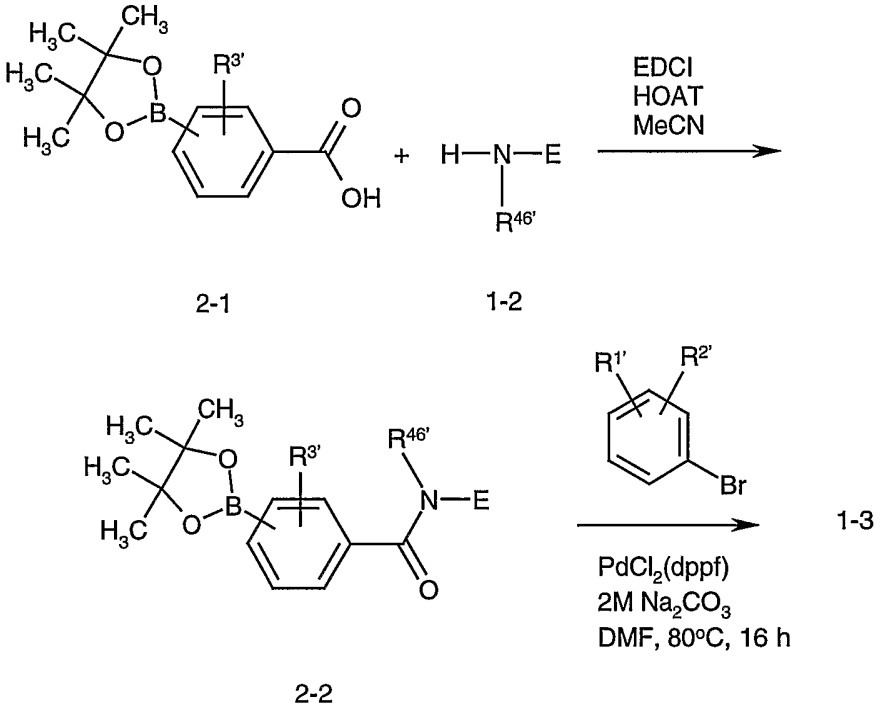
Alternatively, compounds of formula (I) may be obtained as shown in **Scheme 2** by treatment of a suitably substituted aniline **1-2** with a suitably substituted boronobenzoic acid, for example **2-1**, with a suitable coupling reagent, for example 1-(dimethylaminopropyl)-3-ethylcarbodimide hydrochloride 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(diphenyl-phosphino)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



1-1 1-2 1-3

Scheme 2



Compounds 2-2 of Scheme 2 are novel intermediates useful in preparing compounds of formula (I), and as such are also included within the scope of this invention.

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 the methods of international application publication number WO 96/31508 published 10 October 1996.

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 $CONR^{46'}$ and E is represented by group (a), where $R^{46'}$ and R^6 are represented by group D, where D is $(CR^{22}R^{23})_e$, where e is 2, 3 or 4 and R^{22} and R^{23} are independently hydrogen or C_{1-6}alkyl or D is $(CR^{22}R^{23})_f$-G where f is 0, 1, 2 or 3 and G is oxygen, sulfur or $CR^{22}=CR^{23}$, 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 $CONR^{46'}$ 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 $CONR^{46'}$ and E is represented by group (b), where $R^{46'}$ and R^{33} are represented by the group K, where K is $(CR^{34}R^{35})_i$, where i is 2, 3, or 4 and R^{34} and R^{35} are independently hydrogen or C_{1-6}alkyl or K is $(CR^{34}R^{35})_j$-M where j is 0, 1, 2, or 3 and L is oxygen, sulfur or $CR^{34}=CR^{35}$, 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 $CONR^{46'}$ 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 $CONR^{46'}$, NHCO or CH_2NH, 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 $CONR^{46'}$ 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 $CONR^{46'}$, NHCO or CH_2NH, and E represents (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 $CONR^{46'}$, and E represents 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 $CONR^{46'}$, and E represents 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 $CONR^{46'}$ or CH_2NH, and E represents group (i), were prepared according the methods of international application publication number WO 97/19070, published 29 May 1997.

Suitably substituted anilines used to prepare compounds of formula (I) where E is a group or formula (g) are prepared according to the methods of international application publication number WO 96/31508 published 10 October 1996. Other intermediates useful in preparing compounds of formula (I) wherein E is a group (g) are described in international application _____ (Attorney Docket No. P51156, filed July 13, 2001).

Suitably substituted anilines used to prepare compounds of formula (I) where E is a group of formula (h) are prepared according to the methods of international application publication number WO 95/32967, published 7 December 1995 and WO 97/07120, published 27 February 1997, WO 97/07120, published 27 February 1997.

Suitably substituted anilines used to prepare compounds of formula (I) where E is a group of formula (i) are prepared according to 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 4-Methoxy-3-[1-(1-methylethyl)-4-piperidinyl]benzenamine

a) 1-(tert-butoxycarbonyl)-4-hydroxy-4-(2-methoxyphenyl)piperidine

Tert-Butyl 4-oxo-1-piperidinecarboxylate (36 g, 0.18 mol) was added to a solution of 1M 2-methoxyphenylmagnesium bromide in tetrahydrofuran (240 mL, 0.24 mol) stirred at 0°C over 1 h. The mixture was heated to reflux for 1 h and stirred at RT for 5 h. The resulting mixture was carefully quenched with aqueous ammonium chloride (~25 mL) until the supernatant was clear and salts settled. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in dichloromethane, dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by chromatography (silica gel, 20-33% hexane/ethyl acetate) to give the title compound.

b) 1,2,3,6-tetrahydro-4-(2-methoxyphenyl)piperidine

The compound of Preparation 1(a) (37 g, 0.12 mol) dissolved in dichloromethane (225 mL) was treated with trifluoroacetic acid (50 mL) and stirred at RT for 16 h. The resulting mixture was concentrated *in vacuo* to give the title compound, which was used without purification.

c) 4-(2-methoxyphenyl)piperidine

A mixture of the compound of Preparation 1(b) (0.12 mol) dissolved in methanol (125 mL) and 10% palladium-on-carbon (2.5 g) in a Parr bottle was shaken in a hydrogen atmosphere (50 psi) for 3.5 h. The mixture was filtered through Celite®, the filtrate was concentrated *in vacuo*, and the residue was partitioned between ethyl acetate and aqueous sodium hydroxide. The organic phase was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound.

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

Trifluoroacetic anhydride (8.1 g, 39 mmol) was added portionwise over 10 min to a solution of the compound of Preparation 1(c) (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 ($MgSO_4$), and concentrated *in vacuo* to afford 10 g (99%) of the title compound as an amber oil. MS(ES) m/e 288.1 $[M+H]^+$.

e) 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 1(d) (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 organic extracts were combined and washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give 12 g (>100%) of a 2.2:1 mixture of the title compound and 4-(2-methoxy-3-nitrophenyl)-1-(trifluoroacetyl)piperidine. 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 $[M+H]^+$.

f) 4-(2-methoxy-5-nitrophenyl)piperidine

Potassium carbonate (10 g, 74 mmol) was added to a solution of the compound of Preparation 1(e) (4.9 g, 15 mmol) in 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 the aqueous layer was extracted with dichloromethane. The organic extracts were combined and washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give 3.7 g (>100%) of the title compound as an off-white solid. MS(ES) m/e 237.2 $[M+H]^+$.

g) 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 1(f) (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 organic extracts were combined and washed with water (3 × 100 mL) and with brine, dried ($MgSO_4$), and concentrated *in vacuo* to provide 4.0 g (90%) of the title compound as a yellow solid. MS(ES) m/e 279.2 $[M+H]^+$.

h) 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 1(g) (4.0 g, 14 mmol) in ethanol (100 mL) in a Parr bottle. 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 × 100 mL). The ether solution was dried ($MgSO_4$) and concentrated *in vacuo* to provide 3.0 g (84%) of the title compound as a tan solid. MS(ES) m/e 249.2 $[M+H]^+$.

Preparation 2

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 1(h) (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-ethylcarbodimide 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 ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. MS(ES) m/e 478.4 $[M+H]^+$.

Preparation 3

Preparation of 2-Methoxy-3-[1-(1-methylethyl)-4-piperidinyl]benzenamine

Following the general procedure of Example 1(f)(g)(h), except substituting 4-(2-methoxy-3-nitrophenyl)-1-(trifluoroacetyl)piperidine [Preparation 1(e)] for the compound of Preparation 1(e), gave the title compound.

Preparation 4

Preparation of 4-Methoxy-3-[1-cyclopentyl-4-piperidinyl]benzenamine

a) 4-(2-methoxy-5-nitrophenyl)-1-(cyclopentyl)piperidine

A solution of the compound of Preparation 1(f) (3.4 g, 14.4 mmol) in methanol (21 mL) was treated with acetic acid (8.5 g, 0.14 mol), cyclopentanone (6.12 g, 71.4 mmol) and sodium cyanoborohydride (3.74 g, 57.8 mmol). The resulting mixture was heated to reflux for 16 h, concentrated *in vacuo*, and the residue was partitioned between dichloromethane and 2N sodium hydroxide. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound.

b) 4-methoxy-3-[1-cyclopentyl-4-piperidinyl]benzenamine

Following the general procedure of Preparation 1(h), except substituting the compound of Preparation 4(a) for the compound of Preparation 1(g), gave the title compound.

Preparation 5

Preparation of N-[4-Methoxy-3-[1-cyclopentyl-4-piperidinyl]phenyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide Following the general procedure of Preparation 2, except substituting the compound of Preparation 4(b) for

the compound of Preparation 1(h), gave the title compound. MS(ES) m/e 504.4 $[M+H]^+$.

Preparation 6

Preparation of 3-[1,2,3,6-Tetrahydro-1-(1-methylethyl)-4-pyridinyl]-4-methoxyaniline

a) 1,2,3,6-tetrahydro-4-(2-methoxyphenyl)-1-(trifluoroacetyl)piperidine

Following the general procedure of Preparation 1(d), except substituting the compound of Preparation 1(b) for the compound of Preparation 1(c), gave the title compound.

b) 1,2,3,6-tetrahydro-4-(2-methoxy-5-nitrophenyl)-1-(trifluoroacetyl)piperidine

Following the general procedure of Preparation 1(e), except substituting the compound of Preparation 6(a) for the compound of Preparation 1(d), gave the title compound. MS(ES) m/e 235.0 $[M+H]^+$.

c) 1,2,3,6-tetrahydro-4-(2-methoxy-5-nitrophenyl)piperidine

Following the general procedure of Preparation 1(f), except substituting the compound of Preparation 6(b) for the compound of Preparation 1(e), gave the title compound..

d) 1,2,3,6-tetrahydro-4-(2-methoxy-5-nitrophenyl)-1-(1-methylethyl)piperidine

Following the general procedure of Preparation 1(g), except substituting the compound of Preparation 6(c) for the compound of Preparation 1(f), gave the title compound.

e) 3-[1,2,3,6-tetrahydro-1-(1-methylethyl)-4-pyridinyl]-4-methoxyaniline

A solution of stannous chloride dihydrate (0.7 g, 3.1 mmol) in concentrated hydrochloric acid (1 mL) was added in portions to a solution of the compound of Preparation 6(d) in acetic acid (2 mL) over 1 h. The mixture was stirred at RT for 16 h, made alkaline with 10% sodium carbonate and with 10% sodium hydroxide, extracted with dichloromethane, and the organic extracts were combined and washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound.

Preparation 7

Preparation of 3-[1-(1-Methylethyl)-3-pyrrolidinyl]-4-methoxyaniline

a) 1-benzyl-3-hydroxy-3-(2-methoxyphenyl)pyrrolidine

Following the general procedure of Preparation 1(a), except substituting 1-benzyl-3-pyrrolidinone for tert-butyl 4-oxo-1-piperidinecarboxylate, gave the title compound. MS(ES) m/e 284.2 $[M+H]^+$.

b) 1-benzyl-3-(2-methoxyphenyl)-dihydropyrrole

Following the general procedure of Preparation 1(b), except substituting the compound of Preparation 7(a) for the compound of Preparation 1(a), gave the title compound. MS(ES) m/e 266.4 $[M+H]^+$.

c) 1-benzyl-3-(2-methoxyphenyl)pyrrolidine

Following the general procedure of Preparation 1(c), except substituting the compound of Preparation 7(b) for the compound of Preparation 1(b), gave the title compound. MS(ES) m/e 268.2 $[M+H]^+$.

d) 3-(2-methoxyphenyl)pyrrolidine

The compound of Preparation 7(c) (200 mg, 0.7 mmol) was treated with 1-chloroethyl chloroformate (210 mg, 1.5 mmol) and then with methanol to give the title compound.

e) 1-trifluoroacetyl-3-(2-methoxyphenyl)pyrrolidine

Following the general procedure of Preparation 1(d), except substituting the compound of Preparation 7(d) for the compound of Preparation 1(c), gave the title compound.

f) 1-trifluoroacetyl-3-(2-methoxy-5-nitrophenyl)pyrrolidine and 1-trifluoroacetyl-3-(2-methoxy-3-nitrophenyl)pyrrolidine

Following the general procedure of Preparation 1(e), except substituting the compound of Preparation 7(e) for the compound of Preparation 1(d), gave the title compounds in a 3:1 ratio.

g) 3-(2-methoxy-5-nitrophenyl)pyrrolidine and 3-(2-methoxy-3-nitrophenyl)pyrrolidine

Following the general procedure of Preparation 1(f), except substituting the compounds of Preparation 7(f) for the compound of Preparation 1(e), gave the title compounds in a 3:1 ratio. MS(ES) m/e 265.2 $[M+H]^+$.

h) 1-(1-methylethyl)-3-(2-methoxy-5-nitrophenyl)pyrrolidine and 1-(1-methylethyl)-3-(2-methoxy-3-nitrophenyl)pyrrolidine

Following the general procedure of Preparation 1(g), except substituting the compounds of Preparation 7(g) for the compound of Preparation 1(e), gave the title compounds in a 2:1 ratio.

Preparation 8

Preparation of 3-[1-Cyclopropyl-4-piperidinyl]-4-methoxyaniline

Following the general procedure of Preparation 4(a)(b), except substituting [(1-ethoxycyclopropane)oxy]trimethylsilane for cyclopentanone, gave the title compound.

Preparation 9

Preparation of 3-[1-(tert-Butoxycarbonyl)-4-piperidinyl]-4-methoxyaniline

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

Following the general procedure of Preparation 1(h), except substituting the compound of Preparation 1(e) for the compound of Preparation 1(g), gave the title compound.

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

Following the general procedure of Preparation 1(f), except substituting the compound of Preparation 9(a) for the compound of Preparation 1(e), gave the title compound.

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

The compound of Preparation 9(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 $[M+H]^+$.

Preparation 10

Preparation of 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

Following the procedure of Preparation 2, except substituting 4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]benzenamine, (WO 9901127) for the compound of Preparation 1(h), gave the title compound. MS(ES) m/e 536.4 $[M+H]^+$.

Example 1

Preparation of N-[3-[1-(1-Methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide

A mixture of the compound of Preparation 1(h) (20 mg, 0.08 mmol), 1,1'-biphenyl-4-carboxylic acid (16 mg, 0.08 mmol) and diisopropylethylamine (26 mg, 0.2 mmol) in acetonitrile (15 mL) was stirred at RT and treated with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate ("BOP") (40 mg, 0.09 mmol). The resulting solution was stirred for 16 h, concentrated *in vacuo*, and the residue was dissolved in dimethyl sulfoxide and purified by HPLC (YMC GuardPak

ODS-A, 50 × 20 mm, 20 mL/min, A:0.1% trifluoroacetic acid in acetonitrile B:0.1% aqueous trifluoroacetic acid, A:25 to 80% during 10 min, UV detection at 254 nm) to afford the title compound. MS(ES) m/e 429.4 $[M+H]^+$.

Example 2

Preparation of N-[3-[1-(1-Methylethyl)-4-piperidinyl]-2-methoxyphenyl]-1,1'-biphenyl-4-carboxamide

Following the general procedure of Example 1, except substituting the compound of Preparation 3 for the compound of Preparation 1(e), gave the title compound. MS(ES) m/e 429.4 $[M+H]^+$.

Example 3

Preparation of 3'-Methyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide

3'-Methyl-1,1'-biphenyl-4-carboxylic acid (0.1 mmol), the compound of Preparation 1(h) (0.1 mmol) and triethylamine were dissolved in acetonitrile (1 mL) and treated with 1-hydroxy-7-azabenzotriazole ("HOAT") (0.1 mmol) dissolved in dimethylformamide (0.5 mL) followed by 1-(dimethylaminopropyl)-3-ethylcarbodimide hydrochloride ("EDCI")(0.12 mmol) in dimethylformamide/acetonitrile (0.5 mL). The resulting mixture was shaken at RT for 16 h, concentrated, 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 443.4$[M+H]^+$.

Examples 4-9

Following the general procedure of Example 3, except substituting 2'-chloro-1,1'-biphenyl-4-carboxylic acid, 3',5'-dichloro-1,1'-biphenyl-4-carboxylic acid, 4-(cyclohexyl)benzoic acid, 2',6'-dichloro-1,1'-biphenyl-4-carboxylic acid, 4-iodobenzoic acid, and 4-bromobenzoic acid for 3'-methyl-1,1'-biphenyl-4-carboxylic acid, gave the following compounds:

2'-chloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 463.2 $[M+H]^+$;

3',5'-dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 497.2 $[M+H]^+$;

4-cyclohexyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide: MS(ES) m/e 435.4$[M+H]^+$;

2',6'-dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 497.4$[M+H]^+$;
4-iodo-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide: MS(ES) m/e 479.2 $[M+H]^+$; and
4-bromo-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide: MS(ES) m/e 431.2 $[M+H]^+$.

Examples 10-53

A mixture of a solution of the compound of Preparation 2 in dimethylformamide (0.188M, 0.8 mL, 0.15 mmol), a solution of an appropriately substituted aryl bromide in dimethylformamide (1M, 0.3 mL. 0.3 mmol), a solution of [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) ("$PdCl_2$(dppf)") 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 × 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 following compounds:

3'-hydroxymethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 459.1 $[M+H]^+$;

5'-chloro-2'-methyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 477.2 $[M+H]^+$;

3'-fluoro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 447.1 $[M+H]^+$;

3'-hydroxy-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 445.1 $[M+H]^+$;

3'-ethoxycarbonyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 501.4 $[M+H]^+$;

4'-[4-(1H-tetrazol-5-yl)]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 497.4 $[M+H]^+$;

4'-ethoxycarbonyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 501.4 $[M+H]^+$;

2',5'-dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 457.3 $[M+H]^+$;

4'-methyl-2'-nitro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 488.4 $[M+H]^+$;

2'-amino-4'-trifluoromethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 512.2 $[M+H]^+$;

4'-acetamido-3'-methyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 500.4 $[M+H]^+$;

4'-methanesulfonyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 507.2 $[M+H]^+$;

4'-acetamido-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 486.4 $[M+H]^+$;

3'-sulfamoyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 508.2 $[M+H]^+$;

4'-hydroxymethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 459.1 $[M+H]^+$;

4'-acetamido-3'-fluoro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 504.4 $[M+H]^+$;

2'-hydroxymethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 517.4 $[M+H]^+$;

3'-uriedo-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 545.2 $[M+H]^+$;

3'-amino-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 444.3 $[M+H]^+$;

2'-carbamoyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 472.3 $[M+H]^+$;

4'-chloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 463.3 $[M+H]^+$;

4'-methoxy-2'-methyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 473.3 $[M+H]^+$;

3'-chloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 463.3 $[M+H]^+$;

4'-isopropoxy-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 487.3 $[M+H]^+$;

3'-trifluoromethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 497.1 $[M+H]^+$;

4'-dimethylamino-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 472.3$[M+H]^+$;

3'-chloro-4'-methyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 477.3$[M+H]^+$;

4'-fluoro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 447.1 $[M+H]^+$;

3'-isopropoxy-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 487.3 $[M+H]^+$;

3'-cyano-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 454.1 $[M+H]^+$;

3',5'-dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 457.3 $[M+H]^+$;

4'-amino-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 444.3 $[M+H]^+$;

5'-amino-2'-methyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 458.3 $[M+H]^+$;

3'-aminomethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 458.3 $[M+H]^+$;

3'-[4-(1H-tetrazol-5-yl)]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 497.4 $[M+H]^+$;

3'-dimethylamino-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 472.4$[M+H]^+$;

3'-acetyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 471.4 $[M+H]^+$;

3'-butylamino-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 500.6$[M+H]^+$;

3'-methylamino-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 458.4$[M+H]^+$;

3'-acetamido-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 486.4$[M+H]^+$;

3'-methanesulfonamido-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 522.2 $[M+H]^+$;

3'-(5-methyl-1,2,4-oxadiazol-3-yl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 511.4 $[M+H]^+$;

3'-[4-[[(dimethylamino)carbonyl]amino]]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 515.4$[M+H]^+$; and

3'-ethoxy-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 473.2$[M+H]^+$.

Example 54

Preparation of N-[3-[1,2,3,6-Tetrahydro-1-(1-methylethyl)-4-pyridinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide

The compound of Preparation 6(e) (25 mg, 0.1 mmol) was added to a mixture of 1,1'-biphenyl-4-carboxylic acid (20 mg, 0.1 mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (49 mg, 0.11 mmol) and triethylamine (51 mg, 0.5 mmol) in dichloromethane, and stirred at RT for 16 h. The resulting mixture was concentrated *in vacuo* and the residue was dissolved in dimethyl sulfoxide 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 afford the title compound. MS(ES) m/e 427.2 $[M+H]^+$.

Examples 55-56

Preparation of N-[3-[1-(1-Methylethyl)-3-pyrrolidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide) and N-[3-[1-(1-methylethyl)-3-pyrrolidinyl]-2-methoxyphenyl]-1,1'-biphenyl-4-carboxamide

Following the general procedure of Example 54, except substituting the compounds of Preparation 7(h) for the compound of Preparation 6(e), gave the title compounds in a 2:1 ratio which were separated by HPLC. MS(ES) m/e 415.4 $[M+H]^+$.

Examples 57-58

Following the general procedure of Example 54, except substituting the compounds of Preparation 8 and Preparation 4(b) for the compound of Preparation 6(e), gave the following compounds:

N-[3-[1-cyclopropyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 427.2 $[M+H]^+$; and

N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 455.2 $[M+H]^+$.

Example 59

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

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

Following the general procedure of Example 54, except substituting the compound of Preparation 9(c) for the compound of Preparation 6(e), gave the title compound. MS(ES) m/e 487.4 $[M+H]^+$.

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

Following the general procedure of Preparation 1(b), except substituting the compound of Example 59(a) for the compound of Preparation 1(a), gave the title compound. MS(ES) m/e 387.4 $[M+H]^+$.

Examples 60

Preparation of N-[3-[1-Cyclohexyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide

Following the general procedure of Preparation 4(a), except substituting the compound of Example 59(b) for the compound of Preparation 1(f) and substituting cyclohexanone for cyclopentanone, gave the title compound. MS(ES) m/e 469.4 $[M+H]^+$.

Examples 61-62

Following the general procedure of Example 60, except substituting 3-pentanone and 2,2-(dimethyl)propanal for cyclohexanone, gave the following compounds:

N-[3-[1-(3-pentyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 457.4 $[M+H]^+$; and

N-[3-[1-(2,2-dimethylpropyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 457.4 $[M+H]^+$.

Examples 63-64

Following the general procedure of Example 58, except substituting 2-chloro-1,1'-biphenyl-4-carboxylic acid and 3'-methyl-1,1'-biphenyl-4-carboxylic acid for 1,1'-biphenyl-4-carboxylic acid, gave the following compounds:

2'-chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 489.2 $[M+H]^+$; and

3'-methyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 461.2 $[M+H]^+$.

Examples 65-79

Following the general procedure of Example 10, except substituting the compound of Preparation 5 for the compound of Preparation 1(h) and substituting the appropriately substituted aryl bromide for 3-hydroxymethyl-1-bromobenzene, gave the following compounds:

3'-[4-(1H-tetrazol-5-yl)]-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 523.4 $[M+H]^+$;

3'-ethoxycarbonyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 527.3 $[M+H]^+$;

3'-chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 489.3 $[M+H]^+$;

3'-isopropoxy-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 513.5 $[M+H]^+$;

3'-cyano-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 480.3 $[M+H]^+$;

3',5'-dimethyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 483.5 $[M+H]^+$;

3'-acetamido-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 512.5$[M+H]^+$;

3'-acetyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 497.3 $[M+H]^+$;

3'-(3-methyl-1,2,4-oxadiazol-5-yl)-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 537.3 $[M+H]^+$;

3'-methanesulfonamido-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 548.5 $[M+H]^+$;

3',5'-chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 523.3 $[M+H]^+$;

3',5'-di(methoxycarbonyl)-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 571.3 $[M+H]^+$;

3'-sulfamoyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 534.3 $[M+H]^+$;

3'-uriedo-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 513.5 $[M+H]^+$; and

3'-carbamoyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 498.4 $[M+H]^+$.

Example 80

Preparation of 3'-Uriedo-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide

Following the general procedure of Example 10, except substituting the compound of Preparation 10 for the compound of Preparation 1(h) and substituting 3-uriedo-1-bromobenzene for 3-hydroxymethyl-1-bromobenzene, gave the title compound MS(ES) m/e 545.4 $[M+H]^+$.

Biological Data:

CCR5 Receptor Binding Assay

CHO cell membranes (0.25 $x10^6$ cell equivalents) derived from CHO cells stably transfected with CCR5 were incubated with 0.3 ^{125}I-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 % NaN_3. 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 Ca^{2+} mobilization in RBL 2H3 cells stably expressing the hCCR5 receptor (RBL 2H3 hCCR5). Agonist activity is determined by Ca^{2+} mobilization in the same cells which is inhibitable 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 10^6 cells/mL with Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM $NaHCO_3$, 1 mM KH_2PO_4 and 11 mM glucose) containing 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% BSA and centrifuged at 200g for 3 min. Cells were resuspended at 2 X 10^6 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 (10^6 cells/mL) were resuspended in cold KRH with 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ 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 Ca^{2+} attained after 33 nM RANTES stimulation was calculated as described by Grynkiewicz *et al.*, (1985). The percent of maximal RANTES-induced Ca^{2+} was determined for each concentration of antagonist and the IC_{50}, 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 IC_{50} 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 IC_{50} 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.

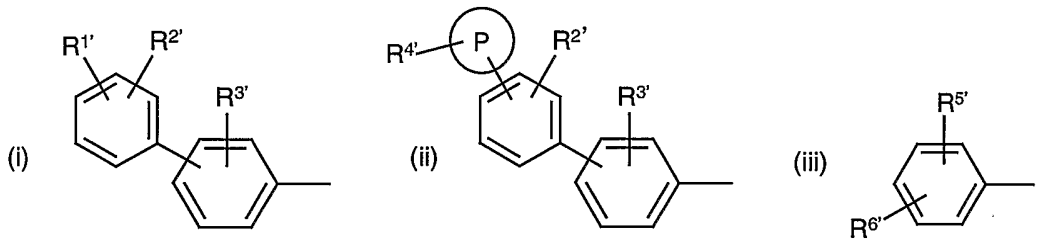
What is claimed is:

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

Ar—A—E

Formula (I)

wherein Ar represents 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 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, $(CH_2)_aNR^{7'}R^{8'}$, $(CH_2)_aNR^{7'}COR^{9'}$, $(CH_2)_aNR^{7'}CO_2R^{10'}$, $(CH_2)_aNR^{7'}SO_2R^{11'}$, $(CH_2)_aCONR^{12'}R^{13'}$, hydroxy$C_{1-6}$alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), $(CH_2)_aCO_2C_{1-6}$alkyl, $(CH_2)_bOC(O)R^{14'}$, $CR^{15'}{=}NOR^{16'}$, $CNR^{15'}{=}NOR^{16'}$, $COR^{17'}$, $CONR^{12'}R^{13'}$, $CONR^{12'}(CH_2)_cOC_{1-4}$alkyl, $CONR^{12'}(CH_2)_aCO_2R^{18'}$, $CONHNR^{19'}R^{20'}$, $CONR^{12'}SO_2R^{21'}$, $CO_2R^{22'}$, cyano, trifluoromethyl, $NR^{7'}R^{8'}$, $NR^{7'}COR^{9'}$, $NR^{23'}CO(CH_2)_aNR^{23'}R^{24'}$, $NR^{23'}CONR^{23'}R^{24'}$, $NR^{7'}CO_2R^{10'}$, $NR^{7'}SO_2R^{11'}$, $N{=}CNR^{23'}NR^{23'}R^{24'}$, nitro, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, $OC(O)NR^{25'}R^{26'}$, $SR^{27'}$, $SOR^{28'}$, $SO_2R^{28'}$, $SO_2NR^{25'}R^{26'}$ or halogen;

$R^{3'}$ and $R^{4'}$ are 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, $CONR^{29'}R^{30'}$, $CO_2R^{31'}$, cyano, aryl, trifluoromethyl, $NR^{29'}R^{30'}$, nitro, hydroxy, C_{1-6}alkoxy, acyloxy, or halogen;

$R^{5'}$ 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}alkynyl, $(CH_2)_d$-$OR^{32'}$, $(CH_2)_d$-$COR^{33'}$, $(CH_2)_d$-$CR^{34'}$=$NOR^{35'}$, $CONR^{36'}R^{37'}$, $CO_2R^{38'}$, hydroxy, $O(CH_2)_e$-$R^{39'}$, $NR^{36'}R^{37'}$, $SR^{40'}$, $SO_2NR^{41'}R^{42'}$ or halogen; or, $R^{5'}$ and $R^{6'}$ form a fused benzo ring optionally substituted with C_{1-6} 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;

$R^{22'}$ is hydrogen or C_{1-6}alkyl optionally substituted with one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or $NR^{7'}R^{8'}$;

$R^{23'}$ and $R^{24'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{25'}$ and $R^{26'}$ are independently hydrogen or C_{1-6}alkyl, 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_{1-6}alkyl;

$R^{28'}$ is C_{1-6}alkyl;

$R^{29'}$, $R^{30'}$ and $R^{31'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{32'}$ 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 $CO_2R^{45'}$, 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_2H, CO_2C_{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;

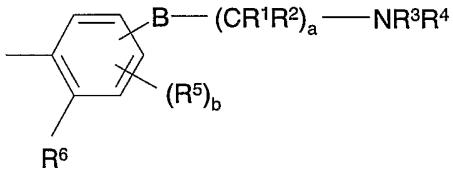
c' is 1, 2 or 3;

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_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

E represents a group (a):



(a);

wherein:

B is oxygen, C≠C, $S(O)_c$, $CR^7{=}CR^8$, 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, 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, $OCOR^{12}$, $NHCOCF_3$, $NHSO_2R^{13}$, $NHCO_2R^{14}$, or $NHCOC_{0-6}$alkyl wherein the alkyl of $NHCOC_{0-6}$alkyl is optionally substituted by OH;

R^5 is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{15}R^{16}$, CO_2R^{17}, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$ or halogen;

R^6 is hydrogen, C_{1-6}alkyl, aryl, trifluoromethyl, hydroxy, C_{1-6}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_{1-6}alkyl;

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

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

a is 1, 2, 3, or 4;

b is 1 or 2;

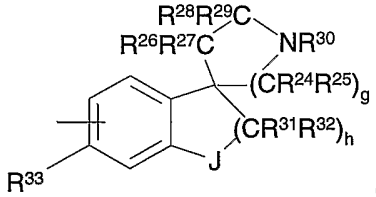
c and d are independently 0, 1 or 2;

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_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

alternatively, E represents a group (b):



(b);

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

R^{30} is hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl;

R^{33} is hydrogen, C_{1-6}alkyl, trifluoromethyl, hydroxy or halogen, or R^{33} and $R^{30'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N;

J is oxygen, $CR^{36}R^{37}$, or NR^{38}, or J is a group $S(O)_k$;

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

g is 1, 2 or 3;

h is 1, 2 or 3;

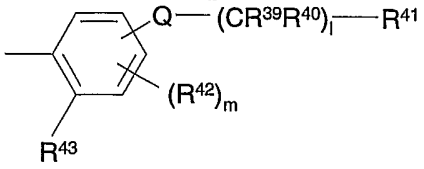
i is 2, 3, or 4;

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 $CONR^{46'}$, NHCO, -$NHCH_2$, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

alternatively, E represents a group (c):



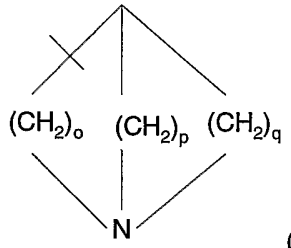
(c);

wherein:

Q is oxygen, $S(O)_n$, $CR^{44}=CR^{45}$, $CR^{44}R^{45}$, or Q is NR^{46};

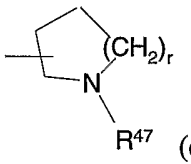
R^{39} and R^{40} are independently hydrogen or C_{1-6}alkyl;

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



(d)

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



(e)

R^{42} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{48}R^{49}$, CO_2R^{50}, trifluoromethyl, $NHCO_2R^{51}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_sR^{52}$, $SO_2NR^{53}R^{54}$, 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 C_{1-6}alkyl;

R^{47} is hydrogen, C_{1-6}alkyl, or C_{3-7} cycloalkyl;

R^{51} and R^{52} are independently C_{1-6}alkyl;

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;

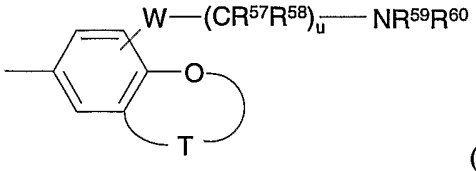
r is 0,1, 2, or 3;

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 CH_2NH,

alternatively, E represents a group (f):



(f);

wherein:

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, 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, $OCOR^{63}$, $NHCOCF_3$, $NHSO_2R^{64}$, $NHCO_2R^{65}$, or $NHCOC_{0-6}$alkyl wherein the alkyl of $NHCOC_{0-6}$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;

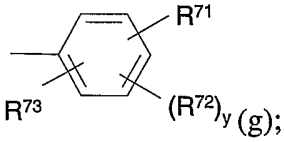
v is 2 or 3;

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_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

alternatively, E represents a group (g):



(g);

wherein:

R^{71} is a 5- to 7-membered saturated or partially saturated heterocyclic ring containing a 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;

R^{72} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{74}R^{75}$, CO_2R^{76}, trifluoromethyl, $NHCO_2R^{77}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_zR^{78}$, $SO_2NR^{79}R^{80}$, 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;

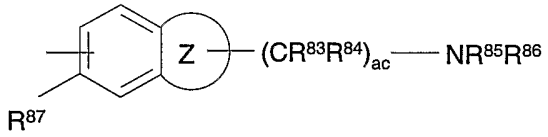
z is 0, 1, or 2;

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 $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

alternatively, E represents a group (h):



(h);

wherein:

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, 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, $OCOR^{92}$, $NHCOCF_3$, $NHSO_2R^{93}$, $NHCO_2R^{94}$, or $NHCOC_{0-6}$alkyl wherein the alkyl of $NHCOC_{0-6}$alkyl is optionally substituted by 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 $(CR^{95}R^{96})_{ad}$ 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_{1-6}alkyl;

R^{93} and R^{94} are independently C_{1-6}alkyl;

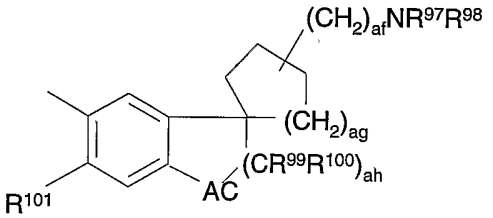
ac is 0 to 4;

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 $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

alternatively, E represents a group (i):



(i);

wherein:

R^{97} and R^{98} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, 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, $CONR^{102}R^{103}$, $NR^{104}R^{105}$, hydroxy, $OCOR^{106}$, $NHCOCF_3$, $NHSO_2R^{107}$, $NHCO_2R^{108}$, or $NHCOC_{0-6}$alkyl wherein the alkyl of $NHCOC_{0-6}$alkyl is optionally substituted by OH;

R^{99} and R^{100} are independently hydrogen or C_{1-6}alkyl;

R^{101} is hydrogen or C_{1-6}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_{1-6}alkyl;

R^{107} and R^{108} are independently C_{1-6}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.

2. A compound selected from:

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

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

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

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

3',5'-Dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

4-Cyclohexyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide;

2',6'-Dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

4-Iodo-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide;

4-Bromo-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide;

N-[3-[1,2,3,6-Tetrahydro-1-(1-methylethyl)-4-pyridinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-(1-Methylethyl)-3-pyrrolidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclopropyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

3'-[4-(1H-Tetrazol-5-yl)]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

4'-[4-(1H-Tetrazol-5-yl)]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

2',5'-Dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3',5'-Dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

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

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

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

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

3'-[4-[[(Dimethylamino)carbonyl]amino]]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

2'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Methyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-[4-(1H-Tetrazol-5-yl)]-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclohexyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

3'-Ethoxycarbonyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Isopropoxy-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Cyano-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Dimethyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Acetamido-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Acetyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

3'-Methanesulfonamido-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Di(methoxycarbonyl)-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Sulfamoyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Uriedo-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Carbamoyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-(3-Methyl-1,2,4-oxadiazol-5-yl)-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide; and

3'-Uriedo-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide, or a pharmaceutically acceptable salt or solvate thereof.

3. A compound selected from:

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

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

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

3',5'-Dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

4-Cyclohexyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide;

2',6'-Dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

4-Iodo-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide;

4-Bromo-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-benzamide;

N-[3-[1,2,3,6-Tetrahydro-1-(1-methylethyl)-4-pyridinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-(1-Methylethyl)-3-pyrrolidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclopropyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

3'-[4-(1H-Tetrazol-5-yl)]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

2',5'-Dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3',5'-Dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

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

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

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

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

3'-[4-[[(Dimethylamino)carbonyl]amino]]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

2'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Methyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-[4-(1H-Tetrazol-5-yl)]-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclohexyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

3'-Ethoxycarbonyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Isopropoxy-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Cyano-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Dimethyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Acetamido-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Acetyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

3'-Methanesulfonamido-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3',5'-Di(methoxycarbonyl)-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Sulfamoyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Uriedo-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Carbamoyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-(3-Methyl-1,2,4-oxadiazol-5-yl)-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide; and

3'-Uriedo-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide or a pharmaceutically acceptable salt or solvate thereof..

4. A compound selected from:

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

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

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

3',5'-Dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

2',6'-Dichloro-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[1-Cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

3'-[4-(1H-Tetrazol-5-yl)]-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

2',5'-Dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3',5'-Dimethyl-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

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

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

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

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

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

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

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

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

2'-Chloro-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Methyl-N-[3-[1-cyclopentyl-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide; and

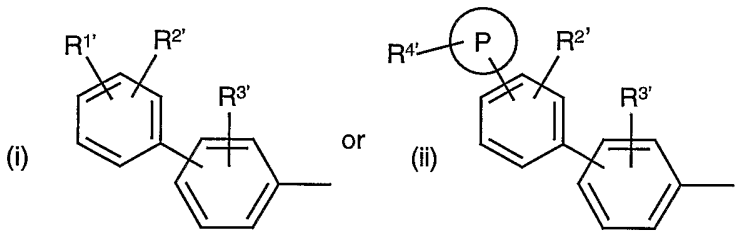
N-[3-[1-(3-Pentyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide, or a pharmaceutically acceptable salt or solvate thereof.

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

Ar—A—E

Formula (I)

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



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 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, $(CH_2)_aNR^{7'}R^{8'}$, $(CH_2)_aNR^{7'}COR^{9'}$, $(CH_2)_aNR^{7'}CO_2R^{10'}$, $(CH_2)_aNR^{7'}SO_2R^{11'}$, $(CH_2)_aCONR^{12'}R^{13'}$, hydroxy$C_{1-6}$alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), $(CH_2)_aCO_2C_{1-6}$alkyl, $(CH_2)_bOC(O)R^{14'}$, $CR^{15'}=NOR^{16'}$, $CNR^{15'}=NOR^{16'}$, $COR^{17'}$, $CONR^{12'}R^{13'}$, $CONR^{12'}(CH_2)_cOC_{1-4}$alkyl, $CONR^{12'}(CH_2)_aCO_2R^{18'}$, $CONHNR^{19'}R^{20'}$, $CONR^{12'}SO_2R^{21'}$, $CO_2R^{22'}$, cyano, trifluoromethyl, $NR^{7'}R^{8'}$, $NR^{7'}COR^{9'}$, $NR^{23'}CO(CH_2)_aNR^{23'}R^{24'}$, $NR^{23'}CONR^{23'}R^{24'}$, $NR^{7'}CO_2R^{10'}$, $NR^{7'}SO_2R^{11'}$, $N=CNR^{23'}NR^{23'}R^{24'}$, nitro, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-}

$_6$alkoxyC_{1-6}alkoxy, OC(O)$NR^{25'}R^{26'}$, $SR^{27'}$, $SOR^{28'}$, $SO_2R^{28'}$, $SO_2NR^{25'}R^{26'}$ or halogen;

$R^{3'}$ and $R^{4'}$ are 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, $CONR^{29'}R^{30'}$, $CO_2R^{31'}$, cyano, aryl, trifluoromethyl, $NR^{29'}R^{30'}$, nitro, hydroxy, C_{1-6}alkoxy, acyloxy, 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;

$R^{22'}$ is hydrogen or C_{1-6}alkyl optionally substituted with one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or $NR^{7'}R^{8'}$;

$R^{23'}$ and $R^{24'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{25'}$ and $R^{26'}$ are independently hydrogen or C_{1-6}alkyl, 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_{1-6}alkyl;

$R^{28'}$ is C_{1-6}alkyl;

$R^{29'}$, $R^{30'}$ and $R^{31'}$ 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;

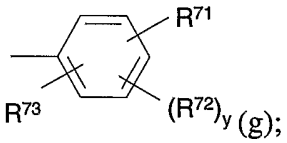
b' is 0, 1, 2 or 3;

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, Ar is (i) or (ii), A is $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl, and E is a group (g):



wherein:

R^{71} is a 5- to 7-membered saturated or partially saturated heterocyclic ring containing a 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;

R^{72} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{74}R^{75}$, CO_2R^{76}, trifluoromethyl, $NHCO_2R^{77}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_zR^{78}$, $SO_2NR^{79}R^{80}$, 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;

aa is 2, 3 or 4; and

ab is 0, 1, 2 or 3.

6. The compound of formula (I) according to claim 5, wherein Ar is (i) or (ii), E is group (g), A is $CONR^{46'}$ and $R^{46'}$ is hydrogen.

7. The compound of formula (I) according to claim 6 wherein, A is attached to group (g) meta to R^{71} and para to R^{72}, and wherein R^{71} is piperidin-4-

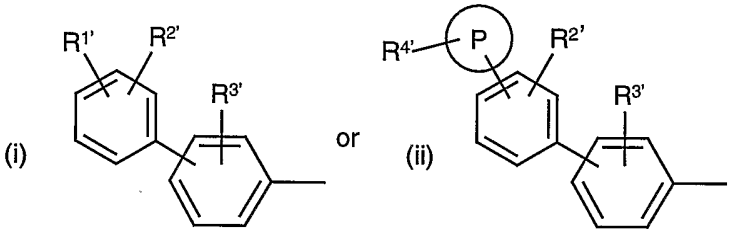
yl, 1,2,3,6-tetrahydropyridin-4-yl, or pyrrolidin-3-yl substituted on nitrogen with isopropyl, 3-pentyl, cyclopropyl, or cyclopentyl, R^{72} is methoxy, y is 1, and R^{73} is hydrogen.

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

Ar—A—E

Formula (I)

wherein Ar represents a group selected from (i) or (ii);



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 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, $(CH_2)_aNR^{7'}R^{8'}$, $(CH_2)_aNR^{7'}COR^{9'}$, $(CH_2)_aNR^{7'}CO_2R^{10'}$, $(CH_2)_aNR^{7'}SO_2R^{11'}$, $(CH_2)_aCONR^{12'}R^{13'}$, hydroxy$C_{1-6}$alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), $(CH_2)_aCO_2C_{1-6}$alkyl, $(CH_2)_bOC(O)R^{14'}$, $CR^{15'}=NOR^{16'}$, $CNR^{15'}=NOR^{16'}$, $COR^{17'}$, $CONR^{12'}R^{13'}$, $CONR^{12'}(CH_2)_cOC_{1-4}$alkyl, $CONR^{12'}(CH_2)_aCO_2R^{18'}$, $CONHNR^{19'}R^{20'}$, $CONR^{12'}SO_2R^{21'}$, $CO_2R^{22'}$, cyano, trifluoromethyl, $NR^{7'}R^{8'}$, $NR^{7'}COR^{9'}$, $NR^{23'}CO(CH_2)_aNR^{23'}R^{24'}$, $NR^{23'}CONR^{23'}R^{24'}$, $NR^{7'}CO_2R^{10'}$, $NR^{7'}SO_2R^{11'}$, $N=CNR^{23'}NR^{23'}R^{24'}$, nitro, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, $OC(O)NR^{25'}R^{26'}$, $SR^{27'}$, $SOR^{28'}$, $SO_2R^{28'}$, $SO_2NR^{25'}R^{26'}$ or halogen;

$R^{3'}$ and $R^{4'}$ are 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, $CONR^{29'}R^{30'}$, $CO_2R^{31'}$, cyano, aryl, trifluoromethyl, $NR^{29'}R^{30'}$, nitro, hydroxy, C_{1-6}alkoxy, acyloxy, 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;

$R^{22'}$ is hydrogen or C_{1-6}alkyl optionally substituted with one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or $NR^{7'}R^{8'}$;

$R^{23'}$ and $R^{24'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{25'}$ and $R^{26'}$ are independently hydrogen or C_{1-6}alkyl, 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_{1-6}alkyl;

$R^{28'}$ is C_{1-6}alkyl;

$R^{29'}$, $R^{30'}$ and $R^{31'}$ 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;

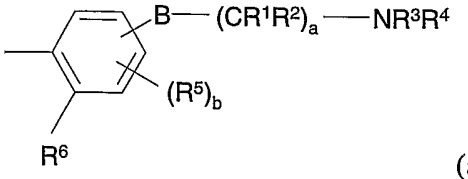
b' is 0, 1, 2 or 3;

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, Ar is (i) or (ii); A is $CONR^{46'}$, NHCO, $-NHCH_2$, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl, and E is a group (a):



(a);

wherein:

B is oxygen, C≡C, $S(O)_c$, $CR^7=CR^8$, 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, 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, $OCOR^{12}$, $NHCOCF_3$, $NHSO_2R^{13}$, $NHCO_2R^{14}$, or $NHCOC_{0-6}$alkyl wherein the alkyl of $NHCOC_{0-6}$alkyl is optionally substituted by OH;

R^5 is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{15}R^{16}$, CO_2R^{17}, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$ or halogen;

R^6 is hydrogen, C_{1-6}alkyl, aryl, trifluoromethyl, hydroxy, C_{1-6}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_{1-6}alkyl;

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

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

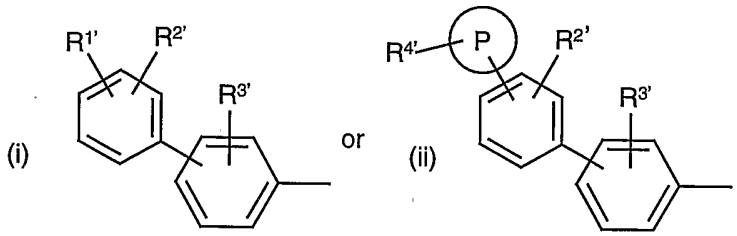
f is 0, 1, 2 or 3.

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

Ar—A—E

Formula (I)

wherein Ar represents a group selected from (i) or (ii);



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 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, $(CH_2)_aNR^{7'}R^{8'}$, $(CH_2)_aNR^{7'}COR^{9'}$, $(CH_2)_aNR^{7'}CO_2R^{10'}$, $(CH_2)_aNR^{7'}SO_2R^{11'}$, $(CH_2)_aCONR^{12'}R^{13'}$, hydroxy$C_{1-6}$alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), $(CH_2)_aCO_2C_{1-6}$alkyl, $(CH_2)_bOC(O)R^{14'}$, $CR^{15'}=NOR^{16'}$, $CNR^{15'}=NOR^{16'}$, $COR^{17'}$, $CONR^{12'}R^{13'}$, $CONR^{12'}(CH_2)_cOC_{1-4}$alkyl, $CONR^{12'}(CH_2)_aCO_2R^{18'}$, $CONHNR^{19'}R^{20'}$, $CONR^{12'}SO_2R^{21'}$, $CO_2R^{22'}$, cyano, trifluoromethyl, $NR^{7'}R^{8'}$, $NR^{7'}COR^{9'}$, $NR^{23'}CO(CH_2)_aNR^{23'}R^{24'}$, $NR^{23'}CONR^{23'}R^{24'}$, $NR^{7'}CO_2R^{10'}$, $NR^{7'}SO_2R^{11'}$, $N=CNR^{23'}NR^{23'}R^{24'}$, nitro, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, $OC(O)NR^{25'}R^{26'}$, $SR^{27'}$, $SOR^{28'}$, $SO_2R^{28'}$, $SO_2NR^{25'}R^{26'}$ or halogen;

$R^{3'}$ and $R^{4'}$ are 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, $CONR^{29'}R^{30'}$, $CO_2R^{31'}$, cyano, aryl, trifluoromethyl, $NR^{29'}R^{30'}$, nitro, hydroxy, C_{1-6}alkoxy, acyloxy, 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;

$R^{22'}$ is hydrogen or C_{1-6}alkyl optionally substituted with one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or $NR^{7'}R^{8'}$;

$R^{23'}$ and $R^{24'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{25'}$ and $R^{26'}$ are independently hydrogen or C_{1-6}alkyl, 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_{1-6}alkyl;

$R^{28'}$ is C_{1-6}alkyl;

$R^{29'}$, $R^{30'}$ and $R^{31'}$ 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;

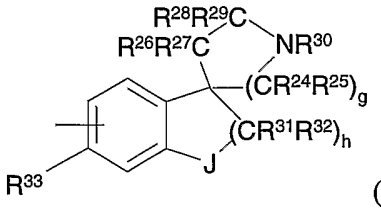
b' is 0, 1, 2 or 3;

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, Ar is (i) or (ii), A is $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl, and E is a group (b):



(b);

wherein:

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

R^{30} is hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl;

R^{33} is hydrogen, C_{1-6}alkyl, trifluoromethyl, hydroxy or halogen, or R^{33} and $R^{30'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N;

J is oxygen, $CR^{36}R^{37}$, or NR^{38}, or J is a group $S(O)_k$;

R^{34}, R^{35}, R^{36}, R^{37}, and R^{38} are independently hydrogen or C_{1-6}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; and

k is 0, 1 or 2.

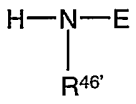
10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier.

11. A method for treating or preventing a CCR5-mediated disease in a mammal by administering to the mammal in need thereof, an effective amount of a CCR5 receptor ligand according to any one of claims 1 to 9, or a pharmaceutically acceptable salt or solvate thereof.

12. The method according to claim 11, wherein the CCR5-mediated disease states are selected from 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.

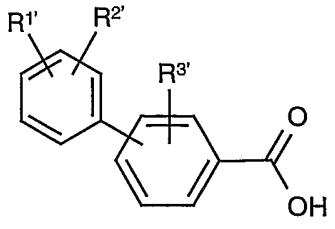
13. A process for preparing a compound of formula (I) according to any one of the preceding claims comprising:

a) coupling a compound of formula (II)



Formula (II)

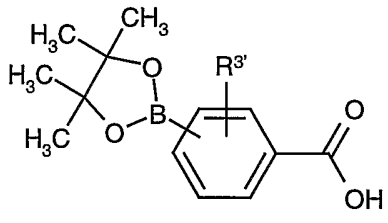
with a compound of formula (III)



Formula (III)

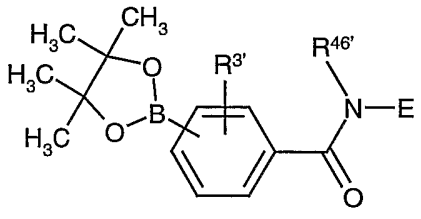
to provide a compound of formula (I); or

b) coupling a compound of formula (II) with a compound of formula (IV)



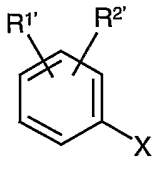
Formula (IV)

to provide a compound of formula (V)



Formula (V)

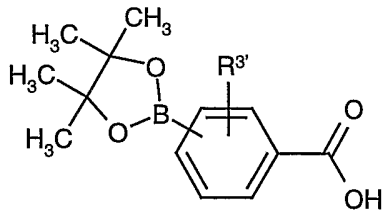
and c) treating the compound of formula (V) with an aryl compound of formula (VI)



Formula (VI)

wherein X is a group selected from bromo, iodo, or [(trifluoromethane)sulfonyl]oxy, to provide a compound of formula (I).

14. A compound of formula (IV):



Formula (IV)

wherein:

R3' is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{1-6}alkyl, $CONR^{29'}R^{30'}$, $CO_2R^{31'}$, cyano, aryl, trifluoromethyl, $NR^{29'}R^{30'}$, nitro, hydroxy, C_{1-6}alkoxy, acyloxy, or halogen.

15. A compound which is:

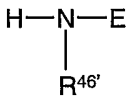
N-[3-(4-Piperidinyl)-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[4-Methoxy-3-[1-(1-methylethyl)-4-piperidinyl]phenyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide;

N-[4-Methoxy-3-[1-cyclopentyl-4-piperidinyl]phenyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide; and

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.

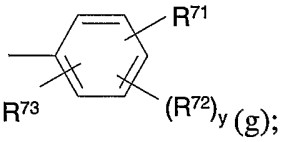
16. A compound of formula (II)



Formula (II)

wherein:

E is a group (g):



$R^{46'}$ is hydrogen or C_{2-6}alkyl;

R^{71} is piperidin-4-yl;

R^{72} is methoxy; and

R^{73} is hydrogen.

17. The compound of formula (II) according to claim 16 selected from:

4-Methoxy-3-[1-(1-methylethyl)-4-piperidinyl]benzenamine;

4-Methoxy-3-[1-cyclopentyl-4-piperidinyl]benzenamine;

3-[1,2,3,6-Tetrahydro-1-(1-methylethyl)-4-pyridinyl]-4-methoxyaniline;

3-[1-(1-Methylethyl)-3-pyrrolidinyl]-4-methoxyaniline; and

3-[1-Cyclopropyl-4-piperidinyl]-4-methoxyaniline.

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