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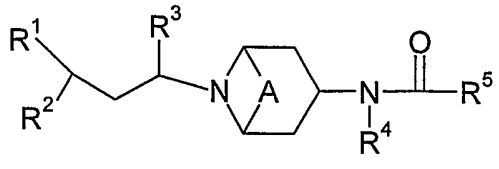
(54) Title: CHEMICAL COMPOUNDS



(I)

(57) Abstract: Compounds of formula (I): [Chemical formula should be inserted here. Please see paper copy] compositions comprising them, processes for preparing them and their use in medical therapy (for example modulating CCR5 receptor activity in a warm blooded animal).

CHEMICAL COMPOUNDS

The present invention relates to heterocyclic derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in PCT/SE01/01053, EP-A1-1013276, WO00/08013, WO99/38514 and WO99/04794.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

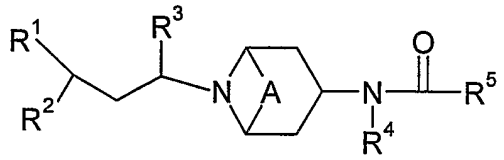
The CCR5 receptor is expressed on T-lymphocytes, monocytes, macrophages, dendritic cells, microglia and other cell types. These detect and respond to several chemokines, principally "regulated on activation normal T-cell expressed and secreted"

(RANTES), macrophage inflammatory proteins (MIP) MIP-1α and MIP-1β and monocyte chemoattractant protein-2 (MCP-2).

This results in the recruitment of cells of the immune system to sites of disease. In many diseases it is the cells expressing CCR5 which contribute, directly or indirectly, to tissue damage. Consequently, inhibiting the recruitment of these cells is beneficial in a wide range of diseases.

CCR5 is also a co-receptor for HIV-1 and other viruses, allowing these viruses to enter cells. Blocking the receptor with a CCR5 antagonist or inducing receptor internalisation with a CCR5 agonist protects cells from viral infection.

The present invention provides a compound of formula (I):



(I)

wherein:

A is CH_2CH_2 or A is absent;

R^1 is C_{3-7} cycloalkyl in which at least one ring carbon is replaced by the same or different O, S, S(O), $S(O)_2$, CHF or CF_2; wherein R^1 is optionally substituted by **halogen, cyano, C_{1-6} alkyl** [optionally substituted by phenyl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, $S(O)(C_{1-4}$ alkyl) or $S(O)_2(C_{1-4}$ alkyl)} or heteroaryl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, $S(O)(C_{1-4}$ alkyl) or $S(O)_2(C_{1-4}$ alkyl)}], **C_{1-6} alkoxy, phenyl** {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, $S(O)(C_{1-4}$ alkyl) or $S(O)_2(C_{1-4}$ alkyl)}, **heteroaryl** {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, $S(O)(C_{1-4}$ alkyl) or $S(O)_2(C_{1-4}$ alkyl)}, **$S(O)_2R^6$, $S(O)_2NR^8R^9$, $C(O)R^7$, $C(O)_2(C_{1-6}$ alkyl)** (such as tert-butoxycarbonyl), **$C(O)_2$(phenyl(C_{1-2} alkyl))** (such as benzyloxycarbonyl) **or $C(O)NHR^{10}$**;

R^2 is phenyl optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3;

R^3 is hydrogen or C_{1-4} alkyl;

R^4 is hydrogen, methyl, ethyl, allyl or cyclopropyl;

R^5 is aryl, aryl(C_{1-4})alkyl, heteroaryl or heteroaryl(C_{1-4})alkyl;

unless stated otherwise aryl and heteroaryl moieties are independently optionally substituted by one or more of halo, cyano, nitro, hydroxy, $OC(O)NR^{11}R^{12}$, $NR^{13}R^{14}$, $NR^{15}C(O)R^{16}$, $NR^{17}C(O)NR^{18}R^{19}$, $S(O)_2NR^{20}R^{21}$, $NR^{22}S(O)_2R^{23}$, $C(O)NR^{24}R^{25}$, CO_2R^{26}, $NR^{27}CO_2R^{28}$, $S(O)_qR^{29}$, $OS(O)_2R^{30}$, C_{1-6} alkyl (optionally mono-substituted by $S(O)_2R^{31}$ or $C(O)NR^{32}R^{33}$), C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy (optionally mono-substituted by CO_2R^{34}, $C(O)NR^{35}R^{36}$, cyano, heteroaryl or $C(O)NHS(O)_2R^{37}$), $NHC(O)NHR^{38}$, C_{1-6} haloalkoxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenylS(O), phenyl$S(O)_2$, phenyl(C_{1-4})alkoxy, heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, S(C_{1-4} alkyl), S(O)(C_{1-4} alkyl), $S(O)_2$(C_{1-4} alkyl), $S(O)_2NH_2$, $S(O)_2NH$(C_{1-4} alkyl), $S(O)_2N$(C_{1-4} alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, C(O)NH(C_{1-4} alkyl), C(O)N(C_{1-4} alkyl)$_2$, CO_2H, CO_2(C_{1-4} alkyl), NHC(O)(C_{1-4} alkyl), $NHS(O)_2$(C_{1-4} alkyl), CF_3 or OCF_3;

q is 0, 1 or 2;

R^6 is C_{1-6} alkyl [optionally substituted by halo (such as fluoro), C_{1-4} alkoxy, phenyl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)} or heteroaryl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)}], C_{3-7} cycloalkyl, phenyl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)} or heteroaryl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)};

R^7 and R^{10} are, independently, hydrogen, C_{1-6} alkyl [optionally substituted by halo (such as fluoro), C_{1-4} alkoxy, phenyl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)} or heteroaryl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)}], C_{3-7} cycloalkyl, phenyl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)} or heteroaryl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)};

R^8 and R^9 are, independently, hydrogen or C_{1-4} alkyl; or R^8 and R^9 join to form a 5- or 6-membered ring which may additionally comprise an oxygen or sulphur atom (for example to form a morpholine, thiomorpholine ring) or NR^{39} group (for example to form a piperazine ring), wherein the ring is optionally substituted with halogen, C_{1-4} alkyl or phenyl (wherein the phenyl ring is optionally substituted by halo, cyano, nitro, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$ alkyl, $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, $NHS(O)_2(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $NHC(O)NH_2$, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3);

R^{11}, R^{13}, R^{15}, R^{17}, R^{18}, R^{20}, R^{22}, R^{24}, R^{27}, R^{32} and R^{35} are, independently, hydrogen or C_{1-6} alkyl;

R^{12}, R^{14}, R^{16}, R^{19}, R^{21}, R^{23}, R^{25}, R^{26}, R^{28}, R^{29}, R^{30}, R^{31}, R^{33}, R^{34}, R^{36}, R^{37} and R^{38} are, independently, C_{1-6} alkyl (optionally substituted by halo, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), heteroaryl, phenyl, heteroaryloxy or phenyloxy), C_{3-7} cycloalkyl, phenyl or heteroaryl; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;

R^{12}, R^{14}, R^{16}, R^{19}, R^{21}, R^{25}, R^{26}, R^{33}, R^{34}, R^{36} and R^{38} may additionally be hydrogen; and,

R^{39} is hydrogen, C_{1-4} alkyl, $C(O)(C_{1-4}$ alkyl) or $S(O)_2(C_{1-4}$ alkyl);

or a pharmaceutically acceptable salt thereof.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate. In addition to these further examples of acid addition salts are succinate, glutarate or malonate.

The invention includes solvates (such as hydrates) of compounds of formula (I) and the present invention covers all such solvates.

Alkyl groups and moieties are straight or branched chain and are, for example, methyl (sometimes abbreviated to Me), ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl or tert-butyl.

Cycloalkyl is for example, cyclopropyl, cyclopentyl or cyclohexyl.

Haloalkyl includes CF_3, and haloalkoxy includes OCF_3.

Fluoroalkyl includes, for example, one to six, such as one to three, fluorine atoms, and comprises, for example, a CF_3 group. Fluoroalkyl is, for example, CF_3 or CH_2CF_3.

Alkoxyalkyl groups include methoxymethyl and ethoxymethyl.

Heterocyclyl is, for example, piperidine, piperazine, pyrrolidine, azetidine, tetrahydrofuran, morpholine or thiomorpholine. Further examples of heterocyclyl are tetrahydropyran and tetrahydrothiopyran.

Aryl includes phenyl and naphthyl. In one aspect of the invention aryl is phenyl.

Heteroaryl is, for example, an aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heteroaryl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, thiazolyl, isothiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, [1,2,4]-triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzo[b]furyl (also known as benzfuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2a]pyridinyl), thieno[3,2-b]pyridin-6-yl, 1,2,3-benzoxadiazolyl (also known as benzo[1,2,3]thiadiazolyl), 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), quinolinyl, isoquinolinyl, a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl), a benzothiazinyl or dibenzothiophenyl (also known as dibenzothienyl); or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

Aryl(C_{1-4} alkyl), aryl(C_{1-4})alkyl, phenyl(C_{1-4})alkyl and phenyl(C_{1-4} alkyl) are, independently, for example, benzyl, 1-(phenyl)eth-1-yl or 1-(phenyl)eth-2-yl.

Heteroaryl(C_{1-4} alkyl)alkyl is, for example, pyridinylmethyl, pyrimidinylmethyl or 1-(pyridinyl)eth-2-yl.

Phenyl(C_{1-4})alkoxy is, for example, benzyloxy

Heteroaryl(C_{1-4})alkoxy is, for example, pyridylmethoxy or pyrimidinylmethoxy.

Heteroaryl rings can carry various substituents including sulphonyl groups. A sulphonyl group on a heteroaryl ring can be a good leaving group (susceptible to nucleophilic

displacement) and examples of such situation are: 2-methanesulphonyl-pyridine and 2- or 4-methanesulphonyl-pyrimidine. The present invention covers compounds including a heteroaryl ring carrying a sulphonyl group which are sufficiently stable (non-reactive) to be isolated using the experimental procedures described.

In one aspect the present invention provides a compound of formula (I) wherein A is absent.

In a further aspect the present invention provides a compound of formula (I) wherein, unless specified otherwise, aryl, phenyl and heteroaryl moieties are independently optionally substituted by one or more of halo, hydroxy, nitro, $S(C_{1-6}$ alkyl), $S(O)(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-6}$ alkyl), $S(O)_2N(C_{1-6}$ alkyl$)_2$, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $CH_2S(O)_2(C_{1-6}$ alkyl), $OS(O)_2(C_{1-6}$ alkyl), OCH_2heteroaryl (such as OCH_2tetrazolyl), OCH_2CO_2H, $OCH_2CO_2(C_{1-6}$ alkyl), $OCH_2C(O)NH_2$, $OCH_2C(O)NH(C_{1-6}$ alkyl), OCH_2CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, $C(O)NH_2$, $C(O)NH(C_{1-6}$ alkyl), $C(O)N(C_{1-6}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3, OCF_3, heteroaryl or heteroaryl(C_{1-4} alkyl); wherein the foregoing heteroaryl group are optionally substituted by halo, hydroxy, nitro, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), CF_3 or OCF_3 {and in a further aspect of the invention the foregoing heteroaryl groups (such as tetrazolyl) are optionally substituted by C_{1-4} alkyl}.

In another aspect the present invention provides a compound of formula (I) wherein, unless specified otherwise, aryl, phenyl and heteroaryl moieties are independently optionally substituted by one or more of halo, hydroxy, nitro, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3.

In one particular aspect of the invention R^1 is C_{3-7} cycloalkyl in which at least one ring carbon is replaced by the same or different O, S, S(O), $S(O)_2$, CHF or CF_2 (for example R^1 is tetrahydropyranyl, tetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl or 1,1-difluorocyclohexyl); wherein R^1 is optionally substituted by halogen or C_{1-6} alkyl.

In another aspect of the invention R^1 is tetrahydropyranyl, tetrahydrothiopyranyl or 1,1-dioxidotetrahydrothiopyranyl, each optionally substituted by halogen or C_{1-4} alkyl (such as methyl).

In a further aspect of the invention R^2 is phenyl optionally substituted in the 2-, 3-, 2,5- or 3,5- position by the same or different: halo (such as fluoro or chloro), C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3; where n is 0, 1 or 2.

In a still further aspect of the invention R^2 is phenyl optionally substituted in the 3- or 3,5- position by the same or different: halo (such as fluoro or chloro), C_{1-4} alkyl or CF_3.

In another aspect R^2 is phenyl, mono-fluorophenyl (for example 3-fluorophenyl), difluorophenyl (for example 3,5-difluorophenyl), mono-chlorophenyl (for example 3-chlorophenyl) or di-halophenyl (such as 3-chloro-5-fluorophenyl).

In yet another aspect of the invention R^3 is hydrogen or methyl. In yet another aspect of the invention R^3 is hydrogen. In a further aspect of the invention R^3 is methyl.

In a further aspect of the invention R^4 is ethyl.

In a still further aspect of the invention R^5 is phenyl or benzyl, either of which is optionally substituted by halogen (such as chloro or fluoro), cyano, C_{1-4} alkyl (mono-substituted by $S(O)_2(C_{1-4}$ alkyl) or $C(O)NH(C_{1-4}$ alkyl)), C_{1-4} alkoxy, $S(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), $OS(O)_2(C_{1-4}$ alkyl), OCH_2COOH, OCH_2-tetrazolyl (itself optionally substituted by C_{1-4} alkyl), carboxamide or tetrazolyl (itself optionally substituted by C_{1-4} alkyl).

In a further aspect of the invention R^5 is phenyl or benzyl, either of which is optionally substituted by halogen (such as chloro or fluoro), cyano, C_{1-4} alkyl (mono-substituted by $S(O)_2(C_{1-4}$ alkyl) or $C(O)NH(C_{1-4}$ alkyl)), C_{1-4} alkoxy, $S(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl) or $OS(O)_2(C_{1-4}$ alkyl).

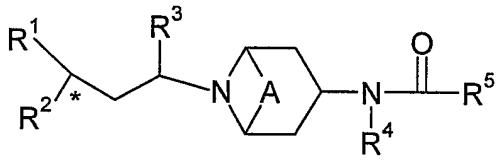
In another aspect the present invention provides a compound of the invention wherein R^5 is phenyl {optionally substituted by $S(O)_2(C_{1-4}$ alkyl) (such as $CH_3S(O)_2$, for example in the 4-position), C_{1-4} alkoxy (such as CH_3O, for example in the 4-position), $OS(O)_2(C_{1-4}$ alkyl) (such as OSO_2CH_3, for example in the 4-position), halogen (such as chloro or fluoro) or cyano}.

In a further aspect the present invention provides a compound of the invention wherein R^5 is benzyl {optionally substituted by $S(O)_2(C_{1-4}$ alkyl) (such as $CH_3S(O)_2$, for example in the 4-position), C_{1-4} alkoxy (such as CH_3O, for example in the 4-position), $OS(O)_2(C_{1-4}$ alkyl) (such as OSO_2CH_3, for example in the 4-position), halogen (such as chloro or fluoro) or cyano}.

In yet another aspect the present invention provides a compound of formula (I) wherein R^1 is tetrahydropyranyl, tetrahydrothiopyranyl or 1,1-dioxidotetrahydrothiopyranyl; R^2 is phenyl optionally substituted by halo (such as fluoro); R^3 is hydrogen; R^4 is ethyl; R^5 is benzyl optionally substuituted by $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2CH_3$).

In a further aspect the present invention provides a compound of formula (I) wherein: R^1 is tetrahydropyranyl, tetrahydrothiopyranyl or 1,1-dioxidotetrahydrothiopyranyl; wherein R^1 is optionally substituted by C_{1-6} alkyl (for example by 1 or 2 CH_3 groups); R^2 is phenyl optionally substituted by halo (for example by 2 chloro atoms or 2 fluoro atoms); R^3 is hydrogen; R^4 is C_{1-4} alkyl (for example ethyl); and R^5 is benzyl optionally substituted by $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$).

The compounds of formula (I) have a chiral centre at * (see below). In one aspect of



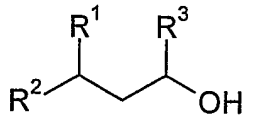
(I)

the invention this chiral centre has the R absolute stereochemistry (as determined by the Cahn-Ingold-Prelog convention).

Compounds of the invention are presented in the Examples.

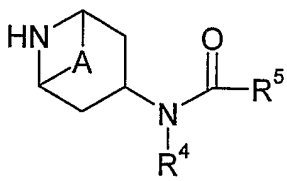
The compounds of the invention can be prepared using one of the proceses described below.

A compound of the invention can be prepared by reacting a compound of formula (II):



(II)

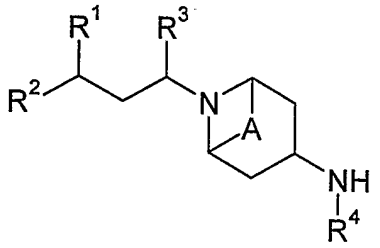
with an oxidizing agent such as the Dess Martin periodinane and then reacting the product so-formed with a compound of formula (III):



(III)

in the presence of a source of triacetoxybobohydride (such as a resin or the sodium salt), in a suitable solvent (such as a C_{1-6} aliphatic alcohol, for example ethanol; or an ether, for example tetrahydrofuran) at room temperature (for example 10-30°C).

Alternatively, a compound of the invention can be prepared by coupling a compound of formula (IV):



(IV)

with a compound R^5-CO_2H in the presence of a suitable coupling agent {for example PyBrOP (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate) or HATU (O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate)} in the presence of a suitable base (such as a tertiary amine, for example diisopropylethylamine) in a suitable solvent (for example *N*-methylpyrrolidinone or a chlorinated solvent, such as dichloromethane) at room temperature (for example 10-30°C).

The starting materials for the preparative methods are either commercially available or can be prepared by literature methods, adapting literature methods or by following or adapting the Method herein described.

In a further aspect the invention provides processes for preparing the compounds of the invention. Many of the intermediates in the processes are novel and these are provided as further features of the invention.

The compounds of the invention have activity as pharmaceuticals, in particular as modulators (such as agonists, partial agonists, inverse agonists or antagonists) of chemokine receptor (especially CCR5) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

The compounds of the present invention are also of value in inhibiting the entry of viruses (such as human immunodeficiency virus (HIV)) into target calls and, therefore, are of value in the prevention of infection by viruses (such as HIV), the treatment of infection by viruses (such as HIV) and the prevention and/or treatment of acquired immune deficiency syndrome (AIDS).

According to a further feature of the invention there is provided a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a warm blooded animal (such as man) by therapy (including prophylaxis).

According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity (especially CCR5 receptor activity) in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

The present invention also provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, as a medicament, especially a medicament for the treatment of transplant rejection, respiratory disease, psoriasis or rheumatoid arthritis (especially rheumatoid arthritis). [Respiratory disease is, for example, COPD, asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)} or rhinitis {acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}; and is particularly asthma or rhinitis].

In another aspect the present invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention also provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use as a medicament, especially a medicament for the treatment of rheumatoid arthritis.

In another aspect the present invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention further provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for

example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a warm blooded animal, such as man.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR5 mediated disease state) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR5 receptor) activity, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the invention, or a pharmaceutically acceptable salt thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of $0.01 mgkg^{-1}$ to $100 mgkg^{-1}$ of the compound, preferably in the range of $0.1 mgkg^{-1}$ to $20 mgkg^{-1}$ of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a

period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of the invention, or a pharmaceutically acceptable salt thereof or a solvent thereof (hereafter Compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.0

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β-cyclodextrin may be used to aid formulation.

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

The invention further relates to combination therapies or compositions wherein a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, is administered concurrently (possibly in the same composition) or sequentially with an agent for the treatment of any one of the above disease states.

In particular, for the treatment of the inflammatory diseases rheumatoid arthritis, psoriasis, inflammatory bowel disease, COPD, asthma and allergic rhinitis a compound of the invention can be combined with a TNF-α inhibitor (such as an anti-TNF monoclonal antibody (such as Remicade, CDP-870 and D.sub2.E.sub7.), or a TNF receptor immunoglobulin molecule (such as Enbrel.reg.)), a non-selective COX-1 / COX-2 inhibitor (such as piroxicam or diclofenac; a propionic acid such as naproxen, flubiprofen, fenoprofen, ketoprofen or ibuprofen; a fenamate such as mefenamic acid, indomethacin, sulindac or apazone; a pyrazolone such as phenylbutazone; or a salicylate such as aspirin), a COX-2 inhibitor (such as meloxicam, celecoxib, rofecoxib, valdecoxib or etoricoxib) low dose methotrexate,

lefunomide; ciclesonide; hydroxychloroquine, d-penicillamine or auranofin, or parenteral or oral gold.

The present invention still further relates to the combination of a compound of the invention together with:

- a leukotriene biosynthesis inhibitor, a 5-lipoxygenase (5-LO) inhibitor or a 5-lipoxygenase activating protein (FLAP) antagonist, such as zileuton, ABT-761, fenleuton, tepoxalin, Abbott-79175, Abbott-85761, an N-(5-substituted)-thiophene-2-alkylsulfonamide, a 2,6-di-tert-butylphenol hydrazones, a methoxytetrahydropyran such as Zeneca ZD-2138, SB-210661, a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; an indole or quinoline compound such as MK-591, MK-886 or BAY x 1005;
- a receptor antagonist for a leukotriene LTB.sub4., LTC.sub4., LTD.sub4. or LTE.sub4. selected from the group consisting of a phenothiazin-3-one such as L-651,392; an amidino compound such as CGS-25019c; a benzoxalamine such as ontazolast; a benzenecarboximidamide such as BIIL 284/260; or a compound such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A) or BAY x 7195;
- a PDE4 inhibitor including an inhibitor of the isoform PDE4D;
- an antihistaminic H.sub1. receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine or chlorpheniramine;
- a gastroprotective H.sub2. receptor antagonist;
- an α.sub1.- and α.sub2.-adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride or ethylnorepinephrine hydrochloride;
- an anticholinergic agent such as ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine;
- a β.sub1.- to β.sub4.-adrenoceptor agonist such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate or pirbuterol, or a methylxanthanine including theophylline and aminophylline; sodium cromoglycate; or a muscarinic receptor (M1, M2, and M3) antagonist;
- an insulin-like growth factor type I (IGF-1) mimetic;

- an inhaled glucocorticoid with reduced systemic side effects, such as prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate or mometasone furoate;
- an inhibitor of a matrix metalloprotease (MMP), such as a stromelysin, a collagenase, or a gelatinase or aggrecanase; such as collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) or MMP-12;
- a modulator of chemokine receptor function such as CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the C-X_3-C family;
- an osteoporosis agent such as roloxifene, droloxifene, lasofoxifene or fosomax;
- an immunosuppressant agent such as FK-506, rapamycin, cyclosporine, azathioprine or methotrexate;
- a compound useful in the treatment of AIDS and/or HIV infection for example: an agent which prevents or inhibits the viral protein gp120 from engaging host cell CD4 {such as soluble CD4 (recombinant); an anti-CD4 antibody (or modified / recombinant antibody) for example PRO542; an anti-group120 antibody (or modified / recombinant antibody); or another agent which interferes with the binding of group120 to CD4 for example BMS806}; an agent which prevents binding to a chemokine receptor, other than CCR5, used by the HIV virus {such as a CXCR4 agonist or antagonist or an anti-CXCR4 antibody}; a compound which interferes in the fusion between the HIV viral envelope and a cell membrane {such as an anti-group 41 antibody; enfuvirtide (T-20) or T-1249}; an inhibitor of DC-SIGN (also known as CD209) {such as an anti-DC-SIGN antibody or an inhibitor of DC-SIGN binding}; a nucleoside/nucleotide analogue reverse transciptase inhibitor {for example zidovudine (AZT), nevirapine, didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir, adefovir or tenofovir (for example as free base or as disoproxil fumarate)}; a non-nucleoside reverse transciptase inhibitor {for example nevirapine, delavirdine or efavirenz}; a protease inhibitor {for example ritonavir, indinavir, saquinavir (for example as free base or as mesylate salt), nelfinavir (for example as free base or as mesylate salt), amprenavir, lopinavir or atazanavir (for

example as free base or as sulphate salt)}; a ribonucleotide reductase inhinbitor {for example hydroxyurea}; or an antiretroviral {for example emtricitabine}; or,

- an existing therapeutic agent for the treatment of osteoarthritis, for example a non-steroidal anti-inflammatory agent (hereinafter NSAID's) such as piroxicam or diclofenac, a propionic acid such as naproxen, flubiprofen, fenoprofen, ketoprofen or ibuprofen, a fenamate such as mefenamic acid, indomethacin, sulindac or apazone, a pyrazolone such as phenylbutazone, a salicylate such as aspirin, a COX-2 inhibitor such as celecoxib, valdecoxib, rofecoxib or etoricoxib, an analgesic or intra-articular therapy such as a corticosteroid or a hyaluronic acid such as hyalgan or synvisc, or a P2X7 receptor antagonist.

The present invention still further relates to the combination of a compound of the invention together with: (i) a tryptase inhibitor; (ii) a platelet activating factor (PAF) antagonist; (iii) an interleukin converting enzyme (ICE) inhibitor; (iv) an IMPDH inhibitor; (v) an adhesion molecule inhibitor including a VLA-4 antagonist; (vi) a cathepsin; (vii) a MAP kinase inhibitor; (viii) a glucose-6 phosphate dehydrogenase inhibitor; (ix) a kinin-B.sub1. - and B.sub2. -receptor antagonist; (x) an anti-gout agent, e.g., colchicine; (xi) a xanthine oxidase inhibitor, e.g., allopurinol; (xii) an uricosuric agent, e.g., probenecid, sulfinpyrazone or benzbromarone; (xiii) a growth hormone secretagogue; (xiv) a transforming growth factor (TGFβ); (xv) a platelet-derived growth factor (PDGF); (xvi) a fibroblast growth factor, e.g., basic fibroblast growth factor (bFGF); (xvii) a granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) a capsaicin cream; (xix) a Tachykinin NK.sub1. and NK.sub3. receptor antagonist selected from the group consisting of NKP-608C; SB-233412 (talnetant); and D-4418; (xx) an elastase inhibitors selected from the group consisting of UT-77 and ZD-0892; (xxi) a TNFα converting enzyme inhibitor (TACE); (xxii) an induced nitric oxide synthase inhibitor (iNOS); or (xxiii) a chemoattractant receptor-homologous molecule expressed on TH2 cells (a CRTH2 antagonist).

The invention will now be illustrated by the following non-limiting Examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI". Where an "Isolute™ SCX column" is referred to, this means a column containing benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd., 1st House, Duffryn Industial Estate, Ystrad Mynach, Hengoed, Mid Glamorgan, UK. Where "Argonaut™ PS-*tris*-amine scavenger resin" is referred to, this means a *tris*-(2-aminoethyl)amine polystyrene resin obtained from Argonaut Technologies Inc., 887 Industrial Road, Suite G, San Carlos, California, USA.

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio DMSO (CD_3SOCD_3) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05% formic acid and B, acetonitrile with 0.05% formic acid. The eluent gradient went from 95% A to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are

reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$ and

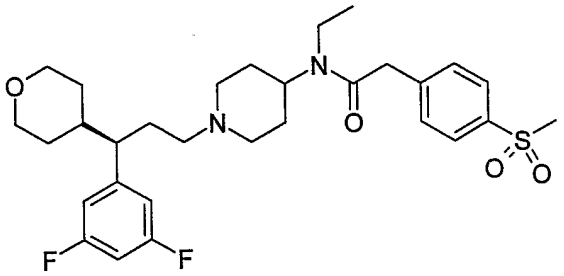
(xi) the following abbreviations are used:

THF tetrahydrofuran;

Boc tert-butoxycarbonyl

EXAMPLE 1

This Example illustrates the preparation of *N*-{1-[(3R)-3-(3,5-difluorophenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propyl]piperidin-4-yl}-*N*-ethyl-2-[4-(methylsulphonyl)phenyl]acetamide.



Step (i): (2*E*)-3-(Tetrahydro-2*H*-pyran-4-yl)acrylic acid

Tetrahydropyran-4-carboxaldehyde (2.47g), malonic acid (2.26g) and piperidine (0.2ml) in pyridine (15ml) was refluxed for 4 hours. The mixture was concentrated and partitioned between ethyl acetate and 1N HCl. The organic layer was dried ($MgSO_4$) and evaporated to give a solid (2.77g), which was used without further purification.

^{1}H NMR ($CDCl_3$): 1.5-1.8 (m, 4H), 2.4 (m, 1H), 3.4-3.5 (m, 2H), 4.0 (m, 2H), 5.8 (d, 1H), 7.0 (dd, 1H).

Step (ii): (4R,5S)-1,5-Dimethyl-4-phenyl-3-[(2*E*)-3-(tetrahydro-2*H*-pyran-4-yl)prop-2-enyl]imidazolidin-2-one

To a solution of (2*E*)-3-(tetrahydro-2*H*-pyran-4-yl)acrylic acid (2.76g) in anhydrous tetrahydrofuran (25ml) was added 1-chloro-*N*,*N*-2-trimethyl-1-propenylamine (2.31ml) and the resulting mixture was stirred for 3 hours to give Solution A.

To a suspension of (4R,5S)-1,5-dimethyl-4-phenyl-2-imidazolidin-2-one (3.32g) in anhydrous tetrahydrofuran (25ml), cooled to 5°C, was added dropwise lithium bis(trimethylsilyl)amide (1M solution in THF). The mixture was stirred at 5°C for 30 minutes before adding Solution A. The resulting mixture was stirred at room temperature for 18

hours. The mixture was quenched with 50% brine and extracted with ethyl acetate. The organics were dried ($MgSO_4$) and evaporated to a gum which was recrystallised from ethanol to give (4R,5S)-1,5-dimethyl-4-phenyl-3-[(2*E*)-3-(tetrahydro-2*H*-pyran-4-yl)prop-2-enyl]imidazolidin-2-one (3.46g).

^{1}H NMR ($CDCl_3$): 0.75 (d, 3H), 1.4 (m, 2H), 1.65 (m, 2H), 2.4 (m, 1H), 2.8 (s, 3H), 3.4 (m, 2H), 3.9 (m, 3H), 5.3 9d, 1H), 6.9 (dd, 1H), 7.1 (m, 2H), 7.25 (m, 3H), 7.4 dd, 1H).

Step (iii): (4S, 5R)-1-[(3R)-3-(3,5-Difluorophenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propanoyl]-3,4-dimethyl-5-phenylimidazolidin-2-one

To a suspension of cuprous iodide (931mg) in tetrahydrofuran (60ml) under argon was added tetramethylethylenediamine (0.81ml). The resulting mixture was stirred for 20 minutes to give a solution. The mixture was cooled to –75°C and 3,5-difluorophenyl magnesium bromide (9.8ml, 0.5M solution in THF) was added dropwise and the resulting mixture was stirred for a further 1 hour. A preformed solution of (4R,5S)-1,5-dimethyl-4-phenyl-3-[(2*E*)-3-(tetrahydro-2*H*-pyran-4-yl)prop-2-enyl]imidazolidin-2-one (800mg) in dichloromethane (2ml) and dibutylboron triflate (2.93ml, 1M solution in dichloromethane) was added and the mixture was stirred at –75°C for 1 hour before allowing to warm slowly to 5°C. The mixture was quenched with saturated ammonium chloride and ethyl acetate. Air was bubble through the mixture for 20 minutes. The organic layer was washed with saturated ethylenediaminetetraacetic acid, dried ($MgSO_4$) and evaporated to a gum which was purified by column chromatography eluting with a gradient of ethyl acetate / isohexane to give (4S, 5R)-1-[(3R)-3-(3,5-difluorophenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propanoyl]-3,4-dimethyl-5-phenylimidazolidin-2-one (887mg) as a solid.

^{1}H NMR ($CDCl_3$): 0.8 (d, 3H), 1.2-1.5 (m, 3H), 2.7 (m, 2H), 2.85 (s, 3H), 3.0 (m, 1H), 3.15-3.4 (m, 3H), 3.8-4.0 (m, 4H), 5.2 (d, 1H), 6.6-6.7 (m, 3H), 6.9 (m, 2H), 7.2 (m, 3H). MS (ES) 443 $(M+H)^+$.

Step (iv): (3R)-3-(3,5-difluorophenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propan-1-ol

To a solution of (4S, 5R)-1-[(3R)-3-(3,5-difluorophenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propanoyl]-3,4-dimethyl-5-phenylimidazolidin-2-one (882mg) in anhydrous tetrahydrofuran (20ml) was added lithium borohydride (1.5ml, 2M solution in THF). The resulting mixture was heated to 60°C under argon for 2 hours. The mixture was cooled, quenched with saturated ammonium chloride and ethyl acetate and then stirred for 20

minutes. The organic layer was dried ($MgSO_4$) and evaporated to give a gum which was purified by column chromatography eluting with an ethyl acetate / isohexane gradient to give (3R)-3-(3,5-difluorophenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propan-1-ol (345mg) as an oil.

^1H NMR ($CDCl_3$): 1.2-1.4 (m, 2H), 1.6-1.9 (m, 4H), 2.15 (m, 1H), 2.55 (m, 1H), 3.25-3.45 (m, 3H), 3.55 (m, 1H), 3.9 (m, 1H), 4.05 (m, 1H), 6.7 (m, 3H).

Step (v): Title compound

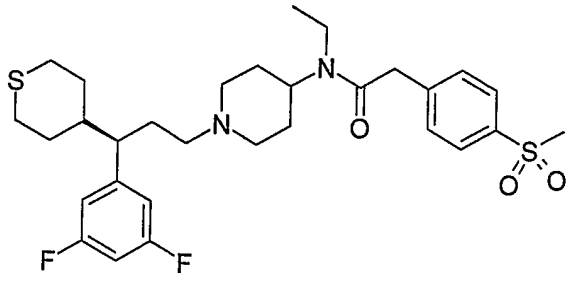
To a solution of (3R)-3-(3,5-difluorophenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propan-1-ol (345mg) in dichloromethane (10ml) was added in one portion Dess Martin periodinane (628mg) and the resulting mixture was stirred for 2 hours. The mixture was partitioned between 1N NaOH and dichloromethane. The organic extracts were dried ($MgSO_4$) and evaporated to give an oil which was then dissolved in anhydrous tetrahydrofuran (10ml). *N*-(4-Piperidinyl)-*N*-ethyl-2-[4-(methylsulphonyl)phenyl]acetamide (221mg; Method A) was added followed by MP-triacetoxyborohydride resin (2mmol/g) (1g). The resulting mixture was stirred for 2 hours. The mixture was filtered, washed with tetrahydrofuran and evaporated to give a gum which was purified by column chromatography eluting with a gradient of methanol / dichloromethane to give the title compound as a glass (325mg).

MS (ES) 563 $(M+H)^+$

NMR ($CDCl_3$): 1.26 (m, 4H), 1.67 (m, 4H), 1.80 (m, 4H), 2.07 (m, 2H), 2.35 (m, 1H), 2.81 (m, 4H), 2.99 (m, 2H), 3.07 (s, 3H), 3.33 (m, 4H), 3.80 (s, 2H), 3.89 (m, 1H), 4.01 (m, 1H), 4.40 (m, 1H), 6.68 (m, 3H), 7.47 (d, 2H), 7.91 (d, 2H).

EXAMPLE 2

This Example illustrates the preparation of *N*-{1-[(3R)-3-(3,5-difluorophenyl)-3-(tetrahydro-2*H*-thiopyran-4-yl)propyl]piperidin-4-yl}-*N*-ethyl-2-[4-(methylsulphonyl)phenyl]acetamide.



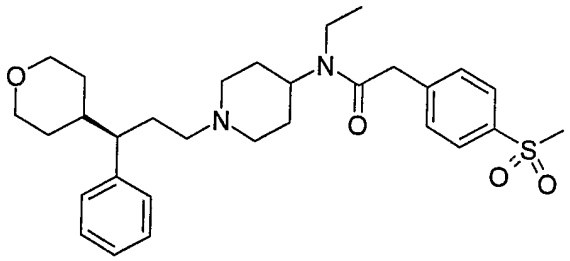
This compound was prepared in a similar manner to Example 1 but starting from tetrahydrothiopyran-4-carboxaldehyde.

MS (ES) 579 $(M+H)^+$.

NMR ($CDCl_3$): 1.24 (m, 3H), 1.42 (m, 3H), 1.67 (m, 5H), 1.78 (m, 2H), 2.01 (m, 6H), 2.36 (m, 2H), 2.59 (m, 1H), 2.82 (m, 3H), 3.03 (s, 3H), 3.31 (q, 2H), 3.79 (s, 2H), 4.36 (m, 1H), 6.62 (m, 3H), 7.45 (t, 2H), 7.89 (d, 2H).

EXAMPLE 3

This Example illustrates the preparation of *N*-{1-[(3R)-3-(phenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propyl]piperidin-4-yl}-*N*-ethyl-2-[4-(methylsulphonyl)phenyl]acetamide.



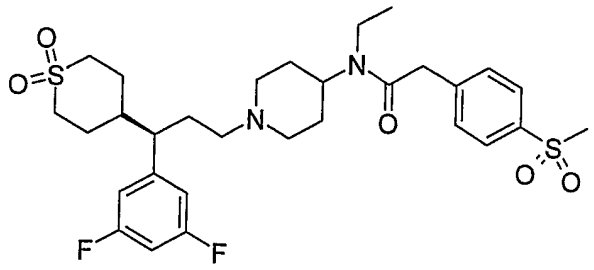
This compound was prepared in a similar manner to Example 1 but using phenyl magnesium bromide.

MS (ES) 527 $(M+H)^+$.

NMR ($CDCl_3$): 1.19 (m, 5H), 1.32 (qd, 1H), 1.42 (m, 1H), 1.71 (m, 7H), 2.04 (m, 4H), 2.30 (t, 1H), 2.97 (m, 2H), 3.03 (s, 3H), 3.31 (m, 4H), 3.77 (s, 2H), 3.83 (m, 1H), 3.99 (dd, 1H), 4.39 (m, 1H), 7.09 (d, 2H), 7.19 (t, 1H), 7.27 (t, 2H), 7.44 (t, 2H), 7.88 (d, 2H).

EXAMPLE 4

This Example illustrates the preparation of *N*-{1-[(3R)-3-(phenyl)-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)propyl]piperidin-4-yl}-*N*-ethyl-2-[4-(methylsulphonyl)phenyl]acetamide.



MS (ES) 611 $(M+H)^+$.

NMR ($CDCl_3$): 1.24 (m, 3H), 1.82 (m, 15H), 2.27 (m, 1H), 2.55 (m, 1H), 2.75 (m, 1H), 2.96 (m, 4H), 3.03 (s, 3H), 3.32 (q, 2H), 3.78 (s, 2H), 4.35 (m, 1H), 6.67 (m, 3H), 7.45 (t, 2H), 7.89 (d, 2H).

This compound was prepared as in Example 2 but with the addition of an oxidation step.

Preparation of (4R,5S)-1,5-dimethyl-4-phenyl-3-[(2*E*)-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)prop-2-enyl]imidazolidin-2-one.

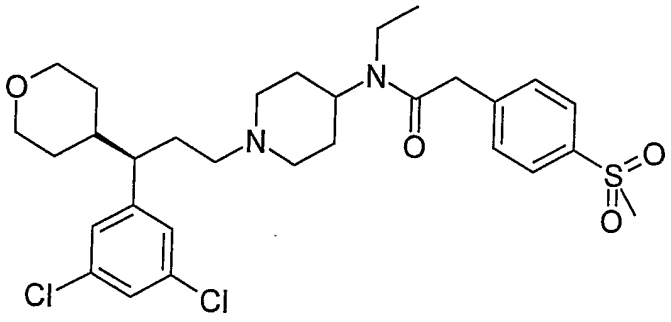
To a solution of (4R,5S)-1,5-dimethyl-4-phenyl-3-[(2*E*)-3-(tetrahydro-2*H*-thiopyran-4-yl)prop-2-enyl]imidazolidin-2-one (712mg) in dichloromethane (60ml) was added meta chloroperbenzoic acid (1.53g, 70% strength). The mixture was stirred for 18 hours and then partitioned between 2N sodium hydroxide and dichloromethane. The organic extracts were dried ($MgSO_4$) and evaporated to give a gum which was purified by column chromatography eluting with a gradient of methanol and dichloromethane to give (4R,5S)-1,5-dimethyl-4-phenyl-3-[(2*E*)-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)prop-2-enyl]imidazolidin-2-one (622mg).

^{1}H NMR ($CDCl_3$): 0.8 (d, 3H), 1.75 (m, 2H), 1.9 (m, 2H), 2.15 (m, 1H), 2.85 (s, 3H), 2.85-3.25 (m, 6H), 2.8 (m, 1H), 3.9 (m, 1H), 5.2 (d, 1H), 6.7 (m, 3H), 6.9 (m, 2H), 7.25 (m, 3H).

MS (ES) 491 $(M+H)^+$.

EXAMPLE 5

This Example illustrates the preparation of *N*-{1-[(3*R*)-3-(3,5-dichlorophenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propyl]piperidin-4-yl}-*N*-ethyl-2-[4-(methylsulfonyl)phenyl]acetamide.

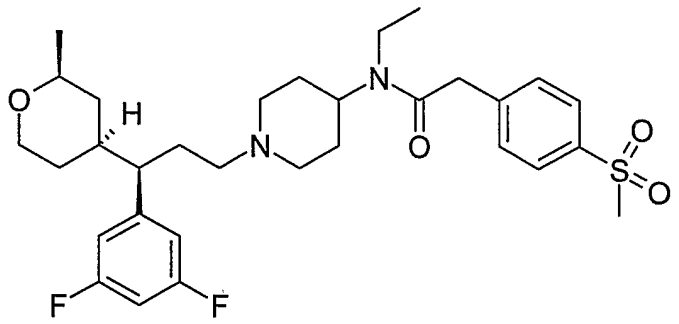


This compound was prepared by a method analogous to that of Example 1using 3,4-dichlorophenyl magnesium bromide in step iii.

NMR ($CDCl_3$): 1.1-1.3 (m, 6H), 1.6-1.8 (m, 9H), 1.9-2.1 (m, 4H), 2.3 (m, 1H), 2.8-2.9 (m, 2H), 3.0 (s, 3H), 3.2-3.4 (m, 3H), 3.8 (m, 2H), 3.85-4.0 (m, 2H), 4.4 (m,1H), 7.0 (s, 2H), 7.2 (s, 1H), 7.4-7.5 (m, 2H), 7.9 (d, 2H).

EXAMPLE 6

This Example illustrates the preparation of *N*-(1-{(3*R*)-3-(3,5-difluorophenyl)-3-[(2*S*,4*S*)-2-methyltetrahydro-2*H*-pyran-4-yl]propyl}piperidin-4-yl)-*N*-ethyl-2-[4-(methylsulfonyl)phenyl]acetamide.



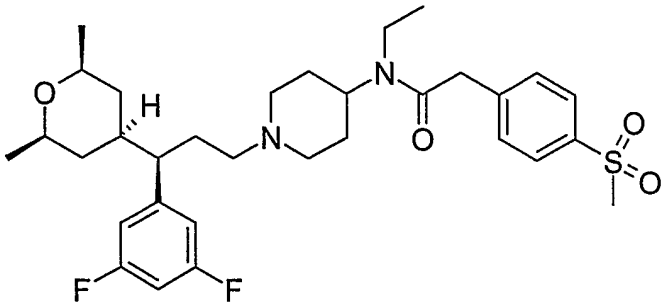
This compound was prepared in a similar manner to Example 1 but using (2*E*)-3-[(2*S*,4*S*)-2-methyltetrahydro-2*H*-pyran-4-yl]acrylic acid (Method B) in step (ii).

MS (ES) 577 $(M+H)^+$

NMR ($CDCl_3$): 0.80 (q, 1H), 1.08 (d, 3H), 1.10-1.27 (m, 3H), 1.44 (m, 1H), 1.56-1.84 (m, 7H), 1.90-2.21 (m, 5H), 2.30 (t, 1H), 2.87-2.99 (m, 2H), 3.02 (s, 3H), 3.22-3.51 (m, 5H), 3.78 (s, 2H), 4.02 (dd, 1H), 4.35-4.44 (m, 1H), 6.60-6.71 (m, 3H), 7.45 (d, 2H), 7.89 (d, 2H).

EXAMPLE 7

This Example illustrates the preparation of *N*-(1-{(3*R*)-3-(3,5-difluorophenyl)-3-[(2*R*,4*R*,6*S*)-2,6-dimethyltetrahydro-2*H*-pyran-4-yl]propyl}piperidin-4-yl)-*N*-ethyl-2-[4-(methylsulfonyl)phenyl]acetamide.



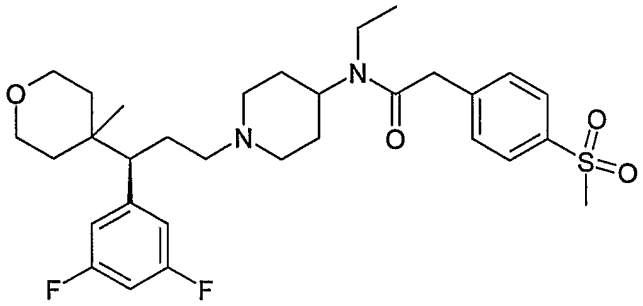
This compound was prepared in a similar manner to Example 1 but using (2*E*)-3-[(2*R*,4*R*,6*S*)-2,6-dimethyltetrahydro-2*H*-pyran-4-yl]acrylic acid (Method B) in step (ii).

MS (ES) 591 $(M+H)^+$

NMR ($CDCl_3$): 0.73 (q, 1H), 0.86 (q, 1H), 1.07-1.16 (m, 4H), 1.18-1.27 (m, 6H), 1.45 (t, 1H), 1.53-1.84 (m, 7H), 1.89-2.14 (m, 4H), 2.28 (t, 1H), 2.80-2.95 (m, 2H), 3.04 (s, 3H), 3.27-3.36 (m, 3H), 3.40-3.50 (m, 2H), 3.78 (s, 2H), 4.35-4.46 (m, 1H), 6.60-6.70 (m, 3H), 7.45 (d, 2H), 7.89 (d, 2H).

EXAMPLE 8

This Example illustrates the preparation of *N*-{1-[(3*R*)-3-(3,5-difluorophenyl)-3-(4-methyltetrahydro-2*H*-pyran-4-yl)propyl]piperidin-4-yl}-*N*-ethyl-2-[4-(methylsulfonyl)phenyl]acetamide.



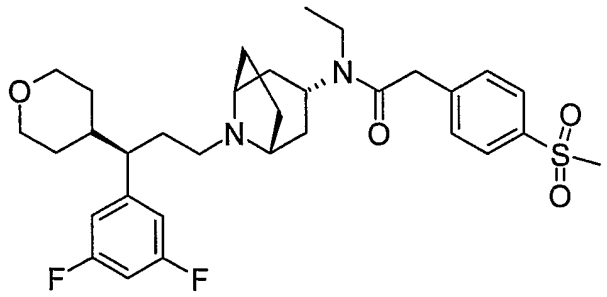
This compound was prepared in a similar manner to Example 1, but starting from 4-methyl-tetrahydropyran-4-carboxaldehyde (Method C).

MS (ES) 577 $(M+H)^+$

NMR ($CDCl_3$): 0.92 (d, 1H), 1.00 (s, 3H), 1.15 (t, 1H minor rotomer), 1.23 (t, 2H, major rotomer), 1.40-1.85 (m, 8H), 1.95-2.06 (m, 4H), 2.41 (d, 1H), 2.83-3.00 (m, 3H), 3.03 (s, 3H), 3.33 (q, 2H), 3.47 (m, 2H), 3.58 (td, 1H), 3.68-3.84 (m, 3H), 4.40 (m, 1H), 6.68 (m, 3H), 7.43 (m, 2H), 7.89 (d, 2H).

EXAMPLE 9

This Example illustrates the preparation of *N*-{(3-*exo*)-8-[3-(3,5-difluorophenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}-*N*-ethyl-2-[4-(methylsulfonyl)phenyl]acetamide.



This compound was prepared in a similar manner to Example 1 step (v) but using *N*-[(3-*exo*)-8-azabicyclo[3.2.1]oct-3-yl]-*N*-ethyl-2-[4-(methylsulfonyl)phenyl]acetamide (Method D).

MS ES 589 $(M+H)^+$

NMR (CDCl3): 1.1-1.3 (m, 8H) 1.4(m, 1H) 1.6(m, 3H) 1.8 (m, 5H) 1.9-2.2 (m, 3H) 2.4(m, 1H) 3.0 (s, 3H) 3.1-3.4 (m, 6H) 3.8 (m, 2H) 3.9 (m, 1H) 4.0 (m, 1H) 4.7 (m, 1H) 6.6 (m, 3H) 7.4 (m, 2H) 7.9 (m, 2H).

Method A

N-(4-Piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide

Step 1: Preparation of 1-phenylmethyl-4-ethylaminopiperidine dihydrochloride

To a solution of 1-phenylmethyl-4-piperidone (25.0g, 132mmol) in THF (250mL) was added ethylamine hydrochloride (12.0g, 147 mol) and methanol (50mL) and the resulting mixture stirred at room temperature for 10min. Sodium triacetoxyborohydride (40g, 189mmol) was added portionwise and the resulting mixture stirred at room temperature for 1h. 2M Sodium hydroxide solution (250mL) was added and the resulting mixture extracted with diethyl ether. The organic extracts were dried (K_2CO_3) and evaporated to give 1-phenylmethyl-4-ethylaminopiperidine as an oil. This was dissolved in ethanol (500mL) and concentrated hydrochloric acid (20mL) was added. The resulting crystals were collected, washed with diethyl ether and dried giving the sub-titled compound as a solid (38 g); NMR: ($CDCl_3$): 1.10 (t, 3H), 1.40 (m, 2H), 1.83 (m, 2H), 2.02 (m, 2H), 2.65 (q, 2H), 2.85 (m, 2H), 3.50 (s, 2H), 3.75 (m, 1H), 7.2 - 7.4 (m, 5H); MS: 219 (MH+).

Step 2: Preparation of *N*-(1-Phenylmethyl-4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide

To a solution of 1-phenylmethyl-4-ethylaminopiperidine dihydrochloride (32.0g, 110mmol) in DCM (500mL) was added *N,N*-diisopropylethylamine (60mL) with stirring to ensure complete dissolution. 4-Methanesulfonylphenylacetic acid (25.0g, 117mmol), 4-Dimethylaminopyridine (2.0g) and dicyclohexylcarbodiimide (25.0g, 121mmol) were added and the resulting mixture was stirred at room temperature for 20h. The precipitate was removed by filtration and the resulting solution was washed successively with 2N aqueous HCl, water and 1N aqueous NaOH, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel chromatography (eluent: 10% MeOH/ethyl acetate) to afford the sub-titled compound (35g, 76%); NMR: 1.00 and 1.14 (t, 3H), 1.45 and 1.70 (m, 2H), 1.95 (br m, 2H), 2.80 (br m, 2H), 3.18 (s, 3H), 3.20 and 3.33 (q, 2H), 3.45 (s, 2H), 3.80 and 3.87 (s, 2H), 3.70 and 4.10 (m, 1H), 7.2 - 7.3 (m, 5H), 7.48 (m, 2H), 7.82 (m, 2H); MS: 415 (MH+).

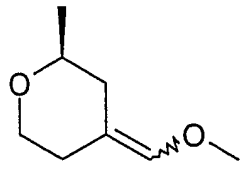
Step 3: Preparation of the title compound

To a solution of *N*-(1-phenylmethyl-4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenyl-acetamide (34g, 82mmol) in ethanol (600mL) was added ammonium formate (40g). The mixture was purged with argon and 30% Pd on carbon (4.2g) was added. The resulting mixture was stirred at reflux for 4h, then allowed to cool and filtered through diatomaceous earth. The filtrate was evaporated to give a thick oil which solidified on standing to yield the title compound (24.9g, 94%); NMR: 1.02 and 1.15 (t, 3H), 1.4 -1.6 (br m, 4H), 2.45 (m, 2H), 2.93 (br m, 2H), 3.18 (s, 3H), 3.20 and 3.32 (q, 2H), 3.72 and 4.18 (m, 1H), 3.80 and 3.87 (s, 2H), 7.50 (m, 2H), 7.85 (m, 2H); MS: 325 (MH+).

Method B

(2*E*)-3-[(2*S*,4*S*)-2-methyltetrahydro-2*H*-pyran-4-yl]acrylic acid

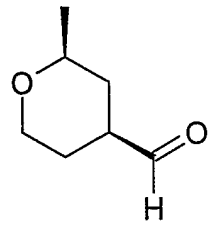
Step 1: Preparation of (2*S*, 4*E/Z*)-4-(methylmethylene)-2-methyltetrahydro-2*H*-pyran



To a suspension of (methoxymethyl)triphenyl phosphine chloride (32g) in anhydrous THF (160ml), cooled to -10°C, was added dropwise sodium bis(trimethylsilyl) amide (46.7ml of 2M solution in THF). The reaction mixture was stirred for 1 hour and then a solution of

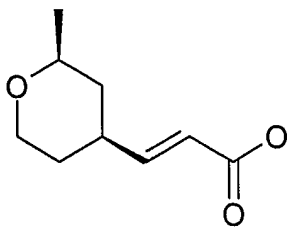
(2*S*)-2-methyltetrahydro-4*H*-pyran-4-one (7.1g)(CAS REG No 82110-21-2) in anhydrous THF (20ml) was added over 5 minutes. The resulting mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction was quenched with water (50ml) and extracted with diethyl ether (3x100ml). The organics were dried and evaporated to dryness. The resulting gum was treated with diethyl ether and filtered. The organics were evaporated to dryness and the resulting residue was purified by chromatography on silica eluting with ethyl acetate / isohexane (1:9) to give the title compound (~1:1 *E/Z* mixture of isomers) as an oil. Yield 6.22g. NMR $CDCl_3$ 1.1 (dd, 3H), 1.45-2.1 (m, 3H), 2.4-2.55 (m, 1H), 3.2 (m, 2H), 3.4 (s, 3H), 3.85 (m,1H) 5.7 (m, 1H).

Step 2: Preparation of (2*S*)-2-methyltetrahydro-2*H*-pyran-4-carboxaldehyde



A mixture of (2*S*, 4*E/Z*)-4-(methylmethylene)-2-methyltetrahydro-2*H*-pyran (6.22g) and formic acid (40ml, 88%) in water (20ml) was heated, under argon, to 90°C for 6 hours. The reaction mixture was cooled, neutralised with 6N sodium hydroxide and extracted with diethyl ether (3x150ml). The organics were dried and evaporated to dryness. The residue was purified by chromatography on silica eluting with ethyl acetate / isohexane (3:7) to give the title compound (4:1 mixture of cis /trans isomers) as an oil. Yield 4.065g. NMR $CDCl_3$ 1.25-1.4 (m, 4H), 1.5-2.2 (m, 3H), 2.45-2.7 (m, 1H), 3.4 3.5 (m, 2H), 3.85-4.1 (m, 1H), 9.65 (s, CHO cis), 9.8 (s, CHO trans).

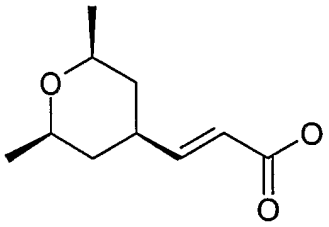
Step 3: Preparation of (2*E*)-3-[(2*S*)-2-methyltetrahydro-2*H*-pyran-4-yl]acrylic acid



A mixture of (2*S*)-2-methyltetrahydro-2*H*-pyran-4-carboxaldehyde (4.0), malonic acid (6.495g) and piperidine (0.1ml) in pyridine (10ml) was heated to 100°C for 4 hours. The

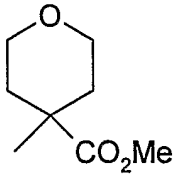
reaction mixture was concentrated and partitioned between ethyl acetate (100ml) and 1N HCl. The organic layer was dried, evaporated and recrystallised form toluene to give the title compound. Yield 2.48g. NMR $CDCl_3$ 1.2 (m, 4H), 1.5 (m, 1H), 1.7 (m, 2H), 2.45 (m, 1H), 3.5 (m, 2H), 4.05 (m, 1H), 5.8 (d, 1H), 7.0 (dd, 1H).

In a similar manner, but starting from 2,6-dimethyltetrahydro-4*H*-pyran-2-one, was prepared (2*E*)-3-(2,6-dimethyltetrahydro-2*H*-pyran-4-yl)acrylic acid. NMR $CDCl_3$ 1.05 (m, 2H), 1.2 (m, 6H), 1.7 (m, 2H), 2.5 (m, 1H), 3.5 (m, 2H), 5.8 (d, 1H), 7.0 (dd, 1H)



Method C

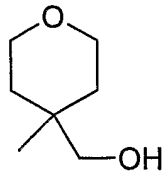
Step 1: Preparation of 4-methyl-tetrahydropyran-4-carboxylic acid methyl ester.



Tetrahydropyran-4-carboxylic acid methyl ester (14.42g) was dissolved in anhydrous tetrahydrofuran (250ml) and cooled to -78°C under an atmosphere of argon. To this stirred solution was added, *via* syringe, lithium bis(trimethylsilyl)amide (1M solution in THF, 100ml). The solution was allowed to warm to 0°C, stirred for 15 minutes, then cooled to -78°C. To the cooled solution was added, dropwise *via* syringe, iodomethane (6.2ml). The solution was stirred for 30 minutes then allowed to warm slowly to room temperature and stirred for a further 3 hours. The reaction was then quenched with saturated aqueous ammonium chloride and partitioned with ethyl acetate. The aqueous portions were further extracted with ethyl acetate then the combined organic fractions were washed with water then brine then dried ($MgSO_4$) and filtered. Evaporation of solvents under reduced pressure gave a yellow oil which was purified by two successive rounds of column chromatography using a gradient of ethyl acetate in *iso*-hexane to give the product (7.25g) as a yellow oil.

NMR ($CDCl_3$): 1.23 (s, 3H), 1.49 (t, 2H), 2.02-2.10 (m, 2H), 3.43-3.51 (m, 2H), 3.71 (s, 3H), 3.75-3.82 (m, 2H).

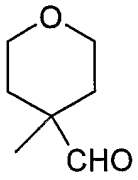
Step 2: Preparation of (4-methyl-tetrahydropyran-4-yl)-methanol.



To a solution of 4-methyl-tetrahydro-pyran-4-carboxylic acid methyl ester (7.75g) in anhydrous dichloromethane cooled to -78°C was added, over 15 minutes *via* syringe, di-*iso*-butylaluminium hydride (1M solution in DCM, 123ml). The reaction solution was left to stir at -78°C for 3 hours then warmed to room temperature and left to stir for a further 2 hours. The reaction was then quenched with saturated ammonium chloride and partitioned with dichloromethane. The aqueous portions were further extracted with dichloromethane then the combined organic fractions were washed with brine, dried ($MgSO_4$) and evaporated to give a clear oil which was purified by column chromatography using a gradient of ethyl acetate in *iso*-hexane as eluent to give the product (5.54g) as a clear oil.

NMR ($CDCl_3$): 1.02 (s, 3H), 1.25-1.21 (m, 2H), 1.58 (ddd, 2H), 2.60 (s, 1H), 3.37 (s, 2H), 3.62 (ddd, 2H), 3.74 (dt, 2H).

Step 3: Preparation of 4-Methyl-tetrahydro-pyran-4-carboxaldehyde.

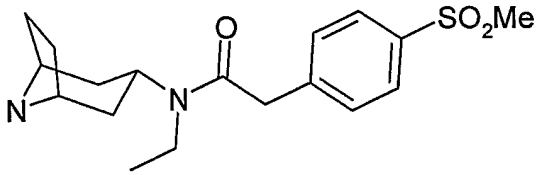


Pyridinium chlorochromate (11.55g) and Celite® (23g) were mixed together and suspended in dichloromethane (250ml) at 0°C. A solution of (4-methyl-tetrahydro-pyran-4-yl)-methanol (4.65g) in dichloromethane (100ml) was added to the stirred suspension and the reaction left to stir for 24 hours. The reaction was diluted with diethyl ether and filtered under suction, washing the filter cake with diethyl ether, to give, after evaporation of solvents under reduced pressure, a brown gum which was purified by column chromatography using a gradient of ethyl acetate in *iso*-hexane to give the product (3.26g) as a clear oil.

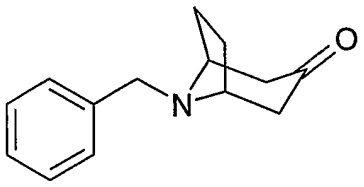
NMR ($CDCl_3$): 1.11 (s, 3H), 1.50 (ddd, 2H), 1.94 (dt, 2H), 3.51 (ddd, 2H), 3.77 (dt, 2H), 9.47 (s, 1H).

Method D

Preparation of *N*-[(3-*exo*)-8-azabicyclo[3.2.1]oct-3-yl]-*N*-ethyl-2-[4-(methylsulfonyl)phenyl]acetamide

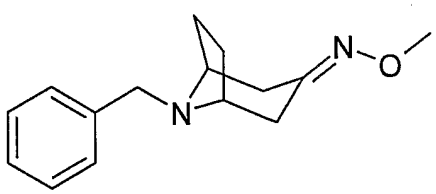


Step 1: Preparation of 8-benzylbicyclo[3.2.1.]octan-3-one



A solution of 2,5-dimethoxytetrahydrofuran (22.2ml) in 0.1M HCl was refluxed for 1 hour and then cooled to 0 °C. 1,3-Acetonedicarboxylic acid (25g), benzylamine (15.6ml) and 10% sodium acetate (95ml) were added in one portion and the resulting mixture was stirred at room temperature for 1 hour, followed by heating to 50 °C for 5 hours. The reaction mixture was cooled, basified with 2M sodium hydroxide and washed with water. The organics were dissolved in 1M hydrochloric acid and washed with dichloromethane. The aqueous layer was rebasified with 2M sodium hydroxide and extracted with ethyl acetate (3x100ml). The organic extracts were dried and evaporated to dryness to give the title compound as a brown oil which was used without further purification. Yield 13.66g M+H 216.

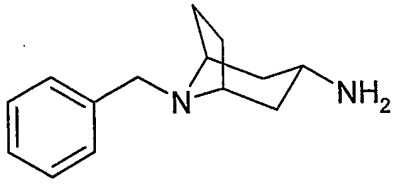
Step 2: Preparation of 8-benzylbicyclo[3.2.1.]octan-3-one-*O*-methyloxime



To a solution of 8-benzylbicyclo[3.2.1.]octan-3-one (13.66g) in ethanol (250ml) was added pyridine (5.69ml) followed by hydroxylamine hydrochloride (4.85g) and the resulting mixture was refluxed for 18 hours. The reaction mixture was allowed to cool to room

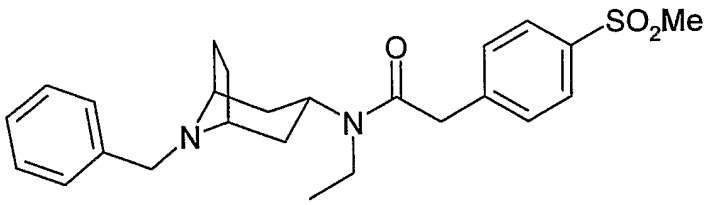
temperature and then partitioned between water and dichloromethane. The organic layer was dried and evaporated to give the title compound as a brown solid which was used without further purification. Yield 10.79g. M+H 231.

Step 3: Preparation of 8-benzyl-8-azo-bicyclo[3.2.1]octan-3-*exo*-amine



A solution of 8-benzylbicyclo[3.2.1.]octan-3-one-*O*-methyloxime (27.78g) in pentanol (500ml) was heated to 165°C. Sodium (10g) was added portionwise over 6 hours. The reaction was heated for a further 4 hours and then cooled to 5 °C. The reaction was acidified with 6M hydrochloric acid and the phases separated. The aqueous extracts were basified with sodium hydroxide and extracted with ethyl acetate (3x100 ml). The combined organic extracts were dried and evaporated to dryness to give the title compound as a pale brown oil. Yield 20.21g. M+H 217.

Step 4: Preparation of *N*-(8-benzyl-8-aza-bicyclo[3.2.1]oct-3-yl)-*N*-ethyl-2-(4-methanesulfonyl-phenyl)-acetamide



To a solution of 8-Benzyl-8-aza-bicyclo[3.2.1]oct-3-yl-exo-amine (2.81g, 13 mmol) in DCM (40mL) was added acetaldehyde (0.69g, 16mmol) and the resulting mixture stirred at room temperature for 1h. Sodium triacetoxyborohydride (3.3 g, 16mmol) was added portionwise and the resulting mixture stirred at room temperature for 16h. The mixture was then washed with water, dried over $MgSO_4$ and concentrated. This material was then dissolved in DCM (50mL) and 4-methanesulfonylphenylacetic acid (3.1g, 14mmol) and diisopropylcarbodiimide (2.1g, 14mmol) were added and the resulting mixture stirred for 2h. The precipitate was removed by filtration and the crude material was adsorbed onto silica. Silica gel chromatography (eluent: 100% DCM to 10% methanol and 1% 0.88 ammonia in DCM) gave the sub-titled compound as a foam (0.37g); NMR ($CDCl_3$): 1.2 and 1.3 (t, 3H),

1.4 (m, 1H), 1.5 (m, 1H), 1.7 (m, 2H), 1.9 (m, 2H), 2.0 (m, 2H), 3.0 (s, 3H), 3.3 (m, 4H), 3.5 (d, 2H), 3.8 (d, 2H), 3.9 and 4.8 (m, 1H), 7.3 (m, 5H), 7.5 (m, 2H), 7.9 (m, 2H); MS: 441 (MH+).

Step 5: Preparation of title compound.

To a solution of *N*-(8-benzyl-8-aza-bicyclo[3.2.1]oct-3-yl)-*N*-ethyl-2-(4-methanesulfonyl-phenyl)-acetamide (0.37g, 0.85mmol) in ethanol (20mL) was added 20% palladium hydroxide on carbon (0.04g) and the resulting mixture was stirred under an atmosphere of hydrogen for 2 days. The catalyst was removed by filtration and the resulting solution was adsorbed onto silica. The residue was purified by silica gel chromatography (eluent: DCM to 10% methanol and 1% 0.88 ammonia in DCM) to afford the titled compound as an oil (0.1g); NMR ($CDCl_3$): 1.1 and 1.2 (t, 3H), 1.3 (m, 1H), 1.4 (m, 2H), 1.7 (m, 5H), 2.1 (br s, 1H), 3.0 (s, 3H), 3.3 (m, 2H), 3.6 (m, 2H), 3.7 and 3.8 (s, 2H), 3.8 and 4.8 (m, 1H), 7.4 (m, 2H), 7.9 (m, 2H); MS 351 (MH+)

EXAMPLE 10

The ability of compounds to inhibit the binding of RANTES was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated RANTES, scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated RANTES bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated RANTES was calculated (IC_{50}). Preferred compounds of formula (I) have an IC_{50} of less than 50μM.

EXAMPLE 11

The ability of compounds to inhibit the binding of MIP-1α was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated MIP-1α , scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated MIP-1α bound to the receptor was determined by scintillation counting. Competition curves were obtained for

compounds and the concentration of compound which displaced 50% of bound iodinated MIP-1α was calculated (IC_{50}). Preferred compounds of formula (I) have an IC_{50} of less than 50μM.

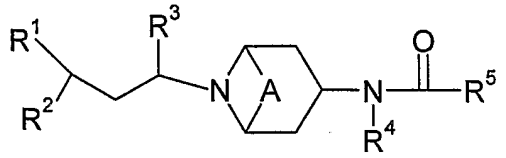
Results from this test for certain compounds of the invention are presented in Table I. In Table I the results are presented as Pic50 values. A Pic50 value is the negative log (to base 10) of the IC_{50} result, so an IC50 of 1μM (that is 1 x 10^{-6}M) gives a Pic50 of 6. If a compound was tested more than once then the data below is an average of the probative tests results.

Table I

Example	Pic50
1	9.1
2	9.3

CLAIMS

1. A compound of formula (I):



(I)

wherein:

A is CH_2CH_2 or A is absent;

R^1 is C_{3-7} cycloalkyl in which at least one ring carbon is replaced by the same or different O, S, S(O), $S(O)_2$, CHF or CF_2; wherein R^1 is optionally substituted by **halogen, cyano, C_{1-6} alkyl** [optionally substituted by phenyl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)} or heteroaryl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)}], **C_{1-6} alkoxy, phenyl** {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)}, **heteroaryl** {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, $S(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or $S(O)_2$(C_{1-4} alkyl)}, **$S(O)_2R^6$, $S(O)_2NR^8R^9$, $C(O)R^7$, $C(O)_2$(C_{1-6} alkyl)** (such as tert-butoxycarbonyl), **$C(O)_2$(phenyl(C_{1-2} alkyl))** (such as benzyloxycarbonyl) **or $C(O)NHR^{10}$**;

R^2 is phenyl optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n$(C_{1-4} alkyl), nitro, cyano or CF_3;

R^3 is hydrogen or C_{1-4} alkyl;

R^4 is hydrogen, methyl, ethyl, allyl or cyclopropyl;

R^5 is aryl, aryl(C_{1-4})alkyl, heteroaryl or heteroaryl(C_{1-4})alkyl;

unless stated otherwise aryl and heteroaryl moieties are independently optionally substituted by one or more of halo, cyano, nitro, hydroxy, $OC(O)NR^{11}R^{12}$, $NR^{13}R^{14}$, $NR^{15}C(O)R^{16}$, $NR^{17}C(O)NR^{18}R^{19}$, $S(O)_2NR^{20}R^{21}$, $NR^{22}S(O)_2R^{23}$, $C(O)NR^{24}R^{25}$, CO_2R^{26}, $NR^{27}CO_2R^{28}$, $S(O)_qR^{29}$, $OS(O)_2R^{30}$, C_{1-6} alkyl (optionally mono-substituted by $S(O)_2R^{31}$ or $C(O)NR^{32}R^{33}$), C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy (optionally mono-substituted by CO_2R^{34},

$C(O)NR^{35}R^{36}$, cyano, heteroaryl or $C(O)NHS(O)_2R^{37}$), $NHC(O)NHR^{38}$, C_{1-6} haloalkoxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenylS(O), phenylS$(O)_2$, phenyl(C_{1-4})alkoxy, heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, S(C_{1-4} alkyl), S(O)(C_{1-4} alkyl), S$(O)_2$(C_{1-4} alkyl), S$(O)_2NH_2$, S$(O)_2$NH(C_{1-4} alkyl), S$(O)_2$N(C_{1-4} alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, C(O)NH(C_{1-4} alkyl), C(O)N(C_{1-4} alkyl)$_2$, CO_2H, CO_2(C_{1-4} alkyl), NHC(O)(C_{1-4} alkyl), NHS$(O)_2$(C_{1-4} alkyl), CF_3 or OCF_3;

q is 0, 1 or 2;

R^6 is C_{1-6} alkyl [optionally substituted by halo (such as fluoro), C_{1-4} alkoxy, phenyl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, S$(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S$(O)_2$(C_{1-4} alkyl)} or heteroaryl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, S$(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S$(O)_2$(C_{1-4} alkyl)}], C_{3-7} cycloalkyl, phenyl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, S$(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S$(O)_2$(C_{1-4} alkyl)} or heteroaryl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, S$(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S$(O)_2$(C_{1-4} alkyl)};

R^7 and R^{10} are, independently, hydrogen, C_{1-6} alkyl [optionally substituted by halo (such as fluoro), C_{1-4} alkoxy, phenyl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, S$(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S$(O)_2$(C_{1-4} alkyl)} or heteroaryl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, S$(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S$(O)_2$(C_{1-4} alkyl)}], C_{3-7} cycloalkyl, phenyl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, OCF_3, (C_{1-4} alkyl)C(O)NH, S$(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S$(O)_2$(C_{1-4} alkyl)} or heteroaryl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF_3, (C_{1-4} alkyl)C(O)NH, S$(O)_2NH_2$, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S$(O)_2$(C_{1-4} alkyl)};

R^8 and R^9 are, independently, hydrogen or C_{1-4} alkyl; or R^8 and R^9 join to form a 5- or 6-membered ring which may additionally comprise an oxygen or sulphur atom (for example to form a morpholine, thiomorpholine ring) or NR^{39} group (for example to

form a piperazine ring), wherein the ring is optionally substituted with halogen, C_{1-4} alkyl or phenyl (wherein the phenyl ring is optionally substituted by halo, cyano, nitro, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$ alkyl, $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, $NHS(O)_2(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)NH_2$, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3);

R^{11}, R^{13}, R^{15}, R^{17}, R^{18}, R^{20}, R^{22}, R^{24}, R^{27}, R^{32} and R^{35} are, independently, hydrogen or C_{1-6} alkyl;

R^{12}, R^{14}, R^{16}, R^{19}, R^{21}, R^{23}, R^{25}, R^{26}, R^{28}, R^{29}, R^{30}, R^{31}, R^{33}, R^{34}, R^{36}, R^{37} and R^{38} are, independently, C_{1-6} alkyl (optionally substituted by halo, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), heteroaryl, phenyl, heteroaryloxy or phenyloxy), C_{3-7} cycloalkyl, phenyl or heteroaryl; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;

R^{12}, R^{14}, R^{16}, R^{19}, R^{21}, R^{25}, R^{26}, R^{33}, R^{34}, R^{36} and R^{38} may additionally be hydrogen; and,

R^{39} is hydrogen, C_{1-4} alkyl, $C(O)(C_{1-4}$ alkyl) or $S(O)_2(C_{1-4}$ alkyl);

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I) as claimed in claim 1 wherein, unless specified otherwise, aryl, phenyl and heteroaryl moieties are independently optionally substituted by one or more of halo, hydroxy, nitro, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3.

3. A compound of formula (I) as claimed in claim 1 or 2 wherein R^1 is C_{3-7} cycloalkyl in which at least one ring carbon is replaced by the same or different O, S, S(O), $S(O)_2$, CHF or CF_2; wherein R^1 is optionally substituted by halogen or C_{1-6} alkyl.

4. A compound of formula (I) as claimed in claim 3 wherein R^1 is tetrahydropyranyl, tetrahydrothiopyranyl or 1,1-dioxidotetrahydrothiopyranyl, each optionally substituted by halogen or C_{1-4} alkyl.

5. A compound as claimed in claim 1, 2, 3 or 4 wherein R^2 is phenyl optionally substituted in the 2-, 3-, 2,5- or 3,5- position by the same or different: halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3; where n is 0, 1 or 2.

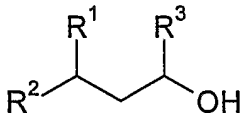
6. A compound as claimed in claim 1, 2, 3, 4 or 5 wherein R^3 is hydrogen.

7. A compound as claimed in claim 1, 2, 3, 4, 5 or 6 wherein R^4 is ethyl.

8. A compound as claimed in claim 1, 2, 3, 4, 5, 6 or 7 wherein R^5 is phenyl or benzyl, either of which is optionally substituted by halogen, cyano, C_{1-4} alkyl (mono-substituted by $S(O)_2(C_{1-4}$ alkyl) or $C(O)NH(C_{1-4}$ alkyl)), C_{1-4} alkoxy, $S(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), $OS(O)_2(C_{1-4}$ alkyl), OCH_2COOH, OCH_2-tetrazolyl (itself optionally substituted by C_{1-4} alkyl), carboxamide or tetrazolyl (itself optionally substituted by C_{1-4} alkyl).

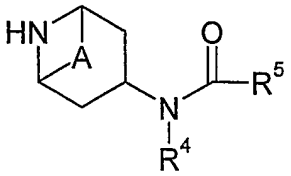
9. A process for preparing a compound of formula (I) as claimed in claim 1, the process comprising:

a. reacting a compound of formula (II):



(II)

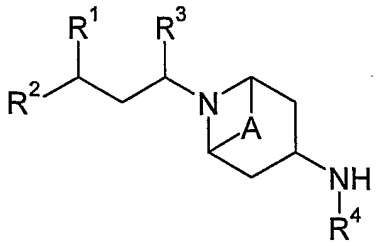
with an oxidizing agent and then reacting the product so-formed with a compound of formula (III):



(III)

in the presence of a source of triacetoxybobohydride, in a suitable solvent at room temperature; or

b. coupling a compound of formula (IV):



(IV)

with a compound R^5-CO_2H in the presence of a suitable coupling agent, in the presence of a suitable base, in a suitable solvent at room temperature.

10. A pharmaceutical composition which comprises a compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

11. A compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof, for use as a medicament.

12. A compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in therapy.

13. A method of treating a CCR5 mediated disease state comprising administering to a patient in need of such treatment an effective amount of a compound as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001860

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 405/06, C07D 409/06, A61K 31/4468
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03042205 A1 (ASTRAZENECA AB), 22 May 2003 (22.05.2003), claim 1, examples, abstract --	1-13
A	WO 2003042177 A1 (ASTRAZENECA AB), 22 May 2003 (22.05.2003), claims 1-13, example 56, abstract --	1-13
A	WO 0187839 A1 (ASTRAZENECA AB), 22 November 2001 (22.11.2001) --	1-13
A	WO 03080574 A1 (ASTRAZENECA AB), 2 October 2003 (02.10.2003), table II, example 3, method D, abstract --	1-13

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 2005	11-03-2005
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anders Wirén/ELY Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001860

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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