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 WO01/87839, WO01/66525, 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.

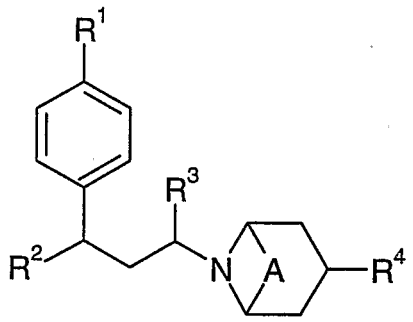
The CCR5 receptor is expressed on T-lymphocytes, monocytes, macrophages, dendritic cells, microglia and other cell types. These detect and respond to several

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 absent or is CH_2CH_2;

R^1 is halo, hydroxy, nitro, $(CH_2)_nS(O)_k(C_{1-6}$ alkyl), $(CH_2)_nS(O)_2NH_2$, $(CH_2)_nS(O)_2NH(C_{1-6}$ alkyl), $(CH_2)_nS(O)_2NHCHO$, $(CH_2)_nS(O)_2N(C_{1-6}$ alkyl)$_2$, $OS(O)_2(C_{1-6}$ alkyl), cyano, C_{1-6} alkyl, C_{1-6} alkoxy, 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)$_2$, C(O)[N-linked heterocyclyl], CO_2H, $CO_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl), $(CH_2)_nNHS(O)_2(C_{1-6}$ alkyl), $C(O)(C_{1-6}$ alkyl), CF_3, OCF_3, phenyl, heteroaryl, $(C_{1-4}$ alkyl)phenyl, $(C_{1-4}$ alkyl)heteroaryl, NHC(O)phenyl, NHC(O)heteroaryl, $NHC(O)(C_{1-4}$ alkyl)phenyl, $NHC(O)(C_{1-4}$ alkyl)heteroaryl, $NHS(O)_2$phenyl, $NHS(O)_2$heteroaryl, $NHS(O)_2(C_{1-4}$ alkyl)phenyl, $NHS(O)_2(C_{1-4}$ alkyl)heteroaryl, $NHC(O)NH(C_{1-6}$ alkyl), $NHC(O)NH(C_{3-7}$ cycloalkyl), NHC(O)NHphenyl, NHC(O)NHheteroaryl, $NHC(O)NH(C_{1-4}$ alkyl)phenyl or $NHC(O)NH(C_{1-4}$ alkyl)heteroaryl;

wherein the foregoing phenyl and heteroaryl groups are optionally substituted by halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ 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^2 is phenyl, halophenyl, thienyl or halothienyl;

R^3 is hydrogen or methyl;

R^4 is a five membered heterocycle containing at least one carbon atom, one to four nitrogen atoms and, optionally, one oxygen or sulphur atom, said heterocycle being optionally substituted by oxo, C_{1-6} alkyl, $H_2NC(O)$, (phenylC_{1-2} alkyl)$HNC(O)$, C_{1-2} alkyl(phenyl) [which is optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, OCF_3, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl) or $S(O)_2(C_{1-4}$ alkyl)], $S(C_{1-4}$ alkyl), $S(C_{1-2}$ alkyl(phenyl)), NH_2 or phenyl; the five membered heterocycle being optionally fused to a cyclohexane, piperidine, benzene, pyridine, pyridazine, pyrimidine or pyrazine ring; the ring carbon atoms of said fused cyclohexane, piperidine, benzene, pyridine, pyridazine, pyrimidine or pyrazine ring being optionally substituted by halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, OCF_3, NH_2, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl) or $S(O)_2(C_{1-4}$ alkyl); and the nitrogen of the fused piperidine ring being optionally substituted by C_{1-4} alkyl {which is optionally substituted by oxo, halogen, OH, C_{1-4} alkoxy, OCF_3, $C(O)O(C_{1-4}$ alkyl), CN, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, NH_2, $NH(C_{1-4}$ alkyl) or $N(C_{1-4}$ alkyl$)_2$}, $C(O)(C_{1-4}$ alkyl) {wherein the alkyl is optionally substituted by C_{1-4} alkoxy or fluoro}, $C(O)O(C_{1-4}$ alkyl), $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ or $S(O)_2(C_{1-4}$ alkyl) {wherein the alkyl is optionally substituted by fluoro};

k, m and n are, independently, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof or a solvate 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 (adducts) such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or, additionally, formate. Acid addition salt is, for example hydrochloride or formate.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Halogen is, for example, chloro, fluoro or bromo; such as chloro or fluoro.

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.

N-Linked heterocyclyl is a nitrogen-linked, non-aromatic 3, 4, 5 or 6 membered ring optionally comprising one further heteroatom (selected from the group comprising nitrogen, oxygen and sulphur). It is, for example, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl.

Heteroaryl is 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, pyridinyl, pyrimidinyl, 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. Heteroaryl is especially pyridyl, pyrimidinyl, indolyl or benzimidazolyl.

The five membered heterocycle of R^4 is, for example, pyrazolyl, imidazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl or thiazolyl. When the five membered heterocycle of R^4 is fused to a benzene or pyridine ring the resulting bicyclic is, for example, benzimidazolyl, benztriazolyl or an imidazopyridinyl (such as imidazo[4,5c]pyridinyl). When the five membered ring heterocycle of R^4 is fused to a saturated cycloalkyl or piperidine the resulting bicyclic is, for example, 4,5,6,7-tetrahydro-1*H*-benzimidazole, 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine or 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine. In one particular aspect of the invention the five membered ring heterocycle of R^4 is, for example, pyrazolyl, imidazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl or 1,3,4-oxadiazolyl. When the five membered ring heterocycle of R^4 is fused to a benzene ring the resulting bicyclic is, for example, benzimidazol-1-yl.

(C_{1-4} Alkyl)phenyl is, for example, benzyl, 2-phenylethyl or 1-phenyleth-1-yl. (C_{1-4} Alkyl)heteroaryl is, for example, pyridylmethyl or pyrimidinylmethyl. NHC(O)Heteroaryl is, for example, NHC(O)pyridyl. NHC(O)(C_{1-4} Alkyl)phenyl is, for example, NHC(O)benzyl. NHC(O)(C_{1-4} Alkyl)heteroaryl is, for example, NHC(O)CH_2pyridyl. NHS(O)$_2$Heteroaryl is, for example, NHS(O)$_2$pyridyl. NHS(O)$_2$(C_{1-4} Alkyl)phenyl is, for example, NHS(O)$_2$benzyl. NHS(O)$_2$(C_{1-4} Alkyl)heteroaryl is, for example, NHS(O)$_2$$CH_2$pyridyl. NHC(O)NHheteroaryl is, for example, NHC(O)NHpyridyl. NHC(O)NH(C_{1-4} Alkyl)phenyl is, for example, NHC(O)NHbenzyl. NHC(O)NH(C_{1-4} Alkyl)heteroaryl is, for example, NHC(O)NHCH$_2$pyridyl.

In another aspect of the invention R^4 is a five membered ring aromatic heterocycle containing at least one carbon atom, one to four nitrogen atoms and, optionally, one oxygen atom, said heterocycle being optionally substituted by C_{1-6} alkyl or benzyl [which is optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, OCF_3, S(C_{1-4} alkyl) or S(O)$_2$(C_{1-4} alkyl)], and being optionally fused to a benzene ring, said fused benzene ring being optionally substituted by halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, OCF_3, S(C_{1-4} alkyl) or S(O)$_2$(C_{1-4} alkyl).

In yet another aspect of the invention k and m are, independently, 0 or 2. In a further aspect of the invention k and m are both 2.

In another aspect of the invention A is absent.

In a further aspect of the invention n is 0.

In a still further aspect of the invention R^1 is halo, S(O)$_k$(C_{1-6} alkyl), OS(O)$_2$(C_{1-6} alkyl), S(O)$_2$NH$_2$, S(O)$_2$NH(C_{1-6} alkyl), S(O)$_2$N(C_{1-6} alkyl)$_2$, cyano, NH$_2$, NH(C_{1-6} alkyl), N(C_{1-6} alkyl)$_2$, 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), NHC(O)phenyl, NHC(O)heteroaryl, NHC(O)(C_{1-4} alkyl)phenyl, NHC(O)(C_{1-4} alkyl)heteroaryl, NHS(O)$_2$phenyl, NHS(O)$_2$heteroaryl, NHS(O)$_2$(C_{1-4} alkyl)phenyl, NHS(O)$_2$(C_{1-4} alkyl)heteroaryl, NHC(O)NH(C_{1-6} alkyl), NHC(O)NH(C_{3-7} cycloalkyl), NHC(O)NHphenyl, NHC(O)NHheteroaryl, NHC(O)NH(C_{1-4} alkyl)phenyl or NHC(O)NH(C_{1-4} alkyl)heteroaryl; wherein the foregoing phenyl and heteroaryl groups are optionally substituted by halo, hydroxy, nitro, S(O)$_m$(C_{1-4} alkyl), S(O)$_2$NH$_2$, 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$_2$H, 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; k and m are, independently, 0 or 2.

In a further aspect of the invention R^1 is halo, cyano, $S(O)_2(C_{1-6}$ alkyl), $OS(O)_2(C_{1-6}$ alkyl), $CO_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), NHC(O)phenyl, NHC(O)heteroaryl, $NHC(O)(C_{1-4}$ alkyl)phenyl, $NHC(O)(C_{1-4}$ alkyl)heteroaryl, $NHS(O)_2$phenyl, $NHS(O)_2$heteroaryl, $NHS(O)_2(C_{1-4}$ alkyl)phenyl or $NHS(O)_2(C_{1-4}$ alkyl)heteroaryl; wherein the foregoing phenyl and heteroaryl groups are optionally substituted by halo, hydroxy, nitro, $S(O)_2(C_{1-4}$ 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.

In a still further aspect of the invention R^1 is halo, cyano, $S(O)_2(C_{1-6}$ alkyl), $OS(O)_2(C_{1-6}$ alkyl), $CO_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl) or $NHS(O)_2(C_{1-6}$ alkyl).

In another aspect R^1 is $S(O)_k(C_{1-4}$ alkyl), wherein k is 0, 1 or 2, (for example SCH_3, $S(O)CH_3$ or $S(O)_2CH_3$), $NHS(O)_2(C_{1-4}$ alkyl) (for example $NHS(O)_2CH_3$) or $NHC(O)(C_{1-4}$ alkyl) (for example $NHC(O)CH_3$). In yet another aspect R^1 is $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$), $NHS(O)_2(C_{1-4}$ alkyl) (for example $NHS(O)_2CH_3$) or $NHC(O)(C_{1-4}$ alkyl) (for example $NHC(O)CH_3$). In a still further aspect R^1 is $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$).

In a further aspect of the invention R^2 is phenyl, halophenyl (for example mono-chlorophenyl, mono-fluorophenyl or di-fluorophenyl; such as 3-fluorophenyl or 3,5-difluorophenyl), thienyl or halothienyl (for example mono-chlorothienyl; such as 4-chlorothien-2-yl or 5-chlorothien-2-yl). In a still further aspect R^2 is halophenyl (for example mono-chlorophenyl, mono-fluorophenyl or di-fluorophenyl; such as 3-fluorophenyl or 3,5-difluorophenyl). In another aspect R^2 is phenyl, halophenyl (for example mono-chlorophenyl, mono-fluorophenyl or di-fluorophenyl; such as 3-fluorophenyl or 3,5-difluorophenyl) or thienyl. In yet another aspect R^2 is 3-fluorophenyl or 3,5-difluorophenyl.

In a still further aspect R^3 is hydrogen.

In another aspect of the invention R^4 is other than an optionally substituted indolyl group.

In another aspect R^4 is imidazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, tetrazolyl, pyrazolyl or 1,3-thiazolyl, isoxazolyl optionally substituted as described above.

In yet another aspect R^4 is 1,2,4-triazolyl, thiazolyl, 1,2,4-oxadiazolyl, imidazolyl or 1,2,3-triazolyl substituted as described above. In a further aspect R^4 is 1,2,4-triazolyl, thiazolyl, 1,2,4-oxadiazolyl, benzimidazolyl, benztriazolyl or an imidazopyridinyl (such as

imidazo[4,5c]pyridinyl), each of which is unsubstituted or substituted by one or two of the same or different C_{1-6} alkyl (for example C_{1-4} alkyl; such as methyl), CF_3, OH (which may tautomerise to the keto form), $S(O)_2(C_{1-4}$ alkyl), $C(O)NH_2$, $C(O)NH(phenyl(C_{1-2}$ alkyl)) or $phenyl(C_{1-2}$ alkyl); wherein the phenyl of the foregoing $phenyl(C_{1-2}$ alkyl) groups is optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano or $S(O)_2(C_{1-4}$ alkyl).

In a further aspect R^4 is pyrazolyl, 1,2,4-triazolyl, tetrazolyl, isoxazolyl or 1,2,4-oxadiazolyl, substituted as described above. In a further aspect R^4 is pyrazolyl, 1,2,4-triazolyl, tetrazolyl, isoxazolyl or 1,2,4-oxadiazolyl each of which is unsubstituted or substituted by one or two of the same or different C_{1-6} alkyl (for example C_{1-4} alkyl; such as methyl, ethyl or iso-propyl) or benzyl (optionally substituted (for example unsubstituted or mono-substituted) by halogen, $S(C_{1-4}$ alkyl) or $S(O)_2(C_{1-4}$ alkyl)).

In a still further aspect R^4 is benzimidazolyl (for example benzimidazol-1-yl) which is optionally substituted on the benzene part (for example mono-substituted at the 5-position of the benzimidazolyl) by halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, OCF_3, $S(C_{1-4}$ alkyl) or $S(O)_2(C_{1-4}$ alkyl). In another aspect R^4 is benzimidazolyl (for example benzimidazol-1-yl) which is optionally substituted on the benzene part (for example mono-substituted at the 5-position of the benzimidazolyl) by $S(O)_2(C_{1-4}$ alkyl).

In another aspect of the invention R^4 is imidazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, tetrazolyl, pyrazolyl or 1,3-thiazolyl, said ring being optionally substituted by oxo, C_{1-6} alkyl (such as methyl or *iso*-propyl), C_{1-2} alkyl(phenyl) {wherein the phenyl is optionally substituted by halo (such as chloro or fluoro) or $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2CH_3$}, $S(C_{1-4}$ alkyl) (such as SCH_3), $S(C_{1-2}$ alkyl(phenyl)) (such as $SCH_2C_6H_5$), NH_2 or phenyl; said ring optionally being fused to a benzene ring, said benzene ring being optionally substituted by cyano or $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2CH_3$).

In yet another aspect the present invention provides a compound of formula (I) wherein A is absent or is CH_2CH_2; R^1 is $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2CH_3$); R^2 is phenyl, halophenyl (such as 3-fluorophenyl, 3,5-difluorophenyl or 3-chloro-5-fluorophenyl), thienyl or halothienyl (such as 5-chlorothien-2-yl or 4-chlorothien-2-yl); R^3 is hydrogen; R^4 is imidazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, tetrazolyl, pyrazolyl or 1,3-thiazolyl, said ring being optionally substituted by oxo, C_{1-6} alkyl (such as methyl or *iso*-propyl), C_{1-2} alkyl(phenyl) {wherein the phenyl is optionally substituted by halo (such as chloro or fluoro) or $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2CH_3$}, $S(C_{1-4}$ alkyl) (such as SCH_3), $S(C_{1-2}$ alkyl(phenyl))

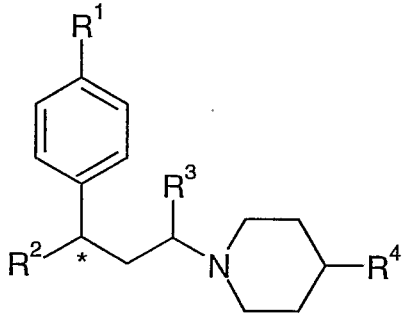
(such as $SCH_2C_6H_5$), NH_2 or phenyl; said ring optionally being fused to a benzene ring, said benzene ring being optionally substituted by cyano or $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2CH_3$).

The compounds listed in Table I illustrate the invention. In another aspect the present invention provides each individual compound recited in Table I.

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TABLE I

Table I comprises compounds of formula (I) wherein A is absent.

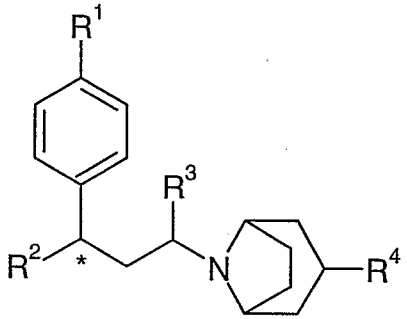


Compound No.	R^1	R^2	R^3	R^4	* Chirality	Adduct	LCMS (MH+)
1	$CH_3S(O)_2$	3-Fluorophenyl	H	5-$CH_3S(O)_2$-benzimidazol-1-yl	R isomer	-	570
2	$CH_3S(O)_2$	3-Fluorophenyl	H	3-CH_3-5-$(CH_3)_2CH$-[1,2,4]triazol-4-yl	R isomer	-	499
3	$CH_3S(O)_2$	Phenyl	H	3-((4-$CH_3S(O)_2$-phenyl)CH_2)[1,2,4]-oxadiazol-5-yl	S isomer	hydrochloride	594
4	$CH_3S(O)_2$	Phenyl	H	3-(benzyl)[1,2,4]-oxadiazol-5-yl	S isomer	hydrochloride	516
5	$CH_3S(O)_2$	Phenyl	H	5-$CH_3S(O)_2$-benzimidazol-1-yl	S isomer	-	552
6	$CH_3S(O)_2$	Phenyl	H	3-((4-CH_3S-phenyl)CH_2)[1,2,4]-oxadiazol-5-yl	S isomer	hydrochloride	562
7	$CH_3S(O)_2$	Thien-3-yl	H	5-$CH_3S(O)_2$-benzimidazol-1-yl	R isomer	-	558
8	$CH_3S(O)_2$	Thien-2-yl	H	5-$CH_3S(O)_2$-benzimidazol-1-yl	R isomer	-	558
9	$CH_3S(O)_2$	5-Chlorothien-2-yl	H	5-$CH_3S(O)_2$-benzimidazol-1-yl	R isomer	-	592
10	$CH_3S(O)_2$	4-Chlorothien-2-yl	H	5-$CH_3S(O)_2$-benzimidazol-1-yl	R isomer	-	592

11	$CH_3S(O)_2$	3,5-Difluorophenyl	H	5-$CH_3S(O)_2$-benzimidazol-1-yl	R isomer	-	588
12	$CH_3S(O)_2$	3,5-Difluorophenyl	H	3-CH_3-5-$(CH_3)_2CH$-[1,2,4]triazol-4-yl	R isomer	-	517
13	$CH_3S(O)_2$	Phenyl	H	3-CH_3-[1,2,4]-oxadiazol-5-yl	S isomer	-	440
14	$CH_3S(O)_2$	3,5-Difluorophenyl	H	2-((4-Chloro-phenyl)CH_2)-2*H*-tetrazol-5-yl	R isomer	-	586
15	$CH_3S(O)_2$	3,5-Difluorophenyl	H	2-((4-$CH_3S(O)_2$-phenyl)CH_2)-2*H*-tetrazol-5-yl	R isomer	-	630
16	$CH_3S(O)_2$	3,5-Difluorophenyl	H	5-Benzyl-2-methyl-2*H*-pyrazol-3-yl	R isomer	hydrochloride	564
17	$CH_3S(O)_2$	3-Cl, 5-F-phenyl	H	5-$CH_3S(O)_2$-benzimidazol-1-yl	R isomer	-	604
18	$CH_3S(O)_2$	3,5-Difluorophenyl	H	2-ethyl-5-(4-fluorobenzyl)-2*H*-pyrazol-3-yl	R isomer	-	596
19	$CH_3S(O)_2$	3,5-Difluorophenyl	H	4-amino-1,3-thiazol-2-yl	R isomer	-	492
20	$CH_3S(O)_2$	3,5-Difluorophenyl	H	5-methylimidazolidine-2,4-one-3-yl	R isomer	-	506
21	$CH_3S(O)_2$	3,5-Difluorophenyl	H	5-phenylimidazolidine-2,4-one-3-yl	R isomer	-	568
22	$CH_3S(O)_2$	3,5-Difluorophenyl	H	2-(4-chlorobenzyl)-1,3-thiazol-5-yl	R isomer	-	601
23	$CH_3S(O)_2$	3,5-Difluorophenyl	H	5-ethylimidazolidine-2,4-one-3-yl	R isomer	-	520
24	$CH_3S(O)_2$	3,5-Difluorophenyl	H	2-methyl-2*H*-tetrazol-5-yl	R isomer	-	476
25	$CH_3S(O)_2$	3,5-Difluorophenyl	H	Indol-1-yl	R isomer	-	509
26	$CH_3S(O)_2$	3,5-Difluorophenyl	H	4*H*-[1,2,4]triazol-4-yl	R isomer	-	461
27	$CH_3S(O)_2$	3,5-Difluorophenyl	H	3,5-dimethyl-[1,2,4]triazol-4-yl	R isomer	-	489
28	$CH_3S(O)_2$	3,5-Difluorophenyl	H	5-cyano-benzimidazol-1-yl	R isomer	-	535
29	$CH_3S(O)_2$	3,5-Difluorophenyl	H	Benzimidazol-1-yl	R isomer	-	510
30	$CH_3S(O)_2$	3,5-Difluorophenyl	H	2-methyl-5-$CH_3S(O)_2$-benzimidazol-1-yl	R isomer	-	602

Table II

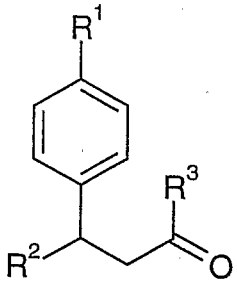
Table II comprises compounds of forluma (I) wherein A is CH_2CH_2.

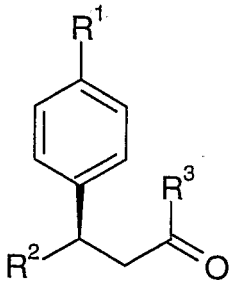


Compound No.	R^1	R^2	R^3	R^4	* Chirality	LCMS (MH+)
1	$CH_3S(O)_2$	3,5-Difluorophenyl	H	3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl (*exo*)	R isomer	543
2	$CH_3S(O)_2$	3,5-Difluorophenyl	H	5-(methylsulfonyl)-1*H*-benzimidazole (*endo*)	R isomer	614
3	$CH_3S(O)_2$	3,5-Difluorophenyl	H	5-(methylsulfonyl)-1*H*-benzimidazole (*exo*)	R isomer	614

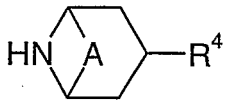
The compounds of the invention can be prepared as shown in the processes on pages marked Schemes 1 and 2 below. (In Schemes 1 and 2 Ac is acetyl; Bu is butyl; LDA is lithium diisopropylamide; TMEDA is *N,N,N',N'*-tetramethylethyenediamine; and, Tf is triflate.)

A compound of the invention can be prepared by reductive amination of a compound of formula (II) or (IIa):


(II)


(IIa)

with a compound of formula (III):

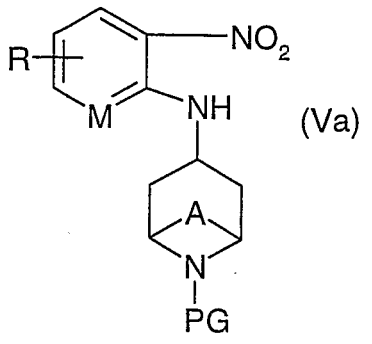

(III)

in the presence of $NaBH(OAc)_3$ (wherein Ac is $C(O)CH_3$) and acetic acid, in a suitable solvent (such as a C_{1-6} aliphatic alcohol, for example ethanol) at room temperature (for example 10-30°C).

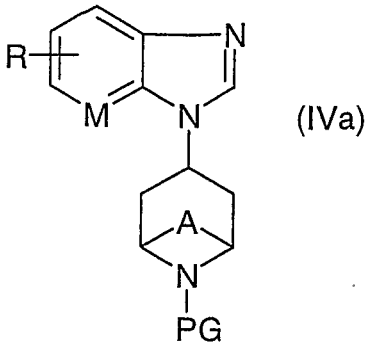
Compounds of formula (III) can be prepared by removal of the protecting group (PG) from a compound of formula (IV), for example where PG is benzyloxylcarbonyl or benzyl removal may be effected by hydrogenation (for example hydrogen in the presence of palladium on carbon catalyst); where PG is tert-butyloxycarbonyl removal may be effected by treatment with acid (such as hydrochloric acid or trifluoroacetic acid).


(IV)

Compounds of formula (IVa) can be made by first reducing a compound of formula (Va):



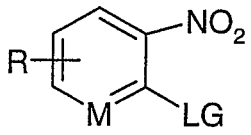
(Va)



(IVa)

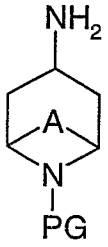
and then cyclising the product so formed. (For example cyclising in the presence of trimethylorthoformate and *para*-toluenesuphonic acid monohydrate.)

A compound of formula (Va) can be prepared by coupling a compound of formula (VIa):



(VIa)

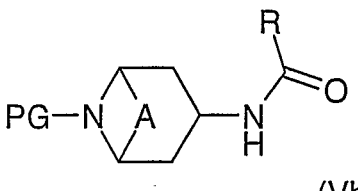
wherein LG is a leaving group (such as fluorine), with a compound of formula (VII):



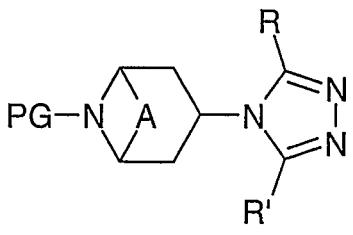
(VII)

in the presence of a base. Compounds of formula (VIa) can be made by nitration of the respective chloroheteroaryl or respective chloroheteroaryl *N*-oxide (followed by reduction to remove the *N*-oxide); or by chlorination of an oxo-nitro-heteroaryl (such as 3-nitropyridin-4-one).

Compounds of formula (IVb) can be prepared from a compound of formula (Vb) using a "one-pot", two-step procedure by first activating the amide with, for example, phosphorous oxychloride in the presence of a base (such as pyridine) and reacting with an acyl hydrazide, then by cyclising in the presence of an acid at elevated temperature (such as *para*-toluenesuphonic acid in refluxing toluene).



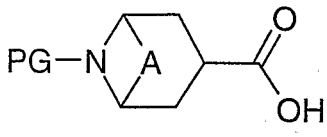
(Vb)



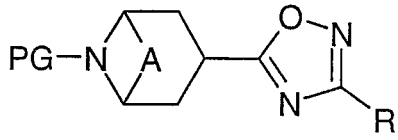
(IVb)

Compounds of formula (Vb) can be prepared from a compound of formula (VII) by reaction with an activated carboxylic acid or with a carbonyl chloride in the presence of a base.

Compounds of formula (IVc) can be prepared by first activating the acid of a compound of formula (Vc) and reacting with an *N*-hydroxy-amidine $RC(NOH)NH_2$, then by cyclisation under elevated temperature in a suitable solvent such as dioxan.

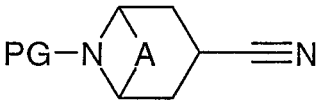


(Vc)

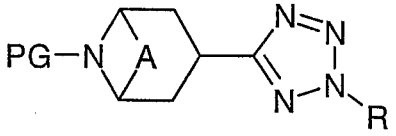


(IVc)

Compounds of formula (IVd) can be prepared by addition of azide to a compound of formula (Vd) then by alkylation of the product so formed.

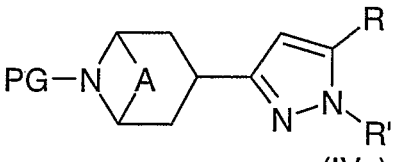


(Vd)

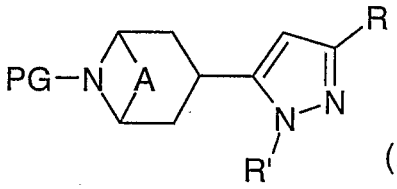


(IVd)

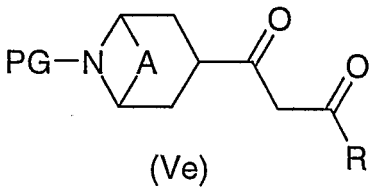
Compounds of formula (IVe) and (IVf) can be prepared by reaction of a compound of formula (Ve) with an alkyl hydrazine $R'NHNH_2$. Compounds of formula (Ve) can be made by condensation of a compound of formula (VIe) with an ester $RC(O)_2R''$.



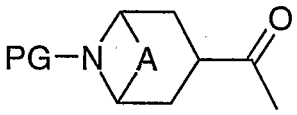
(IVe)



(IVf)

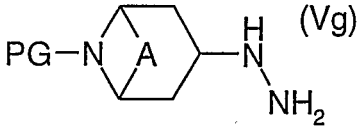


(Ve)

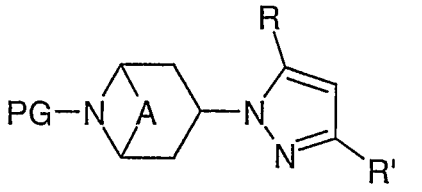


(VIe)

Compounds of formula (IVg) can be prepared by reaction of a compound of formula (Vg) with a 1,3-di-ketone $RC(O)CH_2C(O)R'$.

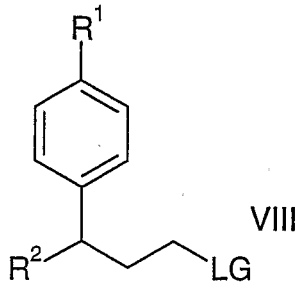


(Vg)

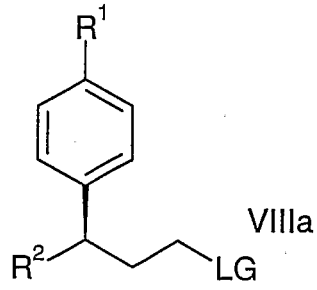


(IVg)

A compound of the invention can be prepared by alkylation of a compound of formula (VIII) or (VIIIa):

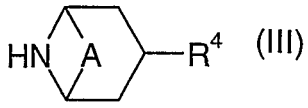


VIII



VIIIa

with a compound of formula (III)



(III)

in the presence of a suitable base, such as potassium carbonate or triethylamine, in a suitable solvent, such as acetonitrile or THF at room temperature (for example 10-30°C).

The starting materials for these preparative methods and Schemes are either commercially available or can be prepared by literature methods, adapting literature methods or by following or adapting Methods 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 or a solvate 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 or a solvate thereof.

The present invention also provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate 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 scrofulous 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 or a solvate 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 or a solvate 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 or a solvate 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 scrofulous 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 or solvate thereof.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate 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 or a solvate 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 0.01mgkg^{-1} to 100mgkg^{-1} of the compound, preferably in the range of 0.1mgkg^{-1} to 20mgkg^{-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 the invention, or a pharmaceutically acceptable salt, solvate or a solvate of a salt thereof, or a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt, solvate or a solvate of a 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 $C\text{-}X_3\text{-}C$ 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 - $(M+H)^+$;

(xi) the compounds of the Examples and Methods were named using the IUPAC name program from Advanced Chemistry Development Inc, version 6.00; and,

(xii) the following abbreviations are used:

DMSO	dimethyl sulfoxide;
DMF	*N*-dimethylformamide;
DCM	dichloromethane;
THF	tetrahydrofuran;
DIPEA	*N*,*N*-diisopropylethylamine;
DIBAL	Di-iso-butyl aluminium hydride
NMP	*N*-methylpyrrolidinone;
HATU	O-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate;
HBTU	O-(7-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate;
Boc	tert-butoxycarbonyl
MeOH	methanol;
EtOH	ethanol; and
EtOAc	ethyl acetate.

EXAMPLE 1

This Example illustrates the preparation of (*R*)-1-{1-[3-(3-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-propyl]-piperidin-4-yl}-5-methanesulfonyl-1*H*-benzoimidazole (Compound No. 1 of Table I).

Under an argon atmosphere (*R*)-3-(3-fluoro-phenyl)-3-(4-methanesulfonylphenyl)-propionaldehyde (0.162g) (Method O) and 5-methanesulfonyl-1-piperidin-4-yl-1*H*-benzoimidazole (0.112g) (Method A) were dissolved in dichloromethane. A drop of acetic acid was added followed by sodium trisacetoxyborohydride (0.254g) and the reaction mixture was stirred at ambient temperature for 18 hours, then partitioned between dichloromethane (2 x 50mL) and 2M aqueous sodium hydroxide solution (50mL). The organic liquors were washed with saturated brine, dried (MgSO4) and evaporated to dryness on the rotary evaporator. The residue was purified on a 20g silica cartridge eluting with a 0 to 30% methanol in ethyl acetate gradient over 30 minutes at 20mL per minute to yield the title compound as a solid (0.056g). NMR ($CDCl_3$): 2.17 (m, 6H), 2.33 (m, 4H), 3.04 (s, 3H), 3.08 (m, 4H), 4.18 (t, 1H), 4.25 (m, 1H), 6.92 (m, 2H), 7.04 (d, 1H), 7.39 (m, 1H), 7.45 (d, 2H), 7.57 (d, 1H), 7.89 (d, 2H), 8.19 (s, 1H), 8.42 (s, 1H).

The procedure described in Example 1 can be repeated using different piperidines or piperidine hydrochlorides (such as 2-methyl-5-(methylsulfonyl)-1-piperidin-4-yl-1*H*-benzimidazole (Method A), 1-piperidin-4-yl-1*H*-benzimidazole-5-carbonitrile (Method A), 4-(3-isopropyl-5-methyl-[1,2,4]triazol-4-yl)-piperidine (Method B), 4-[3-(4-methanesulfonyl-benzyl)-[1,2,4]oxadiazol-5-yl]-piperidine hydrochloride (Method C), 4-(3-benzyl-[1,2,4]oxadiazol-5-yl)-piperidine hydrochloride (Method D), 4-[3-(4-methylsulfanyl-benzyl)-[1,2,4]oxadiazol-5-yl]-piperidine hydrochloride (Method E), 4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidine (Method F), 4-[2-(4-chloro-benzyl)-2*H*-tetrazol-5-yl]-piperidine (Method G), 4-[2-(4-methanesulfonyl-benzyl)-2*H*-tetrazol-5-yl]-piperidine (Method H), or 4-(5-benzyl-2-methyl-2*H*-pyrazol-3-yl)-piperidine (Method I), 4-[2-ethyl-5-(4-fluoro-benzyl)-2*H*-pyrazol-3-yl]-piperidine (Method I), 4-[2-(4-chlorobenzyl)-1,3-thiazol-4-yl]piperidine (Method R), 4-(2-Methyl-2*H*-tetrazol-5-yl)-piperidine (Method S), 2-piperidine-4-yl-1,3-thiazol-4-amine, 5-ethyl-3-piperidin-4-ylimidazolidine-2,4-dione (Method T), 5-phenyl-3-piperidin-4-ylimidazolidine-2,4-dione (Method T), 5-methyl-3-piperidin-4-ylimidazolidine-2,4-dione (Method T), 4-(4*H*-1,2,4-triazol-4-yl)piperidine Method U), 4-(3,5-dimethyl-4*H*-1,2,4-triazol-4-yl)piperidine (Method V), 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-*exo*-8-

azabicyclo[3.2.1]octane (Method W), 1-*endo*-(8-azabicyclo[3.2.1]oct-3-yl)-5-(methylsufonyl)-1*H*-benzamidazole (Method X), 1-*exo*-(8-azabicyclo[3.2.1]oct-3-yl)-5-(methylsufonyl)-1*H*-benzamidazole (Method Y), in place of 5-methanesulfonyl-1-piperidin-4-yl-1*H*-benzoimidazole and different aldehydes (such as (*R*)-3-(4-methanesulfonyl-phenyl)-3-thiophen-2-yl-propionaldehyde (Method J), (*R*)-3-(4-methanesulfonyl-phenyl)-3-thiophen-3-yl-propionaldehyde (Method K), (*R*)-3-(4-methanesulfonyl-phenyl)-3-(5-chlorothiophen-2-yl)-propionaldehyde (Method L), (*R*)-3-(4-methanesulfonyl-phenyl)-3-(4-chlorothiophen-2-yl)-propionaldehyde (Method M), (*S*)-3-phenyl-3-(4-methanesulfonylphenyl)propionaldehyde (Method N), or (*R*)-3-(3,5-difluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye (Method P), or (*R*)-3-(3-chloro-5-fluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye (Method Q), in place of (*R*)-3-(3-fluoro-phenyl)-3-(4-methanesulfonylphenyl)-propionaldehyde.

EXAMPLE 2

This Example illustrates the preparation of 1-(1-{(3*R*)-3-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl)phenyl]propyl}piperidin-4-yl)-1*H*-indole (Compound No. 25 of Table I).

Step 1: Tosyl chloride (3g) was added portionwise to pyridine (50ml) at 5°C, followed by a solution of (3*R*)-3-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]propan-1-ol (3.1g) in pyridine (15ml) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured onto ice / 2N HCl and extracted with diethyl ether (x2). The organic extracts were dried and evaporated to dryness to give (3*R*)-3-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]propyl 4-methylbenzenesulfonate as a solid. Yield 2.9g. NMR ($CDCl_3$): 2.4 (m, 2H), 2.5 (s, 3H), 3.05 (s, 3H), 3.95 (m, 2H), 4.2 (t, 1H), 6.7 9m, 3H), 7.3 9m, 4H), 7.75 (d, 2H), 7.85 (d, 2H).

Step 2: A mixture of 1-piperidin-4-yl-1*H*-indole hydrochloride (450mg), (3*R*)-3-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]propyl 4-methylbenzenesulfonate (760mg) and potassium carbonate (500mg) in acetonitrile (30ml) was refluxed for 18 hours. The reaction mixture was concentrated and partitioned between ethyl acetate and water. The organic extracts were dried and evaporated to dryness. The residue was purified by chromatography on silica eluting with ethyl acetate to give the title compound as a solid. Yield 200mg. NMR

($CDCl_3$): 2.0-2.4 (m, 10H), 3.0-3.05 (m, 2H), 3.05 (s, 3H), 4.2 (m, 2H), 6.55 (d, 1H), 6.7 (m, 3H), 7.1-7.3 (m, 3H), 7.4 (d, 1H), 7.5 (d, 2H), 7.65 (d, 1H), 7.9 (d, 2H).

Additional NMR data:

Compound No. 2 of Table I: NMR ($CDCl_3$): 1.70 – 2.34 (m, 11H), 2.53 (s, 3H), 3.00 (m, 5H), 3.18 (m, 1H), 4.12 (m, 1H), 6.92 (m, 2H), 7.02 (d, 1H), 7.26 (m, 1H), 7.43 (d, 2H), 7.87 (d, 2H).

Compound No. 3 of Table I: NMR: 2.08 (2H, m), 2.22 (2H, m), 2.61(2H, m), 2.92 (2H, m), 3.01 (2H, m), 3.18 (3H, s), 3.21 (2H, s), 3.29 (1H, m), 3.59 (2H, m), 4.20 (1H, t), 4.24 (2H, m).

Compound No. 4 of Table I: NMR: 2.08 (2H, m), 2.21 (2H, m), 2.62 (2H, m), 2.91 (2H, m), 3.01 (2H, m), 3.17 (3H, s), 3.27 (1H, m), 3.58 (2H, m), 4.08 (2H, s), 4.20 (1H, m), 7.32 (10H, m), 7.64 (2H, m), 7.87 (2H, m), 10.90 (1H, br s).

Compound No. 5 of Table I: NMR ($CDCl_3$): 2.19 (m, 8H), 2.36 (m, 4H), 3.03 (s, 3H), 3.06 (m, 1H), 3.10 (s, 3H), 4.18 (m, 1H), 4.25 (m, 1H), 7.24 (m, 5H), 7.47 (d, 2H), 7.60 (d, 1H), 7.84 (d, 2H), 8.19 (s, 1H), 8.40 (s, 1H).

Compound No. 6 of Table I: NMR: 2.07 (2H, m), 2.22 (2H, m), 2.45 (3H, s), 2.60 (2H, m), 2.92 (2H, m), 3.02 (2H, m), 3.59 (2H, m), 3.59 (2H, dd), 4.04 (2H,s), 4.20 (1H, t), 7.24 (2H, m), 7.33 (2H, m) 7.40 (2H, m), 7.87 (2H, m), 10.71 (1H, br s).

Compound No. 7 of Table I: NMR ($CDCl_3$): 2.10 (m, 2H), 2.20 (m, 6H), 2.35 (m, 2H), 2.89 and 4.35 (m, 1H), 3.05 (s, 3H), 3.12 (m, 5H), 4.25 (m, 2H), 6.90 (d, 1H), 7.08 (s, 1H), 7.30 (s, 1H), 7.45 (d, 1H), 7.60 (m, 1H), 7.85 (d, 2H), 8.18 (s, 1H), 8.39 (s, 1H).

Compound No. 8 of Table I: NMR ($CDCl_3$): 2.22 (m, 9H), 2.40 (m, 2H), 3.05 (s, 3H), 3.13 (s, 3H), 4.28 (m, 1H), 4.40 (m, 1H), 6.93 (m, 2H), 7.20 (d, 1H), 7.50 (m, 2H), 7.60 (d, 1H), 7.88 (m, 3H), 8.20 (s, 1H), 8.41 (s, 1H).

Compound No. 9 of Table I: NMR ($CDCl_3$): 2.20 (m, 9H), 2.39 (m, 2H), 3.08 (s, 3H), 3.13 (s, 3H), 4.25 (m, 1H), 4.31 (m, 1H), 6.64 (d, 1H), 6.77 (d, 1H), 7.46 (d, 2H), 7.60 (d, 1H), 7.88 (m, 3H), 8.20 (s, 1H), 8.41 (s. 1H).

Compound No. 10 of Table I: NMR ($CDCl_3$): 2.20 (m, 9H), 2.39 (m, 2H), 3.07 (s, 3H), 3.10 (s, 3H), 4.26 (m, 1H), 4.38 (m, 1H), 6.77 (s, 1H), 7.00 (s, 1H), 7.49 (d, 2H), 7.60 (d, 1H), 7.89 (m, 3H), 8.20 (s, 1H), 8.40 (s, 1H).

Compound No. 11 of Table I: NMR ($CDCl_3$): 2.20 (m, 10H), 2.38 (m, 2H), 3.04 (s, 3H), 3.10 (s, 3H), 4.19 (m, 1H), 4.23 (m, 1H), 6.75 (m, 1H), 6.80 (m, 2H), 7.41 (d, 2H), 7.60 (d, 1H), 7.88 (m, 3H), 8.19 (s, 1H), 8.41 (s, 1H).

Compound No. 12 of Table I: NMR ($CDCl_3$): 1.40 (d, 6H), 1.82 (m, 2H), 2.10 (m, 5H), 2.30 (m, 4H), 2.55 (s, 3H), 3.03 (m, 2H), 3.08 (s, 3H), 3.90 (m, 1H), 4.15 (m, 1H), 6.64 (m, 1H), 6.80 (m, 2H), 7.44 (d, 2H), 7.90 (d, 2H).

Compound No. 13 of Table I: NMR: 2.32(3H, m), 2.60-2.92 (9H, m), 2.95 (3H, s), 3.40 (2H, m), 3.64 (2H, m), 4.06 (1H, m), 7.18 (2H, m), 7.26 (2H, m), 7.42 (2H,m), 7.80 (2H, m).

Compound No. 14 of Table I: NMR ($CDCl_3$): 1.9 (m, 2H), 2.05 (m, 4H), 2.25 (m, 4H), 2.9 (m, 3H), 3.05 (s, 3H), 4.2 (m, 1H), 5.7 (s, 2H), 6.7 (m, 1H), 6.75 (d, 2H), 7.3 (m, 4H), 7.4 (d, 2H), 7.9 (d, 2H).

Compound No. 15 of Table I: NMR ($CDCl_3$): 1.9 (m, 2H), 2.1 (m, 4H), 2.25 (m, 4H), 2.9 (m, 3H), 3.05 (s, 6H), 4.2 (m, 1H), 5.8 (s, 2H), 6.65 (m, 1H), 6.75 (d, 2H), 7.45 (d, 2H), 7.55 (d, 2H), 7.9 (d, 2H), 8.0 (d, 2H).

Compound No. 16 of Table I: NMR ($CDCl_3$): 1.65 (m, 2H), 1.83 (d, 2H), 1.99 (t, 2H), 2.23 (m, 4H), 2.48 (tt, 2H), 2.89 (t, 2H), 3.03 (s, 3H), 3.75 (s, 3H), 3.92 (s, 2H), 4.15 (m, 1H), 5.76 (s, 1H), 6.66 (tt, 1H), 6.75 (m, 2H), 7.19 (m, 1H), 7.26 (m, 4H), 7.41 (d, 2H), 7.87 (d, 2H).

Compound No. 17 of Table I: NMR ($CDCl_3$): 2.2 (m, 9H), 2.35 (m, 2H), 3.05 (s, 3H), 3.1 (s, 3H), 3.1 (m, 1H), 4.2 (m, 1H), 4.25 (m, 1H), 6.85 (dd, 1H), 7.0 (dd, 1H), 7.05 (s, 1H), 7.45 (d, 2H), 7.55 (d, 1H), 7.9 (m, 3H), 8.2 (s, 1H), 8.45 (s, 1H).

Compound No. 18 of Table I: NMR ($CDCl_3$): 1.12-1.15 (t, 3H), 1.54-1.76 (m, 6H), 1.90-1.95 (t, 2H), 2.10-2.21 (m, 2H), 2.38-2.45 (tt, 1H), 2.80-2.86 (t, 2H), 2.97 (s, 3H), 3.83 (s, 2H), 3.94-3.99 (q, 2H), 4.06-4.10 (t, 1H), 5.65 (s, 1H), 6.56-6.62 (tt, 1H), 6.66-6.71 (m, 2H), 6.86-6.91 (m, 2H), 7.11-7.16 (m, 2H), 7.34-7.36 (d, 2H), 7.80-7.82 (d, 2H).

Compound No. 19 of Table I: NMR ($CDCl_3$): 1.6 (m, 2H), 1.9-2.0 (m, 4H,) 2.1-2.2 (m, 4H), 2.4 (m, 1H), 2.8 (m, 2H), 3.0 (s, 3H), 4.1 (m, 1H), 4.7 (bs, 2H), 6.0 (s, 1H), 6.6(m, 1H), 7.0 (m, 2H), 7.4 (d, 2H), 7.8 (d, 2H).

Compound No. 20 of Table I:1 NMR ($CDCl_3$): 1.4 (d, 3H), 1.6 (m, 2H), 2.0 (m, 2H), 2.1 (m, 4H), 2.4-2.5 (m, 2H), 2.9 (m, 2H), 3.0 (s, 3H), 3.9 (m, 1H), 4.0 (q, 1H), 4.2 (m, 1H), 5.5 (s, 1H), 6.6 (m, 1H), 6.8 (m, 2H), 7.4 (d, 2H), 7.8 (d, 2H).

Compound No. 21 of Table I: NMR ($CDCl_3$): 1.6 (m, 2H), 2.0 (m, 2H), 2.2 (m, 4H), 2.4-2.5(m, 2H), 2.9 (m, 2H), 3.0 (m, 3H), 3.9 (m, 1H), 4.2 (m, 1H), 5.0 (s, 1H), 5.8 (s, 1H), 6.6 (m, 1H), 6.8 (m, 2H), 7.3-7.4 (m, 7H), 7.8 (d, 2H).

Compound No. 22 of Table I: NMR ($CDCl_3$): 1.75 (m, 2H), 2.05 (m, 4H), 2.3 (m, 4H), 2.75 (m, 1H), 2.95 (m, 2H), 3.05 (s, 3H), 4.15 (m, 1H), 4.25 (s, 2H), 6.65 (m, 1H), 6.8 (m, 3H), 7.3 (m, 4H), 7.45 (d, 2H), 7.9 (d, 2H).

Compound No. 23 of Table I: NMR ($CDCl_3$): 1.0 (t, 3H), 1.6 (m, 2H), 1.7-1.9 (m, 2H), 2.0 (m, 2H), 2.1 (m, 4H), 2.4-2.5 (m, 2H), 2.9 (m, 2H), 3.0 (m, 3H), 3.8 (m, 1H), 3.9 (m, 1H), 4.2 (m, 1H), 5.5 (s, 1H), 6.6 (m, 1H), 6.8 (m, 2H), 7.4(d, 2H), 7.8 (d, 2H).

Compound No. 24 of Table I: NMR ($CDCl_3$): 1.94-2.17 (6H, m), 2.25-2.42 (5H, m), 2.97 (3H, m), 3.02 (3H, s), 4.27 (3H, s), 6.58 (1H, t), 6.75 (2H, d), 7.43 (2H, d), 7.88 (2H, d).

Compound No. 25 of Table I: NMR ($CDCl_3$): 2.0-2.4 (m, 10H), 3.0-3.05 (m, 2H), 3.05 (s, 3H), 4.2 (m, 2H), 6.55 (d, 1H), 6.7 (m, 3H), 7.1-7.3 (m, 3H), 7.4 (d, 1H), 7.5 (d, 2H), 7.65 (d, 1H), 7.9 (d, 2H).

Compound No. 26 of Table I: NMR ($CDCl_3$): 1.9 (m, 2H), 2.0 (m, 4H), 2.25 9m, 4H), 2.9 (m, 2H), 3.2 (s, 3H), 4.1 9m, 1H), 4.25 (t, 1H), 7.05 (m, 1H), 7.2 (m, 2H), 7.65 (d, 2H), 7.85 9d, 2H), 8.6 (s, 2H).

Compound No. 27 of Table I: NMR ($CDCl_3$): 1.75 (m, 2H), 2.0 (m, 2H), 2.25 (m, 4H), 2.35 (s, 6H), 2.9 (m, 2H), 3.2 (s, 3H), 3.3 (m, 2H), 3.9 (m, 1H), 4.25 (m, 1H), 7.05 (m, 1H), 7.2 (m, 2H), 7.65 (d, 2H), 7.9 (d, 2H).

Compound No. 28 of Table I: NMR ($CDCl_3$): 1.5 (m, 4H), 2.05-2.3 (m, 6H), 3.0 (m, 5H), 4.1 (m, 2H), 6.6 (m, 1H), 6.7 (m, 2H), 7.4 (m, 2H), 7.5 (dd, 2H), 7.85 (d, 2H), 8.1 (m, 2H).

Compound No. 29 of Table I: NMR ($CDCl_3$): 1.5 (m, 2H), 2.05-2.3 (m, 8H), 2.95-3.0 (m, 2H), 3.0 (s, 3H), 4.15 (m, 2H), 6.6 (m, 1H), 6.75 (m, 2H), 7.2 (m, 2H), 7.35 (m, 3H), 7.75 (m, 1H), 7.85 (m, 2H), 7.95 (s, 1H).

Compound No. 30 of Table I: NMR ($CDCl_3$): 1.55 (m, 2H), 1.8 (m, 2H), 2.1 (m, 2H), 2.2 (m, 2H), 2.3 (m, 2H), 2.45 (m, 2H), 2.6 (s, 3H), 3.0 (s, 3H), 3.05 (s, 3H), 4.1 (m, 2H), 6.6 (m, 1H), 6.75 (m, 2H), 7.4 (d, 2H), 7.6 (d, 1H), 7.75 (d, 1H), 7.85 (d, 2H), 8.2 (d, 1H).

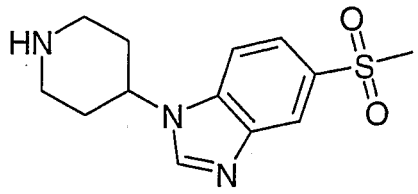
Compound No. 1 of Table II: NMR ($CDCl_3$): 1.31 (d, 6H), 1.58 (m, 4H), 1.94 (m, 2H), 2.13 (m, 4H), 2.25 (m, 2H), 2.466 (s, 3H), 2.92 (m, 1H), 2.966 (s, 3H), 3.24 (m, 2H), 4.2 (m, 2H), 6.61 (m, 1H), 6.7 (m, 2H), 7.366 (m, 2H), 7.825 (m, 2H).

Compound No. 2 of Table II: NMR ($CDCl_3$): 1.6 (m, 2H) 1.9 (m, 2H) 2.1-2.2 (m, 2H) 2.3 (m, 4H) 2.8 (m, 2H) 3.1 (s, 3H) 3.2 (s, 3H) 3.4 (m, 2H) 4.3 (m, 1H) 4.8 (m, 1H) 6.8 (m, 1H) 6.9 (m, 2H) 7.5 (d, 2H) 7,6 (d, 2H) 8.0 (m, 3H) 8.2 (s, 1H) 8.5 (s, 1H).

Compound No. 3 of Table II: NMR ($CDCl_3$): 1.8 (m, 2H) 2.0 (m, 4H) 2.2-2.3 (m, 4H) 2.4 (m, 2H) 3.0 (s, 3H) 3.1 (s, 3H) 3.4 (m, 2H) 4.3 (t, 1H) 4.6 (m, 1H) 6.7 (m, 1H) 6.8 (m, 1H) 7.4 (d, 2H) 7.6 (d, 2H) 7.9 (m, 3H) 8.2 (s, 1H) 8.4 (s, 1H)

Method A

5-Methanesulfonyl-1-piperidin-4-yl-1*H*-benzoimidazole



Step 1: 4-Amino-1-benzylpiperidine (87g) was added slowly during 20 minutes to a stirred mixture of 2-fluoro-5-methylsulphonyl-nitrobenzene (100g) and anhydrous sodium carbonate (35g) in 500mL DMSO, the internal temperature rose from 20°C to 50°C. The mixture was stirred at 90°C for 12 hours, then poured into ice/water and the yellow solid was filtered off, redissolved in dichloromethane, dried and evaporated to give 175g *N*-(1-benzylpiperidin-4-yl)-2-nitro-4-methylsulphonylaniline.

Step 2: The crude material from step 1 (170g) was dissolved in 3 litres of methanol in a pressure vessel, 20g of moist 5%Pd/C catalyst was added and stirred under an atmosphere of hydrogen at 3 bar and 50°C for one hour. The reaction was cooled, filtered and evaporated to give 133g *N*-(1-benzylpiperidin-4-yl)-2-amino-4-methylsulphonylaniline as a brown solid.

Step 3: The crude material from step 2 (130g) was stirred in 300mL trimethylorthoformate containing 4-toluenesulphonic acid (8g) at 90°C for one hour, and collecting the methanol distillate. The reaction was cooled and filtered to give 108g 1-(1-benzylpiperidin-4-yl)-5-methylsulphonyl-1*H*-benzimidazole as a brown solid.

Step 4: The crude material from step 3 (100g) was dissolved in 1 litre of methanol in a pressure vessel, 20g of moist 10% Pd/C catalyst and 100mL acetic acid were added and stirred under an atmosphere of hydrogen at 5 bar and 50°C for 8 hours. The reaction was cooled, filtered and evaporated. The residue was dissolved in water and basified with sodium hydroxide solution, extracted into dichloromethane, dried and evaporated. The brown solid was triturated with isopropanol, filtered, and washed with ether to give the title compound

(60g) as a pale grey solid; NMR: 2.00(m, 4H), 2.75(m, 2H), 3.15(m, 2H), 3.20(s, 3H), 4.60(m, 1H), 7.78 (dd, 1H), 7.85(d, 1H), 8.20(d, 1H), 8.56(s, 1H).

Preparation of 1-piperidin-4-yl-1*H*-benzimidazole-5-carbonitrile

In a similar manner to Method A step 1-3 was prepared *tert*-butyl-4-(5-cyano-1*H*-benzimidazol-1-yl)piperidin-1-carboxylate, except 4-fluoro-3-nitrobenzonitrile and *tert*-butyl 4-aminopiperidine-1-carboxylate was used. The *tert*-butyloxycarbonyl group was removed using the following method.

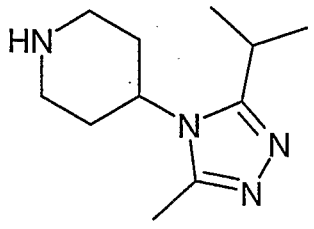
tert-Butyl-4-(5-cyano-1*H*-benzimidazol-1-yl)piperidin-1-carboxylate (326mg) was dissolved in DCM (10ml) and silica gel (10g) was added and the mixture evaporated to dryness. Toluene (100ml) was added and the mixture refluxed for 15 hours. The mixture was evaporated to dryness and the silica was then washed with dichloromethane. The organics were evaporated to a gum which was purified by chromatography on silica eluting with NH_3 / MeOH / dichloromethane (2:18:80) to give the title compound as a solid. Yield 77mg. NMR (d6 DMSO): 2.0 (m, 4H), 2.75 (m, 2H), 3.15 (m, 2H), 4.6 (m, 1H), 7.7 (d, 1H), 7.9 (d, 1H), 8.2 (s, 1H), 8.6 (s, 1H). MS 227 (MH^+).

Preparation of 2-methyl-5-(methylsulfonyl)-1-piperidin-4-yl-1*H*-benzimidazole

In a similar manner to Method A steps 1-4, except using trimethylorthoacetate, was prepared 2-methyl-5-(methylsulfonyl)-1-piperidin-4-yl-1*H*-benzimidazole. MS 293 (MH^+)

Method B

4-(3-Isopropyl-5-methyl-[1,2,4]triazol-4-yl)-piperidine



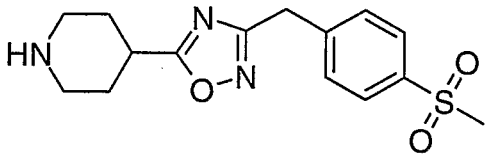
Step 1: To a solution of the 2-methyl-N-[1-(phenylmethyl)-4-piperidinyl]-propanamide (5.89g) in pyridine (11.2mL) and chloroform (15mL) at 0°C under Ar was added phosophorus oxychloride (6.33mL). The mixture was allowed to warm to ambient temperature and stirred for 24 hours then evaporated. The residue was dissolved in chloroform (30mL) and acetic hydrazide (3.36g) added and the mixture heated at reflux for 5 hrs, diluted with saturated

sodium hydrogen carbonate and extracted with dichloromethane, dried ($MgSO_4$) and evepourated. The residue was dissolved in 6M HCl (30mL) and heated at reflux for 21 hours and then evaporated. Saturated potassium carbonate (300mL) was added and extracted with dichloromethane, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The resulting yellow oil was purified on silica (90g) using 2% of a 7M ammonia soln in methanol in 98% dichloromethane to give a yellow solid (3.04g); NMR ($CDCl_3$): 1.40 (d, 6H), 1.80 (m, 2H), 2.0-2.3 (m, 5H), 2.55 (s, 3H), 3.0-3.1 (m, 3H), 3.55 (s, 2H), 3.85 (m, 1H), 7.25-7.35 (m, 5H).

Step 2: The *N*-benzylpiperidine triazole (3.03g) was dissolved in ethanol (50mL) and 20% palladium hydroxide (0.70g) and ammonium formate (3.22g) added and the mixture heated at reflux for 150 minutes. The suspension was filtered through celite and the filtrate evaporated to give the product as a yellow solid (2.20g). NMR ($CDCl_3$): 1.2 (d, 6H), 1.7 (m, 2H), 1.9 (m, 2H), 2.1 (br s, 1H), 2.4 (s, 3H), 2.6 (t, 2H), 3.0 (m, 2H), 3.1 (m, 1H), 4.0 (m, 1H).

Method C

4-[3-(4-Methanesulfonyl-benzyl)-[1,2,4]oxadiazol-5-yl]-piperidine hydrochloride

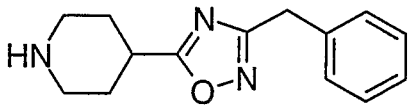


Step 1: *tert*-Butyl 4-{3-[4-(methylthio)benzyl]-1,2,4-oxadiazol-5-yl}piperidine-1-carboxylate (3.10g, 7.96mmol) (Method E, step 1) was dissolved in dichloromethane(100mL), at room temperature, under argon. 3-Chloroperbenzoic acid (60% wt, 6.87g, 23.88mmol) was added portionwise and stirred for 1 hour. Sodium metabisulfite (1M, 250mL) was added and stirred and the organics separated and washed with 1N sodium hydroxide and brine, dried ($MgSO_4$) and solvents evaporated to a clear oil which crystallised upon addition of diethyl ether (50mL). The solid was filtered, washed with a minimum of diethyl ether and dried to give *tert*-butyl 4-{3-[4-(methylsulfonyl)benzyl]-1,2,4-oxadiazol-5-yl}piperidine-1-carboxylate as a white fluffy solid (2.61g, 78% yield); NMR ($CDCl_3$): 1.46 (9H, s), 1.61 (3H, s), 1.79 (2H, m), 2.04 (2H, m), 2.93 (2H, m), 3.04 (3H, s), 4.15 (2H ,s), 7.53 (2H, d), 7.90 (2H, d).

Step 2: A premixed solution of acetyl chloride (0.97mL, 11.86mmol) was added dropwise to methanol (10mL), stirred for 10 minutes and tert-butyl 4-{3-[4-(methylsulfonyl)benzyl]-1,2,4-oxadiazol-5-yl}piperidine-1-carboxylate (2.50g, 5.93mmol) was added and the mixture heated to reflux for 2hours. The solvents were evaporated and the residue triturated with diethyl ether, filtered and dried to give the title compound as a fine white powder (2.05g, 97%); NMR 1.97 (2H, m), 2.17(2H, dd), 3.02(2H, m), 3.31 (2H, m), 3.41 (1H, m), 4.25 (2H, s), 7.59 (2H, d), 7.89 (2H, d), 9.27(1H, br s), 9.35 (1H, br s); MS: 322 (MH+).

Method D

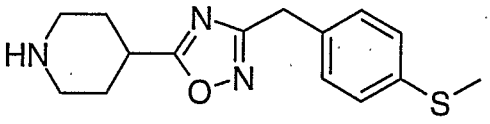
4-(3-Benzyl-[1,2,4]oxadiazol-5-yl)-piperidine hydrochloride



This was prepared from *N'*-hydroxy-2-phenylethanimidamide and 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid using a similar method to that used to prepare 4-{3-[4-(methylthio)benzyl]-1,2,4-oxadiazol-5-yl}piperidine hydrochloride (Method E, Steps 1, 2); NMR: 1.96 (2H, m), 2.15(2H, dd), 3.01(2H, t), 3.24 (2H, dd), 3.40 (1H, m), 4.09 (2H, s), 7.25 (5H, m), 9.31(2H, br s); MS: 244 (MH+).

Method E

4-{3-[4-(methylthio)benzyl]-1,2,4-oxadiazol-5-yl}piperidine hydrochloride



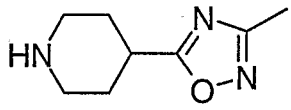
1-(*tert*-Butoxycarbonyl)piperidine-4-carboxylic acid (1.00g, 4.36mmol), 1-hydroxybenzotriazole (589mg, 4.36mmol) and *N*-methylmorpholine(0.97mL, 8.72mmol) were dissolved in dicloromethane (50mL), under argon, and (3-dimethylaminopropyl)carbodiimide hydrochloride (921mg, 8.72mmol) and *N'*-hydroxy-2-[4-(methylthio)phenyl]ethanimidamide (855mg, 4.36mmol) were added. The mixture was stirred at room temperature for 92 hours. The organics were washed with sodium hydroxide (0.1N) and citric acid (0.5M), dried (phase separating filter) and the solvent evaporated to give a yellow oil which was redissolved in 1,4-dioxane (100mL) and heated to reflux for 5 hours, cooled and the solvent evaporated and chromatographed (50g Silica Isolute, eluent 20% ethyl acetate / isohexane) to give a yellow

oil, *tert*-butyl 4-{3-[4-(methylthio)benzyl]-1,2,4-oxadiazol-5-yl}piperidine-1-carboxylate (920mg, 54%); NMR ($CDCl_3$): 1.46 (9H, s), 1.71-1.87 (2H, m), 2.03 (2H, m), 2.48 (3H, m), 2.92 (2H, t), 3.05 (1H, m), 4.00 (2H, s), 4.07 (2H, m), 7.24 (4H, m).

Step 2. Acetyl chloride (86µL, 1.21mmol) was added dropwise to methanol (0.5mL) and stirred for 10 minutes then added to tert-butyl 4-{3-[4-(methylthio)benzyl]-1,2,4-oxadiazol-5-yl}piperidine-1-carboxylate (237mg, 0.61mmol) in MeOH (5mL) and the mixture heated to 60°C for 1hour and the solvents evaporated to give a the title compound as a yellow powder, (199mg, 100%); MS: 290 (MH+).

Method F

4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidine hydrochloride



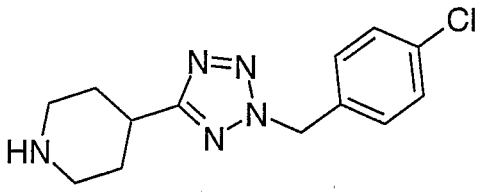
Step 1: Hydroxylamine (50% w/v solution in water, 20mL, 10.0g) was added to acetonitrile (19.0mL, 14.9g, 364mmol, 1.2 equivalents) and the mixture stirred at ambient temperature for 64 hours with the formation of a fine white precipitate, which was filtered and washed with water and diethylether, dried, and combined with the evaporated filtrates and recrystallised from hot methanol (50mL) and dried to give *N'*-hydroxyethanimidamide as white needles; NMR: 1.63(3H, s), 5.32(2H, s), 8.67(1H, s).

Step 2: 1-(*tert*-Butoxycarbonyl)piperidine-4-carboxylic acid (5.00g, 21.83mmol), 1-hydroxybenzotriazole (2.95g, 21.83mmol) and *N*-methylmorpholine(4.8mL, 43.67mmol) were dissolved in dichloromethane (100mL), under argon, and (3-dimethylaminopropyl)carbodiimide hydrochloride (4.60g, 24.0mmol) and *N'*-hydroxyethanimidamide (1.62g, 21.83mmol) were added. The mixture was stirred at room temperature overnight then water (50mL) was added and the mixture stirred for 30minutes. The organics were separated, dried and the solvent evaporated to give a yellow oil which was redissolved in 1,4-dioxane (100mL) and heated to 100°C for 3hours, cooled and the solvent evaporated to give crude *tert*-butyl 4-(3-methyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate as a brown oil (5.74g, 98.5%).

Step 3: Crude *tert*-butyl 4-(3-methyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (5.73g, 21.3mmol) was dissolved in MeOH (100mL) and a premixed solution of acetyl chloride (1.53mL, 42.8mmol) in MeOH (10mL) was added and the mixture heated to 60°C for 1 hour, then the solvents were evaporated and the resultant gum triturated with dichloromethane / diethyl ether (1:1) to give a cream solid which was filtered, washed with diethyl ether and dried, to give the title compound as a solid (1.98g, 55% yield); MS: 168 (MH+).

Method G

4-[2-(4-Chloro-benzyl)-2*H*-tetrazol-5-yl]-piperidine



Step 1: Isonipecotamide (10g) was added portionwise over 15 minutes to phosphorous oxychloride at 0°C. The resulting mixture was refluxed for 2 hours and then cooled and poured slowly onto water keeping the temperature below 20°C. The resulting mixture was neutralised using concentrated potassium hydroxide and extracted with dichloromethane. The organics were dried ($MgSO_4$) and evaporated to give 4-cyanopiperidine as an oil, which was used without further purification.

Step 2: The crude 4-cyanopiperidine was dissolved in methanol (50mL) and di-*tert*-butyldicarbonate (17g) was added. The resulting mixture was stirred for 5 hours. The mixture was concentrated to an oil which was purified by column chromatography eluting with an ethyl acetate / isohexane gradient (10:90 to 40:60 v/v) to give tert-butyl 4-cyanopiperidine-1-carboxylate (9.25g) as an oil; NMR ($CDCl_3$): 1.45 (s, 9H), 1.85 9m, 4H), 2.8 (m, 1H), 3.4 (m, 2H), 3.7 (m, 2H).

Step 3: A mixture of *tert*-butyl 4-cyanopiperidine-1-carboxylate (2.1g), sodium azide (1.95g) and ammonium chloride (1.6g) in dimethylformamide was heated to 100°C for 18 hours. The mixture was cooled and partitioned between 1N HCl and dichloromethane. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to give a gum which was purified by column chromatography eluting with MeOH/dichloromethane (1:99) to give tert-butyl 4-(2*H*-

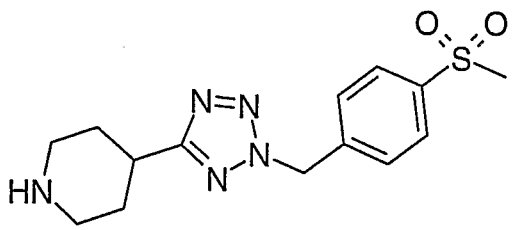
tetrazol-5-yl)piperidine-1-carboxylate (1.31g); NMR ($CDCl_3$): 1.5 (s, 9H), 1.9 (m, 2H), 2.15 (m, 2H), 3.0 (m, 2H), 3.3 (m, 1H), 4.2 (m, 2H).

Step 4: To a solution of *tert*-butyl 4-(2*H*-tetrazol-5-yl)piperidine-1-carboxylate (873mg) in dimethylformamide (5mL), cooled to 5°C, was added sodium hydride (165mg 60% dispersion in oil). The resulting mixture was stirred for 30 minutes before the addition of a solution of 4-chlorobenzyl bromide (780mg) in dimethylformamide (1mL). The mixture was allowed to warm to room temperature and stirred for a further 3 hours. The mixture was poured onto water and extracted with ethyl acetate. The extract was then dried ($MgSO_4$) and evaporated to a gum. Purification by column chromatography eluting with a slow gradient of ethyl acetate / isohexane (10:90 to 70:30) gave firstly *tert*-butyl 4-[2-(4-chlorobenzyl)-2*H*-tetrazole-5-ylpiperidine-1-carboxylate (539mg;) NMR ($CDCl_3$): 1.5 (s, 9H), 1.8 (m, 2H), 2.05 (m, 2H), 2.95 (m, 1H), 3.1 (m, 2H), 4.1 (m, 2H), 5.7 (s, 2H), 7.35 (d, 2H), 7.4 (d, 2H); followed by *tert*-butyl 4-[1-(4-chlorobenzyl)-2*H*-tetrazole-5-ylpiperidine-1-carboxylate (488mg); NMR ($CDCl_3$) 1.5 (s, 9H), 1.7 (m, 2H), 1.9 (m, 2H), 2.9 (m, 3H), 4.15 (m, 2H), 5.55 (s, 2H), 7.15 (d, 2H), 7.4 (d, 2H).

Step 5: To a solution of *tert*-butyl 4-[2-(4-chlorobenzyl)-2*H*-tetrazole-5-ylpiperidine-1-carboxylate (532mg) in dichloromethane (4mL) was added trifluoroacetic acid (4mL) and the resulting mixture was stirred for 3 hours. The mixture was concentrated and azeotroped with 7N NH_3 in methanol. The resulting gum was purified by column chromatography eluting with 7N NH_3 in methanol / dichloromethane (1:99 to 5:95 v/v) to give 4-[2-(4-chlorobenzyl)-2*H*-tetrazol-5-yl]piperidine (328mg); NMR ($CDCl_3$): 1.8 (m, 2H), 2.1 (m, 2H), 2.8 (m, 2H), 3.1 (m, 1H), 3.2 (m, 2H), 5.7 (s, 2H), 7.3-7.4 (dd, 4H).

Method H

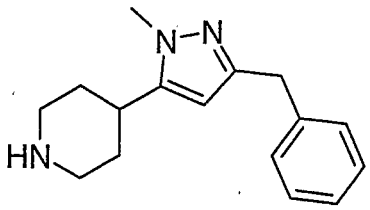
4-[2-(4-Methanesulfonyl-benzyl)-2*H*-tetrazol-5-yl]-piperidine



This was prepared from 4-methanesulphonylbenzyl bromide and *tert*-butyl 4-(2*H*-tetrazol-5-yl)piperidine-1-carboxylate using a similar method to that used to prepare 4-[2-(4-chloro-benzyl)-2*H*-tetrazol-5-yl]-piperidine (Method G, Steps 4 and 5); NMR ($CDCl_3$): 1.8 (m, 2H), 2.05 (m, 2H), 2.8 (m, 2H), 3.05 (s, 3H), 3.1 9m, 1H), 3.2 (m, 2H), 5.8 9s, 2H), 7.55 (d, 2H), 7.95 9d, 2H).

Method I

4-(5-Benzyl-2-methyl-2*H*-pyrazol-3-yl)-piperidine



Step 1: To a stirred solution of methyl magnesium bromide (3.0M in THF, 76mL) was added, *via* cannula over 10 minutes, a solution of 4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester (12.00g; prepared as described in *Chem. Pharm. Bull.*, 2001, **49**, 822) in anhydrous THF (120mL). The green cloudy solution was then left to stir overnight at room temperature. The reaction was quenched by cannula transfer into a rapidly stirred solution of saturated aqueous ammonium chloride (500mL), which was then stirred for 15 minutes before neutralisation to pH 7 by the addition of 1M aqueous HCl. The reaction mixture was then extracted into Et_2O (700mLl) and washed with 10% aqueous citric acid followed by brine. The organic extracts were then dried over magnesium sulfate and filtered under suction before evaporation of solvents under reduced pressure to give the crude product as a mobile yellow oil (7.00g). This was purified by column chromatography on silica gel, eluting with an increasingly polar gradient of Et_2O in DCM as eluent. Evaporation of solvents under reduced pressure gave the desired product as a clear colourless oil (4.00g); NMR ($CDCl_3$): 1.45 (s, 9H), 1.52 (m, 2H), 1.83 (br d, 2H), 2.16 (s, 3H), 2.45 (tt, 1H), 2.79 (br t, 2H), 4.10 (br d, 2H).

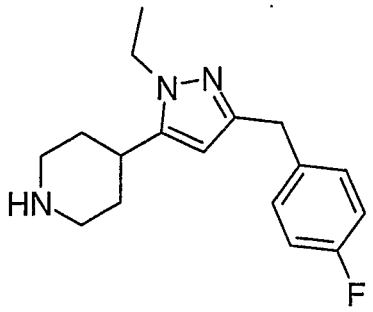
Step 2: 4-Acetyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.00g) was dissolved in anhydrous THF (6mL) and cooled to 0°C. To this was added a solution of lithium hexamethyldisilazane (1.0M in hexanes; 4.84mL). This was left to stir at 0°C for 10 minutes before addition of a THF solution (2mL) of methyl phenylacetate (0.661g). The reaction mixture was left to stir for a total of 4 hours before being quenched by the addition of 1M

aqueous HCl (50mL). The reaction mixture was extracted with Et_2O (3 x 75mL) then the combined organic extracts were dried over magnesium sulfate and filtered. Evaporation of solvents under reduced pressure gave a thick yellow oil which was purified by column chromatography on silica gel, using an increasingly polar gradient of Et_2O in DCM as eluent. Evaporation of solvents under reduced pressure gave the desired 4-(3-oxo-4-phenyl-butyryl)-piperidine-1-carboxylic acid *tert*-butyl ester as a clear oil (0.225g); NMR ($CDCl_3$): 1.45 (s, 9H), 1.54 (m, 2H), 1.76 (d, 2H), 2.28 (tt, 1H), 2.71 (br t, 2H), 3.61 (s, 2H), 4.12 (br d, 2H), 5.44 (s, 1H), 7.12-7.36 (m, 5H), 15.30 (s, 1H); MS: 344 ($M-1^-$).

Step 3: 4-(3-Oxo-4-phenyl-butyryl)-piperidine-1-carboxylic acid *tert*-butyl ester (0.118g) was dissolved in MeOH (4mL) and added to a refluxing solution of methyl hydrazine (0.019g) in methanol (2mL). After 45 minutes at reflux the reaction mixture was cooled to room temperature and solvents evaporated under reduced pressure to give the crude product as a clear oil which was purified by column chromatography on silica using Et_2O as eluent to give 4-(5-benzyl-2-methyl-2*H*-pyrazol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (0.032g) as a clear oil; NMR ($CDCl_3$): 1.46 (s, 9H), 1.46-1.54 (m, 2H), 1.82 (br d, 2H), 2.64 (tt, 1H), 2.78 (br t, 2H), 3.77 (s, 3H), 3.90 (s, 2H), 4.18 (br d, 2H), 5.72 (s, 1H), 7.16-7.29 (m, 5H); MS: 356 (MH+).

Step 4: 4-(5-Benzyl-2-methyl-2*H*-pyrazol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (0.032g) was dissolved in a 25%v/v solution of trifluoroacetic acid in DCM (7mL) and stirred for 30 minutes. The solvents were then evaporated under reduced pressure to give a clear oil which was purified by column chromatography on SCX-2 stationary phase using a gradient of DCM up to 50% 7N NH_3 in MeOH in DCM as eluent. Evaporation of solvent under reduced pressure gave the title compound as a clear oil (0.018g); NMR($CDCl_3$): 1.50-1.60 (qd, 2H), 1.85 (br d, 2H), 2.64 (tt, 1H), 2.66-2.76 (qd, 2H), 3.17 (br d, 2H), 3.76 (s, 3H), 3.91 (s, 2H), 5.76 (s, 1H), 7.16-7.20 (m, 1H), 7.24-7.30 (m 4H); MS: 256 (MH+).

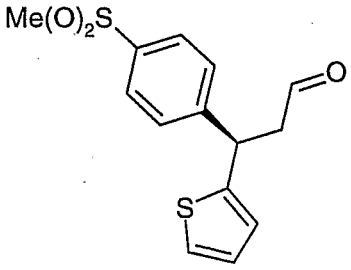
Preparation of 4-[2-ethyl-5-(4-fluoro-benzyl)-2*H*-pyrazol-3-yl]-piperidine



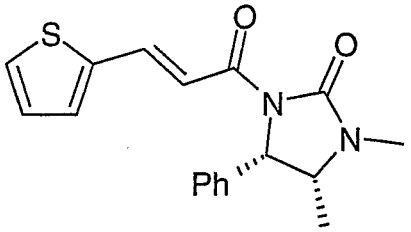
This material was prepared in a fashion similar to that described in **Method I** *except* that the methyl phenylacetate used in Step 2 was substituted with methyl (4-fluorophenyl)acetate, to give 4-[4-(4-fluoro-phenyl)-3-oxo-butyryl]-piperidine-1-carboxylic acid *tert*-butyl ester [NMR ($CDCl_3$): 1.45 (s, 9H), 1.50-1.60 (m, 2H), 1.74-1.80 (br d, 2H), 2.24-2.34 (tt, 1H), 2.68-2.77 (br t, 2H), 3.58 (s, 2H), 4.07-4.18 (br m, 2H), 5.44 (s, 1H), 6.99-7.05 (m, 2H), 7.16-7.22 (m, 2H), 15.30 (s, 1H); MS: 362 ($M-1^-$)], and the methyl hydrazine used in Step 3 was substituted with ethyl hydrazine oxalate and diisopropylethylamine (in equimolar ratio) to give 4-[2-ethyl-5-(4-fluoro-benzyl)-2*H*-pyrazol-3-yl]-piperidine-1-carboxylic acid *tert*-butyl ester [NMR ($CDCl_3$): 1.41-1.45 (t, 3H), 1.46 (s, 9H), 1.49-1.54 (m, 2H), 1.79-1.83 (br d, 2H), 2.60-2.69 (tt, 1H), 2.74-2.82 (br t, 2H), 3.89 (s, 2H), 4.03-4.08 (q, 2H), 4.15-4.25 (br d, 2H), 5.68 (s, 1H), 6.93-6.98 (m, 2H), 7.17-7.21 (m, 2H); MS: 388 (MH^+)], and subsequent removal of the protecting group gave the title compound as a clear gum (0.042g); MS: 288 (MH^+).

Method J

(*R*)-3-(4-Methanesulfonyl-phenyl)-3-thiophen-2-yl-propionaldehyde

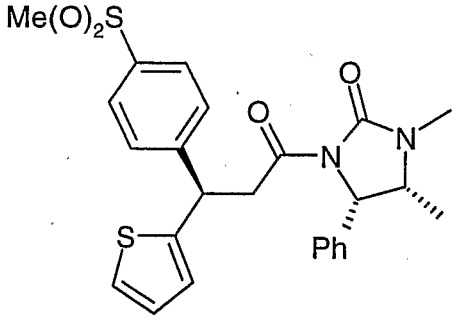


Step 1: Preparation of (4*S*,5*R*)-1,5-dimethyl-4-phenyl-3-(3-thiophen-2-yl-acryloyl)-imidazolidin-2-one



(2-Thiophene)cinnamic acid (1.22g, 7.88 mmol) was suspended in dichloromethane (10mL) and oxalyl chloride (0.86mL, 9.86mmol) was added dropwise. After stirring for 2h, the acid chloride was concentrated in vacuo and azeotroped with toluene to dryness. (4*S*,5*R*)-1,5-Dimethyl-4-phenyl-imidazolidin-2-one (1.25g, 6.57mmol) and DIPEA (2.52mL, 14.5mmol) were premixed in dichloromethane (3 mL) and were added to the acid chloride as one portion. This was then stirred overnight. Aqueous workup (washing with water, then brine and concentrating) followed by column chromatography (hexane to dichloromethane) gave the sub-titled compound (1.13g, 44%) as a yellow oil; NMR ($CDCl_3$): 0.85 (d, 3H), 2.90 (s, 3H), 3.95 (m, 1H), 5.42 (d, 1H), 7.03 (m, 1H), 7.28 (m, 7H), 7.90 (d, 1H), 8.00 (d, 1H); LCMS: 327 (MH+).

Step 2: Preparation of (4*R*, 5*S*)-1-[(*R*)-3-(4-methanesulfonyl-phenyl)-3-thiophen-2-yl-propionyl]-3,4-dimethyl-5-phenyl-imidazolidin-2-one



Copper (I) iodide (1.31g, 6.89mmol) was suspended in tetrahydrofuran (10mL) under argon and TMEDA (1.14mL, 7.58mmol) was added as a single portion. After stirring for 10min the solution was cooled to -78°C and 4-thioanisyl phenylmagnesium bromide (14mL, 6.89mmol) was added dropwise. The resulting solution was then stirred for a further 30min at -78°C. To this mixture was then added slowly a mixture of (4*S*,5*R*)-1,5-dimethyl-4-phenyl-3-(3-thiophen-2-yl-acryloyl)-imidazolidin-2-one (1.13g) and dibutylboron triflate (4.2mL, 4.14mmol) in tetrahydrofuran (10mL) at -78°C and then the resulting mixture was stirred and allowed to warm to room temperature overnight. The reaction was then quenched with saturated aqueous ammonium chloride and washed with concentrated tetrasodium EDTA

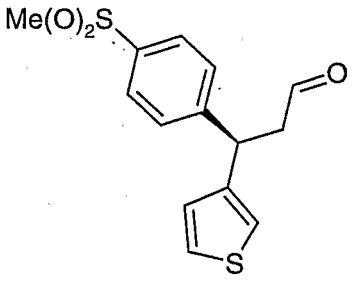
solution. The organics were then separated, concentrated and redissolved in ethyl acetate (100mL). meta-Chloroperbenzoic acid (1.7g, 6.9mmol) was added as a single portion and the solution stirred for 2h. This was then quenched with 2M aqueous sodium hydroxide solution and the resulting precipitate collected by filtration. This gave the sub-titled compound (1.06g, 64%) as a white solid; NMR ($CDCl_3$): 0.80 (d, 3H), 2.83 (s, 3H), 3.00 (s, 3H), 3.72 (dd, 1H), 3.85 (m, 1H), 4.05 (dd, 1H), 4.95 (t, 1H), 5.22 (d, 1H), 6.90 (m, 3H), 7.21 (m, 5H), 7.44 (d, 2H), 7.79 (d, 2H); LCMS: 483 (MH+).

Step 3: Preparation of title compound

(4*R*, 5*S*)-1-[(*R*)-3-(4-Methanesulfonyl-phenyl)-3-thiophen-2-yl-propionyl]-3,4-dimethyl-5-phenyl-imidazolidin-2-one (1.05 g, 2.18 mmol) was dissolved in dichloromethane (40mL) under argon and the solution was cooled to -78°C. DIBAL solution (7mL, 6.53mmol) was then added dropwise and the solution stirred at -78°C for a further 2h. Crushed Glauber's salt (7g) was then added and the reaction stirred vigorously at room temperature for 1h. This was then filtered and stirred with basic alumina (7g) for 4h. Filtration and concentration gave the title compound (0.25g, 38%) as a colourless oil; NMR ($CDCl_3$): 3.05 (s, 3H), 3.24 (m, 2H), 4.96 (t, 1H), 6.85 (m, 1H), 6.93 (m, 1H), 7.20 (m, 1H), 7.48 (d, 2H), 7.90 (d, 2H), 9.76 (s, 1H).

Method K

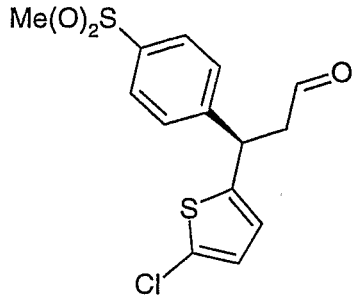
(*R*)-3-(4-Methanesulfonyl-phenyl)-3-thiophen-3-yl-propionaldehyde



This was prepared from (3-thiophene)cinnamic acid using a similar sequence of reactions used to prepare (*R*)-3-(4-Methanesulfonyl-phenyl)-3-thiophen-2-yl-propionaldehyde (Method J); NMR ($CDCl_3$): 3.03 (s, 3H), 3.20 (m, 2H), 4.79 (t, 1H), 6.85 (m, 1H), 7.00 (m, 1H), 7.25 (m, 1H), 7.40 (d, 2H), 7.85 (d, 2H), 9.75 (s, 1H).

Method L

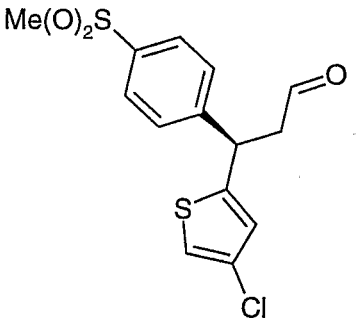
(*R*)-3-(4-Methanesulfonyl-phenyl)-3-(5-chlorothiophen-2-yl)-propionaldehyde



This was prepared from (2-[5-chlorothiophene])cinnamic acid using a similar sequence of reactions used to prepare (*R*)-3-(4-Methanesulfonyl-phenyl)-3-thiophen-2-yl-propionaldehyde (Method J); NMR ($CDCl_3$): 3.05 (s, 3H), 3.20 (m, 2H), 4.82 (t, 1H), 6.62 (m, 1H), 6.72 (m, 1H), 7.45 (d, 2H), 7.89 (d, 2H), 9.73 (s, 1H).

Method M

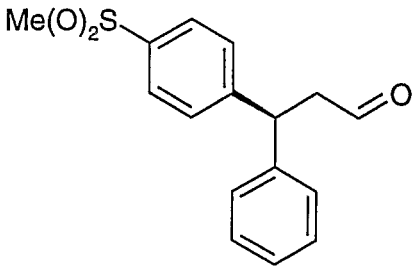
(*R*)-3-(4-Methanesulfonyl-phenyl)-3-(4-chlorothiophen-2-yl)-propionaldehyde



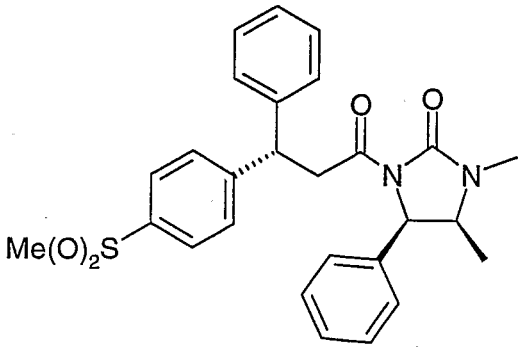
This was prepared from (2-[4-chlorothiophene])cinnamic acid using a similar sequence of reactions used to prepare (*R*)-3-(4-Methanesulfonyl-phenyl)-3-thiophen-2-yl-propionaldehyde (Method J); NMR ($CDCl_3$): 3.04 (s, 3H), 3.23 (m, 2H), 4.86 (t, 1H), 6.70 (m, 1H), 6.95 (m, 1H), 7.45 (d, 2H), 7.87 (d, 2H), 9.75 (s, 1H).

Method N

(*S*)-3-Phenyl-3-(4-methanesulfonylphenyl)propionaldehyde



Step 1: Preparation of (4*S*, 5*R*)-1-[(*S*)-3-(4-methanesulfonyl-phenyl)-3-phenyl-propionyl]-3,4-dimethyl-5-phenyl-imidazolidin-2-one



To a mixture of copper (I) iodide (960mg, 5.0mmol) and THF (20mL) was added *N,N,N',N'*-tetramethylethylenediamine (0.83mL, 5.5mmol) and the resulting mixture was stirred at room temperature for 10min. then cooled to –78°C. Phenylmagnesium bromide (5.0mL, 1M in THF, 5.0mmol) was added and the resulting mixture stirred at –78°C for 15min. A solution of di-n-butylboron triflate (3.0mL, 1M in diethyl ether, 3.0mmol) and (*E*)-(4*S*, 5*R*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (Method D, 1.0g, 2.51mmol) in THF (15mL) was added and the resulting mixture was stirred whilst allowing to warm to room temperature for 18h. The reaction mixture was washed with saturated aqueous ammonium chloride, water and brine, dried ($MgSO_4$) and evaporated. The residue was purified by eluting through a 20g Bond Elut with gradient of isohexane to ethyl acetate giving the sub-titled compound (1.49g, 100%); NMR ($CDCl_3$): 0.78 (d, 3H), 2.82 (s, 3H), 3.00 (s, 3H), 3.78 (dd, 1H), 3.80 (m, 1H), 3.98 (dd, 1H), 4.72 (m, 1H), 5.19 (d, 1H), 6.99 (m, 2H), 7.22 (m, 8H), 7.48 (d, 2H), 7.79 (d, 2H); MS: 477 (MH+).

Step 2: Preparation of (*S*)-3-phenyl-3-(4-methanesulfonylphenyl)propan-1-ol

To a solution of (4*S*,5*R*)-1-[(*S*)-3-(4-methanesulfonyl-phenyl)-3-phenyl-propionyl]-3,4-dimethyl-5-phenyl-imidazolidin-2-one (846mg, 1.78mmol) in THF (20mL) at 0°C was added lithium aluminium hydride (3.6mL, 1M in THF, 3.6mmol) and the resulting mixture was stirred for 15min. The reaction was quenched by the addition of 2M aqueous sodium hydroxide. The phases were separated and the organic phase pre-absorbed onto a Bond Elut and eluted with a gradient of isohexane to ethyl acetate giving the sub-titled compound as a white solid (285mg, 55%); NMR ($CDCl_3$): 1.63 (br s, 1H), 2.33 (m, 2H), 3.00 (s, 3H), 3.59 (t, 2H), 4.28 (t, 1H), 7.23 (m, 5H), 7.43 (d, 2H), 7.82 (d, 2H).

Step 3: Preparation of the title compound

To a solution of (*S*)-3-phenyl-3-(4-methanesulfonylphenyl)propan-1-ol (244mg, 0.84mmol) in DCM (5mL) was added Dess-Martin periodinane (392mg, 0.92mmol) and the resulting mixture was stirred at room temperature for 1.5h. The mixture was washed with 2M aqueous sodium hydroxide (2 x 10mL), dried and evaporated to give the title compound.

Method O

(*R*)-3-(3-Fluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye

This was prepared from (4*S*, 5*R*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one and 3-fluorophenylmagnesium bromide using a method similar to that used to prepare (*S*)-3-phenyl-3-(4-methanesulfonyl-phenyl)propionaldehyde from phenylmagnesium bromide (Method N); NMR ($CDCl_3$): 3.01 (s, 3H), 3.24 (d, 2H), 4.73 (t, 1H), 6.91 (m, 2H), 6.99 (m, 1H), 7.28 (m, 2H), 7.42 (d, 2H), 7.87 (d, 2H), 9.76 (s, 1H).

Method P

(*R*)-3-(3,5-Difluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye

This was prepared from (4*S*, 5*R*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one and 3,5-difluorophenylmagnesium bromide using a method similar to that used to prepare (*S*)-3-phenyl-3-(4-methanesulfonyl-phenyl)propionaldehyde from phenylmagnesium bromide (Method N).

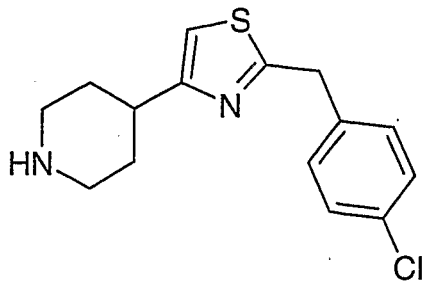
Method Q

(*R*)-3-(3-Chloro-5-fluorophenyl)-3-(4-methanesulfonylphenyl)propionaldehdye

This was prepared from (4*S*, 5*R*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one and 3-chluoro-5-fluorophenylmagnesium bromide using a method similar to that used to prepare (*S*)-3-phenyl-3-(4-methanesulfonyl-phenyl)propionaldehyde from phenylmagnesium bromide (Method N).

Method R

4-[2-(4-Chlorobenzyl)-1,3-thiazol-4-yl]piperidine



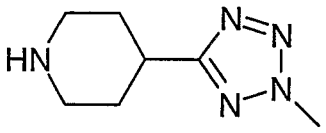
Step 1: To a solution of 1-[(allyloxy)carbonyl]piperidine-4-carboxylic acid (7g) in dichloromethane (60ml) and DMF (4 drops), cooled to 5°C, was added oxalyl chloride (6ml). The reaction mixture was stirred for 2 hours at room temperature, evaporated and azeotroped with anhydrous THF. The resulting residue was dissolved in anhydrous THF (100ml), cooled to 5°C, and trimethylsilyldiazomethane (45.5ml of 2M solution in THF) was added dropwise. The resulting mixture was stirred at room temperature for 1 hour. Diethyl ether (100ml) was added and the organics were washed with saturated sodium bicarbonate (50ml). The organics was separated, dried and evaporated. The residue was dissolved in diethyl ether (60ml), cooled to 5°C and HBr in acetic acid (6.55ml, 33%solution) was added. The resulting mixture was stirred for 1 hour. The reaction was basified with saturated sodium bicarbonate and extracted with diethyl ether (x2). The organics were dried and evaporated to dryness. The residue was purified by chromatography on silica eluting with a gradient of isohexane to ethyl acetate hexane / isohexane (2:5) to give allyl 4-(bromoacetyl)piperidine-1-carboxylate as an oil. Yield 4.92g. NMR ($CDCl_3$): 1.7 (m, 2H), 1.9 (m, 2H), 2.5 (m, 1H), 2.95 (m, 2H), 3.7 (s, 3H), 4.1 (m, 2H), 4.6 (m, 2H), 5.3 (m, 2H), 5.95 (m, 1H).

Step 2: A mixture of allyl 4-(bromoacetyl)piperidine-1-carboxylate (547mg) and 2-(4-chlorophenyl)ethanethioamide (366mg) in ethanol (15ml) was refluxed for 5 hours. The reaction mixture was evaporated to dryness and the residue was purified by chromatography on silica eluting with methanol / dichloromethane (2:98) to give allyl 4-[2-(4-chlorobenzyl)-1,3-thiazol-4-yl]piperidine-1-carboxylate. Yield 698mg. NMR ($CDCl_3$): 1.65 (m, 2H), 2.25 (m, 2H), 2.95 (m, 2H), 3.2 (m, 1H), 4.3 (m, 2H), 4.55 (m, 4H), 5.3 (m, 2H), 6.0 (m, 1H), 6.95 (s, 1H), 7.35 (m, 4H).

Step 3: To a solution of allyl 4-[2-(4-chlorobenzyl)-1,3-thiazol-4-yl]piperidine-1-carboxylate (692mg) in anhydrous THF (20ml) was added dimedone (2.06g) followed by $Pd(PPh_3)_4$ (201mg) and the resulting mixture was stirred at room temperature for 4 hours. A further portion of dimedone (1.03g) and $Pd(PPh_3)_4$ (100mg) was added and the mixture was stirred for a further 18 hours. The reaction mixture was partitioned between 1N sodium hydroxide (50ml) and ethyl acetate (100ml). The organics were separated, dried and evaporated to dryness. The residue was purified by column chromatography on SCX-2 stationary phase using a gradient of DCM up to 50% 7N NH_3 in MeOH in dichloromethane as eluent to give 4-[2-(4-chlorobenzyl)-1,3-thiazol-4-yl]piperidine as a solid. Yield 162mg). NMR ($CDCl_3$): 1.8 (m, 2H), 2.2 (m, 2H), 2.4 (bs, 1H), 2.8-3.0 (m, 3H), 3.3 (m, 2H), 4.4 (s, 2H), 7.4 (m, 5H).

Method S

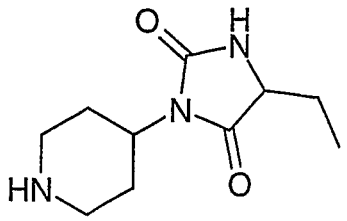
4-(2-Methyl-2*H*-tetrazol-5-yl)-piperidine



To a solution of *tert*-butyl 4-(2*H*-tetrazol-5-yl)piperidine-1-carboxylate (CAS 91419-58-8) (0.98g, 3.89mmol) and triphenylphosphine (3.06g) in THF under a blanket of Ar was added the diisopropyl azodicarboxylate (2.30ml) and the mixture stirred for 10 minutes. Methanol (473µl) was added and the reaction was stirred for 18 hours and then the solution was concentrated *in vacuo*. The residue was purified on silica using a 90g Biotage cartridge and a gradient elution of 25 to 35% ethyl acetate in hexanes. This semi-pure mixture was partially dissolved in a 4M HCl in dioxane solution and stirred for 1 hour, then concentrated *in vacuo*. The residue was partially dissolved in DCM (40ml) and triethylamine (162µl) and MP-Carbonate (4.17g, loading 2.8mmol/g) added and slurry stirred for 64 hours. The resin was filtered off and washed with a 10% solution of methanol in DCM and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on SCX-2 stationary phase using methanol and then a 1M ammonia in methanol solution. Evaporation of the solvent under reduced pressure gave the title compound as a yellow solid (0.502g); NMR ($CDCl_3$): 1.78 (2H, m), 2.06 (2H, d), 2.77 (2H, m), 3.08 (1H, m), 3.19 (2H, d), 3.08 (3H, s).

Method T

5-Ethyl-3-piperidin-4-ylimidazolidine-2,4-dione



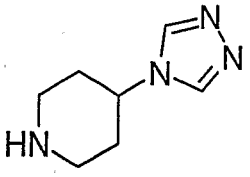
Step 1: To a solution of 5-ethylimidazoline-2,4-dione (1g) in DMF (40ml) was added potassium carbonate (2.16g) followed by *tert*-butyl 4-[(methylsulfonyl)oxy]piperidine-1-carboxylate (2.18g) and the resulting mixture was heated to 100°C for 18 hours. The reaction mixture was concentrated under reduced pressure and then was partitioned between dichloromethane and water. The organic layer was collected, dried and evaporated to dryness. The residue was purified by chromatography on silica eluting with a gradient of isohexane to ethyl acetate / isohexane (1:1) to give *tert*-butyl 4-(4-ethyl-2,5-dioxoimidazolidin-1-yl)piperidine-1-carboxylate as a solid. Yield 1.12g. NMR ($CDCl_3$): 0.95 (t, 3H), 1.5 (s, 9H), 1.9 (m, 2H), 2.35 9m, 2H), 2.7 (m, 2H), 3.8-4.0 (m, 3H), 4.1 (q, 2H), 5.6 (bs, 1H).
Step 2 : To a suspension of *tert*-butyl 4-(4-ethyl-2,5-dioxoimidazolidin-1-yl)piperidine-1-carboxylate (1.12g) in dioxane (10ml) was added a solution of 4M HCl in dioxane (10ml) and the resulting mixture was stirred for 1 hour. Diethyl ether (20ml) was added and the mixture was filtered and washed with diethyl ether to give 5-ethyl-3-piperidin-4-ylimidazolidine-2,4-dione. Yield 687mg. MS 212 MH^+

In a similar manner but using 5-phenylimidazoline-2,4-dione was prepared 5-phenyl-3-piperidin-4-ylimidazolidine-2,4-dione. MS 260 MH^+

In a similar manner but using using 5-methylimidazoline-2,4-dione was prepared 5-methyl-3-piperidin-4-ylimidazolidine-2,4-dione. MS 198 MH^+

Method U

4-(4*H*-1,2,4-Triazol-4-yl)piperidine

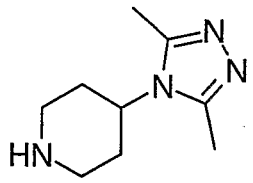


Step 1: To a solution of 1,2 –bis[(dimethylamino)methylene]hydrazine (660mg) in toluene (10ml) was added 1-benzylpiperidin-4-amine (0.8ml) and p-toluenesulfonic acid (75mg) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was refluxed for 8 hours and then evaporated to dryness. The residue was purified by chromatography on silica eluting with a gradient of methanol / ethyl acetate to give 1-benzyl-4-(4*H*-1,2,4-triazol-4-yl)piperidine. Yield 220mgs. NMR (d6 DMSO): 2.0 (m, 4H), 2.1 (m, 2H), 2.9 (m, 2H), 3.5 (s, 2H), 4.2 9m, 1H), 7.35 9m, 5H), 8.65 9s, 2H).

Step 2: To a solution of 1-benzyl-4-(4*H*-1,2,4-triazol-4-yl)piperidine (200mg) in ethanol (10ml) was added palladium hydroxide (170mg) followed by ammonium formate 9262mg). The resulting mixture was refluxed for 1 hour. The mixture was cooled, filtered through Celite and evaporated to dryness to give 4-(4*H*-1,2,4-triazol-4-yl)piperidine as a white solid. Yield 100mg. NMR (d6 DMSO) 1.75 (m, 2H), 1.95 (m, 2H), 2.6 (m, 2H), 3.05 (m, 2H), 3.3 (bs, 1H), 4.2 (m, 1H), 8.6 (s, 2H).

Method V

4-(3,5-Dimethyl-4*H*-1,2,4-triazol-4-yl)piperidine



Step 1: To a solution of 1-benzylpiperidin-4-amine (10g) in dichloromethane (80ml), cooled to 5°C, was added pyridine (5.1ml) followed by acetyl chloride (4.5ml) and the resulting mixture was stirred for 5 hours. The reaction mixture was washed with 1N NaOH (x2) and then the organic layers were dried and evaporated to dryness to give a solid which was recrystallised from ethyl acetate to give *N*-(1-benzylpiperidin-4-yl)acetamide. Yield 8.8g. NMR (d6 DMSO): 1.4 (m, 2H), 1.7 (m, 2H), 1.8 (s, 3H), 2.0 (m, 2H), 2.75 (m, 2H), 3.45 (s, 2H), 3.55 (m, 1H), 7.3 (m, 5H), 7.75 (d, 1H).

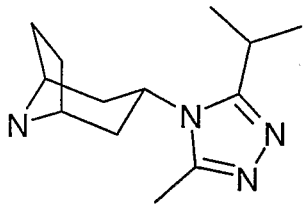
Step 2: To a solution of *N*-(1-benzylpiperidin-4-yl)acetamide (8.8g) in chloroform (30ml), cooled to 5°C was added dropwise phosphorous oxychloride (10.6ml) keeping the temperature below 5°C. The resulting mixture was stirred at 5°C for 18 hours. The reaction mixture was concentrated and azeotroped with toloune. The residue was redissolved in chloroform (30ml)

and acetic hydrazide (4.21g) was added. The resulting mixture was refluxed for 18 hours. The reaction mixture was cooled, basified with saturated sodium bicarbonate, extracted with dichloromethane (x2), dried and evaporated. The residue was dissolved in 7M HCl and refluxed for 8 hours. The reaction mixture was cooled, basified with aqueous potassium carbonate, extracted with dichloromethane (x2), dried and evaporated. The residue was purified by chromatography eluting with ethyl acetate / isohexane (20:80) to give 1-benzyl-4-(4*H*-1,2,4-triazol-4-yl)piperidine. Yield 1g. NMR (d6 DMSO): 1.8 (m, 2H), 2.1 (m, 4H), 2.4 (s, 6H), 2.95 (m, 2H), 3.55 (s, 2H), 3.95 (m, 1H), 7.35 (m, 5H).

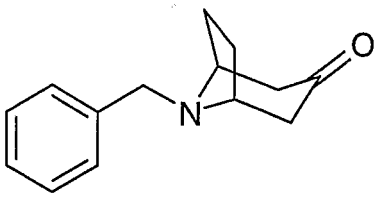
Step 3 : In a similar manner to Method U step 2 was prepared 4-(3,5-dimethyl-4*H*-1,2,4-triazol-4-yl)piperidine. NMR (d6 DMSO): 1.75 (m, 2H), 1.9 (m, 2H), 2.4 (s, 6H), 2.6 (m, 2H), 3.05 (m, 2H), 4.0 (M, 1H).

Method W

Preparation of 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-*exo*-8-azabicyclo[3.2.1]octane



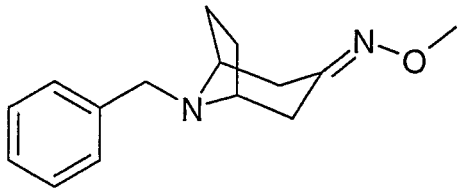
Step 1: Preparation of 8-benzylbicyclo[3.2.1.]octan-3-one



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) was added in one portion and the resulting mixture was stirred at room temperature for 1 hour and then heated to 50 °C for 5 hours. The reaction mixture was cooled, basified with 2M sodium hydroxide, extracted with dichloromethane and washed with water. The organics were extracted with 1M hydrochloric acid and washed with dichloromethane. The aqueous layer was basified with 2M sodium hydroxide and extracted with ethyl acetate (3x100ml). The organic extracts were dried and evaporated to dryness to

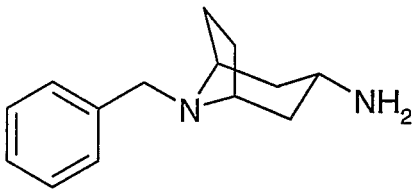
give the title compound as a brown oil which was used without further purification. Yield 13.66g. MS 216 MH^+.

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



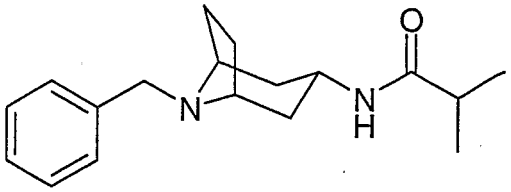
To a solution of 8-benzylbicyclo[3.2.1.]octan-3-one (13.66g) in ethanol (250ml) was added pyridine (5.69ml) followed by hydroxylamine hydrochloride (4.85g) and the resulting mixture was refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature and then partitioned between water 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. MS 231 MH^+.

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



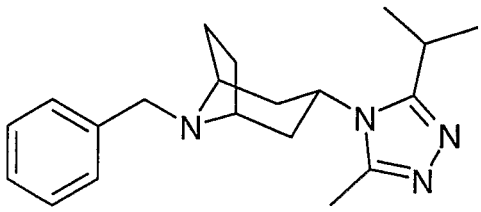
A solution of 8-benzylbicyclo[3.2.1.]octan-3-one-*O*-methyloxime (27.78g) in pentanol (500ml) was heated to 165°C. Sodium (10g) was added portionwise over 6 hours. The reaction was heated for a further 4 hours and then cooled to 5 °C. The reaction was acidified with 6M hydrochloric acid and the phases 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. MS 217 MH^+.

Step 4: Preparation of *N*-(8-benzyl-8-azabicyclo[3.2.1]oct-3-yl-*exo*)-2-methylpropanamide



To a solution of 8-benzyl-8-azobicyclo[3.2.1]octan-3-*exo*-amine (10g) in DMF (20ml) was added triethylamine (9.7ml) and isobutyric acid (6.43ml) followed by *O*-(7-azabenzotriazol-1yl)-*N,N,N'N'*-tetramethyluronium hexafluorophosphate (HATU, 26.36g) and the resulting mixture was allowed to stir for 18 hours. The reaction mixture was poured onto water and extracted with ethyl acetate (3x50 ml). The organics were extracted with 6M hydrochloric acid. The acid extracts were basified with sodium hydroxide and then extracted with ethyl acetae (3x50 ml). The organic extracts were dried and evaporated to dryness to give the title compound as a pale brown solid. Yield 5.99g. MS 287 MH^+; NMR $CDCl_3$ 1.1 (d, 6H), 1.5 (m, 2H), 1.6-2.05 (m, 6H), 2.3 (m, 1H), 3.2 (m,2H), 4.2 (m, 1H), 5.2 (m, 1H), 7.2-7.4 (m, 5H).

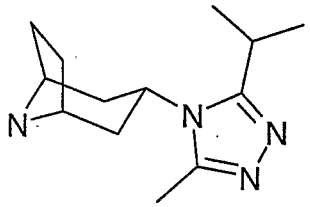
Step 5: Preparation of 8-Benzyl-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-*exo*-8-azabicyclo[3.2.1]octane



Phosphorous oxychloride (13ml) was added slowly to a solution of *N*-(8-benzyl-8-azabicyclo[3.2.1]oct-3-yl-*exo*)-2-methylpropanamide (13.27g) in pyridine (25ml) and chloroform (50ml) at 0 °C. The reaction mixture was allowed to warm to room temperature and then allowed to stir for 18 hours. The mixture was evaporated and azeotroped with toluene. The residue was dissolved in chloroform (50ml) and diisopropylethylamine (24ml) and acetic anhydride (5.15g) was added and the resulting mixture was refluxed for 18 hours. Saturated aqueous sodium carbonate (250ml) was added and the product was extracted with dichloromethane. The organic extracts were dried and evaporated. The residue was dissolved in 6M hydrochloric acid and refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature, basified with 6M sodium hydroxide, extracted with dichloromethane (3x50 ml), dried and evaporated to dryness. The residue was purified by column

chromatography on silica eluting with a gradient of dichloromethane to 5% (7M NH_3 in methanol) in dichloromethane to give the title compound as an off white solid. Yield 2.31g. MS 325 MH^+. NMR $CDCl_3$ 1.4 (d, 6H), 1.7 (m, 4H), 2.1-2.4 (m, 4H), 2.6 (s, 3H), 3.05 (m, 1H), 3.4 (bs, 2H), 3.6 (s, 2H), 4.3 (m, 1H), 7.2-7.4 (m, 5H).

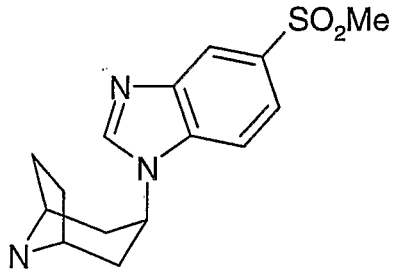
Step 6: Preparation of 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-*exo*-8-azabicyclo[3.2.1]octane



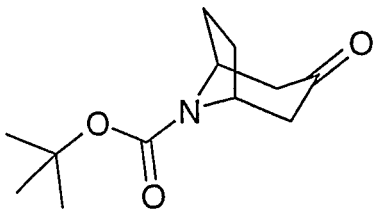
To a solution of 8-benzyl-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-*exo*-8-azabicyclo[3.2.1]octane (2.3g) in ethanol (70ml) was added 20% palladium hydroxide (230mg) and the resulting mixture was stirred under a hydrogen atmosphere for 18 hours. The reaction mixture was filtered and evaporated to give the title compound as a white solid. Yield 1.88g. NMR $CDCl_3$ 1.4(d, 6H), 1.7-1.8 (m, 4H), 1.95 (m, 2H), 2.1-2.3 (m, 4H), 2.55 (s, 3H), 3.05 (m, 1H), 4.35 (m, 1H).

Method X

Preparation of 1-*endo*-(8-azabicyclo[3.2.1]oct-3-yl)-5-(methylsufonyl)-1*H*-benzamidazole



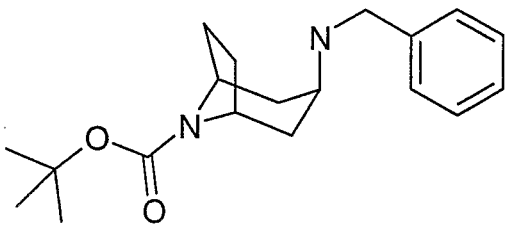
Step 1: Preparation of *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate



To a solution of 8-benzylbicyclo[3.2.1.]octan-3-one (8.48g, Method W, step 1) in ethanol (100ml) was added 30 % palladium on carbon (850mg) followed by ammonium

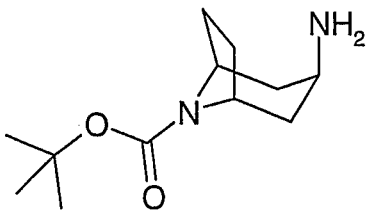
formate (8.5g) and the resulting mixture was refluxed for 4 hours. The mixture was cooled, filtered and evaporated to dryness. The residue was dissolved in THF (50ml) and water (50ml) and d-*tert*-butyl dicarbonate (8.61g) was added. The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated and then partitioned between dichloromethane and 1M citric acid. The organic extracts were washed with saturated sodium bicarbonate, brine, dried and evaporated to dryness. The residue was purified by chromatography on silica eluting with ethyl acetate / isohexane (20:80) to give the title compound as an oil which solidified on standing. Yield 4.43g. NMR $CDCl_3$: 1.5 (s, 9H), 1.7 (m, 2H), 2.1 (m, 2H), 2.35 (m, 2H), 2.7 (m, 2H), 4.5 9m, 2H).

Step 2: Preparation of *tert*-butyl 3-*endo*-(benzylamino)-8-azabicyclo[3.2.1]octane-8-carboxylate



To a solution of of *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (4.43g) in dichloromethane (90ml) and acetic acid (10ml) was added benzylamine (2.37ml) followed by sodium triacetoxyborohydride (6.3g) and the resulting mixture was stirred for 18 hours. The reaction mixture was concentrated, redissolved in ethyl acetate and washed with saturated sodium bicarbonate. The organic layers were dried and evaporated to dryness. The residue was purified by chromatography on silica eluting with a gradient of ethyl acetate / isohexane to give the title compound as a solid. Yield 2.84g. NMR $CDCl_3$: 1.5 (s, 9H), 1.6 (m, 2H), 1.9-2.2 (m, 5H), 3.0 (m, 1H), 3.75 9s, 2H), 4.1 (m, 2H), 7.3 (m, 5H).

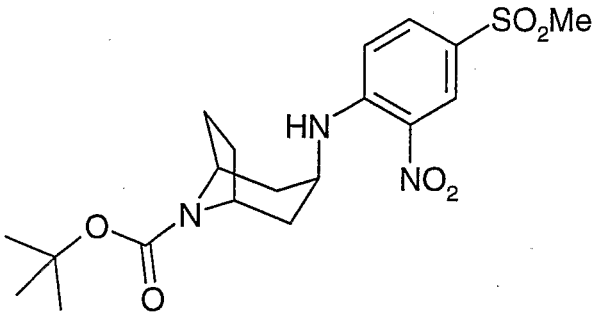
Step 3: Preparation of *tert*-butyl 3-*endo*-amino-8-azabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-*endo*-(benzylamino)-8-azabicyclo[3.2.1]octane-8-carboxylate (2.84g) in ethanol (50ml) was added 30% palladium on carbon (286mg) followed

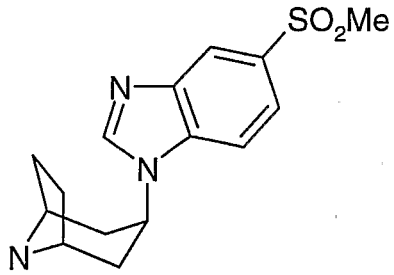
by ammonium formate (3g) and the resulting mixture was refluxed for 2.5 hours. The mixture was cooled, filtered and evaporated to dryness to give the title compound, which was used without further purification. MS 227 MH^+.

Step 4: Preparation of *tert*-butyl 3-{[4-(methylsulfonyl)-2-nitrophenyl]amino}-8-*endo*-azabicyclo[3.2.1]octane-8-carboxylate.



Prepared in a similar manner to Method A, step 1 but using of *tert*-butyl 3-*endo*-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (2.12g) to give the title compound as a foam. Yield 3.24g. NMR $CDCl_3$: 1.5 (s, 9H), 1.8 (m, 2H), 2.0-2.2 (m, 6H), 3.1 (3, 3H), 4.0 (m, 1H), 4.3 (m, 2H), 6.85 (d, 1H), 7.9 (dd, 1H), 8.8 9d, 1H), 9.1 (d, 1H).

Step 5: Preparation of 1-*endo*-(8-azabicyclo[3.2.1]oct-3-yl)-5-(methylsufonyl)-1*H*-benzamidazole

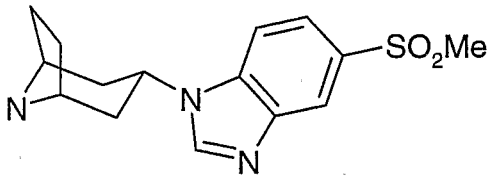


Step A: To a solution of *tert*-butyl 3-{[4-(methylsulfonyl)-2-nitrophenyl]amino}-8-*endo*-azabicyclo[3.2.1]octane-8-carboxylate (3.25g) and trimethyl orthoformate (4.2ml) in ethanol (100ml) was added acetic acid (1ml) and 10% palladium on carbon (100mgl). The mixture was placed under an atmosphere of hydrogen (5bar) and heated to 80°C for 18 hours. The mixture was cooled and filtered to a gum.

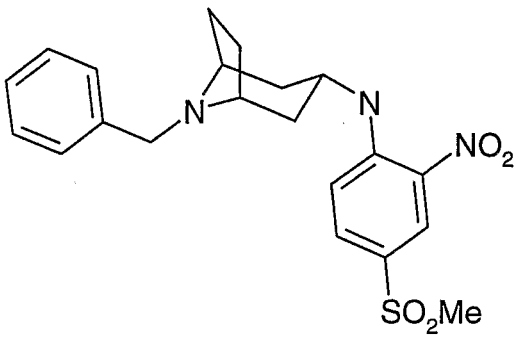
Step B: The product form step A was dissolved in dioxane (20ml) and 4M HCl (20ml) was added. The resulting mixture was stirred for 1 hour. Diethyl ether (50ml) was added and the mixture was filtered and washed with diethyl ether to give the title compound. MS 306 MH^+.

Method Y

Preparation of 1-*exo*-(8-azabicyclo[3.2.1]oct-3-yl)-5-(methylsufonyl)-1*H*-benzamidazole

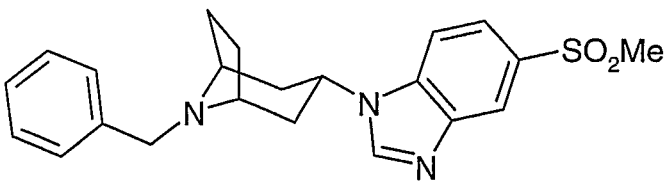


Step 1: Preparation of 8-benzyl-*N*-[4-(methylsulfonyl)-2-nitrophenyl]-8-*exo*-azabicyclo[3.2.1]octan-3-amine



In a similar manner to Method A step 1 but using 8-benzyl-8-azobicyclo[3.2.1]octan-3-*exo*-amine (Method W step 3) was prepared 8-benzyl-*N*-[4-(methylsulfonyl)-2-nitrophenyl]-8-*exo*-azabicyclo[3.2.1]octan-3-amine. NMR $CDCl_3$: 1.8 (m, 4H), 2.1 (m, 2H), 2.3 (m, 2H), 3.15 (s, 3H), 3.45 (m, 2H), 3.7 (s, 2H), 4.0 (m, 1H), 7.1 9d, 1H), 7.4 (m, 4H), 7.95 (dd, 1H), 8.4 (d, 1H), 8.85 (d, 1H).

Step 2: Preparation of 1-(8-benzyl-8-*exo*-azabicyclo[3.2.1]oct-3-yl)-5-(methylsufonyl)-1*H*-benzamidazole



In a similar manner to Method X step 4 was prepared the title compound as oil, which solidified on standing. NMR $CDCl_3$: 1.9 (m, 4H), 2.3 (m, 4H), 3.1 (s, 3H), 3.45 (m, 2H), 3.65 (s, 2H), 4.7 (m, 1H), 7.4 (m, 5H), 7.65 (m, 1H), 7.9 (m, 1H), 8.2 (s, 1H), 8.4 (s, 1H).

Step 3: Preparation of 1-*exo*-(8-azabicyclo[3.2.1]oct-3-yl)-5-(methylsufonyl)-1*H*-benzamidazole

To a solution of 1-(8-benzyl-8-*exo*-azabicyclo[3.2.1]oct-3-yl)-5-(methylsufonyl)-1*H*-benzamidazole (1.1g) in ethanol (50ml) was added 30% palladium on carbon (110mg) followed by ammonium formate (1.1g) and the resulting mixture was heated to 90°C for 5 hours. An additional portion of ammonium formate (1.1g) and 30% palladium on carbon (110mgs) was added and the mixture was heated for a firther 8 hours. The mixture was cooled, filtered and evaporated to give a gum, which was purified on a SCX column to give the title compound as a solid. Yield 750mg. NMR $CDCl_3$: 1.8-2.3 (m, 8H), 3.1 (s, 3H), 3.8 (m, 2H), 4.7 (m, 1H), 7.6 9d, 1H), 7.9 9dd, 1H), 8.2 (s, 1H), 8.4 9s, 1H). MS 306 MH^+.

EXAMPLE 3

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.

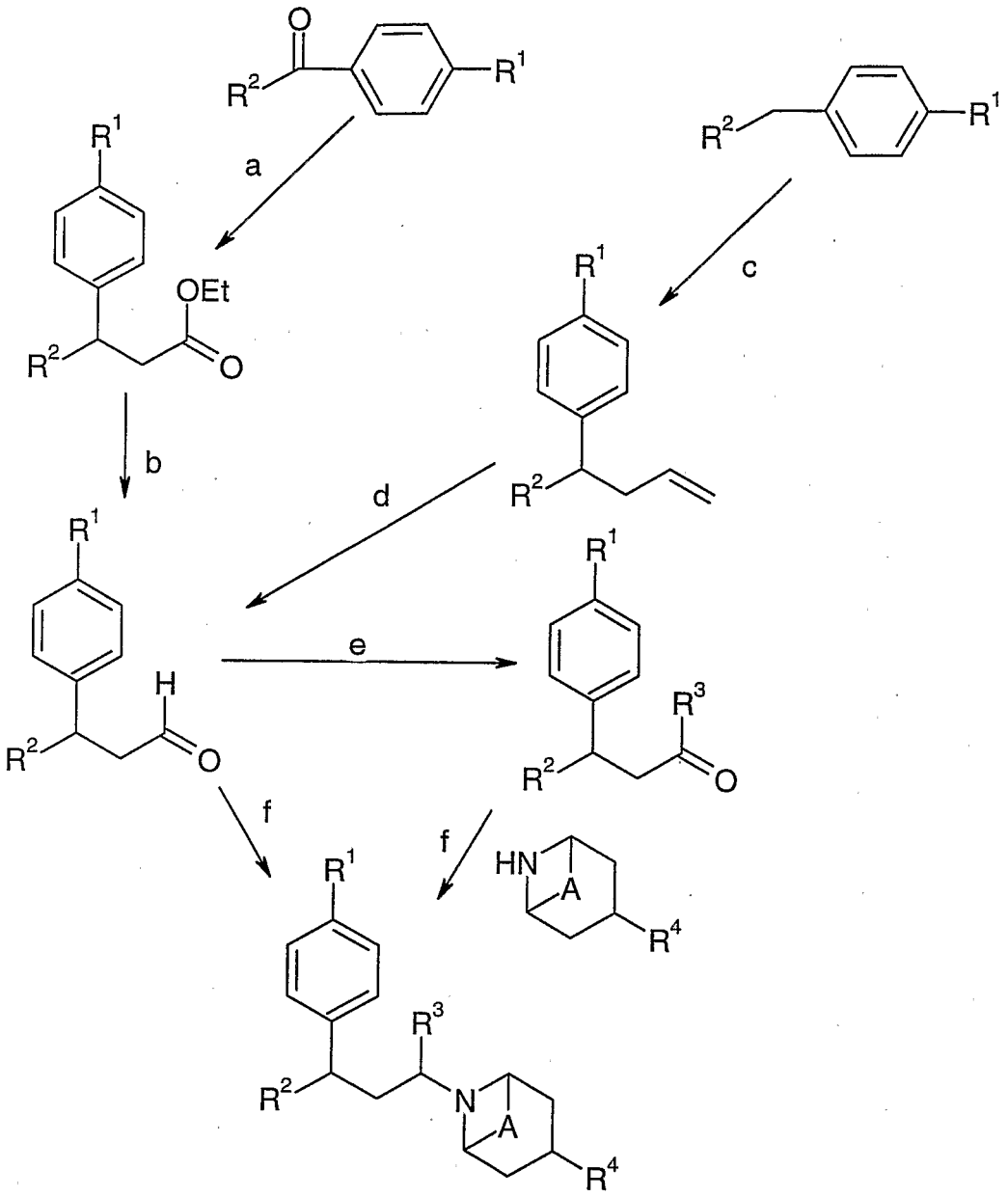
Results from this test for certain compounds of the invention from Table I are presented in Table III. In Table III the results are presented as Pic50 values. A Pic50 value is the negative log (to base 10) of the IC_{50} result, so an IC50 of 1μM (that is 1 x 10^{-6}M) gives a Pic50 of 6. If a compound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

Table III

Compound No.	Pic50
1	9.0
2	7.4
3	8.9
4	7.8
5	8.4
6	7.2
7	8.0

Compound No.	Pic50
8	8.0
9	7.7
10	7.7
11	9.0
12	7.7
13	6.8

SCHEME 1



Conditions

a) (i) $(EtO)_2P(=O)CH_2CO_2Et$, base; (ii) hydrogenation (e.g. $Pd(OH)_2$, H_2)

b) (i) Reduction (e.g. $LiAlH_4$); (ii) Oxidation (e.g. Dess-Martin periodinane)

c) Allyl bromide, base (e.g. LDA)

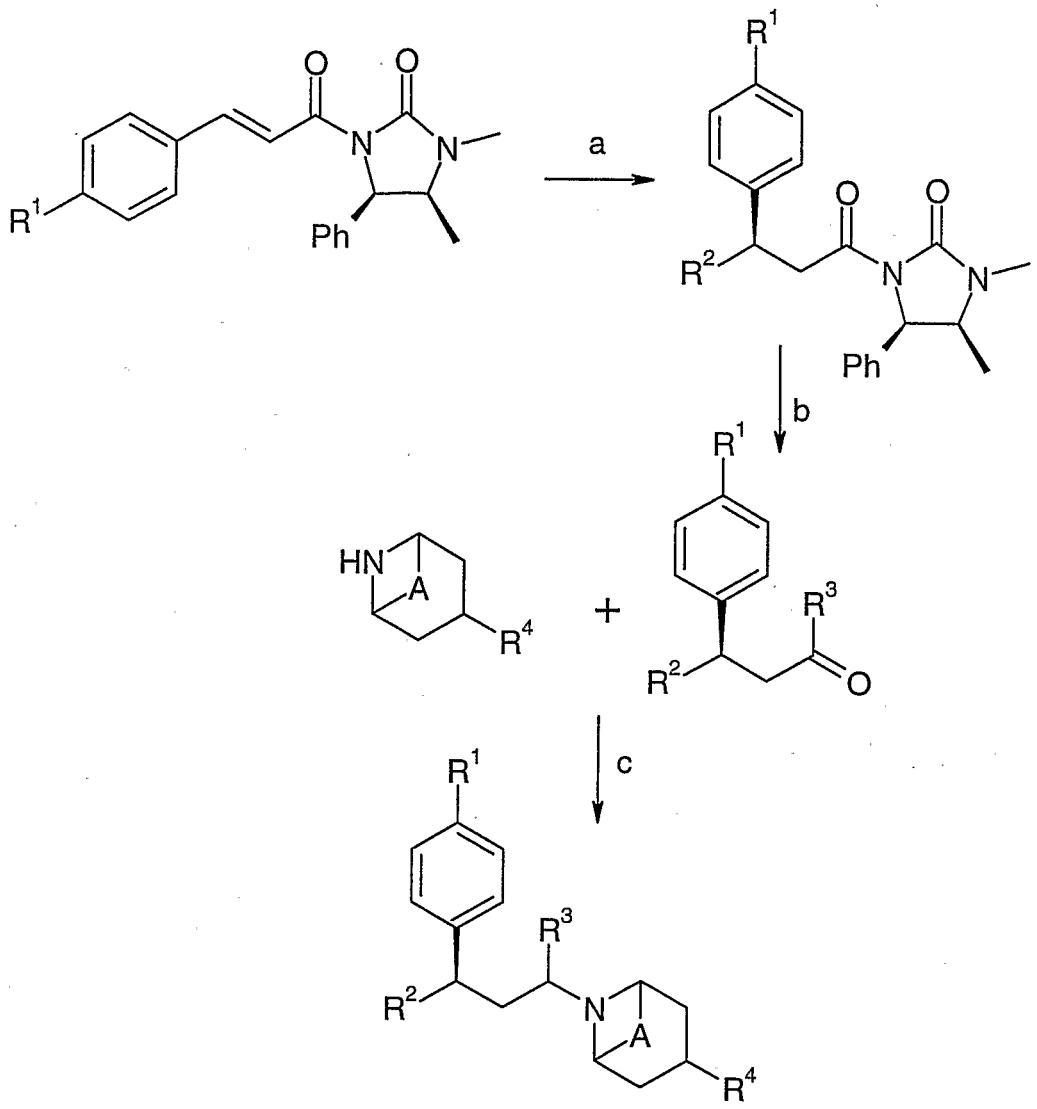
d) O_3 then Me_2S

e) (i) R^3MgBr (ii) Oxidation

f) Reductive amination ($NaBH(OAc)_3$, AcOH)

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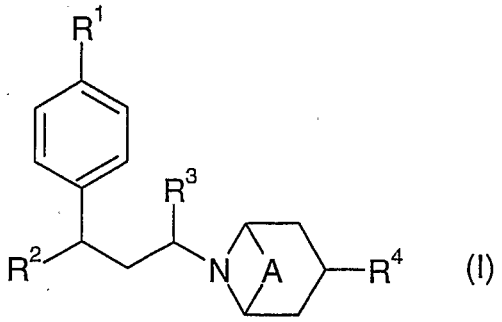
SCHEME 2



Conditions
a) R^2MgBr, CuI, TMEDA, *n*-Bu_2BOTf
b) Reduction-oxidation (for when R^3 is H), or Reduction-oxidation then R^3MgBr (for when R^3 is alkyl) then oxidation
c) Reductive amination ($NaBH(OAc)_3$, AcOH)

CLAIMS

1. A compound of formula (I):



(I)

wherein:

A is absent or is CH_2CH_2;

R^1 is halo, hydroxy, nitro, $(CH_2)_nS(O)_k(C_{1-6}$ alkyl), $(CH_2)_nS(O)_2NH_2$, $(CH_2)_nS(O)_2NH(C_{1-6}$ alkyl), $(CH_2)_nS(O)_2NHCHO$, $(CH_2)_nS(O)_2N(C_{1-6}$ alkyl)$_2$, $OS(O)_2(C_{1-6}$ alkyl), cyano, C_{1-6} alkyl, C_{1-6} alkoxy, 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)$_2$, C(O)[N-linked heterocyclyl], CO_2H, $CO_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl), $(CH_2)_nNHS(O)_2(C_{1-6}$ alkyl), $C(O)(C_{1-6}$ alkyl), CF_3, OCF_3, phenyl, heteroaryl, (C_{1-4} alkyl)phenyl, (C_{1-4} alkyl)heteroaryl, NHC(O)phenyl, NHC(O)heteroaryl, NHC(O)(C_{1-4} alkyl)phenyl, NHC(O)(C_{1-4} alkyl)heteroaryl, $NHS(O)_2$phenyl, $NHS(O)_2$heteroaryl, $NHS(O)_2(C_{1-4}$ alkyl)phenyl, $NHS(O)_2(C_{1-4}$ alkyl)heteroaryl, $NHC(O)NH(C_{1-6}$ alkyl), $NHC(O)NH(C_{3-7}$ cycloalkyl), NHC(O)NHphenyl, NHC(O)NHheteroaryl, $NHC(O)NH(C_{1-4}$ alkyl)phenyl or $NHC(O)NH(C_{1-4}$ alkyl)heteroaryl; wherein the foregoing phenyl and heteroaryl groups are optionally substituted by halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ 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^2 is phenyl, halophenyl, thienyl or halothienyl;

R^3 is hydrogen or methyl;

R^4 is a five membered heterocycle containing at least one carbon atom, one to four nitrogen atoms and, optionally, one oxygen or sulphur atom, said heterocycle being optionally substituted by oxo, C_{1-6} alkyl, $H_2NC(O)$, (phenylC_{1-2} alkyl)$HNC(O)$, C_{1-2}

alkyl(phenyl) [which is optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, OCF_3, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl) or $S(O)_2(C_{1-4}$ alkyl)], $S(C_{1-4}$ alkyl), $S(C_{1-2}$ alkyl(phenyl)), NH_2 or phenyl; the five membered heterocycle being optionally fused to a cyclohexane, piperidine, benzene, pyridine, pyridazine, pyrimidine or pyrazine ring; the ring carbon atoms of said fused cyclohexane, piperidine, benzene, pyridine, pyridazine, pyrimidine or pyrazine ring being optionally substituted by halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, OCF_3, NH_2, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl) or $S(O)_2(C_{1-4}$ alkyl); and the nitrogen of the fused piperidine ring being optionally substituted by C_{1-4} alkyl {which is optionally substituted by oxo, halogen, OH, C_{1-4} alkoxy, OCF_3, $C(O)O(C_{1-4}$ alkyl), CN, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, NH_2, $NH(C_{1-4}$ alkyl) or $N(C_{1-4}$ alkyl)$_2$}, $C(O)(C_{1-4}$ alkyl) {wherein the alkyl is optionally substituted by C_{1-4} alkoxy or fluoro}, $C(O)O(C_{1-4}$ alkyl), $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ or $S(O)_2(C_{1-4}$ alkyl) {wherein the alkyl is optionally substituted by fluoro};

k, m and n are, independently, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof or a solvate thereof.

2. A compound of formula (I) as claimed in claim 1 wherein A is absent.

3. A compound of formula (I) as claimed in claim 1 or 2 wherein R^1 is halo, cyano, $S(O)_2(C_{1-6}$ alkyl), $OS(O)_2(C_{1-6}$ alkyl), $CO_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), NHC(O)phenyl, NHC(O)heteroaryl, $NHC(O)(C_{1-4}$ alkyl)phenyl, $NHC(O)(C_{1-4}$ alkyl)heteroaryl, $NHS(O)_2$phenyl, $NHS(O)_2$heteroaryl, $NHS(O)_2(C_{1-4}$ alkyl)phenyl or $NHS(O)_2(C_{1-4}$ alkyl)heteroaryl; wherein the foregoing phenyl and heteroaryl groups are optionally substituted by halo, hydroxy, nitro, $S(O)_2(C_{1-4}$ 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.

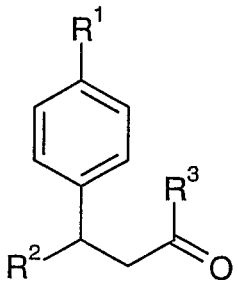
4. A compound of formula (I) as claimed in claim 1, 2 or 3 wherein R^1 is halo, cyano, $S(O)_2(C_{1-6}$ alkyl), $OS(O)_2(C_{1-6}$ alkyl), $CO_2(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl) or $NHS(O)_2(C_{1-6}$ alkyl).

5. A compound of formula (I) as claimed in claim 1, 2, 3 or 4 wherein R^2 is phenyl or halophenyl.

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

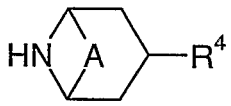
7. A compound of formula (I) as claimed in any one of the preceding claims wherein R^4 is imidazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, tetrazolyl, pyrazolyl or 1,3-thiazolyl, isoxazolyl optionally substituted as described in claim 1.

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



(II)

with a compound of formula (III):



(III)

in the presence of $NaBH(OAc)_3$ (wherein Ac is $C(O)CH_3$) and acetic acid, in a suitable solvent at room temperature;

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

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

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

12. 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.