NOVEL COMPOUNDS

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

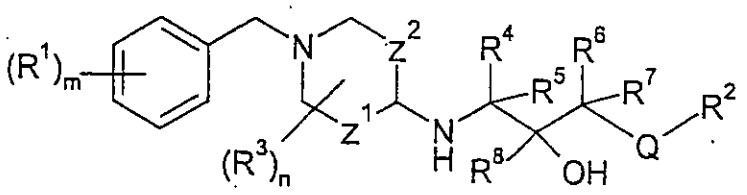
Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins 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) and Cys-Cys (C-C) 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.

In accordance with the present invention, there is therefore provided a compound of general formula



(I)

wherein

m is 0, 1, 2 or 3;

each R^1 independently represents halogen, cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-NR^9R^{10}$, C_3-C_6 cycloalkylamino, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonylamino, sulphonamido ($-SO_2NH_2$), C_1-C_6 alkylsulphonyl, $-C(O)NR^{11}R^{12}$, $-NR^{13}C(O)-(NH)_pR^{14}$, phenyl, or C_1-C_6 alkyl optionally substituted by carboxyl or C_1-C_6 alkoxycarbonyl;

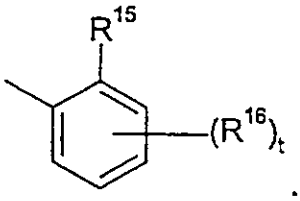
p is 0 or 1;

Z^1 represents a bond or a group $(CH_2)_q$ where q is 1 or 2;

Z^2 represents a bond or a group CH_2, with the proviso that Z^1 and Z^2 do not both simultaneously represent a bond;

Q represents an oxygen or sulphur atom or a group CH_2 or NH;

R^2 represents a group



;

n is 0, 1 or 2;

each R^3 independently represents a C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, $-CH_2OH$ or carboxyl group;

R^4, R^5, R^6 and R^7 each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^4, R^5, R^6 and R^7 together represent a C_1-C_4 alkylene chain linking the two

carbon atoms to which they are attached to form a 4- to 7-membered saturated carbocycle, or R^5, R^6 and R^7 each represent a hydrogen atom and R^4 and R^8 together with the carbon atoms to which they are attached form a 5- to 6-membered saturated carbocycle;

R^8 represents a hydrogen atom, a C_1-C_6 alkyl group or is linked to R^4 as defined above;

R^9 and R^{10} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{11} and R^{12} each independently represent a hydrogen atom or a C_1-C_6 alkyl group optionally substituted by C_1-C_6 alkoxycarbonyl;

R^{13} represents a hydrogen atom or a C_1-C_6 alkyl group;

R^{14} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by carboxyl, C_1-C_6 alkoxy or C_1-C_6 alkoxycarbonyl;

R^{15} represents carboxyl, C_1-C_6 alkoxy, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxycarbonylC_1-C_6 alkyl or a group $-NR^{17}R^{18}$, $-NHSO_2CH_3$, $-C(O)NR^{17}R^{18}$, $-NHC(O)NR^{17}R^{18}$, $-OC(O)NR^{17}R^{18}$, $-OCH_2C(O)NR^{17}R^{18}$, $-NHC(O)OR^{19}$ or $-NHC(O)R^{20}$;

t is 0, 1, 2 or 3;

each R^{16} independently represents halogen, cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-NR^{21}R^{22}$, C_3-C_6 cycloalkylamino, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonylamino, sulphonamido ($-SO_2NH_2$), C_1-C_6 alkylsulphonyl, $-C(O)NR^{23}R^{24}$, $-NR^{25}C(O)(NH)_vR^{26}$, phenyl, or C_1-C_6 alkyl optionally substituted by carboxyl or C_1-C_6 alkoxycarbonyl;

R^{17} and R^{18} each independently represent a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by carboxyl or C_1-C_6 alkoxycarbonyl, or R^{17} and R^{18} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{19} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by carboxyl or C_1-C_6 alkoxycarbonyl;

R^{20} represents a group C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, adamantyl, C_5-C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one heteroatom selected from nitrogen, oxygen and sulphur, each of which may be optionally substituted by one or more substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, phenyl and -NHC(O)-R^{27};

R^{21} and R^{22} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{23} and R^{24} each independently represent a hydrogen atom or a C_1-C_6 alkyl group optionally substituted by C_1-C_6 alkoxycarbonyl;

v is 0 or 1;

R^{25} represents a hydrogen atom or a C_1-C_6 alkyl group;

R^{26} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by carboxyl, C_1-C_6 alkoxy or C_1-C_6 alkoxycarbonyl; and

R^{27} represents a C_1-C_6 alkyl, amino ($-NH_2$) or phenyl group;

or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, an alkyl substituent group or an alkyl moiety in a substituent group may be linear or branched. When R^9 and R^{10} (or R^{17} and R^{18}, or R^{21} and R^{22}) represent a saturated heterocycle, it should be understood that the only heteroatom present is the nitrogen atom to which R^9 and R^{10} (or R^{17} and R^{18}, or R^{21} and R^{22}) are attached. In the definition of R^{20}, it should be noted that the saturated or unsaturated 5- to 10-membered heterocyclic ring system may be aliphatic or aromatic.

The integer m is preferably 1 or 2.

Each R^1 independently represents halogen (e.g. chlorine, fluorine, bromine or iodine), cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl

or cyclohexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl), C_1-C_6, preferably C_1-C_4, haloalkoxy (e.g. trifluoromethoxy), $-NR^9R^{10}$, C_3-C_6 cycloalkylamino (e.g. cyclopropylamino, cyclobutylamino, cyclopentylamino or cyclohexylamino), C_1-C_6, preferably C_1-C_4, alkylthio (e.g. methylthio or ethylthio), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkylcarbonylamino (e.g. methylcarbonylamino or ethylcarbonylamino), sulphonamido, C_1-C_6, preferably C_1-C_4, alkylsulphonyl (e.g. methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, n-butylsulphonyl, n-pentylsulphonyl or n-hexylsulphonyl), $-C(O)NR^{11}R^{12}$, $-NR^{13}C(O)-(NH)_pR^{14}$, phenyl, or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by carboxyl or C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl).

Most preferably, each R^1 independently represents halogen (particularly chlorine or fluorine), cyano, nitro, C_1-C_6 alkoxy (especially methoxy), C_1-C_6 alkylcarbonyl (especially methylcarbonyl) or C_1-C_6 alkylcarbonylamino (particularly methylcarbonylamino). Each R^1 especially represents a halogen atom.

Q preferably represents an oxygen atom.

Each R^3 independently represents a C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), $-CH_2OH$ or carboxyl group. It is preferred that R^3 represents a methyl, methoxycarbonyl, ethoxycarbonyl, $-CH_2OH$ or carboxyl group.

R^4, R^5, R^6 and R^7 each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), or R^4, R^5, R^6 and R^7 together represent a C_1-C_4 alkylene chain linking the two carbon atoms to which they are attached to form a 4- to 7-membered saturated carbocycle (e.g. cyclohexyl or preferably cyclopentyl), or R^5, R^6 and R^7 each represent a hydrogen atom and R^4 and R^8 together with the carbon atoms to which they are attached form a 5- to 6-membered saturated carbocycle (preferably cyclopentyl).

R^8 represents a hydrogen atom, a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) or is linked to R^4 as defined above.

R^9 and R^{10} each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle (preferably pyrrolidinyl or piperidinyl).

R^{11} and R^{12} each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by a C_1-C_6, preferably C_1-C_4, alkoxycarbonyl substituent group.

R^{13} represents a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

R^{14} represents a hydrogen atom, or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by carboxyl, C_1-C_6, preferably C_1-C_4, alkoxy or C_1-C_6, preferably C_1-C_4, alkoxycarbonyl.

R^{15} represents carboxyl, C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C_1-C_6 alkoxycarbonylC_1-C_6 alkyl, preferably C_1-C_4 alkoxycarbonylC_1-C_4 alkyl (e.g. methoxycarbonylmethyl or methoxycarbonylethyl), or a group $-NR^{17}R^{18}$, $-NHSO_2CH_3$, $-C(O)NR^{17}R^{18}$, $-NHC(O)NR^{17}R^{18}$, $-OC(O)NR^{17}R^{18}$, $-OCH_2C(O)NR^{17}R^{18}$, $-NHC(O)OR^{19}$ or $-NHC(O)R^{20}$.

It is preferred that R^{15} represents C_1-C_4 alkoxy (especially methoxy), C_1-C_4 alkylcarbonyl (especially methylcarbonyl or ethylcarbonyl), C_1-C_4 alkoxycarbonylC_1-C_4 alkyl (particularly methoxycarbonylmethyl or methoxycarbonylethyl), $-C(O)NR^{17}R^{18}$, $-NHSO_2CH_3$, $-NHC(O)NR^{17}R^{18}$ or, especially, $-NHC(O)R^{20}$.

Each R^{16} independently represents halogen (e.g. chlorine, fluorine, bromine or iodine), cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl), C_1-C_6, preferably C_1-C_4, haloalkoxy (e.g. trifluoromethoxy), $-NR^{21}R^{22}$, C_3-C_6 cycloalkylamino (e.g. cyclopropylamino, cyclobutylamino, cyclopentylamino or cyclohexylamino), C_1-C_6, preferably C_1-C_4, alkylthio (e.g. methylthio or ethylthio), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkylcarbonylamino (e.g. methylcarbonylamino or ethylcarbonylamino), sulphonamido, C_1-C_6, preferably C_1-C_4, alkylsulphonyl (e.g. methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, n-butylsulphonyl, n-pentylsulphonyl or n-hexylsulphonyl), $-C(O)NR^{23}R^{24}$, $-NR^{25}C(O)-(NH)_vR^{26}$, phenyl, or

C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by carboxyl or C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl).

Preferably, each R^{16} independently represents halogen (particularly chlorine or fluorine), cyano, C_1-C_4 alkoxy (especially methoxy), C_1-C_4 alkoxycarbonyl (especially methoxycarbonyl), C_1-C_4 haloalkyl (especially trifluoromethyl), C_1-C_4 alkylcarbonyl (particularly methylcarbonyl), phenyl or C_1-C_4 alkyl (e.g. methyl or tert-butyl).

R^{17} and R^{18} each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by carboxyl or, more preferably, C_1-C_6, preferably C_1-C_4, alkoxycarbonyl, especially methoxycarbonyl, or R^{17} and R^{18} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle (preferably pyrrolidinyl or piperidinyl).

R^{19} represents a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by carboxyl or, more preferably, C_1-C_6, preferably C_1-C_4, alkoxycarbonyl, especially methoxycarbonyl.

R^{20} represents a group C_1-C_6, preferably C_1-C_5, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_2-C_6, preferably C_2-C_4, alkenyl, C_3-C_6 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), adamantyl, C_5-C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one heteroatom (e.g. one, two, three or four heteroatoms) selected from nitrogen, oxygen and sulphur, each of which may be optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from nitro, hydroxyl, oxo, halogen (e.g. fluorine, chlorine, bromine or iodine), carboxyl, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl,

tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkylthio (e.g. methylthio or ethylthio), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), phenyl and -NHC(O)-R^{27}.

The saturated or unsaturated 5- to 10-membered heterocyclic ring system may be monocyclic or polycyclic (e.g. bicyclic) and may comprise up to four heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of ring systems that may be used include pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl.

R^{21} and R^{22} each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle (preferably pyrrolidinyl or piperidinyl).

R^{23} and R^{24} each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by a C_1-C_6, preferably C_1-C_4, alkoxycarbonyl substituent group.

R^{25} represents a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

R^{26} represents a hydrogen atom, or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally

substituted by carboxyl, C_1-C_6, preferably C_1-C_4, alkoxy or C_1-C_6, preferably C_1-C_4, alkoxycarbonyl.

R^{27} represents a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), amino or phenyl group.

Preferred compounds of the invention include:

N-[2-(3-{[1-(3,4-dichlorobenzylpiperidinyl]aminohydroxypropoxy)phenyl]acetamide,

N-[5-chloro-2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]acetamide,

N-[2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-methylphenyl]acetamide,

N-[4-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)[1,1'-biphenyl]-3-yl]acetamide,

N-[3-acetyl-2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-methylphenyl]acetamide,

N-[2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-fluorophenyl]acetamide,

N-[2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-fluorophenyl]acetamide,

N-[2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-cyanophenyl]acetamide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]-acetamide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amin0}-hydroxypropoxy)phenyl]-isobutyramide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]-2-2-dimethyl-propiomanide,

N-[5-chloro-2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]acetamide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-methylphenyl]acetamide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-methylphenyl]acetamide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-fluorophenyl]acetamide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-cyanophenyl]acetamide,

N-(2-{[(2S)-3-({-[(4-Chlorophenyl)methyl]-4-piperidinyl}amino)-2-hydroxypropyl]oxy}phenyl)acetamide bi(trifluoroacetate),

N-(2-{(2R)-3-[1-(4-Chloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide,

N-(2-{[3-({1-[(4-Chlorophenyl)methyl]-4-piperidinyl}amino)-2-hydroxy-2-methylpropyl]oxy}phenyl)acetamide,

N-(2-{(2S)-3-[1-(4-Chloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide,

N-{2-[((2S)-3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropyl)oxy]phenyl}acetamide,

N-{2-[((2S)-3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropyl)oxy]-4-fluorophenyl}acetamide,

N-{4-fluoro-2-[((2S)-3-{[1-(4-fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropyl)oxy]phenyl}acetamide,

N-{2-[((2S)-3-{[(3S)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxypropyl)oxy]-4-fluorophenyl}acetamide,

N-{2-[((2S)-3-{[(3R)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxypropyl)oxy]-4-fluorophenyl}acetamide,

N-[2-(3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]acetamide,

N-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)-4-fluorophenyl]acetamide,

N-[4-Fluoro-2-(3-{[1-(4-fluorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]acetamide,

N-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-methylphenyl]acetamide,

N-[2-(3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-methylphenyl]acetamide,

N-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide,

N-[2-(3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide,

N-[2-(3-{[(3S)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide,

N-[2-(3-{[(3R)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide,

N-[2-(3-{[1-(4-Bromobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide,

N-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]benzamide,

N-[2-(3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]benzamide,

N-[2-(3-{[(3R)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]benzamide,

N-[2-(3-{[1-(4-Bromobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]benzamide,

N-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-methoxyphenyl]acetamide,

N-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-6-fluorophenyl]acetamide,

N-[2-Fluoro-6-(3-{[1-(4-fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]acetamide,

2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)-N-methylbenzamide,

N-(2-{3-[1-(3,4-Dichloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-benzamide,

N-(2-{3-[1-(3-Chloro-4-fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-benzamide,

N-(2-{3-[1-(3,4-Difluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-benzamide,

N-(2-{3-[1-(3,4-Dichloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-6-methyl-phenyl)-acetamide,

N-(2-{3-[1-(4-Fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-6-methyl-phenyl)-acetamide,

N-(2-{3-[1-(4-Bromo-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide,

N-(2-{3-[1-(3,4-Dichloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide,

N-(2-{3-[1-(3-Chloro-4-fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide,

N-(2-{3-[1-(3,4-Difluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide,

2-{3-[1-(4-Bromo-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-N-methyl-benzamide,

2-{3-[1-(3,4-Dichloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-N-methyl-benzamide,

2-{3-[1-(4-Chloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-N-methyl-benzamide,

2-{3-[1-(4-Fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-N-methyl-benzamide,

3,5-Dimethyl-1H-pyrrole-2-carboxylic acid (2-{3-[1-(4-bromo-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-amide,

3,5-Dimethyl-1H-pyrrole-2-carboxylic acid (2-{3-[1-(3-chloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-amide,

3,5-Dimethyl-1H-pyrrole-2-carboxylic acid (2-{3-[1-(3-fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[1-(4-Bromo-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-acetamide,

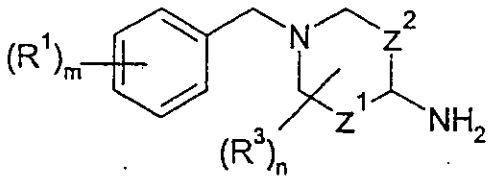
N-(2-{3-[1-(3-Chloro-4-fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-acetamide,

N-(2-{3-[1-(3,4-Difluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-acetamide, and

N-(2-{3-[1-(4-Fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-acetamide.

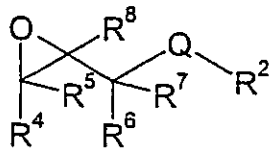
The present invention further provides a process for the preparation of a compound of formula (I) as defined above which comprises

(a) reacting a compound of general formula



(II)

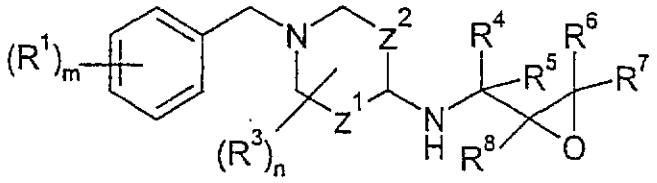
wherein m, n, Z^1, Z^2, R^1 and R^3 are as defined in formula (I), with a compound of general formula



(III)

wherein Q, R^2, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I); or

(b) reacting a compound of general formula



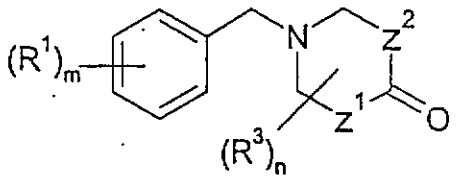
(IV)

wherein m, n, Z^1, Z^2, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I), with a compound of general formula

$$L^1 - Q - R^2 \quad (V)$$

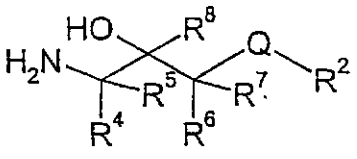
wherein L^1 represents a hydrogen atom or a leaving group (e.g. Li when Q is CH_2) and Q and R^2 are as defined in formula (I); or

(c) reacting a compound of general formula



(VI)

wherein m, n, Z^1, Z^2, R^1 and R^3 are as defined in formula (I), with a compound of general formula



(VII)

wherein Q, R^2, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I);

and optionally after (a), (b) or (c) converting the compound of formula (I) to a further compound of formula (I) and/or forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

The process of the invention may conveniently be carried out in a solvent, e.g. an organic solvent such as an alcohol (e.g. methanol or ethanol), a hydrocarbon (e.g. toluene) or acetonitrile at a temperature of, for example, 15°C or above such as a temperature in the range from 20 to 120°C.

Compounds of formulae (II), (III), (IV), (V), (VI) and (VII) are either commercially available, are well known in the literature or may be prepared easily using known techniques.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures. For example, a compound of formula (I) in which R^{15} represents $-NHC(O)CH_3$ can be converted to a further compound of formula (I) in which R^{15} represents $-NH_2$ by a hydrolysis reaction in the presence of hydrochloric acid.

It will be appreciated by those skilled in the art that in the process of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

Compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Preferred optical isomers are the (S)-enantiomers.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially MIP-1α chemokine receptor) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS).

Examples of these conditions are:

(1) **(the respiratory tract)** airways diseases including chronic obstructive pulmonary disease (COPD) such as irreversible COPD; asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus,

Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura;

(6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(7) cancers, especially non-small cell lung cancer (NSCLC) and squamous sarcoma;

(8) diseases in which angiogenesis is associated with raised chemokine levels (e.g. NSCLC); and

(9) cystic fibrosis, stroke, re-perfusion injury in the heart, brain, peripheral limbs and sepsis.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention also provides a method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

The invention still further provides a method of treating an airways disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I) may be in the range from 0.001 mg/kg to 30 mg/kg.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association 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 present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The invention will now be further explained by reference to the following illustrative examples, in which ^{1}H NMR spectra were recorded on Varian Unity Inova 400. The central solvent peak of chloroform–*d* (δ_H 7.27 ppm) were used as internal standard. Low resolution mass spectra and accurate mass determination were recorded on a Hewlett-Packard 1100 LC-MS system equipped with APCI /ESI ionisation chambers. All solvents and commercial reagents were laboratory grade and used as received. The nomenclature used for the compounds was generated with ACD/IUPAC Name Pro.

Examples 1-16

Starting material: 1-(3,4-Dichlorobenzyl)-4-piperidinylamine

i) tert-Butyl 4-piperidinylcarbamate

Di-tert-butyl-dicarbonate (11.6g, 53.16mmol) was added to a solution of 1-benzyl-4-piperidinamine (13.10g, 68.84mmol) in dichloromethane (100ml) and triethylamine (2ml) and the solution was stirred at room temperature for 2 hrs. Water was added to the solution and the organic layer was separated, dried over natrium sulphate, filtered and concentrated. The resulting residue was taken up into ethanol. Palladium hydroxide 20% (500mg) was added to the solution and the mixture was hydrogenated (parr apparatus) over 50psig hydrogen for 48 hrs. The mixture was filtered over a pad of celite. The solid was washed with two portions of hot ethanol and concentrated in vacuo to give 8.85g product.

APCI-MS: m/z 201[MH+]

^{1}HNMR (400MHz, CD_3OD) δ 2.97-3.39(1H, m), 3 (2H, m), 2.55-2.62 (2H, m), 1.8-1,84 (2H,dd), 1.42 (9H, s), 1.27-1.37 (2H,m)

ii) 1-(3,4-Dichlorobenzyl)-4-piperidinylamine

1,2-dichloro-4-(chloromethyl)benzene (390mg, 1.99mmol)) was added to a solution of tert-butyl 4-piperidinylcarbamate (400mg, 2.0mmol) in DMF (25ml) and triethylamine (2ml). The solution was stirred at room temperature for 3hrs and then concentrated in vacuo. To the solution of the solid in dichloromethane was added (30ml) trifluoroacetic acid (6ml) was added and stirred at room temperature for 2hrs. The solution was diluted with dichloromethane and washed with two portions of water. The combined water washings were treated with 2M NaOH to pH 10 and extracted with ether. The ether was dried (Na_2SO_4), filtered and evaporated to leave a yellow residue (300mg, 1.16mmol).

APCI-MS: m/z 259[MH+]

^{1}HNMR (400MHz, CD_3OD) δ 7.41(1H, d), 7.36 (1H, br d), 7.13 (1H, dd), 3.42 (2H, s), 2.97-3.01 (1H, m), 3 (2H, m), 2.55-2.62 (2H, m), 1.41-1.55 (2H,dd), 1.31-1.54 (2H,m)

Example 1

***N*-[2-(3-{[1-(3,4-dichlorobenzylpiperidinyl]aminohydroxypropoxy)phenyl]acetamide**

The mixture of N-Acetyl-2-(2,3-epoxypropoxy)aniline (120mg, 0,58mmol) and the above starting material (150mg, 0,58mmol) in ethanol (10ml 99.5%) was refluxed for 3hrs. The solvent distilled off under reduced pressure, the resulting residue was purified by silica gel column chromatography (eluant: dichloromethane/methanol 15:1) to give 108mg of the title compound as a gum. Addition of 1.0M ethereal HCl solution gave a white solid product.

APCI-MS:m/z 466[MH^+].

^{1}HNMR (400MHz, CD_3OD) δ 8.0 (1H, dd,), 7.5 (1H, d), 7.45 (1H d), 7.23 (1H, dd), 6.89-7.08 (4H, m), 4.15 (1H, m), 3.9-4.1 (2H, m), 3.40 (2H, S), 2.97-3.11 (1H, m), 3 (2H, m), 2.55-2.68 (2H, m), 1.39-1.55 (2H,dd), 1.31-1.44 (2H,m), 2.17 (3H, s).

The following compounds were synthesised by methods analogous to the method described in Example 1.

Example 2

***N*-[5-chloro-2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]acetamide**

APCI-MS: m/z 500[MH^+]

Example 3

***N*-[2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-methylphenyl]acetamide**

APCI-MS: m/z 480[MH^+]

Example 4

N-[4-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)[1,1'-biphenyl]-3-yl]acetamide

APCI-MS: m/z 542[MH^+]

Example 5

N-[3-acetyl-2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-methylphenyl]acetamide

APCI-MS: m/z 522[MH^+]

Example 6

N-[2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-fluorophenyl]acetamide

APCI-MS: m/z 484[MH^+]

Example 7

N-[2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-fluorophenyl]acetamide

APCI-MS: m/z 484[MH^+]

Example 8

N-[2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-cyanophenyl]acetamide

APCI-MS: m/z 491[MH^+]

Example 9

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]-acetamide

APCI-MS: m/z 432[MH^+]

Example 10

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amin0}-hydroxypropoxy)phenyl]-isobutyramide

APCI-MS: m/z 460[MH^+]

Example 11

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]-2-2-dimethyl-propiomanide

APCI-MS: m/z 474[MH^+]

Example 12

N-[5-chloro-2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]acetamide

APCI-MS: m/z 466[MH^+]

Example 13

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-methylphenyl]acetamide

APCI-MS: m/z 446[MH^+]

Example 14

***N*-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-methylphenyl]acetamide**

APCI-MS: m/z 446[MH^+]

Example 15

***N*-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-fluorophenyl]acetamide**

APCI-MS: m/z 450[MH^+]

Example 16

***N*-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-cyanophenyl]acetamide**

APCI-MS: m/z 457[MH^+]

Starting Materials for Examples 17 to 63.

Epoxide: A

***N*-{2-[(2*S*)Oxiranylmethoxy]phenyl}acetamide**

(2*S*)-2-[(2-nitrophenoxy)methyl]oxirane (1.17 g, 6 mmol) was dissolved in ethyl acetate (50 ml). Platinum on charcoal (0.50 g) was added, and the mixture was stirred in the atmosphere of hydrogen for 3 h at room temperature and atmospheric pressure. The catalyst was filtered and washed on the filter with ethyl acetate (10 ml). Acetic anhydride (1.23g, 1.13 ml, 12 mmol) and ethyldi(*i*-propyl)amine (1.55 g, 2.05 ml, 12 mmol) were added to the solution. The reaction mixture was stirred at room temperature for 3 h, then washed with 1M NaOH (2 x 50 ml) and brine (2 x 50 ml), and dried with Na_2SO_4. Evaporation of the solvent and flash chromatography on silica gel with n-heptane/ethyl

acetate (from 25 to 75 %) afforded the title compound (0.74 g, 3.57 mmol, 60 %) as colourless crystals.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.36 (m, 1H), 7.89 (br. S, 1H), 6.8 – 7.0 (m, 3H), 4.35 (dd, 1H, *J = 2.5, J = 11.3*), 3.95 (dd, 1H, *J = 5.9, J = 11.3*), 3.39 (m, 1H), 2.95 (t, 1H, *J = 4.8*), 2.78 (dd, 1H, *J = 2.7, J = 4.8*), 2.22 (s, 3H).

APCI-MS: m/z 208 [MH^+]

Epoxide: B

i) [(2*R*)-2-Methyloxiranyl]methyl-4-methylbenzenesulfonate

(S)-2-methyl-glycidol (0,10g, 1.13mmol), dimethylaminopyridine (0.5mg, 3.8μmol) in triethylamine (2ml) was cooled on an ice bath and tosyl chloride (0.217g, 1.14mmol) was added in portions during 10 min. The flask was sealed and kept at –10°C over night. The reaction mixture was evaporated and the residue was stirred with dry diethylether (3.5ml). The solid was filtered off and washed with diethylether (3 x 1ml). The filtrate was dried and concentrated in vacuo. The crude product was purified on silica (Heptane/EtOAc 1:2) to give 145mg (53%) of the subtitle compound.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.80 (2H, d, J8.4Hz), 7.36 (2H, d, J8.1Hz), 4.04 (1H, d, J10.7Hz), 3.95 (1H, d, J10.7Hz), 2.70 (1H, d, J4.7Hz), 2.64 (1H, d, J4.6Hz), 2.46 (3H, s), 1.36 (3H, s).

ii) *N*-(2-{[(2*R*)-2-Methyloxiranyl]methoxy}phenyl)acetamide

To 2-acetamidophenol (90.5mg, 0.598mmol) and cesium carbonate(234mg, 0.718mmol) was added [(2*R*)-2-methyloxiranyl]methyl 4-methylbenzene-sulfonate (145mg, 0.598mmol) dissolved in DMF (1ml). The mixture was stirred at room temperature for four hours and then partitioned between ethyl-acetate and water. After extraction the combined organic phases were dried and concentrated in vacuo. The residue was purified on silica (Heptane/EtOAc 3:1 – 2:1) to give 63mg (48%) of the title compound.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.38-8.31 (1H, m), 8.02 (1H, bs), 7.04-6.97 (2H, m), 6.93-6.86 (1H, m), 4.11 (1H, d, J10.9Hz), 4.01 (1H, d, J10.9Hz), 2.95 (1H, d, J4.7Hz), 2.78 (1H, d, J4.7Hz), 2.21 (3H, s), 1.48 (3H, s).

Epoxide: C

i) [(2*S*)-2-Methyloxiranyl]methyl-3-nitrobenzenesulfonate

To an oven-dried 1000 ml three-necked flask was added powdered activated molecular sieves (8.0 g, 4Å) and CH_2Cl_2 (440 ml, dried over molecular sieves). D-(-)-Diisopropyl tartrate (3.0 ml, 14.2 mmol) and 2-methyl-2-propan-1-ol (20 ml, 240 mmol) was added and the mixture was cooled to –20°C. Titanium tetraisopropoxide (3.5 ml, 11.9 mmol) was added with a few ml of CH_2Cl_2 and the mixture was stirred at –20°C for 30 minutes. Cumene hydroperoxide (75 ml, approx. 430 mmol) was added dropwise over 1.5 hours maintaining the temperature at –20°C. The mixture was stirred at this temperature over night. Trimethylphosphite (40 ml, 340 mmol)was added dropwise over 5 hours maintaining the temperature at –20°C. Triethylamine (50 ml, 360 mmol) and DMAP (3.48 g, 28.5 mmol) was added followed by a solution of 3-nitrobenzenesulphonyl chloride (47 g, 212 mmol) in CH_2Cl_2 (400 ml). The temperature was raised to –10°Cand the mixture was stirred at this temperature over night. After removing the external cooling, the reaction mixture was filtered through celite®. The organic phase was washed with 10% tartaric acid (500 ml), saturated $NaHCO_3$ (300 ml) and brine (300 ml). The organic phase was dried ($MgSO_4$) and evaporated to give ca 150 g of a yellow oil. The crude material was chromatographed (1 kg silica, Heptane/EtOAc 100:0 to 50:50 gradually increased polarity) to give 48.8 g (84%) of the sub-title compound as a yellow oil. The compound was pure enough to use further without any additional purification.

^{1}H-NMR (400 MHz, $CDCl_3$): □ 8.79-8.75 (1H, m); 8.52 (1H, ddd, *J* 1.1 2.3 8.3 Hz); 8.25 (1H, ddd, *J* 1.1 1.8 7.8 Hz); 7.81 (1H, t, *J* 8.5 Hz); 4.28 (1H, d, *J* 11.3 Hz); 4.05 (1H, d, *J* 11.3 Hz); 2.73 (1H, d, *J* 4.4 Hz); 2.67 (1H, d, *J* 4.4 Hz); 1.56 (3H, s)

ii) *N*-(2-{[(2*S*)-2-Methyloxiranyl]methoxy}phenyl)acetamide

In a flask was added the compound obtained in a) (24.57 g, 90 mmol), 2-acetamido-phenol (13.59 g, 90 mmol), Cs_2CO_3 (35.1 g, 108 mmol, powdered anhydrous) and DMF (90 ml). The flask was sealed and the mixture was stirred with a magnetic stirrer at room temperature for 2 hours. A heavy precipitate was formed, and the starting materials were converted in 2 hours. The mixture was partitioned between EtOAc/water (400 + 400 ml). The organic phase was collected and the aqueous phase was washed with EtOAc (2 x 200 ml). The combined organic phases were washed with water (200 ml), 1M NaOH (2 x 200 ml) and brine (150 ml). The organic solution was dried over Na_2SO_4, and concentrated in vacuo after filtration. The crude material was purified on silica (Heptane/EtOAc 5:1 to 1:1, gradually increasing the polarity), eluting 18.5 g (92%) of the sub-title compound. The optical purity was 97.4 %, according to chiral HPLC (Chiralpak ™, iso-hexane/iso-propanol 95:5).

^{1}H-NMR (400 MHz, $CDCl_3$): □ 8.39-8.32 (1H, m); 8.00 (1H, bs); 7.05-6.97 (2H, m); 6.95-6.88 (1H, m); 4.12 (1H, d, AB, *J* 11.0 Hz); 4.02 (1H, d, AB, *J* 11.0 Hz); 2.96 (1H, d, *J* 4.6 Hz); 2.79 (1H, d, *J* 4.8 Hz); 2.22 (3H, s); 1.49 (3H, s)

Epoxide: D

***N*-{4-Fluoro-2-[(2*S*)oxiranylmethoxy]phenyl}acetamide**

was prepared from (2*S*)-2-[(5-fluoro-2-nitrophenoxy)methyl]oxirane according to the method described for Epoxide: A.

APCI-MS: m/z 226 [MH+]

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.30 (dd, 1H, *J = 5.2, J = 9.0*), 7.71 (br. S, 1H), 8.6 – 8.8 (m, 2H), 4.36 (dd, 1H, *J = 2.3, J = 11.3*), 3.90 (dd, 1H, *J = 6.3, J = 11.3*), 3.40 (m, 1H), 2.97 (t, 1H, *J = 4.4*), 2.78 (dd, 1H, *J = 2.7, J = 4.8*), 2.21 (s, 3H).

Epoxide: E

***N*-{2-[(2-Methyl-2-oxiranyl)methoxy]phenyl}benzamide**

A mixture of *N*-(2-hydroxyphenyl)benzamide (159 mg, 0.75 mmol), 2-(chloromethyl)-2-methyloxirane (1.60 g, 15 mmol), and benzyltriethylammonium chloride (27 mg, 0.12 mmol) was stirred at 70 – 75 °C for 6 h. After cooling to room temperature, water (2 ml) was added and the mixture was vigorously shaken. It was extracted with dichloromethane (2 x 5 ml), and the combined organic extracts were washed with aq. NaOH (2M, 5 ml) and water (10 ml). Drying with Na_2SO_4, evaporation of the solvent and flash chromatography on silica gel with n-heptane/ethyl acetate (ethyl acetate from 25 to 50 %) afforded title compound as yellowish solid (131 mg, 0.46 mmol, 62 %).

APCI-MS: m/z 284 [MH+]

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.68 (br. S, 1H), 8.54 (m, 1H), 7.94 (m, 2H), 7.4 – 7.6 (m, 3H), 7.07 (m, 2H), 6.92 (m, 1H), 4.19 (d, 1H, *J = 10.7*), 4.06 (d, 1H, *J 10.7*), 2.92 (d, 1H, *J = 4.6*), 2.78 (d, 1H, *J = 4.6*).

Epoxide: F

***N*-Methyl-2-[(2-methyl-2-oxiranyl)methoxy]benzamide**

was prepared from 2-hydroxy-*N*-methylbenzamide (prepared according to Cohen et al, *J. Am. Chem. Soc.*,1998, *20*, 6277 - 6286.) according to the method described for *N*-{2-[(2-methyl-2-oxiranyl)methoxy]phenyl}benzamide.

APCI-MS: m/z 284 [MH+]

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.68 (br. S, 1H), 8.54 (m, 1H), 7.94 (m, 2H), 7.4 – 7.6 (m, 3H), 7.07 (m, 2H), 6.92 (m, 1H), 4.19 (d, 1H, *J = 10.7*), 4.06 (d, 1H, *J 10.7*), 2.92 (d, 1H, *J = 4.6*), 2.78 (d, 1H, *J = 4.6*), 1.51 (s, 3H).

Epoxide: G

***N*-[4-Methyl-2-(2-oxiranylmethoxy)phenyl]acetamide**

A mixture of *N*-(2-hydroxy-4-methylphenyl)acetamide (10 g, 60 mmol), 2-(bromomethyl)oxirane (9.86 g, 72 mmol, 6.0 ml) and potassium carbonate (16.8 g, 120 mmol) in DMF (100 ml) was heated at 55 °C for 2 h. Then the reaction mixture was diluted

with ethyl acetate and washed with aq. HCl (1.5 %), aq. sat. $NaHCO_3$, and brine. Evaporation of the solvent and flash chromatography on silica gel with n-heptane/ethyl acetate (ethyl acetate from 35 to 70 %) afforded the title compound (5.65 g, 25 mmol, 43 %).

APCI-MS: m/z 222 [MH+]

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.20 (d, 1H, *J = 8.2*), 7.78 (br. s, 1H), 6.79 (d, 1H, *J = 8.2*), 6.70 (s, 1H), 4.32 (dd, 1H, *J = 2.5, J = 11.4*), 3.93 (dd, 1H, *J = 5.9, J = 11.4*), 3.38 (m, 1H), 2.94 (t, 1H, *J = 4.8*), 2.77 (dd, 1H, *J = 2.7, J = 4.8*), 2.29 (s, 3H), 2.19 (s, 3H).

Epoxide: H

***N*-[4-Methoxy-2-(2-oxiranylmethoxy)phenyl]acetamide**

Was prepared from *N*-(2-hydroxy-4-methoxyphenyl)acetamide according to the method described for *N*-[4-methyl-2-(2-oxiranylmethoxy)phenyl]acetamide using cesium carbonate instead of potassium carbonate.

APCI-MS: m/z 238 [MH+]

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.20 (d, 1H, *J = 8.8*), 7.62 (br. s, 1H), 6.4 – 6.6 (m, 2H), 6.70 (s, 1H), 4.32 (dd, 1H, *J = 2.5, J = 11.3*), 3.91 (dd, 1H, *J = 6.1, J = 11.3*), 3.77 (s, 3H), 3.37 (m, 1H), 2.94 (t, 1H, *J = 4.8*), 2.76 (dd, 1H, *J = 2.7, J = 4.8*), 2.18 (s, 3H).

Epoxide: I

i) 2-Amino-3-fluorophenol

To a stirred solution of 2,6-difluoronitrobenzene (1100mg, 6.9mmol) in dry methanol (20ml) was added a solution of sodium (180mg, 7.8mmol) in dry methanol (8 ml). The solution was stirred overnight. After concentration, water was added and the solution was extracted with ether, dried over $MgSO_4$, filtered and concentrated to a yellow residue (870mg.5.08 mmol). To the solution of the yellow residue in dichloromethane (10 ml) boron tribromide (1M in dichloromethane, 10 ml) was added and stirred at room temperature overnight. Water was then added and the solution stirred for further 60 min.

The organic phase was separated and the water phase was extracted with ether. The combined organic phase were dried over $MgSO_4$, filtered and concentrated in vacuo to give a brownish residue. The residue was taken up into ether and washed with 2M sodium hydroxide and water. The water and sodium hydroxide washings were combined and neutralised with 6M HCl and extracted with ether, dried over $MgSO_4$ and evaporated to give a yellow residue which was purified by flash chromatography on silica gel with EtOAc:Heptane: 1:3 as eluant to give the product (720mg, 4.6mmol) which was directly suspended with palladium-charcoal (140mg) in water-ethanol (30ml). Sodium borohydride (530mg) was added over a period of 5 min and the suspension was stirred at room temperature (1h). The catalyst was removed by filtration through a Celite pad. The filtrate was acidified with 6M hydrochloric acid to destroy any residual borohydride, neutralised with 2 M sodium hydroxide, and then extracted with ether. The ethereal extracts were dried over $MgSO_4$ and evaporated.

APCI-MS: m/z 128.2 [MH^+]

ii) N-[2-Fluoro-6-(2-oxiranylmethoxy)phenyl]acetamide

To a stirred solution of 2-amino-3-fluorophenol (300 mg, 2.36 mmol) in water-methanol (10 ml) acetic acid anhydride was added until all 2-amino-3-fluorophenol was consumed. The solution was concentrated to a residue of N-(2-fluoro-6-hydroxyphenyl) acetamide. To a mixture of N-(2-fluoro-6-hydroxyphenyl)acetamide (399mg, 2.36mmol) and potassium carbonate (652mg, 4.72mmol) in DMF (5 ml) epibromohydrin (388 mg, 2.8mmol) was added and the mixture was stirred at 70°C for 3hr. Water and ethyl acetate were added, the organic phase separated, dried and concentrated. The resulting residue was purified by RP- HPLC (10- 40 % CH3CN) to give the desired product as a solid (242 mg,1.08mmol).

APCI-MS: m/z 226 [MH+]

^{1}H-NMR (400MHz, $CDCl_3$): □ 7.15 (m, 1H), 6.87 (br. s, 1H), 6.6 - 6.8 (m, 2H), 4.30 (dd, 1H, *J = 2.3, J = 11.3*), 3.93 (dd, 1H, *J = 5.7, J = 11.3*), 3.34 (m, 1H), 2.91 (t, 1H, *J = 4.4*), 2.75 (dd, 1H, *J = 2.8, J = 4.8*), 2.20 (br. s, 3H).

Epoxide: J

***N*-(2-Oxiranylmethoxy-phenyl)-benzamide**

To a stirred solution of N-(2-Hydroxy-phenyl)-benzamide (0.81g, 3.80 mmol), and cesium carbonate (1.61g, 4.94 mmol) in acetonitrile was added epibromohydrin (0.63 ml, 7.60 mmol). After 4 hours the reaction mixture was partitioned between dichloromethane and water. After evaporation of the organic solvent the residue was crystallised from petroleum ether and diethyl ether yielding (0.741g, 73%).

APCI-MS: m/z 227[MH^+]

^{1}H -NMR (400 MHz, $CDCl_3$): δ 8.65 (bs, 1H), 8.55 (bs, 1H), 7.94 (d, 2H), 7.53 (m, 3H), 7.08 (bs, 2H), 6.96 (bs, 1H), 4.42 (d, 1H), 4.02, (m, 1H), 3.41 (bs, 1H), 2.96 (s, 1H), 2.80 (s, 1H).

Epoxide: K

***N*-Methyl-2-oxiranylmethoxy-benzamide**

To a solution of 2-Hydroxy-*N*-methyl-benzamide (0.5g, 3.31 mmol prepared according to Cohen, Seth M et al J. Am. Chem. Soc., (1998), 120(25), 6277-6286.) and cesium carbonate (2.16g, 6.62mmol) in acetonitrile was added epibromohydrin (0.274ml, 3.31mmol). The mixture was heated at 50°C for 2 hours and then after cooling to room temperature partitioned between water(50 ml)and dichloromethane (100ml). The dichloromethane was dried and evaporated . Chromatography (EtOAc) gave 0.43g (64%) of the product as a solid.

APCI-MS: m/z 208[MH^+]

^{1}H -NMR (400 MHz, $CDCl_3$): δ 8.20 (dd, 1H), 7.85 (bs, 1H), 7.42 (m, 1H), 7.11 (m, 1H), 6.95 (dd, 1H), 4.46 (dd, 1H), 4.11 (dd, 1H), 3.41 (m, 1H), 3.02 (d, 3H), 2.97 (t, 1H), 2.84 (dd, 1H).

Epoxide: L

***N*-(2-Methyl-6-oxiranylmethoxy-phenyl)-acetamide**

A mixture of 3-methyl-2-acetamidophenol (0.165g, 1 mmol), and epichlorohydrin (1.84g, 20mmol) was stirred at 70°C to afford a clear solution. Triethylbenzylammonium chloride (0.15g, 1 mmol) was then added and stirring was continued at 125°C for 15 minutes. After cooling to room temperature 1M NaOH solution was added and the solution was extracted with dichloromethane. The organic extract was washed with water and dried. After evaporation of the dichloromethane the resulting brownish oil was purified through silica chromatography 50-70% EtOAc in heptane yielding the product as a colourless oil (0.12g, 0.54mmol).

APCI-MS: m/z 208[MH^+]

Epoxide: M

3,5 Dimethyl-1-*H*-pyrrole-2-carboxylic acid (2-oxiranylmethoxy-phenyl)-acetamide

The compound was prepared from 3,5 Dimethyl-1-*H*-pyrrole-2-carboxylic acid-(2-phenyl)-acetamide (300 mg, 1.3 mmol) analogously to that described for Epoxide: L.

APCI-MS: m/z 287 [MH^+]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.46 (m,1H), 8.31 (m,1H), 6.99 (m,2H), 6.87 (m,1H), 5.85(m,1H), 4.34(m,1H), 3.92 (m, 1H), 3.36 (m,1H), 2.91 (m,2H), 2.71 (m,1H), 2.47 (m, 3H), 2.25 (m,3H).

(i) 3,5 Dimethyl-1-*H*-pyrrole-2-carboxylic acid (2-phenyl)-acetamide

2-Aminofenol (545mg, 5 mmol), 3,5 dimethyl-1-H-pyrrole-2-carboxylic acid **(ii)** (695mg, 5 mmol) and HATU (1900mg, 5 mmol) were stirred in DMF (20 ml).

Diisopropylethylamine was added to pH 8. The mixture was stirred overnight and then concentrated. The residue was purified on C18 (acetonitrile/water 10/90 to 40/60 with 0.5% trifluoroacetic acid) to give the title compound (550 mg, 48%).

APCI-MS: m/z 231 [MH^+]

^{1}H-NMR (400MHz, $CDCl_3$): δ 9.22 (s,1H), 7.63 (s, 1H), 7.11(m, 2H), 7.03 (m, 1H), 6.88 (m,1H), 5.88 (s, 1H), 2.44 (s,1H), 2.24 (s,1H).

(ii) 3,5 Dimethyl-1-*H*-pyrrole-2-carboxylic acid

To a solution of ethyl 3,5-dimethyl-2-pyrrolecarboxylate (Aldrich) (504mg, 3 mmol) in THF/H_20/MeOH (5:1:1, 30ml) was added NaOH (480 mg, 12 mmol) in H_20 (12 ml). The mixture was stirred at 75° C overnight. The homogeneous mixture was washed with ether. To the aqueous layer was added a saturated aqueous $KHSO_4$ solution until the pH was about 3. The solution was then extracted with dichloromethane. The extracts were dried over $MgSO_4$ and evaporated. The residue was purified on silica (ethylacetate /methanol 90/10) to give the title compound (375 mg, 90 %).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.75(s,1H), 5.83(s,1H), 2.25(s,1H), 2.38 (s,1H).

Amine: N

1-(4-Chlorobenzyl)-piperidineamine

1-Chloro-4-(chloromethyl)benzene (1.61 g, 10 mmol) was added to a stirred solution of *tert*-butyl 4-piperidinylcarbamate (2.02 g. 10.1 mmol) and triethylamine (10 ml) in dry DMF (100 ml). The solution was stirred at room temperature overnight and then the solvent was removed in vacuo. The residue was taken in dichloromethane (150 ml) and trifluoroacetic acid (30 ml) was added. After stirring at room temperature for 3 h, the solution was diluted with dichloromethane (150 ml), and extracted with water (2 x 150 ml). The pH of the combined aqueous extracts was adjusted to 10 by addition of 2 M NaOH. The solution was extracted with ether (3 x 100 ml). Drying with sodium sulfate and

evaporation of the solvent afforded the title compound as yellowish oil (1.91 g, 8.5 mmol, 85 %).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.2 –7.3 (m, 4H), 3.41 (s, 2H), 2.76 (m, 2H), 2.63 (m, 1H), 1.98 (m, 2H), 1.76 (m, 2H), 1.3 – 1.6 (m, 4H).APCI-MS: m/z 225 [MH^+]

Amine: O

(3*S*)-1-(4-Chlorobenzyl)-3-pyrrolidinamine

was prepared according the method described for Amine: N from *tert*-butyl (3*S*)pyrrolidinylcarbamate.

APCI-MS: m/z 211 [MH+]

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.2 – 7.3 (m, 4H), 5.55 (d, 2H), 3.49 (m, 1H), 2.66 (m, 2H), 2.41 (m, 1H), 2.29 (dd, 1H), 2.18 (m, 1H), 1.68 (br. s, 2H), 1.48 (m, 1H).

Amine: P

(3*R*)-1-(4-Chlorobenzyl)-3-pyrrolidinamine

Was prepared according the method described for Amine: N from *tert*-butyl (3*R*)pyrrolidinylcarbamate.

APCI-MS: m/z 211 [MH+]

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.2 – 7.3 (m, 4H), 5.55 (d, 2H), 3.49 (m, 1H), 2.66 (m, 2H), 2.41 (m, 1H), 2.29 (dd, 1H), 2.18 (m, 1H), 1.68 (br. s, 2H), 1.48 (m, 1H).

Amine: Q

3-(4-Chlorophenoxy)piperidine

tert-Butyl 3-hydroxy-1-piperidinecarboxylate (1.85 g, 9.18 mmol, prepared according to Costa et al., *J. Med. Chem.* **1992**, *35*, 4334 – 4343) (1.85 g, 9.18 mmol) and triphenyl phosphine (2.41 g, 9.18 mmol) were dissolved in dry THF (25 ml) under nitrogen. The solution was cooled to 0 °C and a solution of 4-chlorophenol (1.18 g, 9.18 mmol) in dry

THF (10 ml) was added followed by diethyl azodicarboxylate (1.60 g, 9.18 mmol, 1.45 ml). After 15 minutes the reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed in vacuo, the residue stirred with ether/n-heptane (1 : 2, 50 ml) mixture. The solid triphenyl phosphine oxide was filtered off, the solution washed with aq. NaOH (1M, 3 x 75 ml). Evaporation of the solvent and flash chromatography on silica gel with ethyl acetate/n-heptane (ethyl acetate from 5 to 25 %) afforded the BOC-protected subtitle compound, which was dissolved in dichloromethane (20ml). Trifluoroacetic acid (10 ml) was added, and the reaction mixture was stirred overnight at room temperature. The solution was concentrated in vacuo and the product was purified by flash chromatography on silica gel ($MeOH/CHCl_3/NH_3$, 100 : 100 : 1) to afford colourless oil (0.23 g, 12%).

APCI-MS: m/z 212 [MH+]

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.19 (m, 2H), 6.84 (m, 2H), 4.25 (m, 1H), 3.17 (m, 1H), 2.7 – 2.9 (m, 4H), 1.97 (m, 1H), 1.7 – 1.9 (m, 2H), 1.53 (m, 1H).

Amine: R

1-(4-Bromobenzyl)-4-piperidinylamine

To a solution of 4-bromo benzylbromide (1.0g, 4.1mmol) in dichloromethane (20ml) and diisopropyletylamine (1ml) was added tert-butyl 4-piperidinylcarbamate (1.0g, 5.0mmol). The solution was then stirred at room temperature over night. The solvent was evaporated and 25 ml of 50% TFA in dichloromethane was added to the resulting white solid. The mixture was then stirred at room temperature for 2h and then evaporated to dryness. The resulting solid was dissolved in water and extracted with toluene. After removal of the toluene the water phase was made basic with 1M NaOH giving a pH of 13. The water phase was then extracted with dichloromethane 3 times and the combined extracts were dried and then evaporated to give the pure product as a slightly yellow oil (0.96g, 3.6mmol)

APCI-MS: m/z 269[M+]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 2H), 7.18 (d, 2H), 3.43 (s, 2H), 2.78 (m, 3H), 2.43 (bs, 2H), 2.10 (t, 2H), 1.82 (m, 2H), 1.44 (m, 2H).

The following Amines (S, T, U) were synthesised by methods analogous to the method described for Amine R.

Amine: S

1-(3,4-Difluorobenzyl)-4-piperidinylamine

APCI-MS: m/z 227[MH^+]

Amine: T

1-(3-Chloro-4-fluorobenzyl)-4-piperidinylamine

APCI-MS: m/z 243[MH^+]

Amine: U

1-(4-Fluorobenzyl)-4-piperidinylamine

APCI-MS: m/z 209[MH^+]

Example 17

***N*-(2-{[(2*S*)-3-({-[(4-Chlorophenyl)methyl]-4-piperidinyl}amino)-2-hydroxypropyl]oxy}phenyl)acetamide bi(trifluoroacetate)**

A solution of 1-(4-chlorobenzyl)-piperidine amine (0.80 g, 3.57 mmol) and *N*-{2-[(2*S*)oxiranylmethoxy]phenyl}acetamide (0.74 g, 3.57 mmol) in ethanol (50 ml, 99.5 %) was refluxed for 4h. The solvent was distilled off under reduced pressure. The residue was purified by preparative HPLC (Kromasil C18 column; eluant: [acetonitrile + 0.1 % TFA/water + 0.1 % TFA]) to afford colourless solid (1.158 g, 1.75 mmol, 49 %).

APCI-MS: m/z 432 [MH^+]

Example 18

N-(2-{(2R)-3-[1-(4-Chloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide

1-(4-chlorobenzyl)-4-piperidinamine (62mg, 0.276mmol) and *N*-(2-{[(2*R*)-2-methyloxiranyl]methoxy}phenyl)acetamide (61mg, 0.276mmol) in ethanol (1.5ml) was stirred in a sealed vial at 80°C for 4 hours. The reaction mixture was diluted with water and purified by reversed phase HPLC to give 130mg (70%) of the title compound as a ditrifluoroacetate after lyophilisation. The optical purity was determined to 86% ee, by chiral HPLC on a Chiralpak AD-column.

APCI-MS: m/z446.1 [M+]

Example 19

N-(2-{[3-({1-[(4-Chlorophenyl)methyl]-4-piperidinyl}amino)-2-hydroxy-2-methylpropyl]oxy}phenyl)acetamide

Prepared by analogy to the method described in Example 18 from racemic epoxide.

APCI-MS: m/z 446.1 [M+]

Example 20

N-(2-{(2S)-3-[1-(4-Chloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide

Prepared according to the method described in Example 18 from N-(2-(((2S)-2-methyloxiranyl)methoxy)phenyl)acetamide, >98% yield was obtained.

APCI-MS: m/z 446.1 [M+]

General Procedure (Examples 21-43)

To a solution of the amine in EtOH (0.1 M, 0.2 ml) a solution of the epoxide in DMSO (0.1 M, 0.2 ml) was added. The reaction mixture was heated at 80 °C for 24 h.

Example 21

N-{2-[((2*S*)-3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropyl)oxy]phenyl}acetamide

APCI-MS: m/z 416 [MH+]

Example 22

N-{2-[((2*S*)-3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropyl)oxy]-4-fluorophenyl}acetamide

APCI-MS: m/z 450 [MH+]

Example 23

N-{4-fluoro-2-[((2*S*)-3-{[1-(4-fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropyl)oxy]phenyl}acetamide

APCI-MS: m/z 434[MH+]

Example 24

N-{2-[((2*S*)-3-{[(3*S*)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxypropyl)oxy]-4-fluorophenyl}acetamide

APCI-MS: m/z 436 [MH+]

Example 25

***N*-{2-[((2*S*)-3-{[(3*R*)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxypropyl)oxy]-4-fluorophenyl}acetamide**

APCI-MS: m/z 436 [MH+]

Example 26

***N*-[2-(3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]acetamide**

APCI-MS: m/z 430 [MH+]

Example 27

***N*-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)-4-fluorophenyl]acetamide**

APCI-MS: m/z 464 [MH+]

Example 28

***N*-[4-Fluoro-2-(3-{[1-(4-fluorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]acetamide**

APCI-MS: m/z 448 [MH+]

Example 29

***N*-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-methylphenyl]acetamide**

APCI-MS: m/z 446 [MH+]

Example 30

***N*-[2-(3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-methylphenyl]acetamide**

APCI-MS: m/z 430 [MH+]

Example 31

***N*-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide**

APCI-MS: m/z 494 [MH+]

Example 32

***N*-[2-(3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide**

APCI-MS: m/z 478 [MH+]

Example 33

***N*-[2-(3-{[(3*S*)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide**

APCI-MS: m/z 480 [MH+]

Example 34

***N*-[2-(3-{[(3*R*)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide**

APCI-MS: m/z 480 [MH+]

Example 35

***N*-[2-(3-{[1-(4-Bromobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide**

APCI-MS: m/z 540 [MH+]

Example 36

***N*-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]benzamide**

APCI-MS: m/z 508 [MH+]

Example 37

***N*-[2-(3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]benzamide**

APCI-MS: m/z 492 [MH+]

Example 38

***N*-[2-(3-{[(3*R*)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]benzamide**

APCI-MS: m/z 494 [MH+]

Example 39

***N*-[2-(3-{[1-(4-Bromobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]benzamide**

APCI-MS: m/z 554 [MH+]

Example 40

***N*-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-methoxyphenyl]acetamide**

APCI-MS: m/z 462 [MH+]

Example 41

***N*-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-6-fluorophenyl]acetamide**

APCI-MS: m/z 450 [MH+]

Example 42

***N*-[2-Fluoro-6-(3-{[1-(4-fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]acetamide**

APCI-MS: m/z 434 [MH+]

Example 43

2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)-*N*-methylbenzamide

APCI-MS: m/z 446 [MH+]

Example 44

N-(2-{3-[1-(3,4-Dichloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-benzamide

To a solution of *N*-(2-Oxiranylmethoxy-phenyl)-benzamide (0.2ml, 0.1M in DMSO) was added (0.2ml, 0.1M in EtOH) of 1-(3,4-Dichloro-benzyl)-piperidin-4-ylamine. The resulting mixture was heated at 75-80°C for 24hours. The ethanol was removed and the product was purified with preparative LC/MS.

APCI-MS: m/z 529[MH^+]

The following Examples 45-63 were synthesised by methods analogous to the method described in Example 44.

Example 45

N-(2-{3-[1-(3-Chloro-4-fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-benzamide

APCI-MS: m/z 513[MH^+]

Example 46

N-(2-{3-[1-(3,4-Difluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-benzamide.

APCI-MS: m/z 496[MH^+]

Example 47

N-(2-{3-[1-(3,4-Dichloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-6-methyl-phenyl)-acetamide

APCI-MS: m/z 481[MH^+]

Example 48

N-(2-{3-[1-(4-Fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-6-methyl-phenyl)-acetamide

APCI-MS: m/z 430[MH^+]

Example 49

N-(2-{3-[1-(4-Bromo-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide

APCI-MS: m/z 490[M+]

Example 50

N-(2-{3-[1-(3,4-Dichloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide

APCI-MS: m/z 481[MH^+]

Example 51

N-(2-{3-[1-(3-Chloro-4-fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide

APCI-MS: m/z 464[MH^+]

Example 52

N-(2-{3-[1-(3,4-Difluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide

APCI-MS: m/z 448[MH^+]

Example 53

2-{3-[1-(4-Bromo-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-N-methyl-benzamide

APCI-MS: m/z 476[M^+]

Example 54

2-{3-[1-(3,4-Dichloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-N-methyl-benzamide

APCI-MS: m/z 467[M^+]

Example 55

2-{3-[1-(4-Chloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-N-methyl-benzamide

APCI-MS: m/z 432[MH^+]

Example 56

2-{3-[1-(4-Fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-N-methyl-benzamide

APCI-MS: m/z 416[MH^+]

Example 57

3,5-Dimethyl-1H-pyrrole-2-carboxylic acid (2-{3-[1-(4-bromo-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS: m/z 456[MH^+]

Example 58

3,5-Dimethyl-1H-pyrrole-2-carboxylic acid (2-{3-[1-(3-chloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS: m/z 512[MH^+]

Example 59

3,5-Dimethyl-1H-pyrrole-2-carboxylic acid (2-{3-[1-(3-fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS: m/z 495[MH^+]

Example 60

N-(2-{3-[1-(4-Bromo-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-acetamide

APCI-MS: m/z 476[M^+]

Example 61

N-(2-{3-[1-(3-Chloro-4-fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-acetamide

APCI-MS: m/z 450[MH^+]

Example 62

N-(2-{3-[1-(3,4-Difluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-acetamide

APCI-MS: m/z 434[MH^+]

Example 63

N-(2-{3-[1-(4-Fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-acetamide

APCI-MS: m/z 416[MH^+]

THP-1 Chemotaxis Assay

Introduction

The assay measured the chemotactic response elicited by MIP-1α chemokine in the human monocytic cell line THP-1. The compounds of the Examples were evaluated by their ability to depress the chemotactic response to a standard concentration of MIP-1α chemokine.

Methods

Culture of THP-1 cells

Cells were thawed rapidly at 37°C from frozen aliquots and resuspended in a 25 cm flask containing 5 ml of RPMI-1640 medium supplemented with Glutamax and 10% heat inactivated fetal calf serum without antibiotics (RPMI+10%HIFCS). At day 3 the medium is discarded and replaced with fresh medium.

THP-1 cells are routinely cultured in RPMI-1640 medium supplemented with 10% heat inactivated fetal calf serum and glutamax but without antibiotics. Optimal growth of the cells requires that they are passaged every 3 days and that the minimum subculture density is 4x10+5 cells/ml.

Chemotaxis assay

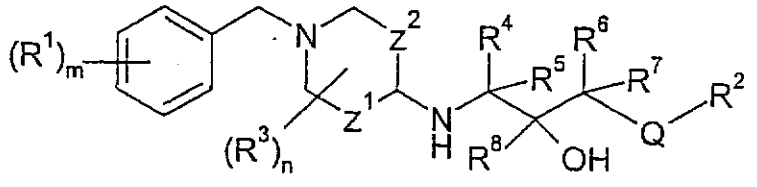
Cells were removed from the flask and washed by centrifugation in RPMI+10%HIFCS+glutamax. The cells were then resuspended at 2x10+7 cells/ml in fresh medium (RPMI+10%HIFCS+glutamax) to which was added calcein-AM (5 µl of stock solution to 1 ml to give a final concentration of $5x10^{-6}$M). After gentle mixing the

cells were incubated at 37°C in a CO_2 incubator for 30 minutes. The cells were then diluted to 50 ml with medium and washed twice by centrifugation at 400xg. Labelled cells were then resuspended at a cell concentration of 1x10+7 cells/ml and incubated with an equal volume of MIP-1α antagonist (10^{-10}M to 10^{-6}M final concentration) for 30 minutes at 37°C in a humidified CO_2 incubator.

Chemotaxis was performed using Neuroprobe 96-well chemotaxis plates employing 8 μm filters (cat no. 101-8). Thirty microlitres of chemoattractant supplemented with various concentrations of antagonists or vehicle were added to the lower wells of the plate in triplicate. The filter was then carefully positioned on top and then 25μl of cells preincubated with the corresponding concentration of antagonist or vehicle were added to the surface of the filter. The plate was then incubated for 2 hours at 37°C in a humidified CO_2 incubator. The cells remaining on the surface were then removed by adsorption and the whole plate was centrifuged at 2000 rpm for 10 minutes. The filter was then removed and the cells that had migrated to the lower wells were quantified by the fluorescence of cell associated calcein-AM. Cell migration was then expressed in fluorescence units after subtraction of the reagent blank and values were standardized to % migration by comparing the fluorescence values with that of a known number of labelled cells. The effect of antagonists was calculated as % inhibition when the number of migrated cells were compared with vehicle.

CLAIMS

1. A compound of general formula



(I)

wherein

m is 0, 1, 2 or 3;

each R^1 independently represents halogen, cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-NR^9R^{10}$, C_3-C_6 cycloalkylamino, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonylamino, sulphonamido, C_1-C_6 alkylsulphonyl, $-C(O)NR^{11}R^{12}$, $-NR^{13}C(O)-(NH)_pR^{14}$, phenyl, or C_1-C_6 alkyl optionally substituted by carboxyl or C_1-C_6 alkoxycarbonyl;

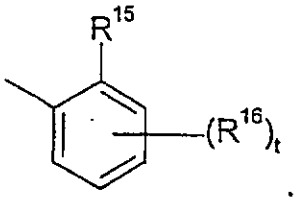
p is 0 or 1;

Z^1 represents a bond or a group $(CH_2)_q$ where q is 1 or 2;

Z^2 represents a bond or a group CH_2, with the proviso that Z^1 and Z^2 do not both simultaneously represent a bond;

Q represents an oxygen or sulphur atom or a group CH_2 or NH;

R^2 represents a group



;

n is 0, 1 or 2;

each R^3 independently represents a C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, $-CH_2OH$ or carboxyl group;

R^4, R^5, R^6 and R^7 each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^4, R^5, R^6 and R^7 together represent a C_1-C_4 alkylene chain linking the two carbon atoms to which they are attached to form a 4- to 7-membered saturated carbocycle, or R^5, R^6 and R^7 each represent a hydrogen atom and R^4 and R^8 together with the carbon atoms to which they are attached form a 5- to 6-membered saturated carbocycle;

R^8 represents a hydrogen atom, a C_1-C_6 alkyl group or is linked to R^4 as defined above;

R^9 and R^{10} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{11} and R^{12} each independently represent a hydrogen atom or a C_1-C_6 alkyl group optionally substituted by C_1-C_6 alkoxycarbonyl;

R^{13} represents a hydrogen atom or a C_1-C_6 alkyl group;

R^{14} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by carboxyl, C_1-C_6 alkoxy or C_1-C_6 alkoxycarbonyl;

R^{15} represents carboxyl, C_1-C_6 alkoxy, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxycarbonylC_1-C_6 alkyl or a group $-NR^{17}R^{18}$, $-NHSO_2CH_3$, $-C(O)NR^{17}R^{18}$, $-NHC(O)NR^{17}R^{18}$, $-OC(O)NR^{17}R^{18}$, $-OCH_2C(O)NR^{17}R^{18}$, $-NHC(O)OR^{19}$ or $-NHC(O)R^{20}$;

t is 0, 1, 2 or 3;

each R^{16} independently represents halogen, cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-NR^{21}R^{22}$, C_3-C_6 cycloalkylamino, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonylamino, sulphonamido, C_1-C_6 alkylsulphonyl, $-C(O)NR^{23}R^{24}$, $-NR^{25}C(O)(NH)_vR^{26}$, phenyl, or C_1-C_6 alkyl optionally substituted by carboxyl or C_1-C_6 alkoxycarbonyl;

R^{17} and R^{18} each independently represent a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by carboxyl or C_1-C_6 alkoxycarbonyl, or R^{17} and R^{18} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{19} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by carboxyl or C_1-C_6 alkoxycarbonyl;

R^{20} represents a group C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, adamantyl, C_5-C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one heteroatom selected from nitrogen, oxygen and sulphur, each of which may be optionally substituted by one or more substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, phenyl and -NHC(O)-R^{27};

R^{21} and R^{22} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{23} and R^{24} each independently represent a hydrogen atom or a C_1-C_6 alkyl group optionally substituted by C_1-C_6 alkoxycarbonyl;

v is 0 or 1;

R^{25} represents a hydrogen atom or a C_1-C_6 alkyl group;

R^{26} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by carboxyl, C_1-C_6 alkoxy or C_1-C_6 alkoxycarbonyl; and

R^{27} represents a C_1-C_6 alkyl, amino (-NH_2) or phenyl group;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein m is 1 or 2.

3. A compound according to claim 2, wherein each R^1 represents a halogen atom.

4. A compound according to any one of claims 1 to 3, wherein Q represents an oxygen atom.

5. A compound according to any one of claims 1 to 4, wherein R^{15} represents a group -NHC(O)R^{20}.

6. A compound according to claim 5, wherein, in R^{20}, the saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one heteroatom selected from nitrogen, oxygen and sulphur, is pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl or pyridinyl.

7. A compound according to any one of claims 1 to 6, wherein each R^{16} independently represents halogen, cyano, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 haloalkyl, C_1-C_4 alkylcarbonyl, phenyl or C_1-C_4 alkyl.

8. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in claim 1 being selected from:

N-[2-(3-{[1-(3,4-dichlorobenzylpiperidinyl]aminohydroxypropoxy)phenyl]acetamide,

N-[5-chloro-2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]acetamide,

N-[2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-methylphenyl]acetamide,

N-[4-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)[1,1'-biphenyl]-3-yl]acetamide,

N-[3-acetyl-2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-methylphenyl]acetamide,

N-[2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-fluorophenyl]acetamide,

N-[2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-fluorophenyl]acetamide,

N-[2-(3-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-cyanophenyl]acetamide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]-acetamide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amin0}-hydroxypropoxy)phenyl]-isobutyramide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]-2-2-dimethyl-propiomanide,

N-[5-chloro-2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]acetamide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-methylphenyl]acetamide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-methylphenyl]acetamide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-fluorophenyl]acetamide,

N-[2-(3-{[1-(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-5-cyanophenyl]acetamide,

N-(2-{[(2S)-3-({-[(4-Chlorophenyl)methyl]-4-piperidinyl}amino)-2-hydroxypropyl]oxy}phenyl)acetamide bi(trifluoroacetate),

N-(2-{(2R)-3-[1-(4-Chloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide,

N-(2-{[3-({1-[(4-Chlorophenyl)methyl]-4-piperidinyl}amino)-2-hydroxy-2-methylpropyl]oxy}phenyl)acetamide,

N-(2-{(2S)-3-[1-(4-Chloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide,

N-{2-[((2S)-3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropyl)oxy]phenyl}acetamide,

N-{2-[((2S)-3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropyl)oxy]-4-fluorophenyl}acetamide,

N-{4-fluoro-2-[((2S)-3-{[1-(4-fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropyl)oxy]phenyl}acetamide,

N-{2-[((2S)-3-{[(3S)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxypropyl)oxy]-4-fluorophenyl}acetamide,

N-{2-[((2S)-3-{[(3R)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxypropyl)oxy]-4-fluorophenyl}acetamide,

N-[2-(3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]acetamide,

N-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)-4-fluorophenyl]acetamide,

N-[4-Fluoro-2-(3-{[1-(4-fluorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]acetamide,

N-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-methylphenyl]acetamide,

N-[2-(3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-methylphenyl]acetamide,

N-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide,

N-[2-(3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide,

N-[2-(3-{[(3S)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide,

N-[2-(3-{[(3R)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide,

N-[2-(3-{[1-(4-Bromobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]benzamide,

N-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]benzamide,

N-[2-(3-{[1-(4-Fluorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]benzamide,

N-[2-(3-{[(3R)-1-(4-Chlorobenzyl)pyrrolidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]benzamide,

N-[2-(3-{[1-(4-Bromobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)phenyl]benzamide,

N-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-methoxyphenyl]acetamide,

N-[2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-6-fluorophenyl]acetamide,

N-[2-Fluoro-6-(3-{[1-(4-fluorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)phenyl]acetamide,

2-(3-{[1-(4-Chlorobenzyl)-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)-N-methylbenzamide,

N-(2-{3-[1-(3,4-Dichloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-benzamide,

N-(2-{3-[1-(3-Chloro-4-fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-benzamide,

N-(2-{3-[1-(3,4-Difluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-benzamide,

N-(2-{3-[1-(3,4-Dichloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-6-methyl-phenyl)-acetamide,

N-(2-{3-[1-(4-Fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-6-methyl-phenyl)-acetamide,

N-(2-{3-[1-(4-Bromo-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide,

N-(2-{3-[1-(3,4-Dichloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide,

N-(2-{3-[1-(3-Chloro-4-fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide,

N-(2-{3-[1-(3,4-Difluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-2-methyl-propoxy}-phenyl)-acetamide,

2-{3-[1-(4-Bromo-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-N-methyl-benzamide,

2-{3-[1-(3,4-Dichloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-N-methyl-benzamide,

2-{3-[1-(4-Chloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-N-methyl-benzamide,

2-{3-[1-(4-Fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-N-methyl-benzamide,

3,5-Dimethyl-1H-pyrrole-2-carboxylic acid (2-{3-[1-(4-bromo-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-amide,

3,5-Dimethyl-1H-pyrrole-2-carboxylic acid (2-{3-[1-(3-chloro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-amide,

3,5-Dimethyl-1H-pyrrole-2-carboxylic acid (2-{3-[1-(3-fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[1-(4-Bromo-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-acetamide,

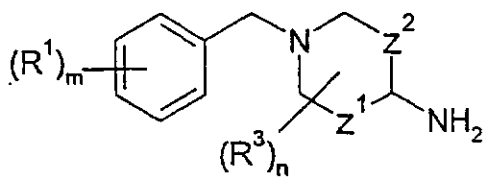
N-(2-{3-[1-(3-Chloro-4-fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-acetamide,

N-(2-{3-[1-(3,4-Difluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-acetamide, and

N-(2-{3-[1-(4-Fluoro-benzyl)-piperidin-4-ylamino]-2-hydroxy-propoxy}-phenyl)-acetamide.

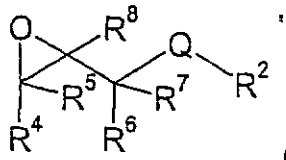
9. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises,

(a) reacting a compound of general formula



(II)

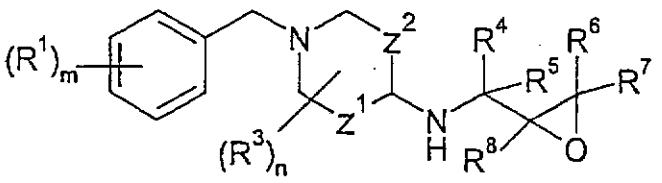
wherein m, n, Z^1, Z^2, R^1 and R^3 are as defined in formula (I), with a compound of general formula



(III)

wherein Q, R^2, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I); or

(b) reacting a compound of general formula



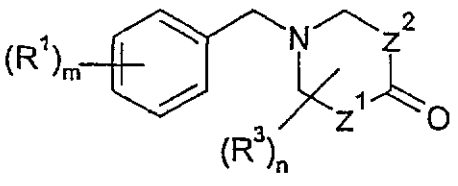
(IV)

wherein m, n, Z^1, Z^2, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I), with a compound of general formula

$$L^1 - Q - R^2 \quad (V)$$

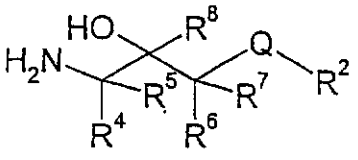
wherein L^1 represents a hydrogen atom or a leaving group and Q and R^2 are as defined in formula (I); or

(c) reacting a compound of general formula



(VI)

wherein m, n, Z^1, Z^2, R^1 and R^3 are as defined in formula (I), with a compound of general formula



(VII)

wherein Q, R^2, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I);

and optionally after (a), (b) or (c) converting the compound of formula (I) to a further compound of formula (I) and/or forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

10. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

11. A process for the preparation of a pharmaceutical composition as claimed in claim 10 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 with a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 for use in therapy.

13. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in therapy.

14. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

15. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in treating rheumatoid arthritis.

16. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in treating chronic obstructive pulmonary disease.

17. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in treating asthma.

18. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in treating multiple sclerosis.