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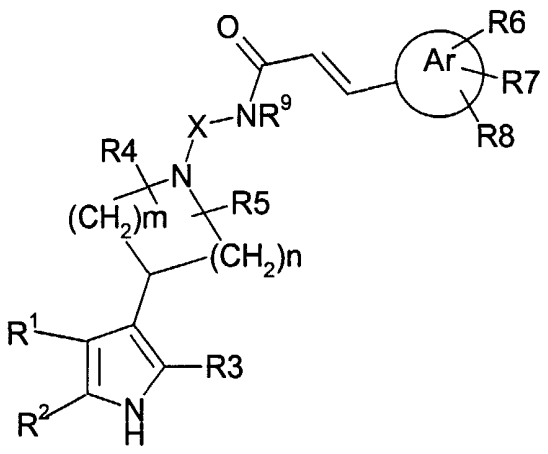
(54) Title: 3-SUBSTITUTED INDOELS OR FUSED PYRROLES AS ANTAGONISTS OF THE CHEMOKINE MCP-1 (CCR2B) RECEPTOR

(57) Abstract: Compounds of the formula (I) are antagonists of the chemokine MCP-1 (CCR2B) receptor and are of use in treating in inflammatory conditions with monocyte and/or lymphocyte involvement.



(I)

WO 02/079151 A1

3-SUBSTITUTED INDOLES OR FUSED PYRROLES AS ANTAGONISTS OF THE CHEMOKINE MCP-1 (CCR2B) RECEPTOR

The present invention relates to a novel class of 3-substituted indoles or fused pyrroles which are antagonists of the chemokine MCP-1 (CCR2B) receptor, processes for their preparation and their use in therapy.

Chemokines are structurally and functionally related 8 to 10 kD polypeptides, involved in the recruitment of white blood cells into areas of inflammation and their subsequent activation (Miller, M.D. and Krangel, M.S. (1992) *Crit. Rev. Immunol.* **12**, 17-46; Baggiolini, M., Dewald, B. and Moser, B.(1994) *Adv. Immunol.* **55**, 97-179). In addition, some chemokines are able to regulate the proliferative potential of hematopoietic progenitor cells, endothelial cells and certain types of transformed cells (Oppenheimer, J.J., Zachariae, C.O.C., Mukaida, N., and Matsushima, K. (1991) *Ann. Rev. Immunol.* **9**, 617-648; Schall, T.J. (1991) *Cytokine* **3**, 165-183). Based on whether the first two cysteine moieties are separated by one amino acid residue or are adjacent, chemokines belong to the α- or CXC chemokine family (e.g interleukin IL-8 or the β- or CC chemokine family (e.g. RANTES and MCP-1).

More recently, two further classes of chemokines have been discovered: the C chemokine family exemplified by lymphotactin (Science, 1994, 266, 1395-1399) and the CX3C chemokine family exemplified by fractalkine/neurotactin (Nature, 1997, 385, 640-44 and Nature, 1997, 387, 611-17)

Chemokines play a key role in the accumulation of various cell types, including neutrophils, monocytes, T-lymphocytes, basophils and fibroblasts at sites of inflammation. These chemokines are implicated in both acute and chronic inflammatory disease states, including rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, asthma, restenosis, psoriasis, various respiratory syndromes, for instance asthma and idiopathic pulmonary fibrosis, and also contribute towards modulation of angiogenesis and fibroplasia. Chemokines are also implicated in various infectious diseases including viral, bacterial and parasital infections, stroke, sarcoidosis, chronic contact dermatitis, as well as organ transplant rejection.

Chemokines express their biological responses through interaction with chemokine receptors (Horuk, R. and Peiper, S.C. (1995) *Exp. Opin. Ther. Patents* **5**, 1185-1200). Several chemokine receptors have already been cloned, for instance, the following human CXC chemokine receptors:

(a) the receptors for IL8 (CXCR1) and IL8/ELR chemokines, (CXCR2, Holmes, W.E., Lee, J., Kuang, W.J., Rice, G.C. and Wood, W.I. (1991) *Science* **253**, 1278-1280; Murphy, P.M. and Tiffany, H.L. (1991) *Science* **253**, 1280-1283);

(b) a receptor for IP10/Mig (CXCR3, Loetscher, M., Gerber, B., Loetscher, P., Jones, S.A., Piali, L., Clark-Lewis, I., Baggiolini, M., and Moser, B. (1996) J. Exp. Med. 184, 963-969.); and

(c) a receptor for SDF-1 (CXCR4 or LESTR, Bleul, C.C., Farzan, M., Choe, H., Parolin, C., Clark-Lewis, I., Sodroski, J., Springer, T.A. (1996) Nature, 382, 829-836.)

In addition, the following human CC chemokine receptors have also been cloned:

(a) MIP-1α/RANTES receptor (CCR-1, Neote, K., Digregorio, D., Mak,J.K., Horuk, R. and Schall, T.J. (1993) *Cell* **72**, 415-425; Gao, B. J-L., Kuhns, D.B., Tiffany, H.L., McDermott, D., Li, X., Francke, U. and Murphy, P.M. (1993) *J. Exp. Med.* **177**, 1421-1427);

(b) MCP-1A and B receptors (CCR-2A and B, Charo, I.F., Myers, S.J., Herman, A., Franci, C., Connolly, A.J. and Coughlin, S.R. (1994) *Proc. Natl. Acad. Sci. USA* **91**, 2752-2756; Yamagami, S., Tokuda, Y., Ishii, K., Tanaka, T. and Endo, N. (1994) *Biochem. Biophys. Res. Commun.* **202**, 1156-1162);

(c) the eotaxin/RANTES receptor (CCR-3, Combadiere, C., Ahuja, S.K. and Murphy, P.M. (1995) *J. Biol. Chem.* **270**, 16491-16494; Daugherry, D.L., Siciliano, S.J., DeMartino, J.A., Malkowitz, L., Sirotina, A. and Springer, M.S. (1996) *J.Exp.Med.* **183**, 2349-2354; Kitaura, M., Nakajima, T., Imai, T., Harada, S., Combadiere, C., Tiffany, H.L., Murphy, P.M. and Yoshie, O. (1996) *J. Biol Chem.* **271**, 7725-7730);

(d) the promiscuous receptor on basophils (CCR-4, Power, C.A., Meyer, A., Nemeth, K., Bacon, K.B., Hoogewerf, A.J., Proudfoot, A.E.I. and Wells, T.N.C. (1995) *J. Biol. Chem.* **270**, 19495-19500);

(e) a new MIP-1α/MIP-1β/RANTES receptor (CCR-5, Samson, M., Labbe, O., Mollereau, C., Vassart, G. and Parmentier, M. (1996) *Biochemistry* **35**, 3362-3367.);

(f) a new receptor for LARC (CCR6, Baba, M., Imai, T., Nishimura, M., Kakizaki, M., Takagi, S., Hieshima, Nomiyuki, H., and Yashie, O. (1997) J. Biol Chem. 272, 14893-14898.);

(g) a new receptor for ELC/exodus3 (CCR7, Yoshida, R., Imai, T., Hieshima, K., Kusuda, J., Baba, M., Kitaura, M., Nishimura, M., Kakizaki, M., Nomiyama, H., and Yoshie, O. (1997) J. Biol. Chem. 272, 13803-13809.); and

(h) a new receptor for I-309 (CCR8, Samson, M., Stordeur, P., Labbe, O., Soularue, P., Vassart, G., and Parmentier, M. (1997) Eur. J. Immunol. 26, 3021-3028; Tiffany, HL, Lautens, LL, Gao,J-L, Pease, J., Locati, M., Combadiere, C., Modi, W., Bonner, T.I. and Murphy, P.M. (1997) *J Exp. Med.* **186**, 165-170; Stuber-Roos, R., Loetscher, M., Legner,

D.F., Clark-Lewis, I., Baggiolini, M. and Moser, B. (1997) J. Biol. Che. 272, 17251-17254).

Recently the receptor for the newly described CX3C chemokine, fractalkine/neurotactin, has also been identified (Imai, T., Hieshima, K., Haskell, C., Baba, M., Nagira, M., Nishimura, M., Kakizaki, M., Takagi, S., Nomiyama, H., Schall, T.J., Yoshie, O. (1997) Cell 91, 521-530.).

Chemokine receptors belong to the group of 7 transmembrane (7TM) spanning receptors and their signal transduction pathway involves pertussus toxin-sensitive G-protein and a rise in $[Ca^{2+}]_i$. Although details about the molecular events are still incomplete, a complex array of intracellular signals ultimately lead to leukocyte activation and chemotaxis (Premack, B.A. and Schall, T.J. (1996) Nature Medicine 2, 1174-1178).

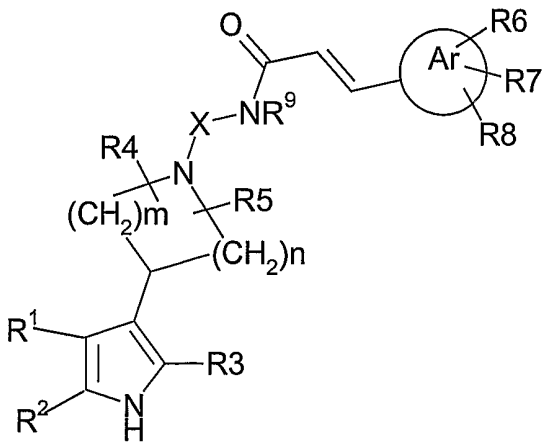
Chemokine receptors are divided into at least three sub-families, the CXC chemokine receptors (CXCR), the CC chemokine receptors (CCR) and the CX3CR, based on their selectivity for either CXC, CC, CX3C chemokines. Ligand cross-selectivity, that is CXCRs that bind CC chemokines or *vice versa*, is not observed. Chemokine receptors consist of 350-368 amino acids and the sequence identity amongst members of the receptor sub-families varies widely, from about 36-77%. Most chemokine receptors recognise more than one chemokine and many chemokines, including IL-8, RANTES, MIP-1α and the MCPs, bind to more than one receptor (Roos *et al*, J Biol Chem, 1997, 272 (28), 17521).

EP-A-0 324 431 (Fujisawa Pharm KK) describes a group of N-substituted indolyl-piperidine derivatives having anti-allergic activity. The N substituent is A-NH-CO-B-R_1 in which R_1 is aryl substituted by optionally protected hydroxy, halo and /or lower alkoxy, A is lower alkylene and B is lower alkylene. In exemplified compounds, A is CH_2CH_2 whilst B is generally butadienyl.

A class of MCP-1 receptor antagonists has recently been disclosed (WO 98/06703, Warner Lambert).

We have now found a new class of indole compounds that are MCP-1 (CC2RB) receptor antagonists.

Accordingly, the present invention provides a compound of the formula (I):



(I)

in which:

Ar is an aryl or heteroaryl group;

R1 and R2 form the residue of a 5 to 7 membered monocyclic heteroaryl ring comprising from one to three hetereoatoms selected from O, S, N and optionally substituted with one or two substitutents which may be the same or different and selected from the group consisting of halogen, cyano, (C_1-$_6$)alkyl, (C_3-$_7$)cycloalkyl, (C_1-$_6$)alkoxy, halo(C_1-$_6$)alkyl, hydroxy, oxo, amino, mono- or di-(C_1-$_6$)alkylamino, acylamino, nitro, carboxy, (C_1-$_6$)alkoxycarbonyl, (C_1-$_6$)alkenyloxycarbonyl, (C_1-$_6$)alkoxycarbonyl(C_1-$_6$)alkyl, carboxy(C_1-$_6$)alkyl, (C_1-$_6$)alkylcarbonyloxy, carboxy(C_1-$_6$)alkyloxy, (C_1-$_6$)alkoxycarbonyl(C_1-$_6$)alkoxy, (C_1-$_6$)alkylthio, (C_1-$_6$)alkylsulphinyl, (C_1-$_6$)alkylsulphonyl, sulphamoyl, mono- and di-(C_1-$_6$)-alkylsulphamoyl, carbamoyl, mono- and di-(C_1-$_6$)alkylcarbamoyl, (C_1-$_6$)alkylsulphonamido, arylsulphonamido, aryl, aryl(C_1-$_6$)alkyl, aryl(C_1-$_6$)alkoxy, aryloxy and heterocyclyl; or

R1 and R2 form the residue of a benzene ring which is optionally substituted with one or two substitutents which may be the same or different are selected from the group consisting of hydrogen, halogen, cyano, (C_1-$_6$)alkyl, (C_3-$_7$)cycloalkyl, (C_1-$_6$)alkoxy, halo(C_1-$_6$)alkyl, hydroxy, amino, mono- or di-(C_1-$_6$)alkylamino, acylamino, nitro, carboxy, (C_1-$_6$)alkoxycarbonyl, (C_1-$_6$)alkenyloxycarbonyl, (C_1-$_6$)alkoxycarbonyl(C_1-$_6$)alkyl, carboxy(C_1-$_6$)alkyl, (C_1-$_6$)alkylcarbonyloxy, carboxy(C_1-$_6$)alkyloxy, (C_1-$_6$)alkoxycarbonyl(C_1-$_6$)alkoxy, (C_1-$_6$)alkylthio, (C_1-$_6$)alkylsulphinyl, (C_1-$_6$)alkylsulphonyl, sulphamoyl, mono- and di-(C_1-$_6$)-alkylsulphamoyl, carbamoyl, mono- and di-(C_1-$_6$)alkylcarbamoyl, (C_1-$_6$)alkylsulphonamido, arylsulphonamido, aryl, aryl(C_1-$_6$)alkyl, aryl(C_1-$_6$)alkoxy, aryloxy and heterocyclyl;

R3 is hydrogen or $C_{(1-6)}$alkyl;

R4 and R5 which may be the same or different are hydrogen or $C_{(1-6)}$alkyl, or together with the carbon atoms of the ring to which they are attached form a bridging 5- to 7 - membered ring;
R6, R7 and R8 which may be the same or different are selected from the group consisting of hydrogen, halogen, cyano, (C_1-6)alkyl, (C_3-7)cycloalkyl, (C_1-6)alkoxy, halo(C_1-6)alkyl, hydroxy, amino, mono- or di-(C_1-6)alkylamino, acylamino, nitro, carboxy, (C_1-6)alkoxycarbonyl, (C_1-6)alkenyloxycarbonyl, (C_1-6)alkoxycarbonyl(C_1-6)alkyl, carboxy(C_1-6)alkyl, (C_1-6)alkylcarbonyloxy, carboxy(C_1-6)alkyloxy, (C_1-6)alkoxycarbonyl(C_1-6)alkoxy, (C_1-6)alkylthio, (C_1-6)alkylsulphinyl, (C_1-6)alkylsulphonyl, sulphamoyl, mono- and di-(C_1-6)-alkylsulphamoyl, carbamoyl, mono- and di-(C_1-6)alkylcarbamoyl, (C_1-6)alkylsulphonamido, arylsulphonamido, aryl, aryl(C_1-6)alkyl, aryl(C_1-6)alkoxy, aryloxy and heterocyclyl, or two adjacent substituents may form $C_{(1-3)}$alkylidenedioxy;
m and n are each integers from 1 to 3;
R9 is H, (C_1-6)alkyl or aryl(C_1-4)alkyl; and
X is a group $(CH_2)_pY(CH_2)_q$ in which Y is $C_{(3-7)}$cycloalkylene, $-C_6H_4-$ (phenylene) or heteroarylene in which each of $(CH_2)_p$, $(CH_2)_q$ may be optionally substituted by (C_1-6)alkyl and Y may be optionally substitued and p and q are each independently 0, 1 or 2; or
a pharmaceutically acceptable salt thereof.

Compounds of the formula (I) are antagonists of the MCP-1 (CC2RB) receptor and also inhibit MCP-1 stimulated chemotaxis in monocytes. They are therefore believed to be of use in the treatment of inflammatory diseases with monocyte and/or lymphocyte involvement such as atherosclerosis and arthritis.

Preferably, R1 and R2 form the residue of a benzene ring, optionally having a 5-hydroxy substituent.

Preferably, R3 is hydrogen.

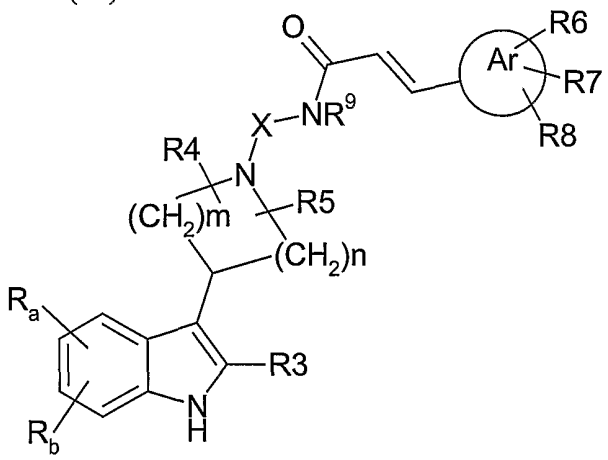
Preferably, R4 and R5 are each hydrogen or R4 and R5 are joined together to form a five membered ring, to give a tropane moiety.

Representative values for n include 1 and 2 and for m include 2. Preferably m and n are each 2, to form a piperidinyl ring.

Representative values of Y include cyclopropylene, *cis* and *trans*-1,4-cyclohexylene, *cis* and *trans*-1,3-cyclohexylene, 1,4- and 1,3-phenylene.

Representative values of Ar include phenyl, naphthyl, furanyl, pyridyl, oxazolyl and indolyl. Preferably Ar is substituted phenyl.

It will be appreciated from the foregoing that a preferred class of compounds of formula (I) are those of formula (IA):



(IA)

in which Ar, R3 to R9, m, n and X are as hereinbefore defined and
R_a and R_b which may be the same or different are selected from the group consisting of hydrogen, halogen, cyano, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, amino, mono- or di-(C_{1-6})alkylamino, acylamino, nitro, carboxy, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkenyloxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, carboxy(C_{1-6})alkyl, (C_{1-6})alkylcarbonyloxy, carboxy(C_{1-6})alkyloxy, (C_{1-6})alkoxycarbonyl(C_{1-6})alkoxy, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, sulphamoyl, mono- and di-(C_{1-6})-alkylsulphamoyl, carbamoyl, mono- and di-(C_{1-6})alkylcarbamoyl, (C_{1-6})alkylsulphonamido, arylsulphonamido, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryloxy and heterocyclyl;
R3 is hydrogen or $C_{(1-6)}$alkyl.
When used herein, the term "alkyl" and similar terms such as "alkoxy" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the term "aryl" includes, unless otherwise defined, phenyl or naphthyl optionally substituted with up to five, preferably up to three substituents.

Suitable substituents for an aryl group include, for example, and unless otherwise defined, halogen, cyano, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy,

amino, mono- or di-(C_{1-6})alkylamino, acylamino, nitro, carboxy, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkenyloxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, carboxy(C_{1-6})alkyl, (C_{1-6})alkylcarbonyloxy, carboxy(C_{1-6})alkyloxy, (C_{1-6})alkoxycarbonyl(C_{1-6})alkoxy, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, sulphamoyl, mono- and di-(C_{1-6})-alkylsulphamoyl, carbamoyl, mono- and di-(C_{1-6})alkylcarbamoyl, (C_{1-6})alkylsulphonamido, arylsulphonamido, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy and heterocyclyl.

When used herein, the term "heterocyclyl" or "heterocyclic" includes single or fused aromatic or non-aromatic rings comprising up to four hetero-atoms in the ring selected from oxygen, nitrogen and sulphur and optionally substituted with up to three substituents. Suitably the heterocyclic ring comprises from 4 to 7, preferably 5 to 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring.

When used herein, the term "heteroaryl" includes an aromatic heterocyclic ring or ring system, preferably with 5 or 6 ring atoms on each ring.

When substituted, a heterocyclyl group may have up to three substituents. Suitable such substituents include those previously mentioned for an aryl group as well as oxo.

When used herein, the terms "halogen" and "halo" include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

Pharmaceutically acceptable salts may be formed from inorganic and organic acids. Representative examples thereof include maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

It will be appreciated that certain compounds of the present invention may comprise one or more chiral centres so that compounds may exist as stereoisomers, including diastereoisomers and enantiomers. The present invention covers all such stereoisomers, and mixtures thereof, including racemates. In particular, the present invention also covers both Z and E-diasteroisomers arising from the double bond of the cinnamide moiety of compounds of formula (I).

Since the compounds of the present invention, in particular compounds of formula (I), are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of formula (I) may be used for preparing the more pure forms used in the pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are obtained in crystalline form.

When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all polymorphic forms of the compounds of formula (I).

Preferred compounds of formula (I) include:
cis-(E)-3-(3,4-Dichlorophenyl)-N-{4-[4-[(1H-indol-3-yl)piperidin-1-yl]methyl]cyclohex-1-yl}acrylamide;
trans-(E)-3-(3,4-Dichlorophenyl)-N-{4-[4-[(1H-indol-3-yl)piperidin-1-yl]methyl]cyclohex-1-yl}acrylamide;
exo-cis-(E)-3-(3,4-Dichlorophenyl)-N-{4-[3-(1H-indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-cyclohexyl}acrylamide; and
cis-(E)-3-(3,4-Dichlorophenyl)-N-{4-[4-(1H-5-hydroxyindol-3-yl)piperidin-1-yl]cyclohex-1-yl} acrylamide.

Compounds of the present invention are antagonists of the MCP-1 (CC2RB) receptor and also inhibit MCP-1 stimulated chemotaxis in monocytes. As such they are expected to be of use in therapy, in particular in the treatment of inflammatory conditions with monocyte and/or lymphocyte involvement, for instance inflammatory diseases such as arthritis and osteoarthritis, and diseases with a clear inflammatory component such as atherosclerosis and stroke. Accordingly, in a further aspect, the present invention provides a compound of formula (I) for use in therapy.

Further diseases which may be treatable with compounds of the present invention include, for instance, psoriasis, chronic contact dermatitis, inflammatory bowel disease, multiple sclerosis, sarcoidosis, idiopathic pulmonary fibrosis, dermatomyositis, skin pemphigoid and related diseases, glomerulonephritis, vasculitis, hepatitis, diabetes, allograft rejection, graft-versus-host diseases, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, and acute and chronic inflammation.

Compounds of the present invention may also be used to inhibit the entry of human immunodeficiency virus (HIV) into monocytes and lymphocytes , thereby having a therapeutic role in the treatment of AIDS.

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides, in a further aspect, a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

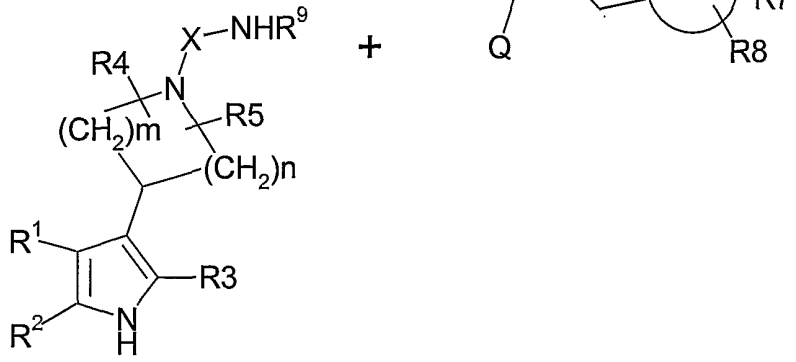
Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository. The compounds of formula (I) which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges. A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent. A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose. A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule. Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration. A typical suppository formulation comprises a compound of formula (I) which is active when administered in this way, with a binding

and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats. Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 500 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I).

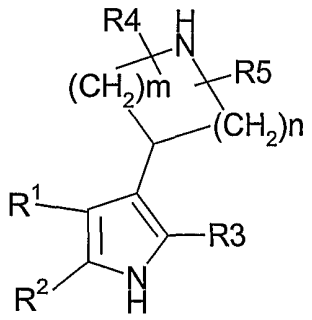
The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I), the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

Compounds of formula (I) may be prepared from convenient starting materials by adapting synthetic procedures well known in the art. Preferably, the final stage involves the formation of an amide bond between a compound of formula (II) and a compound of formula (III):



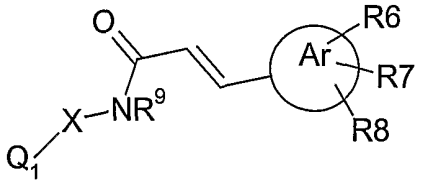
(II) (III)

in which R1 to R9, X, n and m are as hereinbefore defined and Q is hydroxyl or a leaving group such as chloride; or
alkylating or reductively alkylating the nitrogen of the central ring of a compound of formula (IV) with a compound of formula (V):



(IV)

+



(V)

in which R1 to R9, X, n and m are as hereinbefore defined and Q_1 is a leaving group such as chloride, bromide or methanesulphonate, or Q_1 is part of an aldehyde function attached to the terminal carbon of X.

Amide bond forming conditions are well known in the art and include reaction of the amine with an appropriate acid chloride in an inert solvent such as dichloromethane, optionally in the presence of a base such as triethylamine. Alternatively, the amine may be coupled directly with an appropriate carboxylic acid using a carbodi-imide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide.

Alkylation conditions are well known in the art and include reaction of the amine with an appropriate alkylating agent in an inert solvent such as dimethylformamide, optionally with heating and optionally in the presence of an organic base such as triethylamine or an inorganic base such as sodium hydrogen carbonate.

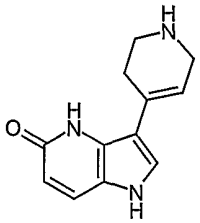
Reductive alkylation conditions are well known in the art and include reaction of the amine with an appropriate aldehyde in the presence of a reducing agent, such as sodium triacetoxyborohydride, in an inert solvent such as dichloromethane.

Compounds of formulae (II) and (IV) are either commerically available or can be made from readily available precursors by using standard synthetic methodology, see for instance, Arz Forsch. 1985, 272. It will be appreciated that compounds of formula (II) may be readily obtained from compounds of formula (IV) by the alkylation thereof with an appropriate alkylating agent QXN* in which Q is a leaving group as hereinbefore defined and N* is a protected amine or a group transformable into an amine, for instance phthalimide, or by reductive alkylation with Q1XN*, where Q1 is part of an aldehyde function attached to the terminal carbon of X.

Compounds of formula (III) are derivatives of (substituted) cinnamic acid which are commercially available or can be readily made using standard methodology (Comprehensive Organic Chemistry, vol 1, 1132). Compounds of formula (V) may be obtained by treating a compound of formula (III) with an appropriate amine $Q'XNH_2$ under amide bond forming conditions, as hereinbefore described in which Q' is a leaving group as hereinbefore described or a group convertible to a leaving group, or aldehyde.

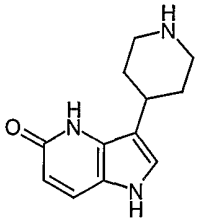
The following Description and Examples illustrate the present invention.

Description 1. 3-(1, 2, 5, 6)-Tetrahydropyrid-4-yl-1,4-dihydro-pyrrolo[3,2-b]pyrid-5-one (D1)



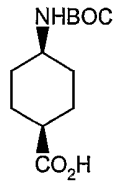
The title compound was prepared according to Macor et al J. Med. Chem. 1990, 2087.

Description 2. 3-Piperidin-4-yl-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one (D2)



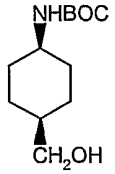
A solution of D1 (1.0 g) in ethanol (50 mL) containing 10% palladium on charcoal (0.4 g) was hydrogenated at 50°C and 50 psi for 18h. The catalyst was then removed by filtration and the solution evaporated to dryness to afford the title compound D2 as a foam (1.1 g) which was used immediately in the next step.

Description 3. cis-4-tert-Butoxycarbonylamino-1-cyclohexane carboxylic acid (D3)



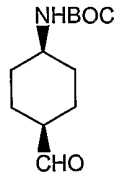
cis-4-amino-1-cyclohexane carboxylic acid (10g) was dissolved in 2M aqueous sodium hydroxide solution (100mL) and dioxane (100mL) and then a solution of Boc anhydride (18.75g) added. The solution was stirred vigorously for 5h and acidified to pH *ca* 4 with dil. HCl. This was extracted with ethyl acetate (3x), the latter dried over $MgSO_4$ and concentrated in vacuo to afford the title compound (20g).

Description 4. *cis*-1-(tert-butoxycarbonylamino)-4-hydroxymethyl cyclohexane (D4)



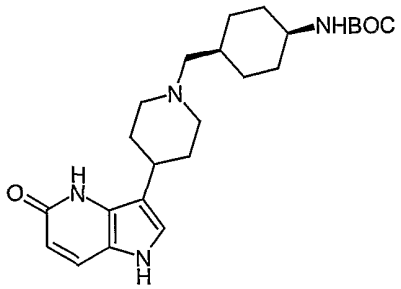
To a stirred solution of *cis*-4-tert-butoxycarbonylamino-1-cyclohexane carboxylic acid (5g) in THF (100mL), under argon, was added dropwise a solution of borane-methyl sulphide complex (3.9mL). This was stirred at room temperature for 30min and then methanol added. The mixture was concentrated and the residue chromatographed on silica using 20-100% ethyl acetate/hexane as eluant. The resulting solid was recrystallised from ethyl acetate/hexane to afford the title compound (2.4g).

Description 5. *cis*-1-(tert-butoxycarbonylamino)-4-formylcyclohexane (D5)



To a stirred solution of oxalyl chloride (2.4g) in THF (60mL) under argon at -78^0C was added dropwise a solution of DMSO (2.0g) in THF (20mL). After ca 5min. a solution of *cis*-1-(tert-butoxycarbonylamino)-4-hydroxymethyl cyclohexane (2.4g) in THF (20mL) was added dropwise over 5min. After stirring for a further 15min. triethylamine (5.3g) was added and the solution then allowed to warm to 0°C. Water was added and the organic phase concentrated and taken up in ethyl acetate. This was washed with 1M HCl, potassium bicarbonate solution and brine and dried over $MgSO_4$. Concentration in vacuo afforded the title compound (2.4g, 100%).

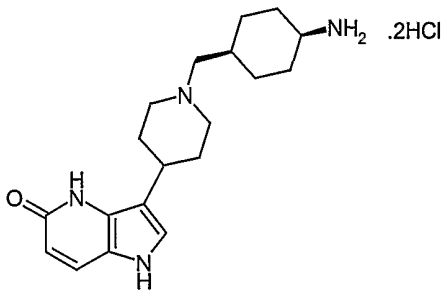
Description 6. cis-{4-[4-(5-Oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)-piperidin-1-ylmethyl]-cyclohexyl}-carbamic acid tert-butyl ester (D6)



A mixture of the piperidine D2 (3 mM) and the aldehyde D5 (0.67 g) were dissolved in dichloromethane (20 mL) and sodium triacetoxyborohydride (1.06 g) added portionwise.

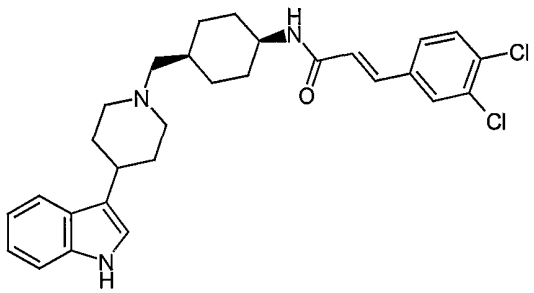
The mixture was stirred for 3h, then poured onto aqueous potassium carbonate and extracted with dichloromethane. Evaporation of the organic layer afforded the title compound D6 (1.1 g). Mass spectrum MH^+ 429

Description 7. cis-3-[1-(4-Amino-cyclohexylmethyl)-piperidin-4-yl]-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one dihydrochloride (D7)



A solution of the BOC compound D6 in ethanolic HCl (25 mL) was stirred at 40 °C for 2h. Evaporation of the solvent afforded the title compound D7 (1.3 g) which was used directly in the preparation of E18.

Example 1: *cis*-(E)-3-(3,4-Dichlorophenyl)-N-{4-[4-[(1H-indol-3-yl)piperidin-1-yl]methyl]cyclohex-1-yl}acrylamide



(a) <u>*cis*-4-tert-Butoxycarbonylamino-1-cyclohexane carboxylic acid</u>

cis-4-amino-1-cyclohexane carboxylic acid (10g) was dissolved in 2M aqueous sodium hydroxide solution (100mL) and dioxane (100mL) and then a solution of Boc anhydride (18.75g) added. The solution was stirred vigorously for 5h and acidified to pH *ca* 4 with dil. HCl. This was extracted with ethyl acetate (3x), the latter dried over $MgSO_4$ and concentrated in vacuo to afford the title compound (20g).

(b) <u>*cis*-1-(tert-butoxycarbonylamino)-4-hydroxymethyl cyclohexane</u>

To a stirred solution of *cis*-4-tert-butoxycarbonylamino-1-cyclohexane carboxylic acid (5g) in THF (100mL), under argon, was added dropwise a solution of borane-methyl sulphide complex (3.9mL). This was stirred at room temperature for 30min and then methanol added. The mixture was concentrated and the residue chromatographed on silica using 20-100% ethyl acetate/hexane as eluant. The resulting solid was recrystallised from ethyl acetate/hexane to afford the title compound (2.4g).

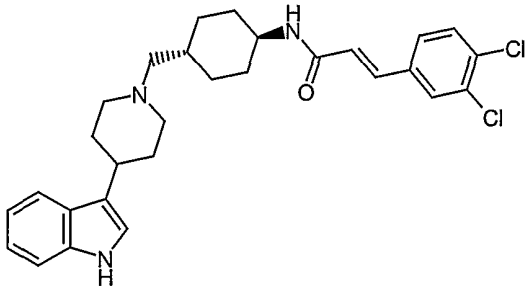
(c) *cis*-1-(tert-butoxycarbonylamino)-4-formylcyclohexane
To a stirred solution of oxalyl chloride (2.4g) in THF (60mL) under argon at -78^0C was added dropwise a solution of DMSO (2.0g) in THF (20mL). After ca 5min. a solution of *cis*-1-(tert-butoxycarbonylamino)-4-hydroxymethyl cyclohexane (2.4g) in THF (20mL) was added dropwise over 5min. After stirring for a further 15min. triethylamine (5.3g) was added and the solution then allowed to warm to 0°C. Water was added and the organic phase concentrated and taken up in ethyl acetate. This was washed with 1M HCl, potassium bicarbonate solution and brine and dried over $MgSO_4$. Concentration in vacuo afforded the title compound (2.4g).

(d) *cis*-1-(tert-butoxycarbonylamino)-4-{4-[(1H-indol-3-yl)piperidin-1-yl]methyl} cyclohexane
To a stirred solution of 4-(indol-3-yl)piperidine (238mg, 1.19mmol) (Arz. Forsch. 1985, 272) and *cis*-1-(tert-butoxycarbonylamino)-4-formylcyclohexane (270mg, 1.19mmol) in dichloromethane (20mL) was added portionwise sodium triacetoxyborohydride (378mg, 1.78mmol). This was stirred at room temperature for 2days, poured into 25% aqueous potassium carbonate solution (100mL) and this extracted with dichloromethane (3x). The combined organic extracts were washed with water, then brine and dried over $MgSO_4$. Concentration in vacuo afforded the title compound (***mg).

(e) *cis*-1-amino-4-{4-[(1H-indol-3-yl))piperidin-1-yl]methyl} cyclohexane To a stirred solution of *cis*-1-(tert-butoxycarbonylamino)-4-{4-[(1H-indol-3-yl)piperidin-1-yl]methyl} cyclohexane (500mg, 1.2mmol) in methanol ((20mL) was added saturated ethanolic HCl (5mL). The solution was heated until effervescence ceased and the solvent removed in vacuo. This was chromatographed on silica gel using 2% methanol/chloroform saturated with ammonia as eluant to afford the title compound (0.27g).

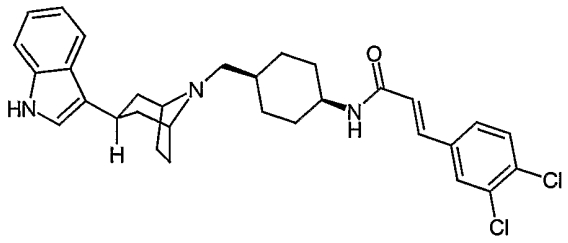
(f) *cis*-(E)-3-(3,4-Dichlorophenyl)-N-{4-[4-[(1H-indol-3-yl)piperidin-1-yl]methyl]cyclohex-1-yl}acrylamide
Under argon, a solution of *cis*-1-amino-4-{4-[(1H-indol-3-yl))piperidin-1-yl]methyl} cyclohexane (242mg, 0.78mmol) in dichloromethane (5mL), containing triethylamine (394mg, 3.9mmol), was added to a stirred solution of 3,4-dichlorocinnamic acid (186mg, 0.86mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (165mg, 0.86mmol), and hydroxybenzotriazole (131mg, 0.86mmol) in dichloromethane (5mL). After stirring overnight at room temperature, the mixture was diluted with dichloromethane (100mL) and washed with 2M aqueous sodium hydroxide solution. The organic layer was dried ($MgSO_4$) and evaporated to dryness. Chromatography of the residue on silica gel using 2% - 5% methanol/chloroform as eluant afforded the title compound (0.13g).

Example 2: *trans*-(E)-3-(3,4-Dichlorophenyl)-N-{4-[4-[(1H-indol-3-yl)piperidin-1-yl]methyl]cyclohex-1-yl}acrylamide



Following the procedures of Example 1(a)-1(f), but starting from *trans*-4-amino-1-cyclohexane carboxylic acid instead of *cis*-4-amino-1-cyclohexane carboxylic acid, the title compound was prepared.

Example 3: exo-cis-(E)-3-(3,4-Dichlorophenyl)-N-{4-[3-(1H-indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-cyclohexyl}acrylamide



(a) 3-(1H-Indol-3-yl)-8-aza-bicyclo[3.2.1]oct-2-ene-8-carboxylic acid tert-butyl ester
To a solution of sodium (1.92 g) in methanol (40 mL) was added indole (1.73 g) followed by commercially available BOC-nortropinone (10 g). The mixture was refluxed under argon for 48h, then cooled to –10°C. Filtration of the precipitate afforded the title compound (2.7 g). Mass spectrum MH^+ 325

(b) Mixture of endo and exo 3-(1H-Indol-3-yl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester
A solution of the compound of example 3(a) (1.9 g) in ethanol (100 mL) was hydrogenated over 10% palladium on charcoal (0.4 g) at 50°C and 50 psi for 18h. Filtration followed by evaporation of the solvent afforded the crude product, which was purified by chromatography on silica using 30% ethyl acetate/hexane as eluent to afford the title compounds as a mixture of isomers (1.2 g). Mass spectrum M^+-H 325

(c) Mixture of endo and exo 3-(8-Aza-bicyclo[3.2.1]oct-3-yl)-1H-indole hydrochloride
The BOC derivative of example 3(b) (1.1 g) was dissolved in ethanolic HCl (20 mL) and the solution stirred for 2h. Evaporation of the solvent afforded the title compounds as a mixture of isomers (1.0 g). Mass spectrum MH^+ 227

(d) Mixture of endo and exo *cis*-{4-[3-(1H-Indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-cyclohexyl}-carbamic acid tert-butyl ester
The tropane derivative of example 3(c) (1.0 g) and *cis*-1-(tert-butoxycarbonylamino)-4-formylcyclohexane (example 1(c)) (0.8 g) were dissolved in dichloromethane (30 mL) and treated with sodium triacetoxyborohydride (1.1 g) portionwise. After 18h additional

aldehyde (0.8 g) and sodium triacetoxyborohydride (1.0 g) were added and solution refluxed for 24h. The mixture was then poured onto aqueous potassium carbonate and extracted with dichloromethane. The organic layer was dried and evaporated to dryness. Chromatography of the residue on silica using 6% methanol/0.6% ammonia/93.4% dichloromethane as eluent afforded the title compounds as a mixture of isomers (0.58 g). Mass spectrum MH^+ 438

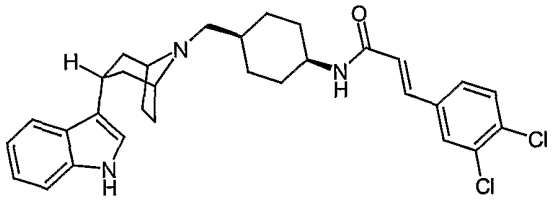
(e) Mixture of endo and exo *cis*-4-[3-(1H-Indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-cyclohexylamine dihydrochloride

The BOC derivative of example 3(d) (0.57 g) was dissolved in ethanolic HCl (10 mL) and stirred at room temperature overnight. Evaporation of the solvent afforded the title compounds as a mixture of isomers (0.6 g). Mass spectrum MH^+ 338

(f) exo-*cis*-(E)-3-(3,4-Dichlorophenyl)-N-{4-[3-(1H-indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-cyclohexyl}acrylamide

The amine of example 3(e) (0.6 g) was dissolved in dichloromethane (5 mL) containing triethylamine (0.85 mL), and treated with a solution of 3,4-dichlorocinnamic acid (0.325 g), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (0.307 g), and hydroxybenzotriazole (0.216 g) in dichloromethane (5 mL). After stirring for 3h at room temperature, the mixture was diluted with dichloromethane and washed with aqueous potassium carbonate. The organic layer was dried and evaporated to dryness. Chromatography of the residue on silica using 6%methanol/0.6% ammonia/93.4% dichloromethane as eluent afforded a mixture of the title compound (exo) and the endo isomer. Preparative HPLC on a Spherisorb column using 0.2% diethylamine/5% dichloromethane/5% methanol/90% hexane afforded the title compound as the faster running component, with the indole substituent equatorial confirmed by 2D NMR studies.

Example 4: endo-*cis*-(E)-3-(3,4-Dichlorophenyl)-N-{4-[3-(1H-indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-cyclohexyl}acrylamide

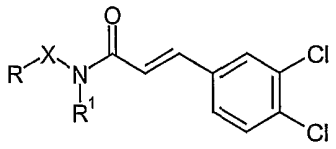


The fractions containing the endo isomer from the procedure of Example 3(f) were concentrated in vacuo to afford the title compound.

Examples 5-13

By analogous procedures to those described for Example 1, using the appropriately substituted indolopiperidine and N-Boc protected amino aldehyde intermediates consistent with the final products, Examples 5-13 were prepared. Where necessary, the required N-Boc protected amino aldehyde intermediates were prepared from appropriate

precursors by analogous procedures to those used for *cis*-1-(tert-butoxycarbonylamino)-4-formylcyclohexane in Example 1.



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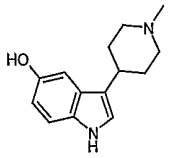
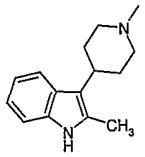
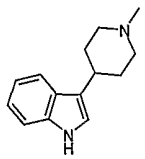
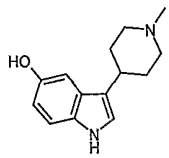
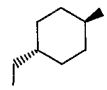
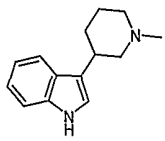
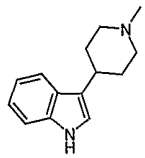
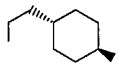
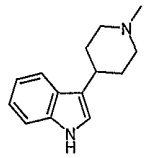
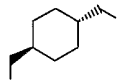
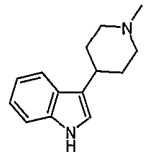
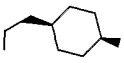
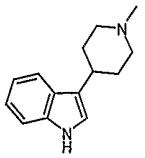
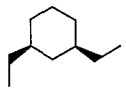
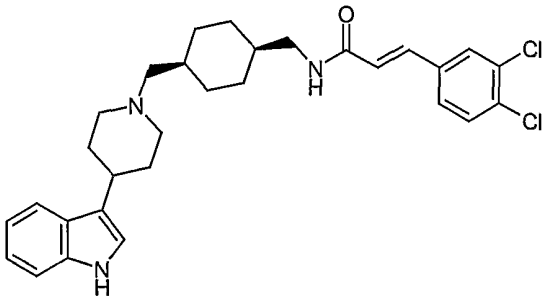
Example	R	R^1	X
5		H	
6		H	
7		CH_3	
8		H	
9		H	
10		H	
11		H	
12		H	

13		H	

Example 14: *cis*-(E)-3-(3,4-Dichlorophenyl)-N-{4-[4-[(1H-indol-3-yl)piperidin-1-yl]methyl]cyclohex-1-ylmethyl} acrylamide



(a) *cis*-1,4-bis(hydroxymethyl)-cyclohexane *cis*-1,4-cyclohexanedioic acid (10g) in THF (100mL) was added dropwise to a refluxing solution of lithium aluminium hydride (4.43g) in THF (100mL). This was refluxed for 4h, cooled to 0°C and then water (4.4mL), 1M NaOH solution (4.4mL) and water (13.2mL) added successively. The mixture was filtered and the filtrate washed with water, then brine and dried over $MgSO_4$. Concentration afforded the title compound (8.1g).

(b) *cis* 1-(hydroxymethyl)-4-(*tert*-butyldimethylsilyloxymethyl)-cyclohexane A solution of *tert*-butyldimethylsilyl chloride (9.74g) in DMF (100mL) was added to a solution of *cis*-1,4-bis(hydroxymethyl)-cyclohexane (9.05g) and imidazole (3.75g) in DMF (200mL) and this stirred under argon at room temperature for 7h. The DMF was removed in vacuo and the residue taken up in ethyl acetate. This was washed with water, dried ($MgSO_4$) and concentrated in vacuo to afford, after chromatography on silica gel using 20% ethyl acetate/hexane as eluant, the title compound (4.86g).

(c) *cis* 1-(mesyloxymethyl)-4-(*tert*-butyldimethylsilyloxymethyl)-cyclohexane Mesyl chloride was added to a solution of *cis* 1-(hydroxymethyl)-4-(*tert*-butyldimethylsilyloxymethyl)-cyclohexane (4.8g) and triethylamine (1.9g) in dry dichloromethane (100mL) at 0°C, and this stirred for 5h. This was diluted with ethyl acetate (200mL), washed with water and dried ($MgSO_4$). Concentration afforded the title compound (5.6g).

(d) *cis* 1-(azidomethyl)-4-(*tert*-butyldimethylsilyloxymethyl)-cyclohexane A mixture of *cis* 1-(mesyloxymethyl)-4-(*tert*-butyldimethylsilyloxymethyl)-cyclohexane (5.6g) and sodium azide (3.3g) in DMF (100mL) was stirred overnight under argon. More sodium azide (3.3g) was added and the reaction stirred for a further 4h. The DMF was removed in vacuo and the residue taken up in ethyl acetate. This was washed with aq. $NaHCO_3$ solution, water, dried ($MgSO_4$) and concentrated in vacuo. Chromatography on silica gel, using 30% ethyl acetate/hexane as eluant, afforded the title compound (3.63g).

(e) *cis* 1-(aminomethyl)-4-(*tert*-butyldimethylsilyloxymethyl)-cyclohexane A solution of *cis* 1-(azidomethyl)-4-(*tert*-butyldimethylsilyloxymethyl)-cyclohexane (3.62g) and triphenyl phosphine (3.74g) in THF (100mL) and water (100mL) was stirred under argon overnight. The reaction mixture was diluted with ethyl acetate (300mL),washed with water and dried over $MgSO_4$. Chromatography on silica gel, using ethyl acetate, followed by 10% methanol/chloroform saturated with ammonia, afforded the title compound (3.2g).

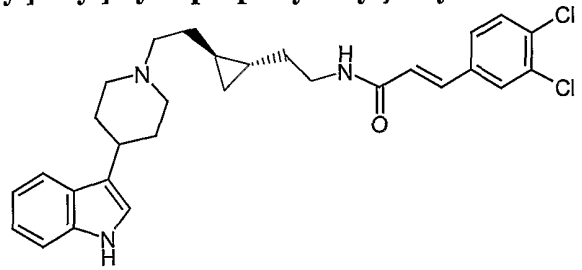
(f) *cis*-(E)-3-(3,4-Dichlorophenyl)-N-{4-(*tert*-butyldimethylsilyloxymethyl) cyclohex-1-ylmethyl}acrylamide Following the procedure of Example 1(f), but substituting *cis* 1-(aminomethyl)-4-(*tert*-butyldimethylsilyloxymethyl)-cyclohexane (1g) for *cis*-1-amino-4-{4-[(1H-indol-3-yl))piperidin-1-yl]methyl}cyclohexane and using corresponding proportions of the other reagents, the title compound (1.3g) was obtained.

(g) *cis*-(E)-3-(3,4-Dichlorophenyl)-N-{4-hydroxymethyl)-cyclohex-1-ylmethyl}acrylamide To a stirred solution of *cis*-(E)-3-(3,4-Dichlorophenyl)-N-{4-(*tert*-butyldimethylsilyloxymethyl) cyclohex-1-yl}acrylamide (1.3g) in THF(50mL), under argon, was added a 1M solution of TBAF in THF (2.9mL). This was stirred at room temperature for 2 days, then washed with brine and dried over $MgSO_4$. Concentration gave a residue which was chromatographed on silica gel, using ethyl acetate as eluant, to afford the title compound (0.62g).

(h) *cis*-(E)-3-(3,4-Dichlorophenyl)-N-{4-formyl)-cyclohex-1-ylmethyl}acrylamide Swern oxidation of *cis*-(E)-3-(3,4-Dichlorophenyl)-N-{4-hydroxymethyl)-cyclohex-1-yl}acrylamide (0.62g), by an analogous procedure to that described in Example 1(c) afforded the title compound (0.61g).

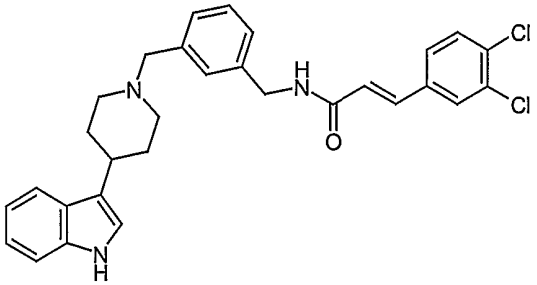
(i) *cis*-(E)-3-(3,4-Dichlorophenyl)-N-{4-[4-[(1H-indol-3-yl)piperidin-1-yl]methyl]cyclohex-1-ylmethyl} acrylamideFollowing the procedure of Example 1(d), but substituting *cis*-(E)-3-(3,4-Dichlorophenyl)-N-{4-formyl)-cyclohex-1-ylmethyl}acrylamide (0.22g) for *cis*-1-(tert-butoxycarbonylamino)-4-formylcyclohexane, and using corresponding proportions of the other reagents, the title compound (0.26g) was obtained.

Example 15: *trans*-(E)-3-(3,4-Dichlorophenyl)-N-{2-[4-[(1H-indol-3-yl)piperidin-1-yl]ethyl]-cycloprop-1-ylethyl}acrylamide



Using analogous procedures to those described in Example 14, but starting from *trans* 1,2-bis-(methoxycarbonylmethyl)-cyclopropane, the title compound was prepared.

Example 16: (E)-3-(3,4-Dichlorophenyl)-N-{3-[4-[(1H-indol-3-yl)piperidin-1-yl]methyl]benzyl}acrylamide

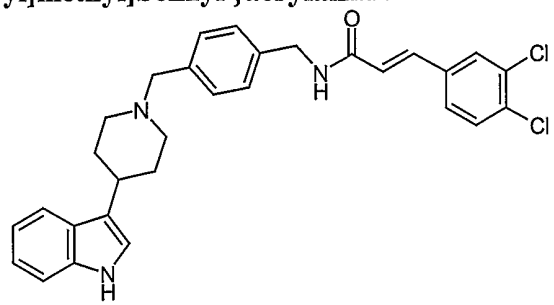


(a) 3-{4-[(1H-indol-3-yl)piperidin-1-yl]methyl}benzonitrile Following the procedure of Example 1(d), but substituting 3-cyanobenzaldehyde (197mg) for *cis*-1-(tert-butoxycarbonylamino)-4-formylcyclohexane, and using corresponding proportions of the other reagents, the title compound (0.47g) was obtained.

(b) 3-{4-[(1H-indol-3-yl)piperidin-1-yl]methyl}benzylamine 3-{4-[(1H-indol-3-yl)piperidin-1-yl]methyl}benzonitrile (0.445g) in ether (10mL) was added dropwise to a refluxing solution of lithium aluminium hydride (0.537g) in ether (10mL). This was refluxed overnight, cooled and then filtered. The filtrate was washed with water then brine and dried over $MgSO_4$. Concentration afforded a residue which was chromatographed on silica gel, using 2% methanol/chloroform saturated with ammonia as eluant, to afford the title compound (0.13g).

(c) (E)-3-(3,4-Dichlorophenyl)-N-{3-[4-[(1H-indol-3-yl)piperidin-1-yl]methyl]benzyl}acrylamide Following the procedure of Example 1(f), but substituting 3-{4-[(1H-indol-3-yl)piperidin-1-yl]methyl}benzylamine (0.12g) for *cis*-1-amino-4-{4-[(1H-indol-3-yl)piperidin-1-yl]methyl}-cyclohexane and using corresponding proportions of the other reagents, the title compound (0.12g) was obtained.

Example 17: (E)-3-(3,4-Dichlorophenyl)-N-{4-[4-[(1H-indol-3-yl)piperidin-1-yl]methyl]benzyl }acrylamide



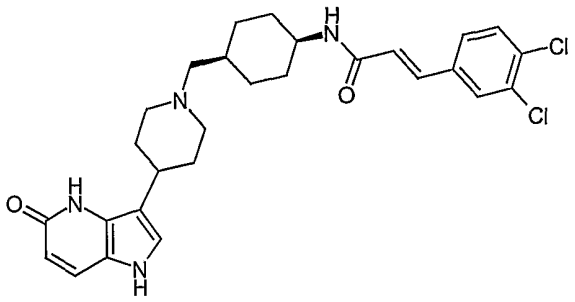
Using analogous procedures to those described in Example 16, but starting from 4-cyanobenzaldehyde, the title compound was prepared.

Spectral Data

Example	Spectral Data

1	Mass spectrum MH^+ 510/512. ^1H NMR: δ DMSO 1.2-1.4 (2H, m), 1.5-1.8 (9H, m), 1.90 (2H, App d), 2.1 (2H, App t), 2.2 (2H, d), 2.7-2.8 (1H, m), 2.9 (2H, d), 3.94 (1H, br s), 6.8 (1H, d), 6.9 (1H, t), 7.0 (1H, t), 7.1 (1H, d), 7.3 (1H, d), 7.4 (1H, d,), 7.5 (2H, App t), 7.7 (1H, d), 7.8 (1H, d), 7.9 (1H, d), 10.8 (1H, s).
2	Mass spectrum MH^+ 510, 512. ^1H NMR: δ DMSO 1.3-1.4 (2H, m), 1.5-1.8 (9H, m), 1.9 (2H, App d), 2.1 (2H, App t), 2.2 (2H, App d), 2.8-2.9 (1H, m), 2.9 (2H, App d), 3.9 (1H, s), 6.8 (1H, d), 6.9 (1H, t), 7.0 (1H, t), 7.1 (1H, d), 7.3 (1H, d), 7.4 (1H, d), 7.5 (2H, App t), 7.7 (1H, d), 7.8 (1H, d), 8.0 (1H, d), 10.7 (1H, s)
3	Mass spectrum MH^+ 536, 538. ^1H NMR $CDCl_3$ δ: 1.3 – 2.1 (20H, m), 2.31 (2H, d), 3.25 (1H, m), 4.20 (1H, m), 5.73 (1H, m), 6.38 (1H, d), 6.98 (1H, d), 7.1-7.2 (2H, m), 7.28-7.39 (3H, m), 7.42 (1H, d),7.50 (1H, d), 7.59 (1H, d), 7.64 (1H, d), 7.90 (1H, s).
4	Mass spectrum MH^+ 536, 538. ^1H NMR $CDCl_3$ δ: 1.2 – 2.0 (19H, m), 2.30 (2H, d), 2.49 (1H, m), 3.40 (1H, m), 4.20 (1H, m), 5.73 (1H, m), 6.38 (1H, d), 7.02 (1H, s), 7.08 (1H, m), 7.17 (1H, m), 7.2-7.35 (2H, m), 7.42 (1H, d), 7.52 (1H, d), 7.55-7.65 (2H, m), 7.88 (1H, s)
5	Mass spectrum MH^+ 526, 528. ^1H NMR: δ DMSO 1.2-1.3 (2H, m), 1.5-1.8 (11H, m), 1.8-1.9 (2H, d), 2.0-2.1 (2H, App t), 2.1 (2H, m), 2.9-3.0 (2H, m), 4.0 (1H, m), 6.5 (1H, dd), 6.8 (1H, dd), 7.0 (1H, d), 7.1 (1H, d), 7.4 (1H, d), 7.5 (1H, d), 7.7 (1H, d), 7.8 (1H, s), 8.0 (1H, d), 8.5 (1H, s), 10.4 (1H, s)
6	Mass spectrum MH^+ 524, 526. ^1H NMR $CDCl_3$ δ: 1.2 (2H, m), 2.60-2.80 (9H, m), 2.01 (2H, m), 2.18-2.28 (4H, m), 2.72 (1H, m), 3.01 (2H, d), 4.21 (1H, m), 5.72 (1H, m), 6.39 (1H, d), 7.00-7.10 (2H, m), 7.2-7.35 (2H, m), 7.44 (1H, d), 7.52 (1H, d), 7.61 (1H, m), 7.69 (2H, s)
7	Mass spectrum MH^+ 524, 526. ^1H NMR: δ DMSO 1.4-1.6 (2H, m), 1.5-1.8 (10H, m), 1.8-2.0 (3H, m), 2.1-2.2 (2H, m), 2.4 (1H, d), 2.7-2.8 (1H, m), 2.8-3.0 (4H, m), 4.2 (1H, m), 7.0 (1H, t), 7.1 (1H, t), 7.1 (1H, d), 7.2 (2H, m), 7.4 (1H, d), 7.5 (1H, d), 7.6 (1H, d), 7.7 (2H, m), 8.1 (1H, s)
8	Mass spectrum MH^+ 526, 528. ^1H NMR: δ DMSO 0.9 (2H, App q), 1.2 (2H, App q), 1.5-1.5 (1H, m), 1.7 (2H, App q), 1.7-1.9 (6H, m), 2.0 (2H, App t), 2.2 (2 H, App d), 2.6-2.7 (1H, m), 2.9 (2H, m), 3.6 (1H, m), 6.5 (1H, dd), 6.7 (1H, d), 6.8 (1H, d), 7.0 (1H, d), 7.1 (1H, d), 7.4 (1H, d), 7.5 (1H, d), 7.7 (1H, d), 7.8 (1H, s), 8.0 (1H, d), 8.5 (1H, s), 10.4 (1H, s)
11	Mass spectrum MH^+ 524, 526. ^1H NMR: δ $CDCl_3$ 0.9-1.1 (4H, m), 1.5 (2H, brs), 1.7-1.91 (m, 6H), 2.0 (4H App t), 2.16 (2H, d), 2.8-2.9 (1H, m), 2.8-3.0 (2H, m), 3.2 (2H, t), 5.9 (1H, t), 6.4 (1H, d, *J* = 15.6 Hz), 6.9 (1H, d), 7.1 (1H, t), 7.2 (1H, t), 7.2-7.6 (6H, m), 7.6 (1H, d), 8.2 (1H, s)
13	Mass spectrum MH^+ 510, 512. ^1H NMR: δ DMSO 0.7-0.9 (2H, m), 1.1-1.3 (1H, m), 1.4-1.6 (2H, m), 1.6-2.0 (11H, m), 2.1 (2H, d), 2.8 (1H, m), 2.9 (2H, br d), 3.1 (2H, br t), 6.7 (1H, d), 6.9 (1H, t), 7.0 (1H, t), 7.1 (1H, d), 7.3 (1H, d), 7.4 (1H, d), 7.5-7.6 (2H, m), 7.7 (1H, d), 7.8 (1H, d), 8.1 (1H, t), 10.8 (1H, s)
15	Mass spectrum MH^+ 510, 512. ^1H NMR: δ DMSO 0.2-0.3 (2H, m), 0.4-0.5 (2H, m), 1.2-1.4 (2H, m), 1.4-1.6 (2H, m), 1.6-1.7 (2H, m), 1.8-1.9 (2H, m), 1.9-2.1 (2H, m), 2.3-2.5 (2H, m), 2.6-2.7 (1H, m), 2.9-3.0 (m, 2H), 3.3 (m, 2H), 6.7 (1H, d), 6.9 (1H, t), 7.0 (1H, t), 7.1 (1H, d), 7.3 (1H, d), 7.4 (1H, d), 7.5 (1H, d), 7.6 (1H, d), 7.7 (1H, d), 7.9 (1H, d), 8.1 (1H, d), 10.8 (1H, t)

Example 18. cis-(E)-3-(3,4-Dichloro-phenyl)-N-{4-[4-(5-oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)-piperidin-1-ylmethyl]-cyclohexyl}-acrylamide (E18)



The amine D7 (1.3 g) in dichloromethane (20 mL) containing diisopropylethylamine (2.1 mL) was treated with 3,4-dichlorocinnamic acid (0.5 g), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (0.46 g), and hydroxybenzotriazole (0.32 g). After stirring for 3h, the mixture was diluted with dichloromethane and extracted with aqueous potassium carbonate. The organic layer was evaporated to dryness to afford the crude product (1.0 g). Chromatography on silica using 5% methanol/0.5% ammonia/94.5% dichloromethane as eluent afforded the title compound E18 as a foam (0.32 g). Mass spectrum MH^+ 527, 529. ^1H NMR DMSO δ: 1.2-3.2 (20H, m), 3.9 (1H, broad s), 5.96 (1H, d), 6.75 (1H, d), 6.98 (1H, d), 7.37 (1H, d), 7.49 (1H, d), 7.54 (1H, dd), 7.68 (1H, d), 7.83 (1H, s), 7.95 (1H, d), 10.85 (1H, s), 11.40 (1H, s).

Biological Data

1. Cell membrane assay, using membranes from transfected CHO cells expressing the CCR2B (MCP-1) receptor.

(a) Generation of CCR2B cell line – A fragment containing a Kozak sequence and the CCR2B coding sequence (ref Berkhout et al, J Biol Chem, 1997, 272, 16404 and references cited therein) was subcloned into the mammalian expression vector pCDN (Aiyar N, Baker E, Wu H-L, Nambi P, Edwards R M, Trill J, Ellis C and Bergsma D J, Human ATI receptor is a single copy gene : Characterisation in a stable cell line, Mol Cell Biochem, 131, 75-86, 1994). The resulting construct was sequenced to confirm the sequence integrity of CCR2B. Stable cell lines were obtained by electroporation of the pCDN:CCR2B vector into Chinese Hamster Ovary (CHO) cells, followed by clonal selection using G418. The resulting clones were screened for high-level receptor expression by ligand binding assays on whole cells. From this screen, the clonal cell line producing the highest number of receptors per cell was choosen for further studies.

(b) ^{125}I- labelled MCP-1 (Amersham International, UK) was incubated with membrane suspension (25μg of protein) in the presence or absence of increasing concentrations of unlabelled human MCP-1 (R + D Systems) or antagonist for 2 hours at room temperature in a 96-well plate with 50 mM HEPES 1mM $CaCl_2$, 5mM $MgCl_2$, BSA (0.5% w/v final conc), pH 7.4.

Following incubation, the membranes were washed and collected onto a 96 well polyethylenimine-treated Packard GF/C filter, using a Packard harvester. The plate was oven dried and radioactivity bound to the filter plate was counted using a Topcount liquid scintillation counter. The IC_{50} values and pK_i values were calculated using Inflexion, a non-linear iterative curve fitting program based on Microsoft Excel (Br J Pharmacol, 1994, 112, 440P)

The compounds of Examples 1-18 had pK_i values in the range 5.0-7.1.

2. Monocyte Chemotaxis

(a) Monocyte isolation

Human peripheral blood monocytes were prepared from the blood of normal healthy volunteers, essentially as described by Boyum (1984, *Methods in Enzymol*ogy (Academic Press, New York and London) 108, 88-102). Blood was collected into anticoagulant (one part 50mM EDTA, pH 7.4, to nine parts blood), then centrifuged for 5 minutes at 600*g*. The upper layer of platelet-rich plasma was removed and centrifuged for 15 minutes at 900*g*, to pellet the platelets. The upper layer of platelet-poor plasma was removed and

added back to the packed red cells; the pelleted platelets were discarded. Dextran T500 was added (10 volumes EDTA blood to one volume 6% (w/v) dextran in 0.9% (w/v) NaCl) and the erythrocytes were allowed to sediment at unit gravity for 30 minutes. The resultant leukocyte-rich plasma was removed and centrifuged for 5 minutes at 400*g*. The cell pellet was resuspended in 5ml of the supernatant, and the suspension was underlayered with 3ml NycoPrep, then centrifuged for 15 minutes at 600*g*. The mononuclear layer at the interface between the plasma and the NycoPrep was removed and washed through PBS by centrifugation for 5 minutes at 400*g*. The mononuclear layer typically contained ≥ 80% monocytes, determined by staining cytocentrifuge preparations for non-specific esterase using α-naphthyl-butyrate. Cell viability (typically >95%) was assessed as the ability to exclude trypan blue.

(b) Chemotaxis

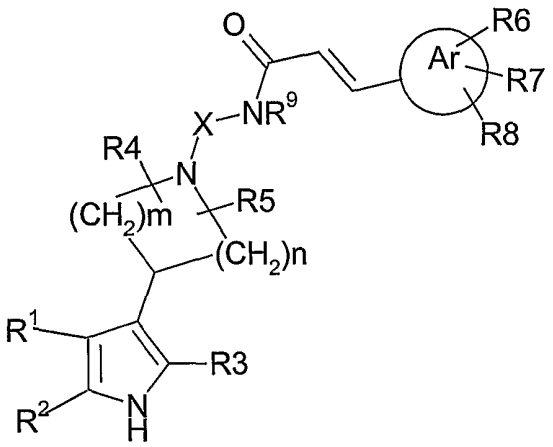
The ability of the MCP-1 antagonists to inhibit the chemoattractant activity of MCP-1 towards freshly isolated human monocytes was determined using a 48-well modified Boyden microchemotaxis chamber. MCP-1 (1nM), was incubated with varying concentrations of the antagonist, and aliquots of these mixtures were placed in the lower wells of the chamber. Monocytes were also incubated with varying concentrations of antagonist and aliquots of these mixtures were placed in the upper wells of the chamber, such that the same concentration of the antagonist was present in both the upper and corresponding lower wells. Numbers of cells migrating from the upper chamber across a polycarbonate filter (5μm pore size) following incubation at 37°C and 5% CO_2 humidified air were quantified by light microscopy of Diff-Quik stained filters, using a x40 objective and x10 ocular containing a 10mm^2 counting grid. Dose-inhibition curves were constructed, and from these, pKb values were determined.

For chemotaxis with immortalised or transfected cell lines, essentially the same format was used, except that a 96-well chemotaxis chamber was employed. Cells which have migrated across a polycarbonate filter (5μm pore size) following incubation at 37°C and 5% CO_2 humidified air were quantified colorimetrically from a standard curve relating cell density to absorbance at 590nm. The colorimetric end point derives from cellular reduction of 3-[4,5, dimethylthiazol-2-yl]-2,5, diphenyltetrazolium bromide from its formazan product.

The compounds of Examples 1, 3 and 5 had pKb's in the range 7.1 to 8.0.

Claims

1. A compound of formula (I):



(I)

in which:

Ar is an aryl or heteroaryl group;

R1 and R2 form the residue of a 5 to 7 membered monocyclic heteroaryl ring comprising from one to three hetereoatoms selected from O, S, N and optionally substituted with one or two substitutents which may be the same or different and selected from the group consisting of halogen, cyano, (C_1-$_6$)alkyl, (C_3-$_7$)cycloalkyl, (C_1-$_6$)alkoxy, halo(C_1-$_6$)alkyl, hydroxy, oxo, amino, mono- or di-(C_1-$_6$)alkylamino, acylamino, nitro, carboxy, (C_1-$_6$)alkoxycarbonyl, (C_1-$_6$)alkenyloxycarbonyl, (C_1-$_6$)alkoxycarbonyl(C_1-$_6$)alkyl, carboxy(C_1-$_6$)alkyl, (C_1-$_6$)alkylcarbonyloxy, carboxy(C_1-$_6$)alkyloxy, (C_1-$_6$)alkoxycarbonyl(C_1-$_6$)alkoxy, (C_1-$_6$)alkylthio, (C_1-$_6$)alkylsulphinyl, (C_1-$_6$)alkylsulphonyl, sulphamoyl, mono- and di-(C_1-$_6$)-alkylsulphamoyl, carbamoyl, mono- and di-(C_1-$_6$)alkylcarbamoyl, (C_1-$_6$)alkylsulphonamido, arylsulphonamido, aryl, aryl(C_1-$_6$)alkyl, aryl(C_1-$_6$)alkoxy, aryloxy and heterocyclyl; or

R1 and R2 form the residue of a benzene ring which is optionally substituted with one or two substitutents which may be the same or different are selected from the group consisting of hydrogen, halogen, cyano, (C_1-$_6$)alkyl, (C_3-$_7$)cycloalkyl, (C_1-$_6$)alkoxy, halo(C_1-$_6$)alkyl, hydroxy, amino, mono- or di-(C_1-$_6$)alkylamino, acylamino, nitro, carboxy, (C_1-$_6$)alkoxycarbonyl, (C_1-$_6$)alkenyloxycarbonyl, (C_1-$_6$)alkoxycarbonyl(C_1-$_6$)alkyl, carboxy(C_1-$_6$)alkyl, (C_1-$_6$)alkylcarbonyloxy, carboxy(C_1-$_6$)alkyloxy, (C_1-$_6$)alkoxycarbonyl(C_1-$_6$)alkoxy, (C_1-$_6$)alkylthio, (C_1-$_6$)alkylsulphinyl, (C_1-$_6$)alkylsulphonyl, sulphamoyl, mono- and di-(C_1-$_6$)-alkylsulphamoyl, carbamoyl, mono- and di-(C_1-$_6$)alkylcarbamoyl,

(C_{1-6})alkylsulphonamido, arylsulphonamido, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryloxy and heterocyclyl;
R3 is hydrogen or $C_{(1-6)}$alkyl;
R4 and R5 which may be the same or different are hydrogen or $C_{(1-6)}$alkyl, or together with the carbon atoms of the ring to which they are attached form a bridging 5- to 7 - membered ring;
R6, R7 and R8 which may be the same or different are selected from the group consisting of hydrogen, halogen, cyano, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, amino, mono- or di-(C_{1-6})alkylamino, acylamino, nitro, carboxy, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkenyloxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, carboxy(C_{1-6})alkyl, (C_{1-6})alkylcarbonyloxy, carboxy(C_{1-6})alkyloxy, (C_{1-6})alkoxycarbonyl(C_{1-6})alkoxy, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, sulphamoyl, mono- and di-(C_{1-6})-alkylsulphamoyl, carbamoyl, mono- and di-(C_{1-6})alkylcarbamoyl, (C_{1-6})alkylsulphonamido, arylsulphonamido, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryloxy and heterocyclyl, or two adjacent substituents may form $C_{(1-3)}$alkylidenedioxy;
m and n are each integers from 1 to 3;
R9 is H, (C_{1-6})alkyl or aryl(C_{1-4})alkyl; and
X is a group $(CH_2)_pY(CH_2)_q$ in which Y is $C_{(3-7)}$cycloalkylene, $-C_6H_4-$ (phenylene) or heteroarylene in which each of $(CH_2)_p$, $(CH_2)_q$ may be optionally substituted by (C_{1-6})alkyl and Y may be optionally substitued and p and q are each independently 0, 1 or 2; or
a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a compound according to claim 1 together with a pharmaceutically acceptable carrier or excipient.

3. A compound according to claim 1 for use in therapy.

4. A compound according to claim 1 for use in the treatment of atherosclerosis or arthritis.

5. Use of a compound according to claim 1 in the manufacture of a medicament for use in the treatment of inflammatory conditions with monocyte and/or lymphocyte involvement.

INTERNATIONAL SEARCH REPORT

	I onal Application No
	rCT/EP 02/03570

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/14 C07D451/02 C07D471/04 A61K31/00 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

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

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

CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FORBES I T ET AL: "CCR2B receptor antagonists: conversion of a weak HTS hit to a potent lead compound" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 16, 21 August 2000 (2000-08-21), pages 1803-1806, XP004216003 ISSN: 0960-894X Compound 14 page 1804 -page 1805; tables 1,3 --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 August 2002	27/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Stroeter, T

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WITHERINGTON, J. ET AL: "Conformationally restricted indolopiperidine derivatives as potent CCR2B receptor antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2001), 11(16), 2177-2180 , XP002208447 Compounds 5b, 8 page 2177 -page 2179; tables 3-5 ---	1-5
A	WO 98 06703 A (CONNOR DAVID THOMAS ;WARNER LAMBERT CO (US); GLASE SHELLY ANN (US)) 19 February 1998 (1998-02-19) cited in the application the whole document -----	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/03570

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		EP 0927167 A1	07-07-1999
		JP 2000516611 T	12-12-2000
		US 2002099054 A1	25-07-2002
		WO 9806703 A1	19-02-1998
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		US 6348487 B1	19-02-2002