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(54) Title: CHEMICAL COMPOUNDS

(57) Abstract: The invention provides compounds of formula (I): as modulators of chemokine and H1 receptor activity. The compounds are especially useful in the treatment of asthma and rhinitis.

# CHEMICAL COMPOUNDS

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

Pharmaceutically active piperidine derivatives are disclosed in WO99/38514, WO99/04794, WO00/29377, WO00/35877, WO0058305 and WO01/14333.

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

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

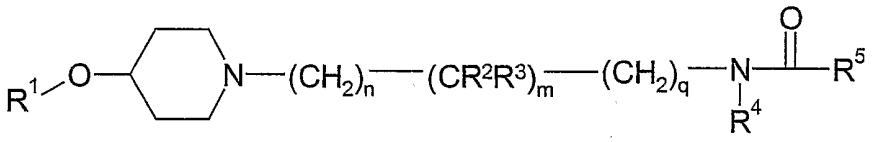
The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α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

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

Histamine is a basic amine, 2-(4-imidazolyl)-ethylamine, and is formed from histidine by histidine decarboxylase. It is found in most tissues of the body, but is present

in high concentrations in the lung, skin and in the gastrointestinal tract. At the cellular level inflammatory cells such as mast cells and basophils store large amounts of histamine. It is recognised that the degranulation of mast cells and basophils and the subsequent release of histamine is a fundamental mechanism responsible for the clinical manifestation of an allergic process. Histamine produces its actions by an effect on specific histamine G-protein coupled receptors, which are of three main types, H1, H2 and H3. Histamine H1 antagonists comprise the largest class of medications used in the treatment of patients with allergic disorders, especially rhinitis and urticaria. H1 antagonists are useful in controlling the allergic response by for example blocking the action of histamine on post-capillary venule smooth muscle, resulting in decreased vascular permeability, exudation and oedema. The antagonists also produce blockade of the actions of histamine on the H1 receptors on c-type nociceptive nerve fibres, resulting in decreased itching and sneezing.

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



(I)

wherein

$R^1$ is phenyl optionally substituted by cyano, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ haloalkyl), halogen, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl or $C_{1-6}$ alkoxy;

n is 0, 1, 2, 3 or 4; m is 0 or 1; when m is 0 then q is 0, and when m is 1 then q is 1, 2 or 3; provided that n + m + q = 1, 2, 3 or 4;

when $R^2$ and $R^3$ are, independently, hydrogen or $C_{1-6}$ alkyl, and $R^4$ is hydrogen, then $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being substituted at least once with a substituent selected from the group comprising: $C_{1-6}$ alkyl (substituted with $NH_2$, $CO_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ hydroxyalkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), $C_{1-6}$ alkoxy (substituted with $C_{1-6}$ alkoxy, hydroxy, $CO_2(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl) or $NH_2$), $C_{2-6}$ alkenyl, pyrrolyl and $\Delta^3$-pyrrolinyl; and optionally further substituted with a substituent selected from the group comprising: halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkoxy, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$

alkylthio, $C_{1-6}$ alkylthio($C_{1-6}$ alkyl), $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido, phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, and $C(O)R^{10}$-substituted $C_{1-6}$ alkyl or $C_{1-6}$ alkoxy groups;

when $R^2$ and $R^3$ are, independently, hydrogen or $C_{1-6}$ alkyl, and $R^4$ is $C_{1-4}$ alkyl or $C_{3-6}$ cycloalkyl($C_{1-4}$ alkyl), then $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl (optionally substituted with halogen, $C_{1-6}$ alkylthio, $NH_2$, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy (substituted with halogen, $C_{1-6}$ alkoxy, hydroxy, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl) or $NH_2$), $C_{2-6}$ alkenyl, $C_{1-6}$ alkoxycarbonyl, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ hydroxyalkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, pyrrolyl or $\Delta^3$-pyrrolinyl;

and when $R^2$ is phenyl (optionally substituted with halogen, $C_{1-4}$ alkyl or $C_{1-4}$ alkoxy), $R^3$ is hydrogen or $C_{1-6}$ alkyl, and $R^4$ is hydrogen, $C_{1-4}$ alkyl or $C_{3-6}$ cycloalkyl($C_{1-4}$ alkyl), then $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl (optionally substituted with halogen, $C_{1-6}$ alkylthio, $NH_2$, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy (substituted with halogen, $C_{1-6}$ alkoxy, hydroxy, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl) or $NH_2$), $C_{2-6}$ alkenyl, $C_{1-6}$ alkoxycarbonyl, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ hydroxyalkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, pyrrolyl or $\Delta^3$-pyrrolinyl;

$R^{10}$ is hydroxy or $NR^{11}R^{12}$ group; and,

$R^6$, $R^7$ $R^8$, $R^9$, $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl;

or a pharmaceutically acceptable salt thereof; or a solvate thereof.

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

Suitable salts include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, acetate, diacetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

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

Halogen includes fluorine, chlorine, bromine and iodine.

Alkyl groups and moieties are straight or branched chain and are, for example, methyl, ethyl, n-propyl, iso-propyl, iso-butyl or tert-butyl.

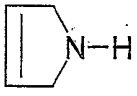
Alkenyl group are, for example, vinyl or allyl.

Cycloalkyl is, for example, cyclopropyl, cyclopentyl or cyclohexyl; and cycloalkylalkyl is, for example cyclopropylmethyl. Alkoxy includes methoxy, ethoxy, n-propoxy, iso-propoxy and tert-butoxy; alkoxycarbonyl includes methoxy- and ethoxy-, carbonyl; haloalkyl includes trifluoromethyl; haloalkoxy includes trifluoromethoxy; cycloalkylamino includes cyclopropyl-, cyclobutyl-, cyclopentyl- or cyclohexylamino; alkylthio includes methyl- or ethylthio; alkylthioalkyl includes methylthiomethyl; alkylcarbonylamino includes methyl- or ethylcarbonylamino; $C(O)NR^8R^9$ includes $C(O)NHCH_3$; dialkylsulphonamido includes dimethylsulphonamido and diethylsulphonamido; alkyl substituted with $NH_2$ includes $CH_2NH_2$; alkyl substituted with $CO_2$(alkyl) includes $CH_2CO_2CH_3$; alkyl substituted with $S(O)_2$(alkyl) includes $CH_2S(O)_2CH_3$ and $CH_2S(O)_2CH_2CH_3$; alkyl substituted with $NHS(O)_2$(alkyl) includes $CH_2NHS(O)_2CH_3$; alkyl substituted with $S(O)_2NR^{13}R^{14}$ includes $CH_2S(O)_2N(CH_3)_2$; $S(O)_2$(alkyl) includes $S(O)_2CH_3$ and $S(O)_2CH_2CH_3$; $S(O)_2$(hydroxyalkyl) includes $S(O)_2CH_2CH_2OH$; $S(O)_2NH$(alkyl) includes $S(O)_2NHCH_3$; NHC(O)(alkyl) includes $NHC(O)CH_3$; $NHS(O)_2$(alkyl) includes $NHS(O)_2CH_3$; alkoxy substituted with alkoxy includes $O(CH_2)_2OCH_3$; alkoxy substituted with hydroxy includes $O(CH_2)_2OH$; alkoxy substituted with $CO_2$(alkyl) $OCH_2CO_2CH_3$; alkoxy substituted with NHC(O)O(alkyl) includes $OCH_2NHCO_2CH_3$; and alkoxy substituted with $NH_2$ includes $OCH_2NH_2$.

The 3- to 10-membered saturated or unsaturated ring system in the group $R^5$ may be monocyclic or polycyclic comprising 2 or more fused rings, examples of which include

cyclobutyl, cyclopentyl, cyclohexyl, norbornylenyl, adamantyl, phenyl, naphthyl, furyl, thienyl, pyrrolyl, 2,5-dihydro-1H-pyrrolyl (also known as $\Delta^3$-pyrroline), thiazolyl, isothiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, piperidinyl, morpholinyl, pyridinyl (for example in 6-oxo-1,6-dihydro-pyridinyl), pyrimidinyl (for example a pyrimidinedione), pyrazinyl, pyridazinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl (for example in 1-dioxo-2,3-dihydrobenz[b]thienyl), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl (for example in 1H-benzthiazol-2-one-yl), 2,3-dihydrobenzthiazolyl (for example in 2,3-dihydrobenzthiazol-2-one-yl), 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2a]pyridinyl), thieno[3,2-b]pyridin-6-yl, benzo[1,2,3]thiadiazolyl, 2,1,3-benzothiadiazolyl, benzofurazan, quinoxalinyl, dihydro-1-benzopyryliumyl (for example in a coumarinyl or a chromonyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example in 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), a purine (for example in 3,7-dihydro-purin-2,6-dione-8-yl), a pyrazolopyrimidinyl, a thienopyrimidinyl, a thiazolopyrimidinyl, quinolinyl, isoquinolinyl (for example in 2H-isoquinolin-1-one-yl), quinoxalinyl (for example 2,4-dioxo-3,4-dihydro-quinazolinyl), a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl or in 1H-[1,8]naphthyridin-4-one-yl), chromonyl, 1,3-benzodioxolyl, a benzothiazinyl (for example in 4H-benzo[1,4]thiazin-3-one-yl), benzo[d]imidazo[2,1-b]thiazol-2-yl or dibenzothiophenyl; or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

Alternatively, the 3- to 10-membered saturated or unsaturated ring system in the group $R^5$ may be monocyclic or polycyclic comprising 2 or more fused rings, examples of which include cyclobutyl, cyclopentyl, cyclohexyl, norbornylenyl, adamantyl, piperidyl, phenyl, naphthyl, naphthyridinyl, 1,3-benzodioxolyl, pyrazolyl, furanyl, pyridyl, thienyl, indolyl, benzthiazolyl, benzthienyl, 1,2,3-benzthiadiazolyl, benzoxazolyl, benzothiazolyl, chromonyl, imidazolyl, quinolinyl, isoquinolinyl, benzimidazolyl, pyrimidinyl, pyrazolopyrimidinyl, thienopyrimidinyl, thiazolopyrimidinyl, pyrimidinedione, pyrazinyl, pyridazinyl, purinyl, quinoxalinyl, thiazolyl, isothiazolyl and 2,4-dioxo-3,4-dihydro-quinazolinyl. $\Delta^3$-Pyrroline is also known as 2,5-dihydro-1*H*-pyrrole and has the structure:



In one aspect m and q are both 0.

In another aspect the present invention provides a compound of formula (I) wherein $R^1$ is phenyl optionally substituted by cyano, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ haloalkyl), halogen, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl or $C_{1-6}$ alkoxy; n is 0, 1, 2, 3 or 4; m is 0 or 1; when m is 0 then q is 0, and when m is 1 then q is 1, 2 or 3; provided that n + m + q = 1, 2, 3 or 4; $R^2$ and $R^3$ are, independently, hydrogen or $C_{1-6}$ alkyl; $R^4$ is hydrogen; $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being substituted at least once with a substituent selected from the group comprising: $C_{1-6}$ alkyl (substituted with $NH_2$, $CO_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ hydroxyalkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), $C_{1-6}$ alkoxy (substituted with $C_{1-6}$ alkoxy, hydroxy, $CO_2(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl) or $NH_2$), $C_{2-6}$ alkenyl, pyrrolyl and $\Delta^3$-pyrrolinyl; and optionally further substituted with a substituent selected from the group comprising: halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkoxy, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylthio($C_{1-6}$ alkyl), $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido, phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, and $C(O)R^{10}$-substituted $C_{1-6}$ alkyl or $C_{1-6}$ alkoxy groups; $R^{10}$ is hydroxy or $NR^{11}R^{12}$ group; and, $R^6$, $R^7$ $R^8$, $R^9$, $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl.

In a further aspect the present invention provides a compound of formula (I) wherein $R^1$ is phenyl optionally substituted by cyano, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ haloalkyl), halogen, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl or $C_{1-6}$ alkoxy; n is 0, 1, 2, 3 or 4; m is 0 or 1; when m is 0 then q is 0, and when m is 1 then q is 1, 2 or 3; provided that n + m + q = 1, 2, 3 or 4; $R^2$ and $R^3$ are, independently, hydrogen or $C_{1-6}$ alkyl; $R^4$ is $C_{1-4}$ alkyl or $C_{3-6}$ cycloalkyl($C_{1-4}$ alkyl); $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl (optionally substituted with halogen, $C_{1-6}$ alkylthio, $NH_2$, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy

(substituted with halogen, $C_{1-6}$ alkoxy, hydroxy, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl) or $NH_2$), $C_{2-6}$ alkenyl, $C_{1-6}$ alkoxycarbonyl, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ hydroxyalkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, pyrrolyl or $\Delta^3$-pyrrolinyl; $R^{10}$ is hydroxy or $NR^{11}R^{12}$ group; and, $R^6$, $R^7$ $R^8$, $R^9$, $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl.

In a still further aspect the present invention provides a compound of formula (I) wherein $R^1$ is phenyl optionally substituted by cyano, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ haloalkyl), halogen, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl or $C_{1-6}$ alkoxy; n is 0, 1, 2, 3 or 4; m is 1; q is 1; provided that n + m + q = 2, 3 or 4; $R^2$ is phenyl (optionally substituted with halogen, $C_{1-4}$ alkyl or $C_{1-4}$ alkoxy); $R^3$ is hydrogen or $C_{1-6}$ alkyl; $R^4$ is hydrogen, $C_{1-4}$ alkyl or $C_{3-6}$ cycloalkyl($C_{1-4}$ alkyl); $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl (optionally substituted with halogen, $C_{1-6}$ alkylthio, $NH_2$, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy (substituted with halogen, $C_{1-6}$ alkoxy, hydroxy, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl) or $NH_2$), $C_{2-6}$ alkenyl, $C_{1-6}$ alkoxycarbonyl, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ hydroxyalkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, pyrrolyl or $\Delta^3$-pyrrolinyl; $R^{10}$ is hydroxy or $NR^{11}R^{12}$ group; and, $R^6$, $R^7$ $R^8$, $R^9$, $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl.

In another aspect $R^1$ is phenyl optionally substituted by halogen (such as chloro or fluoro), $C_{1-4}$ alkyl (such as methyl) or $C_{1-4}$ alkoxy (such as methoxy).

In a further aspect n is 2.

In yet another aspect $R^2$ is hydrogen.

In a still further aspect $R^3$ is hydrogen.

In another aspect $R^4$ is hydrogen or $C_{1-4}$ alkyl; and $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being substituted by at least one of $C_{1-6}$ alkyl (substituted with $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $S(O)_2(C_{1-6}$ alkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl) or $NHS(O)_2(C_{1-6}$ alkyl); and optionally further substituted with a substituent selected from the group comprising: halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkoxy, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylthio($C_{1-6}$ alkyl), $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido and $C(O)R^{10}$-substituted $C_{1-6}$ alkyl or $C_{1-6}$ alkoxy groups; $R^{10}$ is hydroxy or $NR^{11}R^{12}$ group; and, $R^6$, $R^7$ $R^8$, $R^9$, $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl.

In yet another aspect $R^4$ is hydrogen or $C_{1-4}$ alkyl; and $R^5$ is phenyl substituted by at least one of $C_{1-6}$ alkyl (substituted with $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $S(O)_2(C_{1-6}$ alkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl) or $NHS(O)_2(C_{1-6}$ alkyl); and optionally further substituted with a substituent selected from the group comprising: halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkoxy, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylthio($C_{1-6}$ alkyl), $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido and $C(O)R^{10}$-substituted $C_{1-6}$ alkyl or $C_{1-6}$ alkoxy groups; $R^{10}$ is hydroxy or $NR^{11}R^{12}$ group; and, $R^6$, $R^7$ $R^8$, $R^9$, $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl.

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

In a still further aspect $R^5$ is phenyl mono-substituted by $C_{1-6}$ alkyl (substituted with $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $S(O)_2(C_{1-6}$ alkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl) or $NHS(O)_2(C_{1-6}$ alkyl); and $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl.

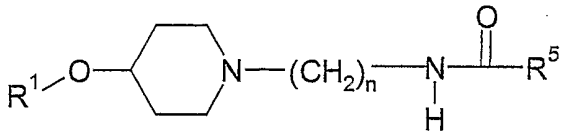
In another aspect the invention provides any compound described in a Table or an Example herein, or a pharmaceutically acceptable salt thereof.

Compounds of the invention are listed in Table I. All the compounds in Table I are compounds of formula (I) wherein m and q are both 0.

TABLE I

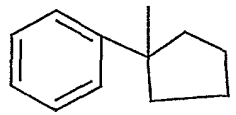
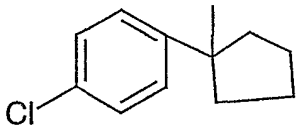
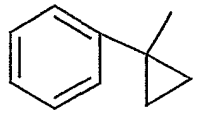
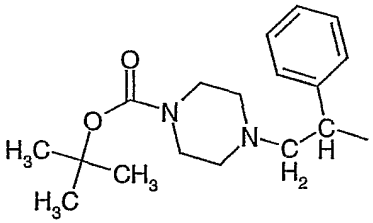
| Compound No. | $R^1$ | n | $R^4$ | $R^5$ | M+H |
|---|---|---|---|---|---|
| 1 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 4-$CH_2NH_2$-$C_6H_4$ | 422 |
| 2 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3,4-$(S(O)_2CH_3)_2$-$C_6H_3$ | 549 |
| 3 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$S(O)_2CH_2CH_2CH_3$-$C_6H_4$ | 499 |
| 4 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$S(O)_2CH_2CH(CH_3)_2$-$C_6H_4$ | 513 |
| 5 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$CH_2S(O)_2CH_3$-$C_6H_4$ | 485 |
| 6 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$S(O)_2CH_2CH_3$-$C_6H_4$ | 485 |
| 7 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 4-$CH_2S(O)_2CH_3$-$C_6H_4$ | 485 |
| 8 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 4-(pyrrol-1-yl)-$C_6H_4$ | 458 |
| 9 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$S(O)_2NHCH_3$-$C_6H_4$ | 486 |
| 10 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 2-$NH_2$-5-$NHC(O)CH_3$-$C_6H_3$ | 465 |
| 11 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$NHC(O)CH_3$-$C_6H_4$ | 450 |
| 12 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$O(CH_2)_2OCH_3$-$C_6H_4$ | 467 |
| 13 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$S(O)_2CH_3$-4-$NH_2$-$C_6H_3$ | 486 |
| 14 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 4-$CH=CH_2$-$C_6H_4$ | 419 |
| 15 | 3,4-$F_2$-$C_6H_3$ | 2 | $CH_2$-cyclopropyl | 3-$OCH_3$-4-F-$C_6H_3$ | |
| 16 | 3,4-$F_2$-$C_6H_3$ | 2 | H | 3-$S(O)_2CH_3$-$C_6H_4$ | |
| 17 | 3,4-$Cl_2$-$C_6H_3$ | 3 | H | 2-($\Delta^3$-pyrrolin-1-yl)-benzthiazol-6-yl | |
| 18 | 3,4-$F_2$-$C_6H_3$ | 2 | $CH_3$ | 3-$OCH_3$-$C_6H_4$ | |
| 19 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$S(O)_2CH_3$-$C_6H_4$ | |
| 20 | 3,4-$Cl_2$-$C_6H_3$ | 3 | H | 3-$S(O)_2CH_3$-$C_6H_4$ | |
| 21 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$O(CH_2)_2OH$-$C_6H_4$ | |
| 22 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$S(O)_2(CH_2)_2OH$-$C_6H_4$ | |
| 23 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$O(CH_2)_2NHC(O)$-$OC(CH_3)_3$-$C_6H_4$ | |
| 24 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$NHS(O)_2CH_3$-$C_6H_4$ | |
| 25 | 3,4-$Cl_2$-$C_6H_3$ | 2 | H | 3-$O(CH_2)_2NH_2$-$C_6H_4$ | |

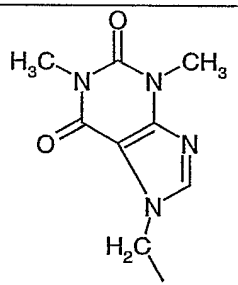
In a further aspect the present invention provides the compounds listed in Table II which are of formula (II):

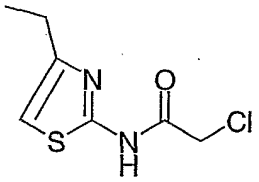


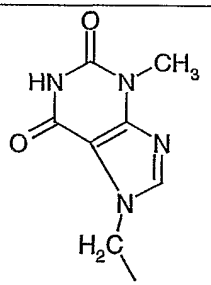
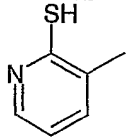
(II)

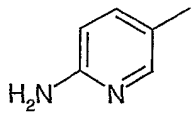
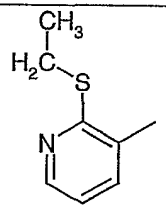
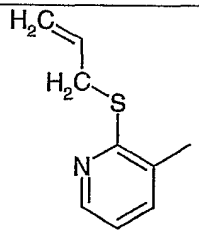
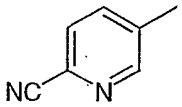
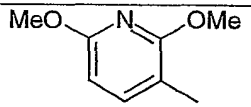
TABLE II

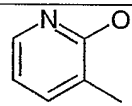
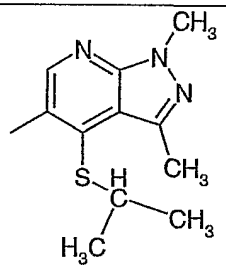
| Compound No. | $R^1$ | x | $R^5$ | M+H |
|---|---|---|---|---|
| 1 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $C(CH_3)_2(4\text{-}Cl\text{-}C_6H_4)$ | 469 |
| 2 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH(CH_2CH_3)(C_6H_5)$ | 435 |
| 3 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 461 |
| 4 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 495 |
| 5 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 433 |
| 6 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 605 |
| 7 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $C(NH_2)(CH(CH_3)_2)(C_6H_5)$ | 464 |
| 8 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH(CH(CH_3)_2)(C_6H_5)$ | 449 |

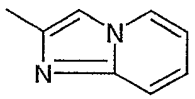
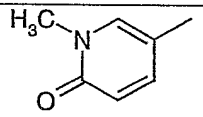
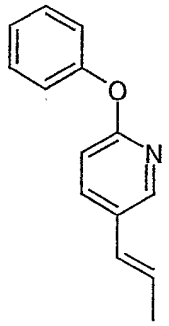
| | | | | |
|---|---|---|---|---|
| 9 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2,4-$(OCH_3)_2$-$C_6H_3$) | 467 |
| 10 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(4-$(OCH_2C_6H_5)$-$C_6H_4$) | 513 |
| 11 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(3-$(OCH_2C_6H_5)$-$C_6H_4$) | 513 |
| 12 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2-$CH_3$-Naphth-1-yl) | 471 |
| 13 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2,4,6-$CH_3$-$C_6H_2$) | 449 |
| 14 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2-$(OCH_2CH_3)$-$C_6H_4$) | 451 |
| 15 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 509 |
| 16 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(3-$(OCH_3)$-4-$(OCH_2CH_3)$-$C_6H_3$) | 481 |
| 17 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(4-$(OCH_2CH_2CH_2CH_3)$-$C_6H_4$) | 479 |
| 18 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(1H-Indol-1-yl) | 446 |
| 19 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2-$NO_2$-$C_6H_4$) | 452 |
| 20 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(3-Cl-4-OH-$C_6H_3$) | 457 |
| 21 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(3,4-$Cl_2$-$C_6H_3$) | 475 |
| 22 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2,6-$Cl_2$-$C_6H_3$) | 475 |
| 23 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2-Br-$C_6H_4$) | 485 |
| 24 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(1,4-$(CH_3)_2$-3-$(CO_2H)$-1H-Pyrrole-2-yl) | 468 |

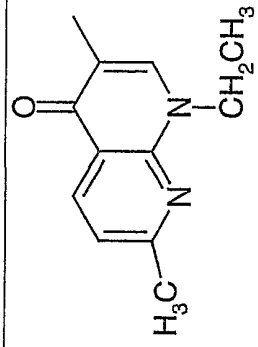
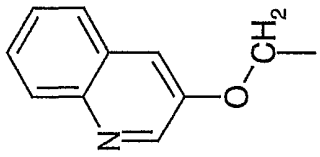
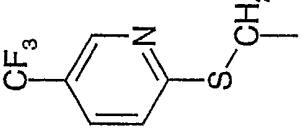
| | | | | |
|---|---|---|---|---|
| 25 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 505 |
| 26 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(3,4-$(OH)_2$-$C_6H_3$) | 439 |
| 27 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2,5-$(OCH_3)_2$-$C_6H_3$ | 467 |
| 28 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(4-OH-$C_6H_4$) | 423 |
| 29 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(1H-indol-3-yl) | 446 |
| 30 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(naphth-2-yl) | 457 |
| 31 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(3,4,5-$(OCH_3)_3$-$C_6H_2$) | 497 |
| 32 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2-(pyrazin-2-yl)-1,3-thiazol-4-yl) | 492 |
| 33 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(5-$(CH(CH_3)_2)$-2-$CH_3$-1H-indol-3-yl) | 502 |
| 34 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(5-(pyrrolidin-1-yl)-2H-tetrazol-2-yl) | 468 |
| 35 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(5-(4-$CH_3$-$C_6H_4$)-2H-tetrazol-2-yl) | 489 |
| 36 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(5-Cl-1-benzothien-3-yl) | 497 |
| 37 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(5-$CH_3$-2-$C_6H_5$-1,3-thiazol-4-yl) | 504 |
| 38 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(3-$NO_2$-4-Cl-5-$CH_3$-1H-pyrazol-1-yl) | 490 |
| 39 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(4-$NO_2$-1-$CH_3$-1H-pyrazol-5-yl) | 456 |
| 40 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2-$CF_3$-1H-benzimidazol-1yl) | 515 |
| 41 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2-(ethylsulfanyl)-1H-benzimidazol-1-yl) | 507 |

| | | | | |
|---|---|---|---|---|
| 42 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(3-$NO_2$-5-$CH_3$-1H-pyrazol-1-yl | 456 |
| 43 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2-$CH_3$-4-$C_6H_5$-1,3-thiazol-5-yl) | 504 |
| 44 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2-$CH_3$-4-(thien-2-yl)-1,3-thiazol-5-yl) | 510 |
| 45 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(3,4-($NO_2$)$_2$-5-$CH_3$-1H-pyrazol-1-yl) | 501 |
| 46 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(4-($OCH_2CH_2CH(CH_3)_2$)-$C_6H_4$) | 493 |
| 47 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2-(*tert*-Butylsulfanyl)-$C_6H_4$) | 495 |
| 48 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(4-Cl-3,5-($CH_3$)$_2$-1H-pyrazol-1-yl) | 459 |
| 49 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 495 |
| 50 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(4-$NO_2$-3,5-($CH_3$)$_2$-1H-pyrazol-1-yl | 470 |
| 51 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2,4-($NO_2$)$_2$-1H-imidazol-1-yl) | 487 |
| 52 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(3,5-($CH_3$)$_2$-1H-pyrazol-1-yl) | 425 |
| 53 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(2-CN-$C_6H_4$) | 432 |
| 54 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 3-OH-pyridin-2-yl | 410 |
| 55 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 426 |

| | | | | |
|---|---|---|---|---|
| 56 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 409 |
| 57 | 3,4-$Cl_2$-$C_6H_3$ | 2 | Pyridin-2-yl | 394 |
| 58 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 454 |
| 59 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 4-$OCH_3$-quinoline-2-yl | 474 |
| 60 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 4-OH-quinoline-4-yl | 460 |
| 61 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 466 |
| 62 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 410 |
| 63 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 454 |

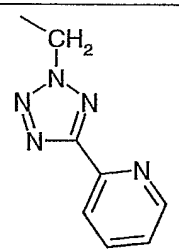
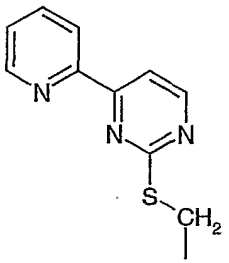
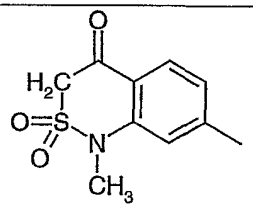
| | | | | |
|---|---|---|---|---|
| 64 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 424 |
| 65 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 536 |
| 66 | 3,4-$Cl_2$-$C_6H_3$ | 2 | Isoquinoline-2-yl | 444 |
| 67 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 6-$CO_2CH_3$-pyridin-2-yl | 452 |
| 68 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 6-$OCH_3$-pyridin-3-yl | 424 |
| 69 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 6-$CH_3$-pyridin-3-yl | 408 |
| 70 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 2-$OCH_2CF_3$-pyridin-3-yl | 492 |
| 71 | 3,4-$Cl_2$-$C_6H_3$ | 2 | Quinoline-2-yl | 444 |
| 72 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 2-Cl-6-$CH_3$-pyridin-4-yl | 442 |
| 73 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 6-$CH_3$-pyridin-2-yl | 408 |
| 74 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 8-OH-quinoline-2-yl | 460 |
| 75 | 3,4-$Cl_2$-$C_6H_3$ | 3 | quinoline-3-yl | 444 |
| 76 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(3-F-$C_6H_4$) | 425 |

| | | | | |
|---|---|---|---|---|
| 77 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 433 |
| 78 | 3,4-$Cl_2$-$C_6H_3$ | 3 | Isoquinoline-3-yl | 444 |
| 79 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 4-(2-$CH_3$-pyridin-4-yl)-$C_6H_4$ | 484 |
| 80 | 3,4-$Cl_2$-$C_6H_3$ | 3 | [1,6]naphthyridine-2-yl | 445 |
| 81 | 3,4-$Cl_2$-$C_6H_3$ | 3 | 2-$CH_3$-[1,6]naphthyridine-3-yl | 459 |
| 82 | 3,4-$Cl_2$-$C_6H_3$ | 3 | 2-$CH_3$- quinoline-3-yl | 458 |
| 83 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 424 |
| 84 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 512 |

| | | | | |
|---|---|---|---|---|
| 85 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 503 |
| 86 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 474 |
| 87 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 508 |

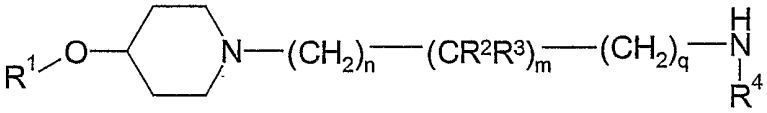
| | | | | |
|---|---|---|---|---|
| 88 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 506 |
| 89 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 1-($CH(CH_3)_2$)-1H-1,2,3-benzotriazole-5-yl | 476 |
| 90 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 2-CN-$C_6H_4$ | 418 |
| 91 | | |  | 485 |
| 92 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 5-(pyridin-2-yl)-2-thiophen-2-yl | 476 |
| 93 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 420 |

| | | | | |
|---|---|---|---|---|
| 94 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 480 |
| 95 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 1-(5-CF3-pyridin-2-yl)-piperidine-4-yl | 545 |
| 96 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 554 |
| 97 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 461 |
| 98 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 2-$CF_3$-[1,8]naphthyridin-3-yl | 513 |
| 99 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 2-$CF_3$-[1,6]naphthyridin-3-yl | 513 |

| | | | | |
|---|---|---|---|---|
| 100 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 476 |
| 101 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 518 |
| 102 | 3,4-$Cl_2$-$C_6H_3$ | 2 | $CH_2$(3-(pyridin-2-yl)-1H-pyrazol-1-yl) | 474 |
| 103 | 3,4-$Cl_2$-$C_6H_3$ | 2 |  | 526 |
| 104 | 3,4-$Cl_2$-$C_6H_3$ | 2 | 6-$CH_3$-2-($SO_2CH_3$)-pyridin-4-yl | 511 |

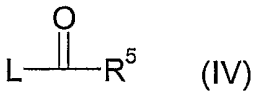
In a further aspect the present invention provides the a compound listed in Table II or a pharmaceutically acceptable salt thereof, or a solvate of a salt thereof. Where compounds of Table II can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers) the present invention covers all such isomers and mixtures thereof in all proportions. Suitable salts include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, acetate, diacetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of the invention can be prepared by reacting a compound of formula (III):



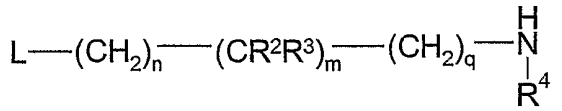
(III)

with a compound of formula (IV):



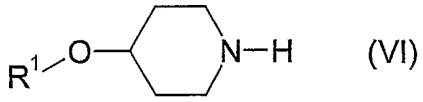
(IV)

wherein L is a leaving group (such as halogen). A compound of formula (III) can be prepared by reacting a compound of formula (V):



(V)

wherein L is a leaving group (such as halogen); with a compound of formula (VI):



(VI)

Alternatively, compounds of the invention can be prepared by adapting the methods provided in the Examples below. Compounds of formula (III), (IV), (V) and (VI) can be prepared by using or adapting methods described in the art or by adapting the methods provided in the Examples below.

In another aspect the present invention provides processes for the preparation of the compounds of the invention.

The compounds of the invention have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CCR3) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or

immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

The compounds of the invention are also H1 antagonists and may be used in the treatment of allergic disorders.

Examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

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

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

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

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

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus

erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle.

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

According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity (especially CCR3 receptor activity) in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound as hereinbefore defined or a pharmaceutically acceptable salt thereof or a solvate thereof.

According to another feature of the present invention there is provided a method for antagonising H1 in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound as hereinbefore defined or a pharmaceutically acceptable salt thereof or a solvate thereof.

The invention also provides a compound as hereinbefore defined or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament.

In a further aspect the present invention provides the use of a compound as hereinbefore defined or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR3 receptor activity) or antagonising H1 in a warm blooded animal, such as man, or both).

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

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis

medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

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

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

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

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

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

in a warm blooded animal, such as man.

In a further aspect a compound of the invention, or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or

pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In a still further aspect a compound of the invention, or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma.

The present invention also provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of asthma or rhinitis.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR3 mediated disease state, especially asthma) or an H1 mediated disease state (such as an allergic disorder) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound as hereinbefore defined or a pharmaceutically acceptable salt thereof or solvate thereof.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR3 receptor) activity or antagonising H1, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

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

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules,

syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

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

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

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

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

(a)

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

(b)

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

(c)

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

(d)

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

(e)

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

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

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

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

(i) when given, $^1$H NMR data is quoted in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard;

(ii) mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(iii) the title and sub-titled compounds of the examples and methods were named using the ACD/name program from Advanced Chemical Development Inc, Canada;

(iv) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry, NovaPak or Ex-Terra reverse phase silica column;

(v) solvents were dried with $MgSO_4$ or $Na_2SO_4$;

(vi) unless otherwise stated reactions were performed at room temperature (RT); and,

(vii) the following abbreviations are used:

| | |
|---|---|
| THF | tetrahydrofuran; |
| DMF | N,N-dimethylformamide |
| DEAD | diethyl-azodicarboxylate |
| TFA | trifluoroacetic acid |
| PyBrop® | Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate |
| HPLC | High pressure liquid chromatography |

Example 1

This Example illustrates the preparation of 4-(3,4-dichlorophenoxy)piperidine.

Step a: *tert*-Butyl 4-(3,4-dichlorophenoxy)-1-piperidinecarboxylate.

Diethyl azodicarboxylate (41.0ml) was added to a solution of triphenylphosphine (62.9g) in THF (800ml) at 0°C. After 15 minutes 3,4-dichlorophenol (39.1g) was added, after a further 15 minutes *tert*-butyl 4-hydroxy-1-piperidinecarboxylate (48.3g) in THF (400ml) was added dropwise over 30 minutes. The solution was stirred at room temperature for 16 hours and concentrated to a small volume. Purification by flash chromatography (ethyl acetate: isohexane 95:5) gave the sub-title compound as an oil (61.3g).

MS: APCI (+ve): 246 (M-BOC+2H)

Step b: 4-(3,4-Dichlorophenoxy)piperidine

The product from Step (a) was dissolved in dichloromethane (600ml) and trifluoroacetic acid (300ml) was added. After 24 hours at room temperature the solution was evaporated and the resultant gum triturated under ether to give the sub-titled product as a solid (36.6g). The free base was liberated by addition of aqueous NaOH (2M) and extraction with ethyl acetate followed by evaporation of solvent to give the title compound as a gum (25g).

$^1$H NMR: ($CDCl_3$): δ 1.77 (1H, br s), 2.05-2.26 (4H, m), 3.20-3.49 (4H, m), 4.61 (1H, s), 6.69-7.52 (3H, m).

Example 2

This Example illustrates the preparation of *N*-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-3-(methylsulfonyl)benzamide hydrochloride (a salt of Compound 20 of Table I).

Step a: *tert*-butyl 3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propylcarbamate

The product from Example 1 Step (b) (10g) was dissolved in DMF (50ml) and triethylamine (14.8ml) was added. *tert*-Butyl 3-bromopropylcarbamate (10g) was added and the solution stirred at room temperature for 24 hrs. The solvent was evaporated and the resulting solid was dissolved in ethyl acetate and water was added, the organic phase separated, dried with $MgSO_4$ and evaporated to a solid (17.51g).

M: ESI (+ve): 403 (M+H)

Step b: 3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propylamine

The product from Step (a) (2g) was dissolved in dioxane (100ml) and 6N HCl (100ml) added. After 18hours at room temperature the solvent was evaporated and the resultant solid basified with NaOH (2N) to pH 11. The aqueous was extracted with ethyl acetate, the organic phase separated, dried with $MgSO_4$ and evaporated to leave the sub-title compound as an oil (1.1g).

MS: ESI (+ve): 303 (M+H)

Step c: *N*-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-3-(methylsulfonyl)benzamide hydrochloride

The product of Step (b) (0.15g) was dissolved in DMF (4ml). 3-Methylsulphonyl-benzoic acid (0.110g), triethylamine (0.250ml) and PyBrop® (0.350g) were added. After 8 hours at room temperature the solvents were evaporated and the residue redissolved in ethyl acetate. The organics were washed with $H_2O$, dried with $MgSO_4$ and concentrated. Purification by reverse phase HPLC (with a gradient eluent system (25% $MeCN/NH_4OAc_{aq}$ (0.1%) to 95% $MeCN//NH_4OAc_{aq}$ (0.1%)) and formation of the hydrochloride salt by addition of HCl dissolved in ether and evaporation of solvent gave the title compound (0.145g).

MS: APCI (+ve): 485 (M+H).

$^1$H NMR (400MHz, DMSO): δ 1.93 - 2.08 (4H, m), 2.14 - 2.26 (2H, m), 3.11 - 3.20 (4H, m), 3.22 (3H, s), 3.33 - 3.39 (1H, m), 3.41 (2H, q), 3.50 - 3.57 (1H, m), 4.76 - 4.80 (1H, m), 7.02 (1H, dd), 7.25 - 7.32 (1H, m), 7.47 - 7.53 (1H, m), 7.74 (1H, t), 8.06 (1H, dt), 8.19 (1H, dt), 8.39 (1H, t), 8.74 - 8.80 (1H, m).

Melting point: 212°C

Example 3

This Example illustrates the preparation of *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-(methylsulfonyl)benzamide hydrochloride (a salt of Compound 19 of Table I).

Step a: *tert*-Butyl 2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethylcarbamate

The product from Example 1 Step (b) (8.6g) was dissolved in DMF (60ml) and triethylamine (12ml) was added. *tert*-Butyl 2-bromoethylcarbamate (7.8g) was added and the solution stirred at room temperature for 12 hours. Diethyl ether/$H_2O$ (1:1 500ml) added and the organic phase separated, dried with $MgSO_4$ and evaporated to a gum. Purification by flash chromatography (dichloromethane: methanol: 880 $NH_3$ (aq) 98.5:1:0.5) gave the sub-title product (10g).

MS: APCI (+ve): 389(M+H)

Step b: 2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethylamine

The product from Step a (10g) was dissolved in dichloromethane (200ml) and trifluoroacetic acid (100ml) added. After 12hours at room temperature the solvent was evaporated and the resultant solid was washed with diethyl ether and filtered. The solid

was redissolved in $H_2O$, basified with NaOH (2N) to pH 11. The aqueous was extracted with dichloromethane, the organic phase separated, dried and evaporated to leave the sub-title compound (3.5g).

MS: APCI (+ve): 289 (M+H)

Step c: *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-(methylsulfonyl)benzamide hydrochloride

The product of Step b (0.200g) was dissolved in DMF (5ml). 3-Methylsulphonyl-benzoic acid (0.132g), triethylamine (0.250ml) and PyBrop® (0.420g) were added. After 24 hours at room temperature the solvents were evaporated and the residue redissolved in ethyl acetate. The organics were washed with $H_2O$, dried with $MgSO_4$ and concentrated. Purification by reverse phase HPLC (with a gradient eluent system (25% $MeCN/NH_4OAc_{aq}$ (0.1%) to 95% $MeCN//NH_4OAc_{aq}$ (0.1%)) (any excess $NH_4OAc$ was removed by dissolving the compound in ethyl acetate and washing with aqueous saturated $NaHCO_3$ followed by drying of the organics with $MgSO_4$ and evaporation of solvent) and formation of the hydrochloride salt by addition of HCl dissolved in ether and evaporation of solvent gave the title compound (0.084g).

MS: APCI (+ve): 471 (M+H)

$^1H$ NMR: (399.979 MHz, $D_2O$) δ 2.09 - 2.19 (2H, m), 2.25 - 2.33 (2H, m), 3.30 (3H, s), 3.38 - 3.46 (2H, m), 3.48 (2H, t), 3.58 - 3.66 (2H, m), 3.80 - 3.91 (3H, m), 6.98 (1H, dd), 7.25 (1H, d), 7.47 (1H, d), 7.82 (1H, t), 8.17 (2H, t), 8.36 (1H, s).

Melting point: 219°C

Example 4

This Example illustrates the preparation of *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-[(methylsulfonyl)methyl]benzamide (Compound 5 of Table I).

The product of Example 3, Step (b) (0.200g) was dissolved in dichloromethane (4ml). 3-[(Methylsulfonyl)methyl]benzoic acid (see WO00/15609; or by hydrolysis of methyl 3-[(methylsulfonyl)methyl]benzoate which is commercially available; 0.132g), triethylamine (0.289ml) and PyBrop® (0.483g) were added. After 24 hours at room temperature $NaHCO_3$(aq) was added and product extracted with diethyl ether. The organics were dried with $MgSO_4$ and concentrated. Purification by reverse phase HPLC (with a gradient eluent system (25% $MeCN/NH_4OAc_{aq}$ (0.1%) to 95% $MeCN//NH_4OAc_{aq}$ (0.1%)) (any excess $NH_4OAc$ was removed by dissolving the compound in

dichloromethane and washing with aqueous saturated $NaHCO_3$ followed by drying of the organics with $MgSO_4$ and evaporation of solvent) gave the title compound (0.101g).

MS: APCI(+ve): 485 (M+H).

$^1$H NMR (299.946 MHz, DMSO) δ 1.58 - 1.67 (2H, m), 1.89 - 1.97 (2H, m), 2.27 - 2.35 (2H, m), 2.49 - 2.53 (2H, m), 2.70 - 2.79 (2H, m), 2.94 (3H, s), 3.38 - 3.43 (2H, m), 4.41 - 4.49 (1H, m), 4.54 (2H, s), 4.81-4.83 (1H, m) 6.96 - 7.00 (1H, m), 7.25 - 7.27 (1H, m), 7.47 - 7.57 (3H, m), 7.82 - 7.87 (2H, m), 8.42 - 8.47 (1H, m).

Melting point: 112-114°C

Example 5

This Example illustrates the preparation of *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4-[(methylsulfonyl)methyl]benzamide (Compound 7 of Table I).

Prepared in a similar manner to the method of Example 4 using 4-[(methylsulfonyl)methyl]benzoic acid (J. Med. Chem. (1997), 40(25), 4030-4052) to give the title compound as a solid (0.160g).

MS: APCI(+ve): 485 (M+H)

$^1$H NMR (299.946 MHz, DMSO) δ 1.56 - 1.65 (2H, m), 1.89 - 1.98 (2H, m), 2.26 - 2.35 (2H, m), 2.65 - 2.82 (2H, m), 2.71 - 2.78 (2H, m), 2.92 (3H, s), 3.37 - 3.41 (2H, m), 4.40 - 4.49 (1H, m), 4.56 (2H, s), 6.96 - 7.00 (1H, m), 7.24 - 7.27 (1H, m), 7.48 - 7.53 (3H, m), 7.82 - 7.86 (2H, m), 8.42 - 8.47 (1H, m).

Melting point: 179-181°C.

Example 6

This Example illustrates the preparation of *N*-(cyclopropylmethyl)-*N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-4-fluoro-3-methoxybenzamide (Compound 15 of Table I).

Step a: *tert*-Butyl 4-(3,4-difluorophenoxy)-1-piperidinecarboxylate

The sub-title compound was prepared according to the method of Example 1, Step a using 3,4-difluorophenol to afford an oil (5.4g).

MS: ESI (+ve): 213 (M-BOC+H)

Step b: 4-(3,4-Difluorophenoxy)piperidine

The sub-title compound was prepared according to the method of Example 1, Step b to afford a pale yellow oil (3g).

MS: ESI (+ve): 214 (M+H)

Step c: *tert*-butyl 2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethylcarbamate

The product of Step b (5g) was dissolved in DMF (27ml) and triethylamine (7.7ml) was added. *tert*-Butyl 2-bromoethylcarbamate (5.8g) was added and the solution stirred at room temperature for 24 hrs. The solvent was evaporated and the residue dissolved in ethyl acetate and washed with water. The organic phase separated, dried and evaporated. Purification by flash chromatography (dichloromethane : methanol 97:3) gave the sub-title product as an oil (10g) containing a small amount of DMF.

MS: APCI(+ve): 357 (M+H)

Step d: 2-[4-(3,4-Difluorophenoxy)-1-piperidinyl]ethylamine

The product of Step c (10g) was dissolved in dioxane (114ml) and HCl (6N) (114ml) was added and the reaction stirred for 2 hours. Organic solvent was evaporated and aqueous NaOH (2M) added. The product was extracted with ethyl acetate, the combined organic extracts dried with $Na_2SO_4$ and concentrated to give the sub-title product as an oil (4.65g).

$^1$H NMR: (400 MHz, $CDCl_3$) δ 1.74-1.83 (2H, m), 1.95-2.00 (2H, m), 2.26-2.31 (2H, m), 2.43 (2H, t), 2.73 (2H, br s), 2.79 (2H, t), 4.17-4.23 (1H, m), 6.58-7.07 (3H, m).

MS: APCI(+ve): 257 (M+H)

Step e: *N*-(Cyclopropylmethyl)-*N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}amine

The product of Step d (0.4g) dissolved in MeOH (6ml) was added to cyclopropanecarbaldehyde (0.116ml) and the resulting mixture was stirred for 4 hours. The solvent was evaporated, the residue re-dissolved in methanol (6ml) and $NaBH_4$ (0.095g) added and the mixture left for 30 minutes. Aqueous sodium hydroxide (1N) was added and the aqueous extracted with diethyl ether. The organic extracts were dried with $Na_2SO_4$, filtered and concentrated to give the sub-title product as an oil (0.493g).

MS: APCI(+ve): 311 (M+H)

Step f: *N*-(Cyclopropylmethyl)-*N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-4-fluoro-3-methoxybenzamide

To a solution of 4-fluoro-3-methoxybenzoic acid (0.082g) in THF (1ml) was added carbonyldiimidazole (0.078g) and the resulting solution stirred at room temperature for 10

minutes before addition of the product of Step e (0.15g) in THF (1.5ml). The mixture was stirred for 2 hours and the solvent removed by evaporation to yield a colourless gum. Purification by reverse phase HPLC (with a gradient eluent system 25% MeCN/$NH_4OAc$(aq) (0.1%) to 95% MeCN//$NH_4OAc$(aq) (0.1%)) gave the title compound (0.011g).

MS: ESI(+ve) 463(M+H)

$^1$H NMR (300 MHz, $CDCl_3$) δ 0.13 - 0.22 (2H, m), 0.52 - 0.58 (2H, m), 0.93 - 1.04 (1H, m), 1.70 - 1.81 (2H, m), 1.88 - 1.99 (2H, m), 2.25 - 2.40 (2H, m), 2.55 - 2.79 (4H, m), 3.22 - 3.33 (2H, m), 3.59 - 3.71 (2H, m), 3.90 (3H, s), 4.14 - 4.22 (1H, m), 6.55 - 6.61 (1H, m), 6.70 (1H, ddd), 6.92 (1H, ddd), 7.01 - 7.06 (2H, m), 7.08 (1H, d).

Example 7

This Example illustrates the preparation of *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-3-(methylsulfonyl)benzamide hydrochloride (a salt of Compound 16 of Table I).

The product of Example 6, Step d (0.200g) was dissolved in THF (4ml), 3-methylsulphonylbenzoic acid (0.156g), N,N-di-isopropylethylamine (0.407ml) and PyBrop® (0.401g) were added. After 18 hours at room temperature ethyl acetate and aqueous $NaHCO_3$ solution were added. The product was extracted with ethyl acetate, the combined organic extracts dried with $MgSO_4$ and concentrated. Purification by reverse phase HPLC (with a gradient eluent system 45% MeCN/$NH_4OAc_{aq}$ (0.1%) to 95% MeCN//$NH_4OAc_{aq}$ (0.1%)) and formation of the hydrochloride salt by addition of HCl dissolved in ether and evaporation of solvent gave the title compound (0.205g).

MS: APCI(+ve) 439 (M+H)

$^1$H NMR (300 MHz, DMSO) δ 1.93-2.26 (4H, m), 3.05-3.76 (10H, m), 4.50-4.60 (1H, m), 4.76 (1H, brs), 6.81-8.50 (7H, m), 9.29-9.33 (1H, m), 10.81 (1H, br s).

Example 8

This Example illustrates the preparation of *N*-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-(2,5-dihydro-1*H*-pyrrol-1-yl)-1,3-benzothiazole-6-carboxamide (Compound 17 of Table I).

Prepared in a similar manner to the method of Example 6, Step f using the product of Example 2, Step b and 2-(2,5-dihydro-1*H*-pyrrol-1-yl)-1,3-benzothiazole-6-carboxylic acid to give the title compound as a solid (0.026g).

MS: ESI(+ve) 531 (M+H)

$^1$H NMR: (399.978 MHz, $CDCl_3$) δ 1.66 - 2.25 (6H, m), 2.11 - 2.24 (2H, m), 2.72 - 2.83 (3H, m), 2.85 - 2.95 (2H, m), 3.64 (2H, q), 4.37 - 4.45 (1H, m), 6.41 (2H, t), 6.75 (1H, dd), 7.00 (1H, d), 7.21 (2H, d), 7.47 (2H, t), 7.89 (1H, d), 7.94 - 7.96 (1H, m), 8.39 (1H, s), 8.42 - 8.47 (1H, m).

Example 9

This Example illustrates the preparation of *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-3-methoxy-*N*-methylbenzamide hydrochloride (Compound 18 of Table I).

Step a: *N*-{2-[4-(3,4-Difluorophenoxy)-1-piperidinyl]ethyl}-2,2,2-trifluoroacetamide

To a solution of the product of Example 6, Step d (1.5g) and triethylamine (2.45ml) at $0^0$C in dichloromethane (20ml) was added trifluoroacetic anhydride (1.24ml) dropwise over 10 minutes. After warming to RT the reaction mixture was partitioned between water (20ml) and dichloromethane (20ml). The organic phase was separated and dried with $MgSO_4$. Purification by flash chromatography (dichloromethane: methanol: 98:2)gave the sub-title compound as a colourless oil (1.64g).

MS: ESI(+ve) 353(M+H)

$^1$H NMR: (299.944 MHz, $CDCl_3$) δ1.75 - 1.86 (2H, m), 1.93 - 2.02 (2H, m), 2.36 (2H, ddd), 2.58 (2H, t), 2.73 (2H, td), 3.44 (2H, q), 4.25 (1H, m), 6.57 - 6.63 (1H, m), 6.72 (1H, ddd), 6.96 - 7.07 (1H, m), 7.05 (1H, q).

Step b: *N*-{2-[4-(3,4-Difluorophenoxy)-1-piperidinyl]ethyl}-2,2,2-trifluoro-*N*-methylacetamide

A solution of the product of Step a (1.64g) in THF (5ml) was added dropwise to a suspension of sodium hydride (0.205g 60% suspension in oil) in THF (20ml) at $0^0$C. The reaction mixture was allowed to warm to RT over 30 min before cooling again to $0^0$C. Methyl iodide (0.29ml) in THF (5ml) was added dropwise. The reaction mixture was left stirring at RT for 18 hours before removal of solvents by evaporation. Purification by flash chromatography (dichloromethane: methanol: 880 $NH_3$ (aq) 98.5:1:0.5) gave the title product (0.3g).

MS: ESI(+ve) 367(M+H)

Step c: *N*-{2-[4-(3,4-Difluorophenoxy)-1-piperidinyl]ethyl}-*N*-methylamine

To a solution of the product of Step b (0.3g) in ethanol (15ml) was added a 2M solution of sodium hydroxide (5ml). The mixture was stirred at RT for 72 hours. The resultant mixture was partitioned between EtOAc (20ml) and water (20ml). The organic layer was separated and dried with $MgSO_4$. Removal of solvent under reduced pressure gave the title compound (0.2g).

MS: ESI(+ve) 367(M+H)

$^1$H NMR (300 MHz, $CDCl_3$) δ 1.74 - 1.84 (2H, m), 1.92 - 2.01 (2H, m), 2.25 - 2.33 (2H, m), 2.46 (3H, s), 2.51 (2H, t), 2.68 - 2.77 (2H, m), 2.68 (2H, t), 4.20 (1H, tt), 6.57 - 6.62 (1H, m), 6.72 (1H, ddd), 7.04 (1H, dt).

Step d: *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-3-methoxy-*N*-methylbenzamide hydrochloride

To a solution of the product of Step c (0.145g) and triethylamine (0.224ml) in THF (3ml) at $0^0$C was added a solution 3-methoxybenzoyl chloride (0.083ml) in THF (2ml). The mixture was stirred for 1 hour then partitioned between ethyl acetate and water. The organic layer was separated and dried with $MgSO_4$ and the solvent removed by evaporation. Purification by reverse phase HPLC (with a gradient eluent system 25% MeCN/$NH_4OAc$(aq) (0.1%) to 95% MeCN//$NH_4OAc$(aq) (0.1%)) evaporation of solvent and the residue was dissolved in diethyl ether and HCl (1ml 1M solution in diethyl ether) added. Filtration gave the title compound (0.137g).

MS: ESI(+ve) 405(M+H)

$^1$H NMR (400 MHz, $D_2O$) δ 1.91 - 2.02 (1H, m), 2.13 (1H, t), 2.30 (1H, d), 2.44 (1H, d), 3.06 (3H, s), 3.24 (1H, t), 3.35 - 3.47 (2H, m), 3.52 (2H, t), 3.65 (1H, d), 3.80 (1H, t), 3.86 (3H, s), 3.97 (2H, t), 6.77 - 6.85 (1H, m), 6.94 - 7.16 (4H, m), 7.20 - 7.27 (1H, m), 7.45 - 7.52 (1H, m)

Melting point: 218°C

## Example 10

This Example illustrates the preparation of *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-hydroxybenzamide (Compound 8 of Table II).

Step a: *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide

The product from Example 3, Step b (2.00g) was dissolved in THF (100ml) and triethylamine (2.10g) added. The solution was then cooled with stirring to 0°C and to it 3-

methoxybenzoyl chloride was added dropwise as a solution in THF (10ml). Reaction was left to warm to room temp and left for 24hours then water was added and the organics extracted into ethyl acetate. The combined organics were dried with $MgSO_4$ and the solvent removed by evaporation. The crude product was purified by flash chromatography to leave the sub-title product as a pale yellow oil (1.38g).

MS: APCI(+ve): 424 (M+H)

Step b: *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-hydroxybenzamide

The product from Step a (1.3g) was dissolved in dichloromethane (40ml) under nitrogen and cooled to –78°C. Boron tribromide was then added slowly and reaction left to warm to room temp and left over 72hours. Methanol was added followed by flash silica (for preabsorption) and purification by flash chromatography (dichloromethane: methanol: 880 $NH_3$ (aq) 96.8:4:0.2) to give the title product (1.1g).

$^1$H NMR (300 MHz, $CDCl_3$) δ 1.80 - 1.91 (2H, m), 1.97 - 2.09 (2H, m), 2.48 (2H, t), 2.69 (2H, t), 2.80 (2H, t), 3.60 (2H, q), 4.33 (1H, quintet), 6.75 (1H, dd), 6.91 (1H, ddd), 7.00 (1H, d), 7.16 (1H, d), 7.21 (1H, d), 7.31 (1H, d), 7.40 (1H, t).

Example 11

The present Example illustrates the preparation of *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-[2-(dimethylamino)-2-oxoethoxy]benzamide acetate (a salt of Compound 86 of Table II).

The product from Example 10, Step b (0.150g) was dissolved with 2-chloro-*N*,*N*-dimethylacetamide (0.045g) in dimethylformamide (10ml) with stirring under nitrogen. Caesium carbonate (0.241g) was then added and reaction left for 24hours. Evaporation of solvent and purification by flash chromatography (dichloromethane: methanol: 880 $NH_3$ (aq) 96.9:3:0.15) followed by reverse phase HPLC (with a gradient eluent system (25% $MeCN/NH_4OAc_{aq}$ (0.1%) to 95% $MeCN//NH_4OAc_{aq}$ (0.1%)) gave the product as an acetate salt (0.090g).

MS: APCI(+ve): 494 (M+H)

$^1$H NMR: (299.944 MHz, $CDCl_3$) δ 1.74 - 1.88 (2H, m), 1.96 - 2.06 (2H, m), 2.17 (3H, s), 2.38 - 2.47 (2H, m), 2.65 (2H, t), 2.73 - 2.85 (1H, m), 2.99 (3H, s), 3.08 (3H, s), 3.56 (2H, q), 3.98 - 4.13 (1H, m), 4.27 - 4.37 (1H, m), 4.75 (2H, s), 6.76 (1H, dd), 6.99-7.04 (2H, m), 7.08 - 7.12 (1H, m), 7.28 - 7.41 (4H, m).

Example 12

This Example illustrates the preparation of methyl{3-[({2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}amino)carbonyl]phenoxy}acetate hydrochloride (a salt of Compound 87 of Table II).

To a solution of the product from Example 10, Step b (0.250g) and methyl chloroacetate (0.066g) in dimethylformamide (10ml) under nitrogen was added caesium carbonate (0.4g). The reaction was left to stir for 24hours. Water was added and organics extracted into ethyl acetate and dried with $MgSO_4$. Evaporation of solvent and purification by reverse phase HPLC (with a gradient eluent system 25% MeCN/$NH_4OAc_{aq}$ (0.1%) to 95% MeCN//$NH_4OAc_{aq}$ (0.1%)) gave the product. The isolated product was then converted to title product by dissolving in diethylether, adding ethereal hydrochloric acid and triturating from diethylether to give the titled product as a white powder (0.050g).

MS: APCI(+ve): 481 (M+H)

$^1$H NMR (300 MHz, $D_2O$) δ 1.94 - 2.02 (2H, m), 2.38 - 2.46 (2H, m), 3.25 (2H, t), 3.41 - 3.44 (2H, m), 3.48 (2H, t), 3.56 - 3.66 (2H, m), 3.84 (3H, s), 4.61 - 4.74 (1H, m), 4.88 (2H, s), 6.99 (1H, dd), 7.21 - 7.27 (2H, m), 7.37 - 7.40 (2H, m), 7.49 (2H, t).

Example 13

This Example illustrates the preparation of *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-(2-hydroxyethoxy)benzamide hydrochloride (a salt of Compound 21 of Table I).

To a solution of the product from Example 10, Step b (0.2g) and 2-(2-bromoethoxy)tetrahydro-2H-pyran (0.209g) in dimethylformamide (10ml) under nitrogen was added caesium carbonate (0.326g). After stirring for 24hours, water was added and organics extracted into ethyl acetate separated and dried with $MgSO_4$. Evaporation of solvent and purification by flash chromatography (eluent 2% MeOH, 0.1% 0.880 ammonia, 97.9% dichloromethane) gave the THP protected titled product. Deprotection of the product was achieved by stirring in trifluoroacetic acid:dichloromethane (1:2) solution (65ml) for 30mins. $NaHCO_3$(aq) was added. The product was extracted with ethyl acetate, the combined organic extracts dried with $MgSO_4$ and concentrated to give the crude titled product. Purification by reverse phase HPLC (with a gradient eluent system 25% MeCN/$NH_4OAc_{aq}$ (0.1%) to 95% MeCN//$NH_4OAc_{aq}$ (0.1%)) was achieved. The isolated product was then converted to title product by dissolving in diethylether, adding ethereal hydrochloric acid and triturating from diethylether to give the titled product (0.069g).

MS: APCI(+ve): 453 (M+H)

$^1$H NMR (400 MHz, DMSO) δ 2.01 – 2.15 (2H,m), 2.27 – 2.34 (2H,m), 3.20 –3.26 (2H,m), 3.32 – 3.41 (2H,m), 3.49- 3.57 (2H,m), 3.69 – 3.90 (4H,m), 4.11 (2H,t), 4.60 – 4.75 (1H,m), 7.05 –7.12 (1H,m), 7.17 (1H,d), 7.41 - 7.47 (2H, m), 7.54 - 7.64 (2H, m) 8.96 (1H,s).

Example 14

This Example illustrates the preparation of *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-[(2-hydroxyethyl)sulfonyl]benzamide acetate (a salt of Compound 22 of Table I).

Step a: 3-{[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]sulfonyl}benzoic acid

To a solution of 3-sulfino-benzoic acid (1g) and 2-iodoethyl tetrahydro-2*H*-pyran-2-yl ether (1.4g) in water (20ml) and ethanol (20ml) was added NaOH solution to give a pH of 9. The resulting mixture was refluxed for 3 hours before evaporation of the ethanol. The aqueous was acidified to pH3 and the product extracted with EtOAc. The organic layer was separated, dried with $MgSO_4$ and solvent removed by evaporation to give the sub-title compound (0.25g).

MS: ESI(+ve) 230(M+H - THP)

Step b: *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-[(2-hydroxyethyl)-sulfonyl]benzamide acetate

To a solution of the product of Step a (0.20g), the product of Example 3, Step b (0.25g) and diisopropylethyl amine (0.33ml) in dichloromethane (5ml) was added PyBrOP® (0.37g) and the mixture stirred for 24 hours. Purification by Biotage® 40M eluting 20% MeCN/2% 880 ammonia/ 78% dichloromethane gave a colourless oil (0.49g) which was dissolved in trifluoroacetic acid (9ml) and water (1ml) and stirred for 15 minutes. The solvents were evaporated under reduced pressure and purification by reverse phase HPLC (with a gradient eluent system 25% MeCN/$NH_4OAc$aq (0.1%) to 95% MeCN//$NH_4OAc$(aq) (0.1%)) (any excess $NH_4OAc$ was removed by dissolving the compound in ethyl acetate and washing with aqueous saturated $NaHCO_3$ followed by drying of the organics with $MgSO_4$ and evaporation of solvent) and formation of the acetate salt by dissolving in acetic acid and evaporation of the excess acid gave the title product (0.050g).

MS: ESI(+ve) 501 (M+H)

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.79 - 1.87 (2H, m), 1.95 - 2.04 (3H, m), 2.42 (2H, t), 2.65 (2H, t), 2.77 (2H, t), 3.43 (2H, t), 3.58 (2H, q), 3.80 (2H, t), 4.29 - 4.35 (1H, m), 6.76 (1H, dd), 6.92 - 6.97 (1H, m), 7.00 (1H, d), 7.31 (1H, d), 7.65 (1H, t), 8.05 (1H, d), 8.10 (1H, d), 8.30 (1H, t)

Example 15

This Example illustrates the preparation of *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-[(methylamino)sulfonyl]benzamide acetate (a salt of Compound 9 of Table I).

Prepared in a similar manner to the method of Example 14, Step b using the product from Example 3, Step b and 3-[(methylamino)sulfonyl]benzoic acid to give the title product (0.269g).

MS: ESI(+ve) 486 (M+H)

$^1$H NMR (500.076 MHz, DMSO) δ 1.57-1.65 (2H, m), 1.91-1.96 (2H, m), 2.31 (2H, t), 2.43(3H, s), 2.49-2.52 (5H, m), 2.72-2.78 (2H, m), 3.41 (2H, q), 4.45 (1H, m), 6.99 (1H, dd), 7.26 (1H, d), 7.50 (1H, d), 7.52-7.58 (1H, m), 7.72 (1H, t), 7.91 (1H, d), 8.09 (1H, d), 8.24(1H, s), 8.69 (1H, t).

Example 16

This Example illustrates the preparation of *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-(2-methoxyethoxy)benzamide hydrochloride (A salt of Compound 12 of Table I).

Prepared in a similar manner to the method of Example 14, Step b using the product from Example 3, Step b and 3-(2-methoxyethoxy)benzoic acid to give the title product after formation of a hydrochloride salt (0.213g).

MS: ESI(+ve) 467 (M+H)

$^1$H NMR: (500.076 MHz, DMSO) δ 1.83 - 1.91 (1H, m), 2.02 - 2.14 (2H, m), 2.22 - 2.31 (1H, m), 3.07 - 3.16 (2H, m), 3.17 - 3.25 (2H, m), 3.32 (3H, s), 3.44 - 3.52 (1H, m), 3.62 - 3.73 (2H, m), 3.68 (2H, t), 4.15 (2H, t), 4.57 - 4.65 (1H, m), 4.81 - 4.85 (1H, m), 7.02 - 7.09 (1H, m), 7.14 (1H, d), 7.35 - 7.38 (1H, m), 7.40 (1H, t), 7.45 - 7.49 (2H, m), 7.56 (1H, t), 8.78 - 8.85 (1H, m).

Example 17

This Example illustrates the preparation of *tert*-butyl 2-{3-[({2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}amino)carbonyl]phenoxy}ethylcarbamate acetate (a salt of Compound 23 of Table I).

Step a: Methyl 3-{2-[(*tert*-butoxycarbonyl)amino]ethoxy}benzoate

To a solution of *tert*-butyl 2-bromoethylcarbamate (5g) and methyl 3-hydroxybenzoate (3.4g) in dimethylformamide (60ml) was added caesium carbonate (14.5g) and the reaction stirred for 12hours before partitioning between water and ethyl acetate. The organic layer was separated, dried with $MgSO_4$ and the solvent removed by evaporation. Purification by flash chromatography (ethyl acetate: isohexane 92.5:7.5) gave the sub-title product as a colourless oil (3g).

$^1$H NMR ($CDCl_3$) δ 1.41 (9H, s), 3.51 (2H, q), 3.87 (3H, s), 4.02 (2H, t), 5.03 - 5.10 (1H, m), 7.05 (1H, ddd), 7.30 (1H, t), 7.50 - 7.51 (1H, m), 7.60 (1H, dt).

Step b: 3-{2-[(*tert*-butoxycarbonyl)amino]ethoxy}benzoic acid

To a solution of the product of Step a (6g) in THF (120ml) was added lithium hydroxide monohydrate (4.9g) and enough water to ensure full disolution. The reaction was stirred for 12 hours, acidified with 2M HCl and partitioned between ethyl acetate and water. The organic layer was separated, dried with $MgSO_4$ and the solvent removed by evaporation to give the title compound (3.9g).

$^1$H NMR (400 MHz, DMSO) δ 1.38 (9H, s), 3.31 (2H, t), 4.01 (2H, t), 7.02 (1H, t), 7.19 (1H, dt), 7.39 - 7.43 (2H, m), 7.53 (1H, d), 12.97 (1H, s).

Step c: *tert*-butyl 2-{3-[({2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}amino)-carbonyl]phenoxy}ethylcarbamate acetate

Prepared in a similar manner to the method of Example 14, Step b using the product from Step b and the product of Example 3, Step b to give the title product (0.234g).

MS: ESI(+ve) 552 (M+H)

$^1$H NMR: (500.076 MHz, DMSO) δ 1.38 (9H, s), 1.57 - 1.64 (2H, m), 1.89 - 1.94 (2H, m), 1.96 (3H, s), 2.29 (2H, t), 2.47 - 2.51 (6H, m), 2.72 - 2.76 (2H, m), 4.00 (2H, t), 4.43 - 4.46 (1H, m), 6.98 (1H, dd), 7.02 (1H, t), 7.07 - 7.09 (1H, m), 7.26 (1H, d), 7.35 - 7.43 (3H, m), 7.50 (1H, d), 8.39 (1H, t).

Example 18

This Example illustrates the preparation of *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-[(methylsulfonyl)amino]benzamide (Compound 24 of Table I).

Step a: 3-amino-*N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide

Prepared in a similar manner to the method of Example 14, Step b using the product from Example 3, Step b and 3-aminobenzoic acid to give the sub-title product (0.183g).

MS: ESI(+ve) 448 (M+H).

Step b: *N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-[(methylsulfonyl)amino]-benzamide

To a solution of the product of Step a in pyridine (2ml) was added methanesulfonyl chloride (0.034ml) and the reaction left to stir for 5 mins. Water (0.5ml) was added and the solvents evaporated. Purification by reverse phase HPLC (with a gradient eluent system (25% MeCN/$NH_4OAc_{aq}$ (0.1%) to 95% MeCN//$NH_4OAc_{aq}$ (0.1%)) (any excess $NH_4OAc$ was removed by dissolving the compound in dichloromethane and washing with aqueous saturated $NaHCO_3$ followed by drying of the organics with $MgSO_4$ and evaporation of solvent) gave the title product (0.091g).

MS: APCI (+ve) 486 (M+H)

$^1H$ NMR (400 MHz, $CDCl_3$) δ 1.80-1.87 (2H, m), 1.96-2.04 (2H, m), 2.38-2.43 (2H, m), 2.64-2.67 (2H, m), 2.79-2.84 (2H, m), 3.02 (3H, s), 3.57-3.62 (2H, m), 4.31-4.32 (1H, m), 6.75-7.90 (9H, m).

Melting point: 150-151°C

Example 19

This Example illustrates the preparation of 3-(2-aminoethoxy)-*N*-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide dihydrochloride (a salt of Compound 25 of Table I).

To a solution of the product of Example 17, Step c (0.163) in dioxane (5ml) was added concentrated HCl (1ml) and the mixture stirred for 3 hours. The solvents were evaporated and excess HCl removed by azeotroping with toluene. The residue was dissolved in water and after freeze drying gave the title compound (0.145g).

MS: ESI(+ve) 452 (M+H).

$^1$H NMR (300 MHz, DMSO) δ 1.96 - 2.10 (2H, m), 2.18 - 2.30 (2H, m), 3.06 - 3.35 (6H, m), 3.42 - 3.50 (1H, m), 3.65 - 3.83 (3H, m), 4.28 (2H, t), 4.58 - 4.70 (1H, m), 4.85 (1H, s), 7.02 - 7.18 (2H, m), 7.33 - 7.45 (2H, m), 7.50 - 7.62 (3H, m), 8.33 (2H, s), 9.04 - 9.11 (1H, m).

Example 20

This Example illustrates the preparation of derivatives of (1*S*)-2-[4-(3,4-difluorophenoxy)-1-piperidinyl]-1-phenylethylamine

Step a: *tert*-butyl (1*S*)-2-[4-(3,4-difluorophenoxy)-1-piperidinyl]-2-oxo-1-phenylethylcarbamate

To (2*S*)-[(*tert*-butoxycarbonyl)amino](phenyl)ethanoic acid (1g) in $CH_2Cl_2$/DMF (1:1) (20ml) was added 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (0.989g) and left to stir for 5 mins. The product of example 6, step b (0.848g) was then added and the reaction left to stir for 24 hrs. Aqueous $NaHCO_3$ solution was added and the product extracted with $CH_2Cl_2$. The organic phase was washed with $H_2O$ dried with $Na_2SO_4$ and purification by flash chromatography (ethyl acetate: isohexane 30:70) gave the sub-title compound (0.650g).

MS: ESI(+ve): 447 (M+H)

Step b: (1*S*)-2-[4-(3,4-difluorophenoxy)-1-piperidinyl]-2-oxo-1-phenylethylamine

The product from Example 20, step a (0.650g) was dissolved in dichloromethane (7ml) and trifluoroacetic acid (2ml) was added. After 3 hr at room temperature the solution was evaporated and aqueous NaOH (2M) added. The product was extracted with ethyl acetate, the combined organic extracts dried with $Na_2SO_4$ and concentrated to give the sub-title product as an oil (0.544g).

MS: ESI(+ve): 347 (M+H)

Step c: (1*S*)-2-[4-(3,4-difluorophenoxy)-1-piperidinyl]-1-phenylethylamine

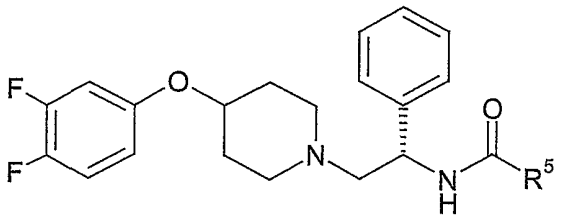
The product from Example 20, step b) (0.544g) was dissolved in THF (5ml) and borane [10.05ml (1M in THF)] was added. The reaction was heated at reflux for 2 hours. The reaction was quenched slowly with MeOH and the solvents evaporated. Aqueous HCl (5ml Concentrated HCl: 5ml $H_2O$) was added and the reaction heated at 70°C for 1hour. NaOH (2M) was added until pH 9 was reached. The product was extracted with $CH_2Cl_2$ and the combined organics washed with saturated aqueous $NaHCO_3$, dried with $Na_2SO_4$

and solvents evaporated. Purification by flash chromatography (dichloromethane: methanol: 880 $NH_3$ (aq) 89:10:1)gave the sub-title compound as an oil (0.377g). $^1H$ NMR: (300MHz, $CDCl_3$) δ 1.76 (6H, m), 2.20-2.92 (6H, m), 4.08-4.13 (1H, m), 4.18-4.21 (1H, m), 6.57-7.40 (8H, m).

This compound was then coupled to various acids, using a similar method to that of Example 7, to provide the compounds listed in Table III.

Table III

The compounds of the invention listed in Table III are compounds having the formula below wherein $R^5$ is as defined in the Table.




| Compound No. | $R^5$ | M+H |
|---|---|---|
| 1 | 4-cyclohexyl-$C_6H_4$ | 519 |
| 2 | 4-n-butyl-$C_6H_4$ | 509 |
| 3 | 3-$N(Me)_2$-$C_6H_4$ | 480 |
| 4 | 4-NHC(O)Me-$C_6H_4$ | 494 |
| 5 | 4-$N(Et)_2$-$C_6H_4$ | 508 |
| 6 | 3-$CO_2$Me-$C_6H_4$ | 495 |
| 7 | 2-$C(O)NH_2$-$C_6H_4$ | 480 |
| 8 | 4-$S(O)_2$-$C_6H_4$ | 515 |
| 9 | 2-I-$C_6H_4$ | 563 |
| 10 | 3-phenoxy-$C_6H_4$ | 529 |
| 11 | 2-Me-$C_6H_4$ | 451 |
| 12 | 3-Me-$C_6H_4$ | 451 |
| 13 | 3-I-$C_6H_4$ | 563 |
| 14 | 2-$NHC_6H_5$-5-$NH_2$-$C_6H_3$ | 543 |
| 15 | 3,5-$F_2$-$C_6H_3$ | 473 |
| 16 | 3-$NO_2$-4-tert-butyl-$C_6H_3$ | 538 |
| 17 | 3-$NO_2$-5-$CO_2$Me-$C_6H_3$ | 540 |

| | | |
|---|---|---|
| 18 | 2-Me-5-$NO_2$-$C_6H_3$ | 496 |
| 19 | 3,5-(tert-butyl)$_2$-$C_6H_3$ | 549 |
| 20 | 2-$NO_2$-5-Me-$C_6H_3$ | 496 |
| 21 | 2-$NO_2$5-SCN-$C_6H_3$ | 539 |
| 22 | 3-OMe-4-Me-$C_6H_3$ | 481 |
| 23 | 4-CN-$C_6H_4$ | 462 |
| 24 | 3-CN-$C_6H_4$ | 462 |
| 25 | 2-$NH_2$-5-I-$C_6H_3$ | 578 |
| 26 | 4-F-$C_6H_4$ | 455 |
| 27 | $CH_2$(2-$NO_2$-$C_6H_4$) | 496 |
| 28 | $CH_2$(2-Cl-$C_6H_4$) | 485 |
| 29 | $CH_2$(4-Cl-$C_6H_4$) | 485 |
| 30 | $OCH_2C_6H_5$ | 557 |
| 31 | $CH_2CH_2$(3,4-(OH)$_2$-$C_6H_3$) | 497 |
| 32 | $CH_2$(4-$NO_2$-$C_6H_4$) | 496 |
| 33 | $(CH_2)_4C_6H_5$ | 493 |
| 34 | $CH_2$(3,4-(OMe)$_2$-$C_6H_3$) | 511 |
| 35 | $CH_2$(4-OEt-$C_6H_4$) | 495 |
| 36 | $CH_2$(3-F-4-OH-$C_6H_3$) | 485 |
| 37 | $(CH_2)_3C_6H_5$ | 479 |
| 38 | $CH_2$(3,4-methylenedioxy-$C_6H_3$) | 495 |
| 39 | $(CH_2)_3$(4-OMe-$C_6H_4$) | 509 |
| 40 | $(CH_2)_2$(4-OH-$C_6H_4$) | 481 |
| 41 | $CH_2$(4-OH-$C_6H_4$) | 467 |
| 42 | $CH_2$(4-phenyl-$C_6H_4$) | 527 |
| 43 | $(CH_2)_2$(3-OH-$C_6H_4$) | 481 |
| 44 | $(CH_2)_2$(4-Me-$C_6H_4$) | 479 |
| 45 | $(CH_2)_3$(4-$NO_2$-$C_6H_4$) | 524 |
| 46 | $(CH_2)_2$(3,4-(OMe)$_2$-$C_6H_3$) | 525 |
| 47 | $(CH_2)_3$(4-Me-$C_6H_4$) | 493 |
| 48 | $(CH_2)_2(C_6F_5)$ | 555 |
| 49 | $(CH_2)_3$(dibenzothiophen-2-yl) | 585 |

| | | |
|---|---|---|
| 50 | $CH_2$(4-Me-$C_6H_4$) | 465 |
| 51 | $(CH_2)_2$(4-SH-$C_6H_4$) | 497 |
| 52 | $CH_2$(4-$OCF_3$-$C_6H_4$) | 535 |
| 53 | $CH_2$(4-OMe-$C_6H_4$) | 481 |
| 54 | $CH_2$(4-(O($CH_2$(4-$NO_2$-$C_6H_4$)))-$C_6H_4$) | 602 |
| 55 | $CH_2$(3-F-4-OMe-$C_6H_3$) | 499 |
| 56 | $(CH_2)_4$(3-Me-$C_6H_4$) | 507 |
| 57 | $CH_2$(3-OH-$C_6H_4$) | 467 |
| 58 | $CH_2$(4-benzyloxy-$C_6H_4$) | 557 |
| 59 | $CH_2$(4-(3-$NO_2$-$C_6H_4$)-$C_6H_4$) | 572 |
| 60 | $CH_2$(2,5-$Me_2$-$C_6H_3$) | 479 |
| 61 | $CH_2$(4-I-$C_6H_4$) | 577 |
| 62 | $CH_2$(4-(4-(OCH(Me)CH(OH)$CH_2CH_2$-pyridin-3-yl)-$C_6H_4$)-$C_6H_4$) | 706 |
| 63 | $CH_2$(3-Br-$C_6H_4$) | 529 |
| 64 | $(CH_2)_2$(3-n-propyl-$C_6H_4$) | 507 |
| 65 | $CH_2$(2-Me-3-$NO_2$-$C_6H_3$) | 510 |
| 66 | $CH_2$(3-OH-4-OMe-$C_6H_3$) | 497 |
| 67 | $CH_2$(3-F-$C_6H_4$) | 469 |
| 68 | $CH_2$(2-F-$C_6H_4$) | 469 |

Example 21

This Example illustrates the preparation of N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-[(methylsulfonyl)amino]benzamide hydrochloride.

Step a: 2-amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide dihydrochloride.

Prepared in a similar manner to Example 7 using the product of Example 3, Step b.

MS: APCI(+ve): 408(M+H).

$^1$H NMR (399.98 MHz, DMSO) δ 1.91 - 1.98 (2H, m), 2.15 – 2.26 (2H, m), 2.58 (2H, m), 3.18-3.29 (3H, m), 3.36 (2H, t), 3.57-3.68(2H, m), 3.72-3.79 (2H, m), 4.66 (1H, s), 6.63-6.71 (2H, m), 6.83 (1H, dd), 7.06 (1H, d), 7.22(1H, dt), 7.51 (1H, dd), 7.90 (1H, s).

Step b: N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-[(methylsulfonyl)amino]-benzamide hydrochloride.

Prepared in a similar manner to Example 18, Step b.

MS: APCI(+ve): 486(M+H)

$^1$HNMR(399.98 MHz, $CDCL_3$) δ 1.82(2H, m), 2.00(2H, m), 2.39(2H, m), 2.63(2H, t), 2.65(2H, m), 3.05(3H, s), 3.52(2H, q), 4.31(1H, m), 6.76(1H, dd), 7.00(1H, m), 7.15(1H, m), 7.32(1H, d), 7.50(2H, m), 7.73(1H, dt)

Example 22

This Example illustrates the preparation of 3-(aminosulfonyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide.

Prepared in a similar manner to Example 7 using the product of Example 3, Step b.

MS: APCI(+ve): 472 (M+H)

$^1$H NMR (399.98 MHz, DMSO) δ 1.57 - 1.65 (2H, m), 1.91 - 1.94 (2H, m), 2.27 - 2.33 (2H, m), 2.48 - 2.52 (2H, m), 2.73 - 2.75 (2H, m), 3.40 (2H, q), 4.45 (1H, m), 6.98 (1H, dd), 7.26 (1H, d), 7.49 (3H, d), 7.67 (1H, t), 7.96 (1H, ddt), 8.03 (1H, tdt), 8.30 (1H, t), 8.65 (1H, t)

Melting point: 168-169°C

Example 23

This Example illustrates the preparation of N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-1-ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxamide.

Prepared in a similar manner to Example 7 using the product of Example 3, Step b.

MS: APCI(+ve): 503 (M+H)

$^1$H NMR (299.946 MHz, DMSO) δ 1.25 - 1.68 (5H, m), 1.72 - 1.81 (2H, m), 1.88 - 1.95 (2H, m), 2.22 (3H, s), 2.31 - 2.40 (2H, m), 2.60 - 2.78 (3H, m), 2.92 - 3.00 (1H, m), 3.44 - 3.52 (1H, m), 4.36 - 4.49 (2H, m), 5.92 - 6.11 (1H, m), 6.91 - 7.06 (1H, m), 7.25 (1H, s), 7.30 - 7.41 (1H, m), 7.44 - 7.54 (1H, m), 11.86 (1H, s).

Melting point: 169-171°C

Example 24

This Example illustrates the preparation of N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-hydroxyphenyl)acetamide.

Prepared in a similar manner to Example 7 using the product of Example 3, Step b.

MS: APCI(+ve):423 (M+H)

$^1$H NMR (399.98 MHz, DMSO) δ 1.53 - 1.61 (2H, m), 1.84 - 1.91 (2H, m), 2.17 - 2.24 (2H, m), 2.29 - 2.37 (2H, m), 2.60 - 2.70 (2H, m), 3.09 - 3.18 (2H, m), 3.28 (2H, s), 4.36 - 4.46 (1H, m), 6.62 - 6.72 (2H, m), 6.93 - 7.00 (1H, m), 7.00 - 7.08 (2H, m), 7.21 - 7.27 (1H, m), 7.43 - 7.53 (1H, m), 7.73 - 7.83 (1H, m), 9.25 (1H, s).

Example 25

This Example illustrates the preparation of N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-[5-(1-pyrrolidinyl)-2H-tetraazol-2-yl]acetamide.

Prepared in a similar manner to Example 7 using the product of Example 3, Step b.

MS: APCI(+ve): 468 (M+H)

$^1$H NMR (399.98 MHz, DMSO) δ 1.56 - 1.63 (2H, m), 1.88 - 1.95 (6H, m), 2.22 - 2.27 (2H, m), 2.37 - 2.42 (2H, m), 2.65 - 2.72 (2H, m), 3.20 - 3.24 (2H, m), 3.31 - 3.37 (4H, m), 4.40 - 4.47 (1H, m), 5.19 (2H, s), 6.96 - 7.01 (1H, m), 7.24 - 7.27 (1H, m), 7.50 (1H, d), 8.15 - 8.24 (1H, m).

Melting point: 114-116°C

Example 26

This Example illustrates the preparation of N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-(2-methyl-4-phenyl-1,3-thiazol-5-yl)acetamide.

Prepared in a similar manner to Example 7 using the product of Example 3, Step b.

MS: APCI(+ve): 504 (M+H)

$^1$H NMR (299.946 MHz, DMSO ) δ 1.54 - 1.63 (2H, m), 1.85 - 1.93 (2H, m), 2.21 - 2.28 (2H, m), 2.33 - 2.39 (2H, m), 2.62 - 2.71 (5H, m), 3.16 - 3.22 (2H, m), 3.74 (2H, s), 4.39 - 4.48 (1H, m), 6.94 - 7.00 (1H, m), 7.23 - 7.27 (1H, m), 7.34 - 7.50 (4H, m), 7.60 - 7.67 (2H, m), 8.08 - 8.15 (1H, m).

Example 27

This Example illustrates the preparation of N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-5-(methylsulfonyl)-2-thiophenecarboxamide.

Prepared in a similar manner to Example 7 using the product of Example 3, Step b.

MS: APCI(+ve): 477 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.54 - 1.65 (2H, m), 1.87 - 1.96 (2H, m), 2.24 - 2.34 (2H, m), 2.68 - 2.77 (2H, m), 3.34 - 3.42 (8H, m), 4.35 - 4.49 (1H, m), 7.25 (1H, d), 7.49 (1H, d), 7.81 (2H, t), 8.80 (1H, t)

Melting point: 142-143°C

Example 28

This Example illustrates the preparation of N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-6-(1H-pyrazol-1-yl)nicotinamide.

Prepared in a similar manner to Example 7 using the product of Example 3, Step b.

MS: APCI(+ve):460 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.54 - 1.69 (2H, m), 1.85 - 2.00 (2H, m), 2.23 - 2.37 (3H, m), 2.68 - 2.81 (2H, m), 3.34 - 3.47 (3H, m), 4.41 - 4.49 (1H, m), 6.60 - 6.64 (1H, m), 6.93 - 7.04 (1H, m), 7.26 (1H, d), 7.46 - 7.55 (1H, m), 7.89 (1H, d), 7.95 - 8.05 (1H, m), 8.32 - 8.42 (1H, m), 8.60 - 8.71 (2H, m), 8.85 - 8.92 (1H, m)

Melting point: 154-155°C

Example 29

This Example illustrates the preparation of N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4-(methylsulfonyl)benzamide.

Prepared in a similar manner to Example 7 using the product of Example 3, Step b.

MS: APCI(+ve): 471 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.55 - 1.67 (2H, m), 1.86 - 1.97 (2H, m), 2.24 - 2.35 (2H, m), 2.69 - 2.79 (2H, m), 3.35 - 3.46 (7H, m), 4.39 - 4.49 (1H, m), 6.94 - 7.03 (1H, m), 7.25 (1H, d), 7.49 (1H, d), 7.99 - 8.10 (4H, m), 8.66 (1H, t)

Melting point: 100-101°C

Example 30

This Example illustrates the preparation of N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}imidazo[1,2-a]pyridine-2-carboxamide.

Prepared in a similar manner to Example 7 using the product of Example 3, Step b.

MS: APCI(+ve): 433 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.53 - 1.70 (2H, m), 1.86 - 2.00 (2H, m), 2.23 - 2.34 (2H, m), 2.66 - 2.80 (2H, m), 3.27 - 3.35 (2H, m), 3.34 - 3.46 (2H, m), 4.41 - 4.50 (1H, m), 6.94 - 7.02 (2H, m), 7.26 (1H, d), 7.29 - 7.39 (1H, m), 7.46 - 7.53 (1H, m), 7.56 - 7.63 (1H, m), 8.22 (1H, t), 8.35 (1H, s), 8.52 - 8.67 (1H, m)

Melting point: 150-151°C

Example 31

This Example illustrates the preparation of 5-(2-chloroanilino)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-1,3,4-oxadiazole-2-carboxamide.

Step a: N-{2-[4-(3,4-dichlorophenoxy)piperidin-1-yl]ethyl}-2-hydrazino-2-oxoacetamide.

To a solution of the product of Example 3, Step b (0.85g) and triethylamine (0.82ml) at RT in dichloromethane (20ml) was added methyl oxalyl chloride (0.30ml) dropwise over 10 minutes. The reaction mixture was partitioned between water (20ml) and dichloromethane (20ml). The organic phase was separated and dried with $MgSO_4$. Evaporation under reduced pressure gave an oil which was dissolved in ethanol (10ml) at RT and treated with hydrazine hydrate (1ml) The reaction mixture was stirred at reflux for 24 hours, filtered and the filtrate evaporated under reduced pressure to leave an oil. Purification by flash chromatography (dichloromethane: methanol 90:10)gave the sub-title compound as a white solid (0.18g).

MS: ESI(+ve): 375 (M+H)

Step b: 5-(2-chloroanilino)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-1,3,4-oxadiazole-2-carboxamide.

2-Chlorophenylisothiocyanate (0.102g) was added to a stirred suspension of the compound from Step a (0.18g) in dimethylformamide (5ml) stirring at RT. After stirring for 1 hour, aminomethylated polystyrene (0.295g) was added and the mixture stirred at RT for 16 hours. N-Cyclohexylcarbodiimide, and N'-methyl polystyrene (0.57g) was then added and the mixture stirred at 80°C for 2 hours. The reaction mixture was cooled to RT, filtered, and the resin washed with dimethylformamide (3 x 5ml). The combined filtrates were evaporated and the residue triturated with diethyl ether, filtration gave the title compound as a white solid (0.14g).

MS: APCI(+ve): 510 (M+H)

$^1$H NMR: (299.98 MHz DMSO) δ 1.51 - 1.70 (2H, m), 1.83 - 1.98 (2H, m), 2.19 - 2.37 (2H, m), 2.42 - 2.55 (1H, m), 2.63 - 2.81 (2H, m), 3.23 - 3.49 (3H, m), 4.32 - 4.53 (1H, m), 6.89 - 7.61 (6H, m), 7.88 - 8.01 (1H, m), 8.80 - 8.99 (1H, m), 10.32 (1H, s)

Melting point: 161-162°C

Example 32

This Example illustrates the preparation of N-{2-[4-(2-chloro-4-fluorophenoxy)-1-piperidinyl]ethyl}-6-(1H-pyrazol-1-yl)nicotinamide.

Step a: 4-(2-Chloro-4-fluorophenoxy)piperidine.

DEAD (0.90ml) was added to a solution of triphenylphosphine (1.44g), 2-chloro-4-fluorophenol (0.806g) and 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (1.0g) in THF at RT. The reaction was stirred for 16hrs, HCl (2ml, 4M in dioxan) added and the mixture stirred at RT for 16 hrs. The mixture was then evaporated to dryness, triethylamine (5ml) added, re-evaporated, dissolved in methanol (10ml) and placed on to a SCX cartridge (Varian, 10g), eluted first with methanol then with 10%$NH_3$ in methanol. The basic fractions were combined and evaporated to give the sub-title compound as an oil (0.98g)

MS: ESI(+ve): 230 (M+H)).

Step b: 2-[4-(2-Chloro-4-fluorophenoxy)piperidin-1-yl]ethylamine.

Potassium carbonate (1.02g, 0.0074 mol) was added to a solution of the 2-chloro-4-fluorophenoxypiperidine (1.7g, 0.0074 mol) and *tert*-butyl 2-bromoethylcarbamate (1.65g, 0.0074 mol) strirring at RT. The resulting mixture was stirred at RT for 24 hours, diluted with ethyl acetate (200ml) and washed with saturated brine solution (3 x 100ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The residual oil was redissolved in dichloromethane (200ml), treated with TFA (20ml) and the solution stirred at RT overnight, evaporation under reduced pressure and purification by flash chromatography (ethyl acetate) gave the sub-title compound as a colourless oil (1.1g).

MS: ESI(+ve): 273 (M+H)).

Step c: N-{2-[4-(2-Chloro-4-fluorophenoxy)-1-piperidinyl]ethyl}-6-(1H-pyrazol-1-yl)nicotinamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 32, step b.

MS: APCI(+ve): 444 (M+H)

$^1$H NMR: (299.98 MHz DMSO) δ 1.48 - 1.77 (2H, m), 1.79 - 1.99 (2H, m), 2.22 - 2.41 (2H, m), 2.45 - 2.57 (2H, m), 2.62 - 2.81 (2H, m), 3.37 - 3.50 (2H, m), 4.33 - 4.50

(1H, m), 6.53 - 6.66 (1H, m), 7.01 - 7.28 (2H, m), 7.33 - 7.47 (1H, m), 7.81 - 7.94 (1H, m), 7.94 - 8.08 (1H, m), 8.30 - 8.43 (1H, m), 8.56 - 8.74 (2H, m), 8.83 - 8.96 (1H, m)

Melting point: 109-110°C

Example 33

This Example illustrates the preparation of N-{2-[4-(2-chloro-4-fluorophenoxy)-1-piperidinyl]ethyl}-3-(methylsulfonyl)benzamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 32, step b.

MS: APCI(+ve): 455 (M+H)

$^1$H NMR: (299.946 MHz DMSO) δ 1.60 - 1.78 (2H, m), 1.83 - 1.98 (2H, m), 2.24 - 2.40 (2H, m), 2.66 - 2.75 (2H, m), 2.94 - 3.06 (1H, m), 3.28 - 3.33 (2H, m), 3.37 - 3.47 (4H, m), 4.36 - 4.50 (1H, m), 7.10 - 7.28 (2H, m), 7.37 - 7.46 (1H, m), 7.67 - 7.82 (1H, m), 8.03 - 8.11 (1H, m), 8.14 - 8.20 (1H, m), 8.33 - 8.39 (1H, m), 8.67 - 8.76 (1H, m)

Melting point: 50-51°C

Example 34

This Example illustrates the preparation of N-{2-[4-(2,4-dichloro-3-methylphenoxy)-1-piperidinyl]ethyl}-4-(methylsulfonyl)benzamide.

Step a: 4-(2,4-Dichloro-3-methylphenoxy)piperidine.

The sub-titled compound was prepared in a similar manner to Example 32, Step a.

MS: ESI(+ve): 260 (M+H)

Step b: 2-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]ethylamine.

The sub-titled compound was prepared in a similar manner to Example 32, Step b.

MS: ESI(+ve): 303 (M+H)

Step c: N-{2-[4-(2,4-Dichloro-3-methylphenoxy)-1-piperidinyl]ethyl}-4-(methylsulfonyl)benzamide.

The sub-titled compound was prepared in a similar manner to Example 7 using the product of Example 34, Step b.

MS: APCI(+ve): 485 (M+H)

$^1$H NMR: (299.98 MHz DMSO) δ 1.57 - 1.73 (2H, m), 1.81 - 1.99 (2H, m), 2.25 - 2.40 (6H, m), 2.61 - 2.80 (2H, m), 3.16 - 3.52 (6H, m), 4.37 - 4.56 (1H, m), 7.02 - 7.16 (1H, m), 7.26 - 7.41 (1H, m), 7.95 - 8.13 (4H, m), 8.57 - 8.74 (1H, m)

Melting point: 171-172°C

Example 35

This Example illustrates the preparation of N-{2-[4-(2,4-dichloro-3-methylphenoxy)-1-piperidinyl]ethyl}-5-(methylsulfonyl)-2-thiophenecarboxamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 34, step b.

MS: APCI(+ve): 491 (M+H)

$^1$H NMR: (299.98 MHz DMSO) δ 1.50 - 1.77 (2H, m), 1.79 - 2.05 (2H, m), 2.23 - 2.58 (6H, m), 2.60 - 2.81 (2H, m), 3.22 - 3.47 (6H, m), 4.35 - 4.65 (1H, m), 7.01 - 7.18 (1H, m), 7.26 - 7.44 (1H, m), 7.71 - 7.91 (2H, m), 8.68 - 8.91 (1H, m)

Melting point:177-178°C

Example 36

This Example illustrates the preparation of N-{2-[4-(2,4-dichloro-3-methylphenoxy)-1-piperidinyl]ethyl}-2-(methylsulfonyl)benzamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 34, step b.

MS: APCI(+ve): 485 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.59 - 1.73 (2H, m), 1.84 - 1.99 (2H, m), 2.29 - 2.43 (6H, m), 2.62 - 2.79 (2H, m), 3.24 - 3.43 (6H, m), 4.42 - 4.61 (1H, m), 7.00 - 7.17 (1H, m), 7.28 - 7.43 (1H, m), 7.45 - 7.60 (1H, m), 7.64 - 7.83 (2H, m), 7.89 - 8.04 (1H, m), 8.53 (1H, t)

Melting point: 71-72°C

Example 37

This Example illustrates the preparation of N-{2-[4-(4-chloro-3-methylphenoxy)-1-piperidinyl]ethyl}-4-(methylsulfonyl)benzamide.

Step a: 4-(4-Chloro-3-methylphenoxy)piperidine.

The sub-titled compound was prepared in a similar manner to Example 32, Step a.

MS: ESI(+ve): 226 (M+H)

Step b: 2-[4-(4-Chloro-3-methylphenoxy)piperidin-1-yl]ethylamine.

The sub-titled compound was prepared in a similar manner to Example 32, Step b.

MS: ESI(+ve): 269 (M+H)

Step c: N-{2-[4-(4-Chloro-3-methylphenoxy)-1-piperidinyl]ethyl}-4-(methylsulfonyl)benzamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 37, Step b.

MS: APCI(+ve): 451 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.53 - 1.67 (2H, m), 1.89 - 1.98 (2H, m), 2.23 - 2.32 (5H, m), 2.67 - 2.83 (2H, m), 3.22 - 3.34 (7H, m), 4.29 - 4.40 (1H, m), 6.74 - 6.84 (1H, m), 6.96 (1H, d), 7.26 (1H, d), 7.97 - 8.11 (4H, m), 8.66 (1H, t)

Melting point: 123-124°C

## Example 38

This Example illustrates the preparation of N-{2-[4-(4-chloro-3-methylphenoxy)-1-piperidinyl]ethyl}-6-(1H-pyrazol-1-yl)nicotinamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 37, Step b.

MS: APCI(+ve): 440 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.55 - 1.67 (2H, m), 1.83 - 2.03 (2H, m), 2.20 - 2.35 (6H, m), 2.69 - 2.87 (2H, m), 3.27 - 3.34 (1H, m), 3.36 - 3.50 (2H, m), 4.29 - 4.42 (1H, m), 6.55 - 6.67 (1H, m), 6.73 - 6.88 (1H, m), 6.96 (1H, d), 7.26 (1H, d), 7.89 (1H, d), 7.94 - 8.06 (1H, m), 8.29 - 8.42 (1H, m), 8.58 - 8.74 (2H, m), 8.80 - 8.94 (1H, m)

Melting point: 183-184°C

## Example 39

This Example illustrates the preparation of N-{2-[4-(4-chloro-3-methylphenoxy)-1-piperidinyl]ethyl}-2-(methylsulfonyl)benzamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 37, Step b.

MS: APCI(+ve): 451 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.52 - 1.68 (2H, m), 1.83 - 2.00 (2H, m), 2.20 - 2.33 (5H, m), 2.68 - 2.79 (2H, m), 3.27 - 3.40 (7H, m), 4.30 - 4.42 (1H, m), 6.77 - 6.85 (1H, m), 6.92 - 6.99 (1H, m), 7.22 - 7.31 (1H, m), 7.48 - 7.56 (1H, m), 7.64 - 7.82 (2H, m), 7.93 - 8.00 (1H, m), 8.49 - 8.64 (1H, m)

Melting point: 63-64°C

Example 40

This Example illustrates the preparation of 3-(aminosulfonyl)-4-chloro-N-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}benzamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 6, Step d.

MS: APCI(+ve): 474 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.54 - 1.65 (2H, m), 1.86 - 1.97 (2H, m), 2.22 - 2.35 (2H, m), 2.64 - 2.82 (2H, m), 3.36 - 3.43 (2H, m), 4.29 - 4.41 (1H, m), 6.73 - 6.83 (1H, m), 7.03 - 7.14 (1H, m), 7.24 - 7.38 (1H, m), 7.70 (2H, s), 7.73 - 7.80 (3H, m), 7.98 - 8.06 (1H, m), 8.44 (1H, d), 8.68 - 8.75 (1H, m)

Melting point: 80-81°C

Example 41

This Example illustrates the preparation of 2-cyano-N-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}benzamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 6, Step d.

MS: APCI(+ve): 386 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.46 - 1.58 (2H, m), 1.78 - 1.94 (2H, m), 2.22 - 2.35 (2H, m), 2.54 - 2.63 (2H, m), 2.70 - 2.83 (2H, m), 3.79 - 3.89 (2H, m), 4.28 - 4.39 (1H, m), 6.72 - 6.81 (1H, m), 7.00 - 7.14 (1H, m), 7.23 - 7.37 (1H, m), 7.65 - 7.84 (3H, m), 8.15 (1H, d), 10.11 (1H, d)

Melting point: 146-147°C

Example 42

This Example illustrates the preparation of 2-chloro-N-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-4-(methylsulfonyl)benzamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 6, Step d.

MS: APCI(+ve): 473 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.55 - 1.65 (2H, m), 1.88 - 1.97 (2H, m), 2.24 - 2.34 (2H, m), 2.69 - 2.79 (2H, m), 3.34 - 3.43 (7H, m), 4.31 - 4.42 (1H, m), 6.74 - 6.82 (1H, m), 7.03 - 7.16 (1H, m), 7.25 - 7.38 (1H, m), 7.68 (1H, t), 7.90 - 7.96 (1H, m), 8.04 (1H, d), 8.56 (1H, t)

Melting point: 108-109°C

Example 43

This Example illustrates the preparation of 3-cyano-N-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}benzamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 6, Step d.

MS: APCI(+ve): 386 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.54 - 1.65 (2H, m), 1.86 - 1.98 (2H, m), 2.22 - 2.34 (2H, m), 2.69 - 2.79 (2H, m), 3.35 - 3.45 (4H, m), 4.32 - 4.40 (1H, m), 6.74 - 6.81 (1H, m), 7.04 - 7.14 (1H, m), 7.25 - 7.37 (1H, m), 7.65 - 7.73 (1H, m), 7.97 - 8.03 (1H, m), 8.10 - 8.16 (1H, m), 8.25 (1H, t), 8.63 (1H, t)

Melting point: 106-107°C

Example 44

This Example illustrates the preparation of N-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-4-[(methylsulfonyl)methyl]benzamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 6, Step d.

MS: APCI(+ve): 453 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.52 - 1.66 (2H, m), 1.69 - 1.77 (2H, m), 1.86 - 1.99 (2H, m), 2.22 - 2.33 (2H, m), 2.69 - 2.79 (2H, m), 2.88 - 2.95 (3H, m), 2.97 - 3.07 (2H, m), 4.29 - 4.41 (1H, m), 4.55 (2H, s), 6.69 - 6.86 (1H, m), 7.01 - 7.16 (1H, m), 7.22 - 7.36 (1H, m), 7.49 (2H, d), 7.84 (2H, d), 8.42 (1H, t)

Melting point: 115-116°C

Example 45

This Example illustrates the preparation of N-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-6-(1H-pyrazol-1-yl)nicotinamide.

The title compound was prepared in a similar manner to Example 7 using the product of Example 6, Step d.

MS: APCI(+ve): 428 (M+H)

$^1$H NMR: (399.98 MHz DMSO) δ 1.50 - 1.68 (2H, m), 1.83 - 2.01 (2H, m), 2.20 - 2.36 (2H, m), 2.69 - 2.83 (2H, m), 3.36 - 3.50 (4H, m), 4.28 - 4.45 (1H, m), 6.56 - 6.66 (1H, m), 6.73 - 6.83 (1H, m), 7.02 - 7.15 (1H, m), 7.25 - 7.38 (1H, m), 7.89 (1H, d), 7.96 - 8.06 (1H, m), 8.33 - 8.41 (1H, m), 8.60 - 8.73 (2H, m), 8.84 - 8.93 (1H, m)

Melting point: 161-162°C

Example 46

Pharmacological Analysis: Calcium flux $[Ca^{2+}]_i$ assay

Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended ($5x10^6$ $ml^{-1}$) and loaded with 5μM FLUO-3/AM + Pluronic F127 2.2μl/ml (Molecular Probes) in low potassium solution (LKS; NaCl 118mM, $MgSO_4$ 0.8mM, glucose 5.5mM, $Na_2CO_3$ 8.5mM, KCl 5mM, HEPES 20mM, $CaCl_2$ 1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $2.5x10^6$ $ml^{-1}$. The cells were then transferred to 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with 5μM fibronectin for two hours) at 25μl/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200μl; room temperature).

A compound of the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an $A_{50}$ concentration of eotaxin and the transient increase in fluo-3 fluorescence ($l_{Ex}$ =490nm and $l_{Em}$ = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

Human eosinophil chemotaxis

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at $10x10^6$ $ml^{-1}$ in RPMI containing 200 IU/ml penicillin, 200 μg/ml streptomycin sulphate and supplemented with 10% HIFCS, at room temperature.

Eosinophils (700 μl) were pre-incubated for 15 mins at 37° C with 7 μl of either vehicle or compound (100x required final concentration in 10% DMSO). The chemotaxis plate (ChemoTx, 3μm pore, Neuroprobe) was loaded by adding 28μl of a concentration of eotaxin (0.1 to 100nM) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 μl of eosinophil suspension were added to the top of the filter. The plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% $CO_2$ atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline

(PBS) containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 µl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Certain compounds of the Examples were found to be antagonists of the eotaxin mediated human eosinophil chemotaxis.

Example 47

Guinea-pig isolated trachea

(See for example, Harrison, R.W.S., Carswell, H. & Young, J.M. (1984) European J. Pharmacol., 106, 405-409.)

Male albino Dunkin-Hartley guinea-pigs (250g) were killed by cervical dislocation and the whole trachea removed. After clearing the adherent connective tissue, the trachea was cut into six ring segments each three cartilage bands wide and then suspended in 20ml organ baths containing Krebs-Henseleit solution of the following composition (mM): NaCl 117.6, $NaH_2PO_4$ 0.9, $NaHCO_3$ 25.0, $MgSO_4$ 1.2, KCl 5.4, $CaCl_2$ 2.6 and glucose 11.1. The buffer was maintained at 37°C and gassed with 5% $CO_2$ in oxygen. Indomethacin (2.8µM) was added to the Krebs solution to prevent development of smooth muscle tone due to the synthesis of cyclo-oxygenase products. The tracheal rings were suspended between two parallel tungsten wire hooks, one attached to an Ormed beam isometric force transducer and the other to a stationary support in the organ bath. Changes in isometric force were recorded on 2-channel Sekonic flat bed chart recorders.

Experimental protocols

At the beginning of each experiment a force of 1g was applied to the tissues and this was reinstated over a 60 minute equilibration period until a steady resting tone was achieved. Subsequently, a cumulative histamine concentration effect (E/[A]) curve was constructed at 0.5 $log_{10}$ unit increments, in each tissue. The tissues were then washed and approximately 30 minutes later, test compound or vehicle (20% DMSO) was added. Following an incubation period of 60 minutes a second E/[A] curve was performed to histamine.

Contraction responses were recorded as a percentage of the first curve maximum.

Data analysis

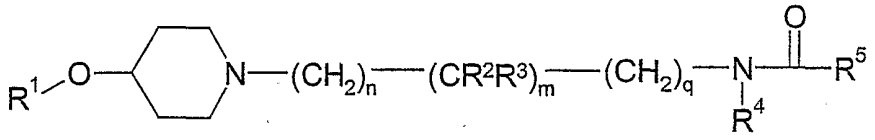
Experimental E/[A] curve data were analysed for the purposes of estimating the potencies ($p[A_{50}]$ values) of histamine in the absence and presence of the test compound. Affinity ($pA_2$) values of test compounds were subsequently calculated using the following equation:

$$\log(r-1) = \log[B] + pA_2$$

where $r = [A]_{50}$ in presence of test compound/$[A]_{50}$ in absence of antagonist and [B] is the concentration of test compound. Compounds were found to be H1 antagonists.

CLAIMS

1. A compound of formula (I):



(I)

wherein

$R^1$ is phenyl optionally substituted by cyano, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ haloalkyl), halogen, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl or $C_{1-6}$ alkoxy;

n is 0, 1, 2, 3 or 4; m is 0 or 1; when m is 0 then q is 0, and when m is 1 then q is 1, 2 or 3; provided that n + m + q = 1, 2, 3 or 4;

when $R^2$ and $R^3$ are, independently, hydrogen or $C_{1-6}$ alkyl, and $R^4$ is hydrogen, then $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being substituted at least once with a substituent selected from the group comprising: $C_{1-6}$ alkyl (substituted with $NH_2$, $CO_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ hydroxyalkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), $C_{1-6}$ alkoxy (substituted with $C_{1-6}$ alkoxy, hydroxy, $CO_2(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl) or $NH_2$), $C_{2-6}$ alkenyl, pyrrolyl and $\Delta^3$-pyrrolinyl; and optionally further substituted with a substituent selected from the group comprising: halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkoxy, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylthio($C_{1-6}$ alkyl), $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido, phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, and $C(O)R^{10}$-substituted $C_{1-6}$ alkyl or $C_{1-6}$ alkoxy groups;

when $R^2$ and $R^3$ are, independently, hydrogen or $C_{1-6}$ alkyl, and $R^4$ is $C_{1-4}$ alkyl or $C_{3-6}$ cycloalkyl($C_{1-4}$ alkyl), then $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by

halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl (optionally substituted with halogen, $C_{1-6}$ alkylthio, $NH_2$, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy (substituted with halogen, $C_{1-6}$ alkoxy, hydroxy, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl) or $NH_2$), $C_{2-6}$ alkenyl, $C_{1-6}$ alkoxycarbonyl, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ hydroxyalkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, pyrrolyl or $\Delta^3$-pyrrolinyl;

and when $R^2$ is phenyl (optionally substituted with halogen, $C_{1-4}$ alkyl or $C_{1-4}$ alkoxy), $R^3$ is hydrogen or $C_{1-6}$ alkyl, and $R^4$ is hydrogen, $C_{1-4}$ alkyl or $C_{3-6}$ cycloalkyl($C_{1-4}$ alkyl), then $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl (optionally substituted with halogen, $C_{1-6}$ alkylthio, $NH_2$, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy (substituted with halogen, $C_{1-6}$ alkoxy, hydroxy, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl) or $NH_2$), $C_{2-6}$ alkenyl, $C_{1-6}$ alkoxycarbonyl, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ hydroxyalkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, pyrrolyl or $\Delta^3$-pyrrolinyl;

$R^{10}$ is hydroxy or $NR^{11}R^{12}$ group; and,

$R^6$, $R^7$ $R^8$, $R^9$, $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl;

or a pharmaceutically acceptable salt thereof; or a solvate thereof.

2. A compound of formula (I) as claimed in claim 1 wherein $R^1$ is phenyl optionally substituted by cyano, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ haloalkyl), halogen, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl or $C_{1-6}$ alkoxy; n is 0, 1, 2, 3 or 4; m is 0 or 1; when m is 0 then q is

0, and when m is 1 then q is 1, 2 or 3; provided that n + m + q = 1, 2, 3 or 4; $R^2$ and $R^3$ are, independently, hydrogen or $C_{1-6}$ alkyl; $R^4$ is hydrogen; $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being substituted at least once with a substituent selected from the group comprising: $C_{1-6}$ alkyl (substituted with $NH_2$, $CO_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ hydroxyalkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), $C_{1-6}$ alkoxy (substituted with $C_{1-6}$ alkoxy, hydroxy, $CO_2(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl) or $NH_2$), $C_{2-6}$ alkenyl, pyrrolyl and $\Delta^3$-pyrrolinyl; and optionally further substituted with a substituent selected from the group comprising: halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkoxy, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylthio($C_{1-6}$ alkyl), $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido, phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, and $C(O)R^{10}$-substituted $C_{1-6}$ alkyl or $C_{1-6}$ alkoxy groups; $R^{10}$ is hydroxy or $NR^{11}R^{12}$ group; and, $R^6$, $R^7$ $R^8$, $R^9$, $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl.

3. A compound of formula (I) as claimed in claim 1 wherein $R^1$ is phenyl optionally substituted by cyano, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ haloalkyl), halogen, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl or $C_{1-6}$ alkoxy; n is 0, 1, 2, 3 or 4; m is 0 or 1; when m is 0 then q is 0, and when m is 1 then q is 1, 2 or 3; provided that n + m + q = 1, 2, 3 or 4; $R^2$ and $R^3$ are, independently, hydrogen or $C_{1-6}$ alkyl; $R^4$ is $C_{1-4}$ alkyl or $C_{3-6}$ cycloalkyl($C_{1-4}$ alkyl); $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl (optionally substituted with halogen, $C_{1-6}$ alkylthio, $NH_2$, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy (substituted with halogen, $C_{1-6}$ alkoxy, hydroxy, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl) or $NH_2$), $C_{2-6}$ alkenyl, $C_{1-6}$

alkoxycarbonyl, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ hydroxyalkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, pyrrolyl or $\Delta^3$-pyrrolinyl; $R^{10}$ is hydroxy or $NR^{11}R^{12}$ group; and, $R^6$, $R^7$ $R^8$, $R^9$, $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl.

4. A compound of formula (I) as claimed in claim 1 wherein $R^1$ is phenyl optionally substituted by cyano, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ haloalkyl), halogen, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl or $C_{1-6}$ alkoxy; n is 0, 1, 2, 3 or 4; m is 1; q is 1; provided that n + m + q = 2, 3 or 4; $R^2$ is phenyl (optionally substituted with halogen, $C_{1-4}$ alkyl or $C_{1-4}$ alkoxy); $R^3$ is hydrogen or $C_{1-6}$ alkyl; $R^4$ is hydrogen, $C_{1-4}$ alkyl or $C_{3-6}$ cycloalkyl($C_{1-4}$ alkyl); $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl (optionally substituted with halogen, $C_{1-6}$ alkylthio, $NH_2$, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy (substituted with halogen, $C_{1-6}$ alkoxy, hydroxy, $C(O)R^{10}$, $CO_2(C_{1-6}$ alkyl), $NHC(O)O(C_{1-6}$ alkyl) or $NH_2$), $C_{2-6}$ alkenyl, $C_{1-6}$ alkoxycarbonyl, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido, $S(O)_2(C_{1-6}$ alkyl), $S(O)_2(C_{1-6}$ hydroxyalkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, pyrrolyl or $\Delta^3$-pyrrolinyl; $R^{10}$ is hydroxy or $NR^{11}R^{12}$ group; and, $R^6$, $R^7$ $R^8$, $R^9$, $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl.

5. A compound of formula (I) as claimed in claim 1, 2 or 3 wherein m and q are both 0.

6. A compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 wherein $R^1$ is phenyl optionally substituted by halogen, $C_{1-4}$ alkyl or $C_{1-4}$ alkoxy.

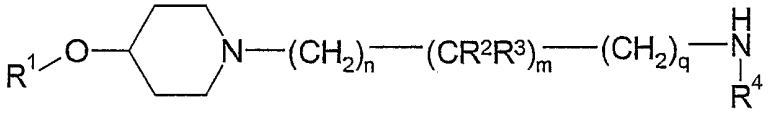
7. A compound of formula (I) as claimed in claim 1, 2, 3, 4, 5 or 6 wherein n is 2.

8. A compound of formula (I) as claimed in claim 1, 2, 3, 4, 5, 6 or 7 wherein $R^4$ is hydrogen or $C_{1-4}$ alkyl; and $R^5$ is a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being substituted by at least one of $C_{1-6}$ alkyl (substituted with $S(O)_2(C_{1-6}$ alkyl), $NHS(O)_2(C_{1-6}$ alkyl) or $S(O)_2NR^{13}R^{14}$), $S(O)_2(C_{1-6}$ alkyl), $S(O)_2NH(C_{1-6}$ alkyl), $NHC(O)(C_{1-6}$ alkyl) or $NHS(O)_2(C_{1-6}$ alkyl); and optionally further substituted with a substituent selected from the group comprising: halogen, cyano, nitro, hydroxy, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkoxy, $NR^6R^7$, $C_{3-6}$ cycloalkylamino, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylthio($C_{1-6}$ alkyl), $C_{1-6}$ alkylcarbonylamino, $C(O)NR^8R^9$, sulphonamido ($S(O)_2NH_2$), (di)$C_{1-6}$ alkylsulphonamido and $C(O)R^{10}$-substituted $C_{1-6}$ alkyl or $C_{1-6}$ alkoxy groups; $R^{10}$ is hydroxy or $NR^{11}R^{12}$ group; and, $R^6$, $R^7$ $R^8$, $R^9$, $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl.

9. A compound of formula (I) as claimed in any one of the preceding claims wherein the 3- to 10-membered saturated or unsaturated ring system in the group $R^5$ is cyclobutyl, cyclopentyl, cyclohexyl, norbornylenyl, adamantyl, phenyl, naphthyl, furyl, thienyl, pyrrolyl, 2,5-dihydro-1H-pyrrolyl, thiazolyl, isothiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, piperidinyl, morpholinyl, a pyridinyl, a pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl, indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 2,3-dihydrobenzthiazolyl, 1,2,3-benzothiadiazolyl, an imidazopyridinyl, thieno[3,2-b]pyridin-6-yl, benzo[1,2,3]thiadiazolyl, 2,1,3-benzothiadiazolyl, benzofurazan, quinoxalinyl, a dihydro-1-benzopyryliumyl, 3,4-dihydro-1H-2,1-benzothiazinyl, a pyrazolopyridine, a purine, a pyrazolopyrimidinyl, a thienopyrimidinyl, a thiazolopyrimidinyl, quinolinyl, isoquinolinyl (for example in 2H-isoquinolin-1-one-yl), quinoxalinyl, a naphthyridinyl, chromonyl, 1,3-benzodioxolyl, a

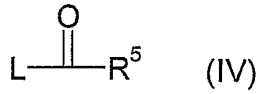
benzothiazinyl, benzo[d]imidazo[2,1-b]thiazol-2-yl or dibenzothiophenyl; or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

10. A process for preparing a compound of formula (I) as claimed in claim 1 comprising reacting a compound of formula (III):



(III)

with a compound of formula (IV):



(IV)

wherein L is a leaving group.

11. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A compound of the formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament.

13. The use of a compound of the formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy.

14. The use of a compound of a formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in the treatment of asthma or rhinitis in a warm blooded animal.

15. A method of treating a CCR3 mediated disease state comprising administering to a patient in need of such treatment an effective amount of a compound of formula (I) as claimed in claim 1.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01869

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 211/46, C07D 401/12, A61K 31/445
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

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

SE,DK,FI,NO classes as above

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | WO 0058305 A1 (ASTRAZENECA AB), 5 October 2000 (05.10.00) | 1-14 |
| X | WO 9710207 A1 (KYORIN PHARMACEUTICAL CO., LTD.), 20 March 1997 (20.03.97) | 1-14 |
| X | EP 0515240 A1 (ELF SANOFI), 25 November 1992 (25.11.92) | 1,5-7,9-14 |

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 29 November 2001 | 04 -12- 2001 |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Göran Karlsson/BS<br>Telephone No. +46 8 782 25 00 |

Form PCT/ISA/210 (second sheet) (July 1998)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01869

**Box I** **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body therapy, see rule 39.1

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

06/11/01

International application No.
PCT/SE 01/01869

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 0058305 A1 | 05/10/00 | AU 4157500 A | 16/10/00 |
| | | AU 4942599 A | 17/01/00 |
| | | EP 1100637 A | 23/05/01 |
| | | SE 9901117 D | 00/00/00 |
| | | AU 2013500 A | 13/06/00 |
| | | EP 1133431 A | 19/09/01 |
| | | SE 9902194 D | 00/00/00 |
| WO 9710207 A1 | 20/03/97 | AU 6944596 A | 01/04/97 |
| | | JP 9077742 A | 25/03/97 |
| EP 0515240 A1 | 25/11/92 | SE 0515240 T3 | |
| | | AT 158574 T | 15/10/97 |
| | | AU 657321 B | 09/03/95 |
| | | AU 1591892 A | 05/11/92 |
| | | BR 9201655 A | 15/12/92 |
| | | CA 2067924 A | 04/11/92 |
| | | CS 9201328 A | 18/11/92 |
| | | CZ 282919 B | 12/11/97 |
| | | DE 69222352 D,T | 09/04/98 |
| | | DK 515240 T | 11/05/98 |
| | | ES 2109987 T | 01/02/98 |
| | | FI 103041 B | 00/00/00 |
| | | FI 921950 A | 04/11/92 |
| | | FR 2676054 A,B | 06/11/92 |
| | | GR 3025277 T | 27/02/98 |
| | | HU 65273 A | 02/05/94 |
| | | HU 213915 B | 28/11/97 |
| | | HU 9201459 D | 00/00/00 |
| | | IE 921365 A | 04/11/92 |
| | | IL 101762 A | 16/10/96 |
| | | JP 3108719 B | 13/11/00 |
| | | JP 5140103 A | 08/06/93 |
| | | KR 244063 B | 02/03/00 |
| | | MX 9202026 A | 01/11/92 |
| | | NO 178572 B,C | 15/01/96 |
| | | NO 921733 D | 00/00/00 |
| | | NZ 242584 A | 27/04/95 |
| | | RU 2089547 C | 10/09/97 |
| | | US 5411971 A | 02/05/95 |
| | | US 5606065 A | 25/02/97 |
| | | ZA 9203176 A | 28/04/93 |