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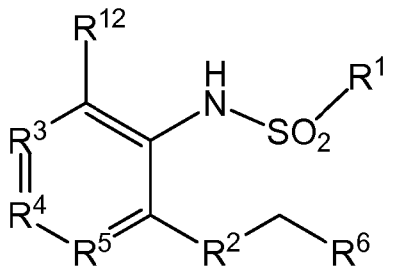
(54) Title: PYRIDINYL AND PYRIMIDINYL SULFONAMIDE DERIVATIVES AS CHEMOKINE RECEPTOR MODULATORS



(I)

(57) Abstract: The present invention relates to novel pyridine or pyrimidine derivatives of the Formula I, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals as modulators of chemokine receptors. The invention relates specifically to the use of these compounds and their pharmaceutical compositions to treat disorders associated with chemokine receptor modulation, such as ocular inflammatory diseases or skin inflammatory diseases.

SULFONAMIDE DERIVATIVES AS CHEMOKINE RECEPTOR MODULATORS

RELATED APPLICATIONS

This application claims the benefit of United States Provisional Patent Application Serial No. 61/777,371 filed March 12, 2013, the disclosure of which is hereby incorporated in its entirety by reference.

FIELD OF THE INVENTION

The present invention relates to novel pyridine or pyrimidine derivatives, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals as modulators of chemokine receptors. The invention relates specifically to the use of these compounds and their pharmaceutical compositions to treat disorders associated with chemokine receptor modulation.

BACKGROUND OF THE INVENTION

Chemokines are a group of 7- to 14-kd peptides that play an important role in orchestrating leukocyte recruitment and migration during inflammation, and therefore represent an important target for anti-inflammatory therapies (Wells et al., 2006). They act by binding to seven-transmembrane, G protein-coupled receptors, the chemokine receptors. The chemokine system is complex, with about 50 chemokines and 20 chemokine receptors identified in humans, often acting with redundancy, making selection of specific antagonists difficult (Gerard and Rollins, 2001). Genetic knockout strategies have confirmed the importance of chemokines as regulators of immune function, but the deletion of specific chemokines has led to only specific and relatively mild defects in the inflammatory response further emphasizing the complex redundancy of the system. Selectivity is crucial for use of chemokine receptor antagonists in systemic diseases where a single chemokine-receptor system is implicated such as atheroscelorsis where the macrophage/monocyte system is the major player in order to allow a subtle and specific control over immune function (Weisberg et al., 2006; Feria and Diaz

Gonzalez et al., 2006).

Many ocular conditions are characterized by inappropriate migration and infiltration of cells such as leukocytes and endothelial cells into the eye with deleterious effects to ocular structures (Wallace et al., 2004). Chemokines have been identified in such diseases and misregulation of the chemokine system is apparent in corneal graft rejection, diabetic retinopathy, age-related macular degeneration (ARMD), chronic inflammatory diseases such as uveitis, dry eye etc. Mice lacking CCR2 or MCP-1 develop features of ARMD with age, including drusen deposits, choroidal neovascularization and photoreceptor atrophy indicating a crucial role for this chemokine and its receptor signaling (Amabati et al., 2003). Thus CCR2 receptor-specific inhibitor might have potential therapeutic benefit in ocular diseases like ARMD. In contrast, various human and animal studies have identified several chemokines in different forms of uveitis, produced both by resident and infiltrating cells, that strongly suggests a prominent role for these molecules in its pathogenesis. Studies in rat and mice models of uveitis have demonstrated up-regulation of monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1), RANTES, stromal derived factor-1 (SDF-1) which are powerful chemoattractants for monocytes and T-cells (Fang et al., 2004; Keino et al., 2003). Similar findings have been reported in peripheral blood mononuclear cells in patients with acute anterior uveitis (AAU), the most common form of human uveitis (Klitgaard et al., 2004). MCP-1 knockout mice and CCR5 knockout mice show reduced endotoxin-induced uveitis, which is the animal model for AAU (Takeuchi et al., 2005; Tuallion et al., 2002). It has also been demonstrated that blocking the chemokine system upstream with the use of NF-κB blockers significantly attenuates experimental AAU in rats (Yang et al., 2005). Blockage of NF-κB results in transcriptional inhibition of multiple chemokines. Given the complexity of pathogenesis in uveitis it is unlikely that a selective inhibition of a chemokine receptor in monotherapy will offer therapeutic benefit. A similar role of multiple chemokines have been shown to be correlated with clinical stage of disease in diabetic retinopathy and dry eye (Meleth et al., 2005; Yamagami et al., 2005). In these ocular diseases the use of broad spectrum chemokine receptor inhibitor which inhibits the function of a wide range of chemokines may be beneficial.

The first broad spectrum chemokine inhibitor (BSCI) to be reported was termed Peptide 3, which was derived from the sequence of human chemokine MCP-

1 and was shown to block the migration of monocytes in response to MCP-1, MIP-1, RANTES and SDF-1 (Reckless and Grainger. 1999). A cyclic retro inverse analogue of Peptide 3, constructed of D-amino acids in the reverse sequence, called NR58-3.14.3 was observed to be a more potent chemokine inhibitor (Beech et al., 2001). NR58-3.14.3 has been used to test for anti-inflammatory activities in animal models of atherosclerosis, lung inflammation, irritable bowel syndrome etc (Beech et al., 2001; Grainger and Reckless. 2003; Tokuyama et al., 2005). However there are several disadvantages to using these BSCI as a long-term therapeutic strategy. The known BSCIs which are peptides which have relatively low potency, poor pharmacokinetics, and are unstable in vivo. In addition, systemic use of broad spectrum chemokine receptor inhibitors could potentially lead to deleterious side effects due to their systemic anti-inflammatory activity. However in ocular diseases, a local or topical application would prevent the broad spectrum inhibitor to be taken up systemically. Identification of a small molecule inhibitor of several chemokine receptors could be very useful for treatment of inflammatory ocular diseases. Given the evidence for the role of multiple chemokines in several ocular diseases and these results, we propose that the use of small and large molecule broad spectrum chemokine receptor inhibitors will have utility in the local treatment of ocular inflammatory diseases including, but not limited to, uveitis, dry eye, diabetic retinopathy, allergic eye disease and proliferative retinopathies. Manipulation of multiple chemokines therefore represents a novel therapeutic approach in treating ocular diseases.

WO/2008/008431 A2 discloses Heteroaryl Sulfonamides.

WO/2009/009740 A1 discloses fused heteroaryl pyridyl and phenyl benzenesulfonamides as ccr-2 modulators for the treatment of inflammation.

WO2008008374 discloses CCR2 inhibitors and methods of use thereof.

WO03/099773 discloses CCR9 inhibitors and methods of use thereof.

US7622583 discloses heteroaryl sulfonamides as antagonists of the CCR2 receptor.

US7335653 discloses bis-aryl sulfonamides as antagonists of chemokine receptors.

US 2008/0293720 discloses pyridinyl sulfonamide modulators of chemokine receptors.

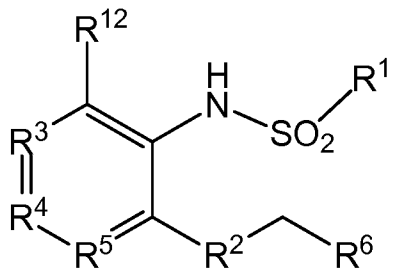
US7393873 discloses arylsulfonamide derivatives.

SUMMARY OF THE INVENTION

We have now discovered a group of novel sulphur derivatives which are potent and selective chemokine receptor modulators. As such, the compounds described herein are useful in treating a wide variety of disorders associated with modulation of chemokine receptors. The term "modulator" as used herein, includes but is not limited to: receptor agonist, antagonist, inverse agonist, inverse antagonist, partial agonist, partial antagonist.

This invention describes compounds of Formula I, which have chemokine receptor biological activity. The compounds in accordance with the present invention are thus of use in medicine, for example in the treatment of humans with diseases and conditions that are alleviated by chemokine receptor modulation.

In one aspect, the invention provides a compound having **Formula I** or a pharmaceutically acceptable salt thereof or stereoisomeric forms thereof, or the individual geometrical isomers, enantiomers, diastereoisomers, tautomers, zwitterions and pharmaceutically acceptable salts thereof:



Formula I

wherein:

R^1 is substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^2 is –S-, -S(O)-, or -$S(O)_2$-;

R^3 is CR^7, N or N-oxide;

R^4 is CR^7, N or N-oxide;

R^5 is CR^7, N or N-oxide;

R^6 is substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^7 is H, substituted or unsubstituted C_{1-6} alkyl, halogen, substituted or unsubstituted $-OR^8$, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, $C(O)R^9$, $NR^{10}R^{11}$, amide, urea, sulfonamide, sulfone, sulfoxide , sulfide, sulfonic acid, nitro, phosphate or phosphonic acid;

R^8 is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^9 is H, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^{10} is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, is substituted or unsubstituted C_{6-10} aryl or together with R^{11} can form a 3-10 membered ring;

R^{11} is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, is substituted or unsubstituted C_{6-10} aryl or together with R^{10} can form a 3-10 membered ring;

R^{12} is H, substituted or unsubstituted C_{1-6} alkyl, halogen, substituted or unsubstituted $-OR^8$, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, $C(O)R^9$, $NR^{10}R^{11}$, amide, urea, sulfonamide, sulfone, sulfoxide , sulfide, sulfonic acid, nitro, phosphate or phosphonic acid;

with the provisios

at least one of R^3, R^4 or R^5 is N or N-oxide; and

R^1 is not benzofuran-2-yl, when R^3 is CR^7 and R^4 is CR^7 and R^5 is N.

In another aspect, the invention provides a compound having **Formula I**, wherein:

R^1 is substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^2 is –S-, -S(O)-, or $-S(O)_2-$;

R^3 is N;

R^4 is CR^7;

R^5 is N;

R^6 is substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl or is substituted or

unsubstituted C_{6-10} aryl;

R^7 is H, substituted or unsubstituted C_{1-6} alkyl, halogen, substituted or unsubstituted $-OR^8$, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, $C(O)R^9$, $NR^{10}R^{11}$, amide, urea, sulfonamide, sulfone, sulfoxide , sulfide, sulfonic acid, nitro, phosphate or phosphonic acid;

R^8 is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^9 is H, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^{10} is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, is substituted or unsubstituted C_{6-10} aryl or together with R^{11} can form a 3-10 membered ring;

R^{11} is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, is substituted or unsubstituted C_{6-10} aryl or together with R^{10} can form a 3-10 membered ring; and

R^{12} is H, substituted or unsubstituted C_{1-6} alkyl, halogen, substituted or unsubstituted $-OR^8$, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, $C(O)R^9$, $NR^{10}R^{11}$, amide, urea, sulfonamide, sulfone, sulfoxide , sulfide, sulfonic acid, nitro, phosphate or phosphonic acid.

In another aspect, the invention provides a compound having **Formula I**, wherein:

R^1 is substituted or unsubstituted heterocycle or substituted or unsubstituted C_{6-10} aryl;

R^2 is –S-, -S(O)- or $-S(O)_2$-;

R^3 is N;

R^4 is CR^7;

R^5 is N;

R^6 is substituted or unsubstituted C_{6-10} aryl;

R^7 is H; and

R^{12} is H.

In another aspect, the invention provides a compound having **Formula I**, wherein:

R^1 is substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;
R^2 is –S-, -S(O)-, or -$S(O)_2$-;
R^3 is CR^7;
R^4 is N or N-oxide;
R^5 is CR^7;
R^6 is substituted or unsubstituted C_{6-10} aryl;
R^7 is H; and
R^{12} is H.

In another aspect, the invention provides a compound having **Formula I**, wherein:
R^1 is substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;
R^2 is –S-, -S(O)- or -$S(O)_2$-;
R^3 is CR^7;
R^4 is N-oxide;
R^5 is CR^7;
R^6 is substituted or unsubstituted C_{6-10} aryl;
R^7 is H; and
R^{12} is H.

In another aspect, the invention provides a compound having **Formula I**, wherein:
R^1 is substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;
R^2 is –S-, -S(O)- or -$S(O)_2$-;
R^3 is CR^7;
R^4 is N;
R^5 is CR^7;
R^6 is substituted or unsubstituted C_{6-10} aryl;
R^7 is H; and
R^{12} is H.

In another aspect, the invention provides a compound having **Formula I**, wherein:

R^1 is substituted or unsubstituted heterocycle, or is substituted or unsubstituted C_{6-10} aryl;

R^2 is –S-, -S(O)-, or -$S(O)_2$-;

R^3 is CR^7;

R^4 is CR^7;

R^5 is, N;

R^6 is substituted or unsubstituted C_{6-10} aryl;

R^7 is H or halogen;

R^{12} is H; and

with the proviso

R^1 is not benzofuran-2-yl, when R^3 is CR^7 and R^4 is CR^7 and R^5 is N.

In another aspect, the invention provides a compound having **Formula I**, wherein:

R^1 is substituted or unsubstituted heterocycle;

R^2 is –S-, -S(O)-, or -$S(O)_2$-;

R^3 is CR^7;

R^4 is CR^7;

R^5 is N;

R^6 is unsubstituted C_{6-10} aryl;

R^7 is H or halogen;

R^{12} is H; and

with the proviso

R^1 is not benzofuran-2-yl, when R^3 is CR^7 and R^4 is CR^7 and R^5 is N.

In another aspect, the invention provides a compound having **Formula I**, wherein:

R^1 is substituted or unsubstituted C_{6-10} aryl;

R^2 is –S-, -S(O)-, or -$S(O)_2$-;

R^3 is CR^7;

R^4 is CR^7;

R^5 isN;

R^6 is unsubstituted C_{6-10} aryl;

R^7 is H or halogen; and

R^{12} is H.

The term "alkyl", as used herein, refers to saturated, monovalent or divalent hydrocarbon moieties having linear or branched moieties or combinations thereof and containing 1 to 6 carbon atoms. One or more methylene ($-CH_2-$) groups, of the alkyl can be replaced by oxygen, sulfur, carbonyl, sulfoxide, nitrogen, sulfonyl, or by a divalent C_{3-6} cycloalkyl. Hydrogen atoms on alkyl groups can be substituted by groups including, but not limited to: halogens, hydroxyls, cycloalkyls, heterocycles, aryls, ethers, amines, nitros, amides, sulfonamides, esters, aldehydes, carboxylic acids, ketones.

The term "cycloalkyl", as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms, derived from a saturated cyclic hydrocarbon. Cycloalkyl groups can be monocyclic or polycyclic. Cycloalkyl can be substituted by groups including, but not limited to: halogens, hydroxyls, cycloalkyls, heterocycles, aryls, ethers, amines, nitros, amides, sulfonamides, esters, aldehydes, carboxylic acids, ketones.

The term "cycloalkenyl", as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms, derived from a saturated cycloalkyl having one or more double bonds. Cycloalkenyl groups can be monocyclic or polycyclic. Cycloalkenyl groups can be substituted by groups including, but not limited to halogens, hydroxyls, cycloalkyls, heterocycles, aryls, ethers, amines, nitros, amides, sulfonamides, esters, aldehydes, carboxylic acids, ketones.

The term "halogen", as used herein, refers to an atom of chlorine, bromine, fluorine, iodine.

The term "alkenyl", as used herein, refers to a monovalent or divalent hydrocarbon radical having 2 to 6 carbon atoms, derived from a saturated alkyl, having at least one double bond. C_{2-6} alkenyl can be in the E or Z configuration. Alkenyl groups can be substituted by C_{1-3} alkyl.

The term "alkynyl", as used herein, refers to a monovalent or divalent hydrocarbon radical having 2 to 6 carbon atoms, derived from a saturated alkyl, having at least one triple bond.

The term "heterocycle" as used herein, refers to a 3 to 10 membered ring, which can be aromatic or non-aromatic, saturated or non-saturated, containing at least one heteroatom selected form O or N or S or combinations of at least two

thereof, interrupting the carbocyclic ring structure. The heterocyclic ring can be interrupted by a C=O; the S heteroatom can be oxidized. Heterocycles can be monocyclic or polycyclic. Heterocyclic ring moieties can be substituted groups including, but not limited to: halogens, hydroxyls, cycloalkyls, heterocycles, -aminos, amides, ethers, esters, ketones, carboxylic acids, aldehydes, sulfonamides.

The term "aryl" as used herein, refers to an organic moiety derived from an aromatic hydrocarbon consisting of a ring containing 6 to 10 carbon atoms by removal of one hydrogen. Aryl can be substituted by groups including, but not limited to: halogens, hydroxyls, cycloalkyls, heterocycles, -aminos, nitros, amides, ethers, esters, carboxylic acids, aldehydes, ketones, sulfonamides groups. Aryl can be monocyclic or bicyclic.

The term "amine" as used herein, represents a group of formula "-NR^xR^y ",wherein R^x and R^y can be the same or independently H, alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

The term "amide" as used herein, represents a group of formula or "-$C(O)N(R^x)(R^y)$" or -"$NR^xC(O)R^y$" wherein R^x and R^y can be the same or independently H, alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

The term "sulfonamide" as used herein, represents a group of formula "-$S(O)_2N(R^x)(R^y)$" or "-$NR^xS(O)_2R^y$" wherein R^x and R^y can be the same or independently H, alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

The term "ester" as used herein, represents a group of formula "-$C(O)O(R^x)$", wherein R^x is alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

The term "aldehyde" as used herein, represents a group of formula "-C(O)H".

The term "ketone" as used herein, represents a group of formula "-$C(O)R^x$" wherein R^x is C_{1-6} alkyl.

The term "hydroxyl" as used herein, represents a group of formula "–OH".

The term "amino" as used herein, represents a group of formula "–NH_2".

The term "carbonyl" as used herein, represents a group of formula "-C(O)-".

The term "carboxyl" as used herein, represents a group of formula "-C(O)O-".

The term "sulfonyl" as used herein, represents a group of formula "-SO_2-".

The term "sulfate" as used herein, represents a group of formula "-O-$S(O)_2$-O-".

The term "carboxylic acid" as used herein, represents a group of formula "-C(O)OH".

The term “sulfoxide” as used herein, represents a group of formula “-S=O”.

The term “phosphonic acid” as used herein, represents a group of formula “-$P(O)(OH)_2$”.

The term “phosphoric acid” as used herein, represents a group of formula “-$(O)P(O)(OH)_2$”.

The term “sulphonic acid” as used herein, represents a group of formula “-$S(O)_2OH$”.

The term “nitro” as used herein, represents a group of formula “-NO_2“.

The term “ether” as used herein, represents a group of formula “-Oalkyl“.

The formula “H “, as used herein, represents a hydrogen atom.

The formula “O “, as used herein, represents an oxygen atom.

The formula “N “, as used herein, represents a nitrogen atom.

The formula “S “, as used herein, represents a sulfur atom.

The term “N-oxide” is repsresented by formulae “N=O” or “$^{+}N\text{-}O^{-}$“.

Compounds of the invention are:

N-[4-(benzylsulfanyl)pyrimidin-5-yl]-1-benzofuran-2-sulfonamide;

N-[4-(benzylsulfonyl)pyrimidin-5-yl]-1-benzofuran-2-sulfonamide;

N-[4-(benzylsulfinyl)pyrimidin-5-yl]-1-benzofuran-2-sulfonamide;

N-[3-(benzylsulfanyl)pyridin-4-yl]-1-benzofuran-2-sulfonamide;

N-[3-(benzylsulfonyl)pyridin-4-yl]-1-benzofuran-2-sulfonamide;

N-[3-(benzylsulfanyl)-1-oxidopyridin-4-yl]-1-benzofuran-2-sulfonamide;

N-[2-(benzylsulfanyl)-5-chloropyridin-3-yl]-3,4-dichlorobenzenesulfonamide;

N-[2-(benzylsulfanyl)-5-chloropyridin-3-yl]-5-chlorothiophene-2-sulfonamide;

N-[2-(benzylsulfonyl)-5-chloropyridin-3-yl]-3,4-dichlorobenzenesulfonamide;

N-[2-(benzylsulfinyl)-5-chloropyridin-3-yl]-3,4-dichlorobenzenesulfonamide;

N-[2-(benzylsulfonyl)-5-chloropyridin-3-yl]-5-chlorothiophene-2-sulfonamide;

N-[2-(benzylsulfinyl)-5-chloropyridin-3-yl]-5-chlorothiophene-2-sulfonamide;

N-[2-(benzylthio)pyridin-3-yl]-1-benzothiophene-2-sulfonamide;

N-[2-(benzylsulfonyl)pyridin-3-yl]-1-benzothiophene-2-sulfonamide;

N-[2-(benzylsulfinyl)pyridin-3-yl]-1-benzothiophene-2-sulfonamide.

Some compounds of Formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in an R or S configuration, said R and S notation is used in correspondence with the

rules described in Pure Appli. Chem. (1976), 45, 11-13.

The term "pharmaceutically acceptable salts" refers to salts or complexes that retain the desired biological activity of the above identified compounds and exhibit minimal or no undesired toxicological effects. The "pharmaceutically acceptable salts" according to the invention include therapeutically active, non-toxic base or acid salt forms, which the compounds of Formula I are able to form.

The acid addition salt form of a compound of Formula I that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, a hydrohalic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; or an organic acid such as for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, fumaric acid, maleic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, citric, methylsulfonic, ethanesulfonic, benzenesulfonic, formic acid and the like (Handbook of Pharmaceutical Salts, P.Heinrich Stahal& Camille G. Wermuth (Eds), Verlag Helvetica Chemica Acta-Zürich, 2002, 329-345).

The base addition salt form of a compound of Formula I that occurs in its acid form can be obtained by treating the acid with an appropriate base such as an inorganic base, for example, sodium hydroxide, magnesium hydroxide, potassium hydroxide, calcium hydroxide, ammonia and the like; or an organic base such as for example, L-Arginine, ethanolamine, betaine, benzathine, morpholine and the like. (Handbook of Pharmaceutical Salts, P.Heinrich Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta- Zürich, 2002, 329-345).

Compounds of Formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

With respect to the present invention reference to a compound or compounds, is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically.

Compounds according to the present invention may exist in different polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

The compounds of the invention are indicated for use in treating or preventing conditions in which there is likely to be a component involving the chemokine

receptors.

In another embodiment, there are provided pharmaceutical compositions including at least one compound of the invention in a pharmaceutically acceptable carrier.

In a further embodiment of the invention, there are provided methods for treating disorders associated with modulation of chemokine receptors. Such methods can be performed, for example, by administering to a subject in need thereof a pharmaceutical composition containing a therapeutically effective amount of at least one compound of the invention.

These compounds are useful for the treatment of mammals, including humans, with a range of conditions and diseases that are alleviated by chemokine receptor modulation.

Therapeutic utilities of chemokine receptor modulators are skin inflammatory diseases and conditions, including, but are not limited to: rosacea (dilation of the blood vessels just under the skin), sunburn, chronic sun damage, discreet erythemas, psoriasis, atopic dermatitis, menopause-associated hot flashes, hot flashes resulting from orchiectomyatopic dermatitis, photoaging, seborrheic dermatitis, acne, allergic dermatitis, irritant dermatitis, telangiectasia (dilations of previously existing small blood vessels) of the face, rhinophyma (hypertrophy of the nose with follicular dilation), red bulbous nose, acne-like skin eruptions (may ooze or crust), burning or stinging sensation of the face, irritated and bloodshot and watery eyes, cutaneous hyperactivity with dilation of blood vessels of the skin, Lyell's syndrome, Stevens-Johnson syndrome, erythema multiforme minor, erythema multiforme major and other inflammatory skin diseases, actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema, wound healing.

Therapeutic utilities of chemokine receptor modulators are ocular inflammatory diseases including, but not limited to, uveitis, retinal degenerative conditions, angiogenesis, dry eye, Keratitis, allergic eye disease and conditions affecting the posterior part of the eye, such as maculopathies and retinal degeneration including non-exudative age related macular degeneration, exudative age related macular degeneration, choroidal neovascularization, diabetic retinopathy, acute macular neuroretinopathy, central serous chorioretinopathy, cystoid macular edema, and diabetic macular edema; uveitis, retinitis, and choroiditis

such as acute multifocal placoid pigment epitheliopathy, Behcet's disease, birdshot retinochoroidopathy, infectious (syphilis, lyme, tuberculosis, toxoplasmosis), intermediate uveitis (pars planitis), multifocal choroiditis, multiple evanescent white dot syndrome (mewds), ocular sarcoidosis, posterior scleritis, serpiginous choroiditis, subretinal fibrosis and uveitis syndrome, Vogt-Koyanagi-and Harada syndrome; vasuclar diseases/ exudative diseases such as retinal arterial occlusive disease, central retinal vein occlusion, disseminated intravascular coagulopathy, branch retinal vein occlusion, hypertensive fundus changes, ocular ischemic syndrome, retinal arterial microaneurysms, Coat's disease, parafoveal telangiectasis, hemi-retinal vein occlusion, papillophlebitis, central retinal artery occlusion, branch retinal artery occlusion, carotid artery disease (CAD), frosted branch angiitis, sickle cell retinopathy and other hemoglobinopathies, angioid streaks, familial exudative vitreoretinopathy, and Eales disease; traumatic/ surgical conditions such as sympathetic ophthalmia, uveitic retinal disease, retinal detachment, trauma, conditions caused by laser, conditions caused by photodynamic therapy, photocoagulation, hypoperfusion during surgery, radiation retinopathy, and bone marrow transplant retinopathy; proliferative disorders such as proliferative vitreal retinopathy and epiretinal membranes, and proliferative diabetic retinopathy; infectious disorders such as ocular histoplasmosis, ocular toxocariasis, presumed ocular histoplasmosis syndrome (POHS), endophthalmitis, toxoplasmosis, retinal diseases associated with HIV infection, choroidal disease associate with HIV infection, uveitic disease associate with HIV infection, viral retinitis, acute retinal necrosis, progressive outer retinal necrosis, fungal retinal diseases, ocular syphilis, ocular tuberculosis, diffuse unilateral subacute neuroretinitis, and myiasis; genetic disorders such as retinitis pigmentosa, systemic disorders with accosiated retinal dystrophies, congenital stationary night blindness, cone dystrophies, Stargardt's disease and fundus flavimaculatus, Best's disease, pattern dystrophy of the retinal pigmented epithelium, X-linked retinoschisis, Sorsby's fundus dystrophy, benign concentric maculopathy, Bietti's crystalline dystrophy, and pseudoxanthoma elasticum; retinal tears/ holes such as retinal detachment, macular hole, and giant retinal tear; tumors such as retinal disease associated with tumors, congenital hypertrophy of the retinal pigmented epithelium, posterior uveal melanoma, choroidal hemangioma, choroidal osteoma, choroidal metastasis, combined hamartoma of the retina and retinal pigmented epithelium, retinoblastoma, vasoproliferative tumors of

the ocular fundus, retinal astrocytoma, and intraocular lymphoid tumors; and miscellaneous other diseases affecting the posterior part of the eye such as punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, myopic retinal degeneration, and acute retinal pigement epitheliitis.

In still another embodiment of the invention, there are provided methods for treating disorders associated with modulation of chemokine receptors. Such methods can be performed, for example, by administering to a subject in need thereof a therapeutically effective amount of at least one compound of the invention, or any combination thereof, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual isomers, enantiomers, and diastereomers thereof.

The present invention concerns the use of a compound of Formula I or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of ocular inflammatory diseases including, but not limited to, uveitis, dry eye, Keratitis, allergic eye disease and conditions affecting the posterior part of the eye, such as maculopathies and retinal degeneration including non-exudative age related macular degeneration, exudative age related macular degeneration, choroidal neovascularization, diabetic retinopathy, acute macular neuroretinopathy, central serous chorioretinopathy, cystoid macular edema, and diabetic macular edema; uveitis, retinitis, and choroiditis such as acute multifocal placoid pigment epitheliopathy, Behcet's disease, birdshot retinochoroidopathy, infectious (syphilis, lyme, tuberculosis, toxoplasmosis), intermediate uveitis (pars planitis), multifocal choroiditis, multiple evanescent white dot syndrome (mewds), ocular sarcoidosis, posterior scleritis, serpiginous choroiditis, subretinal fibrosis and uveitis syndrome, Vogt-Koyanagi-and Harada syndrome; vasuclar diseases/ exudative diseases such as retinal arterial occlusive disease, central retinal vein occlusion, disseminated intravascular coagulopathy, branch retinal vein occlusion, hypertensive fundus changes, ocular ischemic syndrome, retinal arterial microaneurysms, Coat's disease, parafoveal telangiectasis, hemi-retinal vein occlusion, papillophlebitis, central retinal artery occlusion, branch retinal artery occlusion, carotid artery disease (CAD), frosted branch angiitis, sickle cell retinopathy and other hemoglobinopathies, angioid streaks, familial exudative vitreoretinopathy, and Eales disease; traumatic/ surgical conditions such as sympathetic ophthalmia, uveitic retinal disease, retinal detachment, trauma, conditions caused by laser, conditions caused by photodynamic therapy, photocoagulation, hypoperfusion during surgery, radiation

retinopathy, and bone marrow transplant retinopathy; proliferative disorders such as proliferative vitreal retinopathy and epiretinal membranes, and proliferative diabetic retinopathy; infectious disorders such as ocular histoplasmosis, ocular toxocariasis, presumed ocular histoplasmosis syndrome (POHS), endophthalmitis, toxoplasmosis, retinal diseases associated with HIV infection, choroidal disease associate with HIV infection, uveitic disease associate with HIV infection, viral retinitis, acute retinal necrosis, progressive outer retinal necrosis, fungal retinal diseases, ocular syphilis, ocular tuberculosis, diffuse unilateral subacute neuroretinitis, and myiasis; genetic disorders such as retinitis pigmentosa, systemic disorders with accosiated retinal dystrophies, congenital stationary night blindness, cone dystrophies, Stargardt's disease and fundus flavimaculatus, Best's disease, pattern dystrophy of the retinal pigmented epithelium, X-linked retinoschisis, Sorsby's fundus dystrophy, benign concentric maculopathy, Bietti's crystalline dystrophy, and pseudoxanthoma elasticum; retinal tears/ holes such as retinal detachment, macular hole, and giant retinal tear; tumors such as retinal disease associated with tumors, congenital hypertrophy of the retinal pigmented epithelium, posterior uveal melanoma, choroidal hemangioma, choroidal osteoma, choroidal metastasis, combined hamartoma of the retina and retinal pigmented epithelium, retinoblastoma, vasoproliferative tumors of the ocular fundus, retinal astrocytoma, and intraocular lymphoid tumors; and miscellaneous other diseases affecting the posterior part of the eye such as punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, myopic retinal degeneration, and acute retinal pigement epitheliitis.

The actual amount of the compound to be administered in any given case will be determined by a physician taking into account the relevant circumstances, such as the severity of the condition, the age and weight of the patient, the patient's general physical condition, the cause of the condition, and the route of administration.

The patient will be administered the compound orally in any acceptable form, such as a tablet, liquid, capsule, powder and the like, or other routes may be desirable or necessary, particularly if the patient suffers from nausea. Such other routes may include, without exception, transdermal, parenteral, subcutaneous, intranasal, via an implant stent, intrathecal, intravitreal, topical to the eye, back to the eye, intramuscular, intravenous, and intrarectal modes of delivery. Additionally, the formulations may be designed to delay release of the active compound over a given

period of time, or to carefully control the amount of drug released at a given time during the course of therapy.

In another embodiment of the invention, there are provided pharmaceutical compositions including at least one compound of the invention in a pharmaceutically acceptable carrier thereof. The phrase "pharmaceutically acceptable" means the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an emulsion, a dispersion, a patch, a micelle, a liposome, and the like, wherein the resulting composition contains one or more compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for enteral or parenteral applications. Invention compounds may be combined, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. Invention compounds are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

Pharmaceutical compositions containing invention compounds may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets containing invention compounds in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as

calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the invention compounds are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the invention compounds are mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Invention compounds and their pharmaceutically-acceptable salts may be administered through different routes, including but not limited to topical eye drops, direct injection, application at the back of the eye or formulations that may further enhance the long duration of actions such as a slow releasing pellet, suspension, gel, or sustained delivery devices such as any suitable drug delivery system (DDS) known in the art. While topical administration is preferred, this compound may also be used in an intraocular implant as described in U.S. U.S. Patent 7,931,909.

Invention compounds may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the invention compounds with a suitable non-irritating excipient, such as cocoa

butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner.

The compounds and pharmaceutical compositions described herein are useful as medicaments in mammals, including humans, for treatment of diseases and/or alleviations of conditions which are responsive to treatment by agonists or functional antagonists of chemokine receptors. Thus, in further embodiments of the invention, there are provided methods for treating a disorder associated with modulation of chemokine receptors. Such methods can be performed, for example, by administering to a subject in need thereof a pharmaceutical composition containing a therapeutically effective amount of at least one invention compound. As used herein, the term "therapeutically effective amount" means the amount of the pharmaceutical composition that will elicit the biological or medical response of a subject in need thereof that is being sought by the researcher, veterinarian, medical doctor or other clinician. In some embodiments, the subject in need thereof is a mammal. In some embodiments, the mammal is human.

The present invention concerns also processes for preparing the compounds of Formula I. The compounds of formula I according to the invention can be prepared analogously to conventional methods as understood by the person skilled in the art of synthetic organic chemistry.

DETAILED DESCRIPTION OF THE INVENTION

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention claimed. As used herein, the use of the singular includes the plural unless specifically stated otherwise.

It will be readily apparent to those skilled in the art that some of the compounds of the invention may contain one or more asymmetric centers, such that the compounds may exist in enantiomeric as well as in diastereomeric forms. Unless it is specifically noted otherwise, the scope of the present invention includes all enantiomers, diastereomers and racemic mixtures. Some of the compounds of the invention may form salts with pharmaceutically acceptable acids or bases, and

such pharmaceutically acceptable salts of the compounds described herein are also within the scope of the invention.

The present invention includes all pharmaceutically acceptable isotopically enriched compounds. Any compound of the invention may contain one or more isotopic atoms enriched or different than the natural ratio such as deuterium ^{2}H (or D) in place of protium ^{1}H (or H) or use of ^{13}C enriched material in place of ^{12}C and the like. Similar substitutions can be employed for N, O and S. The use of isotopes may assist in analytical as well as therapeutic aspects of the invention. For example, use of deuterium may increase the in vivo half-life by altering the metabolism (rate) of the compounds of the invention. These compounds can be prepared in accord with the preparations described by use of isotopically enriched reagents.

As will be evident to those skilled in the art, individual isomeric forms can be obtained by separation of mixtures thereof in conventional manner. For example, in the case of diasteroisomeric isomers, chromatographic separation may be employed.

Compound names were generated with ACD version 12.0 and some intermediates' and reagents' names used in the examples were generated with software such as Chem Bio Draw Ultra version 12.0 or Auto Nom 2000 from MDL ISIS Draw 2.5 SP1. In general, characterization of the compounds is performed according to the following methods:

NMR spectra are recorded on *Varian* 600 or *Varian* 300, in the indicated solvent at ambient temperature; chemical shifts in [ppm], coupling constants in [Hz].

All the reagents, solvents, catalysts for which the synthesis is not described are purchased from chemical vendors such as Sigma Aldrich, Fluka, Bio-Blocks, Combi-blocks, TCI, VWR, Lancaster, Oakwood, Trans World Chemical, Alfa, Fisher, Maybridge, Frontier, Matrix, Ukrorgsynth, Toronto, Ryan Scientific, SiliCycle, Anaspec, Syn Chem, Chem-Impex, MIC-scientific, Ltd; however some known intermediates, were prepared according to published procedures. Solvents were purchased from commercial sources in appropriate quality and used as received. Air and/or moisture-sensitive reactions were run under an Ar- or N_2- atmosphere.

Usually the compounds of the invention were purified by chromatography: CombiFlash Companion and RediSep Rf silica gel 60 (0.04-0.063 mm); Preparative thin layer chromatography (PTLC): *Analtech* (silica gel 60 F_{254}, 500 or 1000 μm).

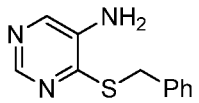
The following abbreviations are used in the examples:

$Na_2S•9H_2O$	sodium sulfide nanohydride
$NaHCO_3$	sodium bicarbonate
HOAc	acetic acid
DMAP	4-dimethylaminopyridine
CH_2Cl_2	dichloromethane
NaOH	sodium hydroxide
MeOH	methanol
HCl	hydrochloric acid
Na_2SO_4	sodium sulfate
Na_2CO_3	sodium carbonate
EtOAc	ethyl acetate
mCPBA	meta-chloroperoxybenzoic acid

The following examples are for illustrative purposes only and are not intended, nor should they be construed as limiting the invention in any manner. Those skilled in the art will appreciate that variations and modifications of the following examples can be made without exceeding the spirit or scope of the invention.

Intermediate 1

4-(benzylthio)pyrimidin-5-amine

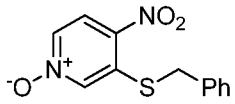


To a solution of 4-chloropyrimidin-5-amine (226 mg, 1.74 mmol) in dioxane (2 ml) and H_2O (2 ml) was added $Na_2S•9H_2O$ (522 mg, 2.17 mmol) and the reaction was stirred at 100 °C for 2 hours, cooled to room temperature, and saturated aqueous $NaHCO_3$ (2 ml) and (bromomethyl)benzene (0.21 ml, 1.74 mmol) was added. The reaction was continued at room temperature for 1 hour, diluted with brine, extracted with EtOAc (×2). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (40-50% EtOAc in hexane) to yield **Intermediate 1** (198 mg, 52%).

^1H NMR (METHANOL-d4) δ 8.33 (s, 1H), 7.85 (s, 1H), 7.40 (d, J = 7.3 Hz, 2H), 7.24 - 7.30 (m, 2H), 7.19 - 7.24 (m, 1H), 4.51 (s, 2H).

Intermediate 2

3-(benzylthio)-4-nitropyridine 1-oxide

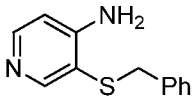


To NaH (60% on mineral oil, 276 mg, 6.9 mmol) in dioxane (25 ml) was added phenylmethanethiol (0.73 ml, 6.3 mmol), after stirred at room temperature for 2 hours, 3-bromo-4-nitropyridine 1-oxide (1.1 g, 5.0 mmol) was added. The mixture was stirred for 3 days, acidified with 1M HCl, extracted with EtOAc (×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (10-100% EtOAc in hexane) to yield **Intermediate 2** (688 mg, 53%).

^{1}H NMR (METHANOL-d4) δ 8.41 (d, J = 1.8 Hz, 1H), 8.24 (d, J = 7.3 Hz, 1H), 8.10 - 8.13 (m, 1H), 7.47 (d, J = 7.3 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.29 - 7.33 (m, 1H), 4.37 (s, 2H).

Intermediate 3

3-(benzylthio)pyridin-4-amine

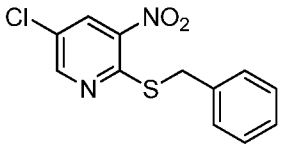


To a solution of **Intermediate 2** (635 mg, 2.49 mmol) in HOAc (12 ml) was added iron powder (977 mg, 17.4 mmol). The suspension was stirred at 100 °C for 3 hours and was filtered and concentrated. The residue was diluted with EtOAc, basified with aqueous NaOH and treated with Celite. After filtration, the organic layer was separated and concentrated. The crude product was purified by flash column chromatography on silica gel (EtOAc) to yield **Intermediate 3** (525 mg, 98%).

^{1}H NMR (METHANOL-d4) δ 7.86 (d, J = 6.2 Hz, 1H), 7.75 (s, 1H), 7.13 - 7.21 (m, 3H), 7.04 - 7.09 (m, 2H), 6.66 (d, J = 6.2 Hz, 1H), 3.85 (s, 2H).

Intermediate 4

2-(benzylthio)-5-chloro-3-nitropyridine



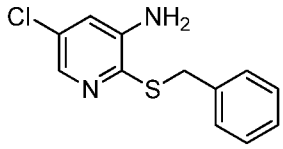
To a solution of 2,5-dichloro-3-nitropyridine (2.25 g, 11.7 mmol) in dioxane (6 ml) was added a solution of $Na_2S•9H_2O$ (2.80 g, 11.7 mmol) in H_2O (6 ml) and the

reaction was stirred at room temperature for 2 hours, then benzyl bromide (1.40 ml, 11.7 mmol) and Na_2CO_3 (1.24 g, 11.7 mmol) was added and the reaction was continued for 3 hours, diluted with water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (0 - 2% EtOAc in hexane) to yield **Intermediate 4** (2.10 g, 64%).

^{1}H NMR (CHLOROFORM-d) δ 8.67 (d, J = 2.3 Hz, 1H), 8.48 (d, J = 2.3 Hz, 1H), 7.39 - 7.43 (m, 2H), 7.25 - 7.34 (m, 3H), 4.44 (s, 2H).

Intermediate 5

2-(benzylthio)-5-chloropyridin-3-amine

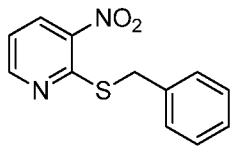


To a solution of **Intermediate 4** (2.0 g, 7.1 mmol) in HOAc (35 ml) was added iron powder (2.0 g, 35.7 mmol). The suspension was stirred at room temperature for 1 hour and was concentrated. The residue was diluted with EtOAc, basified with aqueous NaOH and treated with Celite. After filtration, the organic layer was separated and concentrated. The crude product was purified by flash column chromatography on silica gel (5-10% EtOAc in hexane) to yield **Intermediate 5** (1.83 g, 89%).

^{1}H NMR (CHLOROFORM-d) δ 7.94 (d, J = 2.1 Hz, 1H), 7.22 - 7.38 (m, 5H), 6.86 (d, J = 2.1 Hz, 1H), 4.42 (s, 2H), 3.96 (br. s., 2H).

Intermediate 6

2-(benzylthio)-3-nitropyridine

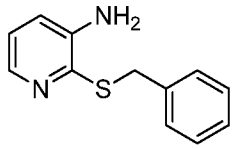


To a solution of 3-nitropyridine-2-thiol (0.50 g, 3.2 mmol) in DMF (4 ml) was added benzyl bromide (0.38 ml, 3.2 mmol) and K_2CO_3 (0.89 g, 6.4 mmol). The mixture was stirred at room temperature for 2 hours, diluted with H_2O, extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by recrystallization from MeOH and minimal amount of CH_2Cl_2 to yield the title compound (0.72 g, 91%).

^{1}H NMR ($CDCl_3$) δ: 8.72 (dd, J=4.5, 1.6 Hz, 1H), 8.49 (dd, J=8.2, 1.8 Hz, 1H), 7.43 (d, J=7.3 Hz, 2H), 7.20-7.34 (m, 4H), 4.48 (s, 2H).

Intermediate 7

2-(benzylthio)pyridin-3-amine

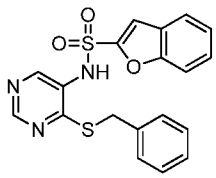


To a solution of **Intermediate 6** (0.35 g, 1.4 mmol) in MeOH (10 ml) was added saturated aqueous NH_4Cl (5 ml) and zinc dust (2.3 g, 35.6 mmol). The suspension was stirred at room temperature for 1 hour and was filtered. The filtrate was extracted with EtOAc, the organic layer was separated and washed with H_2O, brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product (0.24 g) was used without further purification.

^{1}H NMR ($CDCl_3$) δ: 8.01 (dd, J=4.7, 1.2 Hz, 1H), 7.34-7.37 (m, 2H), 7.16-7.32 (m, 3H), 6.92 (dd, J=6.3 Hz, 1H), 6.86 (dd, J=12.1 Hz, 1H), 4.45 (s, 2H), 3.81 (br. s., 2H).

Compound 1

N-[4-(benzylsulfanyl)pyrimidin-5-yl]-1-benzofuran-2-sulfonamide



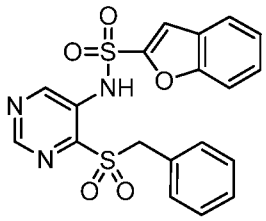
To a solution of **Intermediate 1** (325 mg, 1.50 mmol) in pyridine (2 ml) was added 1-benzofuran-2-sulfonyl chloride (325 mg, 1.50 mmol). The reaction was stirred at room temperature for 4 hours, and additional 1-benzofuran-2-sulfonyl chloride (325 mg, 1.50 mmol) was added. The reaction was continued for 16 hours and was concentrated. The crude mixture was diluted with MeOH, treated with 4M NaOH (2 ml) at 100 °C for 15 minutes, cooled to room temperature, acidified with 6M HCl, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (40-50% EtOAc in hexane) to yield **Compound 1** (311 mg, 52%).

^{1}H NMR (METHANOL-d4) δ 8.76 (s, 1H), 8.35 (s, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 3.8 Hz, 2H), 7.37 (dt, J = 8.1, 3.9 Hz, 1H), 7.29 (s, 1H), 7.08 - 7.17

(m, 3H), 6.93 (d, J = 6.7 Hz, 2H), 4.17 (s, 2H).

Compound 2

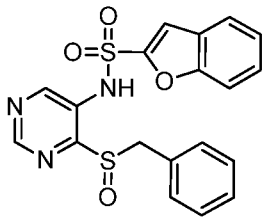
N-[4-(benzylsulfonyl)pyrimidin-5-yl]-1-benzofuran-2-sulfonamide



And

Compound 3

N-[4-(benzylsulfinyl)pyrimidin-5-yl]-1-benzofuran-2-sulfonamide



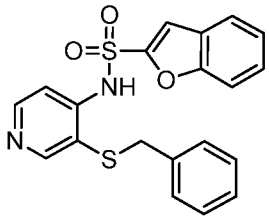
To a solution of **Compound 1** (283 mg, 0.71 mmol) in CH_2Cl_2 (7 ml) was added mCPBA (343 mg, ~1.43 mmol) and the reaction was stirred at room temperature for 2 hours. The reaction mixture was directly loaded onto Celite and purified by flash column chromatography on silica gel (50-100% EtOAc in hexane, then 10-20% MeOH in CH_2Cl_2) to yield **Compound 2** (167 mg, 55%) and **Compound 3** (71 mg, 24%).

Compound 2: ^{1}H NMR (acetone) δ 9.28 (s, 1H), 8.47 (br. s., 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.37 - 7.43 (m, 2H), 7.26 - 7.32 (m, 1H), 7.24 (d, J = 7.3 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.5 Hz, 2H), 4.93 (s, 2H).

Compound 3: ^{1}H NMR (METHANOL-d4) δ 8.81 (s, 1H), 8.41 (s, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.33 - 7.37 (m, 1H), 7.32 (s, 1H), 7.25 - 7.29 (m, 1H), 7.17 - 7.21 (m, 1H), 7.06 - 7.13 (m, 4H), 4.56 (d, J = 13.2 Hz, 1H), 4.38 (d, J = 12.9 Hz, 1H).

Compound 4

N-[3-(benzylsulfanyl)pyridin-4-yl]-1-benzofuran-2-sulfonamide

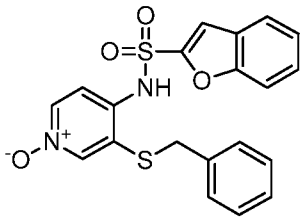


To a solution of **Intermediate 3** (315 mg, 1.46 mmol) in pyridine (3 ml) was added 1-benzofuran-2-sulfonyl chloride (316 mg, 1.46 mmol). The reaction was stirred at room temperature for 16 hours, and additional 1-benzofuran-2-sulfonyl chloride (316 mg, 1.46 mmol) was added. The reaction was continued for 24 hours and was concentrated. The crude mixture was diluted with MeOH, treated with 4M NaOH (2 ml) at 100 °C for 15 minutes, cooled to room temperature, acidified with 6M HCl, and extracted with EtOAc (×2). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (50-100% EtOAc in hexane) to yield **Compound 4** (242 mg, 42%).

^{1}H NMR (METHANOL-d4) δ 7.86 (d, J = 7.0 Hz, 1H), 7.78 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 7.0 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.40 - 7.44 (m, 2H), 7.29 - 7.34 (m, 1H), 7.15 - 7.20 (m, 2H), 7.09 - 7.13 (m, 3H), 4.17 (s, 2H).

Compound 5

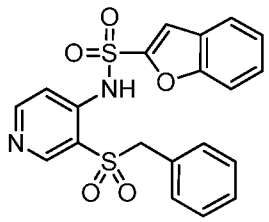
N-[3-(benzylsulfanyl)-1-oxidopyridin-4-yl]-1-benzofuran-2-sulfonamide



And

Compound 6

N-[3-(benzylsulfonyl)pyridin-4-yl]-1-benzofuran-2-sulfonamide



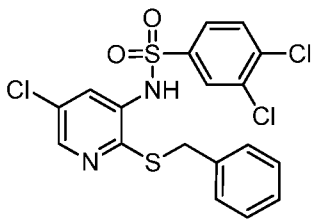
To a solution of **Compound 4** (161 mg, 0.41 mmol) in CH_2Cl_2 (10 ml) was added mCPBA (147 mg, ~0.61 mmol) and the reaction was stirred at room temperature for 4 hours. The volume of the resulting suspension was reduced to about half and was filtered, the solid was rinsed with CH_2Cl_2, triturated with acetone to yield **Compound 5** (85 mg, 51%). The combined filtrate was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by trituration in CH_2Cl_2 followed by PTLC on silica gel (EtOAc) to yield **Compound 6** (35 mg, 20%).

Compound 5: ^{1}H NMR (METHANOL-d4) δ 8.03 (d, J = 7.0 Hz, 1H), 7.72 - 7.76 (m, 1H), 7.69 (d, J = 7.0 Hz, 1H), 7.48 - 7.55 (m, 3H), 7.41 - 7.46 (m, 1H), 7.30 - 7.36 (m, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 2H), 6.90 (d, J = 7.6 Hz, 2H), 4.45 (s, 2H).

Compound 6: ^{1}H NMR (METHANOL-d4) δ 8.18 (br. s., 1H), 8.06 (br. s., 1H), 7.70 (dd, J = 7.9, 0.6 Hz, 1H), 7.58 - 7.64 (m, 1H), 7.43 - 7.48 (m, 2H), 7.36 - 7.41 (m, 1H), 7.28 - 7.32 (m, 1H), 7.09 - 7.15 (m, 3H), 6.97 - 7.02 (m, 2H), 4.94 (s, 2H).

Compound 7

N-[2-(benzylsulfanyl)-5-chloropyridin-3-yl]-3,4-dichlorobenzenesulfonamide



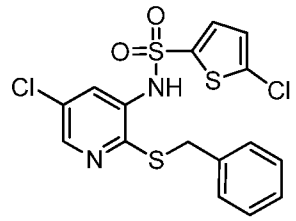
To a solution of **Intermediate 5** (410 mg, 1.64 mmol) in pyridine (5 ml) was added 3,4-dichlorobenzene-1-sulfonyl chloride (0.26 ml, 1.64 mmol) and catalytic amount of DMAP. The reaction was stirred at room temperature for 6 hours, and additional 3,4-dichlorobenzene-1-sulfonyl chloride (0.26 ml, 1.64 mmol) was added. The reaction was continued for 16 hours and was concentrated. The crude mixture was diluted with MeOH, treated with 4M NaOH (1.6 ml) at 100 °C for 10 minutes, cooled to room temperature, acidified with 6M HCl, and extracted with EtOAc (×2). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (0-25% EtOAc in hexane) to yield **Compound 7** (408 mg, 54%).

^{1}H NMR (CHLOROFORM-d) δ 8.29 (d, J = 2.3 Hz, 1H), 7.86 (dd, J = 2.1, 0.6 Hz, 1H), 7.81 (d, J = 2.3 Hz, 1H), 7.48 (dd, J = 4.8, 1.3 Hz, 2H), 7.24 - 7.28 (m, 3H),

7.16 - 7.21 (m, 2H), 6.57 (s, 1H), 4.30 (s, 2H).

Compound 8

N-[2-(benzylsulfanyl)-5-chloropyridin-3-yl]-5-chlorothiophene-2-sulfonamide

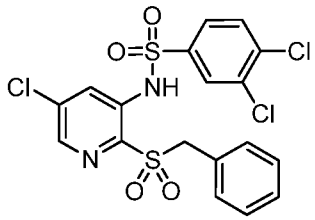


To a solution of **Intermediate 5** (410 mg, 1.64 mmol) in pyridine (5 ml) was added 5-chlorothiophene-2-sulfonyl chloride (356 mg, 1.64 mmol) and catalytic amount of DMAP. The reaction was stirred at room temperature for 6 hours, and additional 5-chlorothiophene-2-sulfonyl chloride (356 mg, 1.64 mmol) was added. The reaction was continued for 16 hours and was concentrated. The crude mixture was diluted with MeOH, treated with 4M NaOH (1.6 ml) at 100 °C for 10 minutes, cooled to room temperature, acidified with 6M HCl, and extracted with EtOAc (×2). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (0-25% EtOAc in hexane) to yield **Compound 8** (424 mg, 60%).

^{1}H NMR (METHANOL-d4) δ 8.35 (d, J = 2.3 Hz, 1H), 7.67 (d, J = 2.3 Hz, 1H), 7.21 - 7.28 (m, 6H), 6.91 (d, J = 3.8 Hz, 1H), 4.29 (s, 2H).

Compound 9

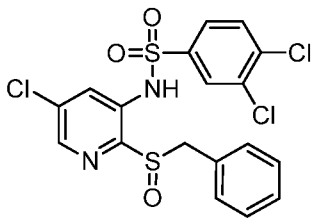
N-[2-(benzylsulfonyl)-5-chloropyridin-3-yl]-3,4-dichlorobenzenesulfonamide



And

Compound 10

N-[2-(benzylsulfinyl)-5-chloropyridin-3-yl]-3,4-dichlorobenzenesulfonamide



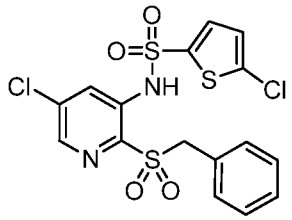
To a solution of **Compound 7** (326 mg, 0.71 mmol) in CH_2Cl_2 (5 ml) was added mCPBA (256 mg, ~1.06 mmol) and the reaction was stirred at room temperature for 2 hours. Additional mCPBA (43 mg, ~0.18 mmol) was added and the reaction was continued for 2 hours. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (50-100% EtOAc in hexane), followed by PTLC (75% EtOAc in hexane) to yield **Compound 9** (264 mg, 76%) and **Compound 10** (16 mg, 5%).

Compound 9: ^{1}H NMR (acetone) δ 8.20 (d, J = 2.1 Hz, 1H), 7.89 - 7.99 (m, 3H), 7.62 (d, J = 8.5 Hz, 1H), 7.19 - 7.27 (m, 5H), 4.81 (s, 2H).

Compound 10: ^{1}H NMR (acetone) δ 10.85 (br. s., 1H), 8.30 (br. s., 1H), 7.97 - 8.11 (m, 1H), 7.85 - 7.97 (m, 1H), 7.67 - 7.85 (m, 2H), 7.18 - 7.44 (m, 3H), 7.08 (d, J = 6.7 Hz, 2H), 4.52 (d, J = 13.2 Hz, 1H), 4.25 (d, J = 13.2 Hz, 1H).

Compound 11

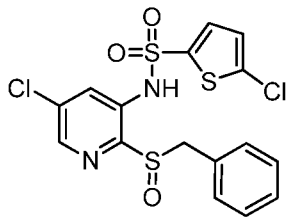
N-[2-(benzylsulfonyl)-5-chloropyridin-3-yl]-5-chlorothiophene-2-sulfonamide



And

Compound 12

N-[2-(benzylsulfinyl)-5-chloropyridin-3-yl]-5-chlorothiophene-2-sulfonamide



To a solution of **Compound 8** (352 mg, 0.82 mmol) in CH_2Cl_2 (5 ml) was added mCPBA (295 mg, ~1.23 mmol) and the reaction was stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (50-100%

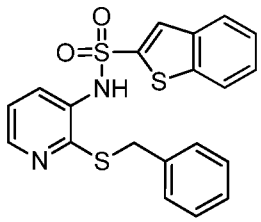
EtOAc in hexane) to yield **Compound 11** (121 mg, 32%) and **Compound 12** (156 mg, 43%).

Compound 11: ^{1}H NMR (acetone) δ 8.05 (d, J = 2.1 Hz, 1H), 7.97 (br. s., 1H), 7.48 (d, J = 3.8 Hz, 1H), 7.18 - 7.32 (m, 5H), 6.99 (d, J = 3.8 Hz, 1H), 4.81 (s, 2H)

Compound 12: ^{1}H NMR (acetone) δ 8.00 (br. s., 1H), 7.88 (s, 1H), 7.42 (d, J = 3.5 Hz, 1H), 7.08 - 7.34 (m, 5H), 6.99 (d, J = 3.8 Hz, 1H), 4.76 (d, J = 12.9 Hz, 1H), 4.25 (d, J = 12.6 Hz, 1H).

Compound 13

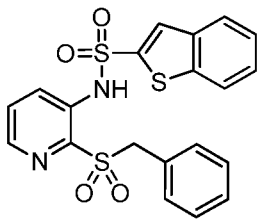
N-[2-(benzylthio)pyridin-3-yl]-1-benzothiophene-2-sulfonamide



To a solution of **Intermediate 7** (243 mg, 1.13 mmol) in pyridine (3 ml) was added benzo[b]thiophene-2-sulfonyl chloride (262 mg, 1.13 mmol). The reaction was stirred at room temperature for 40 hours, and was concentrated. The crude mixture was diluted with EtOAc, washed with aqueous NH_4Cl, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (0-30% EtOAc in hexane) to yield the title compound (230 mg, 49%).
^{1}H NMR ($cdcl_3$) δ: 8.33 (dd, J=4.8, 1.6 Hz, 1H), 7.76-7.87 (m, 4H), 7.42-7.52 (m, 2H), 7.14-7.19 (m, 3H), 7.04-7.14 (m, 3H), 6.89 (br. s., 1H), 4.26 (s, 2H).

Compound 14

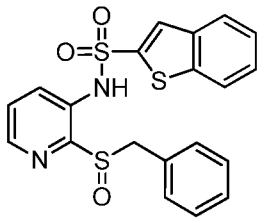
N-[2-(benzylsulfonyl)pyridin-3-yl]-1-benzothiophene-2-sulfonamide



And

Compound 15

N-[2-(benzylsulfinyl)pyridin-3-yl]-1-benzothiophene-2-sulfonamide



To a solution of **Compound 13** (190 mg, 0.46 mmol) in CH_2Cl_2 (2 ml) was added mCPBA (120 mg, ~0.69 mmol) and the reaction was stirred at room temperature for 2 hours. The reaction mixture was directly loaded to Celite and was purified by flash column chromatography on silica gel (0-100% EtOAc in hexane) followed by PTLC (50% EtOAc in hexane) to yield **Compound 14** (49 mg, 24%) and **Compound 15** (50 mg, 25%).

Compound 14: ^{1}H NMR (DMSO-d_6) δ: 8.22-8.60 (m, 1H), 8.05 (d, J=7.9 Hz, 2H), 7.99 (br. s., 2H), 7.65 (br. s., 1H), 7.46-7.56 (m, 2H), 7.16-7.26 (m, 3H), 7.12 (dd, J=7.2, 1.9 Hz, 2H), 4.84 (br. s., 2H).

Compound 15: ^{1}H NMR (acetone) δ: 7.72-8.35 (m, 5H), 7.43 (br. s., 3H), 6.81-7.28 (m, 5H), 4.53 (br. s., 1H), 4.14 (br. s., 1H).

Biological Data

HEK-Gqi5 cells stably expressing CCR2 were cultured in DMEM high glucose, 10% FBS, 1% PSA, 400 μg/ml geneticin and 50 μg/ml hygromycin. Appropriate positive control chemokines (MCP-1, MIP1A or RANTES) was used as the positive control agonist for screening compound-induced calcium activity assayed on the FLIPR^{Tetra}. The drug plates were prepared in 384-well microplates using the EP3 and the MultiPROBE robotic liquid handling systems. Compounds were synthesized and tested for CCR2 activity.

Table 1 shows activity at CCR2 receptor (IC_{50}) nM

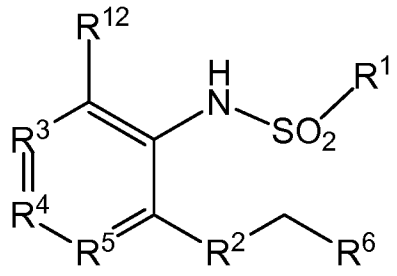
Table 1

IUPAC Name	IC50 (nM)	% ANTAGONISM
N-[4-(benzylsulfanyl)pyrimidin-5-yl]-1-benzofuran-2-sulfonamide	nd	44
N-[4-(benzylsulfonyl)pyrimidin-5-yl]-1-	135	101

benzofuran-2-sulfonamide		
N-[4-(benzylsulfinyl)pyrimidin-5-yl]-1-benzofuran-2-sulfonamide	588	95
N-[3-(benzylsulfanyl)pyridin-4-yl]-1-benzofuran-2-sulfonamide	485	100
N-[3-(benzylsulfonyl)pyridin-4-yl]-1-benzofuran-2-sulfonamide	17	95
N-[3-(benzylsulfanyl)-1-oxidopyridin-4-yl]-1-benzofuran-2-sulfonamide	8	94
N-[2-(benzylsulfanyl)-5-chloropyridin-3-yl]-3,4-dichlorobenzenesulfonamide	nd	46
N-[2-(benzylsulfanyl)-5-chloropyridin-3-yl]-5-chlorothiophene-2-sulfonamide	nd	60
N-[2-(benzylsulfonyl)-5-chloropyridin-3-yl]-3,4-dichlorobenzenesulfonamide	37	97
N-[2-(benzylsulfinyl)-5-chloropyridin-3-yl]-3,4-dichlorobenzenesulfonamide	119	87
N-[2-(benzylsulfonyl)-5-chloropyridin-3-yl]-5-chlorothiophene-2-sulfonamide	263	89
N-[2-(benzylsulfinyl)-5-chloropyridin-3-yl]-5-chlorothiophene-2-sulfonamide	nd	77

What is claimed is:

1. A compound represented by Formula I, an enantiomer, a diastereoisomer, a tautomer or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

R^1 is substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{3-8}$ cycloalkyl, substituted or unsubstituted C $_{3-8}$ cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^2 is –S-, -S(O)-, or -$S(O)_2$-;

R^3 is CR^7, N or N-oxide;

R^4 is CR^7, N or N-oxide;

R^5 is CR^7, N or N-oxide;

R^6 is substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{3-8}$ cycloalkyl, substituted or unsubstituted C $_{3-8}$ cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^7 is H, substituted or unsubstituted C_{1-6} alkyl, halogen, substituted or unsubstituted –OR^8, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, $C(O)R^9$, $NR^{10}R^{11}$, amide, urea, sulfonamide, sulfone, sulfoxide , sulfide, sulfonic acid, nitro, phosphate or phosphonic acid;

R^8 is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{3-8}$ cycloalkyl, substituted or unsubstituted C $_{3-8}$ cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^9 is H, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{3-8}$ cycloalkyl, substituted or unsubstituted C $_{3-8}$ cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^{10} is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{3-8}$ cycloalkyl, substituted or unsubstituted C $_{3-8}$ cycloalkenyl, is substituted or unsubstituted C_{6-10} aryl or together with R^{11} can form a 3-10 membered ring;

R^{11} is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{3-8}$ cycloalkyl, substituted or unsubstituted C $_{3-8}$ cycloalkenyl, is substituted or unsubstituted C_{6-10} aryl or together with R^{10} can form a 3-10 membered ring;

R^{12} is H, substituted or unsubstituted C_{1-6} alkyl, halogen, substituted or unsubstituted $–OR^8$, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, $C(O)R^9$, $NR^{10}R^{11}$, amide, urea, sulfonamide, sulfone, sulfoxide , sulfide, sulfonic acid, nitro, phosphate or phosphonic acid;

with the provisios

at least one of R^3, R^4 or R^5 is N or N-oxide; and,

R^1 is not benzofuran-2-yl, when R^3 is CR^7 and R^4 is CR^7 and R^5 is N.

2. The compound according to claim 1, wherein:

R^3 is N;

R^4 is CR^7; and

R^5 is N.

3. The compound according to claim 1, wherein:

R^1 is substituted or unsubstituted heterocycle or substituted or unsubstituted C_{6-10} aryl;

R^3 is N;

R^4 is CR^7;

R^5 is N;

R^6 is substituted or unsubstituted C_{6-10} aryl;

R^7 is H; and

R^{12} is H.

4. The compound according to claim 1, wherein:

R^3 is CR^7;

R^4 is N or N-oxide;

R^5 is CR^7;

R^6 is substituted or unsubstituted C_{6-10} aryl;

R^7 is H; and

R^{12} is H.

5. The compound according to claim 1, wherein:

R^3 is CR^7;

R^4 is N-oxide;

R^5 is CR^7;

R^6 is substituted or unsubstituted C_{6-10} aryl;

R^7 is H; and

R^{12} is H.

6. The compound according to claim 1, wherein:

R^3 is CR^7;

R^4 is N;

R^5 is CR^7;

R^6 is substituted or unsubstituted C_{6-10} aryl;

R^7 is H; and

R^{12} is H.

7. The compound according to claim 1, wherein:

R^1 is substituted or unsubstituted heterocycle, or is substituted or unsubstituted C_{6-10} aryl;

R^3 is CR^7;

R^4 is CR^7;

R^5 is, N;

R^6 is substituted or unsubstituted C_{6-10} aryl;

R^7 is H or halogen;

R^{12} is H; and

with the proviso

R^1 is not benzofuran-2-yl, when R^3 is CR^7 and R^4 is CR^7 and R^5 is N.

8. The compound according to claim 1, wherein:

R^1 is substituted or unsubstituted heterocycle;

R^3 is CR^7;

R^4 is CR^7;

R^5 is N;

R^6 is unsubstituted C_{6-10} aryl;

R^7 is H or halogen;

R^{12} is H; and

with the proviso

R^1 is not benzofuran-2-yl, when R^3 is CR^7 and R^4 is CR^7 and R^5 is N.

9. The compound according to claim 1, wherein:

R^1 is substituted or unsubstituted C_{6-10} aryl;

R^3 is CR^7;

R^4 is CR^7;

R^5 isN;

R^6 is unsubstituted C_{6-10} aryl;

R^7 is H or halogen; and

R^{12} is H.

10. The compound according to claim 1, selected from:

N-[4-(benzylsulfanyl)pyrimidin-5-yl]-1-benzofuran-2-sulfonamide;

N-[4-(benzylsulfonyl)pyrimidin-5-yl]-1-benzofuran-2-sulfonamide;

N-[4-(benzylsulfinyl)pyrimidin-5-yl]-1-benzofuran-2-sulfonamide;

N-[3-(benzylsulfanyl)pyridin-4-yl]-1-benzofuran-2-sulfonamide;

N-[3-(benzylsulfonyl)pyridin-4-yl]-1-benzofuran-2-sulfonamide;

N-[3-(benzylsulfanyl)-1-oxidopyridin-4-yl]-1-benzofuran-2-sulfonamide;

N-[2-(benzylsulfanyl)-5-chloropyridin-3-yl]-3,4-dichlorobenzenesulfonamide;

N-[2-(benzylsulfanyl)-5-chloropyridin-3-yl]-5-chlorothiophene-2-sulfonamide;

N-[2-(benzylsulfonyl)-5-chloropyridin-3-yl]-3,4-dichlorobenzenesulfonamide;

N-[2-(benzylsulfinyl)-5-chloropyridin-3-yl]-3,4-dichlorobenzenesulfonamide;

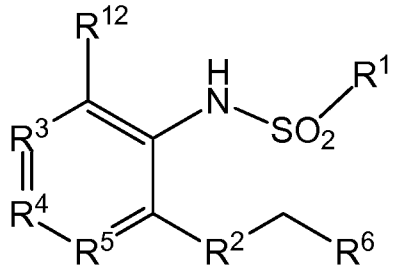
N-[2-(benzylsulfonyl)-5-chloropyridin-3-yl]-5-chlorothiophene-2-sulfonamide;

N-[2-(benzylsulfinyl)-5-chloropyridin-3-yl]-5-chlorothiophene-2-sulfonamide;

N-[2-(benzylthio)pyridin-3-yl]-1-benzothiophene-2-sulfonamide;

N-[2-(benzylsulfonyl)pyridin-3-yl]-1-benzothiophene-2-sulfonamide;
N-[2-(benzylsulfinyl)pyridin-3-yl]-1-benzothiophene-2-sulfonamide.

11. A method of treating a disorder associated with chemokine receptor modulation, which comprises administering to a mammal in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of Formula I



Formula I

wherein:

R^1 is substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{3-8}$ cycloalkyl, substituted or unsubstituted C $_{3-8}$ cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^2 is –S-, -S(O)-, or -$S(O)_2$-;

R^3 is CR^7, N or N-oxide;

R^4 is CR^7, N or N-oxide;

R^5 is CR^7, N or N-oxide;

R^6 is substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{3-8}$ cycloalkyl, substituted or unsubstituted C $_{3-8}$ cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^7 is H, substituted or unsubstituted C_{1-6} alkyl, halogen, substituted or unsubstituted –OR^8, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, $C(O)R^9$, $NR^{10}R^{11}$, amide, urea, sulfonamide, sulfone, sulfoxide , sulfide, sulfonic acid, nitro, phosphate or phosphonic acid;

R^8 is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{3-8}$ cycloalkyl, substituted or unsubstituted C $_{3-8}$ cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^9 is H, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, substituted or

unsubstituted heterocycle, substituted or unsubstituted C $_{3-8}$ cycloalkyl, substituted or unsubstituted C $_{3-8}$ cycloalkenyl or is substituted or unsubstituted C_{6-10} aryl;

R^{10} is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{3-8}$ cycloalkyl, substituted or unsubstituted C $_{3-8}$ cycloalkenyl, is substituted or unsubstituted C_{6-10} aryl or together with R^{11} can form a 3-10 membered ring;

R^{11} is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{3-8}$ cycloalkyl, substituted or unsubstituted C $_{3-8}$ cycloalkenyl, is substituted or unsubstituted C_{6-10} aryl or together with R^{10} can form a 3-10 membered ring;

R^{12} is H, substituted or unsubstituted C_{1-6} alkyl, halogen, substituted or unsubstituted $–OR^8$, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, $C(O)R^9$, $NR^{10}R^{11}$, amide, urea, sulfonamide, sulfone, sulfoxide , sulfide, sulfonic acid, nitro, phosphate or phosphonic acid;

with the provisios

at least one of R^3, R^4 or R^5 is N or N-oxide; and,

R^1 is not benzofuran-2-yl, when R^3 is CR^7 and R^4 is CR^7 and R^5 is N.

12. The method of claim 11, wherein the pharmaceutical composition is administered to the mammal to treat ocular inflammatory diseases or skin inflammatory diseases.

13. The method of claim 11 wherein the mammal is a human.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/024610

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/10 A61K31/416 A61P3/04 C07D213/75 C07D405/12
C07D409/12
ADD.
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)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	WO 2013/130962 A1 (ALLERGAN INC [US]; YUAN HAIQING [US]; BEARD RICHARD L [US]; LIU XIAOXI) 6 September 2013 (2013-09-06) page 1 - page 5; claims; examples	1-13
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 June 2014	11/06/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Härtinger, Stefan

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/024610

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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PCT/US2014/024610

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