

IL-8 RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to novel sulfone compounds, pharmaceutical compositions, processes for their preparation, and use thereof in treating IL-8, GRO α , GRO β , GRO γ ,

5 NAP-2, and ENA-78 mediated diseases.

BACKGROUND OF THE INVENTION

Many different names have been applied to Interleukin-8 (IL-8), such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor.

10 Interleukin-8 is a chemoattractant for neutrophils, basophils, and a subset of T-cells. It is produced by a majority of nucleated cells including macrophages, fibroblasts, endothelial and epithelial cells exposed to TNF, IL-1 α , IL-1 β or LPS, and by neutrophils themselves when exposed to LPS or chemotactic factors such as FMLP. M. Baggiolini et al., J. Clin. Invest. 84, 1045 (1989); J. Schroder et al, J. Immunol. 139, 3474 (1987) and J. Immunol. 144, 2223 (1990) ; Strieter, et al., Science 243, 1467 (1989) and J. Biol. Chem. 264, 10621 (1989); Cassatella et al., J. Immunol. 148, 3216 (1992).

GRO α , GRO β , GRO γ and NAP-2 also belong to the chemokine α family. Like IL-8, these chemokines have also been referred to by different names. For instance GRO α , β , γ have been referred to as MGSA α , β and γ respectively (Melanoma Growth Stimulating Activity), see Richmond et al., J. Cell Physiology 129, 375 (1986) and Chang et al., J. Immunol 148, 451 (1992). All of the chemokines of the α -family which possess the ELR motif directly preceding the CXC motif bind to the IL-8 B receptor (CXCR2).

IL-8, GRO α , GRO β , GRO γ , NAP-2, and ENA-78 stimulate a number of functions in vitro. They have all been shown to have chemoattractant properties for neutrophils, while IL-8 and GRO α have demonstrated T-lymphocyte and basophilic chemotactic activity. In addition, IL-8 can induce histamine release from basophils from both normal and atopic individuals. GRO- α and IL-8 can, in addition, induce lysosomal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis.

30 This may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many known diseases are characterized by massive neutrophil infiltration. As IL-8, GRO α , GRO β , GRO γ and NAP-2 promote the accumulation and activation of neutrophils, these chemokines have been implicated in a wide range of acute and chronic inflammatory

disorders including psoriasis and rheumatoid arthritis, Baggiolini et al., FEBS Lett. 307, 97 (1992); Miller et al., Crit. Rev. Immunol. 12, 17 (1992); Oppenheim et al., Annu. Rev. Immunol. 9, 617 (1991); Seitz et al., J. Clin. Invest. 87, 463 (1991); Miller et al., Am. Rev. Respir. Dis. 146, 427 (1992); Donnelly et al., Lancet 341, 643 (1993). In addition the ELR
5 chemokines (those containing the amino acids ELR motif just prior to the CXC motif) have also been implicated in angiostasis, Strieter et al., Science 258, 1798 (1992).

In vitro, IL-8, GRO α , GRO β , GRO γ and NAP-2 induce neutrophil shape change, chemotaxis, granule release, and respiratory burst, by binding to and activating receptors of the seven-transmembrane, G-protein-linked family, in particular by binding to IL-8
10 receptors, most notably the IL-8 β receptor (CXCR2). Thomas et al., J. Biol. Chem. 266, 14839 (1991); and Holmes et al., Science 253, 1278 (1991). The development of non-peptide small molecule antagonists for members of this receptor family has precedent. For a review, see R. Freidinger in: Progress in Drug Research, Vol. 40, pp. 33-98, Birkhauser Verlag, Basel 1993. Hence, the IL-8 receptor represents a promising target for the
15 development of novel anti-inflammatory agents.

Two high affinity human IL-8 receptors (77% homology) have been characterized: CXCR1, which binds only IL-8 with high affinity, and CXCR2, which has high affinity for IL-8 as well as for GRO α , GRO β , GRO γ and NAP-2. See Holmes et al., supra; Murphy et al., Science 253, 1280 (1991); Lee et al., J. Biol. Chem. 267, 16283 (1992);
20 LaRosa et al., J. Biol. Chem. 267, 25402 (1992); and Gayle et al., J. Biol. Chem. 268, 7283 (1993).

There remains a need for treatment, in this field, for compounds, which are capable of binding to the CXCR1 and/or CXCR2 receptors. Therefore, conditions associated with an increase in IL-8 production (which is responsible for chemotaxis of neutrophil and T-
25 cells subsets into the inflammatory site) would benefit by compounds which are inhibitors of IL-8 receptor binding.

SUMMARY OF THE INVENTION

The present invention comprises novel IL-8 receptor antagonists represented by Formula (I), and compositions comprising the present compounds and a pharmaceutically
30 acceptable carrier or diluent.

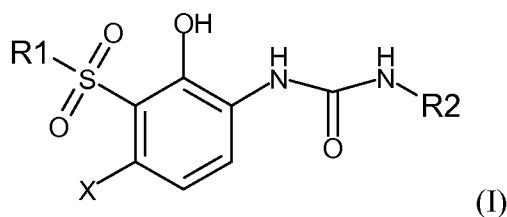
The present invention also comprises novel IL-8 receptor antagonists represented by Formula (I) and combinations comprising the present compounds and one or more additional therapeutic ingredients.

The present invention further comprises a method of treating a chemokine mediated disease wherein the chemokine is one which binds to an IL-8 α or β receptor, and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method of inhibiting the binding of IL-8 to its receptors in a mammal, particularly in a human, in need thereof which comprises administering an effective amount of a compound of Formula (I).

DETAILED DESCRIPTION OF THE INVENTION

Compounds of Formula (I) useful in the present invention are represented by the structure:



wherein

X is selected from the group consisting of halogen, C_{1-3} alkyl, C_{1-3} alkoxy, cyano, CF_3 , and OCF_3 ;

R2 is selected from the group consisting of C_{3-6} cycloalkyl, phenyl and heteroaryl, wherein the phenyl or heteroaryl moieties are optionally substituted, once or twice, independently, by a substituent selected from the group consisting of C_{1-3} alkyl, halogen, CF_3 , OCF_3 , phenyloxy and benzyloxy; or

R2 is phenyl substituted by methylenedioxy or by (di-halo-substituted)-methylenedioxy;

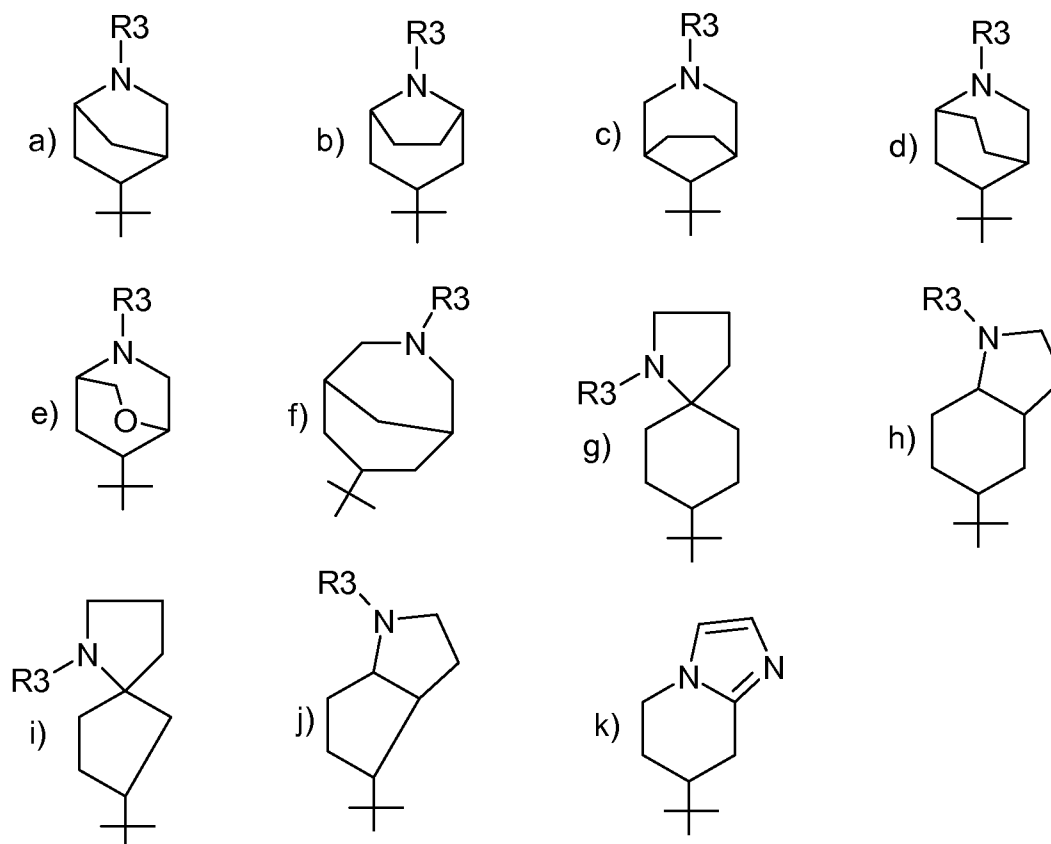
R1 represents C_{4-8} heterocyclyl $(CH_2)_n$ wherein the heterocyclyl moiety is optionally substituted, independently, once or twice, by a substituent selected from the group consisting of C_{1-3} alkyl, $C(O)OR_4$ and $C(O)R_5$;

R_4 and R_5 are independently C_{1-3} alkyl; and

n is 0 or 1;

or

R1 is selected from the following ring systems (a-k):



- 5 wherein R3 is H or C₁₋₃alkyl;
or a pharmaceutically acceptable salt thereof.

As used herein, "C₁₋₃alkyl" refers to a linear or branched saturated hydrocarbon group containing 1 to 3 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, or isopropyl.

- 10 As used herein "cycloalkyl" refers to a saturated monocyclic hydrocarbon ring of 3 to 6 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

- As used herein, "heterocyclyl" refers to a 4-8 membered saturated or non aromatic, unsaturated monocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulphur. Examples of such rings include pyrrolidinyl, azetidiny, pyrazolidinyl, piperidinyl, piperazinyl, and the like.
- 15

As used herein "heteroaryl" refers to a 5-6 membered monocyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Examples of

such monocyclic aromatic rings include pyridyl, pyrrolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, and the like.

As used herein, "halogen" or "halo" refers to F, Cl, Br or I.

As used herein, "C₁₋₃alkoxy" refers to a straight or branched alkoxy moiety
5 containing 1 to 3 carbon atoms. Examples of alkoxy included herein are methoxy, ethoxy, propoxy and prop-2-oxy and the like.

As used herein, "optionally substituted," unless specifically defined, means substituted, independently, at each occurrence, one to three times, by such groups as halogen, C₁₋₃alkyl, C₁₋₃alkoxy, heterocyclyl, aryl, and heteroaryl, such that the optional
10 substituents may be further substituted, except for halogen, one to three times, independently, by halogen or C₁₋₂alkyl.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

15 Suitably, X is selected from the group consisting of halogen, C₁₋₃alkyl, C₁₋₃alkoxy cyano, CF₃, and OCF₃.

In one embodiment, X is halogen.

In another embodiment, X is selected from the group consisting of F, Cl and Br.

In another embodiment, X is Cl.

20 Suitably, R₂ is selected from the group consisting of C₃₋₆cycloalkyl, phenyl and heteroaryl, wherein the phenyl or heteroaryl moieties are optionally substituted, once or twice, independently, by a substituent selected from the group consisting of C₁₋₃alkyl, halogen, CF₃, OCF₃, phenyloxy and benzyloxy; or

R₂ is phenyl substituted by methylenedioxy or by (di-halo-substituted)-methylenedioxy.

25 In one embodiment, R₂ represents phenyl, optionally substituted, independently, once or twice, by a substituent selected from the group consisting of C₁₋₃alkyl, halogen, OCF₃ or phenyloxy.

In one embodiment, R₂ represents pyridyl, optionally substituted once by halogen.

30 In another embodiment, R₂ represents pyridyl substituted by chloro.

In another embodiment, R₂ represents phenyl substituted by difluoromethylenedioxy.

In another embodiment, R₂ represents C₃₋₆cycloalkyl.

In another embodiment, R2 represents halomethylphenyl, trihalomethoxyphenyl, dihalophenyl, ethylphenyl or phenyloxyphenyl.

In another embodiment, R2 represents 3-fluoro-2-methylphenyl, 2-trifluoromethoxyphenyl, 2-chloro-3-fluorophenyl, 2-ethylphenyl or 2-phenyloxyphenyl.

5 In another embodiment, R2 represents halopyridyl.

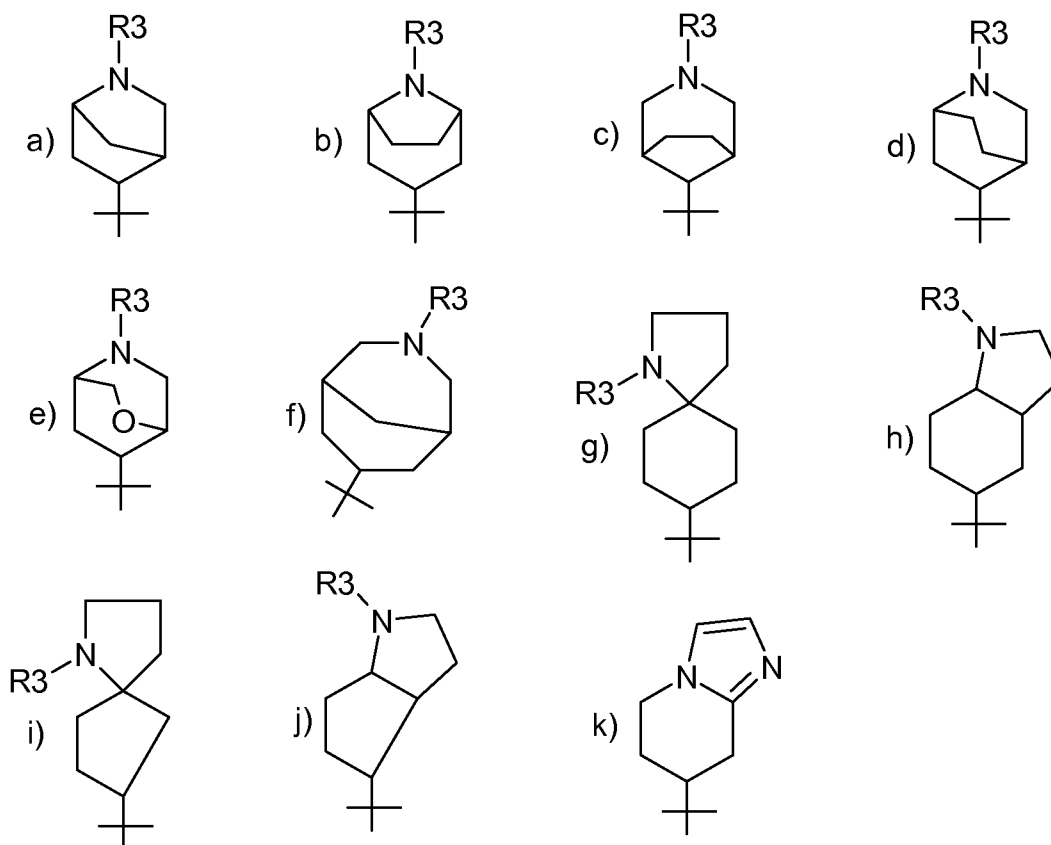
In another embodiment, R2 represents 2-chloro-3-pyridyl.

Suitably, R1 represents C_{4-8} heterocyclyl(CH₂)_n, wherein the heterocyclyl moiety is optionally substituted, independently, once or twice, by a substituent selected from the group consisting of C₁₋₃alkyl, C(O)OR4 and C(O)R5; and

10 in which R4 and R5 are, independently, C₁₋₃alkyl; and n is 0 or 1;

or

R1 is selected from a group consisting of the following ring systems (a-k):



wherein R3 is H or C₁₋₃alkyl.

15 In one embodiment, the R1 heterocyclyl moiety is pyrrolidinyl.

In one embodiment, the R1 heterocyclyl moiety is selected from the group consisting of azetidiny, piperidiny and pyrrolidinyl.

In another embodiment, R1 is selected from the group consisting of pyrrolidinylmethyl, azetidiny, piperidiny, pyrrolidinyl and ethyl-1-piperidinylcarboxylate.

In another embodiment, R1 is selected from the group consisting of 3-pyrrolidinylmethyl, 3-azetidiny, 4-piperidiny, 3-piperidiny, 3-pyrrolidinyl and ethyl-1-piperidinylcarboxylate.

Suitably, n is 0 or 1.

In one embodiment, n is 0.

In another embodiment, n is 1.

In one embodiment, R1 represents a heterocyclyl moiety selected from the group consisting of 2-azabicyclo[2.2.1]heptyl, 8-azabicyclo[3.2.1]octyl, 8-methyl-8-azabicyclo[3.2.1]octyl, 3-azabicyclo[3.2.1]octyl, 2-azabicyclo[2.2.2]octyl, and 2-oxa-5-azabicyclo[2.2.2]octyl.

In another embodiment, R1 represents 3-exo-8-methyl-8-azabicyclo [3.2.1] oct-3-yl or 3-exo-8-azabicyclo [3.2.1]oct-3-yl.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic salts, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonc acid, ethane sulphonc acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

Illustrative compounds of the present invention include, but are not limited to:

N-(4-chloro-2-hydroxy-3-[(3-exo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfonyl}phenyl)-N'-(3-fluoro-2-methylphenyl)urea;

N-{4-chloro-2-hydroxy-3-[(3-pyrrolidinylmethyl)sulfonyl]phenyl}-N'-(2-[(trifluoromethyl)oxy]phenyl)urea;

N-[3-(3-azetidiny)sulfonyl]-4-chloro-2-hydroxyphenyl]-N'-(2-chloro-3-pyridiny)urea;

N-{4-chloro-2-hydroxy-3-[(3-pyrrolidinylmethyl)sulfonyl]phenyl}-N'-(3-fluoro-2-methylphenyl)urea;

N-[3-(3-azetidiny)sulfonyl]-4-chloro-2-hydroxyphenyl]-N'-(2-chloro-3-fluorophenyl)urea;

N-[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)phenyl]-N'-(2,2-difluoro-1,3-benzodioxol-4-yl)urea;

N-[3-(3-azetidinylsulfonyl)-4-chloro-2-hydroxyphenyl]-N'-(3-fluoro-2-methylphenyl)urea;

5 N-[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)phenyl]-N'-(2-chloro-3-pyridinyl)urea;

N-{3-[(3-exo)-8-azabicyclo[3.2.1]oct-3-ylsulfonyl]-4-chloro-2-hydroxyphenyl}-N'-(2-chloro-3-pyridinyl)urea;

N-(2-chloro-3-fluorophenyl)-N'-{4-chloro-2-hydroxy-3-[(3-pyrrolidinylmethyl)sulfonyl]phenyl}urea;

10 N-[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)phenyl]-N'-(2-ethylphenyl)urea;

N-[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)phenyl]-N'-{2-[(trifluoromethyl)oxy]phenyl}urea;

N-{4-chloro-2-hydroxy-3-[(3R)-3-pyrrolidinylsulfonyl]phenyl}-N'-(2-ethylphenyl)urea;

15 N-{3-[(3-exo)-8-azabicyclo[3.2.1]oct-3-ylsulfonyl]-4-chloro-2-hydroxyphenyl}-N'-(3-fluoro-2-methylphenyl)urea;

N-{4-chloro-2-hydroxy-3-[(3R)-3-pyrrolidinylsulfonyl]phenyl}-N'-(2,2-difluoro-1,3-benzodioxol-4-yl)urea;

20 N-[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)phenyl]-N'-(3-fluoro-2-methylphenyl)urea;

N-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]-N'-(2-ethylphenyl)urea;

N-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]-N'-(2-chloro-3-pyridinyl)urea;

N-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]-N'-{2-[(trifluoromethyl)oxy]phenyl}urea;

25 N-{4-chloro-2-hydroxy-3-[(3R)-3-pyrrolidinylsulfonyl]phenyl}-N'-{2-[(trifluoromethyl)oxy]phenyl}urea;

N-{4-chloro-2-hydroxy-3-[(3S)-3-pyrrolidinylsulfonyl]phenyl}-N'-(2-chloro-3-pyridinyl)urea;

30 N-{3-[(3-exo)-8-azabicyclo[3.2.1]oct-3-ylsulfonyl]-4-chloro-2-hydroxyphenyl}-N'-[2-(phenyloxy)phenyl]urea;

N-[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)phenyl]-N'-[2-(phenyloxy)phenyl]urea;

ethyl 4-{[6-chloro-3-({[(3-fluoro-2-methylphenyl)amino]carbonyl}amino)-2-hydroxyphenyl]sulfonyl}-1-piperidinecarboxylate;

N-{3-[(3-exo)-8-azabicyclo[3.2.1]oct-3-ylsulfonyl]-4-chloro-2-hydroxyphenyl}-N'-(2-chloro-3-fluorophenyl)urea;

5 N-{4-chloro-2-hydroxy-3-[(3S)-3-pyrrolidinylsulfonyl]phenyl}-N'-(3-fluoro-2-methylphenyl)urea;

ethyl 4-({6-chloro-2-hydroxy-3-({[2-(phenyloxy)phenyl]amino}carbonyl)amino]phenyl)sulfonyl)-1-piperidinecarboxylate;

10 N-{4-chloro-2-hydroxy-3-[(3R)-3-pyrrolidinylsulfonyl]phenyl}-N'-[2-(phenyloxy)phenyl]urea;

N-(2-chloro-3-fluorophenyl)-N'-[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)phenyl]urea;

ethyl 4-{[6-chloro-3-({[(2-chloro-3-fluorophenyl)amino]carbonyl}amino)-2-hydroxyphenyl]sulfonyl}-1-piperidinecarboxylate;

15 N-(2-chloro-3-fluorophenyl)-N'-{4-chloro-2-hydroxy-3-[(3S)-3-pyrrolidinylsulfonyl]phenyl}urea;

N-(2-chloro-3-fluorophenyl)-N'-{4-chloro-2-hydroxy-3-[(3R)-3-pyrrolidinylsulfonyl]phenyl}urea;

20 N-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}-N'-(3-fluoro-2-methylphenyl)urea;

N-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}-N'-(2-chloro-3-pyridinyl)urea;

N-(2-chloro-3-fluorophenyl)-N'-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}urea;

25 N-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]-N'-(3-fluoro-2-methylphenyl)urea;

N-(2-chloro-3-fluorophenyl)-N'-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]urea; and

N-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]-N'-(2,3-dichlorophenyl)urea;

30 or a pharmaceutically acceptable salt thereof.

Suitably the salt is the hydrochloride salt.

In one embodiment, compounds of the present invention include, but are not limited to:

N-[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)phenyl]-N'-(3-fluoro-2-methylphenyl)urea;

N-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]-N'-(2-chloro-3-pyridinyl)urea;

5 N-{4-chloro-2-hydroxy-3-[(3S)-3-pyrrolidinylsulfonyl]phenyl}-N'-(2-chloro-3-pyridinyl)urea;

N-[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)phenyl]-N'-[2-(phenyloxy)phenyl]urea;

ethyl 4-{[6-chloro-3-({[(3-fluoro-2-methylphenyl)amino]carbonyl}amino)-2-hydroxyphenyl]sulfonyl}-1-piperidinecarboxylate;

10 N-{3-[(3-exo)-8-azabicyclo[3.2.1]oct-3-ylsulfonyl]-4-chloro-2-hydroxyphenyl}-N'-(2-chloro-3-fluorophenyl)urea;

N-{4-chloro-2-hydroxy-3-[(3S)-3-pyrrolidinylsulfonyl]phenyl}-N'-(3-fluoro-2-methylphenyl)urea;

15 ethyl 4-({6-chloro-2-hydroxy-3-([2-(phenyloxy)phenyl]amino}carbonyl)amino]phenyl)sulfonyl)-1-piperidinecarboxylate;

N-{4-chloro-2-hydroxy-3-[(3R)-3-pyrrolidinylsulfonyl]phenyl}-N'-[2-(phenyloxy)phenyl]urea;

N-(2-chloro-3-fluorophenyl)-N'-[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)phenyl]urea;

20 ethyl 4-{[6-chloro-3-({[(2-chloro-3-fluorophenyl)amino]carbonyl}amino)-2-hydroxyphenyl]sulfonyl}-1-piperidinecarboxylate;

N-(2-chloro-3-fluorophenyl)-N'-{4-chloro-2-hydroxy-3-[(3S)-3-pyrrolidinylsulfonyl]phenyl}urea;

25 N-(2-chloro-3-fluorophenyl)-N'-{4-chloro-2-hydroxy-3-[(3R)-3-pyrrolidinylsulfonyl]phenyl}urea;

N-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}-N'-(3-fluoro-2-methylphenyl)urea;

N-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}-N'-(2-chloro-3-pyridinyl)urea;

30 N-(2-chloro-3-fluorophenyl)-N'-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}urea;

N-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]-N'-(3-fluoro-2-methylphenyl)urea;

N-(2-chloro-3-fluorophenyl)-N'-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]urea; and

N-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]-N'-(2,3-dichlorophenyl)urea;
or a pharmaceutically acceptable salt thereof.

5 In another embodiment, compounds of the present invention include, but are not limited to:

N-{3-[(3-exo)-8-azabicyclo[3.2.1]oct-3-ylsulfonyl]-4-chloro-2-hydroxyphenyl}-N'-(2-chloro-3-fluorophenyl)urea;

10 N-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}-N'-(3-fluoro-2-methylphenyl)urea;

N-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}-N'-(2-chloro-3-pyridinyl)urea;

N-(2-chloro-3-fluorophenyl)-N'-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl} urea;

15 N-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]-N'-(3-fluoro-2-methylphenyl)urea;

N-(2-chloro-3-fluorophenyl)-N'-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]urea; and

20 N-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]-N'-(2,3-dichlorophenyl)urea;
or a pharmaceutically acceptable salt thereof.

In another embodiment, compounds of the present invention include, but are not limited to:

N-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}-N'-(3-fluoro-2-methylphenyl)urea;

25 N-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}-N'-(2-chloro-3-pyridinyl)urea; and

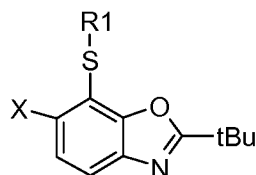
N-(2-chloro-3-fluorophenyl)-N'-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl} urea;

or a pharmaceutically acceptable salt thereof.

METHODS OF PREPARATION

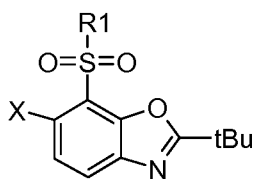
The present compounds may be synthesized by a method comprising the steps of:

A) oxidizing a sulfide according to Formula (II):



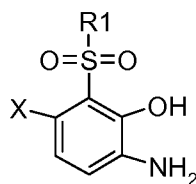
(II)

5 to a sulfone according to Formula (III):



(III)

B) hydrolyzing the sulfone to an aminophenol according to Formula (IV):

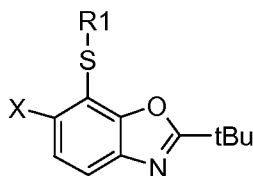


(IV)

and

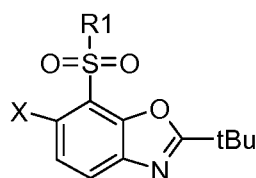
10 C) exposing the aminophenol to an isocyanate or isocyanate precursor to yield the final product.

The present invention also involves novel intermediates selected from the group consisting of Formulas (II):



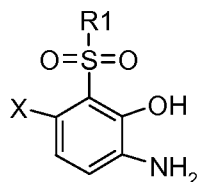
(II)

15 (III):



(III)

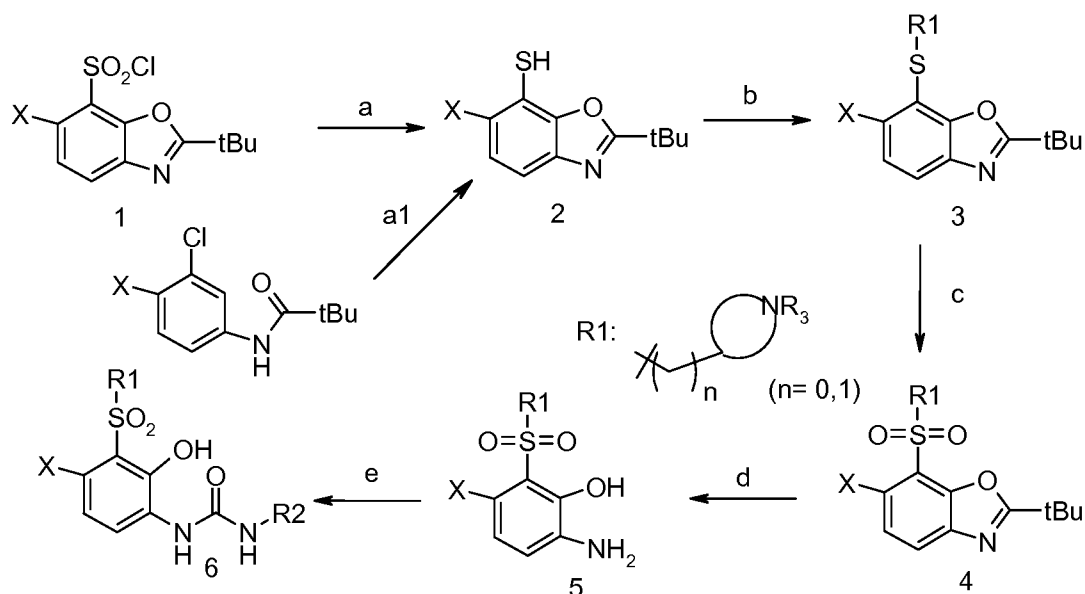
and (IV):



(IV)

5

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Scheme 1 below. The synthesis provided for in these Schemes is applicable for the producing compounds of Formula (I) having a variety of different groups which are reacted, employing optional substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent
10 deprotection, in those cases, then affords compounds of the nature generally disclosed. Once the urea nucleus has been established, further compounds of these formulas may be prepared by applying standard techniques for functional group interconversion, well known in the art.

Scheme 1.

a) aryl phosphine, DMF; a1) i. BuLi, ii. sulfur; b) R1-LG, base; c) Oxidation agent;
 d) H₂SO₄ or HCl; e) R₂C=N=O or R₂CON₃

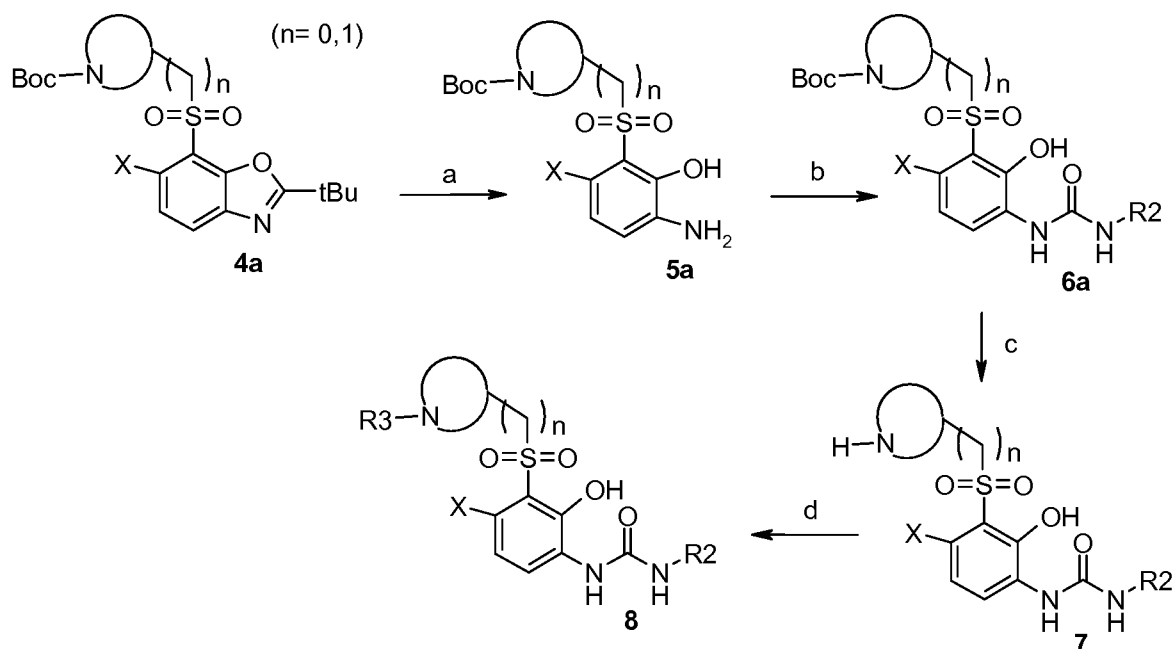
In examples where R1 contain a 3° or an aromatic amine moiety or moieties, the compounds of Formula (I) may be prepared according to Scheme 1.

The sulfonyl chloride **1** (prepared according to WO 01/68033A2, incorporated herein by reference to the extent it teaches how to prepare Scheme 1, **1** compounds) is reduced to the corresponding thiol **2** under conditions such as triphenylphosphine in DMF. Alternatively, the compound **2** may be prepared by quenching the corresponding lithium anion (see WO 01/68033A2, incorporated herein by reference to the extent it teaches how to prepare Scheme 1, **1** compounds) with sulfur (S₈). Alkylation of **2** is then accomplished by treatment with R1-LG, where LG denotes a leaving group such chloro, bromo, iodo or sulfonate, in the presence of base. The resulting sulfides **3** are then oxidized to the sulfones **4** by exposure to an oxidizing agent such as hydrogen peroxide. Hydrolysis of the benzoxazole moiety yields the aminophenols **5** which, in turn, is exposed to an isocyanate or a suitable isocyanate precursor which may be transformed to the isocyanate *in situ*. This reaction produces the final urea **6**.

In cases where R1 contains a 1° or 2° amine protected by a Boc group or a similar acid labile protecting group, the compounds can be prepared as outlined in Scheme 2. The sulfone formation and hydrolysis is performed as described above, however, since the latter

will result in removal of the Boc group, it has to be reintroduced which can be accomplished under suitable reaction conditions such as Boc anhydride and sodium hydroxide yielding compound **5a**. Following urea formation, the Boc group is then removed for the desired product **7** under acidic conditions such as 4N hydrochloric acid in 1,4-dioxane. Finally, the resulting amine may be further elaborated by an operation known to those skilled in the art as reductive amination to form the 2° or 3° amines **8**.

Scheme 2



a) i) $\text{H}_2\text{SO}_4/\text{aq. 1,4-dioxane}$ ii) $\text{NaOH, Boc}_2\text{O}$; b) $\text{R}_2\text{C=N=O}$ or R_2CON_3
 c) 4NHCl, 1,4dioxane ; d) NaCNBH_3 , aldehyde or ketone

Intermediates **4a**, **5a**, **6a**, **7** and **8** represent novel intermediates in Scheme 2.

SYNTHETIC EXAMPLES

The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention. While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl, DCM refers to dichloromethane, THF refers to tetrahydrofuran,

EtOAc refers to ethyl acetate, Hex and Hx refers to hexane, IMS refers to industrial methylated spirit, TBME refers to *tert*-butylmethyl ether, DMF refers to dimethylformamide, BOC and Boc refers to *tert*-butoxycarbonyl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted.

¹H NMR spectra were recorded on a Jeol Delta2 (300 MHz) spectrometer. Chemical shifts are expressed in parts per million (ppm, δ units). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad).

Unless otherwise stated, "flash" and "column chromatography" refers to flash column chromatography on silica using the stated solvent systems.

LC-MS data were obtained on either a PE Sciex Single Quadrupole LC/MS API-150 combined with a Shimadzu LC system (SCL-10A Controller and dual UV detector) or on a Waters micromass ZQ combined with a Waters 2695 separation module.

Starting Material 1:

***N*-(3,4-dichlorophenyl)-2,2-dimethylpropanamide:**

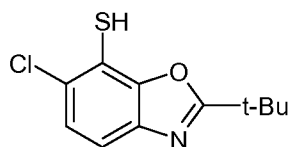
3,4-dichloroaniline (150 g) was dissolved in 1.0 L TBME and the solution was cooled to 10 °C. Sodium hydroxide (140.7 g of a 30% aqueous solution) was added under mechanical stirring. Pivaloyl chloride (125.9 mL) was added dropwise while keeping the internal temperature under 35 °C. After the addition, the temperature of the reaction was maintained at 30-35 °C for a further 30 min. The reaction mixture was then allowed to cool to room temperature and subsequently kept at 0-5 °C for 1 h. The resulting precipitate was filtered off and washed with 600 mL water/MeOH (90/10) and then with 900 mL water. The resulting solid was dried in a vacuum oven at 55 °C for 4 days. Yield: 162 g. ¹H-NMR (DMSO-d₆) δ 9.46(s, 1H), 8.04 (d, J= 2.4 Hz, 1H), 7.65 (dd, J= 9.0, 2.4 Hz, 1H), 7.54 (d, J= 9.0 Hz, 1H), 1.22 (9H, s).

Starting Material 2:

6-chloro-2-(1,1-dimethylethyl)-1,3-benzoxazole-7-sulfonyl chloride:

N-(3,4-dichlorophenyl)-2,2-dimethylpropanamide (121 g) was dissolved in 720 mL THF and the solution was cooled to -50 °C. Butyllithium (433 mL, 2.5N in hex) was added while keeping the internal temperature between -45 °C and -35 °C. (final temp.: -35 °C). Held at -25 °C for 40 min. An hplc check of the reaction mixture revealed that 5-10 % of

the starting material remained. An additional 35 mL of butyllithium was added at -30 °C and the reaction was at -30 to -25 °C for a further 30 min (HPLC: no significant change). The reaction mixture was cooled to -45 °C and SO₂ was bubbled through the solution until saturation appeared to have been reached. Subsequently, the reaction mixture was stirred at
5 -10 to 0 °C for 45 min. Argon (2 double-balloon volumes) was bubbled through the solution following which the reaction mixture was cooled to -5 °C. Sulfuryl chloride (58.8 mL) was added while keeping the temperature below 22 °C. Subsequently, the reaction mixture was kept at 10-15 °C for 1 h (HPLC: complete). EtOAc was added and the mixture was concentrated, washed with water, saturated aqueous sodium bicarbonate and brine,
10 dried over MgSO₄ and the solvent was evaporated *in vacuo*. The crude material crystallized and was triturated with hot hexane. Yield: 87.2 g ¹H-NMR (DMSO-d₆) δ 7.60(d, J= 8.4Hz, 1H), 7.34(d, J= 8.4Hz, 1H), 1.43(9H, s).

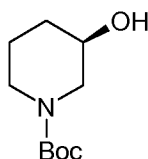
Intermediate 1:

15 Starting Material 1, N-(3,4-dichlorophenyl)-2,2-dimethylpropanamide (prepared according to WO01/68033A2, incorporated herein by reference, to the extent that it teaches the synthesis of Starting Material 1, also described above) was dissolved in dry THF (400 mL), then cooled to -75 °C) under an argon atmosphere. n-BuLi (160 mL, 2.5M in hexane, 5 eq.) was added dropwise while keeping the temperature below -60 °C. Once all the n-BuLi
20 was added, the reaction was stirred at -5 °C for 1.5h, then cooled to -70 °C and sulfur ("sulfur flowers") (13g) was added followed by stirring at -70 °C to room temperature overnight. After stirring the reaction mixture at -10°C, the solution changed color from yellow to brown/orange. The reaction mixture was cooled to 0 °C, the quenched with 2N HCl solution (200 mL) and stirred for 10 min. The organic layer was separated and basified
25 with 2N NaOH solution to pH 12-13, then washed with EtOAc. The aqueous layer was reacidified with 2M HCl solution to about pH 1 and extracted with dichloromethane (2X) which was washed with water, dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography using 1:5 (EtOAc/Hex). Yield: 6 g (30%, orange oil).
¹H-NMR (CDCl₃) δ 7.39-7.30 (m, 2H), 4.08 (s, 1H), 1.50 (9H, s).

30 Alternatively, Intermediate 1 is prepared in the following way:

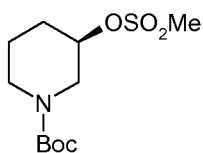
Triphenylphosphine (89g) was dissolved in DCM (200ml) and DMF (2.2ml). The solution was cooled in an ice/methanol bath to -1°C. To this was added a solution of the 6-chloro-2-(1,1-dimethylethyl)-1,3-benzoxazole-7-sulfonyl chloride, Starting Material 2, (prepared according to WO01/68033A2, incorporated herein by reference, to the extent that it teaches the synthesis of Starting Material 2, also described above) (35g) in DCM (100ml) over 30 minutes maintaining the temperature below 15°C. The reaction mixture was stirred at room temperature under nitrogen for 18 hours. The reaction mixture was quenched using 2N hydrochloric acid (200ml). The phases were separated and the organic phase was evaporated in vacuo. The residue was suspended in 2N sodium hydroxide (400ml) and stirred rapidly for 3 hours. The solid was removed by filtration and washed with water. The combined filtrate and washings were cooled in an ice/water bath and acidified using 5N hydrochloric acid to ~pH 1. This was extracted using TBME (400ml). The organic phase was dried over magnesium sulfate and evaporated in vacuo to give Intermediate 1 (22.85g) as a brown solid.

Intermediate 2: (General procedure A)



To a suspension of (R)-(+)-3-hydroxypiperidine hydrochloride (1 g) in DCM (20 mL) was added Et₃N (3.04 mL) followed by BOC₂O (1.75 g) at 0°C which was left over the weekend. Water (50 mL) was added and extracted with DCM (100 mL). Combined organics were washed with water (2 x 50 mL) then brine (50 mL), dried (Na₂SO₄) and concentrated. The residue was columned (flash, eluted with a gradient of 0 – 10% MeOH/DCM). Yield: 1.55 g. ¹H-NMR (CDCl₃) δ 3.74-3.69 (2H, m), 3.56-3.48 (1H, m), 3.18-3.03 (2H, m), 1.92-1.83 (1H, m), 1.79-1.71(2H, m), 1.55-1.45 (1H, m), 1.43 (9H, s).

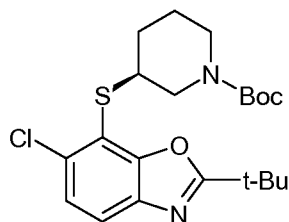
Intermediate 3: (General procedure B)



To a solution of Intermediate 2 (1 g) in DCM (10 mL) was added Et₃N (1.38 mL) followed by MsCl (0.46 mL) dropwise at 0°C. After stirring at 0°C for 1 hour the reaction was warmed to room temperature, quenched with water (10 mL) and separated. The aqueous

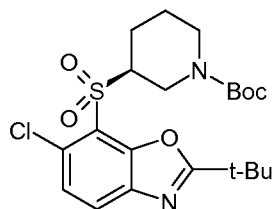
layer was extracted with DCM (2 x 20 mL). Combined organics were washed with water (40 mL), a spatula of silica added, dried (NaSO₄) and concentrated. Yield: 1.4148 g. ¹H-NMR (CDCl₃) δ 4.71 (1H, br s), 3.62 (2H, br d), 3.49-3.27 (2H, m), 3.04 (3H, s), 2.01-1.76 (3H, m), 1.79-1.71(2H, m), 1.55-1.45 (1H, m), 1.45 (9H, s).

5 **Intermediate 4: (General procedure C)**

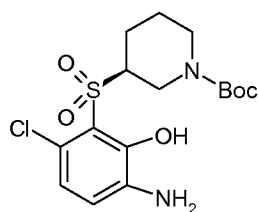


To a suspension of NaH (0.30 g) in THF (20 mL) was added Intermediate 1 (using Starting Material 1) (1.22 g) dropwise. After stirring for 1 hour, Intermediate 3 (1.41 g) in THF was added and the reaction heated to 80°C and left overnight. The reaction mixture was cooled to room temperature then quenched with aqueous saturated NaHCO₃ (50 mL). Reaction mixture was extracted with DCM (2 x 50 mL). Combined organics were washed with water (100 mL), dried (NaSO₄) and concentrated. Residue columned (flash, 20% EtOAc/Hx, silica). Yield: 946.9 mg. ¹H-NMR (CDCl₃) δ 7.50 (d, J= 7.9Hz, 1H), 7.38 (d, J= 7.9Hz, 1H), 3.82 (d, J= 13.4Hz, 1H), 3.55-3.45 (m, 1H), 3.00-2.80 (m, 2H).

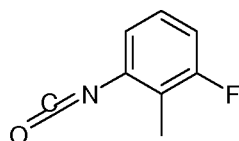
15 **Intermediate 5: (General procedure D)**



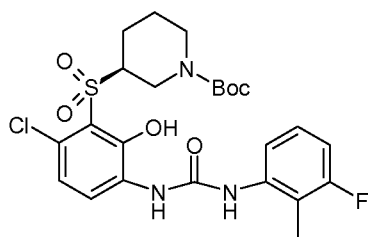
To a solution of intermediate 4 (946.9 mg) in DCM (10mL) was added mCPBA (2.31 g) in DCM (10 mL) at -10 °C. The reaction was stirred at -10 °C for 1h, then warmed to room temperature. The reaction mixture was quenched with aqueous saturated NaHCO₃ (50mL) then extracted with DCM (2 x 70 mL). Combined organics were washed with water (50mL), dried (Na₂SO₄) and concentrated. Residue columned (flash, 30% EtOAc/Hx, silica). Yield 353.6 mg (35%, yellow oil). MS (m/z, ES⁺, M+H): 457.08.

Intermediate 6: (General procedure E)

To a solution of Intermediate 5 (353 mg) in IMS (5 mL) was added aqueous concentrated HCl (5 mL). The reaction was then heated to 80°C and left overnight. Reaction mixture was cooled to room temperature and was concentrated to remove IMS. Residue was basified to pH 12 with aqueous saturated NaOH, EtOAc (30 mL), BOC₂O (1 eq., 0.17 g) added at 0°C and left overnight. Reaction mixture was separated, and aqueous layer extracted with EtOAc (2 x 30 mL). Combined organics were dried (with Na₂SO₄) and concentrated. Residue was columned (flash, eluted with a gradient of 10% - 30% EA/Hx). Yield: Two product containing fractions were isolated: 58.0 mg and 180.9 mg. MS (m/z, ES⁺, M+H): 291.01.

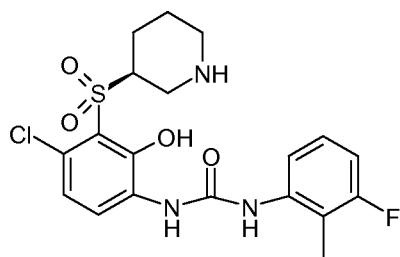
Intermediate 7: (General procedure F)

3-fluoro-2-methylaniline (7.4g) was dissolved in DCM (220 mL) at room temperature under an argon atmosphere. After cooling to 0 °C, aqueous saturated NaHCO₃ (220 mL) was added followed by triphosgene (5.85g). The reaction was left to stir at 0 °C for 1h. After this time, the product was extracted with DCM (2 x 50 mL). The organic fractions were combined, dried over MgSO₄ and the solvent removed in vacuo to yield a yellow oil. Addition of hexane allowed precipitation of a white salt which was filtered off. Removal of the hexane in vacuo yielded a yellow oil (7.69g, 86%). ¹H-NMR (CDCl₃) δ 7.09 (dd, 1H), 6.92-6.85 (m, 2H), 2.24 (s, 3H).

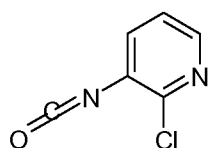
Intermediate 8: (General procedure G)

To a solution of Intermediate 6 (60 mg) in DCM (3 mL) was added Intermediate 7 (70 mg) and the reaction was left over the weekend. Reaction mixture was concentrated and the residue columned (flash, eluted with a gradient of 20% - 30% EtOAc/Hx). Yield: 56.2 mg. MS (m/z, ES⁺, M+H): 542.01.

Example 1: N-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}-N'-(3-fluoro-2-methylphenyl)urea. (General procedure H)

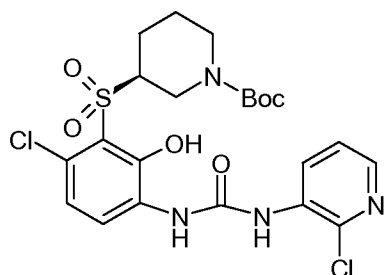


Intermediate 8 (56.2 mg) and 4N HCl/dioxane (3 mL) were stirred together at room temperature and left overnight. Intermediates 6, 5, 4, 3 and 2 were made as described above. Intermediate 1 was made using Starting Material 1 for synthesizing Example 1. The reaction mixture was concentrated and residue dissolved in minimum amount of MeOH and Et₂O was added. Solid crashed out which was filtered and dried. Crude yield: 28.4 mg. The crude product was dissolved in a minimum amount of MeOH and Et₂O added. Solid crashed out, the solvent was decanted and solid dried. Yield: 18.8 mg. MS (m/z, ES⁺, M+H): 441.98. NMR (MeOD) δ 8.40 (1H, d, ArH), 7.46 (1H, d, ArH), 7.19-7.15 (2H, m, ArH), 6.85 (1H, t, ArH), 4.14 (1H, dt, CH), 3.66 (1H, dd, CH), 3.37 (2H, d, CH₂), 3.04 (1H, dt, CH), 2.19 (3H, s, ArCH₃), 2.14-1.69 (4H, m, 2xCH₂).

Intermediate 9:

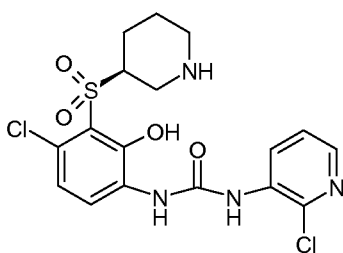
Triphosgene (7.7g) in DCM (40mL) was added to 3-amino-2-chloropyridine (10g) in DCM (200mL) and saturated aqueous NaCHO₃ (200mL) at 0 °C. The reaction was then left to stir at for 1h. The product was then extracted with DCM (2 x 50 mL), dried over Na₂SO₄ and the solvent removed in vacuo to yield an off-white solid. Trituration with hexane followed by filtration of the solids and removal of the solvent from the eluant yielded the product as a colorless oil. After flushing the product with argon and placing it in the refrigerator, a white crystalline solid appeared (6g). ¹H-NMR (CDCl₃) δ 8.22 (br s, 1H), 7.45 (d, 1H), 7.27-7.20 (m, 1H).

Intermediate 10:



To a solution of Intermediate 6 (60 mg) in DCM (3 mL) was added the Intermediate 9 (71 mg) and the reaction was left over the weekend. The reaction mixture was concentrated and the residue columned (flash, 20-30% EtOAc/Hx, silica). Yield: 60.0 mg. MS (m/z, ES⁺, M+H): 544.97

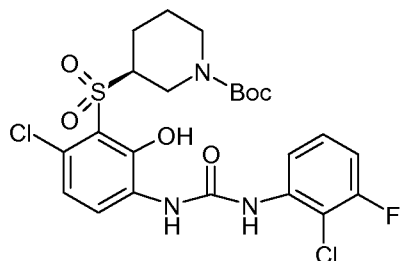
Example 2. N-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}-N'-(2-chloro-3-pyridinyl)urea



Intermediate 10 (60 mg) and 4N HCl/dioxane (3 mL) were stirred together at room temperature and left overnight. Intermediates 6, 5, 4, 3 and 2 were made as described above. Intermediate 1 was made using Starting Material 1 for synthesizing Example 2. Reaction mixture was concentrated and the residue dissolved in a minimum amount of MeOH and EtOAc was added. Solid crashed out, solvent was decanted and solid dried. Yield: 9.1 mg. MS (m/z, ES⁺, M+H): 444.91. NMR (MeOD) δ 8.57 (1H, dd, ArH), 8.45

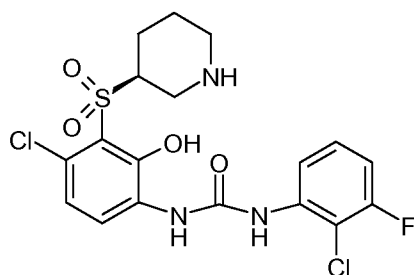
(1H, d, ArH), 8.04 (1H, dd, ArH), 7.35 (1H, dd, ArH), 7.19 (1H, d, ArH), 4.17-4.09 (1H, m, CH), 3.64 (1H, dd, CH), 3.39-3.33 (2H, m, CH₂), 3.05 (1H, dt, CH), 2.15-1.74 (4H, m, 2xCH₂).

Intermediate 11:



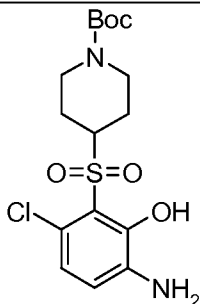
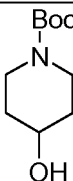
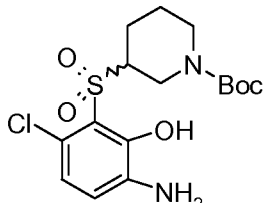
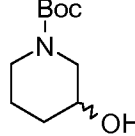
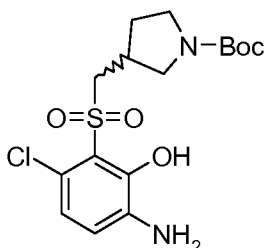
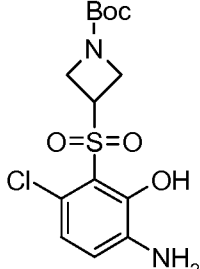
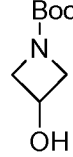
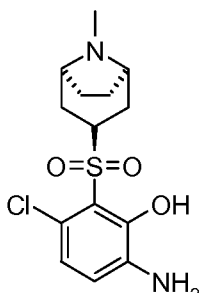
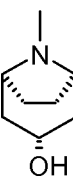
To a solution of Intermediate 6 (60 mg) in DCM (3 mL) was added the 2-chloro-3-fluorophenyl isocyanate (79 mg) and the reaction was left over the weekend. Reaction mixture was concentrated and residue columned (flash, eluted with a gradient of 0 - 30% EtOAc/Hx). Yield: 71.2 mg. R_f: 0.51 (50% EA/Hx). MS (m/z, ES⁺, M+H): 561.95.

Example 3. N-(2-chloro-3-fluorophenyl)-N'-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}urea

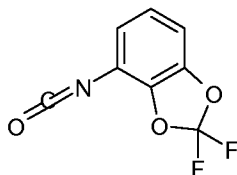


Intermediate 11 (71.2 mg) and 4N HCl/dioxane (3 mL) were stirred together at room temperature and left overnight. Intermediates 6, 5, 4, 3 and 2 were made as described above. Intermediate 1 was made using Starting Material 1 for synthesizing Example 3. The reaction mixture was concentrated and the residue dissolved in a minimum amount of MeOH and Et₂O added. Solid crashed out and was filtered and dried. Yield: 50.1 mg (off-white solid). MS (m/z, ES⁺, M+H): 461.96. NMR (MeOD) δ 8.42 (1H, d, ArH), 7.93 (1H, d, ArH), 7.26 (1H, dt, ArH), 7.18 (1H, d, ArH), 6.95 (1H, dt, ArH), 4.21-4.11 (1H, m, CH), 3.66 (1H, dd, CH), 3.39-3.31 (2H, m, CH₂), 3.03 (1H, dt, CH), 2.17-1.72 (4H, m, 2xCH₂).

Table 1. Intermediates made according to general procedures A-E.

Intermediate	Structure	Starting material (commercially available)	Preparation: general procedures:	Overall yield, characterization.
12			B-E	53%, LCMS (m/z, (M+H)): 391.
13			B-E	16%, MS (m/z, ES ⁺ , M+H): 290.97
14			B-E	11%, MS (m/z, ES ⁺ , M+H): 290.97
15			B-E	5%, LCMS m/z, (M+H)): 363.
16			B-D, E (without re- boc'ing procedure)	37%, R _f : 0.20 (MeOH)

17			B-E	44%, MS (m/z, ES ⁺ , M+H-t-Bu): 321.00
----	--	--	-----	---

Intermediate 18:

Two batches of 2,2-difluoro-1,3-benzodioxol-4-amine (1g and 3.58 g) were treated with triphosgene (566mg and 2.04 mg) and saturated aqueous NaHCO₃ (20 mL and 80 mL) in DCM (20 mL and 80 mL) according to the procedure described for Intermediate 9 yielding 3.27 g of the desired product after the 2 batches had been combined. ¹H-NMR (CDCl₃) δ 7.05 (t, 1H), 6.90 (d, 1H), 6.82 (d, 1H).

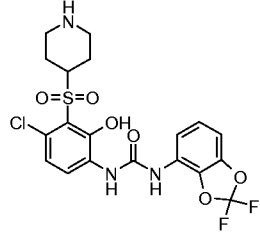
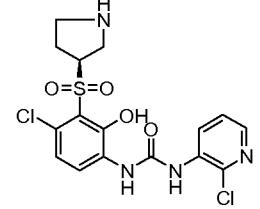
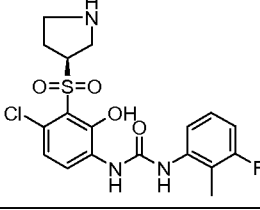
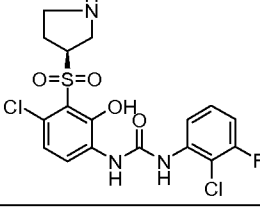
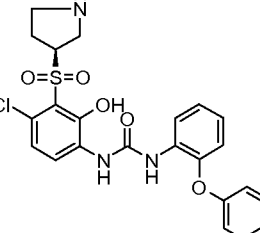
Intermediate 1 was prepared using Starting Material 1 for all syntheses.

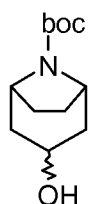
10 **Table 2. Examples prepared from intermediates in Table 1.**

Ex	Structure	Name	Starting materials: Prepared from intermediates	Preparation: general procedures:	Amount of final product, overall % yield, characterization.
4		<i>N</i> -(4-chloro-2-hydroxy-3-[[3-(3- <i>exo</i>)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]sulfonyl]phenyl)- <i>N'</i> -(3-fluoro-2-methylphenyl)urea	16, 7	I	400 mg, 56%, MS (m/z, ES ⁺ , M+H): 482.04
5		<i>N</i> -{4-chloro-2-hydroxy-3-[(3-pyrrolidinylmethyl)sulfonyl]-phenyl}- <i>N'</i> -{2-[(trifluoromethyl)oxy]phenyl}-urea	14, 2-(trifluoromethoxy)phenyl isocyanate	G-H	52 mg, 53%, MS (m/z, ES ⁺ , M+H): 493.92
6		<i>N</i> -[3-(3-azetidylsulfonyl)-4-chloro-2-hydroxyphenyl]- <i>N'</i> -(2-chloro-3-pyridinyl)urea	15, 9	G-H	16 mg, 25%, MS (m/z, ES ⁺ , M+H): 416.88

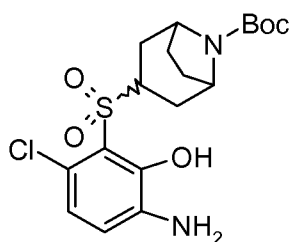
7		<i>N</i> -{4-chloro-2-hydroxy-3-[(3-pyrrolidinylmethyl)sulfonyl]phenyl}- <i>N'</i> -(3-fluoro-2-methylphenyl)urea	14, 7	G-H	76 mg, 87%, MS (m/z, ES ⁺ , M+H): 441.98
8		<i>N</i> -[3-(3-azetidinylsulfonyl)-4-chloro-2-hydroxyphenyl]- <i>N'</i> -(2-chloro-3-fluorophenyl)urea	15 , 2-chloro-3-fluoro phenyl isocyanate	G-H	11 mg, 17%, MS (m/z, ES ⁺ , M+H): 433.86
9		<i>N</i> -[3-(3-azetidinylsulfonyl)-4-chloro-2-hydroxyphenyl]- <i>N'</i> -(3-fluoro-2-methylphenyl)urea	15, 7	G-H	18 mg, 24%, MS (m/z, ES ⁺ , M+H): 413.93
10		<i>N</i> -(2-chloro-3-fluorophenyl)- <i>N'</i> -{4-chloro-2-hydroxy-3-[(3-pyrrolidinylmethyl)sulfonyl]phenyl}urea	14 , 2-chloro-3-fluoro phenyl isocyanate	G-H	100 mg, ~100%, MS (m/z, ES ⁺ , M+H): 461.90
11		<i>N</i> -[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]- <i>N'</i> -(2-ethylphenyl)urea	13 , 2-ethylphenyl isocyanate	G-H	52 mg, 60%, MS (m/z, ES ⁺ , M+H): 437.97
12		<i>N</i> -[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]- <i>N'</i> -(2-chloro-3-pyridinyl)urea	13, 9	G-H	56 mg, 61%, MS (m/z, ES ⁺ , M+H): 444.91
13		<i>N</i> -[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]- <i>N'</i> -{2-[(trifluoromethyl)oxy]phenyl}urea	13 , 2-(trifluoromethoxy)phenyl isocyanate	G-H	37 mg, 40%, MS (m/z, ES ⁺ , M+H): 493.92
14		<i>N</i> -[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)phenyl]- <i>N'</i> -(3-fluoro-2-methylphenyl)urea	13, 7	G-H	24 mg, 26%, MS (m/z, ES ⁺ , M+H): 441.98

15		<i>N</i> -(2-chloro-3-fluorophenyl)- <i>N'</i> -[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)-phenyl]urea	13 , 2-chloro-3-fluoro phenyl isocyanate	G-H	43 mg, 61%, MS (m/z, ES ⁺ , M+H):461.90
16		<i>N</i> -[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)-phenyl]- <i>N'</i> -(2,3-dichlorophenyl)urea	13 , 2,3-dichlorophenyl isocyanate	I, H	6 mg, 5%, LCMS (m/z, (M+H)): 478
17		<i>N</i> -(2-chloro-3-fluorophenyl)- <i>N'</i> -[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)-phenyl]urea	12 , 2,3-dichlorophenyl isocyanate	G-H	135 mg, 46%, MS (m/z, ES ⁺ , M+H): 461.96
18		<i>N</i> -[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)-phenyl]- <i>N'</i> -(3-fluoro-2-methylphenyl)urea	12 , 7	G-H	145 mg, 53%, MS (m/z, ES ⁺ , M+H): 442.04
19		<i>N</i> -[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)-phenyl]- <i>N'</i> -{2-[(trifluoromethyl)oxy]-phenyl}urea	12 , 2-(trifluoromethoxy)phenyl isocyanate	G-H	103 mg, 47%, MS (m/z, ES ⁺ , M+H): 493.92
20		<i>N</i> -[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)-phenyl]- <i>N'</i> -(2-ethylphenyl)urea	12 , 2-ethylphenyl isocyanate	G-H	27 mg, 15%, MS (m/z, ES ⁺ , M+H): 437.90
21		<i>N</i> -[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)-phenyl]- <i>N'</i> -(2-chloro-3-pyridinyl)urea	12 , 9	G-H	70 mg, 25%, MS (m/z, ES ⁺ , M+H): 445.03

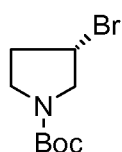
22		<i>N</i> -[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)-phenyl]- <i>N'</i> -(2,2-difluoro-1,3-benzodioxol-4-yl)urea	12, 18	G-H	23 mg, 7%, MS (<i>m/z</i> , ES ⁺ , M+H): 489.97
23		<i>N</i> -{4-chloro-2-hydroxy-3-[(3 <i>S</i>)-3-pyrrolidinylsulfonyl]-phenyl}- <i>N'</i> -(2-chloro-3-pyridinyl)urea	17, 9	G-H	201 mg, 54%, MS (<i>m/z</i> , ES ⁺ , M+H): 430.97
24		<i>N</i> -{4-chloro-2-hydroxy-3-[(3 <i>S</i>)-3-pyrrolidinylsulfonyl]-phenyl}- <i>N'</i> -(3-fluoro-2-methylphenyl)urea	17, 7	G-H	60 mg, 89%, MS (<i>m/z</i> , ES ⁺ , M+H): 428.00
25		<i>N</i> -(2-chloro-3-fluorophenyl)- <i>N'</i> -{4-chloro-2-hydroxy-3-[(3 <i>S</i>)-3-pyrrolidinylsulfonyl]-phenyl}urea	17, 2-chloro-3-fluoro phenyl isocyanate	G-H	76 mg, 20%, MS (<i>m/z</i> , ES ⁺ , M+H): 447.96
26		<i>N</i> -{4-chloro-2-hydroxy-3-[(3 <i>S</i>)-3-pyrrolidinylsulfonyl]-phenyl}- <i>N'</i> -[2-(phenyloxy)phenyl]urea	17, 2-phenoxyphenyl isocyanate	G-H	109 mg, 26%, MS (<i>m/z</i> , ES ⁺ , M+H): 488.06

Intermediate 19:

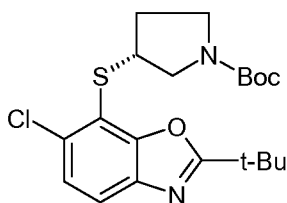
N-Boc-nortropinone (6.3 g) was dissolved in MeOH (150 mL) and cooled to 0 °C. NaBH₄ was added in portions and the reaction mixture was stirred at 0 °C for 2.5h. The reaction was quenched with water, acidified to pH3 and extracted with DCM (x3). The combined organic layers were dried over Na₂SO₄ and concentrated yielding the desired product (5.0g, 79%, white solid). R_f: 0.38 (EtOAc/Hx: 1/1).

Intermediate 20:

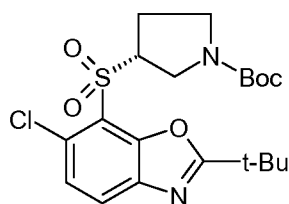
Intermediate 19 was prepared from Intermediate 18 and Intermediate 1 (using Starting Material 1) according to the general procedures B, C, D and E. Overall yield: 29%, MS (m/z, ES⁺, M+H): 316.99.

Intermediate 21:

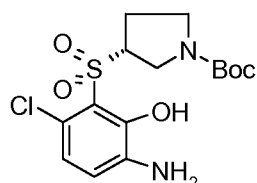
To a 100 mL round bottom flask was added (R)-(-)-N-Boc-3-pyrrolidinol (1.5g) under an argon atmosphere. CBr₄ (1.5g) was then added followed by dry THF (50mL) and the mixture was cooled to 5 °C. PPh₃ was then added over 5 min and the progress was followed by TLC. The solid was removed by filtration and washed with ether. The filtrate was concentrated and purified by column chromatography eluting with 1:3 EtOAc:Hx. Yield: 2.3g (>100%, used without further purification). ¹H-NMR (CDCl₃) δ 4.48 (br s, 1H), 3.82-3.65 (m, 2H), 3.62-3.46 (m, 2H), 2.38-2.18 (m, 2H), 1.46 (s, 9H).

Intermediate 22: (General Procedure I)

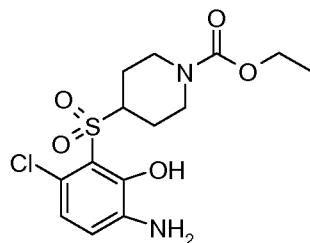
Intermediate 1 (1.0g), Intermediate 21 (1.24g) and K₂CO₃ (0.49g) in methylethylketone (10mL) was stirred at room temperature overnight. Intermediate 1 was made using Starting Material 1. The reaction was quenched with water, extracted with EtOAc and the organic layers were dried over Na₂SO₄ and the concentrated. The crude product was purified by column chromatography eluting with 1:4 EtOAc:Hx. Yield: 0.60g (36%, brown oil). ¹H-NMR (CDCl₃) δ 7.53 (d, J= 8.3Hz, 1H), 7.39 (d, J= 8.3 Hz, 1H), 4.15-4.05 (m, 1H), 3.70-3.50 (m, 2H), 3.50-3.27 (m, 2H), 2.28-2.10 (m, 1H), 1.90-1.77 (m, 1H), 1.47 (s, 9H), 1.44 (s, 9H).

Intermediate 23:

Intermediate 22 (0.40g) was stirred in DCM (4mL) at -10 °C and mCPBA (0.68g) was added. The resulting mixture was stirred at -10 °C for 30 min. The reaction was quenched with NaHCO₃ solution, extracted with DCM, washed with water. The organic layers were dried over Na₂SO₄, concentrated and purified by column chromatography eluting with 1:3 EtOAc:Hx. Yield: 0.30g (69%, white solid). LCMS (m/z, M+H): 443.

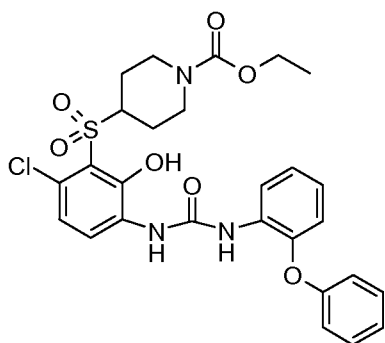
Intermediate 24: (General Procedure J)

Intermediate 23 (0.30g) was stirred in THF (2mL), then added conc. HCl and heated to 80 °C overnight. The reaction mixture was cooled, the solvent removed and the remaining mixture was basified with 50% aqueous NaOH solution. The mixture was cooled to 0 °C and EtOAc was added followed by BOC₂O (0.155g) and the resulting mixture was then stirred at room temperature overnight. The mixture was then diluted with EtOAc and the organic phase was separated, dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography eluting with a gradient of 33-75% EtOAc in hexane. 0.25g (quantitative). LCMS (m/z, M+H-tBu): 321.00

Intermediate 25:

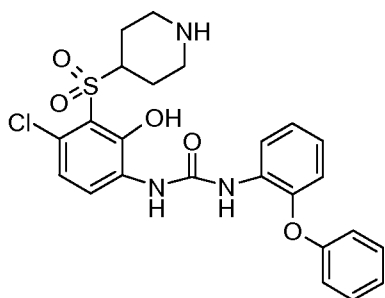
Intermediate 25 was prepared from Intermediate 1 (0.5g) and N-Boc-4-bromopiperidine (0.59g) according to the general procedures I, D and J. Yield: 0.50g (58% overall). Intermediate 1 was made using Starting Material 1.

Example 27. Ethyl 4-({6-chloro-2-hydroxy-3-[(2-(phenyloxy)phenyl]amino}carbonyl)amino}phenyl)sulfonyl)-1-piperidinecarboxylate.
(General Procedure K)



- 5 Intermediate 25 (0.25g) and 2-phenoxyphenyl isocyanate (0.175g) were dissolved in DMF (3mL) and the reaction mixture was stirred at room temperature overnight. The excess DMF was evaporated and the remaining mixture was loaded onto a column and eluted with 1:3 EtOAc:Hx. Yield: 400mg (quantitative, white solid) MS (m/z, ES⁺, M+H): 574.17.

10 **Example 28. N-[4-chloro-2-hydroxy-3-(4-piperidinylsulfonyl)phenyl]-N'-[2-(phenyloxy)phenyl]urea**



- Example 27 (0.20g) was stirred in CHCl₃ (2mL) at room temperature under an argon atmosphere. Iodotrimethylsilane (0.21g) was added and the mixture was heated to reflux
 15 overnight. The reaction did not proceed, however, until two batches of chlorotrimethylsilane (0.037g pr. batch) and NaI (0.051g pr. batch) were added and the reaction was heated to 75 °C for a further 6 h. At this time, MeOH was added and the mixture was stirred for a further 30 min after which the solvents were removed, ammonia in methanol added. The mixture was extracted with DCM, the organic layer washed with
 20 water, dried over Na₂SO₄ and concentrated. The crude product was triturated with DCM/ether and then purified by column chromatography eluting with methanol. Yield: 10 mg (6%, light brown solid) MS (m/z, ES⁺, M+H): 502.06.

Intermediates 4-6, 8, 10-17, 20, 22-25 are novel intermediates.

Table 3. Examples prepared from intermediates 20, 24 and 25.

Example	Structure	Name	Starting materials: Prepared from intermediates	Preparation: general procedures:	Amount of final product, overall % yield, characterization
29		<i>N</i> -(2-chloro-3-fluorophenyl)- <i>N'</i> -{4-chloro-2-hydroxy-3-[(3 <i>R</i>)-3-pyrrolidinylsulfonyl]-phenyl}urea	24, 2-chloro-3-fluoro phenyl isocyanate	G-H	400 mg, 58%, MS (m/z, ES ⁺ , M+H): 447.93
30		ethyl 4-{[6-chloro-3-({[(2-chloro-3-fluorophenyl)amino]-carbonyl}amino)-2-hydroxyphenyl]sulfonyl}-1-piperidinecarboxylate	25, 2-chloro-3-fluoro phenyl isocyanate	G	100 mg, 42%, MS (m/z, ES ⁺ , M+H): 533.95
31		<i>N</i> -{3-[(1 <i>R</i> ,5 <i>S</i>)-8-azabicyclo[3.2.1]oct-3-ylsulfonyl]-4-chloro-2-hydroxyphenyl}- <i>N'</i> -(2-chloro-3-fluorophenyl)urea	20, 2-chloro-3-fluoro phenyl isocyanate	G-H	285 mg, 42%, MS (m/z, ES ⁺ , M+H): 487.93
32		ethyl 4-{[6-chloro-3-({[(3-fluoro-2-methylphenyl)amino]-carbonyl}amino)-2-hydroxyphenyl]sulfonyl}-1-piperidinecarboxylate	25, 7	G	12mg, 5%, MS (m/z, ES ⁺ , M+H): 513.98
33		<i>N</i> -{3-[(1 <i>R</i> ,5 <i>S</i>)-8-azabicyclo[3.2.1]oct-3-ylsulfonyl]-4-chloro-2-hydroxyphenyl}- <i>N'</i> -[2-(phenyloxy)phenyl]urea	20, 2-phenoxyphenyl isocyanate	G-H	20 mg, 6%, MS (m/z, ES ⁺ , M+H): 528.14

34		<i>N</i> -{4-chloro-2-hydroxy-3-[(3 <i>R</i>)-3-pyrrolidinylsulfonyl]-phenyl}- <i>N'</i> -{2-[(trifluoromethyl)oxy]-phenyl}urea	14, 2-(trifluoromethoxy)phenyl isocyanate	G-H	25 mg, 9%, MS (m/z, ES ⁺ , M+H): 479.91
35		<i>N</i> -{4-chloro-2-hydroxy-3-[(3 <i>R</i>)-3-pyrrolidinylsulfonyl]-phenyl}- <i>N'</i> -(2,2-difluoro-1,3-benzodioxol-4-yl)urea	13, 18	G-H	8 mg, 3%, MS (m/z, ES ⁺ , M+H): 475.87
36		<i>N</i> -{3-[(1 <i>R</i> ,5 <i>S</i>)-8-azabicyclo[3.2.1]oct-3-ylsulfonyl]-4-chloro-2-hydroxyphenyl}- <i>N'</i> -(3-fluoro-2-methylphenyl)urea	20, 7	G-H	43 mg, 15%, MS (m/z, ES ⁺ , M+H): 468.09
37		<i>N</i> -{4-chloro-2-hydroxy-3-[(3 <i>R</i>)-3-pyrrolidinylsulfonyl]-phenyl}- <i>N'</i> -(2-ethylphenyl)urea	24, 2-ethylphenyl isocyanate	G-H	53 mg, 56%, MS (m/z, ES ⁺ , M+H): 423.97
38		<i>N</i> -{3-[(1 <i>R</i> ,5 <i>S</i>)-8-azabicyclo[3.2.1]oct-3-ylsulfonyl]-4-chloro-2-hydroxyphenyl}- <i>N'</i> -(2-chloro-3-pyridinyl)urea	20, 9	G-H	24 mg, 12%, MS (m/z, ES ⁺ , M+H): 471.04

METHOD OF TREATMENT

Compounds of Formula (I), or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicine for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated IL-8 cytokine production by such mammal's cell, such as, but not limited to,

monocytes and/or macrophages, or other chemokines which bind to the IL-8 α or β receptor, also referred to as the type I or type II receptor.

Accordingly, the present invention provides a method of treating a chemokine mediated disease, wherein the chemokine is one which binds to an IL-8 α or β receptor and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In particular, the chemokines are IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78.

The compounds of Formula (I) are administered in an amount sufficient to inhibit cytokine function, in particular IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78, such that they are biologically regulated down to normal levels of physiological function, or in some case to subnormal levels, so as to ameliorate the disease state. Abnormal levels of IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78, for instance, in the context of the present invention, constitute: (i) levels of free IL-8 greater than or equal to 1 picogram per mL; (ii) any cell associated IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78 above normal physiological levels; or (iii) the presence of IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78 above basal levels in cells or tissues in which IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78 respectively, is produced.

There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. Chemokine mediated diseases include psoriasis, atopic dermatitis, osteo arthritis, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, stroke, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, graft vs. host reaction, alzheimers disease, allograft rejections, malaria, restinosis, angiogenesis, atherosclerosis, osteoporosis, gingivitis, viral diseases such as rhinovirus or undesired hematopoietic stem cell release.

These diseases are primarily characterized by massive neutrophil infiltration, T-cell infiltration, or neovascular growth, and are associated with increased IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78 production which is responsible for the chemotaxis of neutrophils into the inflammatory site or the directional growth of endothelial cells. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78 have the unique property of promoting neutrophil chemotaxis,

enzyme release including but not limited to elastase release as well as superoxide production and activation. The α -chemokines, but particularly, GRO α , GRO β , GRO γ , NAP-2 or ENA-78, working through the IL-8 type I or II receptor, can promote the neovascularization of tumors by promoting the directional growth of endothelial cells.

5 Therefore, the inhibition of IL-8 induced chemotaxis or activation would lead to a direct reduction in the neutrophil infiltration.

Recent evidence also implicates the role of chemokines in the treatment of HIV infections, Littleman *et al.*, Nature 381, pp. 661 (1996) and Koup *et al.*, Nature 381, pp. 667 (1996).

10 Present evidence also indicates the use of IL-8 inhibitors in the treatment of atherosclerosis. The first reference, Boisvert *et al.*, J. Clin. Invest., 1998, 101:353-363 shows, through bone marrow transplantation, that the absence of IL-8 receptors on stem cells (and, therefore, on monocytes/macrophages) leads to a reduction in the development of atherosclerotic plaques in LDL receptor deficient mice. Additional supporting references
15 are: Apostolopoulos, *et al.*, Arterioscler. Thromb. Vasc. Biol. 1996, 16:1007-1012; Liu, *et al.*, Arterioscler. Thromb. Vasc. Biol., 1997, 17:317-323; Rus, *et al.*, Atherosclerosis, 1996, 127:263-271.; Wang *et al.*, J. Biol. Chem. 1996, 271:8837-8842; Yue, *et al.*, Eur. J. Pharmacol. 1993, 240:81-84; Koch, *et al.*, Am. J. Pathol., 1993, 142:1423-1431.; Lee, *et al.*, Immunol. Lett., 1996, 53, 109-113.; and Terkeltaub *et al.*, Arterioscler. Thromb., 1994,
20 14:47-53.

The present invention also provides for a means of treating CNS injuries by the chemokine receptor antagonist compounds of Formula (I). Such treatment is provided in an acute setting, as well as for prevention of injury in those individuals deemed susceptible to injury.

CNS injuries as defined herein include both open or penetrating head trauma, such
25 as by surgery, or a closed head trauma injury, such as by an injury to the head region. Also included within this definition is ischemic stroke, particularly to the brain area.

Ischemic stroke may be defined as a focal neurologic disorder that results from insufficient blood supply to a particular brain area, usually as a consequence of an embolus, thrombi, or local atheromatous closure of the blood vessel. The role of
30 inflammatory cytokines in this area has been emerging and the present invention provides means for the potential treatment of these injuries. Relatively little treatment, for an acute injury such as these has been available.

TNF- α is a cytokine with proinflammatory actions, including endothelial leukocyte adhesion molecule expression. Leukocytes infiltrate into ischemic brain lesions and hence compounds which inhibit or decrease levels of TNF would be useful for treatment of ischemic brain injury. See Liu *et al.*, Stroke, Vol. 25., No. 7, pp. 1481-88 (1994) whose disclosure is incorporated herein by reference.

Models of closed head injuries and treatment with mixed 5-LO/CO agents is discussed in Shohami *et al.*, J. of Vasc & Clinical Physiology and Pharmacology, Vol. 3, No. 2, pp. 99-107 (1992). Treatment which reduced edema formation was found to improve functional outcome in those animals treated.

Compounds of Formula (I) are administered in an amount sufficient to inhibit IL-8, binding to the IL-8 alpha or beta receptors, from binding to these receptors, such as evidenced by a reduction in neutrophil chemotaxis and activation. The discovery that the compounds of Formula (I) are inhibitors of IL-8 binding is based upon the effects of the compounds of Formula (I) in the *in vitro* receptor binding assays which are described herein. Compounds of Formula (I) have been shown to be inhibitors of type II IL-8 receptors.

As used herein, the term "IL-8 mediated disease or disease state" refers to any and all disease states in which IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78 plays a role, either by production of IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78 themselves, or by IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78 causing another monokine to be released, such as but not limited to IL-1, IL-6 or TNF. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to IL-8, would therefore be considered a disease state mediated by IL-8.

As used herein, the term "chemokine mediated disease or disease state" refers to any and all disease states in which a chemokine which binds to an IL-8 α or β receptor plays a role, such as but not limited to IL-8, GRO- α , GRO- β , GRO γ , NAP-2 or ENA-78. This would include a disease state in which, IL-8 plays a role, either by production of IL-8 itself, or by IL-8 causing another monokine to be released, such as but not limited to IL-1, IL-6 or TNF. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to IL-8, would therefore be considered a disease stated mediated by IL-8.

As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a
5 monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples
10 of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF- α) and Tumor Necrosis Factor beta (TNF- β).

As used herein, the term "chemokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune,
15 inflammatory or hematopoietic response, similar to the term "cytokine" above. A chemokine is primarily secreted through cell transmembranes and causes chemotaxis and activation of specific white blood cells and leukocytes, neutrophils, monocytes, macrophages, T-cells, B-cells, endothelial cells and smooth muscle cells. Examples of chemokines include, but are not limited to IL-8, GRO- α , GRO- β , GRO- γ , NAP-2, ENA-78, IP-10, MIP-1 α , MIP- β , PF4, and
20 MCP 1, 2, and 3.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of
25 Formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of Formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in
30 conventional dosage forms prepared by combining a compound of Formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I) may also be administered in conventional dosages in combination with a

known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Compounds of Formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula (I) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the Formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the Formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying
5 and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or
10 suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The
15 formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily
20 solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100⁰C for half an hour. Alternatively, the
25 solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

30 Compounds of Formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral

administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of Formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration.

Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

For all methods of use disclosed herein for the compounds of Formula (I) the daily oral dosage regimen will preferably be from about 0.01 to about 80 mg/kg of total body weight. The daily parenteral dosage regimen about 0.001 to about 80 mg/kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

Combinations:

The compound and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an $M_1/M_2/M_3$ receptor antagonist), β_2 -adrenoreceptor agonists, antiinfective agents, such as antibiotics, antivirals, or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of Formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent, such as a corticosteroid or an NSAID, an anticholinergic agent, a β_2 -adrenoreceptor agonist, an antiinfective agent, such as an antibiotic or an antiviral, or an antihistamine. One embodiment of the invention encompasses combinations comprising a compound of

Formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a β_2 -adrenoreceptor agonist, and/or an anticholinergic, and/or a PDE-4 inhibitor, and/or an antihistamine.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, for example as alkali metal or amine salts or as acid addition salts, or prodrugs, or as esters, for example lower alkyl esters, or as solvates, for example hydrates to optimise the activity and/or stability and/or physical characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that, where appropriate, the therapeutic ingredients may be used in optically pure form.

In one embodiment, the invention encompasses a combination comprising a compound of the invention together with a β_2 -adrenoreceptor agonist.

Examples of β_2 -adrenoreceptor agonists include salmeterol (which may be a racemate or a single enantiomer such as the *R*-enantiomer), salbutamol (which may be a racemate or a single enantiomer such as the *R*-enantiomer), formoterol (which may be a racemate or a single diastereomer such as the *R,R*-diastereomer), salmefamol, fenoterol, carmoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerbuterol, reproterol, bambuterol, indacaterol, terbutaline and salts thereof, for example the xinafoate (1-hydroxy-2-naphthalenecarboxylate) salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. In one embodiment the β_2 -adrenoreceptor agonists are long-acting β_2 -adrenoreceptor agonists, for example, compounds which provide effective bronchodilation for about 12 hours or longer. Other β_2 -adrenoreceptor agonists include those described in WO2002/066422, WO2002/070490, WO2002/076933, WO2003/024439, WO2003/072539, WO2003/091204, WO2004/016578, WO2004/022547, WO2004/037807, WO2004/037773, WO2004/037768, WO2004/039762, WO2004/039766, WO2001/42193 and WO2003/042160.

Further examples of β_2 -adrenoreceptor agonists include:

3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl} amino) hexyl] oxy} butyl) benzenesulfonamide;

3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl] phenyl] ethyl}-amino) heptyl] oxy} propyl) benzenesulfonamide;

4-{{(1R)-2-[(6-{2-[(2, 6-dichlorobenzyl) oxy] ethoxy} hexyl) amino]-1-hydroxyethyl}-2-(hydroxymethyl) phenol};

4-{{(1R)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy} hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol};

- 5 N-[2-hydroxyl-5-[(1R)-1-hydroxy-2-[[2-4-[(2R)-2-hydroxy-2-phenylethyl]amino]phenyl]ethyl]amino]ethyl]phenyl]formamide;
N-2{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1H)-quinolinon-5-yl)ethylamine; and
5-[(R)-2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one.

- The β_2 -adrenoreceptor agonist may be in the form of a salt formed with a pharmaceutically acceptable acid selected from sulphuric, hydrochloric, fumaric, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), cinnamic, substituted cinnamic, triphenylacetic, sulphamic, sulphanilic, naphthaleneacrylic, benzoic,
15 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic and 4-phenylbenzoic acid.

Suitable anti-inflammatory agents include corticosteroids. Examples of corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity.

- 20 Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester (fluticasone furoate), 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy- androsta-1,4-diene-17 β -carbothioic acid S-
25 (2-oxo-tetrahydro-furan-3S-yl) ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(2,2,3,3- tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid S-cyanomethyl ester and 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methylcyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-
30 fluoromethyl ester, beclomethasone esters (for example the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (for example mometasone furoate), triamcinolone acetonide, rofleponide, ciclesonide (16 α ,17-[[[(R)-

cyclohexylmethylene]bis(oxy)]-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione), butixocort propionate, RPR-106541, and ST-126. In one embodiment corticosteroids include fluticasone propionate, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-
 5 fluoromethyl ester, 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(2,2,3,3-tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid S-cyanomethyl ester and 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-
 10 methycyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester. In one embodiment the corticosteroid is 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester.

Examples of corticosteroids also include those described in WO2002/088167,
 15 WO2002/100879, WO2002/12265, WO2002/12266, WO2005/005451, WO2005/005452, WO2006/072599 and WO2006/072600.

Non-steroidal compounds having glucocorticoid agonism that may possess selectivity for transrepression over transactivation and that may be useful in combination therapy include those covered in the following published patent applications and patents:
 20 WO2003/082827, WO1998/54159, WO2004/005229, WO2004/009017, WO2004/018429, WO2003/104195, WO2003/082787, WO2003/082280, WO2003/059899, WO2003/101932, WO2002/02565, WO2001/16128, WO2000/66590, WO2003/086294, WO2004/026248, WO2003/061651, WO2003/08277, WO2006/000401, WO2006/000398 and WO2006/015870.

Non-steroidal compounds having glucocorticoid agonism that may possess selectivity for transrepression over transactivation and that may be useful in combination therapy include those covered in the following patents: WO2003/082827, WO1998/54159, WO2004/005229, WO2004/009017, WO2004/018429, WO2003/104195, WO2003/082787, WO2003/082280, WO2003/059899, WO2003/101932, WO2002/02565,
 30 WO2001/16128, WO2000/66590, WO2003/086294, WO2004/026248, WO2003/061651 and WO2003/08277.

Examples of anti-inflammatory agents include non-steroidal anti-inflammatory drugs (NSAID's).

Examples of NSAID's include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (for example, theophylline, PDE4 inhibitors or mixed
5 PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis (for example montelukast), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (for example chemokine antagonists, such as a CCR3 antagonist) or inhibitors of cytokine synthesis, or 5-lipoxygenase inhibitors. In one embodiment, the
10 invention encompasses iNOS (inducible nitric oxide synthase) inhibitors for oral administration. Examples of iNOS inhibitors include those disclosed in WO1993/13055, WO1998/30537, WO2002/50021, WO1995/34534 and WO1999/62875. Examples of CCR3 inhibitors include those disclosed in WO2002/26722.

In one embodiment the invention provides the use of the compounds of Formula (I)
15 in combination with a phosphodiesterase 4 (PDE4) inhibitor, for example in the case of a formulation adapted for inhalation. The PDE4 inhibitor useful in this aspect of the invention may be any compound that is known to or which is discovered to act as a PDE4 inhibitor, e.g. as an inhibitor of PDE4B and/or PDE4D.

PDE4 inhibitory compounds include cis-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]. Also, cis-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomilast) and its salts, esters, pro-drugs or physical forms, which is described in U.S.
25 patent 5,552,438, issued 03 September, 1996.

Other PDE4 inhibitory compounds include AWD-12-281 (N-(3,5-dichloro-4-pyridinyl)-1-[4-fluorophenyl)methyl]-5-hydroxy- α -oxo-1H-indol-3-acetamide) from Elbion (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated
30 NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-

23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)benzamide) (see EP 0 706 513 B1 to Byk Gulden Lomberg, e.g. see Example 5 thereof); a phthalazinone (WO1999/47505) from Byk-Gulden; Pumafentrine, (-)-p-[(4aR*,10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther, 1998, 284(1): 162), and T2585.

Further PDE4 inhibitory compounds are disclosed in the published international patent applications WO2004/024728, WO2004/056823, WO2004/103998 (e.g. Example 399 or 544 disclosed therein), WO2005/058892, WO2005/090348, WO2005/090353, and WO2005/090354, all in the name of Glaxo Group Limited.

Examples of anticholinergic agents are those compounds that act as antagonists at the muscarinic receptors, in particular those compounds which are antagonists of the M₁ or M₃ receptors, dual antagonists of the M₁/M₃ or M₂/M₃ receptors or pan-antagonists of the M₁/M₂/M₃ receptors. Exemplary compounds for administration via inhalation include ipratropium (for example, as the bromide, CAS 22254-24-6, sold under the name Atrovent), oxitropium (for example, as the bromide, CAS 30286-75-0) and tiotropium (for example, as the bromide, CAS 136310-93-5, sold under the name Spiriva). Also of interest are revatropate (for example, as the hydrobromide, CAS 262586-79-8) and LAS-34273 which is disclosed in WO2001/04118. Exemplary compounds for oral administration include pirenzepine (CAS 28797-61-7), darifenacin (CAS 133099-04-4, or CAS 133099-07-7 for the hydrobromide sold under the name Enablex), oxybutynin (CAS 5633-20-5, sold under the name Ditropan), terodiline (CAS 15793-40-5), tolterodine (CAS 124937-51-5, or CAS 124937-52-6 for the tartrate, sold under the name Detrol), otilonium (for example, as the bromide, CAS 26095-59-0, sold under the name Spasmomen), trospium chloride (CAS 10405-02-4) and solifenacin (CAS 242478-37-1, or CAS 242478-38-2 for the succinate also known as YM-905 and sold under the name Vesicare).

Additional compounds are disclosed in WO 2005/037280, WO 2005/046586 and WO 2005/104745. The present combinations include, but are not limited to: (3-*endo*)-3-(2,2-di-2-thienylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane iodide;

(3-*endo*)-3-(2-cyano-2,2-diphenylethyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide; and

- 5 (1*R*,5*S*)-3-(2-cyano-2,2-diphenylethyl)-8-methyl-8-{2-[(phenylmethyl)oxy]ethyl}-8-azoniabicyclo[3.2.1]octane bromide.

Other anticholinergic agents include compounds which are disclosed in US patent application 60/487981, incorporated herein in its entirety by reference. These include, for example:

- 10 (endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile;
 (endo)-8-methyl-3-(2,2,2-triphenyl-ethyl)-8-aza-bicyclo[3.2.1]octane;
 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;
 15 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid;
 (endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
 (endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;
 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propan-1-ol;
 20 N-benzyl-3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;
 (endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
 1-benzyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
 1-ethyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
 25 N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-acetamide;
 N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide;
 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile;
 (endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
 30 N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzenesulfonamide;
 [3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;

N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-methanesulfonamide; and/or
(endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

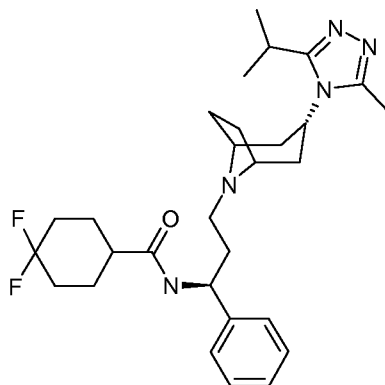
5 Further compounds include:

(endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane
10 bromide;
(endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; and/or
15 (endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

In one embodiment the invention provides a combination comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof together with an H1 antagonist. Examples of H1 antagonists include, without limitation, amexanox, astemizole,
20 azatadine, azelastine, acrivastine, brompheniramine, cetirizine, levocetirizine, efletirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, olopatadine, picumast, pyrilamine,
25 promethazine, terfenadine, tripeleminamine, temelastine, trimeprazine and triprolidine, particularly cetirizine, levocetirizine, efletirizine and fexofenadine. In a further embodiment the invention provides a combination comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof together with an H3 antagonist (and/or inverse agonist). Examples of H3 antagonists include, for example, those compounds
30 disclosed in WO2004/035556 and in WO2006/045416. Other histamine receptor antagonists which may be used in combination with the compounds of the present invention include antagonists (and/or inverse agonists) of the H4 receptor, for example, the compounds disclosed in Jablonowski et al., J. Med. Chem. 46:3957-3960 (2003).

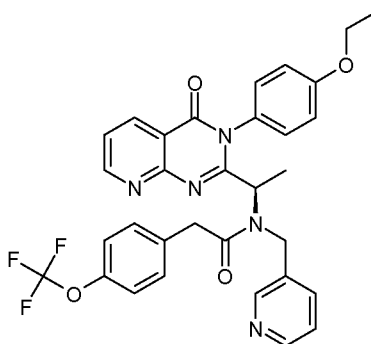
In one embodiment, the invention provides a combination comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof together with a CCR5 receptor antagonist, such as 4,4-difluoro-N-((1S)-3-{3-[3-methyl-5-(1-methylethyl)-4H-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]oct-8-yl}-1-phenylpropyl)cyclohexanecarboxamide:

5



In one embodiment, the invention provides a combination comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof together with a CXCR3 receptor antagonist such as N-((1R)-1-{3-[4-(ethyloxy)phenyl]-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl}ethyl)-N-(3-pyridinylmethyl)-2-{4-[(trifluoromethyl)oxy]phenyl}acetamide:

10



The invention thus provides, in a further aspect, a combination comprising a compound of Formula (I) and/or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor.

15

The invention thus provides, in a further aspect, a combination comprising a compound of Formula (I) and/or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a β_2 -adrenoreceptor agonist.

The invention thus provides, in a further aspect, a combination comprising a compound of Formula (I) and/or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid.

5 The invention thus provides, in a further aspect, a combination comprising a compound of Formula (I) and/or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a non-steroidal GR agonist.

The invention thus provides, in a further aspect, a combination comprising a compound of Formula (I) and/or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

10 The invention thus provides, in a further aspect, a combination comprising a compound of Formula (I) and/or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of Formula (I) and/or a pharmaceutically acceptable salt, solvate or
15 physiologically functional derivative thereof together with a PDE4 inhibitor and a β_2 -adrenoreceptor agonist.

The invention thus provides, in a further aspect, a combination comprising a compound of Formula (I) and/or a pharmaceutically acceptable salt, solvate or
20 physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

25 The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. In one embodiment, the individual compounds will be administered simultaneously in a combined pharmaceutical formulation. Appropriate doses of known therapeutic agents will readily be appreciated by those skilled in the art.

30 The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with another therapeutically active agent.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with a β_2 -

5 adrenoreceptor agonist.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with a corticosteroid.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with a non-steroidal
10 GR agonist.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with an anticholinergic.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with an antihistamine.

15 The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with CXCR3 receptor antagonist.

The invention thus provides, in a further aspect, a pharmaceutical combination of the invention together with a CCR5 receptor antagonist.

20 The invention will now be described by reference to the following biological examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

BIOLOGICAL EXAMPLES

The IL-8, and GRO- α chemokine inhibitory effects of compounds of the present
25 invention are determined by the following *in vitro* assay:

Receptor Binding Assays:

[¹²⁵I] IL-8 (human recombinant) was obtained from GE Healthcare, with specific activity 2000 Ci/mmol. All other chemicals were of analytical grade. High levels of recombinant human CXCR1 (IL-8 type α) and CXCR2 (IL-8 type β) receptors were
30 individually expressed in non-adherent Chinese Hamster Ovary (CHO) cells as described previously (Holmes, *et al.*, Science, **1991**, 253, 1278). The membranes were prepared according to a previously described protocol, Haour, *et al.*, J. Biol. Chem., 249 pp 2195-

2205 (1974)), incorporated herein by reference to the extent required to prepare the present membranes, except that the homogenization buffer was modified to 40mM Tris-HCL (pH 7.5), 1mM MgSO₄, 0.5 mM EGTA (ethylene- glycol-bis(2-aminoethylether)- N,N,N',N' tetra-acetic acid), 1mM PMSF (α -toluenesulphonyl fluoride), 2.5 mg/L leupeptin and 0.1 mg/ml aprotinin. Cells were homogenized and centrifuged at 2,000 rpm for 10 min. The supernatant was centrifuged at 100,000 x g for 1 hour. Supernatant discarded and membranes stored at -80°C. Membrane protein concentration was determined using BioRad reagent according to manufactures protocol using bovine serum albumin (BSA) as a standard.

All IL-8 binding was conducted using Scintillation Proximity Assays (SPA) using wheatgerm agglutinin beads in a 96-well plate format. Membranes CHO-CXCR1 or CHO-CXCR2 were preincubated with the beads in the binding buffer for 30 min. for 4°C Buffer contained 20 mM Bis-Trispropane buffer, pH 8.0, containing 1 mM MgSO₄, 0.1 mM EDTA and 25 mM NaCl. Compounds were diluted in DMSO at 20X the final dilution (final compound concentration between 1 nM and 30 uM and final DMSO concentration of 5%). Assay was performed in 96-well plates (optiplate 96, Packard) at room temperature, in 0.1 ml binding buffer with membranes and 0.04% CHAPS (3-[(3-cholamidopropyl) dimethylammonio]-1-propanesulfonate), 0.0025% BSA and 0.23 nM [¹²⁵I] IL-8. Plates were shaken on a platform for 1 hour, at the end of incubation the plates were spun at 2,000 rpm for 5 min and counted in a Top Count counter The recombinant IL-8 R α , CXCR1 or Type I, receptor is also referred to herein as the non-permissive receptor and the recombinant IL-8 R β , CXCR2 or Type II, receptor is referred to as the permissive receptor.

Exemplified compounds of Formula (I), Examples 1 through 38, exhibited positive inhibitory activity in this assay at IC₅₀ levels < 30 uM, and would be considered active.

Chemotaxis Assay :

The *in vitro* inhibitory properties of these compounds were determined in a neutrophil chemotaxis assay. Primary human neutrophils were isolated from peripheral whole blood using percoll discontinuous gradient centrifugation, dextran sedimentation and hypotonic lysis. The chemoattractants IL-8 (CXCL8) or GRO- α (CXCL1) were placed in the bottom chamber of a 96 multi-well chamber (ChemoTx System, Neuro Probe, Gaithersburg, MD). The agonist concentration used was an EC80 concentration. The two

chambers are separated by a 5 μ m polycarbonate membrane. When compounds of this invention were tested, they were preincubated with the cells prior to placement on the top of the filter. Chemotaxis was allowed to proceed for 45 minutes in a humidified incubator at 37°C with 5% CO₂. At the end of the incubation period, the membrane was removed and the migrated cells in the bottom chamber were transferred to a 96-well plate. These cells were measured using a luminescent cell viability assay (Celltiter-Glo, Promega, Madison, WI). Each sample was tested in duplicate and each compound repeated at least three times. Positive control cells were cells without compound added and represent the maximum chemotactic response. The negative control (unstimulated) was with no chemokine added to the bottom chamber. The difference between the positive control and the negative control represents the chemotactic activity of the cells.

Examples 1 to 3 were tested in this assay. A compound would be considered active if IC₅₀ values were <5 μ M.

CD11b Human Whole Blood assay:

The compounds indicated were tested for their ability to inhibit the GRO α -induced expression of the integrin CD11b on neutrophils in human whole blood.

Blood was drawn (9 ml) using a butterfly line and a 10 ml syringe containing 0.2 ml of working Sodium Heparin. The blood was kept at 37°C until placed on ice in step 5 below. Compound stock solutions were then diluted to 12 times the maximum final concentration, 120 μ M. Half Log serial dilutions were then performed in vehicle. Ten microliters of the compound dilutions or vehicle were then added to the appropriate 12x75 polypropylene tubes. One hundred microliters of whole blood was added per tube and incubated for 10 minutes, in a 37°C water bath with initial (gentle) agitation and again at 5 minutes. The GRO α stock was diluted 1:166.66 in 0.1% BSA-DPBS to "12x"

concentration of 120 nM and 10 μ l of the GRO α dilution or 0.1% BSA-DPBS was added to the appropriate tubes so that the final GRO α concentration equaled 10 nM. The tubes were incubated for 10 min at 37°C with gentle hand agitation and again at 5 minutes. Samples were then placed on ice and 250 μ l of ice cold CellFix working dilution was added followed by a one minute incubation on ice. 1.5 ml Eppendorf tubes were readied during GRO α incubation by adding the appropriate antibodies. Every tube received 10 μ l of CD11b-FITC and 5 μ l of CD16-PE, except for the isotype control which received 10 μ l of IgG2a-FITC instead of CD11b. Addition of 50 μ l of the fixed blood from each tube was

added to the appropriate Eppendorf tube. Samples were allowed to then incubate for 20 min at 4°C in the dark. Addition of the blood/antibody mixtures to 500 ul of cold DPBS were added to the appropriately labeled 12x75 polystyrene tube. The resulting mixture was kept on ice. LDS stock (10 ul) was added and the mixture was incubated for 10 min at 4°C. before flow analysis. Samples were kept in a darkened environment. The LDS addition was staggered as the samples were collected on the flow cytometer so that all samples were run ~10-20 minutes post-LDS addition.

Medium flow rate was used for flow collection and FL3 threshold increased to eliminate red blood cells from analysis using the LDS signal. The color compensation was properly set using unlabeled samples and one-color samples to subtract LDS spill into PE and the PE spill into FITC and FITC into PE. For the BD LSR cytometer, LDS=FL3, PE=FL2, FITC=FL1. A minimum of 2000-3000 events that satisfy the granulocyte gate by SSC vs. FSC and were CD16 positive by the FL2 signal were collected.

Exemplified compounds of Formula (I), Examples 1-3, 12, 17, 18, 23 and 26 exhibited positive inhibitory activity in this assay at IC₅₀ values of <5uM, and would be considered active. Compounds of Examples 1-3, 12, 17, 18, 23 and 26 tested in the above assay had an IC₅₀ value from about 2uM to about 0.5uM.

Calcium Mobilization in CHO-K1 cells stably expressing CXCR2 and Gα16:

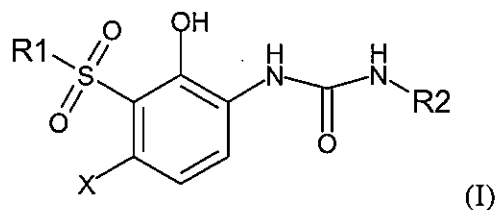
CHO-K1 cells stably expressing CXCR2 and Gα16 were grown to 80% confluency in DMEM/F12 (HAM's) 1:1, w/ 10% FCS (heat inactivated), w/ 2 mM L-glutamine, w/ 0.4 mg/ml G418 while maintained at 37°C in a 5% CO₂ incubator. Twenty four hours previous to assay, cells were harvested and plated, 40,000 cells per well, in a 96 well, black wall, clear bottom plate (Packard View) and returned to CO₂ incubator. On the day of assay, compounds were serially diluted in 100% DMSO to 300X the desired assay concentration. Growth media is aspirated off cells and replaced with 100 ul of load media (EMEM with Earl's salts w/L-Glutamine, 0.1% BSA, (Bovuminar Cohen Fraction V from Seriologicals Corp.), 4 uM Fluo-4-acetoxymethyl ester fluorescent indicator dye (Fluo-4 AM, from Molecular Probes), and 2.5 mM probenecid) and incubated for 1 hour at 37°C in CO₂ incubator. Load media was aspirated and replaced with 100 uL of EMEM with Earl's salts w/L-Glutamine, 0.1% gelatin, and 2.5 mM probenecid and incubated for an additional 10 min. Serially diluted compound (3 ul) in DMSO at 300X was transferred to a 96 well plate containing 297 micro liters of KRH (120 mM NaCl, 4.6mM KCl, 1.03 mM KH₂PO₄,

25 mM NaHCO₃, 1.0mM CaCl₂, 1.1mM MgCl₂, 11mM Glucose, 20 mM HEPES (pH 7.4)) w/ 2.5 mM probenecid and 0.1% gelatin (compound now at 3X). Media was aspirated off cells, and cells washed 3 times with KRH w/ 2.5 mM probenecid, w/ 0.1% gelatin. KRH (100 ul) w/ 2.5 mM probenecid with 0.1% gelatin was added to wells then 50 ul of 3X
5 compound in KRH w/ 2.5 mM probenecid and 0.1% gelatin was added to wells (compound now at 1X) and incubated at 37°C in CO₂ incubator for 10 min. Plates were placed onto FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale CA) for analysis as described previously (Sarau et al., 1999). The percent of maximal human IL-8 induced Ca²⁺ mobilization induced by 1.0 nM IL-8, an EC₈₀ conc. for CXCR2, was
10 determined for each concentration of compound and the IC₅₀ calculated as the concentration of test compound that inhibits 50% of the maximal response induced by 1.0 nM IL-8. Examples 1-38 exhibited positive inhibitory activity in this assay at IC₅₀ values of <10uM and would be considered active. Compounds 1-38 tested by the above assay had an IC₅₀ from about 6000nM to about 5nM.

15 The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the
20 present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

CLAIMS

1. A compound according to Formula (I):



wherein

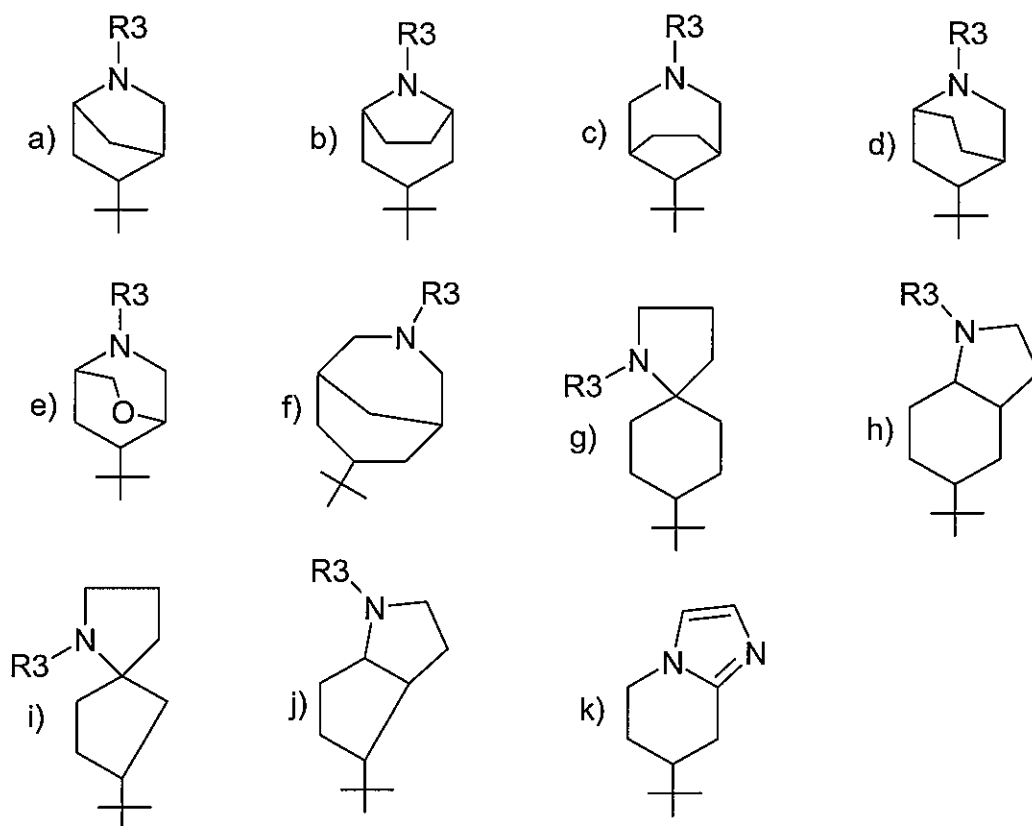
X is selected from the group consisting of halogen, C₁₋₃alkyl, C₁₋₃alkoxy, cyano, CF₃, and OCF₃;

R₂ is selected from the group consisting of C₃₋₆cycloalkyl, phenyl and heteroaryl, wherein the phenyl or heteroaryl moieties are optionally substituted, once or twice, independently, by a substituent selected from the group consisting of C₁₋₃alkyl, halogen, CF₃, OCF₃, phenoxy and benzyloxy; or

R₂ is phenyl substituted by methylenedioxy or phenyl substituted by (di-halo-substituted)-methylenedioxy;

R₁ is a C₄₋₈heterocyclyl(CH₂)_n - moiety -wherein the C₄₋₈heterocyclyl is an optionally substituted pyrrolidin-3-yl, piperidin-4-yl, piperidin-3-yl, or azetidin-3-yl, the heterocyclyl moieties being optionally substituted independently, once or twice, by a substituent selected from the group consisting of C₁₋₃alkyl, C(O)OR₄ and C(O)R₅; or

R₁ is selected from the following ring systems (a-k):



R⁴ and R⁵ are, independently, C₁₋₃alkyl;

n is 0 or 1; and

R³ is H or C₁₋₃alkyl;

or a pharmaceutically acceptable salt thereof,

wherein the compound is:

N-{4-chloro-2-hydroxy-3-[(3S)-3-piperidinylsulfonyl]phenyl}-N'-(3-fluoro-2-methylphenyl)urea, or

N-[4-chloro-2-hydroxy-3-(3-piperidinylsulfonyl)-phenyl]-N'-(3-fluoro-2-methylphenyl)urea,
a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein the pharmaceutically acceptable salt is a hydrochloride salt.

3. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier or diluent.