The present invention is directed to compounds of formula (I) compositions comprising them and their use.
NOVEL HETEROCYCLIC METHYLENE PIPERIDINE DERIVATIVES AND THEIR USE

The present invention relates to pharmaceutically active piperidine derivatives and their use as agonists of CC chemokine receptor activity, more specifically of CCR5 activity. Chemokines are chemotactic cytokines which play an important role in immune and inflammatory responses.

[BACKGROUND OF THE INVENTION]

The Chemokines comprise a large family of proteins which have common important structural features and which have the ability to attract leukocytes. The chemokine family is divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (CXC) and Cys-Cys (CC) subfamilies.

CC chemokine receptors are integral membrane proteins that specifically bind and respond to cytokines of the CC chemokine family. They represent one subfamily of chemokine receptors, a large family of G protein-linked receptors that are known as seven transmembrane (7-TM) proteins since they span the cell membrane seven times. To date, ten true members of the CC chemokine receptor subfamily have been described. These are named CCR1 to CCR10 according to the IUIS/WHO Subcommittee on Chemokine Nomenclature.

Among the CC chemokine receptors, CCR5 is defined as a major co-receptor implicated in susceptibility to HIV-I infection and disease. CCR5 is
a receptor expressed on several cell types including T-lymphocytes, peripheral blood-derived dendritic cells, CD34+ hematopoietic progenitor cells and certain activated/memory ThI lymphocytes.

Because of this well-known activity as HIV-I co-receptor, antagonists for CCR5 have been developed with the aim of inhibiting CCR5-mediated HIV entry. The most advanced of these, Maraviroc, from Pfizer, is in good way to obtain the final FDA approval for entry on the market.

In the prior art, such as in WO0276948, for example, blocking this receptor with a CCR5 antagonist or inducing receptor internalization with a CCR5 agonist was considered of great interest to protect cells from viral infection by HIV-I.

WO0276948 describe compounds having activity as pharmaceuticals, in particular as modulators (such as agonists, partial agonists, inverse agonists or antagonists) of chemokine receptor (especially CCR5) activity.

This invention proposes alternative compounds having activity as pharmaceuticals, in particular as modulators (such as agonists, partial agonists, inverse agonists or antagonists) of chemokine receptor (especially CCR5) for use in the treatment of autoimmune, inflammatory, infectious, proliferative, hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).
[SUMMARY OF THE INVENTION]

The invention encompasses compounds of general formula (I) and methods of use of such compounds or compositions as chemokine receptor modulators.

In a general aspect, the invention provides compounds of general formula I:

\[
\begin{array}{c}
\text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \\
\text{R}^4 \\ 
\text{X} \\
\text{A} \\
\text{N} \\
\text{L}^1 \\
\text{R}^5 \\
\end{array}
\]

and pharmaceutically acceptable salts and solvates thereof, wherein

A is -CH\(_2\)-CH\(_2\)- or absent;

R\(^1\) and R\(^2\) independently are H, halo, optionally substituted alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclyl;

R\(^3\) and R\(^4\) independently are a group selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl, each group being optionally substituted by one or more substituent(s) selected from halo, oxo, nitro, cyano, azido, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, thiol, alkylthio, thioalkyl, haloalkylthio, acyl,
thioacryl, aroyl, amino, alkylamino, aminoalkyl, carboxy, alkoxy carbonyl, cycloalkyl oxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, arylalkyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocyclylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkylcarbonylamoalkyl, acylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylc arbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, sulfino, alkylsulf inyl, sulfo, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsuf onyl, arylsulf onyl, heteroarylsulf onyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulf amoyl, alkylsulf onlamino, cycloalkylsulf onlamino, heterocyclylsulf onlamino, arylsulf onlamino, heteroarylsulf onlamino, and haloalkylsulf onlamino, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the cycloalkyl, aryl, or heterocyclyl group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl group, each of said group being optionally substituted by one or more further substituent(s) selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, and sulfonyl; more preferably, $R^3$ and $R^4$ independently are a group selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl, each group being optionally substituted by one or more
substituent(s) selected from halo, cyano, SO2R, or SO2NR'R' wherein R is an alkyl and R', R'' are H or alkyl;

L¹ is NRCO, NRSO₂, CO, CONR, CONRCH₂, CH₂CO, COCH₂CH₂CO, CH₂COCH₂, COCH₂CH₂, SO₂, SO₂NR, SO₂CH₂, SO₂CH₂CH₂, a single bond or a group selected from C₁-C₃ alkylene, C₂-C₄ alkenylene and C₂-C₄ alkynylene, each group being optionally substituted with one or more substituent(s) selected from alkyl, aryl, heteroaryl, halo, alkylcarbonyl, alkylamino, alkoxy, alkylcarbonylamino, and alkylcarbonylalkyl, wherein R is hydrogen or C₁-C₆ alkyl;

X is CR⁶ or N;

R⁵ is R⁷⁻L²⁻R⁸;

R⁶ is selected from hydrogen, hydroxyl, halo, C₁-C₆ alkyl, cyano, alkoxy, allyl, and COOR, wherein R is selected from hydrogen or C₁-C₃ alkyl, and CON'R'', wherein R' and R'' independently are selected from hydrogen and C₁-C₆ alkyl, with the proviso that CON'R'' is not CON(Me)₂;

R⁷ is a group selected from heteroaryl, and heterocyclyl, each group being optionally substituted by one or more substituent(s) selected from halo, oxo, nitro, cyano, azido, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, thiol, alkylthio, thioalkyl, haloalkylthio, acyl, thioacyl, aroyl, amino, alkylamino, aminoalkyl,
carboxy, alkoxycarbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, arylalkyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocyclylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkylcarbonylalkyl, acylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylalkyl, carbamoyl amino, alky carbamoylamino, sulfino, alkylsulfinyl, sulfo, alkylsulfonfyl, haloalkylsulfonfyl, cycloalkylsulfonfyl, heterocyclylsulf onyl, arylsulf onyl, heteroaryl sulf onyl, sulfamoyl, alkylsulfamoyl, arylsulf amoyl, heteroaryl sulf amoyl, alkylsulf onylamino, cycloalkylsulf onylamino, heterocyclylsulf onylamino, arylsulf onylamino, heteroaryl sulf onylamino, and haloalkylsulf onylamino, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the heteroaryl or heterocyclyl group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl group, each of said groups being optionally substituted by one or more further substituent(s) selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonfyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, and sulfonfyl; more preferably, R⁷ is a group selected from heteroaryl, and heterocyclyl, each group being optionally substituted by one or more substituent(s) selected from halo, cyano, SO₂R, or SO₂NR'R'' wherein R is an alkyl and
R', R'' are H or alkyl.

L²-R⁸ is

Absent; or

L² is a single bond or C₁-C⁴ alkylene, optionally substituted by one or more substituent(s) selected from halo, oxo, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl and alkoxy, or L² is CRᵃRᵇ, wherein Rᵃ and Rᵇ form together with the carbon to which they are attached a carbocycle having 3 to 6 ring atoms; and

R⁸ is a group selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl, each group being optionally substituted by one or more substituent(s) selected from halo, oxo, nitro, cyano, azido, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, thiol, alkylthio, thioalkyl, haloalkyl thio, acyl, thioacyl, aroyl, amino, alkylamino, aminoalkyl, carboxy, alkoxy carbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkycarbonyloxy, cycloalkyl carbonyloxy, heterocyclyl carbonyloxy, aryl carbonyloxy, heteroaryl carbonyloxy, aryl alkyl oxy, alkyl carbonylamino, haloalkyl carbonylamino, cycloalkyl carbonylamino, heterocyclyl carbonylamino, aryl carbonylamino, heteroaryl carbonylamino, alkyl carbonylaminoalkyl, acylamino, carbamoyl,
The invention also relates to the use of the above compounds or their pharmaceutically acceptable salts and solvates as modulators of CCR5, preferably as...
antagonists or agonists of CCR5, and even more preferably as agonists of CCR5.

The invention further provides methods for the treatment or prevention of autoimmune, inflammatory, infectious, proliferative, hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

[DETAILED DESCRIPTION OF THE INVENTION]

As noted above, the invention relates to compounds of formula I, as well as their pharmaceutically acceptable salts and solvates.

Preferred compounds of formula I and pharmaceutically acceptable salts and solvates thereof are those wherein

A is absent;

R₁ and R² independently are hydrogen or C₁-C₄ alkyl, preferably hydrogen, methyl or ethyl, and even more preferably hydrogen or methyl;

R₅ is R⁷-L²-R⁸;

R³, R⁴, R⁸, X and L¹ are as defined above in respect of general formula I;

L² is a single bond or C₁-C₄ alkylene;

R⁷ is defined as above in respect of Formula I, preferably R' is a five membered aromatic heterocycle having at least one carbon atom and 1 to 4 heteroatoms, which are independently selected from nitrogen, oxygen,
and sulphur each group being optionally substituted by
one or more substituent(s) selected from halo, oxo,
nitro, cyano, azido, alkyl, hydroxyalkyl, haloalkyl,
cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl,
heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl,
aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy,
haloalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy,
thiol, alkylthio, thioalkyl, haloalkylthio, acyl,
thioacyl, aroyl, amino, alkylamino, aminooalkyl,
carboxy, alkoxy carbonyl, cycloalkyloxy carbonyl,
heterocyclyloxy carbonyl, aryloxy carbonyl,
heteroaryloxy carbonyl, alkylcarbonyloxy,
cycloalky lcarbonyloxy, heterocyclylcarbonyloxy,
arylcarbonyloxy, heteroarylcarbonyloxy, arylalkyloxy,
selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, aribamo, ariloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarylbond, heterocyclyl, hydroxyl, nitro, oxo, and sulfonyl; more preferably, $R^7$ is a five membered aromatic heterocycle having at least one carbon atom and 1 to 4 heteroatoms, which are independently selected from nitrogen, oxygen, and sulfur optionally substituted by one or more substituent(s) selected from halo, cyano, $SO_2R$, or $SO_2NR'R''$ wherein $R$ is an alkyl and $R', R''$ are $H$ or alkyl.

Even more preferred compounds of Formula I and pharmaceutically acceptable salts and solvates thereof are those wherein

$A$ is absent;

$R^1$ is methyl;

$R^2$ is hydrogen;

$R^3$ and $R^4$ independently are a group selected from aryl, and heteroaryl, each group being optionally substituted by one or more substituent(s) selected from halo, oxo, nitro, cyano, azido, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylmalkyl, hydroxyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, thiol, alkylthio, thioalkyl, haloalkylthio, acyl, thioacyl, aroyl, amino, alkylamino, aminoalkyl, carboxy, alkoxycarbonyl, cycloalkyloxy carbonyl, heterocyclyloxy carbonyl, aryloxycarbonyl,
heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclcarbonyloxy, arylcarbonyloxy, heteroary1carbonyloxy, arylalkyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocyclcarbonylamino, arylcarbonylamino, heteroary1carbonylamino, alkylcarbonylaminoalkyl, acylamino, carbamoyl, hydroxycarbamoyl, alkyl carbamoyl, aryl carbamoyl, heteroaryl carbamoyl, carbamoylalkyl, carbamoylamino, haloalkyl carbamoylamino, sulfino, alkylsulf inyl, sulfo, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclsulfonyl, arylsulfonyl, heteroarylsulfonyl sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, heterocyclsulfonylamino, arylsulfonyl amino, heteroarylsulf onylamino, and haloalkylsulfonylamino, or two substituents form an alkyl enedioxy group or a haloalkylenedioxy group, or fused to the aryl, and heteroaryl groups may be one or more cycloalkyl, aryl, heterocycl or heteroaryl group, each of said groups being optionally substituted by one or more further substituent(s) selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroary1alkyl, heteroary1carbonyl, heterocycl, hydroxyl, nitro, oxo, and sulfonyl; more preferably, $R^3$ and $R^4$ independently are a group selected from aryl, heteroaryl, each group being optionally substituted by one or more substituent(s) selected from halo, cyano, S02R, or S02NR'R'' whereby R is an alkyl and $R'$, $R''$ are H or alkyl;
L² is NR, NR₂, CO, CONR, CONRCH₂, CH₂CO, COCH₂
CH₂CH₂CO, CH₂COCH₂, COCH₂CH₂, SO₂, SO₂NR, SO₂CH₂, SO₂CH₂CH₂,
a single bond or a group selected from C₁-C₃ alkenylene,
C₂-C₄ alkylene and C₂-C₄ alkylnylene, each group being
optionally substituted with one or more substituent (s)
selected from alkyl, aryl, heteroaryl, halo,
alkylcarbonyl, alkylamino, alkoxy, alkylcarbonylamino,
and alkylcarbonylalkyl, wherein R is hydrogen or C₁-C₉
alkyl;

X is CH or N;

R⁵ is R⁷-L²-R⁸;

R⁷ is a group selected from oxazolyl, oxadiazolyl, and
benzoxazolyl, each group being optionally substituted
by one or more substituent (s) selected from halo, oxo,
nitro, cyano, azido, alkyl, hydroxyalkyl, haloalkyl,
cycloalkyl, and cycloalkylalkyl;

L²-R⁸ is

Absent; or

L² is a single bond; and

R⁸ is defined as above in respect of formula I,
preferably R⁸ is a group selected from aryl,
heteroaryl, cycloalkyl, and heterocyclyl, each
group being optionally substituted by one or more
substituent (s) selected from OR', C₁-C₄ alkyl, NO₂,
Cl, F, OCF₃, CF₃, CN, COR', COCF₃, SO₂R', SO₂CF₃,
SO₂NR'R'', COR', CONR'R'', NR'SO₂R'', and NR'COR''
wherein R' and R'' independently are selected from
hydrogen and C₁-C₄ alkyl.
In one embodiment, preferred compounds of Formula I are those of Formula Ia:

\[
\begin{align*}
\text{R}^5 & \quad \text{N} \quad \text{R}^1 \\
\text{X} & \quad \text{L}^1 \quad \text{R}^3 \\
\text{R}^4 & 
\end{align*}
\]

and pharmaceutically acceptable salts and solvates thereof, wherein

- \( \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^8, \text{X}, \text{R}^1, \text{L}^1 \)
- are defined as above in respect of general formula I;

- \( \text{R}^1 \) is \( \text{H}, \text{halo}, \text{optionally substituted alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, or heterocyclyl} \); and

- \( \text{L}^1 \) is \( \text{NRCO, NRSO}_2, \text{CO, CONR, CONRCH}_2, \text{CH}_2\text{CO, COCH}_2\text{CH}_2\text{CO, CH}_2\text{COCH}_2, \text{COCH}_2\text{CH}_2, \text{SO}_2, \text{SO}_2\text{NR, SO}_2\text{CH}_2, \text{SO}_2\text{CH}_2\text{CH}_2, \) a single bond or a group selected from \( \text{C}_1-\text{C}_3 \) alkylene, \( \text{C}_2-\text{C}_4 \) alkenylene and \( \text{C}_2-\text{C}_4 \) alkynylene, each group being optionally substituted with one or more substituent(s) selected from alkyl, aryl, heteroaryl, halo, alkylcarbonyl, alkylamino, alkoxy, alkylcarbonylamino, and alkylcarbonylalkyl, wherein \( \text{R} \) is hydrogen or \( \text{C}_1-\text{C}_6 \) alkyl;

Preferred compounds of formula Ia are those wherein

- \( \text{R}^3, \text{R}^4, \text{R}^8, \text{X}, \text{L}^1 \) are as defined above in respect of general formula I;
R\(^1\) is hydrogen or C\(_1\)-C\(_4\) alkyl, preferably hydrogen, methyl or ethyl, and even more preferably hydrogen or methyl;

R\(^5\) is R\(^7\)-L\(^2\)-R\(^8\);

L\(^2\)-R\(^8\) is absent; or

L\(^2\) is a single bond or C\(_1\)-C\(_4\) alkylene;

R\(^7\) is defined as above in respect of Formula I, preferably R\(^7\) is a five membered aromatic heterocycle having at least one carbon atom and 1 to 4 heteroatoms, which are independently selected from nitrogen, oxygen, and sulphur each group being optionally substituted by one or more substituent (s) selected from halo, oxo, nitro, cyano, azido, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, thiol, alkylthio, thioalkyl, haloalkylthio, acyl, thioacyl, aroyl, amino, alkylamino, aminoalkyl, carboxy, alkoxy carbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkyl carbonyloxy, heterocyclylcarbonyloxy, aryl carbonyloxy, heteroaryl carbonyloxy, arylalkyl, alkoxy carbamoyl, alkoxy carbamoyl, haloalkyl carbamoyl, cycloalkyl carbamoyl, heterocyclyl carbamoyl, aryl carbamoyl, heteroaryl carbamoyl, carbamoyl, alkyl carbamoyl, aryl carbamoyl, heteroaryl carbamoyl, carbamoyl, alkyl carbamoyl, aryl carbamoyl, sulfino,
alkylsulf inyl, sulfo, alkylsulfonyl, haloalkylsulf onyl, cycloalkylsulf onyl, heterocyclylsulfonyl, arylsulf onyl, heteroarylsulf onyl sulfamoyl, alkylsulf amoyl, arylsulf amoyl, heteroarylsulf amoyl, alkylsulf onylamino, cycloalkylsulfonylamino, heterocyclylsulfonylamino, arylsulf onylamino, heteroarylsulf onylamino, and haloalkylsulf onylamino, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the five membered aromatic heterocycle group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl group, each of said groups being optionally substituted by one or more further substituent(s) selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, arylamino, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylamino, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, and sulfonyl.

In another embodiment, preferred compounds of formula I are those of formula Ib:

![Diagram](image)

and pharmaceutically acceptable salts and solvates thereof, wherein

R³, R⁴, X, L², and R⁸ are defined as above in respect of Formula I;

R¹ is H, halo, optionally substituted alkyl, aryl,
heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclyl;

R^1 is defined as above in respect of formula I, preferably L^1 is CO, CONH, CONHCH₂, CH₂CO, COCH₂CH₂CO, CH₂COCH₂, COCH₂CH₂, SO₂NH, SO₂CH₂, SO₂, SO₂CH₂CH₂,
a single bond or a group selected from C₁-C₃ alkyylene, C₂-C₄ alkenylene and C₂-C₄ alkynylene, each group being optionally substituted with one or more substituent(s) selected from alkyl, aryl, heteroaryl, halo, alkylcarbonyl, alkylamino, alkoxy, alkylcarbonylamino, and alkyl carbonyl alkyl; and

R⁷ is a five membered saturated, aromatic, or partially unsaturated heterocycle containing at least one carbon atom and 1 to 4 heteroatoms, which are independently selected from nitrogen, oxygen, and sulphur, said at least one carbon atom being optionally substituted by oxo or =S, wherein the heterocycle is optionally substituted by C₁-C₃ alkyl and/or the five membered saturated, aromatic, or partially unsaturated heterocycle is optionally fused to a five or six membered cycloalkyl, aryl, heterocyclyl or heteroaryl group, each of said groups being optionally substituted by one or more further substituent(s) selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroaryl carbonyl, heterocyclyl, hydroxyl, nitro, oxo, and sulfonyl.

Preferred compounds of formula Ib are those wherein

R³, R⁴, X, L¹, L², and R⁸ are defined as above in respect of Formula Ib;
R\(^1\) is hydrogen or C\(_1\)-C\(_4\) alkyl, preferably hydrogen, methyl or ethyl, and even more preferably methyl; and

R\(^7\) is a five membered aromatic heterocycle having at least one carbon atom and 1 to 4 heteroatoms, which are independently selected from nitrogen, oxygen, or sulphur, preferably 1 oxygen atom and 1 or 2 nitrogen atoms.

In still another embodiment, preferred compounds of formula I are those of formula Ic:

![Chemical Structure](image)

Ic

and pharmaceutically acceptable salts and solvates thereof, wherein

R\(^3\) \(_{R}\) R\(^4\), and X are defined as above in respect of Formula I;

R\(^1\) is hydrogen or C\(_1\)-C\(_4\) alkyl, preferably hydrogen, methyl or ethyl, and even more preferably methyl;

L\(^1\) is defined as above in respect of formula I, preferably L\(^1\) is CO, CONH, CONHCH\(_2\), CH\(_2\)CO, COCH\(_2\)
CH₂CH₂CO, CH₂COCH₂, COCH₂CH₂, SO₂NH, SO₂, SO₂CH₂, SO₂CH₂CH₂, a single bond or a group selected from C₁-C₃ alkylene, C₂-C₄ alkenylene and C₂-C₄ alkynylene, each group being optionally substituted with one or more substituent(s) selected from alkyl, aryl, heteroaryl, halo, alkylcarbonyl, alkylamino, alkoxy, alkylcarbonylamino, and alkyl carbonylalkyl;

สาระนี้เป็นกลุ่มที่สามารถเป็นการเชื่อมต่อหรือเป็นกลุ่มที่เลือกจาก Ci-C₃ alkylene, C₂-C₄ alkenylene และ C₂-C₄ alkynylene แต่ละกลุ่มสามารถถูกแทนที่ด้วยกลุ่มหนึ่งหรือมากกว่าหนึ่งที่เลือกจาก alkyl, aryl, heteroaryl, halo, alkylcarbonyl, alkylamino, alkoxy, alkylcarbonylamino, และ alkyl carbonylalkyl;

__U__ นี้เป็นการเลือกจาก CR°R¹, NR², O, C=O, C=S, หรือ S, ที่นั่น R° และ R¹ นั้นเป็นการเลือกจาก hydrogen และ C1-C3 alkyl;

__Y__ นี้เป็นการเลือกจาก CR°R¹, CR², NR², C=O, C=S, หรือ O, ที่นั่น R° และ R¹ นั้นเป็นการเลือกจาก hydrogen และ C1-C₃ alkyl;

__Z__ นี้เป็นการเลือกจาก CR³, C, หรือ N, ที่นั่น R³ นี้เป็นการเลือกจาก hydrogen และ C₁-C₃ alkyl;

__R₁⁰ และ R₁¹__ นี้เป็นการเลือกจาก OR¹, R¹, NO₂, Cl, F, CF₃, CN, SO₂R¹, SO₂CF₃, SO₂NR¹R¹, CONR¹'R¹, NR¹SO₂R¹', ที่นั่น R¹ และ R¹' นั้นเป็นการเลือกจาก hydrogen และ C₁-C₄ alkyl และ

__R₈__ นี้ถูกกำหนดไว้ที่เดิมในที่นี้ในความหมายของข้อความ I และสามารถเป็นกลุ่มที่เลือกจาก aryl, heteroaryl, cycloalkyl และ heterocyclyl แต่ละกลุ่มสามารถถูกแทนที่ด้วยกลุ่มหนึ่งหรือมากกว่าหนึ่งที่เลือกจาก OR¹, R¹, NO₂, Cl, F, CF₃, CN, SO₂R¹, SO₂CF₃, SO₂NR¹R¹, CONR¹'R¹, และ NR¹SO₂R¹', ที่นั่น R¹ และ R¹' นั้นเป็นการเลือกจาก hydrogen และ C₁-C₃ alkyl.

Preferred compounds of formula Ic are those wherein
R³ and R⁴, are defined as above in respect of Formula
Ic;

R¹ is hydrogen or Cl-C₄ alkyl, preferably hydrogen, methyl or ethyl, and even more preferably methyl;

L¹ is CO, CONH, CONHCH₂, CH₂CO, COCH₂CH₂CO, CH₂COCH₂, COCH₂CH₂, SO₂NH, SO₂, SO₂CH₂, SO₂CH₂CH₂, a single bond or a group selected from Cl-C₃ alkylene, C₂-C₄ alkenylene and C₂-C₄ alkynylene, each group being optionally substituted with one or more substituent(s) selected from alkyl, aryl, heteroaryl, halo, alkylcarbonyl, alkylamino, alkoxy, alkylcarbonylamino, and alkylcarbonylalkyl;

X is CH or N;

−−

is a double bond;

U is 0;

Y is CH or N, preferably N; and

Z is C.

Particularly preferred compounds of the invention are those listed in Table 1 hereafter:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
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<tbody>
<tr>
<td>1</td>
<td>![Structure Image]</td>
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<td></td>
<td>Chemical Structure</td>
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The compounds of formula I can be prepared by different ways with reactions known by the person skilled in the art. Reaction schemes I to VI. Example section), illustrate by way of example different possible approaches.

The invention further provides the use of the compounds of the invention or pharmaceutically acceptable salts or solvates thereof as modulators of chemokine receptor activity, especially as modulators of CCR5 activity. In a preferred embodiment the compounds of Formula I or pharmaceutically acceptable salts or solvates thereof are used as CCR5 antagonists or CCR5 agonists.

In still another embodiment the administration of agonists only, may be advantageous in comparison with the antagonist approach because a CCR5-
agonist may reduce the generation of certain types of HIV variants. Indeed, agonist molecules will promote CCR5 receptor disappearance from the cell surface by inducing its internalization. This would prevent the emergence of variants of the type able to bind the antagonist-bound CCR5, as previously observed for example with the small molecule antagonist Maraviroc (Westby M et al (2007) J Virol 81(5):2359-71). Avoiding generation of HIV variants, for example variants of the type able to bind the antagonist-bound CCR5, and therefore avoiding therapeutic resistance is one of the goal of this invention.

Accordingly, in a particularly preferred embodiment, the invention relates to the use of compounds of formula I, Ia, Ib and Ic or pharmaceutically acceptable salts or solvates thereof, as CCR5 agonists. Examples of such compounds are represented in Table 2:

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[APPLICATIONS]

The invention further provides methods for the treatment or prevention of autoimmune, inflammatory, infectious, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)); examples of these conditions are:

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

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

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasiculitides erythermas, cutaneaus eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);
(Allorgraft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung bone marrow, skin or cornea; or chronic graft versus host disease; and/or (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, inhibiting the entry of viruses into target cells, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematous, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Periotal disease, Sezary syndrome, idiopathic thrombocytopenia purpura, disorders of the menstrual cycle, glomerulonephritis or cerebral malaria, acute and chronic hepatitis B Virus (HBV) and HCV infection.

The treatment or prevention of these diseases comprises the administration of a therapeutically effective amount of a compound or pharmaceutically acceptable salt or solvate of the compounds of the invention, to a patient in need thereof. Preferably the patient is a warm-blooded animal, more preferably a human.

Preferred diseases are AIDS (HIV-1 or -2 infection), inflammatory and immunoregulatory disorders and diseases including asthma, pulmonary emphysema, allergic diseases and graft rejection as well as autoimmune pathologies such as rheumatoid arthritis, atherosclerosis, psoriasis, systemic lupus.
erythematous, ulcerative colitis, multiple sclerosis, glomerulonephritis, together with chronic obstructive pulmonary disease (COPD, including pulmonary fibrosis). Additional fields of application concern certain sort of metastatic cancers and renal diseases.

In a particular preferred embodiment the disease is AIDS (HIV-I or -2 infection).

The compounds of the present invention are also of value in inhibiting the entry of viruses (such as human immunodeficiency virus (HIV)) into target cells and, therefore, are of value in the prevention of infection by viruses (such as HIV), the treatment of infection by viruses (such as HIV) and the prevention and/or treatment of acquired immune deficiency syndrome (AIDS).

According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity, especially CCR5 receptor activity, in a patient, preferably a warm blooded animal, and even more preferably a human, in need of such treatment, which comprises administering to said animal an effective amount of compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof.

According to one embodiment, the compounds of the invention, their pharmaceutical acceptable salts or solvates may be administered as part of a combination therapy. Thus included within the scope of the present invention are embodiments comprising coadministration of, and compositions and medicaments which contain, in addition to a compound of the present invention, a
pharmacologically acceptable salt or solvate thereof as active ingredient, additional therapeutic agents and/or active ingredients. Such multiple drug regimens, often referred to as combination therapy, may be used in the treatment and prevention of any of the diseases or conditions mediated by or associated with CCR5 chemokine receptor modulation, particularly infection by human immunodeficiency virus, HIV. The use of such combinations of therapeutic agents is especially pertinent with respect to the treatment and prevention of infection and multiplication of the human immunodeficiency virus, HIV, and related pathogenic retroviruses within a patient in need of treatment or one at risk of becoming such a patient. The ability of such retroviral pathogens to evolve within a relatively short period of time into strains resistant to any monotherapy which has been administered to said patient is well known in the literature.

In addition to the requirement of therapeutic efficacy, which may necessitate the use of active agents in addition to the CCR5 chemokine receptor modulating compounds of Formula I or their pharmaceutical acceptable salts or solvates thereof, there may be additional rationales which compel or highly recommend the use of combinations of drugs involving active ingredients which represent adjunct therapy, i.e., which complement and supplement the function performed by the CCR5 chemokine receptor modulating compounds of the present invention. Such supplementary therapeutic agents used for the purpose of auxiliary treatment include drugs which, instead of directly treating or preventing a disease or condition
mediated by or associated with CCR5 chemokine receptor modulation, treat diseases or conditions which directly result from or indirectly accompany the basic or underlying CCR5 chemokine receptor modulated disease or condition. For example, where the basic CCR5 chemokine receptor modulated disease or condition is HIV infection and multiplication, it may be necessary or at least desirable to treat opportunistic infections, neoplasms, and other conditions which occur as the result of the immune-compromised state of the patient being treated. Other active agents may be used with the compounds of Formula I or their pharmaceutical acceptable salts or solvates thereof, e.g., in order to provide immune stimulation or to treat pain and inflammation which accompany the initial and fundamental HIV infection.

Thus, the methods of treatment and pharmaceutical compositions of the present invention may employ the compounds of Formula I or their pharmaceutical acceptable salts or solvates thereof in the form of monotherapy, but said methods and compositions may also be used in the form of multiple therapy in which one or more compounds of Formula I or their pharmaceutically acceptable salts or solvates are coadministered in combination with one or more other therapeutic agents such as those described in detail further herein.

Preferred combinations of the present invention include simultaneous, or sequential treatments with a compound of Formula I, or a pharmaceutical acceptable salt or solvate thereof, and one or more inhibitors of HIV protease and/or
inhibitors of HIV reverse transcriptase, preferably selected from the class of non-nucleoside reverse transcriptase inhibitors (NNRTI), including but not limited to nevirapine, delavirdine and efavirenz; from among the nucleoside/nucleotide inhibitors, including but not limited to zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, adefovir and dipivoxil; and from among the protease inhibitors, including but not limited to indinavir, ritonavir, saquinavir, nelfinavir, lopinavir, and amprenavir.

Other agents useful in the above-described preferred embodiment combinations of the present invention include current and to-be-discovered investigational drugs from any of the above classes of inhibitors, including but not limited to FTC, PMPA, fozivudinetidoxil, talviraline, S-1153, MKC-442, MSC-204, MSH-372, DMP450, PNU-140690, ABT-378, KNI-764, TMC120 and TMC125.

There is also included within the scope of the preferred embodiments of the present invention, combinations of a compound of Formula I, or a pharmaceutical acceptable salt or solvate thereof, together with a supplementary therapeutic agent used for the purpose of auxiliary treatment, wherein said supplementary therapeutic agent comprises one or more members independently selected from the group consisting of proliferation inhibitors, e.g., hydroxyurea; immunomodulators, e.g., sargramostim, and various forms of interferon or interferon derivatives; fusion inhibitors, e.g., AMD3100, T-20, T-1249, PRO-140, PRO-542, AD-349, BB-10010 and other chemokine receptor agonists/antagonists; tachykinin receptor
modulators, e.g., NKI antagonists; integrase inhibitors, e.g., AR177; RNaseH inhibitors; inhibitors of viral transcription and RNA replication; and other agents that inhibit viral infection or improve the condition or outcome of HIV-infected individuals through different mechanisms.

Preferred methods of treatment of the present invention for the prevention of HIV infection, or treatment of aviremic and asymptomatic subjects potentially or effectively infected with HIV, include but are not limited to administration of a member independently selected from the group consisting of:

(i) a compound within the scope of Formula I or a pharmaceutical acceptable salt or solvate thereof as disclosed herein,
(ii) one NNRTI in addition to a compound of (i);
(iii) two NRTI in addition to a compound of (i);
(iv) one NRTI in addition to the combination of (ii);
(v) a compound selected from the class of protease inhibitors used in place of a NRTI in combinations (iii) and (iv).

The preferred methods of the present invention for therapy of HIV-infected individuals with detectable viremia or abnormally low CD4 counts further include as a member to be selected: (vi) treatment according to (i) above in addition to the standard recommended initial regimens for the therapy of established HIV infections. Such standard regimens include but are not limited to an agent from the class of protease inhibitors in combination with two NRTIs; and (vii) a standard recommended initial regimens for the therapy of established HIV infections, where either the protease inhibitor component, or one or both of the
NRTIs is/are replaced by a compound within the scope of Formula I as disclosed herein.

The preferred methods of the present invention for therapy of HIV-infected individuals that have failed antiviral therapy further include as a member to be selected: (viii) treatment according to (i) above, in addition to the standard recommended regimens for the therapy of such patients; and (ix) a standard recommended initial regimens for the therapy of patients who have failed antiretroviral therapy, where either one of the protease inhibitor components, or one or both of the NRTIs is/are replaced by a compound within the scope of Formula I or a pharmaceutical acceptable salt or solvate thereof as disclosed herein.

Additional combinations for use according to the invention include combination of a compound of Formula I, or a pharmaceutical acceptable salt or solvate thereof with another CCR5 modulator, such as a CCR5 agonist; a CCR5 antagonist, such as N-(3R)-3-[3-(3-isopropyl-5-methyl-4H-1, 2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]~-l-phenylpropyl}-4,4-difluorocyclohexanecarboxamide; a CCR1 antagonist, such as BX-471; a beta adrenoceptor agonist, such as salmeterol; a corticosteroid agonist, such as fluticasone propionate; a LTD4 antagonist, such as asmontelukast; a muscarinic antagonist, such as tiotropium bromide; a PDE4 inhibitor, such as ascilomilast or roflumilast; a COX-2 inhibitor, such as asclecloxic, valdecoxib or rofecoxib; an alpha-2-delta ligand, such as gabapentin or pregabalin,- a beta-interferon, such as REBIF; a TNF receptor modulator, such as aTNF-alpha inhibitor (e.g.
adalimumab); a HMG CoA reductase inhibitor, such as a statin (e.g. atorvastatin); or an immunosuppressant, such as cyclosporine; or a macrolide such as tacrolimus.

In the above-described preferred embodiment combinations of the present invention, the compound of formula I, a pharmaceutically acceptable salt or solvate thereof and other therapeutic active agents may be administered in terms of dosage forms either separately or in conjunction with each other, and in terms of their time of administration, either serially or simultaneously. Thus, the administration of one component agent may be prior to, concurrent with, or subsequent to the administration of the other component agent(s).

The invention also provides pharmaceutical compositions comprising a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and at least one pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant. As indicated above, the invention also covers pharmaceutical compositions which contain, in addition to a compound of the present invention, a pharmaceutically acceptable salt or solvate thereof as active ingredient, additional therapeutic agents and/or active ingredients.

Another object of this invention is a medicament comprising at least one compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, as active ingredient.

The invention also provides the use of a compound of formula I or a pharmaceutically acceptable
salt or solvate thereof for the manufacture of a medicament. Preferably, the medicament is used for the treatment or prevention of autoimmune, inflammatory, infectious, proliferative or hyperproliferative diseases, or immunologically mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)); examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); pulmonary fibrosis; asthma (such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyperresponsiveness)); bronchitis (such as eosinophilic bronchitis); acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertonic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

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

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

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

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

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, inhibiting the entry of viruses into target cells, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia purpura, disorders of the menstrual cycle, glomerulonephritis or cerebral
 Preferred diseases are AIDS (HIV-I or -2 infection), inflammatory and immunoregulatory disorders and diseases including asthma, pulmonary emphysema, allergic diseases and graft rejection as well as autoimmune pathologies such as rheumatoid arthritis, atherosclerosis, psoriasis, systemic lupus erythematosus, ulcerative colitis, multiple sclerosis, glomerulonephritis, together with chronic obstructive pulmonary disease (COPD, including pulmonary fibrosis). Additional fields of application concern certain sort of metastatic cancers and renal diseases.

In a particular preferred embodiment the disease is AIDS (HIV-I or -2 infection).

The invention also provides the use of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for inhibiting the entry of viruses (such as human immunodeficiency virus (HIV)) into target cells and, therefore, for the prevention of infection by viruses (such as HIV), the treatment of infection by viruses (such as HIV) and the prevention and/or treatment of acquired immune deficiency syndrome (AIDS).

According to a further feature of the present invention there is provided the use of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for modulating chemokine receptor activity, especially CCR5 receptor activity, in a patient, in need of such
treatment, which comprises administering to said patient an effective amount of compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof.

Preferably, the patient is a warm-blooded animal, more preferably a human.

As set forth above, the compounds of the invention, their pharmaceutically acceptable salts or solvates may be used in monotherapy or in combination therapy, such as bi- or tritherapy. Thus, according to one embodiment, the invention provides the use of a compound of the invention for the manufacture of a medicament for at least one of the purposes described above, wherein said medicament is administered to a patient in need thereof, preferably a warm-blooded animal, and even more preferably a human, in combination with at least one additional therapeutic agent and/or active ingredient. The benefits and advantages of such a multiple drug regimen, possible administration regimens as well as suitable additional therapeutic agents and/or active ingredients are those described above.

Generally, for pharmaceutical use, the compounds of the inventions may be formulated as a pharmaceutical preparation comprising at least one compound of the invention and at least one pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds.

By means of non-limiting examples, such a formulation may be in a form suitable for oral
administration, for parenteral administration (such as by intravenous, intramuscular or subcutaneous injection or intravenous infusion), for topical administration (including ocular), for administration by inhalation, by a skin patch, by an implant, by a suppository, etc. Such suitable administration forms - which may be solid, semi-solid or liquid, depending on the manner of administration - as well as methods and carriers, diluents and excipients for use in the preparation thereof, will be clear to the skilled person; reference is made to the latest edition of Remington's Pharmaceutical Sciences.

Some preferred, but non-limiting examples of such preparations include tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, cremes, lotions, soft and hard gelatin capsules, suppositories, drops, sterile injectable solutions and sterile packaged powders (which are usually reconstituted prior to use) for administration as a bolus and/or for continuous administration, which may be formulated with carriers, excipients, and diluents that are suitable per se for such formulations, such as lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, polyethylene glycol, cellulose, (sterile) water, methylcellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, edible oils, vegetable oils and mineral oils or suitable mixtures thereof. The formulations can optionally contain other substances that are commonly
used in pharmaceutical formulations, such as lubricating agents, wetting agents, emulsifying and suspending agents, dispersing agents, desintegrants, bulking agents, fillers, preserving agents, sweetening agents, flavoring agents, flow regulators, release agents, etc... The compositions may also be formulated so as to provide rapid, sustained or delayed release of the active compound(s) contained therein.

The pharmaceutical preparations of the invention are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 0.05 and 1000 mg, and usually between 1 and 500 mg, of the at least one compound of the invention, e.g. about 10, 25, 50, 100, 200, 300 or 400 mg per unit dosage.

Usually, depending on the condition to be prevented or treated and the route of administration, the active compound of the invention will usually be administered between 0.01 to 100 mg per kilogram, more often between 0.1 and 50 mg, such as between 1 and 25 mg, for example about 0.5, 1, 5, 10, 15, 20 or 25 mg, per kilogram body weight day of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses, or essentially continuously, e.g. using a drip infusion.
[DEFINITIONS]

The definitions and explanations below are for the terms as used throughout the entire application, including both the specification and the claims.

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless indicated otherwise.

Where groups may be substituted, such groups may be substituted with one or more substituents, and preferably with one, two or three substituents. Substituents may be selected from but not limited to, for example, the group comprising halogen, hydroxyl, oxo, nitro, amido, carboxy, amino, cyano haloalkoxy, and haloalkyl.

As used herein the terms such as "alkyl, aryl, or cycloalkyl, each being optionally substituted with..." or "alkyl, aryl, or cycloalkyl, optionally substituted with..." encompasses "alkyl optionally substituted with...", "aryl optionally substituted with..." and "cycloalkyl optionally substituted with...".

The term "halo" or "halogen" means fluoro, chloro, bromo, or iodo.

The term "alkyl" by itself or as part of another substituent refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number greater than or equal to 1. Generally, alkyl groups of this invention comprise from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms, more preferably from 1 to 3 carbon...
atoms, still more preferably 1 to 2 carbon atoms. Alkyl
groups may be linear or branched and may be substituted
as indicated herein.

Suitable alkyl groups include methyl, ethyl,
5 n-propyl, i-propyl, n-butyl, i-butyl, s-butyl and t-
butyl, pentyl and its isomers (e.g. n-pentyl, iso-
pentyl), and hexyl and its isomers (e.g. n-hexyl, iso-
hexyl).

The term "hydroxyalkyl" includes but is not
10 limited to hydroxymethyl, 1-hydroxyethyl, 2-
hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 2-
hydroxy-2-methylethyl, 1-hydroxypropyl, 2-
hydroxypropyl, 3-hydroxypropyl, 1-hydroxybutyl, 2-
hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-
15 hydroxy-2-methylpropyl, 1-(hydroxymethyl)-2-
methylpropyl, 1,1-dimethyl-2-hydroxyethyl, 5-
hydroxypentyl, 2-methyl-3-hydroxypropyl, 3,4-
dihydroxybutyl, and so forth "Alkoxyalkyl" refers to an
alkyl group substituted with one to two \( R^b \), wherein \( R^b \)
is alkoxy as defined below. For example
heterocyclylalkyl refers to an alkyl group substituted
with one to two \( R^f \), wherein \( R^f \) is heterocyclyl as
defined below. For example, "aralkyl" or "arylalkyl"
refers to a substituted alkyl group as defined above
wherein at least one of the alkyl substituents is an
aryl as defined below, such as benzyl. For example,
"heteroarylalkyl" refers to a substituted alkyl group
as defined above, wherein at least one of the alkyl
substituents is a heteroaryl as defined below, such as
pyridinyl.
The term "haloalkyl" alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen as defined above. Non-limiting examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like.

The term "cycloalkyl" as used herein is a cyclic alkyl group, that is to say, a monovalent, saturated, or unsaturated hydrocarbyl group having 1 or 2 cyclic structures. Cycloalkyl includes monocyclic or bicyclic hydrocarbyl groups. Cycloalkyl groups may comprise 3 or more carbon atoms in the ring and generally, according to this invention comprise from 3 to 10, more preferably from 3 to 8 carbon atoms still more preferably from 3 to 6 carbon atoms. Examples of cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, with cyclopropyl being particularly preferred. An "optionally substituted cycloalkyl" refers to a cycloalkyl having optionally one or more substituent(s) (for example 1 to 3 substituent(s), for example 1, 2 or 3 substituent(s)), selected from those defined above for substituted alkyl. When the suffix "ene" is used in conjunction with a cyclic group, this is intended to mean the cyclic group as defined herein having two single bonds as points of attachment to other groups.

The term "cycloalkylalkyl" includes but is not limited to cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopentyl ethyl, 1-cyclohexyl ethyl, 2-
cyclopentylethyl, 2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl, 3-cyclopentylbutyl, cyclohexylbutyl and the like.

The term "alkenyl" as used herein refers to an unsaturated hydrocarbyl group, which may be linear or branched, comprising one or more carbon-carbon double bonds. Suitable alkenyl groups comprise between 2 and 6 carbon atoms, preferably between 2 and 4 carbon atoms, still more preferably between 2 and 3 carbon atoms. Examples of alkenyl groups are ethenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl and its isomers, 2-hexenyl and its isomers, 2,4-pentadienyl and the like. The term "alkynyl" as used herein refers to a class of monovalent unsaturated hydrocarbyl groups, wherein the unsaturation arises from the presence of one or more carbon-carbon triple bonds. Alkynyl groups typically, and preferably, have the same number of carbon atoms as described above in relation to alkenyl groups. Non limiting examples of alkynyl groups are ethynyl, 2-propynyl, 2-butynyl, 3-butynyl, 2-pentynyl and its isomers, 2-hexynyl and its isomers— and the like. The term "alkylene" includes methylene, ethylene, methylmethylene, propylene, ethylethylene, and 1,2-dimethylene. "Cycloalkylene" herein refers to a saturated homocyclic hydrocarbyl biradical of Formula \( \text{C}_n\text{H}_{2n-2} \). Cycloalkylene groups of this invention preferably comprise the same number of carbon atoms as their cycloalkyl radical counterparts.

Suitable cycloalkylene groups are \( \text{C}_{3-6} \) cycloalkylene group, preferably a \( \text{C}_{3-5} \) cycloalkylene (i.e. 1,3-cyclopropylene, 1,1-cyclopropylene, 1,1-cyclobutylene, 1,2-cyclobutylene, 1,3-cyclopentylene, or
1,1-cyclopentylene), more preferably a C3-4 cycloalkylene (i.e. 1,3-cyclopropylene, 1,1-cyclopropylene, 1,1-cyclobutylene, 1,2-cyclobutylene).

The terms "heterocyclyl" or "heterocyclo" as used herein by itself or as part of another group refer to non-aromatic, fully saturated or partially unsaturated cyclic groups (for example, 3 to 7 member monocyclic, 7 to 11 member bicyclic, or containing a total of 3 to 10 ring atoms) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen, oxygen and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system, where valence allows. The rings of multi-ring heterocycles may be fused, bridged and/or joined through one or more spiro atoms. Non-limiting exemplary heterocyclic groups include aziridinyl, oxiranyl, thiirany1, piperidinyl, azetidinyl, 2-imidazolinyl, pyrazolidinyl, imidazolidinyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidinyl, succinimidyl, 3H-indolyl, indoliny1, isoindoliny1, 2H-pyrroly1, 1-pyrroliny1, 2-pyrrol iny1, 3-pyrrol iny1, pyrrol idinyl, 4H-quinoliziny1, 2-oxopiperaziny1, piperaziny1, homopiperaziny1, 2-pyrazolinyl, 3-pyrazolinyl, tetrahydro-2H-pyran yl, 2H-pyran y1, 4H-pyran y1, 3,4-dihydro-2H-pyran yl, oxetany1, thietan y1, 3-dioxolany1, 1,4-dioxany1, 2,5-dioximidazolidinyl, 2-oxopiper idinyl,
2-oxopyrrolodinyl, indolinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydroisoquinolin-1-yl, tetrahydroisoquinolin-2-yl, tetrahydroisoquinolin-3-yl, tetrahydroisoquinolin-4-yl, thiomorpholin-4-yl, thioroformylpiperazinyl, and morpholin-4-yl.

The term "aryl" as used herein refers to a polyunsaturated, aromatic hydrocarbyl group having a single ring (i.e. phenyl) or multiple aromatic rings fused together (e.g. naphtyl) or linked covalently, typically containing 5 to 12 atoms; preferably 6 to 10, wherein at least one ring is aromatic. The aromatic ring may optionally include one to two additional rings (either cycloalkyl, heterocyclyl or heteroaryl) fused thereto. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated herein. Non-limiting examples of aryl comprise phenyl, biphenylyl, biphenylenyl, 5- or 6-tetralinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-azulenyl, naphthalen-1- or -2-yl, 4-, 5-, 6 or 7-indenyl, 1- 2-, 3-, 4- or 5-acenaphtylenyl, 3-, 4- or 5-acenaphthenyl, 1-, 2-, 3-, 4- or 10-phenanthryl, 1- or 2-pentalenyl, 4- or 5-indanyl, 5-, 6-, 7- or 8-tetrahydronaphthyl, 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl, 1-, 2-, 3-, 4- or 5-pyrenyl.

The term "arylene" as used herein is intended to include divalent carbocyclic aromatic ring systems such as phenylene, biphenylylene, naphthylene,
indenylene, pentalenylene, azulenylene and the like. Arylene is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthylene, 1,4-dihydronaphthylene and the like.

Where at least one carbon atom in an aryl group is replaced with a heteroatom, the resultant ring is referred to herein as a heteroaryl ring.

The term "heteroaryl" or "aromatic heterocycle" as used herein by itself or as part of another group refers but is not limited to 5 to 12 carbon-atom aromatic rings or ring systems containing 1 to 2 rings which are fused together or linked covalently, typically containing 5 to 6 atoms; at least one of which is aromatic, in which one or more carbon atoms in one or more of these rings is replaced by oxygen, nitrogen and/or sulfur atoms where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. Such rings may be fused to an aryl, cycloalkyl, heteroaryl or heterocyclyl ring. Non-limiting examples of such heteroaryl, include: pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxadiazolyl, thia triazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl, imidazo [2,1-b] [1,3] thiazolyl, thieno [3,2-b] furanyl, thieno [3,2-b] thiophenyl, thieno [2,3-d] [1,3] thiazolyl, thieno [2,3-d] imidazolyl, tetrazolo [1,5-a] pyridinyl,
indolyl, indolizinyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, isobenzothiophenyl, indazolyl, benzimidazolyl, 1,3-benzoazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, 1,3-benzothiazolyl, 1,2-benzoisothiazolyl, 2,1-benzoisothiazolyl, benzotriazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, thienopyridinyl, purinyl, imidazo[1,2-a]pyridinyl, 6-oxopyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 6-oxopyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 1,3-benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl.

The bonds from an asymmetric carbon in compounds of the present invention may be depicted herein using a solid line (—), a zigzag line (ΛΛΛΛ), a solid wedge (~~ ~), or a dotted wedge (~~~). The use of either a solid or dotted wedge to depict bonds from an asymmetric carbon atoms is meant to indicate that only the stereoisomer shown is meant to be included.

The compounds of the invention may also contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds from asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included, unless it is clear from the context that a specific stereoisomer is intended.

The compounds of the invention may be in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the compounds of formula I include the acid addition and base salts thereof. Suitable acid addition salts are formed from
acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts. Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts. Preferred, pharmaceutically acceptable salts include hydrochloride/chloride, hydrobromide/bromide, bisulphate/sulphate, nitrate, citrate, and acetate.

When the compounds of the invention contain an acidic group as well as a basic group the compounds of the invention may also form internal salts, and such compounds are within the scope of the invention. When the compounds of the invention contain a hydrogen-donating heteroatom (e.g. NH), the invention also covers salts and/or isomers formed by transfer of said hydrogen atom to a basic group or atom within the molecule.
Pharmaceutically acceptable salts of compounds of Formula I may be prepared by one or more of these methods:

(i) by reacting the compound of Formula I with the desired acid;

(ii) by reacting the compound of Formula I with the desired base,

(iii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of Formula I or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid; or

(iv) by converting one salt of the compound of Formula I to another by reaction with an appropriate acid or by means of a suitable ion exchange column.

All these reactions are typically carried out in solution. The salt, may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized.

The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

All references to compounds of formula I include references to salts, solvates, multi-component complexes and liquid crystals thereof and to solvates,
mult I-component complexes and liquid crystals of salts thereof.

The compounds of the invention include compounds of formula I as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) and isotopically-labeled compounds of formula I.

In addition, although generally, with respect to the salts of the compounds of the invention, pharmaceutically acceptable salts are preferred, it should be noted that the invention in its broadest sense also included non-pharmaceutically acceptable salts, which may for example be used in the isolation and/or purification of the compounds of the invention. For example, salts formed with optically active acids or bases may be used to form diastereoisomeric salts that can facilitate the separation of optically active isomers of the compounds of Formula I above.

The invention also generally covers all pharmaceutically acceptable predrugs and prodrugs of the compounds of Formula I.

The term "pro-drug" as used herein means the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting in vivo biotransformation product of the derivative is the active drug. Pro-drugs are characterized by increased bio-availability and are readily metabolized into the active inhibitors in vivo. The term "pre-drug", as used herein, means any compound that will be modified to form a drug species, wherein the
modification may take place either inside or outside of
the body, and either before or after the pre-drug
reaches the area of the body where administration of
the drug is indicated.

The term "patient" refers to a warm-blooded
animal, more preferably a human, who/which is awaiting
or receiving medical care or is or will be the object
of a medical procedure.

The term "human" refers to subject of both
genders and at any stage of development (i.e. neonate,
infant, juvenile, adolescent, adult).

The term "transplant" refers to the grafting,
implantation or transplantation of organs, tissues,
cells (e.g., bone marrow) and/or biocompatible
materials onto or into the body of an animal. The term
encompasses the transfer of tissues from one part of
the animal's body to another part and the transfer of
organs, tissues, and/or cells obtained from a donor
animal (either directly or indirectly such as an organ
or tissue produced in vitro by culturing cells obtained
from the animal) into a recipient animal. The animal is
suitably a warm-blooded vertebrate, is typically a
mammal, and is especially a primate (e.g., a human).
The term "transplant rejection" means any immune
reaction in the recipient directed against grafted
organs, tissues, cells, and/or biocompatible materials.

The term "therapeutically effective amount"
(or more simply an "effective amount") as used herein
means the amount of active agent or active ingredient
(e.g., chemokine receptor CCR5 modulator, i.e. a CCR5
agonist or a CCR5 antagonist, especially a CCR5
agonist) which is sufficient to achieve the desired therapeutic or prophylactic effect in the individual to which it is administered.

The term "administration", or a variant thereof (e.g., "administering"), means providing the active agent or active ingredient (e.g., a CCR5 modulator), alone or as part of a pharmaceutically acceptable composition, to the patient in whom/which the condition, symptom, or disease is to be treated or prevented.

By "pharmaceutically acceptable" is meant that the ingredients of a pharmaceutical composition are compatible with each other and not deleterious to the recipient thereof.

The term "agonist" as used herein means a ligand that activates an intracellular response when it binds to a receptor. An agonist according to the invention may promote internalization of a cell surface receptor such that the cell surface concentration of a receptor is decreased or remove.

The term "antagonist" as used herein means a ligand which competitively binds to a receptor at the same site as an agonist, but does not activate an intracellular response initiated by an active form of the receptor. An antagonist thereby inhibits the intracellular response induced by an agonist.

The term "pharmaceutical vehicle" as used herein means a carrier or inert medium used as solvent or diluent in which the pharmaceutically active agent is formulated and/or administered. Non-limiting examples of
pharmaceutical vehicles include creams, gels, lotions, solutions, liposomes.

The present invention will be better understood with reference to the following examples. These examples are intended to represent specific embodiments of the invention, and are not intended as limiting the scope of the invention.

[EXAMPLES]

CHEMISTRY EXAMPLES

All temperatures are expressed in °C and all reactions were carried out at room temperature unless otherwise stated.

Analytical thin layer chromatography (TLC) was used to monitor reactions, establish flash chromatography conditions and verify purity of intermediates or final products. TLC plates used were Merck TLC aluminium sheet silica gel 60 F\textsubscript{254} purchased from VWR International. TLC plates were revealed using ultraviolet irradiation (wavelength=254nm) at room temperature or bromocresol green spray reagent at 0.1% in propan-2-ol purchased from VWR International upon heating at 160°C or KMnO\textsubscript{4} revelator upon heating at 160°C. The KMnO\textsubscript{4} revelator was prepared by dissolving 3g of potassium permanganate, 20g of sodium carbonate, 0.5g of sodium hydroxide in 100mL of distilled water.

HPLC-MS spectra were obtained on Waters instruments using Electrospray ionization (ESI). Samples are injected by a Waters 2767 sample manager. A Waters 2525 binary pump module is linked to a Waters
2996 photodiode array detector and a Waters micromass ZQ-2000. The column used is a Sunfire C18 5µ; 4.6 * 50mm. Eluent is a mixture of solution A (0.1% TFA in H₂O) and solution B (0.1% TFA in ACN): 5% solution B for 1min, gradient from 5% solution B to 95% solution B over 4 min, 95% solution B for 0.2 min and 5% solution B for 0.8min.

¹H and ¹³C NMR spectra were recorded on a Bruker 300MHz. Chemical shifts are expressed in parts per million, (ppm, δ units). Coupling constants are expressed in Hertz units (Hz). Splitting patterns describe apparent multiplicities and are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad).

Solvents, reagents and starting materials were purchased from well known chemical suppliers such as for example Sigma Aldrich, Acros Organics, Eurisotop, VWR International, Sopachem and Polymer labs and the following abbreviations are used

ACN : Acetonitrile,
DCM : Dichloromethane,
DMF : N,N-dimethylformamide,
EtOAc: Ethyl acetate,
EtOH : Ethanol,
HOBr : 1-hydroxybenzotriazole,
MeOH : Methanol,
RT : Room temperature,
TEA : Triethylamine,

TBTU : 0-(1H-Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate,

Y : Yield,

5 g : Grams,

mg : Milligrams,

L : Liters,

mL : Milliliters,

µL : Microliters,

10 mol : Moles,

mmol : Millimoles,

h : Hours,

min : Minutes,

TLC : Thin layer chromatography,

15 MW : Molecular weight,

eq : Equivalent,

µwave : Microwave,

THF : Tetrahydrofuran,

TFA : Trifluoroacetic acid,

20 Ac : Acetyl,

EDC : 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.
SCHEME I

Conditions:
i) $K_2CO_3$, nBu$_3$NI, DMF
ii) NH$_2$OH in water, EtOH, reflux
iii) $K_2CO_3$, MeOH, Toluene, 130°C under microwave irradiation
SCHEME II

Conditions:
i) NH₂OH in water, EtOH, reflux
ii) K₂CO₃, MeOH, Toluene, 130°C under microwave irradiation,
iii) HCl, dioxane 40°C
iv) NaBH₃(OAc)₃, AcOH, DCM
**SCHEME III**

\[
\begin{align*}
\text{O-SO}_2-\text{N} & \xrightarrow{\text{i)}} \text{O-SO}_2-\text{NH}_2^	ext{+} \text{ON} \\
\text{MeSO}_2-\text{N} & \xrightarrow{\text{iii)}} \text{MeSO}_2-\text{N} \\
\text{MeSO}_2-\text{N} & \xrightarrow{\text{iv)}} \text{MeSO}_2-\text{N} \\
\text{MeSO}_2-\text{N} & \xrightarrow{\text{v)}} \text{MeSO}_2-\text{N} \\
\text{MeSO}_2-\text{N} & \xrightarrow{\text{vi)}} \text{MeSO}_2-\text{N}
\end{align*}
\]

**Conditions:**
- i) NH₂OH in water, EtOH, reflux
- ii) K₂CO₃, MeOH, Toluene, 130°C under microwave irradiation
- iii) HCl, dioxane 40°C
- iv) NaI, DIEA, ACN
- v) SOCl₂, toluene
- vi) NaI, DIEA, ACN, 160°C under microwave irradiation
SCHEME IV

Conditions:

i) \( \text{NH}_2\text{OH in water, EtOH, reflux} \)

ii) \( \text{K}_2\text{CO}_3, \text{MeOH, Toluene, 130°C under microwave irradiation} \)

iii) \( \text{HCl, dioxane 40°C} \)

iv) \( \text{Nal, DIEA, ACN, 160°C under microwave irradiation} \)

v) \( \text{SOCl}_2, \text{toluene,} \)

vi) \( \text{Nal, DIEA, ACN, 160°C under microwave irradiation} \)

vii) \( \text{Nal, DIEA, ACN, 160°C under microwave irradiation} \)
**SCHEME V**

1. $\text{NH}_2\text{OH}$ in water, EtOH, reflux
2. $\text{K}_2\text{CO}_3$, MeOH, Toluene, 130°C under microwave irradiation,
3. HCl, dioxane 40°C
4. NaI, DIEA, ACN, 160°C under microwave irradiation
5. SOCl$_2$, toluene
6. NaI, DIEA, AC, 160°C under microwave irradiation
7. HOBr, TBTU, TEA, DMF
SCHEME VI

Conditions:
i) \( \text{K}_2\text{CO}_3, \text{nBu}_4\text{Ni, DMF} \)
ii) \( \text{NaOH, H}_2\text{O, EtOH} \)
iii) \( \text{MeSO}_3\text{H, toluene, 130 °C under microwave irradiation} \)
Synthesis of intermediate 1: \(\text{[1-(3,3-diphenyl-propyl)-piperidin-4-yl]-acetic acid methyl ester}\)

To a solution of piperidine-4-acetic acid methyl ester (2.4 g; 15.1 mmol) in ACN (100 ml) was added 3,3-diphenylpropyl bromide (5.0 g; 18.2 mmol), tetrabutylammonium iodide (558 mg; 1.51 mmol) and potassium carbonate (6.28 g; 45.4 mmol). The mixture was refluxed overnight. The reaction mixture was cooled and filtered over silica gel and concentrated. The residue was purified by silica gel chromatography (eluent: DCM and MeOH/DCM: 5/95) to afford after dry evaporation under vacuum the title intermediate as an Oil (3.0 g; Y: 57%).

\[\text{MS: } (M+H)^+ = 352.\]

Synthesis of intermediate 2: \(\text{[1-(3,3-Diphenyl-propyl)-piperidin-4-yl]-acetic acid}\)

To a solution of 1-(3,3-diphenyl-propyl)-piperidine-4-carboxylic acid methyl ester (3.0 g; 8.6 mmol) in an EtOH/Water 1/1 mixture (80 ml) was added sodium
hydroxide (6 eq). The reaction mixture was stirred overnight at RT. Water was added and the mixture was extracted with DCM. The aqueous phase was collected, acidified with HCl (1M), and extracted with EtOAc. The organic layer was dried with MgSO4 and then concentrated under vacuum to afford the title intermediate (1.8 g; Y: 62%).

MS: (M+H)+ = 338.

Synthesis of intermediate 3: 2-[1-(3,3-Diphenyl-propyl)-piperidin-4-yl]-acetamide

To the vessel were added [1-(3,3-diphenyl-propyl)-piperidin-4-yl]-acetic acid (149.6 mg, 0.4 mmol), TBTU (141.3 mg, 0.44 mmol), HOBt (67.4 mg, 0.44 mmol), and TEA (278 µL, 2 mmol) in DMF (2 mL). To the mixture was added aq. ammonium hydroxide (300 µL). The mixture was stirred at RT for 1 hr and then concentrated under vacuum. The residue was diluted in DCM and washed (3 x) in aq. NaHCO3. The mixture was transferred to PEAX column, eluted with MeOH. The mixture was then transferred to a SCX column, eluted with MeOH. The title compound was eluted with a solution of MeOH/NH4OH (4 mL, 20/1). The organic layer was then concentrated under vacuum to afford the title intermediate (50 mg; Y: 37%).

MS: (M+H)+ = 337.
Synthesis of intermediate 4: \([1-(3,3\text{-diphenyl-propyl)}-piperidin-4-yl] -acetonitrile\)

![Chemical Structure](image)

Thionyl chloride (3 eq) was added to a solution of 2-[1-((3,3-diphenyl-propyl)-piperidin-4-yl)]-acetamide (39.8 mg, 0.118 mmol) in 1 mL anhydrous toluene and 500 µL THF. The resultant mixture was heated under reflux for 2 hrs. The crude was concentrated under vacuum. The residue was diluted in DCM/Aq. NaHCO₃ and extracted with DCM. The organic layer was dried with MgSO₄ and then concentrated under vacuum to afford the title intermediate (37 mg; Y: 95%).

**MS:** \( (M+H)^+ = 315 \)

Synthesis of intermediate 5: \([1-(3,3\text{-Diphenyl-propyl})-piperidin-4-yl] -acetic acid hydrazide\)

![Chemical Structure](image)

A vial was charged with a stir bar, hydrazine monohydrate (1 mL, 20.6 mmol) and [1-(3,3-diphenyl-propyl)-piperidin-4-yl] -acetic acid ethyl ester (365 mg, 1 mmol) in methanol (1 mL). The reaction vessel was sealed and heated to 80°C for 95 min under microwave (200W). After cooling the reaction vessel was uncapped and the mixture was evaporated under vacuum. The
residue was diluted in DCM/Aq. NaNHCO3 and extracted (3x) with DCM. The organic layer was washed with aq. NaHCO3, transferred to a phase separator cartridge, and then evaporated under vacuum to afford the title intermediate as a yellow pale oil (364 mg; Y: 97%).

MS: (M+H)+ = 315.

**Synthesis of intermediate 6:** [1-(2-diphenylamino-ethyl)-piperidin-4-yl]-acetic acid methyl ester

To a solution of piperidine-4-acetic acid methyl ester (162.8 mg; 1.04 mmol), in ACN (4 ml) was added (2-Chloro-ethyl)-diphenyl-amine (J. Med. Chem. 1992, 35, 1042-1049) (240 mg; 1.04 mmol), tetrabutylammonium iodide (38.4 mg; 0.11 mmol) and potassium carbonate (430 mg; 3.11 mmol). The mixture was refluxed during 3 days. The reaction mixture was cooled and filtered over silica gel and concentrated. The residue was purified by silica gel chromatography (eluent: DCM and MeOH/DCM : 5/95) to afford after dry evaporation the title intermediate as an oil (128 mg; Y: 35%).

MS: (M+H)+ = 353.
Synthesis of intermediate 7: 1-(2-diphenylamino-ethyl)-piperidine-4-acetic acid dihydrochlorid salt

The resin Amberlyst® A26(OH) (1.3 g) was added to a solution of 1-(2-diphenylamino-ethyl)-piperidine-4-acetic acid methyl ester (128 mg; 0.36 mmol) in MeOH (2 ml). The reaction mixture was stirred at room temperature overnight. The mixture was filtered and washed 3 times with MeOH and 3 times with ACN. The resin was added to a solution of ACN (1 ml) and aqueous 1 M HCl (4 ml). The mixture was stirred for 3 hours. The mixture was filtered and washed 3 times with ACN. The residue was evaporated to give the title intermediate as an oil (87 mg; Y: 73%).

MS; (M+H)+ = 339.

Synthesis of intermediate 8: 4-[3-(4-Methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester
To a solution of N-Hydroxy-4-methanesulfonylbezπzamide (1 mmol) in a mixture of methanol (5 ml) and toluene (5 ml) was added the 4-Methoxycarbonylmethyl-piperidine-1-carboxylic acid tert-butyl ester (1 mmol) and K$_2$CO$_3$ (5 mmol). The reaction mixture was heated during one hour at 130°C under microwave irradiation. Water was added to the reaction mixture and the mixture was extracted with DCM (3 times). The combined organics were washed with an aqueous solution of NaHCO$_3$ and water and dried (MgSO$_4$). The residue was purified by silica gel chromatography (eluent: DCM and MeOH/DCM: 5/95) to afford after dry evaporation the title intermediate.

Synthesis of intermediate 9: 4-[3-(4-Methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidine hydrochloride salt

To a solution of 4-[3-(4-Methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester (0.77 mmol) in 5 mL of ethanol, was added hydrogen chloride in dioxane (4M solution) (2.5 mL, 10 mmol, 15 eq). The reaction mixture was stirred for 2.5 hours at 40°C and then concentrated under vacuum to afford the title intermediate (217 mg, Y: 88%). MS: (M+H)$^+$ = 322.
Synthesis of intermediate 10: 2-(4-[3-(4-Methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-1-yl)-ethanol

To a solution of 2-(4-cyano-phenyl)-N-piperidin-4-yl-acetamide 4-[3-(4-Methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidine hydrochloride salt (179 mg, 0.5 mmol) in ACN (19 mL) were added 2-chloroethanol (40 mg; 0.5 mmol), powdered sodium iodide (75 mg; 0.5 mmol) and DIEA (165 µL; 1 mmol). The mixture was heated at 150°C for 25 minutes then filtered over silica gel and concentrated under reduce pressure to afford the title intermediate.

Synthesis of intermediate 11: 1-(2-Chloro-ethyl)-4-[3-(4-Methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidine

To a solution of 2-(4-[3-(4-Methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-1-yl)-ethanol (0.4 mmol) in anhydrous toluene (0.5 mL) was added
while stirring a solution of thionyl chloride (60 µL, 0.85 mmol) in anhydrous toluene (0.5 mL) so that the temperature remained between 25 and 30°C. The reaction was stirred overnight at RT and then concentrated under reduce pressure. The hydrochloride salt was scratched in Et₂O, filtered and washed with Et₂O to afford the title intermediate. 

\[(M+H)^+ = 384\]

Synthesis of intermediate 12: 4-[2-\{4-[3-(4-Methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-1-yl\}-ethyl]-phenyl-amine

A mixture of 1-(2-Chloro-ethyl)-4-[3-(4-methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidine (0.3 mmol), aniline (0.6 mmol), powdered sodium iodide (88.4 mg, 0.59 mmol) and DIEA (204 µL, 1.18 mmol) in ACN (1 mL) were heated at 100 °C for 10 minutes in a microwave. The crude reaction mixture was filtered through a cotton wool plug and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent: DCM/MeOH) to afford after dry evaporation under vacuum the title intermediate.
Synthesis of intermediate 13: (3-Fluoro-phenyl) - (2-([3- (4-methanesulfonyl-phenyl) -[1,2,4] oxadiazol-5-ylmethyl] -piperidin-1-yl) -ethyl) -amine

A mixture of 1-(2-Chloro-ethyl) -4- [3- (4-methanesulfonyl-phenyl) -[1,2,4] oxadiazol-5-ylmethyl] -piperidine (0.3 mmol), 3-fluoroaniline (0.6 mmol), powdered sodium iodide (88.4 mg, 0.59 mmol) and DIEA (204 µL, 1.18 mmol) in ACN (1 ml) were heated at 100 ºC for 10 minutes in a microwave. The crude reaction mixture was filtered through a cotton wool plug and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent : DCM/MeOH) to afford after dry evaporation under vacuum the title intermediate.
Synthesis of intermediate 14: (4-Methanesulfonyl-phenyl)-(2-{4-[3-(4-methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-1-yl}-ethyl)-amine

A mixture of 1-(2-chloro-ethyl)-4-[3-(4-methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidine (0.3 mmol), 4-methanesulfonylaniline (0.6 mmol), powdered sodium iodide (88.4 mg, 0.59 mmol) and DIEA (204 µL, 1.18 mmol) in ACN (1 ml) were heated at 100 °C for 10 minutes in a microwave. The crude reaction mixture was filtered through a cotton wool plug and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent: DCM/MeOH) to afford after dry evaporation under vacuum the title intermediate.

Synthesis of intermediate 15: 1-methanesulfonyl-piperidine-4-carbonitri Ie

To a stirred solution of 4-cyanopiperidine (500 mg, 4.54 mmol) and TEA (945 µL, 6.81 mmol) in dry DCM (10
mL) at 0°C, was carefully added methanesulfonylchloride (422 µL, 5.45 mmol). The reaction mixture was stirred overnight at RT, and concentrated under reduced pressure. The crude was dissolved in DCM and washed several times with a saturated aqueous solution of NaHCO₃. The organic layer was extracted, dried over MgSO₄ and concentrated under vacuum to afford the title intermediate.

Synthesis of intermediate 16: 4-cyano-piperidine-1-carboxylic acid tert-butyl ester

To a stirred solution of 4-cyanopiperidine (500 mg, 4.54 mmol) and TEA (945 µL, 6.81 mmol) in dry DCM (10 mL) at 0°C, was carefully added di-tertbutyldicarbonate (1.19 g, 5.45 mmol). The reaction mixture was stirred overnight at RT, and concentrated under reduced pressure. The crude was dissolved in DCM and washed several times with a saturated aqueous solution of NaHCO₃. The organic layer was extracted, dried over MgSO₄ and concentrated under vacuum to afford the title intermediate.
Synthesis of intermediate 17: 2-[1-[(3,3-diphenyl-propyl)-piperidin-4-yl]-N-hydroxy-acetamidine

A solution of hydroxyl amine (0.1 mmol) 50% in water was added to a solution of [1-[(3,3-diphenyl-propyl)-piperidin-4-yl]-acetonitrile (0.1 mmol) in EtOH (1 ml). The reaction mixture was heated at reflux overnight. The resulting mixture was concentrated and dry under vacuum to afford the title intermediate.

Synthesis of intermediate 18: thiobenzimidic acid methyl ester

A mixture containing thiobenzamide (500 mg, 3.65 mmol) and iodomethane (272 µL, 4.38 mmol) in acetone (10 mL) was heated at reflux for 5 hrs. The crude was evaporated under vacuum to afford the title intermediate. The reaction was quantitative. (551 mg).
General Method A: amidoxime preparation

A solution of hydroxylamine (10 mmol) 50% in water was added to a solution of R-CN (10 mmol) in EtOH (10 ml). The reaction mixture was heated at reflux overnight. The resulting mixture was concentrated and dry under vacuum to afford the different amidoximes (Table 3). Intermediates of the invention that were synthesized according to General Method A are listed in Table 3 below:

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>Structure</th>
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| 30 | ![Chemical Structure 30](image)
| 31 | ![Chemical Structure 31](image)
| 32 | ![Chemical Structure 32](image)
| 33 | ![Chemical Structure 33](image)
| 34 | ![Chemical Structure 34](image)
| 35 | ![Chemical Structure 35](image)
| 36 | ![Chemical Structure 36](image)
| 37 | ![Chemical Structure 37](image)
| 38 | ![Chemical Structure 38](image)
| 39 | ![Chemical Structure 39](image)
| 40 | ![Chemical Structure 40](image)
| 41 | ![Chemical Structure 41](image)
| 42 | ![Chemical Structure 42](image)
| 43 | ![Chemical Structure 43](image)
| 44 | ![Chemical Structure 44](image)
| 45 | ![Chemical Structure 45](image)
| 46 | ![Chemical Structure 46](image)
| 47 | ![Chemical Structure 47](image)
General Method B: Synthesis of 1,2,4-oxadiazole

To a solution of the intermediate amidoxime (0.2 mmol) in a mixture of methanol (1 ml) and toluene (1mI) was added the 1-(3,3-diphenyl-propyl)-piperidin-4-yl]-acetic acid methyl ester (0.2 mmol) and K₂CO₃ (1 mmol). The reaction mixture was heated during one hour at 130°C under microwave irradiation. Water was added to the reaction mixture and the mixture was extracted with AcOEt (3 times). The combined organics were washed with an aqueous solution of NaHCO₃ and water and dried (MgSO₄). The residue was purified by silica gel chromatography (eluent: DCM and MeOH/DCM : 5/95) to afford after dry evaporation the different compounds. (Table 4).

Compounds of the invention that were synthesized according to General Method B are listed in Table 4 below:

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<td>48</td>
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</tbody>
</table>
General Method C:

A mixture of l-(2-Chloro-ethyl)-4-[3-(4-methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidine (0.1 mmol), amine : RR'NH (0.2 mmol), powdered sodium iodide (44.2 mg, 0.3 mmol) and DIEA (100 µL, 0.6 mmol) in acetonitrile (1 ml) were heated at 100 °C for 10 minutes in a microwave. The crude reaction mixture was filtered through a cotton wool plug and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent: DCM/MeOH) to afford after dry evaporation under vacuum the different compounds. Compounds of the invention that were synthesized according to General Method C are listed in Table 5 below:

Table 5

<table>
<thead>
<tr>
<th>Compound</th>
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<tbody>
<tr>
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<td>56</td>
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<tr>
<td></td>
<td><img src="image3" alt="Molecule 56" /></td>
</tr>
</tbody>
</table>
A mixture of (2-{4- [3- (4-methanesulfonyl -phenyl) -[1,2,4] oxadiazol-5-ylmethyl] -piper idin-1-yl} -ethyl) -phenyl-amine (0.1 mmol), Alkyl-halide R-X (0.1 mmol), powdered sodium iodide (44.2 mg, 0.3 mmol) and DIEA (100 µL, 0.6 mmol) in acetonitrile (1 ml) were heated at 100 °C for 10 minutes in a microwave. The crude reaction mixture was filtered through a cotton wool plug and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent : DCM/MeOH) to afford after dry evaporation under vacuum the different compounds. (Table 6). Compounds of the invention that were synthesized according to General Method D are listed in Table 6 below:

Table 6

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>![Structure Image]</td>
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</tbody>
</table>
General Method Ξ:

To a mixture of (2-{4-[[3-(4-methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-1-yl]-ethyl}-phenyl-amine (0.11 mmol), TEA (30.5 µL, 0.22 mmol) in DCM (1 ml) was added dropwise at 0°C the acid chloride RCO-Cl (14.8 µL, 0.11 mmol). The mixture was then stirred overnight at RT. The crude reaction mixture was washed with a saturated aqueous NaHCO₃ solution, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: DCM/MeOH) to afford after dry evaporation under vacuum the different compounds. Compounds of the invention that were synthesized according to General Method Ξ are listed in Table 7 below:
Table 7

<table>
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<th>Compound</th>
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<td>61</td>
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<tr>
<td>62</td>
<td><img src="image4" alt="Structure 62" /></td>
</tr>
</tbody>
</table>
Synthesis of compound 51: 4-\{4-\[3-\{(4\text{-}methanesulfonyl-}
\text{-}
\text{phenyl})\]-\[1,2,4\]oxadiazol-5-ylmethyl\] -piperidin-1-yl\} -
2,2-di\text{phenyl}-butyronitrile

To a solution of piperidine-4-acetic acid methyl ester (2.4 g; 15.1 mmol) in ACN (100 ml) was added 4-bromo-2,2-diphenyl-butyronitrile (5.3 g; 18.2 mmol), tetrabutylammonium iodide (558 mg; 1.51 mmol) and potassium carbonate (6.28 g; 45.4 mmol). The mixture was refluxed 3 days. The reaction mixture was cooled and filtered over silica gel and concentrated. The residue was purified by silica gel chromatography (eluents: DCM and MeOH/DCM: 5/95) to afford after dry evaporation under vacuum the title compound as an oil (3.0 g; Y: 57%). MS: (M+H)+ = 541.

General Synthesis: Scheme VI

To a solution of [1-(3,3-diphenyl-propyl)-piperidin-4-yl]-acetic acid (0.1 mmol) in toluene (1 ml) were added methylsulfonic acid (0.3 µL) and the aminopenols derivatives (0.22 mmol). The reaction mixture was heated during 0.5 hour at 130°C under microwave irradiation. Water was added to the reaction mixture and the mixture was extracted with AcOEt (3 times). The combined organics were washed with an aqueous solution of NaHCO3 and water and dried (MgSO4). The residue was
purified by silica gel chromatography (eluent: DCM and MeOH/DCM: 5/95) to afford after dry evaporation the different compounds. (Table 8).

Table 8

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>![Structure 16]</td>
</tr>
<tr>
<td>22</td>
<td>![Structure 22]</td>
</tr>
<tr>
<td>23</td>
<td>![Structure 23]</td>
</tr>
<tr>
<td>24</td>
<td>![Structure 24]</td>
</tr>
</tbody>
</table>
Synthesis of compound 72: 1-(3,3-Diphenyl-propyl)-4-(4-phenyl-4,5-dihydro-oxazol-2-ylmethyl)-piperidine

To a solution of 2-[1-(3,3-diphenyl-propyl)-piperidin-4-yl]-acetic acid (0.05 mmol), 2-amino-2-phenyl-ethanol (0.06 mmol) and triethylamine (0.15 mmol) in anhydrous THF (2 ml) was added PL-Mukaiyama resin (from Polymerlabs, Reference: 3495-1698; 1.18 mmol/g 150-300 µM). The reaction mixture was stirred during 2 hours. (Polystyrene) tosyl chloride resin and pyridine (0.5ml) were added to the reaction mixture. After 48 h, the resin was removed by filtration, and water was added. The mixture was extracted with AcOEt (3 times). The combined organics were washed with an aqueous solution of NaHCO₃ and water and dried (MgSO₄). The residue was purified by silica gel chromatography (eluent: DCM and MeOH/DCM: 5/95) to afford after dry evaporation the title compound.
Synthesis of compound 71: 1-(3,3-Diphenyl-propyl)-4-(4-phenyl-oxazol-2-ylmethyl)-piperidine

To a solution of 2-[1-(3,3-diphenyl-propyl)-piperidin-4-yl]-acetamide (0.05 mmol) in toluene (1 ml) were added methylsulfonic acid (0.3 µL) and 2-Bromo-1-phenyl-ethanederivatives (0.05 mmol). The reaction mixture was heated during 1 hour at 150°C under microwave irradiation. Water was added to the reaction mixture and the mixture was extracted with AcOEt (3 times). The combined organics were washed with an aqueous solution of NaHCCb and water and dried (MgSC>4). The residue was purified by silica gel chromatography (eluent :DCM and MeOH/DCM : 5/95) to afford after dry evaporation the title compound.

Synthesis of compound 29: 1-(3,3-Diphenyl-propyl)-4-(5-phenyl-4H-[1,2,4]triazol-3-ylmethyl)-piperidine
A vial was charged with a stirred bar, thiobenzimidic acid methyl ester (9 mg, 0.057 mmol), and [l-(3,3-diphenyl-propyl)-piperidin-4-yl]-acetic acid hydrazide (20 mg, 0.057 mmol). The reaction vessel was sealed and heated under microwave (200W) to 130°C for 30 min. The mixture was evaporated under vacuum and extracted with AcOEt/aq. NaHCO₃. The organic layer was concentrated under vacuum to afford the title compound (12 mg, Y: 97%).

MS: (M+H)⁺ = 438.

**Synthesis of compound 15:** 1-(3,3-Diphenyl-propyl)-4-(5-phenyl- [1,3,4]oxadiazol-2-ylmethyl) -piperidine

To a vial charged with a stir bar, trimethoxymethyl-benzene (51.4 µL, 0.3 mmol), and [1-(3,3-Diphenyl-propyl)-piperidin-4-yl]-acetic acid hydrazide (35.1 mg, 0.1 mmol) was added methylsulfonic acid (1.3 µL). The reaction vessel was sealed and heated under microwave to 100°C for 30 min. After LC/MS analysis the reaction was heated under microwave for further 30 min. After LC/MS intermediate were still observed. 0.2 eq. of methylsulfonic acid were then added and the reaction vessel was heated under microwave to 130°C for further 30 min. The mixture was evaporated under vacuum and the residue was extracted in DCM/aq. NaHCO₃. The organic layer was dried and transferred to a SCX-2 column, eluted with MeOH (3x) and the title compound was eluted.
using a solution of MeOH/NH₄OH (20/i; 14 mg; Y: 30%).
MS: (M+H)+ = 438 (>90%).

Synthesis of compound 27: 1-(3,3-diphenyl-propyl)-4-(5-phenyl-[1,2,4]oxadiazol-3-ylmethyl)-piperidine

\[
\begin{align*}
\text{A vial was charged with a stir bar, 2-} & \text{[1-(3,3-diphenyl-propyl)-piperidin-4-yl]-N-hydroxy-acetamidine (30 mg, 0.08 mmol), benzoyl chloride (11.2 mg, 0.08 mmol), K₂CO₃ (0.8 mmol) in a solution of MeOH/Toluene (2/1; 2 mL).} \\
\text{The reaction vessel was sealed and heated under microwave to 120°C for 1 hr. After cooling the mixture was evaporated under vacuum and the residue was extracted (2x) in AcOEt/aq. NaHCO₃. The organic layer was dried (MgSO₄) and the residue was purified by silica gel chromatography (AcOEt/Hexane gradient) to obtain the title compound (6 mg; Y: 17%). MS: (M+H)+ = 438.}
\end{align*}
\]
Synthesis of compound 18; 2-[(1-(3,3-diphenyl-propyl)-piperidin-4-ylmethyl]-1H-benzoimidazole

To a solution of benzene-1,2-diamine di-hydrochloride (18 mg, 0.1 mmol), TBTU (0.11 mmol), HOBt (16.83 mg, 0.11 mmol) is added [1-(3,3-diphenyl-propyl)-piperidin-4-yl]-acetic acid (37.4 mg, 0.1 mmol) and TEA (25.25 mg, 0.5 mmol). The reaction mixture was stirred at RT for 1 hr. The mixture was concentrated under vacuum and diluted with DCM. The organic layer was washed (2x) with a solution of aq. NaHCO₃. The organic layer was dried over MgSO₄ and concentrated under vacuum. The residue was dissolved in AcOEt (1mL) heated to 140°C for 40 min. The mixture was then concentrated, diluted in AcOEt, extracted with a solution of AcOET/aq. NaHCO₃. The organic layer is dried over MgSO₄ and the residue was purified by silica gel column (cyclohexan, AE gradient 100% to 0%) to afford the title compounds (6 mg, Y: 15%). MS: (M+H)⁺ = 410.
Synthesis of compound 21: 2-[(1-(3,3-diphenyl-propyl)-piperidin-4-ylmethyl)-1-methyl-1H-benzoimidazole

To a solution of 2-[(1-(3,3-diphenyl-propyl)-piperidin-4-ylmethyl]-1H-benzoimidazole (0.05 mmol) in THF (1 ml) at 0°C was added sodium hydride (0.06 mmol). After 1 hour, methyl iodide (0.1 mol) was added to the reaction mixture. After one hour, water was added to the reaction mixture and the mixture was extracted with AcOEt (3 times). The combined organics were washed with an aqueous solution of NaHCO₃ and water and dried (MgSO₄). The residue was purified by silica gel chromatography (eluent: DCM and MeOH/DCM : 5/95) to afford after dry evaporation the title compound.
Synthesis of compound 38: 4-{5-[1- (3,3-Diphenyl-propyl) -piperidin-4- γlmeth γl] -[1,2, 4]oxadiazol-3-yl}-benzoic acid.

To a solution of 4-{5-[1- (3,3-diphenyl-propyl) -piperidin-4-ylmethyl] -[1,2,4]oxadiazol-3-yl} -benzoic acid methyl ester (0.09 mmol) in an EtOH/Water 1/1 mixture (1 ml) was added lithium hydroxide (6 eq). The reaction mixture was stirred overnight at RT. Water was added and the mixture was extracted with DCM. The aqueous phase was collected, acidified with HCl (1M), and extracted with EtOAc. The organic layer was dried with MgSO4 and then concentrated under vacuum to afford the title compound.
Synthesis of compound 39: 4-{5-[1-(3,3-Diphenyl-propyl)-piperidin-4-ylmeth γ]-[1,2,4] oxadiazol-3-yl}-N,N-dimethyl-benzamide

To a solution of 4-{5-[1-(3,3-Diphenyl-propyl)-piperidin-4-ylmethyl]-[1,2,4] oxadiazol-3-yl} -benzoic acid (0.05 mmol) in DMF (0.5 inL) were added while stirring HOBr (0.06 mmol), TBTU (0.06 mmol), dimethyl amine solution in THF (1 ml). The reaction mixture was stirred overnight. The resulting mixture was concentrated under vacuum. The residue was dissolved in DCM and washed with an aqueous solution of NaHCO₃ and water. The organic phase was transferred to an ISOLUTE® PEA-X/SCX2 column and washed with DCM. The organic fraction was then concentrated under reduced pressure to afford the title compound as an oil.
Synthesis of compound 43: 1-(3,3-diphenyl-propyl)-4-(3-piperidin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)-piperidine dihydrochloride.

To a solution of 4-{(5-[(1-(3,3-diphenyl-propyl)-piperidin-4-ylmethyl]-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl)-2,2,2-trifluoro-ethanone in ethanol (0.5 M), was added hydrogen chloride in dioxane (4M solution) (1 mmol, 15 eq). The reaction mixture was stirred for 2.5 hours at 40°C and then concentrated under vacuum to afford the title compound as an oil.

Synthesis of compound 44: 1-(4-{5-[(1-(3,3-Diphenyl-propyl)-piperidin-4-ylmethyl]-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl)-2,2,2-trifluoro-ethanone
To a stirred solution of 1-(3,3-diphenyl-propyl)-4-(3-piperidin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)-piperidine (0.04 mmol) and TEA (0.07 mmol) in dry DCM (1 mL) at 0°C, was carefully added trifluoroacetic anhydride (0.05 mmol). The reaction mixture was stirred overnight at RT, and concentrated under reduced pressure. The crude was dissolved in DCM and washed several times with a saturated aqueous solution of NaHCO₃. The organic layer was extracted, dried over MgSO₄ and concentrated under vacuum to afford the title compound.

**Synthesis of compound 40:** 1-(4-{5-[1-(3,3-Diphenyl-propyl)-piperidin-4-ylmethyl]-[1,2,4]oxadiazol-3-yl}-piperidin-1-yl)-1-methanesulfonyl

To a stirred solution of 1-(3,3-diphenyl-propyl)-4-(3-piperidin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)-piperidine (0.04 mmol) and TEA (0.07 mmol) in dry DCM (1 mL) at 0°C, was carefully added methanesulfonylchloride (0.05 mmol). The reaction mixture was stirred overnight at RT, and concentrated under reduced pressure. The crude was dissolved in DCM and washed several times with a saturated aqueous solution of NaHCO₃. The organic layer was extracted, dried over MgSO₄ and concentrated under vacuum to afford the title compound.
Synthesis of compound 67:

4-[[3-(4-Methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-1-(1-methyl-3,3-diphenyl-propyl)-piperidine

$\text{NaBH(OAc)}_3$ was added to a solution of 4-[[3-(4-methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidine hydrochloride salt (3.14 mmol), 4,4-diphenyl-butan-2-one (53.8 mg; 0.24 mmol), acetic acid (11.4 $\mu$l; 0.2 mmol) in DCM (2 ml). The reaction mixture was stirred during 7 days at RT. The solution was neutralized with a solution of NaOH 1M. The residue was extracted with DCM and dried ($\text{MgSO}_4$). The residue was purified by silica gel chromatography (eluent: DCM and MeOH/DCM: 5/95) to afford after dry evaporation the title compound as an oil.
Synthesis of compound 20: 4-{5-[1-(3,3-diphenyl-propyl)-piperidin-4-ylmethyl]-[1,2,4]oxadiazol-3-yl}-benzonitrile

Thionyl chloride (3 eq) was added to a solution of 4-\{5-[1-(3,3-Diphenyl-propyl)-piperidin-4-ylmethyl]-[1,2,4]oxadiazol-3-yl\}-benzamide (0.05 mmol) in anhydrous toluene (0.5 ml) and THF (0.2 ml). The resultant mixture was heated under reflux for 2 hrs. The crude was concentrated under vacuum. The residue was diluted in DCM/Aq. NaHCO₃ and extracted with DCM. The organic layer was dried with MgSO₄ and then concentrated under vacuum to afford the title compound.
**Synthesis of compound 50**: (2-{4-[(3-(4-Methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-1-yl}-ethyl)-diphenyl-amine

A mixture of 1-(2-chloro-ethyl) -4-[(3-(4-methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl] -piperidine (0.13 mmol), diphenylamine (44.2 mg, 0.26 mmol), powdered sodium iodide (19.5 mg, 0.13 mmol) and DIEA (45.3 µL, 0.26 mmol) in ACN (0.5 ml) were heated at 100 °C for 10 minutes under microwave irradiation. The crude reaction mixture was filtered through a cotton wool plug and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent : EtOAc/Cyclohexane) to afford after dry evaporation under vacuum the title compound.
Synthesis of compound 65: Benzyl-(3-fluoro-phenyl)-(2-(4-(3-(4-methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-1-yl)-ethyl)-amine

A mixture of (3-fluoro-phenyl)-(2-(4-(3-(4-methanesulfonyl-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-1-yl)-ethyl)-amine (0.1 mmol), benzyl bromide (0.1 mmol), powdered sodium iodide (44.2 mg, 0.3 mmol) and DIEA (100 µL, 0.6 mmol) in ACN (1 ml) were heated at 100 °C for 10 minutes in a microwave. The crude reaction mixture was filtered through a cotton wool plug and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent: DCM/MeOH) to afford after dry evaporation under vacuum the title compounds.
Synthesis of compound 66; Benzyl-\{(4-methanesulfonyl-phenyl)- (2-\{(4- [3- (4-αethanesulfonyl-phenyl) -[1,2,4] oxadiazol-5-ylmethyl]- piperidin-1-yl]-ethyl\}-amine

A mixture of \{(4-methanesulfonyl-phenyl)- (2-\{(4- [3- (4-methanesulfonyl-phenyl) -[1,2,4] oxadiazol-5-ylmethyl]- piperidin-1-yl]-ethyl\}-amine (0.1 mmol), benzyl bromide (0.1 mmol), powdered sodium iodide (44.2 mg, 0.3 mmol) and DIEA (100 μL, 0.6 mmol) in ACN (1 ml) were heated at 100 °C for 10 minutes in a microwave. The crude reaction mixture was filtered through a cotton wool plug and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent: DCM/MeOH) to afford after dry evaporation under vacuum the title compounds.
BIOLOGY EXAMPLES

Cell based assay: Calcium flux. The Aequorin-based assay.

The aequorin assay uses the responsiveness of aequorin to intracellular calcium release induced by the activation of G Protein Coupled Receptors (Stables et al., 1997, Anal. Biochem. 252:115-126; Detheux et al., 2000, J. Exp. Med., 192 1501-1508). Briefly, Chinese hamster ovary cells expressing the CCR5 receptor are transfected to coexpress apoaequorin and Ga1β. Cells are incubated with 5 µM Coelenterazine H (Promega) overnight at room temperature, and resuspended at a concentration of 0.1x 10⁶ cells/ml.

Cells are then mixed with test agonist compounds and light emission by the aequorin is recorded with a luminometer (FDSS 6000 - Hamamatsu) for 30 sec. Results are expressed as Relative Light Units (RLU). Controls include cells not expressing CCR5 in order to exclude possible non-specific effects of the test compound.

An agonist response is defined as an increase of light emission by aequorin corresponding to 10% or more of the light emitted by a reference sample of cells expressing CCR5 and treated with a the reference agonist ligand MIP-1β. The results of the tested compounds are reported as the concentration of compound required to reach 50% (EC50) of the maximum level of light emission induced by these compounds.

When tested in the assay described above and by way of illustration the compounds n° 20, 25, 28, 13,
19, 31, 30, 2, 4, 40 and 3 have an EC50 ranging from 161.6 nM to 2.9 µM (table 9).

Inhibitory effect on HIV infection to MAGI-CCR5 cells

The inhibitory activity of the compounds of the invention on HIV infection is measured on the human MAGI R5 recombinant cell line coexpressing the human CCR5 receptor and CD4 at their extracellular membrane. MAGI R5 cells are plated in black view plates at 10,000 cells/well and incubated with the appropriate concentrations of the compounds of the invention during 1 hour. This is followed by a 24 hours infection period with the recombinant and non-replicative HIV virus coding for the firefly luciferase (Bona et al., 2006, Antimicrob. Agents Chemother. 50: 3407-3417). The inhibitory effect of the tested compound on virus entry in MAGI R5 cells is measured by a reduction of luciferase signal (TopCount-NXT reader (Packard) and detection luciferase kit: Steadylite HTS assay kit (Perkin Elmer)) in the presence of the compound of the invention relative to the maximum signal obtained from cells infected with the virus without any added compound. The results of the tested compounds are reported as the concentration of compound required to inhibit 50% (IC50) of the maximum luciferase signal.

When tested in the assay described above and by way of illustration the compounds n° 20, 25, 28, 13, 19, 31, 30 and 40 have an IC50 ranging from 909.8 nM to 3.3 µM (Table 9).
The ability of the compounds of the invention to inhibit the binding of MIP-1$\beta$ was assessed by an in vitro radioligand binding assay. Membranes were prepared from Chinese hamster ovary recombinant cells which express the human CCR5 receptor. The membranes were incubated with 0.05nM $^{125}$I- MIP-1$\beta$ in a HEPES 25mM/ CaCl$_2$ 5mM/MgCl$_2$ 1mM buffer and various concentrations of the compounds of the invention. The amount of iodinated MIP-1$\beta$ bound to the receptor was determined after filtration by the quantification of membrane associated radioactivity using the TopCount-NXT reader (Packard). Competition curves were obtained for compounds of the invention and the concentration of compound which displaced 50% of bound radioligand (IC$_{50}$) was calculated.

According to the method described above and by way of illustration the compounds 20, 25, 28, 13, 19, 31, 30, 2, 4, 40 and 3 have an IC$_{50}$ ranging from 27.6 nM to 134.5 nM (table 9).

Table 9

<table>
<thead>
<tr>
<th>Compound</th>
<th>Aequorin/ Ca$^{2+}$ assay EC50 (nM)</th>
<th>$^{125}$I-MIP-1$\beta$ binding assay IC50 (nM)</th>
<th>HIV-Infection assay IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>652.70</td>
<td>27.61</td>
<td>1603.86</td>
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<td>25</td>
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<td>34.75</td>
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<td>161.66</td>
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<td>100.32</td>
<td>2328.07</td>
</tr>
<tr>
<td>2</td>
<td>2976.33</td>
<td>111.17</td>
<td>+115%*</td>
</tr>
<tr>
<td>4</td>
<td>2390.81</td>
<td>129.22</td>
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</tr>
<tr>
<td>40</td>
<td>238.62</td>
<td>102.24</td>
<td>2192.59</td>
</tr>
<tr>
<td>3</td>
<td>1325.12</td>
<td>134.50</td>
<td>+108%*</td>
</tr>
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</table>
activity levels in a range that do not allow the accurate calculation of IC50 values and \(^a\) means level of inhibition of luciferase activity at a concentration of 10\(\mu\)M of the compound of the invention compared to the inhibition induced by Rantes at 100\(n\)M

The aequorin-based assay quantitatively determines if the compounds exhibit agonist activity by inducing activation of the CCR5 receptor. The values mentioned in the table 9 clearly indicate that this is the case. Indeed these values show that the compounds of the invention are able to activate the CCR5 receptor and therefore exhibit agonist activity.

The results of the inhibition of MIP-1\(\beta\) (a reference CCR5 ligand) binding assay represented in table 9 evidences that the compounds of the invention are able to specifically and competitively interact with CCR5 receptor.

In addition to the above-mentioned functional and binding activities on the CCR5 receptor, the compounds of the invention are also able to protect a human recombinant cell line (MAGI R5 cell) from the infection by a recombinant HIV virus (see table 9, column HIV-Infection assay), which is known to correlate closely with infection of human leukocytes with pathological strains of HIV.

In other words the above-mentioned results demonstrate that the compounds of the invention are of value in inhibiting the entry of HIV viruses into target cells and therefore are of value in the prevention of infection by HIV viruses, the treatment of infection by HIV viruses and the prevention and/or
the treatment of acquired immune deficiency syndrome (AIDS).
1. A Compound of general formula I:

\[
\text{I}
\]

and pharmaceutically acceptable salts and solvates thereof, wherein

A is \(-\text{CH}_2\text{-CH}_2\)- or absent;

\(E^1\) and \(R^2\) independently are \(\text{H}, \text{halo}, \text{optionally substituted alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, or heterocyclyl;}

\(R^3\) and \(R^4\) independently are a group selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl, each group being optionally substituted by one or more substituent \((s)\) selected from halo, oxo, nitro, cyano, azido, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylated, hydroxyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, thiol, alkylthio, thioalkyl, haloalkylthio, acyl, thioacyl, aroyl, amino, alkylamino, aminoalkyl, carboxy, alkoxy carbonyl, cycloalkyloxy carbonyl, heterocyclyloxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylcarbonyloxy,
alkylcarbonyl, alkylamino, alkoxy, alkylcarbonylamino, and alkylcarbonylalkyl, wherein R is hydrogen or C1-C6 alkyl;

X is CR6 or N;

R5 is R7-1,2-R8;

R8 is selected from hydrogen, hydroxyl, halo, C1-C8 alkyl, cyano, alkoxy, allyl, COOH, and COOR, wherein R is selected from C1-C3 alkyl, CON'R''', wherein R' and R''' independently are selected from hydrogen and C1-C3 alkyl, with the proviso that CON'R''' is not CON(Me)2;

R7 is a group selected from heteroaryl, and heterocyclyl, each group being optionally substituted by one or more substituent (s) selected from halo, oxo, nitro, cyano, azido, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy, cycloalkyl oxy, heterocyclyloxy, aryloxy, thiol, alkylthio, thioalkyl, haloalkylthio, acyl, thioacyl, aroyl, amino, alkylamino, aminoalkyl, carboxy, alkoxy carbonyl, cycloalkyloxy carbonyl, heterocyclyloxy carbonyl, aryloxycarbonyl, heteroaryl oxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, aryloxycarbonyl, heteroaryl oxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, arylcarbonyl oxy, heteroarylcarbonyloxy, arylalkylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocyclylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamo, alkylcarbonylaminoalkyl, acylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyle, arylcarbamoyle, heteroarylcarbamoyle, carbamoylalkyl, carbamoylamino,
alkylcarbamoylamino, sulfino, alkylsulf inyl, sulfo, alkylsulfonyl, haloalkylsulf onyl, cycloalkylsulf onyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl sulfamoyl, alkylsulf amoyl, arylsulfamoyl, heteroarylsulfamoyl, cycloalkylsulf onyl, heterocyclylsulf onyl, arylsulfonyl amino, heteroarylsulfonyl amino, and haloalkylsulfonyl onylamino, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the heteroaryl or heterocyclyl group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl group, each of said groups being optionally substituted by one or more further substituent (s) selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylhetereoaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylsulfonyl, heterocyclyl, hydroxyl, nitro, oxo, and sulfonyl;

L²-R⁸ is

absent, or

L² is a single bond or C1-C4 alkylene, optionally substituted by one or more substituent (s) selected from halo, oxo, cyano, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl and alkoxy, or L² is CRᵃRᵇ, wherein Rᵃ and Rᵇ form together with the carbon to which they are attached a carbocycle having 3 to 6 ring atoms, and

R⁸ is a group selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl, each group being optionally substituted by one or more substituent (s) selected from halo, oxo, nitro,
cyano, azido, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylmethyl, hydroxyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocyclyl oxy, aryloxy, thiol, alkylthio, thioalkyl, haloalkylthio, acyl, thioacyl, aroyl, amine, alkylamine, aminoalkyl, carboxy, alkoxy carbonyl, cycloalkyloxycarbonyl, heterocyclyl oxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, aryl carbonyl oxy, heteroaryl carbonyl oxy, arylalkyloxy, alkylcarbonylamo, haloalkyl carbonylamino, cycloalkyl carbonylamino, heterocyclyl carbonylamino, aryl carbonylamino, heteroaryl carbonylamino, carbamoyl, hydroxycarbamoyl, alkyl carbamoyl, cycloalkyl carbamoyl, heteroaryl carbamoyl, carbamoyl amino, alkyl carbamoyl amino, sulfinyl, alkyl sulf inyl, haloalkyl sulf inyl, cycloalkyl sulf inyl, heterocyclyl sulf inyl, heteroaryl sulf inyl, sulfamoyl, alkyl sulf amoyl, aryl sulf amoyl, heteroaryl sulf amoyl, alkyl sulf onyl, cycloalkyl sulf onyl, heterocyclyl sulf onyl, aryl sulf onyl, haloalkyl sulf onyl, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the cycloalkyl, aryl, or heterocyclyl group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl group, each of said groups being optionally substituted by one or more further substituent(s) selected from halo, alkoxy, alkyl, alkylamine, alkylcarbonyl,
alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, and sulfonyl.

2. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof, wherein

A is absent;

R¹ and R² independently are hydrogen or C¹-C⁴ alkyl;

R⁵ is R⁷-L²-R⁸;

R³, R⁴, R⁸, X and L¹ are defined as in Claim 1;

L² is a single bond or C¹-C⁴ alkylene;

R⁷ is a five membered aromatic heterocycle having at least one carbon atom and 1 to 4 heteroatoms, which are independently selected from nitrogen, oxygen, and sulphur each group being optionally substituted by one or more substituent (s) selected from halo, oxo, nitro, cyano, azido, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, heteroaryl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, thiol, alkylthio, thioalkyl, haloalkylthio, acyl, thioacyl, aroyl, amino, alkylamino, aminooalkyl, carboxy, alkoxyacarbonyl, cycloalkyloxyacarbonyl, heterocyclyloxyacarbonyl, aryloxyacarbonyl, heteroaryl oxycarbonyl, alkylcarbonyloxy, cycloalkyl carbyloxy, heterocyclylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, arylalkyloxy, alkylcarbonylamino, haloalkylcarbonylamino,
cycloalkylcarbonylamino, heterocyclylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkylcarbonylaminoalkyl, acylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, sulfino, alkylsulfinyl, sulfo, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroaryl sulfonamoyl, alkylsulfonamoyl, arylsulfonamoyl, halosulfonamoyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, heterocyclylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, and haloalkylsulfonylamino, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the five membered aromatic heterocycle group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl group, each of said groups being optionally substituted by one or more further substituent(s) selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, and sulfonyl.

3. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof, wherein

A is absent;

$R^1$ is methyl;

$R^2$ is hydrogen;

$R^3$ and $R^4$ independently are a group selected from aryl, and heteroaryl, each group being optionally substituted
by one or more substituent(s) selected from halo, oxo, nitro, cyano, azido, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylcycloalkyl, haloalkoxy, cycloalkyl oxy, heterocyclyloxy, arylxy, thiol, alkylthio, thioalkyl, haloalkyl thio, acyl, thioacyl, aroyl, amino, alky lamino, aminoalkyl, carboxy, alkoxy carbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryl oxycarbonyl, arylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, arylcarbonyl oxy, heteroarylcycloalkyloxy, arylalkyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocyclylcarbonylamino, arylcarbonyl amino, heteroarylcycloalkylamin o, alkylcarbonylaminoalkyl, acylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcycloalkylamin o, carbamoyl alkyl, alkyl carbamoylamino, sulfino, alkylsulf inyl, sulfo, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulf onyl sulfamoyl, alkyl sulfamoyl, arylsulfamoyl, heteroaryl sulfamoyl, alkylsulfonylamino, cycloalkylsulf onlamino, heterocyclylsulfonylamino, arylsulf onlamino, heteroarylsulf onlamino, and haloalkylsulf onlamino, or two substituents form an alkyl enedioxy group or a haloalkylenedioxy group, or fused to the aryl, and heteroaryl group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl group, each of said group being optionally substituted by one or more further substituent(s) selected from halo, alkoxy, alkyl, alky lamino, alkyl carbonyl,
alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, and sulfonyl;

$L^1$ is NRCO, NRSO$_2$, CO, CONR, CONRCH$_2$, CH$_2$CO, COCH$_2$CH$_2$CO, CH$_2$COCH$_2$, COCH$_2$CH$_2$, SO$_2$, SO$_2$NR, SO$_2$CH$_2$, SO$_2$CH$_2$CH$_2$, a single bond or a group selected from C$_1$-C$_3$ alkenylene, C$_2$-C$_4$ alkenylene and C$_2$-C$_4$ alkynylene, each group being optionally substituted with one or more substituent(s) selected from alkyl, aryl, heteroaryl, halo, alkylcarbonyl, alky lamino, alkoxy, alkylcarbonylamino, and alkylcarbonyl alkyl, wherein $R$ is hydrogen or C$_1$-C$_e$ alkyl;

$X$ is CH or N;

$R^5$ is $R^7$-$L^2$-$R^8$;

$R^7$ is a group selected from oxazolyl, oxadiazolyl, benzoazolyl, each group being optionally substituted by one or more substituent(s) selected from halo, oxo, nitro, cyano, azido, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

$L^2$-$R^8$ is

absent; or

$L^2$ is a single bond; and

$R^8$ is a group selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl, each group being optionally substituted by one or more substituent(s) selected from OR', C$_1$-C$_4$ alkyl, NO$_2$, Cl, F, OCF$_3$, CF$_3$, CN, COR', COCF$_3$, SO$_2$R', SO$_2$CF$_3$, SO$_2$NR'R'', COOR', CONR'R'', NR'SO$_2$R'', and NR'COR''
wherein \( R' \) and \( R'' \) independently are selected from hydrogen and \( C_1-C_4 \) alkyl.

4. A compound according to Claim 1 having formula Ia

\[
\text{Ia}
\]

and pharmaceutically acceptable salts and solvates thereof, wherein

10 \( R^3, R^4, R^5, \) and \( X \) are defined as in Claim 1;

\( R^1 \) is \( H, \) halo, optionally substituted alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, or heterocyclyl; and

\( L^1 \) is \( NRCO, \) \( NRSO_2, \) \( CO, \) \( CONR, \) \( CONRC_2H, \) \( CH_2CO, \) \( COCH_2 \)

\( CH_2CH_2CO, \) \( CH_2COCH_2, \) \( COCH_2CH_2, \) \( SO_2, \) \( SO_2NR, \) \( SO_2CH_2, \) \( SO_2CH_2CH_2, \)

a single bond or a group selected from \( C_1-C_3 \) alkylene, \( C_2-C_4 \) alkenylene and \( C_2-C_4 \) alkynylene, each group being optionally substituted with one or more substituent(s) selected from alkyl, aryl, heteroaryl, halo, alkylcarbonyl, alkylamino, alkoxy, alkylcarbonylamino, and alkylcarbonylalkyl, wherein \( R \) is hydrogen or \( C_1-C_6 \) alkyl;

5. A compound according to Claim 4 or a pharmaceutically acceptable salt or solvate thereof, wherein

\( R^3, R^4, R^8, X \) and \( L^1 \) are defined as in Claim 4;
R¹ is hydrogen or C₁-C₄ alkyl;
R⁵ is R²-L²-R⁸;
L²-R⁸ is absent; or
L² is a single bond or C₁-C₄ alkenylene; and

R⁷ is defined as in Claim 1.

6. A compound according to Claim 1 having formula Ib

\[
\text{Ib}
\]

and pharmaceutically acceptable salts and solvates thereof, wherein
R³, R⁴, x, L², and R⁸ are defined as in Claim 1;
R¹ is H, halo, optionally substituted alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclyl;
L¹ is NRCO, NRSO₂, CO, CONR, CONRCH₂, CH₂CO, COCH₂,
CH₂CH₂CO, CH₂COCH₂, COCH₂CH₂, SO₂, SO₂NR, SO₂CH₂,
SO₂CH₂CH₂, a single bond or a group selected from C₁-C₃ alkylene,
C₂-C₄ alkenylene and C₂-C₄ alkynylene, each group being
optionally substituted with one or more substituent(s) selected from alkyl, aryl, heteroaryl, halo,
alkylcarbonyl, alkylamino, alkoxy, alkylcarbonylamino,
and alkylcarbonylalkyl, wherein R is hydrogen or C₁-Ce alkyl; and

R⁷ is a five membered saturated, aromatic, or partially
unsaturated heterocycle containing at least one carbon atom and 1 to 4 heteroatoms, which are independently selected from nitrogen, oxygen, and sulphur, said at least one carbon atom being optionally substituted by oxo or =S, wherein the heterocycle is optionally substituted by C₁-C₃ alkyl and/or the five membered saturated, aromatic, or partially unsaturated heterocycle is optionally fused to a five or six membered cycloalkyl, aryl, heterocyclyl or heteroaryl group, each of said groups being optionally substituted by one or more further substituent(s) selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, ary1, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, and sulfonyl.

7. A compound according to Claim 6 or a pharmaceutically acceptable salt or solvate thereof, wherein

R°, R^4, X, L^2, and R^8 are defined as in Claim 6;

R° is hydrogen or C₁-C₄ alkyl; and

R^7 is a five membered aromatic heterocycle having at least one carbon atom and 1 to 4 heteroatoms, which are independently selected from nitrogen, oxygen, and sulphur.
8. A compound according to Claim 1 having formula Ic

and pharmaceutically acceptable salts and solvates thereof, wherein

R³, R⁴, and X are defined as in Claim 1;

R¹ is H, halo, optionally substituted alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclyl;

L¹ is NRCO, NRSO₂, CO, CONR, CONRCH₂, CH₂CO, COCH₂
CH₂CH₂CO, CH₂COCH₂, COCH₂CH₂, SO₂, SO₂NR, SO₂CH₂, SO₂CH₂CH₂,
single bond or a group selected from C₁-C₃ alkenylene, C₂-C₄ alkenylene and C₂-C₄ alkynylene, each group being
optionally substituted with one or more substituent(s) selected from alkyl, aryl, heteroaryl, halo, alkylcarbonyl, alkylamino, alkoxy, alkylcarbonylamino,
and alkylcarbonylalkyl, wherein R is hydrogen or C₁-Ce alkyl;
is a single or a double bond;

\[ \text{is selected from } \text{CR}^\text{c} \text{R}^{d}, \text{NR}^\text{c}, \text{O}, \text{or S, wherein } \text{R}^\text{c} \text{ and } \text{R}^{a} \text{ independently are selected from hydrogen and } \text{C}_{1}-\text{C}_{3} \text{ alkyl;} \]

\[ \text{Y is } \text{CR}^\text{c} \text{R}^{d}, \text{CR}^\text{c}, \text{NR}^\text{c}, \text{N, or O, wherein } \text{R}^\text{c} \text{ and } \text{R}^{d} \text{ independently are selected from hydrogen and } \text{C}_{1}-\text{C}_{3} \text{ alkyl;} \]

\[ \text{Z is } \text{CR}^\text{c}, \text{C, or N, wherein } \text{R}^\text{o} \text{ is selected from hydrogen and } \text{C}_{1}-\text{C}_{3} \text{ alkyl;} \]

\[ \text{R}^{\text{a}0} \text{ and } \text{R}^{\text{a}1} \text{ independently are selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, and sulfonyl.} \]

9. A compound according to claim 1, selected from the group consisting of

\[ \text{a compound structure diagram} \]

\[ \text{another compound structure diagram} \]
a pharmaceutical composition comprising a compound according to any of Claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof and its pharmaceutically acceptable salts and solvates thereof.

10. A pharmaceutical composition comprising a compound according to any of Claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof and
at least one pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

11. Medicament comprising a compound according to any of Claims 1 to 9.

12. Use of a compound according to any of Claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment or prevention of autoimmune, inflammatory, infectious, proliferative or hyperproliferative diseases, or immunologically mediated diseases.

13. Use according to Claim 12, wherein the disease is selected from AIDS, inflammatory and immunoregulatory disorders and diseases including asthma, pulmonary emphysema, allergic diseases and graft rejection as well as autoimmune pathologies such as rheumatoid arthritis, atherosclerosis, psoriasis, systemic lupus erythematosus, ulcerative colitis, multiple sclerosis, glomerulonephritis, together with chronic obstructive pulmonary disease, metastatic cancers and renal diseases.

14. Use according to Claim 13, wherein the disease is AIDS.

15. Use of a compound according to any of Claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for inhibiting the entry of viruses into target cells and, therefore, for the prevention of infection by viruses, the treatment of infection by viruses.
16. Use according to Claim 15, wherein the virus is human immunodeficiency virus.

17. Use according to Claim 16, wherein the medicament is intended for the prevention and/or treatment of acquired immune deficiency syndrome.

18. Use of a compound according to any of Claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for modulating chemokine receptor activity, in a patient, in need of such treatment, which comprises administering to said patient an effective amount of said compound, or a pharmaceutically acceptable salt or solvate thereof.

19. Use according to Claim 18, wherein the chemokine is CCR5.

20. Use according to any of Claims 12 to 19, wherein said medicament is administered to a patient in need thereof in combination with at least one additional therapeutic agent and/or active ingredient.

21. A method of treating and/or preventing autoimmune, inflammatory, infectious, proliferative or hyperproliferative diseases, or immunologically mediated diseases, comprising administering a therapeutically effective amount of a compound according to any of Claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition according to Claim 10 to a patient in need thereof.
22. The method according to Claim 21, wherein the disease is selected from AIDS (HIV-1 or -2 infection), inflammatory and immunoregulatory disorders and diseases including asthma, pulmonary emphysema, allergic diseases and graft rejection as well as autoimmune pathologies such as rheumatoid arthritis, atherosclerosis, psoriasis, systemic lupus erythematosus, ulcerative colitis, multiple sclerosis, glomerulonephritis, together with chronic obstructive pulmonary disease (COPD, including pulmonary fibrosis), metastatic cancers and renal diseases.

23. The method according to Claim 22, wherein the disease is AIDS.

24. A method of inhibiting the entry of viruses into target cells and, therefore, for the prevention of infection by viruses, the treatment of infection by viruses, comprising administering a therapeutically effective amount of a compound according to any of Claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition according to Claim 10 to a patient in need thereof.

25. The method according to Claim 24, wherein the virus is human immunodeficiency virus.

26. The method according to Claim 25 for the prevention and/or treatment of acquired immune deficiency syndrome.

27. A method of modulating chemokine receptor activity in a patient comprising administering a therapeutically effective amount of a compound according to any of Claims 1 to 9 or a pharmaceutically acceptable salt or
solvate thereof or a pharmaceutical composition according to Claim 10 to a patient in need thereof.

28. The method according to Claim 27, wherein the chemokine is CCR5.

29. The method according to any of Claims 21 to 28, wherein compound according to any of Claims 1 to 9 or the pharmaceutically acceptable salt or solvate thereof or the pharmaceutical composition according to Claim 10 is administered in combination with at least one additional therapeutic agent and/or active ingredient.