Title: OPHTHALMIC USES OF S1P RECEPTOR MODULATORS

Abstract: The present invention pertains to the use of a S1P receptor agonist in the manufacture of a medicament in the treatment of an ocular disorder.
Ophthalmic uses of S1P receptor modulators

The present invention relates to the use of an S1P receptor agonist in the manufacture of a medicament for the treatment of ocular disorders.

Ocular disorders which may be treated according to this invention include typically an ocular disease and disorder which may directly or indirectly involve the degeneration of retinal or corneal cells, in particular by apoptosis. Ocular disorders, as used herein, include ischemic retinopathies in general, anterior ischemic optic neuritis, age-related macular degeneration (AMD), in its dry forms (dry AMD) and wet forms (wet AMD), diabetic retinopathy, diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), cystoid macular edema (CME), retinal detachment, retinitis pigmentosa (RP), Stargardt's disease, Best's vitelliform retinal degeneration, Leber's congenital amaurosis and other hereditary retinal degenerations, pathologic myopia, retinopathy of prematurity, and Leber's hereditary optic neuropathy, the after effects of corneal transplantation or of refractive corneal surgery, keratoconjunctivitis sicca (KCS) or dry eye and herpes keratitis.

Preferably, said ocular disorders are selected from:

Dry AMD, wet AMD, diabetic retinopathy, diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), retinitis pigmentosa (RP), and keratoconjunctivitis sicca (KCS),

and even more preferably, said ocular disorders are selected from:

Dry AMD, wet AMD, DME and PDR.

Also preferably said ocular disorder is PDR.

Also preferably said ocular disorder is DME.

Also preferably said ocular disorder is keratoconjunctivitis sicca (KCS).

Highly preferably, said ocular disorders are selected from dry AMD and wet AMD.

In the present description the terms "treatment" or "treat" refer to both prophylactic or preventive treatment as well as curative or disease-modifying treatment, including treatment of patients at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition.
S1P receptor agonists are compounds which signal as agonists at one or more sphingosine-1 phosphate receptors, e.g. S1P1 to S1P8. Agonist binding to a S1P receptor may e.g. result in dissociation of intracellular heterotrimeric G-proteins into Gα-GTP and Gβγ-GTP, and/or increased phosphorylation of the agonist-occupied receptor and activation of downstream signaling pathways/kinases.

S1P receptor agonists are typically sphingosine analogues, such as 2-substituted 2-amino-propane-1,3-diol or 2-amino-propanol derivatives, e.g. a compound comprising a group of formula X

![Chemical Structure X](image)

wherein Z is H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl, phenyl substituted by OH, C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8} cycloalkyl, phenyl and phenyl substituted by OH, or CH_{2}-R_{4z} wherein R_{4z} is OH, acyloxy or a residue of formula (a)

![Chemical Structure a](image)

wherein Z_{1} is a direct bond or O, preferably O;
each of R_{6z} and R_{6z} independently, is H, or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms;
R_{1z} is OH, acyloxy or a residue of formula (a); and each of R_{2z} and R_{3z} independently, is H, C_{1-4}alkyl or acyl.

Group of formula X is a functional group attached as a terminal group to a moiety which may be hydrophilic or lipophilic and comprise one or more aliphatic, alicyclic, aromatic and/or heterocyclic residues, to the extent that the resulting molecule wherein at least one of Z and R_{1z} is or comprises a residue of formula (a), signals as an agonist at one of more sphingosine-1-phosphate receptor.

Examples of preferred S1P receptor agonists are, for example:
Compounds as disclosed in EP627406A1, e.g. a compound of formula I

\[
\begin{align*}
& \text{CH}_2\text{OR}_3 \\
& \text{R}_4\text{R}_5\text{N} = \text{CH}_2\text{OR}_2 \\
& \text{R}_1
\end{align*}
\]

wherein \( \text{R}_1 \) is a straight- or branched (C\(_{12-22}\)) chain

- which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR\(_6\), wherein R\(_6\) is H, alkyl, aralkyl, acyl or alkoxy carbonyl, and carbonyl, and/or
- which may have as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylanimo, alkoxy carbonyl, alkoxy carbonylamino, acyloxy, alkyl carbamoyl, nitro, halogen, amino, hydroxy imino, hydroxy or carboxy; or

\( \text{R}_1 \) is
- a phenylalkyl wherein alkyl is a straight- or branched (C\(_{6-20}\)) carbon chain; or
- a phenylalkyl wherein alkyl is a straight- or branched (C\(_{1-30}\)) carbon chain wherein said phenylalkyl is substituted by
- a straight- or branched (C\(_{6-20}\)) carbon chain optionally substituted by halogen,
- a straight- or branched (C\(_{6-20}\)) alkoxy chain optionally substituted by halogen,
- a straight- or branched (C\(_{6-20}\)) alkenyloxy,
- phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl,
- cycloalkylalkyl substituted by C\(_{6-20}\) alkyl,
- heteroarylalkyl substituted by C\(_{6-20}\) alkyl,
- heterocyclic C\(_{6-20}\) alkyl or
- heterocyclic alkyl substituted by C\(_{2-20}\) alkyl,

and wherein the alkyl moiety may have
- in the carbon chain, a bond or a hetero atom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR\(_6\), wherein R\(_6\) is as defined above, and
- as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylanimo, alkoxy carbonyl, alkoxy carbonylamino, acyloxy, alkyl carbamoyl, nitro, halogen, amino, hydroxy or carboxy, and

each of R\(_2\), R\(_3\), R\(_4\) and R\(_6\), independently, is H, C\(_{1-4}\) alkyl or acyl or a pharmacologically acceptable salt, solvate or hydrate thereof;

- Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II
wherein m is 1 to 9 and each of R'₂, R'₃, R'₄ and R'₅, independently, is H, alkyl or acyl, or a pharmacologically acceptable salt, solvate or hydrate thereof;

- Compounds as disclosed in EP0778263 A1, e.g. a compound of formula III

wherein W is H; C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl; unsubstituted or by OH substituted phenyl; R''₁, O(CH₂)ₙ; or C₅₋₆ alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C₃₋₅ cycloalkyl, phenyl and phenyl substituted by OH;

X is H or unsubstituted or substituted straight chain alkyl having a number p of carbon atoms or unsubstituted or substituted straight chain alkoxy having a number (p-1) of carbon atoms, e.g. substituted by 1 to 3 substituents selected from the group consisting of C₁₋₆ alkyl, OH, C₁₋₆ alkoxy, acyloxy, amino, C₁₋₆ alkylamino, acylamino, oxo, haloC₁₋₆ alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of C₁₋₆ alkyl, OH, C₁₋₆ alkoxy, acyloxy, amino, C₁₋₆ alkylamino, acylamino, haloC₁₋₆ alkyl and halogen; Y is H, C₁₋₆ alkyl, OH, C₁₋₆ alkoxy, acyl, acyloxy, amino, C₁₋₆ alkylamino, acylamino, haloC₁₋₆ alkyl or halogen, Z is a single bond or a straight chain alkyne having a number or carbon atoms of q,

each of p and q, independently, is an integer of 1 to 20, with the proviso of 6≤p+q≤23, m' is 1, 2 or 3, n is 2 or 3,

each of R''₁, R''₂, R''₃ and R''₄, independently, is H, C₁₋₆ alkyl or acyl,
or a pharmacologically acceptable salt, solvate or hydrate thereof;

- Compounds as disclosed in WO02/18395, e.g. a compound of formula IVa or IVb
wherein $X_a$ is O, S, NR$_{1b}$ or a group $-(\text{CH}_2)_n-\text{R}_{1b}$, which group is unsubstituted or substituted by 1 to 4 halogen; $n_b$ is 1 or 2, $R_{1b}$ is H or (C$_{1-4}$)alkyl, which alkyl is unsubstituted or substituted by halogen; $R_{1b}$ is H, OH, (C$_{1-4}$)alkyl or O(C$_{1-4}$)alkyl wherein alkyl is unsubstituted or substituted by 1 to 3 halogen; $R_{1b}$ is H, OH or (C$_{1-4}$)alkyl, wherein alkyl is unsubstituted or substituted by halogen; each $R_{2a}$ is independently selected from H or (C$_{1-4}$)alkyl, which alkyl is unsubstituted or substituted by halogen; $R_{3a}$ is H, OH, halogen or O(C$_{1-4}$)alkyl wherein alkyl is unsubstituted or substituted by halogen; and $R_{3b}$ is H, OH, halogen, (C$_{1-4}$)alkyl wherein alkyl is unsubstituted or substituted by hydroxy, or O(C$_{1-4}$)alkyl wherein alkyl is unsubstituted or substituted by halogen; $Y_a$ is $-\text{CH}_2-$, $-\text{C(O)}-$, $-\text{CH(OH)}-$, $-\text{C(=NOH)}-$, O or S, and $R_{4a}$ is (C$_{4-14}$)alkyl or (C$_{4-14}$)alkenyl; or a pharmacologically acceptable salt, solvate or hydrate thereof;

- Compounds as disclosed in WO 02/076995, e.g. a compound of formula V

$$\text{V}$$

wherein

$m_c$ is 1, 2 or 3;

$X_c$ is O or a direct bond;

$R_{1c}$ is H; C$_{1-6}$ alkyl optionally substituted by OH, acyl, halogen, C$_{3-10}$cycloalkyl, phenyl or hydroxy-phenylene; C$_{2-6}$alkenyl; C$_{2-6}$alkynyl; or phenyl optionally substituted by OH;

$R_{2c}$ is

\[ \text{OR}_{6c} \]
wherein $R_{6c}$ is $H$ or $C_{1-4}$alkyl optionally substituted by 1, 2 or 3 halogen atoms, and $R_{6c}$ is $H$ or $C_{1-4}$alkyl optionally substituted by halogen;

each of $R_{3c}$ and $R_{4c}$, independently, is $H$, $C_{1-4}$alkyl optionally substituted by halogen, or acyl, and

$R_{c}$ is $C_{13-20}$alkyl which may optionally have in the chain an oxygen atom and which may optionally be substituted by nitro, halogen, amino, hydroxy or carboxy; or a residue of formula (a)

![Chemical structure image]

wherein $R_{7c}$ is $H$, $C_{1-4}$alkyl or $C_{1-4}$alkoxy, and $R_{8c}$ is substituted $C_{1-20}$alkanoyl, phenyl$C_{1-14}$alkyl wherein the $C_{1-14}$alkyl is optionally substituted by halogen or $OH$, cycloalkyl$C_{1-14}$alkoxy or phenyl$C_{1-14}$alkoxy wherein the cycloalkyl or phenyl ring is optionally substituted by halogen, $C_{1-4}$alkyl and/or $C_{1-4}$alkoxy, phenyl$C_{1-14}$alkoxy-$C_{1-14}$alkyl, phenoxy$C_{1-14}$alkoxy or phenoxy$C_{1-14}$alkyl,

$R_{c}$ being also a residue of formula (a) wherein $R_{8c}$ is $C_{1-14}$alkoxy when $R_{1c}$ is $C_{1-4}$alkyl, $C_{2-8}$alkenyl or $C_{2-8}$alkynyl,

or a compound of formula VI

![Chemical structure image]

wherein

$n_x$ is 2, 3 or 4

$R_{1x}$ is $H$; $C_{1-8}$alkyl optionally substituted by $OH$, acyl, halogen, cycloalkyl, phenyl or hydroxy-phenylene; $C_{2-8}$alkenyl; $C_{2-8}$alkynyl; or phenyl optionally substituted by $OH$;

$R_{2x}$ is $H$, $C_{1-4}$alkyl or acyl

each of $R_{3x}$ and $R_{4x}$, independently, is $H$, $C_{1-4}$alkyl optionally substituted by halogen or acyl,

$R_{5x}$ is $H$, $C_{1-4}$alkyl or $C_{1-4}$alkoxy, and
$R_{8x}$ is $C_{1-20}$ alkanoyl substituted by cycloalkyl; cyloalkyl$C_{1-14}$alkoxy wherein the cycloalkyl ring is optionally substituted by halogen, $C_{1-4}$alkyl and/or $C_{1-4}$alkoxy; phenyl$C_{1-4}$alkoxy wherein the phenyl ring is optionally substituted by halogen, $C_{1-4}$alkyl and/or $C_{1-4}$alkoxy, $R_{6x}$ being also $C_{4-14}$alkoxy when $R_{1x}$ is $C_{2-4}$alkyl substituted by OH, or pentyloxy or hexyloxy when $R_{1x}$ is $C_{1-4}$alkyl,

provided that $R_{6x}$ is other than phenyl-butylenoxy when either $R_{6x}$ is H or $R_{1x}$ is methyl, or a pharmacologically acceptable salt, solvate or hydrate thereof;

- Compounds as disclosed in WO02/06268AI, e.g. a compound of formula VII

\[
\begin{array}{c}
\text{\(R_{4d}\)} \\
\text{\(\text{\(R_{3d}\)}\)} \\
\text{\(\text{\(R_{1d}\)}\)} \\
\text{\(\text{\(R_{2d}\)}\)} \\
\text{\(\text{\(R_{6d}\)}\)} \\
\text{\(\text{\(R_{7d}\)}\)} \\
\text{\(\text{\(X_d\)}\)} \\
\text{\(\text{\(Y_d\)}\)} \\
\text{\(\text{\(R_{5d}\)}\)} \\
\end{array}
\]

wherein each of $R_{1d}$ and $R_{2d}$, independently, is H or an amino-protecting group;

$R_{3d}$ is hydrogen, a hydroxy-protecting group or a residue of formula

\[
\begin{array}{c}
\text{\(R_{sd}\)} \\
\text{\(n_d\)} \\
\text{\(X_d\)} \\
\text{\(Y_d\)} \\
\text{\(R_{5d}\)} \\
\text{\(R_{7d}\)} \\
\end{array}
\]

$R_{sd}$ is lower alkyl;

$n_d$ is an integer of 1 to 6;

$X_d$ is ethylene, vinylene, ethynylene, a group having a formula $-\text{D-CH}_2$ (wherein D is carbonyl, $-\text{CH(OH)}$, $O$, $S$ or $N$), aryl or aryl substituted by up to three substituents selected from group a as defined hereinafter;

$Y_d$ is single bond, $C_{1-10}$alkylene, $C_{1-10}$alkylene which is substituted by up to three substituents selected from groups a and b, $C_{1-10}$alkylene having $O$ or $S$ in the middle or end of the carbon chain, or $C_{1-10}$alkylene having $O$ or $S$ in the middle or end of the carbon chain which is substituted by up to three substituents selected from groups a and b;

$R_{5d}$ is hydrogen, cycloalkyl, aryl, heterocycle, cycloalkyl substituted by up to three substituents selected from groups a and b, aryl substituted by up to three substituents selected from groups a and b, or heterocycle substituted by up to three substituents selected from groups a and b;

each of $R_{9d}$ and $R_{7d}$, independently, is H or a substituent selected from group a;

each of $R_{9d}$ and $R_{9d}$, independently, is H or $C_{1-4}$alkyl optionally substituted by halogen;
<group a> is halogen, lower alkyl, halogeno lower alkyl, lower alkoxy, lower alkylthio, carboxyl, lower alkoxy carbonyl, hydroxy, lower aliphatic acyl, amino, mono-lower alkylamino, di-lower alkylamino, lower aliphatic acylamino, cyano or nitro; and

<group b> is cycloalkyl, aryl, heterocycle, each being optionally substituted by up to three substituents selected from group a;

with the proviso that when \(R_{5d}\) is hydrogen, \(Y_d\) is a either a single bond or linear \(C_{1-10}\) alkylene, or a pharmacologically acceptable salt or ester thereof;

-Compounds as disclosed in JP-14316985 (JP2002316985), e.g. a compound of formula VIII

\[
\begin{align*}
\text{VIII} & \\
\text{wherein } R_{1e}, R_{2e}, R_{3e}, R_{4e}, R_{5e}, R_{6e}, R_{7e}, n_e, X_e, \text{ and } Y_e \text{ are as disclosed in JP-14316985; or a pharmacologically acceptable salt, solvate or hydrate or ester thereof;}
\end{align*}
\]

-Compounds as disclosed in WO 03/29184 and WO 03/29205, e.g. compounds of formula IX

\[
\begin{align*}
\text{IX} & \\
\text{wherein } X_i \text{ is } O \text{ or } S, \text{ and } R_{1f}, R_{2f}, R_{3f} \text{ and } n_i \text{ are as disclosed in WO 03/29184 and WO 03/29205, each of } R_{4f} \text{ and } R_{5f}, \text{ independently is } H \text{ or a residue of formula}
\end{align*}
\]

\[
\begin{align*}
\text{wherein each of } R_{4f} \text{ and } R_{5f}, \text{ independently, is } H \text{ or } C_{1-4} \text{ alkyl optionally substituted by halogen; e.g. 2-amino-2-[4-(benzylxyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propane-diol or 2-amino-2-[4-(benzylxyloxyphenoxythio)-2-chlorophenyl]propyl-1,3-propane-diol, or a pharmacologically acceptable salt, solvate or hydrate thereof;}
\end{align*}
\]

-Compounds as disclosed in WO03/062252A1, e.g. a compound of formula X'
wherein

Ar is phenyl or naphthyl; each of m and n independently is 0 or 1; A is selected from COOH, PO₃H₂, PO₂H, SO₃H, PO(C₁₃alkyl)OH and 1H-tetrazol-5-yl; each of R₁ and R₂ independently is H, halogen, OH, COOH or C₁₄alkyl optionally substituted by halogen; R₃ is H or C₁₄alkyl optionally substituted by halogen or OH; each R₄ independently is halogen, or optionally halogen substituted C₁₄alkyl or C₁₃alkoxy; and each of R₉ and M has one of the significances as indicated for B and C, respectively, in WO03/062252A1; or a pharmacologically acceptable salt, solvate or hydrate thereof;

- Compounds as disclosed in WO 03/062248A2, e.g. a compound of formula XI

wherein Ar is phenyl or naphthyl; n is 2,3 or 4; A is COOH, 1H-tetrazol-5-yl, PO₃H₂, PO₂H₂, -SO₃H or PO(R₉)OH wherein R₉ is selected from C₁₄alkyl, hydroxyC₁₄alkyl, phenyl, -CO-C₁₃alkoxy and -CH(OH)-phenyl wherein said phenyl or phenyl moiety is optionally substituted; each of R₁ and R₂ independently is H, halogen, OH, COOH, or optionally halogen substituted C₁₃alkyl or phenyl; R₃ is H or C₁₄alkyl optionally substituted by halogen and/ OH; each R₄ independently is halogen, OH, COOH, C₁₄alkyl, S(O)₉₆₉₂C₁₃alkyl, C₁₃alkoxy, C₃-acycloalkyl, aryl or aralkoxy, wherein the alkyl portions may optionally be substituted by 1-3 halogens; and each of R₉ and M has one of the significances as indicated for B and C, respectively, in WO03/062248A2;

- Compounds as disclosed in WO 04/026817A, e.g. compounds of formula XII
wherein

$R_{ij}$ is halogen, trihalomethyl, C$_{1-4}$-alkyl, C$_{1-4}$-alkoxy, C$_{1-4}$-alkylthio, C$_{1-4}$-alkylsulfilinyl, C$_{1-4}$-alkylsulfonyl, aralkyl, optionally substituted phenoxy or aralkyloxy, $R_{ij}$ is H, halogen, trihalomethyl, C$_{1-4}$-alkyl, C$_{1-4}$-alkoxy, aralkyl or aralkyloxy, $R_{3j}$ is H, halogen, CF$_3$, C$_{1-4}$-alkyl, C$_{1-4}$-alkoxy, C$_{1-4}$-alkylthio or benzoxo, $R_{4j}$ is H, C$_{1-4}$-alkyl, phenyl, optionally substituted benzyl or benzoyl, or lower aliphatic C$_{1-5}$-acyl, $R_{5j}$ is H, monohalomethyl, C$_{1-4}$-alkyl, C$_{1-4}$-alkoxymethyl, C$_{1-4}$-alkylthiomethyl, hydroxyethyl, hydroxypropyl, phenyl, aralkyl, C$_{2-4}$-alkenyl or -alkynyl, each of $R_{ij}$ and $R_{nj}$, independently, is H or C$_{1-4}$-alkyl, or $R_{nj}$ being also a residue of formula

$$\begin{array}{c}
\text{P}\\
\text{O}\\
\text{OR}_{ij}
\end{array}$$

wherein each of $R_{ij}$ and $R_{nj}$, independently, is H or C$_{1-4}$-alkyl optionally substituted by halogen $X_{ij}$ is O, S, SO or SO$_2$ and $n_{ij}$ is an integer of 1 to 4, e.g. 2-amino-4-[4-(3-benzoxoxygenylthio)-2-chlorophenyl]-2-methylbutane-1-ol or 2-amino-4-[4-(3-benzoxoxygenylthio)-2-chlorophenyl]-2-ethylbutane-1-ol;

- Compounds as disclosed in WO 04/103306A, WO 05/000833, WO 05/103309 or WO 05/113330, e.g. compounds of formula XIIIa or XIIIb

wherein

$A_{k}$ is COOR$_{5k}$, OPO(OR$_{5k}$)$_2$, PO(OR$_{5k}$)$_2$, SO$_2$OR$_{5k}$, POR$_{5k}$OR$_{5k}$ or 1H-tetrazol-5-yl, $R_{5k}$ being H or C$_{1-4}$-alkyl;

$W_{k}$ is a bond, C$_{1-3}$-alkylene or C$_{2-3}$-alkenylenes;

$Y_{k}$ is C$_{6-10}$-aryl or C$_{3-8}$-heteroaryl, optionally substituted by 1 to 3 radicals selected from halogene, OH, NO$_2$, C$_{1-4}$-alkyl, C$_{1-4}$-alkoxy; halo-substituted C$_{1-4}$-alkyl and halo-substituted C$_{1-4}$-alkoxy;
Zₖ is a heterocyclic group as indicated in WO 04/103306A, e.g. azetidine;
R₁ₖ is C₆-₁₀aryl or C₃-₅heteroaryl, optionally substituted by C₁-₅alkyl, C₆-₁₀aryl, C₆-₁₀arylC₁-₅alkyl,
C₃-₅heteroaryl, C₃-₅heteroaryLC₁-₅alkyl, C₃-₅cycloalkyl, C₃-₅cycloalkylC₁-₅alkyl,
C₃-₅heterocycloalkyl or C₃-₅heterocycloalkylC₁-₅alkyl; wherein any aryl, heteroaryl, cycloalkyl
or heterocycloalkyl of R₁ₖ may be substituted by 1 to 5 groups selected from halogen, C₁-₅alkyl,
C₆alkoxy and halo substituted-C₁-₅alkyl or -C₁-₅alkoxy;
R₂ₖ is H, C₁-₅alkyl, halo substituted C₁-₅alkyl, C₂-₅alkenyl or C₂-₅alkynyl; and
each of R₃ₖ or R₄ₖ, independently, is H, halogen, OH, C₁-₅alkyl, C₁-₅alkoxy or halo substituted
C₁-₅alkyl or C₁-₅alkoxy;
and the N-oxide derivatives thereof or prodrugs thereof,
or a pharmacologically acceptable salt, solvate or hydrate thereof.

According to a further embodiment of the invention, a S1P receptor agonist for use in the
invention may also be a selective S1P1 receptor, e.g. a compound which possesses a
selectivity for the S1P1 receptor over the S1P3 receptor of at least 20 fold, e.g. 100, 500,
1000 or 2000 fold, as measured by the ratio of EC₅₀ for the S1P1 receptor to the EC₅₀ for the
S1P3 receptor as evaluated in a ³⁵S-GTPγS binding assay, said compound having an EC₅₀
for binding to the S1P1 receptor of 100 nM or less as evaluated by the ³⁵S-GTPγS binding
assay. Representative S1P1 receptor agonists are e.g. the compounds listed in WO
03/061567, the contents of which being incorporated herein by reference, for instance a
compound of formula XIV or XV

![Formula XIV](image)

![Formula XV](image)

When the compounds of formulae I to XV have one or more asymmetric centers in the
molecule, the present invention is to be understood as embracing the various optical
isomers, as well as racemates, diastereoisomers and mixtures thereof are embraced.
Compounds of formula III or IVb, when the carbon atom bearing the amino group is
asymmetric, have preferably the R-configuration at this carbon atom.
The compounds of above formulae may exist in free or salt form. Examples of pharmaceutically acceptable salts of the compounds of the above formulae include salts with inorganic acids, such as hydrochloride, hydrobromide and sulfate, salts with organic acids, such as acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate and benzenesulfonate salts, or, when appropriate, salts with metals such as sodium, potassium, calcium and aluminium, salts with amines, such as triethylamine and salts with dibasic amino acids, such as lysine. The compounds and salts of the present invention encompass hydrate and solvate forms.

Acyl as indicated above may be a residue $R_y$-CO- wherein $R_y$ is C$_{1-6}$alkyl, C$_{3-6}$cycloalkyl, phenyl or phenyl-C$_{1-4}$alkyl. Unless otherwise stated, alkyl, alkoxy, alkenyl or alkynyl may be straight or branched.

When in the compounds of formula I the carbon chain as $R_1$ is substituted, it is preferably substituted by halogen, nitro, amino, hydroxy or carboxy. When the carbon chain is interrupted by an optionally substituted phenylene, the carbon chain is preferably unsubstituted. When the phenylene moiety is substituted, it is preferably substituted by halogen, nitro, amino, methoxy, hydroxy or carboxy.

Preferred compounds of formula I are those wherein $R_1$ is C$_{13-20}$alkyl, optionally substituted by nitro, halogen, amino, hydroxy or carboxy, and, more preferably those wherein $R_1$ is phenylalkyl substituted by C$_{6-14}$alkyl chain optionally substituted by halogen and the alkyl moiety is a C$_{1-6}$alkyl optionally substituted by hydroxy. More preferably, $R_1$ is phenyl-C$_{1-6}$alkyl substituted on the phenyl by a straight or branched, preferably straight, C$_{6-14}$alkyl chain. The C$_{6-14}$alkyl chain may be in ortho, meta or para, preferably in para.

Preferably each of $R_2$ to $R_5$ is H.

A preferred compound of formula I is 2-amino-2-tetradecyl-1,3-propanediol. A particularly preferred S1P receptor agonist of formula I is FTY720, i.e. 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form (referred to hereinafter as Compound A), e.g. the hydrochloride, as shown:

![Chemical structure diagram]
A preferred compound of formula II is the one wherein each of $R'_2$ to $R'_5$ is H and $m$ is 4, i.e. 2-amino-2-[2-[4-(1-oxo-5-phenylpentyl)phenyl]ethyl]propane-1,3-diol, in free form or in pharmaceutically acceptable salt form (referred to hereinafter as Compound B), e.g. the hydrochloride.

A preferred compound of formula III is the one wherein $W$ is CH$_3$, each of $R''_1$ to $R''_3$ is H, $Z_2$ is ethylene, $X$ is heptyloxy and $Y$ is H, i.e. 2-amino-4-(4-heptyloxyphenyl)-2-methyl-butanol, in free form or in pharmaceutically acceptable salt form (referred to hereinafter as Compound C), e.g. the hydrochloride. The R-enantiomer is particularly preferred.

A preferred compound of formula IVa is the FTY720-phosphate ($R_{2a}$ is H, $R_{3a}$ is OH, $X_a$ is O, $R_{1a}$ and $R_{1b}$ are OH). A preferred compound of formula IVb is the Compound C-phosphate ($R_{2a}$ is H, $R_{3b}$ is OH, $X_a$ is O, $R_{1a}$ and $R_{1b}$ are OH, $Y_a$ is O and $R_{1a}$ is heptyl). A preferred compound of formula V is Compound B-phosphate.

A preferred compound of formula V is phosphoric acid mono-[(R)-2-amino-2-methyl-4-(4-pentylloxy-phenyl)-butyl]ester.

A preferred compound of formula VIII is (2R)-2-amino-4-[3-(4-cyclohexylloxybutyl)]-benzo[b]thien-6-yl]-2-methylbutan-1-ol.

A preferred compound of formula IX is a compound wherein $X_i$ is S or O, $R_{1f}$ is benzylloxy, $R_{2f}$, $R_{4f}$ and $R_{9f}$ are each H, $R_{3f}$ is Cl and $n_f$ is 2.

A preferred compound of formula XII is a compound wherein $X_i$ is S or O, $R_{1f}$ is benzylloxy, $R_{2i}$, $R_{4i}$, $R_{9i}$ and $R_{7i}$ are each H, $R_{3i}$ is Cl, $R_{9i}$ is hydroxyethyl or hydroxypropyl and $n_i$ is 2.

Binding affinity of S1P receptor agonists to individual human S1P receptors may be determined in following assays:

**Transient transfection of human S1P receptors into HEK293 cells**

EDG receptors and G$_i$ proteins are cloned, and equal amounts of 4 cDNAs for the EDG receptor, G$_i$-α, G$_i$-β and G$_i$-γ are mixed and used to transfect monolayers of HEK293 cells using the calcium phosphate precipitate method (M. Wigler et al., Cell. 1977;11;223 and DS. Im et al., Mol. Pharmacol. 2000;57;753). Briefly, a DNA mixture containing 25 μg of DNA and 0.25 M CaCl$_2$ is added to HEPES-buffered 2 mM Na$_2$HPO$_4$. Subconfluent monolayers of HEK293 cells are poisoned with 25 mM chloroquine, and the DNA precipitate is then applied to the cells. After 4 h, the monolayers are washed with phosphate-buffered saline and refed media (90% 1:1 Dulbecco's modified essential media (DMEM):F-12 + 10% fetal bovine serum). The cells are harvested 48-72 h after addition of the DNA by scraping in HME buffer.
(in mM: 20 HEPES, 5 MgCl₂, 1 EDTA, pH 7.4) containing 10% sucrose on ice, and disrupted using a Dounce homogenizer. After centrifugation at 800×g, the supernatant is diluted with HME without sucrose and centrifuged at 100,000×g for 1h. The resulting pellet is rehomogenized and centrifuged a second hour at 100,000×g. This crude membrane pellet is resuspended in HME with sucrose, aliquoted, and snap-frozen by immersion in liquid nitrogen. The membranes are stored at 70°C. Protein concentration is determined spectroscopically by Bradford protein assay.

**GTPγS binding assay using S1P receptor/HEK293 membrane preparations**

GTPγS binding experiments are performed as described by DS. Im et al., Mol. Pharmacol. 2000; 57:753. Ligand-mediated GTPγS binding to G-proteins is measured in GTP binding buffer (in mM: 50 HEPES, 100 NaCl, 10 MgCl₂, pH 7.5) using 25 µg of a membrane preparation from transiently transfected HEK293 cells. Ligand is added to membranes in the presence of 10 µM GDP and 0.1 nM [³⁵S]GTPγS (1200 Ci/mmoll) and incubated at 30°C for 30 min. Bound GTPγS is separated from unbound using the Brandel harvester (Gaithersburg, MD) and counted with a liquid scintillation counter.

Compounds of formula A are disclosed e.g. in WO 94/09010, WO 95/16691, WO 96/41807, USP 5,362,718 or WO 99/15530 which are incorporated herein by reference. They may be prepared as disclosed or by analogy to the procedures described in these references.

In a series of further specific or alternative embodiments, the present invention also provides:

1.1. A method for treating an ocular disorder, said method comprising administering to an affected individual a therapeutically effective amount of a S1P receptor agonist. Preferred S1P receptor agonist is Compound A, B or C, (2R)-2-amino-4-[3-(4-cyclohexyloxybutyl)-benzo[b][thien-6-yl]-2-methylbutan-1-ol, or a compound of formula IX wherein X₁ is S or O, R₁₁ is benzylxy, R₂₂, R₄₄ and R₅₅ are each H, R₃₃ is Cl and n₁ is 2.

As used herein, administration is preferably pertaining to oral, rectal, parenteral and topical administration. An even more preferred administration pertains to topical administration.
Efficacy in the described ocular disorders might be established for example in the following animal models:


2) Experimental retinal degeneration induced by

3) Experimental model for the injury of the optic nerve (ON)
   - by experimental transient (acute) retinal ischemia in rats after ophthalmic vessel ligature (as described in Lafuente et al., Invest. Ophthalmol. Vis. Sci. 2001; 42:2074-2084) or cannulation of the anterior chamber (Buchi et al., Ophthalmologica 1991; 203:138-147)

The pharmaceutical compositions of this invention comprise, for example, enteral or parenteral administration forms from approximately 5% to approximately 90%, preferably from approximately 10% to approximately 80%, active ingredient. Pharmaceutical compositions according to the invention for enteral or parenteral administration are, for example, in unit dose form, such as in the form of dragées, tablets, capsules or suppositories, and also ampoules. They are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or...
lyophilising processes. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture or granules, if desired or necessary, after the addition of appropriate excipients, into tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, if desired disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow agents, flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Other orally administrable pharmaceutical compositions are hard gelatin capsules and also soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The hard gelatin capsules may comprise the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and if desired with stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it likewise being possible for stabilisers to be added.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base material. Suitable suppository base materials are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Gelatin rectal capsules that
comprise a combination of the active ingredient with a base material may also be used. Suitable base materials include, for example, liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

There are suitable for parenteral administration by infusion and/or injection especially aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, and also suspensions of the active ingredient, such as corresponding oily suspensions, there being used suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous suspensions that comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and optionally also stabilisers.

The compounds may also be administered topically in or around the eye, for example as eyedrops, ophthalmic suspensions or ointments, subconjunctival, peribulbar, retrobulbar or intravitreal injections, possibly with the use of slow-release devices, such as conjunctival inserts, microspheres or other periocular or intraocular depot devices.

The dosage of the active ingredient depends on the species of warm-blooded animal, the age and the individual condition and also on the mode of administration. Normally the estimated approximate daily dose in the case of oral administration to a patient weighing approximately 75 kg is from approximately 10 mg to approximately 500 mg. In the case of topical administration, the approximate estimated daily dosage may vary from 0.001 to 10 mg, depending on the mode of administration. The amount of active ingredient in a topical formulation is typically much lower than in oral or parenteral formulations. Typically the active in a topical formulation would range from 0.01% - 10% by weight of total weight.
CLAIMS

1. Use of an S1P receptor agonist in the manufacture of a medicament for the treatment of an ocular disorder.

2. Method to treat an ocular disorder which is treatable by an S1P receptor agonist, said method comprising the administration of an effective amount of an S1P receptor agonist to a subject suffering from said ocular disorder.

3. A method, or use according to any preceding claims, wherein said ocular disorder is selected from the group of ischemic retinopathies in general, anterior ischemic optic neuropathy, all forms of optic neuritis, age-related macular degeneration (AMD), in its dry forms (dry AMD) and wet forms (wet AMD), diabetic retinopathy, diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), cystoid macular edema (CME), retinal detachment, retinitis pigmentosa (RP), Stargardt's disease, Best's vitelliform retinal degeneration, Leber's congenital amaurosis and other hereditary retinal degenerations, pathologic myopia, retinopathy of prematurity, and Leber's hereditary optic neuropathy, the after effects of corneal transplantation or of refractive corneal surgery, keratoconjunctivitis sicca (KCS) or dry eye and herpes keratitis.

4. A method, or use according to any preceding claims, wherein the S1P receptor agonist is or comprises a group of formula X

\[
\text{Z} \quad R_{32} R_{22} N\quad \text{CH}_2 R_{12} \quad \text{(X)}
\]

wherein Z is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl, phenyl substituted by OH, C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}cycloalkyl, phenyl and phenyl substituted by OH, or CH_{2-R_{42}} wherein R_{42} is OH, acyloxy or a residue of formula (a)

\[
\text{Z}_1\quad \text{P}\quad \text{OR}_{32} \quad \text{OR}_{32} \quad \text{(a)}
\]

wherein Z_{1} is a direct bond or O, preferably O;
each of \( R_{2z} \) and \( R_{3z} \), independently, is \( H \), or \( C_{1-4} \)-alkyl optionally substituted by 1, 2 or 3 halogen atoms;

\( R_{1z} \) is \( \text{OH} \), acyloxy or a residue of formula (a); and each of \( R_{2z} \) and \( R_{3z} \)

independently, is \( H \), \( C_{1-4} \)-alkyl or acyl, and

wherein the group of formula \( X \) is a functional group attached as a terminal group to a moiety which may be hydrophilic or lipophilic and comprise one or more aliphatic, alicyclic, aromatic and/or heterocyclic residues, to the extent that the resulting molecule wherein at least one of \( Z \) and \( R_{1z} \) is or comprises a residue of formula (a), signals as an agonist at one of more sphingosine-1-phosphate receptor,

in free form or in a pharmaceutically acceptable salt form, as solvate or hydrate thereof.

5. A method, or a use according to claim 4 wherein the S1P receptor agonist is 2-amino-2-[[2-(4-octyloxyphenyl)]ethyl]propane-1,3-diol, Compound B or C, (2R)-2-amino-4-[[3-(4-cyclohexyloxybutyl)]benzo[b][thien-6-yl]]-2-methylbutan-1-ol, or a compound of formula IX as defined hereinbefore wherein \( X_1 \) is \( S \), or \( O \), \( R_{11} \) is benzylxoy, \( R_{16} \), \( R_{14} \) and \( R_{11} \) are each \( H \), \( R_{31} \) is \( Cl \) and \( n_1 \) is 2,

in free form or in a pharmaceutically acceptable salt form.

6. A method, or a use according to according to any of the preceding claims, wherein the S1P receptor agonist is 2-amino-2-[[2-(4-octyloxyphenyl)]ethyl]propane-1,3-diol (compound A) in free form or in a pharmaceutically acceptable salt form.

7. A method, or a use according to according to any of the preceding claims, wherein said S1P receptor agonist is administered topically in or around the eye.

8. A method, or a use according to according to any of the preceding claims, wherein said S1P receptor agonist is or comprises a group of formula (I):

\[
\begin{align*}
\text{CH}_2\text{OR}_3 \\
\text{R}_3\text{N} \quad \text{CH}_2\text{OR}_2 \\
\text{R}_1
\end{align*}
\]

wherein \( R_1 \) is a straight- or branched \( (C_{12-42}) \) chain

which may have in the chain a bond or a hetero atom selected from a double bond, a
tripe bond, \( O \), \( S \), \( N \text{R}_6 \), wherein \( R_6 \) is \( H \), alkyl, aralkyl, acyl or dialkylcarbonyl, and
carbonyl, and/or

SUBSTITUTE SHEET (RULE 26)
which may have as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxy carbonyl, alkoxy carbonylamino, acyloxy, alkyl carbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy; or

R<sub>1</sub> is

a phenylalkyl wherein alkyl is a straight- or branched (C<sub>6-20</sub>) carbon chain; or

a phenylalkyl wherein alkyl is a straight- or branched (C<sub>1-30</sub>) carbon chain wherein said phenylalkyl is substituted by

a straight- or branched (C<sub>6-20</sub>) carbon chain optionally substituted by halogen,

a straight- or branched (C<sub>6-20</sub>) alkoxy chain optionally substituted by halogen,

a straight- or branched (C<sub>2-20</sub>) alkenyloxy,

phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl,

cycloalkylalkyl substituted by C<sub>6-20</sub>alkyl,

heteroarylalkyl substituted by C<sub>3-30</sub>alkyl,

heterocyclic C<sub>3-20</sub>alkyl or

heterocyclic alkyl substituted by C<sub>2-20</sub>alkyl,

and wherein

the alkyl moiety may have in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR<sub>6</sub>, wherein R<sub>6</sub> is as defined above, and as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxy carbonyl, alkoxy carbonylamino, acyloxy, alkyl carbamoyl, nitro, halogen, amino, hydroxy or carboxy, and each of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>9</sub>, independently, is H, C<sub>1-4</sub> alkyl or acyl; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

A method, or use according to any preceding claims, wherein said ocular disorder is age-related macular degeneration (AMD), in its dry forms (dry AMD) and wet forms (wet AMD).
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/13 A61P27/02

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2004/103306 A (IRM LLC; PAN, SHIFENG; GAO, WENQI; GRAY, NATHANIEL; S; MI, YUAN; FAN,) 2 December 2004 (2004-12-02) cited in the application page 12, line 23 - page 13, line 23</td>
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</tr>
<tr>
<td>X</td>
<td>WO 02/18395 A (MERCK &amp; CO., INC; MANDALA, SUZANNE; BERGSTROM, JAMES; HAJOU, RICHARD,) 7 March 2002 (2002-03-07) cited in the application page 10, lines 22-26</td>
<td>1-10</td>
</tr>
<tr>
<td>X</td>
<td>WO 2004/096757 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; ALBERT, RAINER; EHRRARDT, CLAUS; ET) 11 November 2004 (2004-11-11) page 32, line 8 - page 33, line 24</td>
<td>1-10</td>
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Further special features of cited documents:

* Special features of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier document but published on or after the International filing date
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *O* document relating to an oral disclosure, use, exhibition or other means
  *P* document published prior to the International filing date but later than the priority date claimed

Date of the actual completion of the International search

4 July 2006

Date of mailing of the International search report

27/07/2006

Name and mailing address of the ISA

European Patent Office, P. B. 5818, Pauwelaan 2, NL-2280 HV Rijswijk, Tel: (+31-70) 340-2040, Tx: 31 651 epo nl, Fxn: (+31-70) 340-3016

Authorized officer

Cattell, James
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<td>WO 2004/110979 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; EHRHARDT, CLAUS; HINTERDING, KLAUS) 23 December 2004 (2004-12-23) page 11, line 1 - page 12, line 14</td>
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<td>WO 03/061567 A (MERCK &amp; CO., INC; DOHERTY, GEORGE, A; FORREST, MICHAEL, J; HAJDU, RICH) 31 July 2003 (2003-07-31) page 1, lines 5-10 - page 11, lines 17-22</td>
<td>1-10</td>
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<tr>
<td>X</td>
<td>WO 2005/014525 A (MITSUBISHI PHARMA CORPORATION; KOHARA, TOSHIYUKI; ADACHI, KUNITOMO; TA) 17 February 2005 (2005-02-17) page 27, lines 24-26</td>
<td>1-10</td>
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<td>KUROSE ETAL: &quot;Effects of FTY720 a novel immunosuppressant on Experimental Autoimmune Uveoretinitis in rats.&quot; EXP. EYE. RES., vol. 70, no. 7, 2000, - 2000 pages 7-15, XP002382822 abstract</td>
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INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(e) for the following reasons:

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

2. □ Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. claims: 1-10 (partially)

   The diseases of claim 3

1. □ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

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

3. □ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

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

□ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10 (partially)

   The diseases of claim 3
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<td></td>
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<tr>
<td>WO 0218395 A</td>
<td>07-03-2002</td>
<td>AU 8533101 A</td>
<td>13-03-2002</td>
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<td></td>
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<td>CA 2421893 A1</td>
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<td>11-03-2004</td>
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<tr>
<td>WO 2004110979 A</td>
<td>23-12-2004</td>
<td>AU 2004247384 A1</td>
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<td>CA 2527977 A1</td>
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<td>EP 1636717 A2</td>
<td>22-03-2006</td>
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<td>CN 1620461 A</td>
<td>25-05-2005</td>
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<td>CZ 20023560 A3</td>
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<td>WO 02076995 A2</td>
<td>03-10-2002</td>
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