Compositions comprising sphingosine 1 phosphate (S1P) receptor modulators

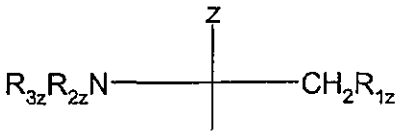
The present invention relates to a composition comprising a sphingosine 1 phosphate (S1P) receptor modulator.

In particular, the present invention relates to stable compositions comprising a sphingosine 1 phosphate (S1P) receptor modulator suitable for use as a dosage form.

S1P receptor modulators 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 Y.

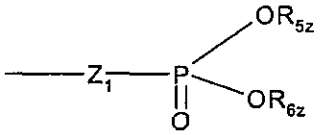
S1P receptor modulators

Sphingosine-1 phosphate (hereinafter "S1P") is a natural serum lipid. Presently there are eight known S1P receptors, namely S1P1 to S1P8. S1 P receptor modulators 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 Y



(Y)

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_{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)



(a)

wherein Z_1 is a direct bond or O, preferably O;

each of R_{5z} 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.

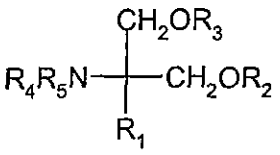
Group of formula Y is a functional group attached as a terminal group to a moiety which may be hydrophilic or lipophilic and comprise one or more aliphatic, alicyclic, aromatic and/or heterocyclic residues, to the extent that the resulting molecule wherein at least one

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.

S1P receptor modulators 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.

Examples of appropriate S1P receptor modulators, comprising a group of formula Y are, for example:

Compounds as disclosed in EP627406A1, e.g. a compound of formula I



I

wherein 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, C_{1-4}alkyl, aryl-C_{1-4}alkyl, acyl or (C_{1-4}alkoxy)carbonyl, and carbonyl, and/or
  - which may have as a substituent C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, arylC_{1-4}alkyl-oxy, acyl, C_{1-4}alkylamino, C_{1-4}alkylthio, acylamino, (C_{1-4}alkoxy)carbonyl, (C_{1-4}alkoxy)-carbonylamino, acyloxy, (C_{1-4}alkyl)carbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy; or

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 substitued by halogen,
- a straight- or branched (C_{6-20})alkenyloxy,
- phenyl-C_{1-14}alkoxy, halophenyl-C_{1-4}alkoxy, phenyl-C_{1-14}alkoxy-C_{1-14}alkyl, phenoxy-C_{1-4}alkoxy or phenoxy-C_{1-4}alkyl,
- 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

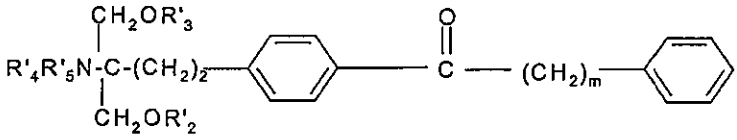
the alkyl moiety may have

- in the carbon chain, a bond or a heteroatom 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 C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, arylC_{1-4}alkyloxy, acyl, C_{1-4}alkyl-amino, C_{1-4}alkylthio, acylamino, (C_{1-4}alkoxy)carbonyl, (C_{1-4}alkoxy)carbonylamino, acyloxy, (C_{1-4}alkyl)carbamoyl, nitro, halogen, amino, hydroxy or carboxy, and

each of R_2, R_3, R_4 and R_5, independently, is H, C_{1-4} alkyl or acyl

or a pharmaceutically acceptable salt or hydrate thereof;

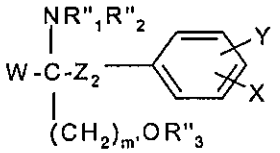
Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II



II

wherein m is 1 to 9 and each of R'_2, R'_3, R'_4 *and* R'_5, *independently, is H,* C_{1-6}*alkyl or acyl,* or a pharmaceutically acceptable salt or hydrate thereof;

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



III

wherein W is H; C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl; unsubstituted or by OH substituted phenyl; $R''_4O(CH_2)_n$; or 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;

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 substitutents selected from the group consisting of C_{1-6}alkyl, OH, C_{1-6}alkoxy, acyloxy, amino, C_{1-6}alkylamino, acylamino, oxo, haloC_{1-6}alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of C_{1-6}alkyl, OH, C_{1-6}alkoxy, acyl, acyloxy, amino, C_{1-6}alkylamino, acylamino, haloC_{1-6}alkyl and halogen; Y is H, C_{1-6}alkyl, OH, C_{1-6}alkoxy, acyl, acyloxy,

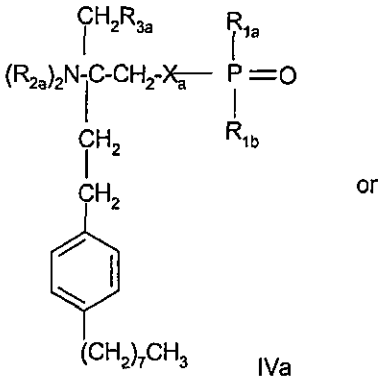
amino, C_{1-6}alkylamino, acylamino, haloC_{1-6}alkyl or halogen, Z_2 is a single bond or a straight chain alkylene having a number or carbon atoms of q,

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

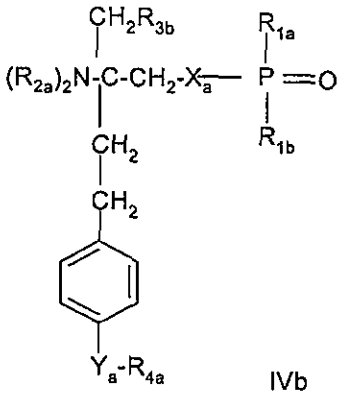
each of R''_1, R''_2, R''_3 and R''_4, independently, is H, C_{1-4}alkyl or acyl,

or a pharmaceutically acceptable salt or hydrate thereof,

Compounds as disclosed in WO02/18395, e.g. a compound of formula IVa or IVb



or



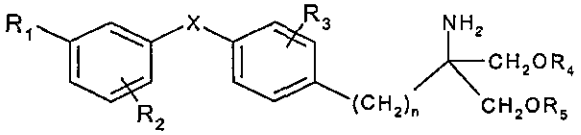
IVa IVb

wherein X_a is O, S, NR_{1s} or a group $-(CH_2)_{na}-$, which group is unsubstituted or substituted by 1 to 4 halogen; n_a is 1 or 2, R_{1s} is H or (C_{1-4})alkyl, which alkyl is unsubstituted or substituted by halogen; R_{1a} 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 substitued 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 $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O or S, and R_{4a} is

(C_{4-14})alkyl or (C_{4-14})alkenyl;

or a pharmaceutically acceptable salt or hydrate thereof;

Amino alcohol compounds of formula V



V

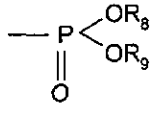
wherein X is O, S, SO or SO_2;

R_1 is halogen, trihalomethyl, OH, C_{1-7}alkyl, C_{1-4}alkoxy, trifluoromethoxy, phenoxy, cyclohexylmethyloxy, pyridylmethoxy, cinnamyloxy, naphthylmethoxy, phenoxymethyl, CH_2-OH, CH_2-CH_2-OH, C_{1-4}alkylthio, C_{1-4}alkylsulfinyl, C_{1-4}alkylsulfonyl, benzylthio, acetyl, nitro or cyano, or phenyl, phenylC_{1-4}alkyl or phenyl-C_{1-4}alkoxy each phenyl group thereof being optionally substituted by halogen, CF_3, C_{1-4}alkyl or C_{1-4}alkoxy;

R_2 is H, halogen, trihalomethyl, C_{1-4}alkoxy, C_{1-7}alkyl, phenethyl or benzyloxy;

R_3 H, halogen, CF_3, OH, C_{1-7}alkyl, C_{1-4}alkoxy, benzyloxy, phenyl or C_{1-4}alkoxymethyl;

each of R_4 and R_5, independently is H or a residue of formula (a)



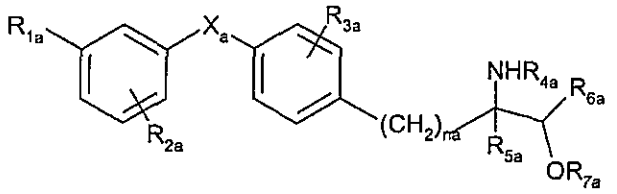
(a)

wherein each of R_8 and R_9, independently, is H or C_{1-4}alkyl optionally substituted by halogen; and

n is an integer from 1 to 4;

or a pharmaceutically acceptable salt thereof;

or a compound of formula VI



VI

wherein

R_{1a} is halogen, trihalomethyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-4}alkylsulifinyl, C_{1-4}alkyl-sulfonyl, aralkyl, optionally substituted phenoxy or aralkyloxy;

R_{2a} is H, halogen, trihalomethyl, C_{1-4}alkyl, C_{1-4}alkoxy, aralkyl or aralkyloxy;

R_{3a} is H, halogen, CF_3, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio or benzyloxy;

R_{4a} is H, C_{1-4}alkyl, phenyl, optionally substituted benzyl or benzoyl, or lower aliphatic C_{1-5}acyl;

R_{5a} is H, monohalomethyl, C_{1-4}alkyl, C_{1-4}alkoxy-methyl, C_{1-4}alkyl-thiomethyl, hydroxyethyl, hydroxypropyl, phenyl, aralkyl, C_{2-4}alkenyl or –alkynyl;

R_{6a} is H or C_{1-4}alkyl;

R_{7a} is H, C_{1-4}alkyl or a residue of formula (a) as defined above,

X_a is O, S, SO or SO_2; and

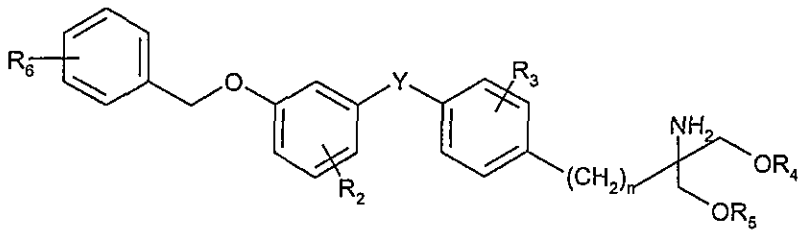
n_a is an integer of 1 to 4;

or a pharmaceutically acceptable salt thereof.

With regard to the compounds of formulae (I) and (II), the term "halogen" encompasses fluorine, chlorine, bromine and iodine. The term "trihalomethyl group" encompasses

trifluoromethyl and trichloromethyl. "C_{1-7} alkyl" encompasses straight-chained or branched alkyl, e.g. methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, pentyl, hexyl or heptyl. The phrase "substituted or unsubstituted phenoxy group" encompasses those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine, trifluoromethyl, C_{1-4}alkyl or C_{1-4}alkoxy. The term "aralkyl group" as in "aralkyl group" or "aralkyloxy group" encompasses benzyl, diphenylmethyl, phenethyl and phenylpropyl. Any alkyl moiety as present in "C_{1-4}alkoxy", "C_{1-4}alkylthio", "C_{1-4}alkylsulfinyl " or "C_{1-4}alkylsulfonyl encompasses straight-chained or branched C_{1-4}alkyl, e.g. methyl, ethyl, propyl, isopropyl or butyl. The phrase "substituted or unsubstituted aralkyl group" encompasses those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine, trifluoromethyl, lower alkyl having 1-4 carbon atoms, or lower alkoxy having 1-4 carbon atoms.

Other compounds of formula V are compounds of formula Va



(Va)

wherein

R_2, R_3, R_4, R_5 and n are as defined above; and Y is O or S and

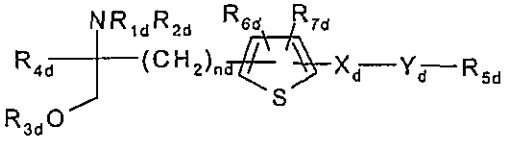
R_6 is hydrogen, halogen, C_{1-7}alkyl, C_{1-4}alkoxy or trifluoromethyl.

Compounds of formulae V and Va are known and are disclosed e.g. in WO03/029205, WO 03/029184 and WO04/026817, respectively, the phosphorylated derivatives being disclosed e.g. in WO04/074297, the contents of which being incorporated herein by reference in their entirety. Compounds disclosed may be prepared as disclosed in the cited references herein.

Phosphorylated derivatives of compounds described herein can be prepared utilizing the procedures for synthesizing phosphorylated compounds described known in the art, e.g., in WO 2005/021503 (see, e.g., pages 11 and 12).

Optically active compounds of and phosphorylated derivatives thereof can be prepared in high purity utilizing procedure described in the art, e.g. in Hinterding et al., *Synthesis*, Vol. 11, pp.1667-1670 (2003).

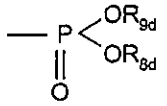
Compounds as disclosed in WO02/06268Al, e.g. a compound of formula VI



VI

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



R_{4d} is C_{1-4}alkyl;

n_d is an integer of 1 to 6;

X_d is ethylene, vinylene, ethynylene, a group having a formula – D-CH_2- (wherein D is carbonyl, – 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, C_{3-6}cycloalkyl, aryl, heterocyclic group, C_{3-6}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 heterocyclic group substituted by up to three substituents selected from groups a and b;

each of R_{6d} and R_{7d}, independently, is H or a substituents selected from group a;

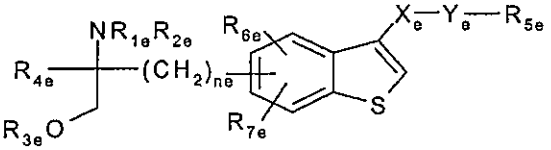
each of R_{8d} and R_{9d}, independently, is H or C_{1-4}alkyl optionally substituted by halogen;

<group a > is halogen, lower alkyl, halogeno lower alkyl, lower alkoxy, lower alkylthio, carboxyl, lower alkoxycarbonyl, hydroxy, lower aliphatic acyl, amino, mono-lower alkylamino, di-C_{1-4}alkylamino, acylamino, cyano or nitro; and

<group b > is C_{3-6}cycloalkyl, aryl or heterocyclic group, 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, ester or hydrate thereof;

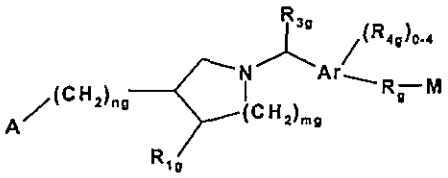
-Compounds as disclosed in JP-14316985 (JP2002316985), e.g. a compound of formula VII



VII

wherein R_{1e},R_{2e},R_{3e},R_{4e},R_{5e},R_{6e},R_{7e}, n_e, X_e and Y_e are as disclosed in JP-14316985;
or a pharmacologically acceptable salt, ester or hydrate thereof;

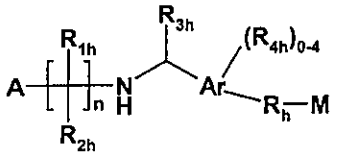
-Compounds as disclosed in WO03/062252A1, e.g. a compound of formula VIII



VIII

wherein
Ar is phenyl or naphthyl; each of m_g and n_g independently is 0 or 1; A is selected from COOH, PO_3H_2, PO_2H, SO_3H, $PO(C_{1-3}alkyl)OH$ and 1*H*-tetrazol-5-yl; each of R_{1g} and R_{2g} independently is H, halogen, OH, COOH or C_{1-4}alkyl optionally substituted by halogen; R_{3g} is H or C_{1-4}alkyl optionally substituted by halogen or OH; each R_{4g} independently is halogen, or optionally halogen substituted C_{1-4}alkyl or C_{1-3}alkoxy; and each of R_g 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;

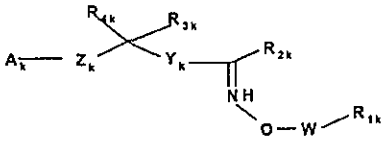
-Compounds as disclosed in WO 03/062248A2, e.g. a compound of formula IX



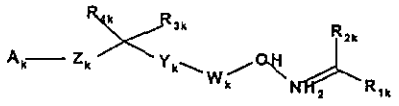
IX

wherein Ar is phenyl or naphthyl; n is 2,3 or 4; A is COOH, 1*H*-tetrazol-5-yl, PO_3H_2, PO_2H_2, $-SO_3H$ or $PO(R_{5h})OH$ wherein R_{5h} is selected from C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl, $-CO-C_{1-3}$alkoxy and –CH(OH)-phenyl wherein said phenyl or phenyl moiety is optionally substituted; each of R_{1h} and R_{2h} independently is H, halogen, OH, COOH, or optionally halogeno substituted C_{1-6}alkyl or phenyl; R_{3h} is H or C_{1-4}alkyl optionally substituted by halogen and/ OH; each R_{4h} independently is halogen, OH, COOH, C_{1-4}alkyl, $S(O)_{0,1\ or2}C_{1-3}$alkyl, C_{1-3}alkoxy, C_{3-6}cycloalkoxy, aryl or aralkoxy, wherein the alkyl portions may optionally be substituted by 1-3 halogens; and each of R_h and M has one of the significances as indicated for B and C, respectively, in WO03/062248A2
or a pharmacologically acceptable salt, solvate or hydrate thereof.

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



Xa



Xb

wherein

A_k is $COOR_{5k}$, $OPO(OR_{5k})_2$, $PO(OR_{5k})_2$, SO_2OR_{5k}, $POR_{5k}OR_{5k}$ or 1*H*-tetrazol-5-yl, R_{5k} being H or C_{1-6}alkyl;

W_k is a bond, C_{1-3}alkylene or C_{2-3}alkenylene;

Y_k is C_{6-10}aryl or C_{3-9}heteroaryl, optionally substituted by 1 to 3 radicals selected from halogene, OH, NO_2, C_{1-6}alkyl, C_{1-6}alkoxy; halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy;

Z_k is a heterocyclic group as indicated in WO 04/103306A, e.g. azetidine;

R_{1k} is C_{6-10}aryl or C_{3-9}heteroaryl, optionally substituted by C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, C_{3-9}heteroaryl, C_{3-9}heteroarylC_{1-4}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, C_{3-8}heterocycloalkyl or C_{3-8}heterocycloalkylC_{1-4}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{1k} may be substituted by 1 to 5 groups selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy and halo substituted-C_{1-6}alkyl or -C_{1-6}alkoxy;

R_{2k} is H, C_{1-6}alkyl, halo substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl: and

each of R_{3k} or R_{4k}, independently, is H, halogen, OH, C_{1-6}alkyl, C_{1-6}alkoxy or halo substituted C_{1-6}alkyl or C_{1-6}alkoxy;

and the N-oxide derivatives thereof or prodrugs thereof,

or a pharmacologically acceptable salt, solvate or hydrate thereof.

The compounds of formulae I to Xb may exist in free or salt form. Examples of pharmaceutically acceptable salts of the compounds of the formulae III to VIII 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 combination 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.

Aryl may be phenyl or naphthyl, preferably phenyl.

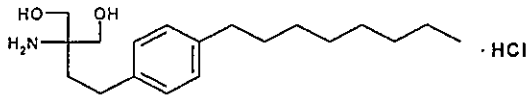
When in the compounds of formula I the carbon chain as R_1 is substituted, it is preferably substituted by halogen, nitro, amino, hydroxy or carboxy. When the carbon chain is interrupted by an optionally substituted phenylene, the carbon chain is preferably unsubstituted. When the phenylene moiety is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

In the above formula of VII "heterocyclic group" represents a 5- to 7 membered heterocyclic group having 1 to 3 heteroatoms selected from S, O and N. Examples of such heterocyclic groups include the heteroaryl groups indicated above, and heterocyclic compounds corresponding to partially or completely hydrogenated heteroaryl groups, e.g. furyl, thienyl, pyrrolyl, azepinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl or pyrazolidinyl. Preferred heterocyclic groups are 5-or 6-membered heteroaryl groups and the most preferred heteocyclic group is a morpholinyl, thiomorpholinyl or piperidinyl group.

A preferred compound of formula I is 2-amino-2-tetradecyl-1,3-propanediol. A particularly preferred S1P receptor agonist of formula III 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:



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_{4a} is heptyl). A preferred compound of formula V is Compound B-phosphate.

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

A preferred compound of formula Xa is e.g. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a prodrug thereof.

It will be appreciated that the compounds as described herein may be the direct active substances, or may be prodrugs. For example, the compounds may be phosphorylated forms.

Oral Formulations

The dosage form of a composition of the present invention, e.g. the final dosage form, may be a solid dosage form, e.g. a tablet. In another embodiment of the present invention the dosage form is granular, e.g. powder form and may comprise part of a suspension or gel. Another dosage forms may comprise of small multiparticulate pellets/beads. Other dosage forms may comprise a solid or granular composition which is soluble in a liquid to

produce a liquid formulation prior to administration. Examples of such formulations are soluble tablets, capsules and sachets. The final liquid formulation may be consumed as a drink.

The oral route is often the most convenient route for drug administration. This may be in the form of a standard tablet, a conventional orally disintegrating tablet, a lyophilized tablet, or a thin film.

It has been found that compounds comprising a group of formula Y, e.g. amino- propane-1,3-diols, e.g. those that have S1P agonist activity, are not easy to formulate. In particular, these are not easy to formulate in a solid oral formulation.

As such, the present inventors have surprisingly found that only a limited number of excipients are potentially feasible with such amino diols.

The Maillard Reaction

The Maillard reaction is a chemical reaction between an amino acid and a reducing sugar [Sugars that contain aldehyde groups that are oxidised to carboxylic acids are classified as reducing sugars.

Reducing sugars include glucose, glyceraldehyde, lactose, arabinose and maltose], usually requiring the addition of heat. Like caramelization, it is a form of non-enzymatic browning. The reactive carbonyl group of the sugar interacts with the nucleophilic amino group of the amino acid, and interesting but poorly characterized odor and flavor molecules result. This process accelerates in an alkaline environment because the amino groups do not neutralize. This reaction is the basis of the flavouring industry, since the type of amino acid determines the resulting flavour.

The potentially feasible excipients are classified into e.g. fillers, binders, disintegrants, lubricants, flow regulators, plastisizers, and matrix formers. Some excipients can be listed in more than one class.

Typical ranges found in a final formulation comprising a compound as described herein are as follows:

Fillers: 10 – 97 %
Binders: 1 – 15 %
Disintegrants: 1 – 15 %
Lubricants: 0.5 – 2 %

Flow regulators: 0.5 – 3 %
Matrix formers: 3 - 50 %
Plastisizers: 5 - 30 %
Flavoring agents: 1 – 20 %
Sweeteners: 1 – 20 %

The present invention therefore relates to stable blends comprising a compound having a group of formula Y and at least one other excipient.

The compound having a group of formula Y may, in one embodiment, be mixed together with one or more of the following excipients:

(a) Fillers selected from Lactose monohydrate, Lactose anhydrous, Maize starch, Mannitol, Xylitol, sorbitol, sucrose, Microcrystalline cellulose,, e.g. Avicel PH101, Dibasic calcium phosphate, Maltodextrin , gelatin, e.g. DE 12
and/or

(b)Binders selected from HPMC, e.g. 3cPs, L-HPC, e.g. HP-Cellulose LH-22, Povidone.
and/or

(c)Disintegrants selected from Maize starch, Crospovidone, Croscarmellose sodium, Sodium carboxymethylstarch e.g. Primojel, pregelatinized starch, e.g. Starch 1500 (Sta RX), calcium silicate
and/or

(d)Lubricants selected from Hydrogenated e.g. ricinoleic, castor oil, e.g. Cutina, magnesium stearate, calcium stearate, zinc stearate, mineral oil, silicone fluid, sodium lauryl sulfate, L-leucine, sodium stearyl fumarate,
and/or

(e)Flow regulators selected from Aerosil 200Colloidal silicone dioxide, e.g. Aerosil 200, Talc
and/or

(f)Matrix formers selected from Hydroxypropyl methyl cellulose, Hydroxypropyl cellulose, Methyl cellulose, Ethyl cellulose, Pullulan, Starch, e.g. Pure Cote, Povidone
and/or

(g)Plastisizers selected from PEG 400, Dibutyl sebacate, Sorbitol and/or

(h)Flavoring agents selected from Menthol, tutti fruti and/or

(i)Sweeteners selected from Sucralose, Sodium saccharine.

Fillers are preferably selected from Fillers selected from Lactose monohydrate, Lactose anhydrous, Maize starch, Xylitol, sorbitol, sucrose, Microcrystalline cellulose, e.g. Avicel PH101, Dibasic calcium phosphate, Maltodextrin and gelatin.

According to one embodiment of the invention preferred fubricants are selected from magnesium stearate and calcium stearate.

In a second embodiment, the present invention relates to a binary blend comprising a compound having a group of formula Y and one excipient selected from:

Sorbitol, Xylitol, dicalcium phosphate, Lactose, microcrystalline cellulose, HPMC, HPC, Crospovidone, croscarmellose sodium, starch, preferably an hydrous, calcium silicate, colloidal silicone dioxide, talc, magnesium stearate, calcium stearate.

Preferably, no moisture is present.

In particular, the excipients are selected from :

Dicalcium phosphate, HPC, crospovidone, calcium silicate, magnesium stearate.

In particular, the formulation or blend of the present invention does not comprise a reducing sugar, e.g glucose, glyceraldehyde, lactose, arabinose and maltose.

In a further preference, the formulation or blend of the present invention does not comprise PEG, stearic acid,

Where necessary, stabilizers may be added to increase or decrease the pH . By modifying the pH, the composition may be adapted to optimize the reduction of likelihood of a

malliard reaction, or other side reactions taking place. An example of a stabilizer is citric acid.

In a preferred embodiment of the compositions o fthe present invention are binary blends, i.e. a mixture of a compound comprising a group of formula Y and one excipient as listed herein.

A particular advantage of the stable binary blends as disclosed herein is that they may be transported and stored prior to final formulation, without forming degredation products. The blends of the present invention, e.g. binary blends, therefore provide a commercially viable option for storing the S1P modulator as described herein in stable conditions.

Prior to the surprising findings of the present invention, the instability of the compounds comprising a group Y would not have been able to be safely stored, without the possibility of impurities being formed. With the present invention, the skilled person is now shown which excipients may be used with the S1P modulators for storage and, most importantly, which ecipients may be used to reduce the risk of impurities contaminating a final drug product, such impurities being formed by a malliard reaction.

Levels of impurities tolerated:

Compositions of the present invention, e.g. binary blends and/or final dosage forms, are preferably free from impurities. It will be understood that the level of impurities tolerated will be judged using pharmaceutically acceptable standards.

However, it is also understood the pharmaceutical standards may only apply to a final dosage form, i.e. the final product. The present invention, in a preferred embodiment provides binary blends containing an S1P receptor modulator as definated herein, i.e. a compound comprising a group of formula Y, which are low, e.g. free, of impurities. Preferably the binary blends of the present invention meet the following criteria for level of impurities:

- No more than 4.5wt% of impurities and/or but no more than 2wt% for an individual impurity.

- Preferably, impurities are at 2wt% or lower with no individual impurity being more than 0.5wt%

The "wt%" measurements above are indicators of amount of impurities tolerated. The term "wt%" means the percentage in relation to the amount of the whole formulation, for example 4wt% means 4mg in a 100mg tablet.

Example of impurity tolerances, using the compound FTY720 as a reference

There are three qualified degradation products observed in a dosage form: acetyl amide, palmitate amide and stearate amide.

The mechanism for the formation of these degradation products is postulated to be due to a nucleophilic attack of the primary amine of the FTY720 molecule at the carbonyl carbon of the acetic, palmitic or stearic acid.

Based on tox qualification study, the three primary degradation products, acetyl amide, palmitate amide and stearate amide were qualified at levels of 4.6%, 4.5% and 4.8%, respectively.

In order to adequately control the quality and efficacy of the final dosage product each qualified degradation product was assigned a specification of equal to or less than 2.0% of label strength.

The specified degradation products were assigned a specification of equal to or less than 1.0% of label strength.

The unspecified degradation products were assigned a specification of equal to or less than 0.5% of label strength as per the Novartis drug product purity policy.

The sum of all the degradation products above the limit of quantitation (0.1% label strength) was set at equal or less than a total of 4.5%.

FTY720: An example of a compound comprising a group of formula Y:

A chemical stability program using binary mixtures of FTY720 and excipients (1 % drug substance was stored for 1 month in closed vials at 50°C) was performed using FTY720 drug substance.

General method to prepare binary mixtures:

1. 10 mg drug substance and 1000 mg excipient were filled into a glass vial (= binary mixture).
2. The closed vials were stored for 1 month at 50°C.

The analytical characterization was performed using gradient HPLC with UV detection. For the analysis, the stored samples were dissolved in 40 ml of 0.0005N hydrochloric acid in isopropanol and stirred with a magnetic stirrer for 30 minutes. This solution was centrifuged and an aliquot of the clear supernatant was used as the test solution.

The limit of quantitation (loq) of the method was 0.1 %. The rel. standard deviation s_{rel} of the assay determinations was ≤ 2 %.

Apparatus	HPLC system with gradient capability, autosampler and UV detector
Column	Waters Xterra™ MS C_8 Length 50 mm, internal diameter 4.6 mm, particle size 2.5 µm, Part number 186000603.
Chromatographic conditions	
Mobile phase A	100 mM $NaClO_4$ buffer, pH 2.8:methanol = 93:7 (v/v)
Mobile phase B	Acetonitrile

Gradient program (linear)

Time [min.]	Phase A [%]	Phase B [%]
0	70	30
1.0	70	30
15.0	58	42
28.0	5	95
30.0	5	95
30.1	70	30
35.0	70	30

Flow rate	1.5 ml/min
Detection	UV detection at 215 nm
Column temperature	30°C

Auto-sampler Temperature	Ambient
Injection volume	10 µl
Run time	35 min

The tables below provide a list of potentially feasible excipients including the results of the stability program.

Example 1: FTY720 stability test with selected fillers

Excipient	Assay in %	Σ impurities in %
Lactose anhydrous	101.4	0.0
Maize starch	102.2	0.0
Mannitol	102.3	0.0
Mannitol granulated (SD 200)	99.5	0.3
Avicel	97.9	0.2
Citric acid + Mannitol (10+90)	102.4	0.0
Sodium hydrogen carbonate + Mannitol (10+90)	102.7	0.0

Example 2: FTY720 stability test with selected binders

Excipient	Assay in %	Σ impurities in %
HPMC 3cPs	97.8	0.0
HP-Cellulose LH-22	99.8	0.4

Example 3: FTY720 stability test with selected disintegrants:

Excipient	Assay in %	Σ impurities in %
Maize starch	102.2	0.0
Crosscarmellose sodium	102.4	0.0
Sodium carboxymethylstarch (Primojel)	103.2	0.0
Starch 1500 (Sta RX)	101.3	0.0

Example 4: FTY720 stability test with selected lubricants:

Excipient	Assay in %	Σ impurities in %

Hydrogenated ricinoleic oil (Cutina)	103.6	0.0
Mg stearate + Manitol (1+99)	103.5	0.5

Example 5: FTY720 stability test with selected flow regulators:

Excipient	Assay in %	Σ impurities in %
Aerosil 200	101.5	0.6

Example 6: FTY720 stability test with selected matrix formers:

Excipient	Assay in %	Σ impurities in %
Hydroxypropyl methyl cellulose	97.8	0.0
Hydroxypropyl cellulose	99.8	0.4
Methyl cellulose	-	-
Ethyl cellulose	-	-
Pullulan	-	-
Starch, e.g. Pure Cote	102.2	0.0
Povidone	95.4	0.5

Polymers having different molecular weights may be used in the same formulation, e.g. having a low and a high molecular weight, i.e. one can use a mixture of e.g. cellulose type polymers having a low and a high MW to provide for different properties.

Example 7: FTY720 stability test with selected plastisizers:

Excipient	Assay in %	Σ impurities in %
PEG 400	-	-
Dibutyl sebacate	-	-
Sorbitol	-	-

Example 8: FTY720 stability test with selected flavoring agents:

Excipient	Assay in %	Σ impurities in %
Menthol	-	-
Tutti frutti		

Example 9: FTY720 stability test with selected sweeteners:

Excipient	Assay in %	Σ impurities in %

Sucralose	-	-
Sodium saccharine	-	-

Example 10: Non-feasible excipients

An example of a non-feasible excipient is shown below. The method to prepare the binary mixtures and the analytical characterization are the same as describe before.

Excipient	Assay in %	Σ impurities in %
Glycerylbehenat (Compritol)	96.2	> 2

Example 10: S1P Assays

The binding affinity of S1P receptor modulators to individual human S1P receptors may be determined in following assay:

S1P receptor modulator activities of compounds are tested on the human S1P receptors $S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$ and $S1P_5$. Functional receptor activation is assessed by quantifying compound induced GTP [γ-^{35}S] binding to membrane protein prepared from transfected CHO or RH7777 cells stably expressing the appropriate human S1P receptor. The assay technology used is SPA (scintillation proximity based assay). Briefly, DMSO dissolved compounds are serially diluted and added to SPA- bead (Amersham-Pharmacia) immobilised S1P receptor expressing membrane protein (10-20µg/well) in the presence of 50 mM Hepes, 100 mM NaCl, 10 mM $MgCl_2$, 10 µM GDP, 0.1% fat free BSA and 0.2 nM GTP [γ-^{35}S] (1200 Ci/mmol). After incubation in 96 well microtiterplates at RT for 120 min, unbound GTP [γ -^{35}S] is separated by a centrifugation step. Luminescence of SPA beads triggered by membrane bound GTP [γ-^{35}S] is quantified with a TOPcount plate reader (Packard). EC_{50}s are calculated using standard curve fitting software. In this assay, the S1P receptor modulators preferably have a binding affinity to S1P receptor <50 nM.

Preferred S1P receptor modulators are e.g. compounds which in addition to their S1P binding properties also have accelerating lymphocyte homing properties, e.g. compounds which elicit a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression. Naïve cells are sequestered; CD4 and CD8 T-cells and B-cells from the blood are stimulated to migrate into lymph nodes (LN) and Peyer's patches (PP).

The lymphocyte homing property may be measured in following Blood Lymphocyte Depletion assay:

A S1P receptor modulator or the vehicle is administered orally by gavage to rats. Tail blood for hematological monitoring is obtained on day –1 to give the baseline individual values, and at 2, 6, 24, 48 and 72 hours after application. In this assay, the S1P receptor agonist or modulator depletes peripheral blood lymphocytes, e.g. by 50%, when administered at a dose of e.g. < 20 mg/kg.

Final Product Manufacture:

The manufacture of final pharmaceutical products may be carried out using conventional techniques. Examples of such techniques are described below, by way of example.

Compressed tablets

Compressed tablets are exerted to great pressure in order to compact the material. If a sufficiently homogeneous mix of components cannot be obtained with simple mixing, the ingredients must be granulated prior to compression to ensure an even distribution of the active compound in the final tablet. Two basic techniques are used to prepare powders for granulation into a tablet: wet granulation and dry granulation.

Powders that can be mixed well and therefore do not require granulation can be compressed in to a tablet through a technique called Direct Compression.

Lyophilised Tablets

These tablets may be manufactured by way of creating a suspension containing the active ingredient and other excipients, for example Gelatin in an amount, for example, of about 3wt%, structure forming agents, such as mannitol or sorbitol, for example and in an amount, for example, of about 1.5wt%, sweeteners and flavouring agents.

An example of a lyophilised tablet formulation is provided below:

The Gelatin/Mannitol solution is cooled to 23°C and mixed with the active substance. The total solid content is preferably less than 50%. The suspension is then cooled to 15°C to prevent sedimentation of the suspension before the start of lyophilisation.

Thin Films

The compositions of the present invention may be further mixed with additional excipients to form final products. The final products may be made from the binary compositions using standard techniques, such as the ones below:

Possible manufacturing comprises casting, drawing, extrusion or coating/lamination processes:

Casting is a manufacturing process by which the drug/excipient mixture is introduced into a mold, allowed to solidify within the mold, and then ejected or broken out to make the individual thin film.

Drawing produces a roll by pulling on a molten drug/excipient mixture until it increases in length. This is typically accompanied by a thinning out of the material. The single units are then cut or punched out ot these roles and packed, e.g. into pouches.

Extrusion creates rolls by pushing and/or drawing through a die of the desired profile shape. Extrusion may be continuous (producing indefinitely long material) or semi-continuous (producing many short pieces). The single units are then cut or punched out of these roles and packed, e.g. into pouches.

Coating/lamination could be described as manufacturing a laminate first by coating and lamination. The resulting roll is then splitted into smaller rolls. The single units are then cut or punched out of these roles and packed, e.g. into pouches.

According to the invention, the compositions of the present invention, e.g. the final dosage form, are useful for:

a) treatment and prevention of organ or tissue transplant rejection, for example for the treatment of the recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants, and the prevention of graft-versus-host disease, such as sometimes occurs following bone marrow transplantation; particularly in the treatment of acute or chronic allo- and xenograft rejection or in the transplantation of insulin producing cells, e.g. pancreatic islet cells;

b) treatment and prevention of autoimmune disease or of inflammatory conditions, e.g. multiple sclerosis, arthritis (for example rheumatoid arthritis), inflammatory bowel disease, hepatitis, etc.;

c) treatment and prevention of viral myocarditis and viral diseases caused by viral mycocarditis, including hepatitis and AIDS.

d) treatment and prevention of cancer, e.g. solid tumors, carcinoma, e.g. for preventing metastatic spread of tumours or for preventing or inhibiting growth of micrometastasis

By "solid tumors" are meant tumors and/or metastasis (whereever located) other than lymphatic cancer, e.g. brain and other central nervous system tumors (eg. tumors of the meninges, brain, spinal cord, cranial nerves and other parts of central nervous system, e.g. glioblastomas or medulla blastomas); head and/or neck cancer; breast tumors; circulatory system tumors (e.g. heart, mediastinum and pleura, and other intrathoracic organs, vascular tumors and tumor-associated vascular tissue); excretory system tumors (e.g. kidney, renal pelvis, ureter, bladder, other and unspecified urinary organs); gastrointestinal tract tumors (e.g. oesophagus, stomach, small intestine, colon, colorectal, rectosigmoid junction, rectum, anus and anal canal), tumors involving the liver and intrahepatic bile ducts, gall bladder, other and unspecified parts of biliary tract, pancreas, other and digestive organs); oral cavity (lip, tongue, gum, floor of mouth, palate, and other parts of mouth, parotid gland, and other parts of the salivary glands, tonsil, oropharynx, nasopharynx, pyriform sinus, hypopharynx, and other sites in the lip, oral cavity and pharynx); reproductive system tumors (e.g. vulva, vagina, Cervix uteri, Corpus uteri, uterus, ovary, and other sites associated with female genital organs, placenta, penis, prostate, testis, and other sites associated with male genital organs); respiratory tract tumors (e.g. nasal cavity and middle ear, accessory sinuses, larynx, trachea, bronchus and lung, e.g. small cell lung cancer or non-small cell lung cancer); skeletal system tumors (e.g. bone and articular cartilage of limbs, bone articular cartilage and other sites); skin tumors (e.g. malignant melanoma of the skin, non-melanoma skin cancer, basal cell carcinoma of skin, squamous cell carcinoma of skin, mesothelioma, Kaposi's sarcoma); and tumors involving other tissues incluing peripheral nerves and autonomic nervous system, connective and soft tissue, retroperitoneum and peritoneum, eye and adnexa, thyroid, adrenal gland and other endocrine glands and related structures, secondary and unspecified malignant neoplasm of lymph nodes, secondary malignant neoplasm of respiratory and digestive systems and secondary malignant neoplasm of other sites.

Where hereinbefore and subsequently a tumor, a tumor disease, a carcinoma or a cancer is mentioned, also metastasis in the original organ or tissue and/or in any other location are implied alternatively or in addition, whatever the location of the tumor and/or metastasis is.

Accordingly, in further aspects the present invention provides:

1. A composition as defined above, for use in treating or preventing a disease or condition as defined above.

2. A method of treating a subject in need of immunomodulation, comprising administering to the subject an effective amount of a composition as defined above.

3. A method of treating or preventing a disease or condition as defined above, comprising administering to the subject a composition as defined above.

4. Use of a pharmaceutical composition as defined above for the preparation of a medicament for the prevention or treatment of a disease or condition as defined above.

CLAIMS:

1. A binary blend consisting of:

(i) 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol (FTY720) in free form or as a pharmaceutically acceptable salt thereof; and

(ii) one excipient selected from the group consisting of Lactose, HPMC, HPC, crospovidone, Croscarmellose sodium, starch, and Colloidal silicone dioxide.

2. The blend according to claim 1, wherein the compound is 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride salt.

3. The blend according to claim 1 or 2, wherein the level of impurities is not more than 4.5 wt% or no more than 2 wt% for an individual impurity.

4. The blend according to any one of claims 1 to 3 for use as a pharmaceutical.

5. The blend according to any one of claims 1 to 3 for the manufacture of a medicament for the treatment of organ or tissue transplant rejection, graft versus host disease, an autoimmune disease, an inflammatory condition, viral myocarditis, a viral disease caused by viral myocarditis or a cancer.

6. The blend according to any one of claims 1 to 3, for use in the preparation of a medicament for the treatment of an autoimmune disease.