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(54) **SOLID PHARMACEUTICAL COMPOSITIONS
 COMPRISING A SIP RECEPTOR AGONIST
 AND A SUGAR ALCOHOL**

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 application No. PCT/EP2004/003656 on Apr. 6, 2004,
 now abandoned.

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 8, 2003.

(51) **Int. Cl.**

A01N 33/02 (2006.01)

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(58) **Field of Classification Search** 514/649
 See application file for complete search history.

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(57) **ABSTRACT**

A solid pharmaceutical composition suitable for oral administration, comprising:

- (a) a SIP receptor agonist; and
- (b) a sugar alcohol.

32 Claims, No Drawings

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**SOLID PHARMACEUTICAL COMPOSITIONS
COMPRISING A S1P RECEPTOR AGONIST
AND A SUGAR ALCOHOL**

This is a divisional of application Ser. No. 10/552,005 filed on Nov. 14, 2005, which is National Stage of International Application No. PCT/EP2004/003656 filed on Apr. 6, 2004, which claims benefit of provisional Application 60/461,215 filed on Apr. 8, 2003, the entire disclosures of which are hereby incorporated by reference.

The present invention relates to pharmaceutical compositions comprising a sphingosine-1 phosphate receptor agonist. Sphingosine-1 phosphate (hereinafter "S1P") is a natural serum lipid. Presently there are 8 known S1P receptors, namely S1P1 to S1P8. S1P receptor agonists have accelerating lymphocyte homing properties.

S1P receptor agonists are immunomodulating compounds which elicit a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, evoking a generalized immunosuppression. Naive 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), and thus infiltration of cells into transplanted organs is inhibited.

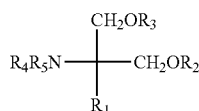
The various known S1P receptor agonists show structural similarities, which result in related problems in providing a suitable formulation. In particular, there is a need for an S1P receptor agonist containing formulation which is well-adapted for oral administration in a solid form, e.g. as a tablet or capsule.

Accordingly, the present invention provides a solid pharmaceutical composition suitable for oral administration, comprising a S1P receptor agonist and a sugar alcohol.

It has surprisingly been found that solid compositions comprising a sugar alcohol provide formulations which are particularly well suited to the oral administration of S1P receptor agonists. The compositions provide a convenient means of systemic administration of S1P receptor agonists, do not suffer from the disadvantages of liquid formulations for injection or oral use, and have good physicochemical and storage properties. In particular, the compositions of the present invention may show a high level of uniformity in the distribution of the S1P receptor agonist throughout the composition, as well as high stability. The compositions of the invention may be manufactured on high speed automated equipment, and thus do not require hand encapsulation.

S1P receptor agonists are typically sphingosine analogues, such as 2-substituted 2-amino-propane-1,3-diol or 2-amino-propanol derivatives. Examples of appropriate S1P receptor agonists are, for example:

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



wherein R₁ is a straight- or branched (C₁₂₋₂₂) carbon chain which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR₆,

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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

R₁ is

a phenylalkyl wherein alkyl is a straight- or branched (C₆₋₂₀) carbon chain; or

a phenylalkyl wherein alkyl is a straight- or branched (C₁₋₃₀) carbon chain wherein said phenylalkyl is substituted by

a straight- or branched (C₆₋₂₀) carbon chain optionally substituted by halogen,

a straight- or branched (C₆₋₂₀) alkoxy chain optionally substituted by halogen,

a straight- or branched (C₆₋₂₀) alkenyloxy, phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl,

cycloalkylalkyl substituted by C₆₋₂₀alkyl,

heteroarylalkyl substituted by C₆₋₂₀alkyl,

heterocyclic C₆₋₂₀alkyl or

heterocyclic alkyl substituted by C₂₋₂₀alkyl,

and wherein

the alkyl moiety may have

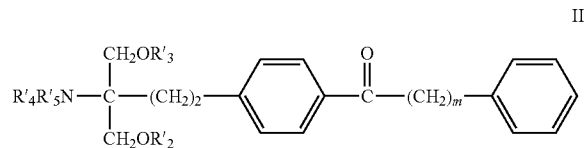
in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR₆, wherein R₆ is as defined above, and

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 R₂, R₃, R₄ and R₅, independently, is H, C₁₋₄ alkyl or acyl

or a pharmaceutically acceptable salt thereof;

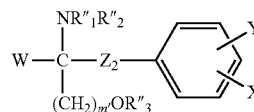
Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II



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 pharmaceutically acceptable salt thereof;

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



wherein W is H; C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl; unsubstituted or by OH substituted phenyl; R''₄O(CH₂)_n; or C₁₋₆alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C₃₋₈cycloalkyl, phenyl and phenyl substituted by OH;

X is H or unsubstituted or substituted straight chain alkyl

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wherein

n_x is 2, 3 or 4

$R_{1,x}$ is H; C_{1-6} alkyl optionally substituted by OH, acyl, halogen, cycloalkyl, phenyl or hydroxy-phenylene; C_{2-6} alkenyl; C_{2-6} alkynyl; or phenyl optionally substituted by OH;

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

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

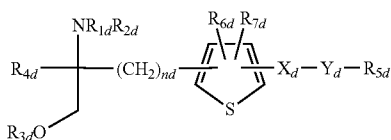
$R_{5,x}$ is H, C_{1-4} alkyl or C_{1-4} alkoxy, and

$R_{6,x}$ is C_{1-20} alkanoyl substituted by cycloalkyl; cycloalkyl- C_{1-4} 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,

$R_{6,x}$ being also C_{4-14} alkoxy when $R_{1,x}$ is C_{2-4} alkyl substituted by OH, or pentyloxy or hexyloxy when $R_{1,x}$ is C_{4-14} alkyl, provided that $R_{6,x}$ is other than phenyl-butyloxy when either $R_{5,x}$ is H or $R_{1,x}$ is methyl,

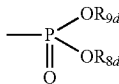
or a pharmaceutically acceptable salt thereof;

Compounds as disclosed in WO02/06268A1, e.g. a compound of formula VII



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

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



$R_{4,d}$ is lower 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;

$R_{5,d}$ 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 $R_{6,d}$ and $R_{7,d}$, independently, is H or a substituent selected from group a;

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

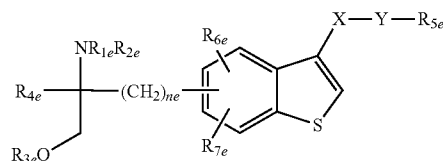
<group a> is halogen, lower alkyl, halogeno lower alkyl, lower alkoxy, lower alkylthio, carboxyl, lower alkoxy-carbonyl, hydroxy, lower aliphatic acyl, amino, mono-lower alky-

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

with the proviso that when $R_{5,d}$ is hydrogen, Y_d is a group exclusive of single bond and linear C_{1-10} alkylene, or a pharmacologically acceptable salt or ester thereof;

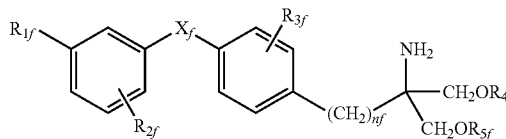
Compounds as disclosed in JP-14316985 (JP2002316985), e.g. a compound of formula VII:



wherein $R_{1,e}$, $R_{2,e}$, $R_{3,e}$, $R_{4,e}$, $R_{5,e}$, $R_{6,e}$, $R_{7,e}$, n_e , X_e and Y_e are as disclosed in JP-14316985;

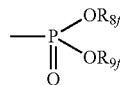
or a pharmaceutically acceptable salt or ester thereof;

Compounds as disclosed in WO 03/29184 and WO 03/29206, e.g. compounds of formula IX



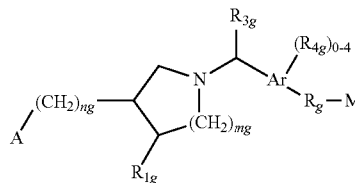
wherein X_f is O or S, and $R_{1,f}$, $R_{2,f}$, $R_{3,f}$ and n_f are as disclosed in WO 03/29184 and 03/29205,

each of $R_{4,f}$ and $R_{5,f}$, independently, is H or a residue of formula



wherein each of $R_{8,f}$ and $R_{9,f}$, independently, is H or C_{1-4} alkyl optionally substituted by halogen; e.g. 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propane-diol or 2-amino-2-[4-(benzyloxyphenylthio)-2-chlorophenyl]propyl-1,3-propane-diol, or a pharmacological salt thereof.

Compounds as disclosed in WO03062252A1, e.g. a compound of formula X



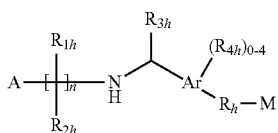
wherein

Ar is phenyl or naphthyl; each of m_g and n_g independently is 0 or 1; A is selected from COOH, PO3H2, PO2H, SO3H, PO(C1-3alkyl)OH and 1H-tetrazol-5-yl; each of $R_{1,g}$ and

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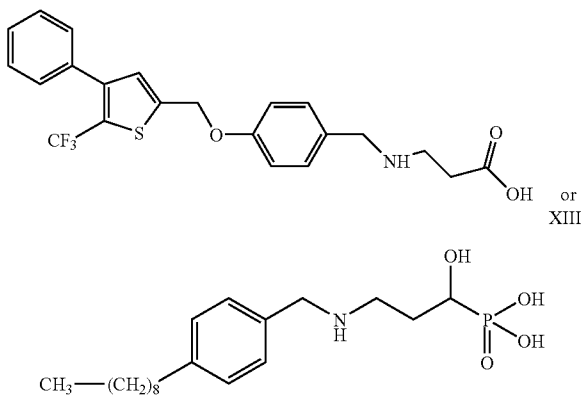
optionally substituted by halogen or OH; each R4g independently is halogen, or optionally halogen substituted C1-4alkyl or C1-3alkoxy; and each of R9 and M has one of the significances as indicated for B and C, respectively, in WO03/062252A1;

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(R5h)OH wherein R5h is selected from C1-4alkyl, hydroxyC1-4alkyl, phenyl, —CO—C1-3alkoxy and —CH(OH)-phenyl wherein said phenyl or phenyl moiety is optionally substituted; each of R1h and R2h independently is H, halogen, OH, COOH, or optionally halogeno substituted C1-6alkyl or phenyl; R3h is H or C1-4alkyl optionally substituted by halogen and/OH; each R4h independently is halogeno, OH, COOH, C1-4alkyl, S(O)0, 1 or 2C1-3alkyl, C1-3alkoxy, C3-6cycloalkoxy, aryl or aralkoxy, wherein the alkyl portions may optionally be substituted by 1-3 halogens; and each of Rg and M has one of the significances as indicated for B and C, respectively, in WO03/062248A2.

According to a further embodiment of the invention, a S1P receptor agonist for use in a combination of 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



In each case where citations of patent applications are

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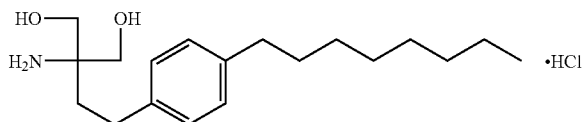
Acyl may be a residue R_y—CO— wherein R_y is C₁₋₄alkyl, C₃₋₆cycloalkyl, phenyl or phenyl-C₁₋₄alkyl. Unless otherwise stated, alkyl, alkoxy, alkenyl or alkynyl may be straight or branched.

When in the compounds of formula I the carbon chain as R₁ 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 R₁ is C₁₃₋₂₀alkyl, optionally substituted by nitro, halogen, amino, hydroxy or carboxy, and, more preferably those wherein R₁ is phenylalkyl substituted by C₆₋₁₄-alkyl chain optionally substituted by halogen and the alkyl moiety is a C₁₋₆alkyl optionally substituted by hydroxy. More preferably, R₁ is phenyl-C₁₋₆alkyl substituted on the phenyl by a straight or branched, preferably straight, C₆₋₁₄alkyl chain. The C₆₋₁₄alkyl chain may be in ortho, meta or para, preferably in para.

Preferably each of R₂ to R₅ 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:



A preferred compound of formula II is the one wherein each of R'₂ to R'₆ is H and m is 4, i.e. 2-amino-2-{2-[(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 CH₃, each of R'₁ to R'₃ is H, Z₂ is ethylene, X is heptyloxy and Y is H, i.e. 2-amino-4-(4-heptyloxyphenyl)-2-methylbutanol, 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 V is phosphoric acid mono-[(R)-2-amino-2-methyl-4-(4-pentyloxy-phenyl)butyl]ester.

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

When the compounds of formulae I to XIII have one or more asymmetric centers in the molecule, the various optical isomers, as well as racemates, diastereoisomers and mixtures thereof are embraced.

Examples of pharmaceutically acceptable salts of the compounds of formulae I to XIII include salts with inorganic acids, such as hydrochloride, hydrobromide and sulfate, salts

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