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

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(51) **Int. Cl.**
A01N 33/02 (2006.01)
A61K 31/135 (2006.01)

(52) **U.S. Cl.** **514/649**

(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 S1P receptor agonist; and
(b) a sugar alcohol.

32 Claims, No Drawings

SOLID PHARMACEUTICAL COMPOSITIONS COMPRISING A SIP 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.

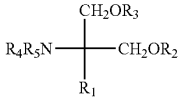
The various known S1P receptor agonists show structural similarities, which result in related problems in providing a suitable formulation. In particular, there is a need for an S1P receptor agonist containing formulation which is well-adapted for oral administration in a solid form, e.g. as a tablet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



I

wherein R_1 is a straight- or branched (C_{12-22})carbon chain which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR_6, wherein R_6 is H, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, and/or

which may have as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, 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 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 heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR_6, wherein R_6 is as defined above, and

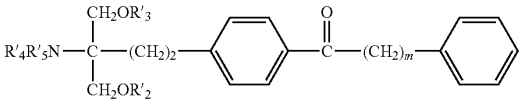
as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxy or carboxy, and

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 thereof;

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

II

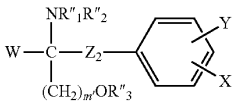


wherein m is 1 to 9 and each of R'_2, R'_3, R'_4 and R'_5, independently, is H, alkyl or acyl,

or a pharmaceutically acceptable salt 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_{1-4}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,

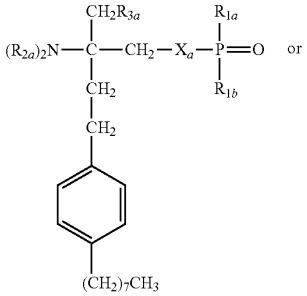
each of p and q, independently, is an integer of 1 to 20, with the proviso of $6 \leqq p+q \leqq 23$, m' is 1, 2 or 3, n is 2 or 3,

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 thereof,

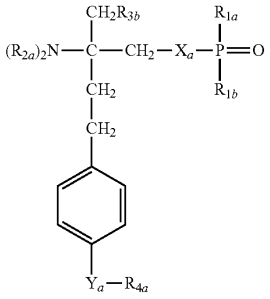
Compounds as disclosed in WO02/18395, e.g. a compound of formula IVa or IVb

IVa



or

IVb

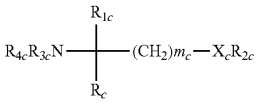


wherein X_a is O, S, NR_{1s} or a group $—(CH_2)_{na}—$, which group is unsubstituted or substituted by 1 to 4 halogen; n_a is 1 or 2, R_{1s} is H or (C_{1-4})alkyl, which alkyl is unsubstituted or substituted by halogen; R_{1a} is H, OH, (C_{1-4})alkyl or $O(C_{1-4})$ alkyl wherein alkyl is unsubstituted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

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

V



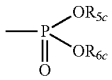
wherein

m_c is 1, 2 or 3;

X_c is O or a direct bond;

R_{1c} is H; CO_{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

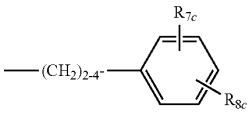


wherein R_{5c} is H or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms, and R_{6c} is H or C_{1-4}alkyl optionally substituted by halogen;

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)

(a)

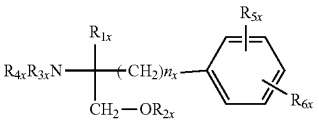


wherein R_{7c} is H, C_{1-4}alkyl or C_{1-4}alkoxy, and r is substituted C_{1-20}alkanoyl, phenylC_{1-14}alkyl wherein the C_{1-14}alkyl is optionally substituted by halogen or OH, cycloalkylC_{1-14}alkoxy or phenylC_{1-14}alkoxy wherein the cycloalkyl or phenyl ring is optionally substituted by halogen, C_{1-4}alkyl and/or CO_{1-4}alkoxy, phenylC_{1-14} alkoxy-C_{1-14}alkyl, phenoxyC_{1-14}alkoxy or phenoxyC_{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_{2-6}alkenyl or C_{2-6}alkynyl,

or a compound of formula VI

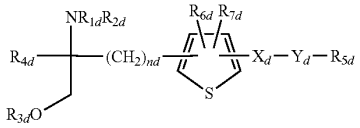
VI



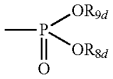
wherein
n_x is 2, 3 or 4
R_{1x} is H; C_{1-6}alkyl optionally substituted by OH, acyl, halogen, cycloalkyl, phenyl or hydroxy-phenylene; C_{2-6}alkenyl; C_{2-6}alkynyl; or phenyl optionally substituted by OH;
R_{2x} is H, C_{1-4} alkyl or acyl
each of R_{3x} and R_{4x}, independently is H, C_{1-4}alkyl optionally substituted by halogen or acyl,
R_{5x} is H, C_{1-4}alkyl or C_{1-4}alkoxy, and
R_{6x} is C_{1-20}alkanoyl substituted by cycloalkyl; cycloalkylC_{1-14}alkoxy wherein the cycloalkyl ring is optionally substituted by halogen, C_{1-4}alkyl and/or C_{1-4}alkoxy; phenylC_{1-14}alkoxy wherein the phenyl ring is optionally substituted by halogen, C_{1-14}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_{4-14}-alkyl,
provided that R_{6x} is other than phenyl-butylenoxy when either R_{5x} is H or R_{1x} is methyl,
or a pharmaceutically acceptable salt thereof;

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

VII



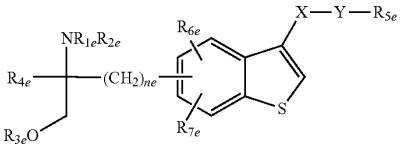
wherein each of R_{1d} and R_{2d}, independently, is H or an amino-protecting group;
R_{3d} is hydrogen, a hydroxy-protecting group or a residue of formula



R_{4d} is 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 substitutents 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 substitutents 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_{6d} and R_{7d}, independently, is H or a substituent 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-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 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:

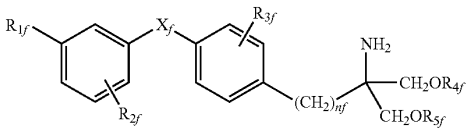
VIII



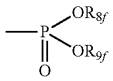
wherein R_{1e}, R_{2e}, R_{3e}, R_{4e}, R_{5e}, R_{6e}, R_{7e}, n_e, X_e and Y_e are as disclosed in JP-14316985;
or a pharmacologically acceptable salt or ester thereof;

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

IX



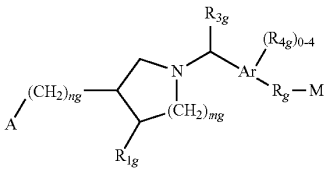
wherein X_f is O or S, and R_{1f}, R_{2f}, R_{3f} and n_f are as disclosed in WO 03/29184 and 03/29205,
each of R_{4f} and R_{5f}, independently is H or a residue of formula



wherein each of R_{8f} and R_{9f}, 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

X

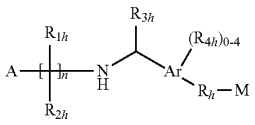


wherein
Ar is phenyl or naphthyl; each of mg and ng independently is 0 or 1; A is selected from COOH, PO3H2, PO2H, SO3H, PO(C1-3alkyl)OH and 1H-tetrazol-5-yl; each of R1g and R2g independently is H, halogen, OH, COOH or C1-4alkyl optionally substituted by halogen; R3g is H or C1-4alkyl

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

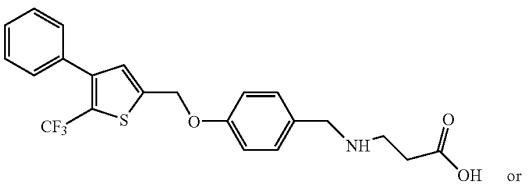
XI



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.

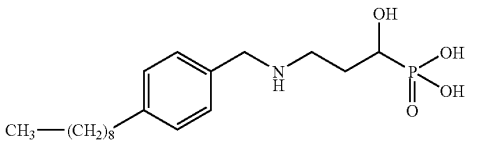
According to a further embodiment of the invention, a S1P receptor agonist for use in a combination of the invention may also be a selective S1P1 receptor, e.g. a compound which possesses a selectivity for the S1P1 receptor over the S1P3 receptor of at least 20 fold, e.g. 100, 500, 1000 or 2000 fold, 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

XII



or

XIII



In each case where citations of patent applications are given, the subject matter relating to the compounds is hereby incorporated into the present application by reference.

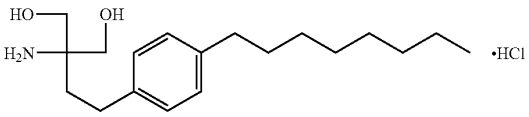
Acyl may be a residue R_y—CO— wherein R_y is C_{1-4}alkyl, C_{3-6}cycloalkyl, phenyl or phenyl-C_{1-4}alkyl. Unless otherwise stated, alkyl, alkoxy, alkenyl or alkynyl may be straight or branched.

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:



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 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-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 with organic acids, such as acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate and benzene-

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