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Hiestand et al.

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(54) **S1P RECEPTOR MODULATORS FOR TREATING RELAPSING-REMITTING MULTIPLE SCLEROSIS**

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Christian Schnell, Helsingue (FR)

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(72) Inventors: **Peter C. Hiestand**, Austria (CH);
Christian Schnell, Helsingue (FR)

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(73) Assignee: **Novartis AG**, Basel (CH)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(21) Appl. No.: **14/257,342**

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(22) Filed: **Apr. 21, 2014**

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(65) **Prior Publication Data**

US 2014/0228446 A1 Aug. 14, 2014

Related U.S. Application Data

(60) Division of application No. 13/149,468, filed on May 31, 2011, now Pat. No. 8,741,963, which is a continuation of application No. 12/303,765, filed as application No. PCT/EP2007/005597 on Jun. 25, 2007, now abandoned.

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(30) **Foreign Application Priority Data**

Jun. 27, 2006 (GB) 0612721.1

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(51) **Int. Cl.**

A61K 31/13 (2006.01)

C07C 215/08 (2006.01)

A61K 31/137 (2006.01)

A61K 31/397 (2006.01)

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(Continued)

(52) **U.S. Cl.**

CPC *C07C 215/08* (2013.01); *A61K 31/137* (2013.01); *A61K 31/397* (2013.01); *A61K 31/13* (2013.01)

Primary Examiner — Kevin E Weddington

(74) *Attorney, Agent, or Firm* — Jim Lynch

(58) **Field of Classification Search**

CPC A61K 31/13; A61K 31/137

USPC 514/667, 903

See application file for complete search history.

(57) **ABSTRACT**

The present invention relates uses of an S1P receptor modulator 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

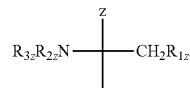
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for the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis.

6 Claims, No Drawings

(56)

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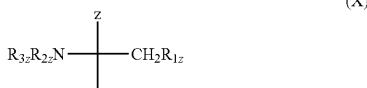
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**S1P RECEPTOR MODULATORS FOR
TREATING RELAPSING-REMITTING
MULTIPLE SCLEROSIS**

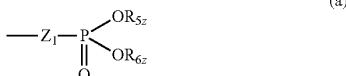
The present invention relates to the use of an S1P receptor modulator in the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis.

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 X.

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



wherein Z is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, phenyl, phenyl substituted by OH, C₁₋₆alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C₃₋₈cycloalkyl, phenyl and phenyl substituted by OH, or CH₂-R_{4z} wherein R_{4z} is OH, acyloxy or a residue of formula (a)



wherein Z₁ is a direct bond or O, preferably O; each of R_{5z} and R_{6z}, independently, is H, or C₁₋₄alkyl 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, C₁₋₄alkyl 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.

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 G α -GTP and G $\beta\gamma$ -GTP, and/or increased phosphorylation of the agonist-occupied receptor and activation of downstream signaling pathways/kinases.

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 S1P₁, S1P₂, S1P₃, S1P₄ and S1P₅. Functional receptor activation is assessed by quantifying compound induced GTP [γ -³⁵S] binding to membrane protein prepared from transfected CHO or RH7777 cells sta-

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bly 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 (10-20 $\mu\text{g}/\text{well}$) in the presence of 50 mM HEPES, 100 mM NaCl, 10 mM MgCl₂, 10 μM GDP, 0.1% fat free BSA and 0.2 nM GTP [γ -³⁵S] (1200 Ci/mmol). After incubation in 96 well microtiterplates at RT for 120 min, unbound GTP [γ -³⁵S] is separated by a centrifugation step. Luminescence of SPA beads triggered by membrane bound GTP [γ -³⁵S] is quantified with a TOPcount plate reader (Packard). EC₅₀s are calculated using standard curve fitting software. In this assay, the S1P receptor modulators preferably have a binding affinity to S1P receptor <50 nM.

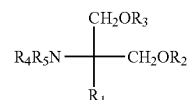
Preferred S1P receptor modulators are e.g. compounds which in addition to their S1P binding properties also have accelerating lymphocyte homing properties, e.g. compounds which elicit a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression. Nave 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.

Examples of appropriate S1P receptor modulators are, for example:

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



wherein R₁ is a straight- or branched (C₁₂₋₂₂) chain which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR₆, wherein R₆ is H, C₁₋₄alkyl, aryl-C₁₋₄alkyl, acyl or (C₁₋₄alkoxy)carbonyl, and carbonyl, and/or which may have as a substituent C₁₋₄alkoxy, C₂₋₄alkenyl, C₂₋₄alkynyl, aryl(C₁₋₄alkyl)-oxy, acyl, C₁₋₄alkylamino, acylamino, (C₁₋₄alkoxy)carbonyl, (C₁₋₄alkoxy)-carbonylamino, acyloxy, (C₁₋₄alkyl) 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,

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a straight- or branched (C₆₋₂₀)alkenyloxy, phenyl-C₁₋₁₄alkoxy, halophenyl-C₁₋₁₄alkoxy, phenyl-C₁₋₁₄alkoxy-C₁₋₁₄alkyl, phenoxy-C₁₋₁₄alkoxy or phenoxy-C₁₋₁₄alkyl, cycloalkylalkyl substituted by C₆₋₂₀alkyl, heteroarylalkyl substituted by C₆₋₂₀alkyl, heterocyclic C₆₋₂₀alkyl or heterocyclic alkyl substituted by C₂₋₂₀alkyl,

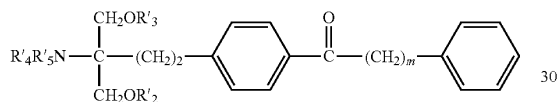
and wherein

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 C₁₋₄alkoxy, C₂₋₄alkenyloxy, C₂₋₄alkynyl, arylC₁₋₄alkoxy, acyl, C₁₋₄alkylamino, C₁₋₄alkylthio, acylamino, (C₁₋₄alkoxy)carbonyl, (C₁₋₄alkoxy)carbonylamino, acyloxy, (C₁₋₄alkyl)carbamoyl, nitro, halogen, amino, hydroxy or carboxy, and each of R₂, R₃, R₄ and R₅, independently, is H, C₁₋₄alkyl or acyl

or a pharmaceutically acceptable salt or hydrate thereof;

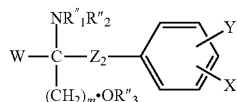
Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II



wherein m is 1 to 9 and each of R'₂, R'₃, R'₄ and R'₅, independently, is H, C₁₋₆alkyl or acyl,

or a pharmaceutically acceptable salt or hydrate 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 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 C₁₋₆alkyl, OH, C₁₋₆alkoxy, acyloxy, amino, C₁₋₆alkylamino, acylamino, oxo, haloC₁₋₆alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of C₁₋₆alkyl, OH, C₁₋₆alkoxy, acyl, acyloxy, amino, C₁₋₆alkylamino, acylamino, haloC₁₋₆alkyl and halogen; Y is H, OH, C₁₋₆alkoxy, acyl, acyloxy, amino, C₁₋₆alkylamino, acylamino, haloC₁₋₆alkyl or halogen, Z₂ is a single bond or a straight chain alkylene having a number or carbon atoms of q,

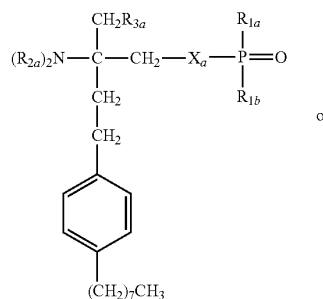
each of p and q, independently, is an integer of 1 to 20, with the proviso of 6 ≤ p + q ≤ 23, m' is 1, 2 or 3, n is 2 or 3,

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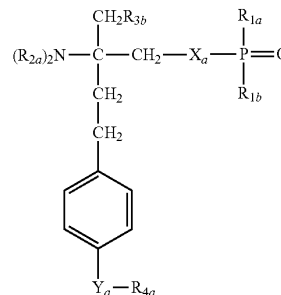
each of R''₁, R''₂, R''₃ and R''₄, independently, is H, C₁₋₄alkyl or acyl,

or a pharmaceutically acceptable salt or hydrate thereof,

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



IVa

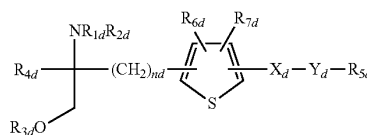


IVb

wherein X_a is O, S, NR_{1a} or a group —(CH₂)_{na}—, which group is unsubstituted or substituted by 1 to 4 halogen; n_a is 1 or 2, R_{1a} is H or (C₁₋₄)alkyl, which alkyl is unsubstituted or substituted by halogen; R_{1b} is H, OH, (C₁₋₄)alkyl or O(C₁₋₄)alkyl wherein alkyl is unsubstituted or substituted by 1 to 3 halogen; R_{1c} is H, OH or (C₁₋₄)alkyl, wherein alkyl is unsubstituted or substituted by halogen; each R_{2a} is independently selected from H or (C₁₋₄)alkyl, which alkyl is unsubstituted or substituted by halogen; R_{3a} is H, OH, halogen or O(C₁₋₄)alkyl wherein alkyl is unsubstituted or substituted by halogen; and R_{3b} is H, OH, halogen, (C₁₋₄)alkyl wherein alkyl is unsubstituted or substituted by hydroxy, or O(C₁₋₄)alkyl wherein alkyl is unsubstituted or substituted by halogen; Y_a is —CH₂—, —C(O)—, —CH(OH)—, —C(=NOH)—, O or S, and R_{4a} is (C₄₋₁₄)alkyl or (C₄₋₁₄)alkenyl;

or a pharmaceutically acceptable salt or hydrate thereof;

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

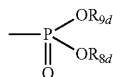


V

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

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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 substituent selected from group a;

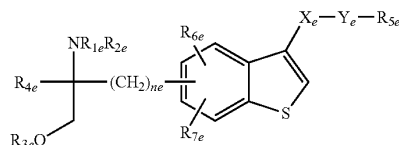
each of R_{8d} and R_{9d} , independently, is H or C_{1-4} alkyl optionally substituted by halogen;

<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- 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 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 VI

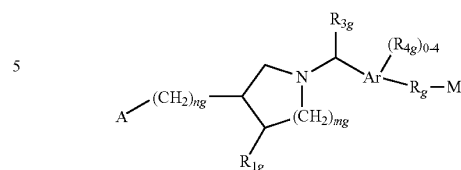


wherein R_{1e} , R_{2e} , R_{3e} , R_{4e} , R_{5e} , R_{6e} , R_{7e} , n_e , X_e and Y_e are as disclosed in JP-14316985;

or a pharmacologically acceptable salt, ester or hydrate thereof;

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

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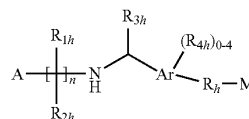


wherein

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 1H-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;

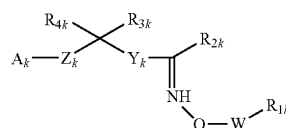
Compounds as disclosed in WO 03/062248A2, e.g. a compound of formula VIII



wherein Ar is phenyl or naphthyl; n is 2, 3 or 4; A is COOH, 1H-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, hydroxy C_{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 halogeno, OH, COOH, $S(O)_{0, 1 \text{ or } 2}C_{1-3}$ 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 IXa or IXb



VII

VIII

IXa

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