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

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(51) **Int. Cl.**

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A61K 31/137	(2006.01)
A61K 31/397	(2006.01)

(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)

(58) **Field of Classification Search**

CPC A61K 31/13; A61K 31/137
USPC 514/667, 903
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2006/0046979	A1	3/2006	Hiestand
2014/0228446	A1	8/2014	Hiestand et al.

FOREIGN PATENT DOCUMENTS

RU	2199339 C2	2/2003
RU	2278687 C1	6/2006
WO	03/097028	11/2003
WO	03/099192	12/2003
WO	2004/028521	4/2004
WO	2004/050073	6/2004
WO	2006/055809	5/2006
WO	2006/058316	6/2006
WO	2006/066086	6/2006

OTHER PUBLICATIONS

Xie et al., "Sphingosine-1-Phosphate Receptor Agonism Impairs the Efficiency of the Local Immune Response by Altering Trafficking of Naive and Antigen-Activated CD + T Cells", J Immunol; vol. 170, pp. 3662-3670, 2003.

Budde et al., "First Human Trial of FTY720, a Novel Immunomodulator, in Stable Renal Transplant Patients". J Am Nephrol, vol. 13, pp. 1073-1083, 2002.

Kataoka et al., "FTY720, Sphingosine 1-Phosphate Receptor Modulator, Ameliorates Experimental Autoimmune Encephalomyelitis by Inhibition of T Cell Infiltration", Cellular & Molecular Immunology, vol. 2, No. 6, pp. 439-448, Dec. 2005.

Forrest et al., "Immune Cell Regulation and Cardiovascular Effects of Sphingosine 1-Phosphate Receptor Agonist in Rodents Are Mediated via Distinct Receptor Subtypes", The Journal of pharmacology and experimental therapeutics (U.S Government work not protected by U.S. copyright), vol. 309, pp. 758-768, 2004.

Suzuki et al., "An immunosuppressive regimen using FTY720 combined with cyclosporin in canine kidney transplantation", Transpl Int., vol. 11, No. 2, pp. 95-101, 1998

Webb et al., "Sphingosine 1-phosphate receptor agonists attenuate relapsing-remitting experimental autoimmune encephalitis in SJL mice", J. Neuroimmun., vol. 153, No. 1, pp. 108-121 (2004).

Brinkmann V. â€œ The immune modulator FTY720 . . . â€• Journal of Biol. Chemistry, Americ. Society of Biolochem. Biol. vol. 277, No. 24. pp. 21453-21457.

Miller et al., Neurol. & Neurosci. Reports, (Sep. 2010), 10(5), pp. 397-406.

Hla, T., FASEB Journal, (Mar. 6, 2006), 20(4), Part 1, A20.

Maschkowskij M.D. Pharmaceuticals, Moscow, Nowaja Wolna, 2001, in 2 volumes, vol. 1 p. 11.

LaMontagne K. â€ž Antagonism of Sphingosine-1-Phosphate Receptors by FTY720 Inhibits Angiogenesis . . . â€œ Cancer Research, Jan. 2006, 66, 221-231. Found on: URL:http://cancerres.aacrjournals.org/content/66/1/221.ful.

Hla. T. Physiological and pathological actions of sphingosine 1-phosphateâ€ Seminars in Cell & Developmental Biology, Oct. 2004, 15(5), 513-520.

Kappos L et al. â€ž FTY720 in relapsing MS . . . â€œ Jun. 23, 2005 online (found Jun. 2, 2011) URL:http://www.ms-in-europe.com/printversion/index.php?anr=105&cnr=4/>.

(Continued)

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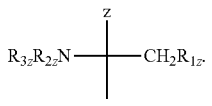
(57) **ABSTRACT**

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

(X)



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

(56) **References Cited**

OTHER PUBLICATIONS

Ho J.W et al. â€ž Effects of a novel immunomodulating agent . . . â€œ Molecular cancer theraputics, 2005 Set, 4(9), 1430-1438. Found: http://mct.aacrjournals.org/content/4/9/1430.full.pdf+html.

Virely D.J. â€œ Developing therapeutics for the treatment of multiple sclerosis.â€· Journal of American Society for Experimental Neuro Therapeutics. Oct. 2005, 2, 638-649. Found on: http://pubget.com/paper/16489371.

Fujino et al. â€˜ Amelioration of experimental autoimmune encephalomyelitis . . . â€™ The Journal of Pharmacology and Experimental Therapeutics, vol. 305, No. 1, pp. 70-77.

K. Rammohan et al, Poster on â€˜ Long-Term Safety of Fingolimod in Patients with Relapsing-Remitting Multiple Sclerosis: Results from Phase 3 FREEDOMS II Extension Studyâ€™ Mar. 16-23, 2013, San Diego, US, 65th American Academy of Neurology Annual Meeting.

Ludwik Kappos et Al : "A place controlled trial of oral Fingolimod in relapsing multiple sclerosis", New England Journal of Medecine, Boston, MA , USA, vol. 362, No. 5, Feb. 4, 2010, pp. 387-401.

Thompson A., "FTY720 in multiple sclerosis: the emerging evidence of its therapeutic value", Core Evidence, 2006, No. 1, 3, pp. 157-167.

T.E. Schmidt et al., Multiple Sclerosis, Guide for Physicians, 2nd edition—M., MED press-inform 2010, pp. 15-16 (English Translation).

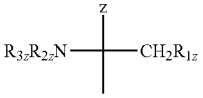
S1P RECEPTOR MODULATORS FOR TREATING RELASPING-REMITTING MULTIPLE SCLEROSIS

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.

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 X.

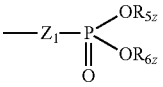
Sphingosine-1 phosphate (hereinafter "S1P") is a natural serum lipid. Presently there are eight known S1P receptors, namely S1P1 to S1P8. S1 P receptor modulators are typically sphingosine analogues, such as 2-substituted 2-amino-propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula X

(X)



wherein Z is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl, phenyl substituted by OH, C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{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 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 Gα-GTP and Gβγ-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 $S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$ and $S1P_5$. Functional receptor activation is assessed by quantifying

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 μg/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. 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).

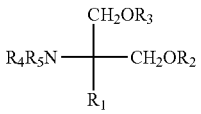
The lymphocyte homing property may be measured in following Blood Lymphocyte Depletion assay:

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

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, 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

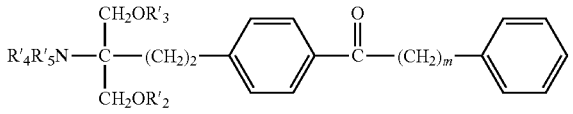
a phenylalkyl wherein alkyl is a straight- or branched (C_{1-30})carbon chain wherein said phenylalkyl is substituted by

a straight- or branched (C_{6-20})carbon chain optionally substituted by halogen,

a straight- or branched (C_{6-20})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}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, 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

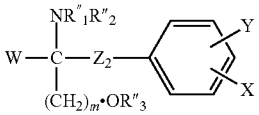
II



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

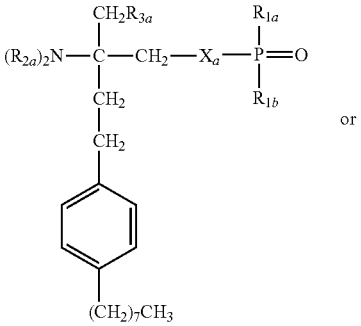


wherein W is H; C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl; unsubstituted or by OH substituted phenyl; $R''_4O(CH_2)_n$; or C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8}cycloalkyl, phenyl and phenyl substituted by OH;
X is H or unsubstituted 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, 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 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,

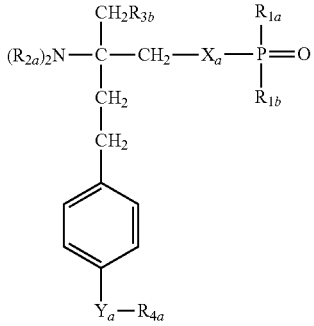
Compounds as disclosed in WO02/18395, e.g. a compound of formula IVa or IVb

IVa



or

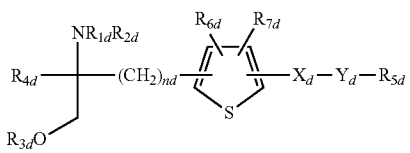
IVb



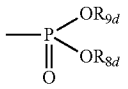
wherein X_a is O, S, NR_{1a} or a group $—(CH_2)_{na}—$, which group is unsubstituted or substituted by 1 to 4 halogen; n_a is 1 or 2, R_{1a} is H or (C_{1-4})alkyl, which alkyl is unsubstituted or substituted by halogen; R_{1a} is H, OH, (C_{1-4})alkyl or O(C_{1-4})alkyl wherein alkyl is unsubstituted 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 WO02/06268AI, e.g. a compound of formula V

V



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 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, 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;

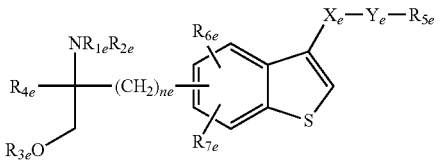
<group a> is halogen, lower alkyl, halogeno lower alkyl, lower alkoxy, lower alkylthio, carboxyl, lower alkoxycarbonyl, hydroxy, lower aliphatic acyl, amino, mono-lower alkylamino, di-C_{1-4}alkylamino, acylamino, cyano or nitro; and

<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 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 VI

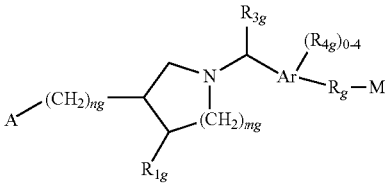
VI



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;

VII



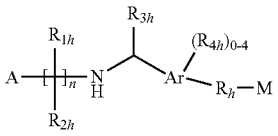
wherein

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

VIII

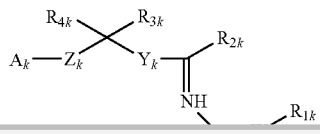


wherein Ar is phenyl or naphthyl; n is 2, 3 or 4; A is COOH, 1H-tetrazol-5-yl, PO_3H_2, PO_2H_2, —SO_3H or $PO(R_{5h})OH$ wherein R_{5h} is selected from C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl, —CO—C_{1-3}alkoxy and —CH(OH)-phenyl wherein said phenyl or phenyl moiety is optionally substituted; each 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 halogeno, OH, COOH, $S(O)_{0,\ 1\ or\ 2}C_{1-3}$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

IXa



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