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(54) Title: USE OF S1P RECEPTOR MODULATOR

(57) Abstract: Use of an S1P receptor modulator in the treatment or prevention of a disease or condition dependent on brain-derived neurotrophic factor (BDNF) expression.

Use of S1P receptor modulator

The present invention relates to the use of an S1P receptor modulator in the treatment or prevention of a disease or condition dependent on brain-derived neurotrophic factor (BDNF) expression.

One of the neurotrophic factors, a brain-derived neurotrophic factor (hereinafter, often referred to as BDNF), is a protein, which is provided from target cells or neurons and glial cells and Schwann cells in the living body, and shows activities to maintain the survival and differentiation of neurons.

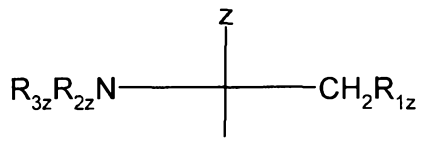
It has now been surprisingly shown that S1P receptor modulators can induce BDNF production.

BDNF has been known as a therapeutic agent for treatment of neurodegenerative diseases (e.g., ALS) or diabetic peripheral neuropathy. BDNF has also been described to be useful as a therapeutic agent for treatment of diabetic mellitus.

Therefore, by inducing BDNF production (or stimulating BDNF expression) S1P receptor modulators can be employed to treat such conditions affected by BDNF, i.e. conditions which can be treated, delayed or prevented by the increased expression of BDNF.

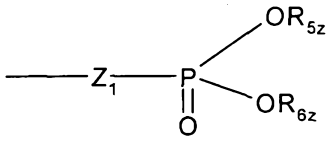
S1P receptor modulators are typically sphingosine analogues, such as 2-substituted 2-amino- propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula Y.

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.

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)

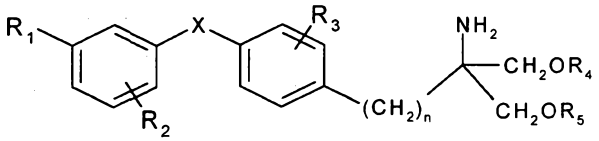
immobilised S1P receptor expressing membrane protein (10-20µg/well) in the presence of 50 mM Hepes, 100 mM NaCl, 10 mM $MgCl_2$, 10 µM GDP, 0.1% fat free BSA and 0.2 nM GTP [γ-^{35}S] (1200 Ci/mmol). After incubation in 96 well microtiterplates at RT for 120 min, unbound GTP [γ -^{35}S] is separated 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.

Examples of appropriate S1P receptor modulators are, for example:

Amino alcohol compounds of formula I



I

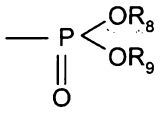
wherein X is O, S, SO or SO_2;
R_1 is halogen, trihalomethyl, OH, C_{1-7}alkyl, C_{1-4}alkoxy, trifluoromethoxy, phenoxy, cyclohexylmethyloxy, pyridylmethoxy, cinnamyloxy, naphthylmethoxy, phenoxymethyl, CH_2-OH, CH_2-CH_2-OH, C_{1-4}alkylthio, C_{1-4}alkylsulfinyl, C_{1-4}alkylsulfonyl, benzylthio, 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)



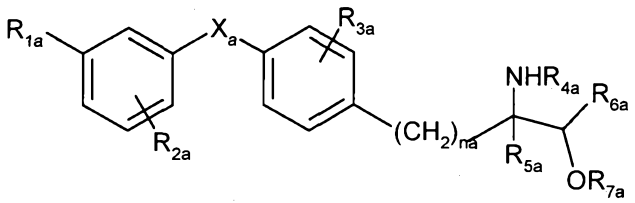
(a)

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 II



II

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

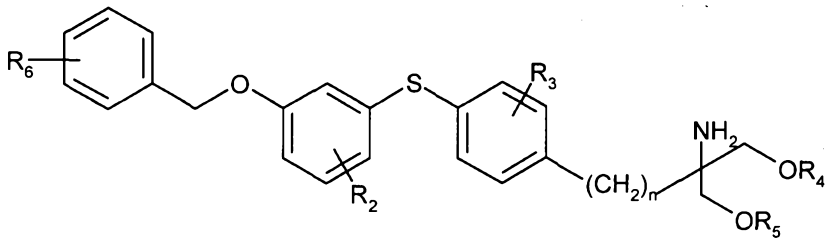
n_a is an integer of 1 to 4;

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 I are compounds of formula Ia



(Ia)

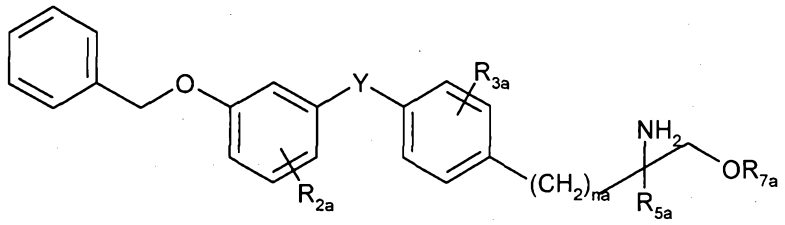
wherein

R_2, R_3, R_4, R_5 and n are as defined above; and

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

Further preferred compounds of formula (Ia) are those wherein R_3 is chlorine, e.g., 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-propane-1,3-diol, 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propane-diol or 2-amino- 2- [4-(3-benzyloxyphenylthio)-2- chlorophenyl]propyl-1,3-propane-diol or a pharmacological salts or hydrates thereof and theirs corresponding phosphate derivatives. Also exemplified is phosphoric acid mono-2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-propyl] ester. The phosphoric acid mono-2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-propyl] ester can be prepared enantiomerically pure by the procedures described in WO 2005/021503.

Other compounds of formula II are compounds of formula (IIa)



IIa

wherein

Y is O or S; and

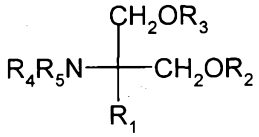
R_{2a}, R_{3a}, R_{5a}, R_{7a} and n_a are as defined above.

Preferred compounds of formula (IIa) are those wherein R_3 is chlorine, e.g., 2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylbutane-1-ol; the corresponding phosphoric acid mono-2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylbutyl] ester; 2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethylbutane-1-ol; and the corresponding phosphoric acid mono-2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethylbutyl] ester.

Compounds of formulae I and II 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 of formulae I and II may be prepared as disclosed in above cited references.

Phosphorylated derivatives of compounds of formula (I), e.g., phosphoric acid mono-2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-propyl] ester, can be prepared utilizing the procedures for synthesizing phosphorylated compounds described e.g., in WO 2005/021503 (see, e.g., pages 11 and 12). Optically active compounds of structural formula (I) and phosphorylated derivatives thereof, in particular of formula (Ia) can be prepared in high purity utilizing the procedure described, e.g., in Hinterding et al., *Synthesis*, Vol. 11, pp.1667-1670 (2003). As an example, an optically active compound of structural formula (Ia), phosphoric acid mono-2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-propyl] ester, can be prepared as described in the scheme below utilizing the procedures of Hinterding et al. (2003) *supra*.

Also included are compounds as disclosed in EP627406A1, e.g. a compound of formula III



III

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

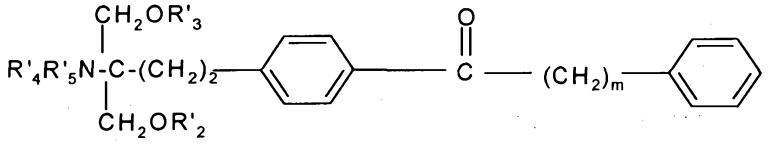
the alkyl moiety may have

- 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;

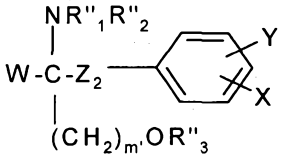
- Compounds as disclosed in EP 1002792A1, e.g. a compound of formula IV



IV

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 V



V

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;

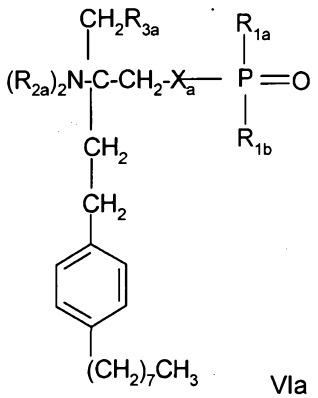
X is H or unsubstituted or substituted straight chain alkyl having a number p of carbon atoms or unsubstituted or substituted straight chain alkoxy having a number (p-1) of carbon atoms, e.g. substituted by 1 to 3 substitutents selected from the group consisting of C_{1-6}alkyl, OH, C_{1-6}alkoxy, acyloxy, 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,

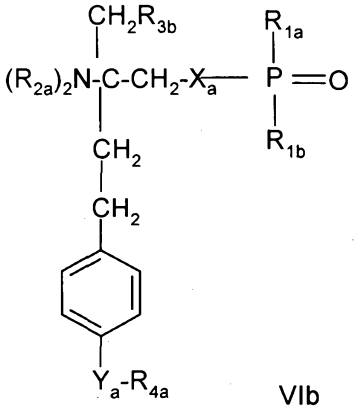
or a pharmaceutically acceptable salt or hydrate thereof,

- Compounds as disclosed in WO02/18395, e.g. a compound of formula VIa or VIb



VIa

or

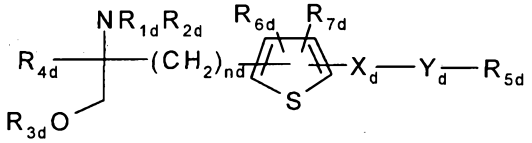


VIb

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;

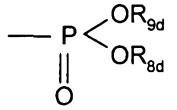
- Compounds as disclosed in WO02/06268Al, e.g. a compound of formula VII



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 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;

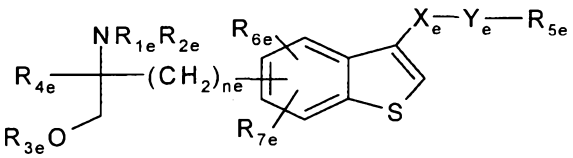
each of R_{8d} and R_{9d}, independently, is H or C_{1-4}alkyl optionally substituted by halogen;

<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 VII

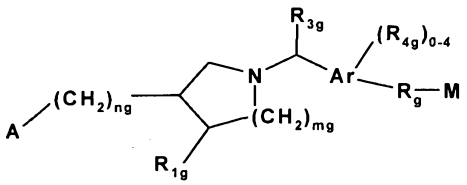


VIII

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, ester or hydrate thereof;

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



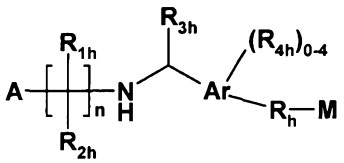
IX

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 X

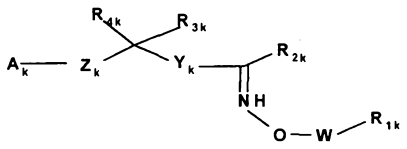


X

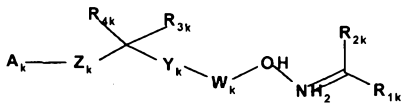
wherein Ar is phenyl or naphthyl; n is 2,3 or 4; A is COOH, 1*H*-tetrazol-5-yl, PO_3H_2, PO_2H_2, SO_3H or $PO(R_{5h})OH$ wherein R_{5h} is selected from C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl, -CO-C_{1-3}alkoxy and –CH(OH)-phenyl wherein said phenyl or phenyl moiety is optionally substituted; each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



XIa



XIb

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 III to XIb 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.

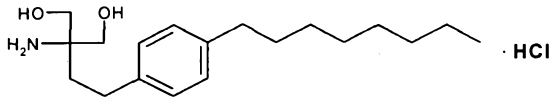
Preferred compounds of formula III are those wherein R_1 is C_{13-20}alkyl, optionally substituted by nitro, halogen, amino, hydroxy or carboxy, and, more preferably those wherein R_1 is phenylalkyl substituted by C_{6-14}-alkyl chain optionally substituted by halogen and the alkyl moiety is a C_{1-6}alkyl 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 III 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 IV 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 V 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 VIa 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 VIII is (2R)-2-amino-4-[3-(4-cyclohexyloxybutyl)-benzo[b]thien-6-yl]-2-methylbutan-1-ol.

A preferred compound of formula XIa 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.

It has now been found that S1P receptor modulators have an inhibitory, preventative or delaying effect on conditions associated with or dependent on or affected by levels of BDNF.

In one particular aspect of the present invention, the compounds as described herein, representing the genus of S1P receptor modulators, increase the levels of BDNF, for example, the compounds as described herein stimulate BDNF production.

A compound which induces brain-derived neurotrophic factor (BDNF) expression can be used as a therapeutic agent for treatment of nervous system disorders and diseases, or treatment of diabetes mellitus.

More particularly, it is useful for nervous system injured by wound, surgery, ischemia, infection, metabolic diseases, malnutrition, malignant tumor, or toxic drug, etc. Especially, it can be used in the treatment of conditions wherein sensory neurons or retinal ganglion cells are injured.

More especially, the compounds can be used in the treatment of congenital conditions or neurodegenerative diseases, for example, Alzheimer's disease, Parkinson's disease (the symptoms of Parkinson's disease may be caused by the degeneration of dopaminergic neuron), Parkinson-Plus syndromes (e.g., progressive spranuclear palsy (Steele-Richardson-Olszewski syndromes), olivopontocerebellar atrophy (OPCA), Shy-Drager syndromes (Multiple Systems Atrophy), and Parkinson dementia complex of Guam), Huntington's disease (Huntington's chorea), and Rett Syndrome, but are not limited thereto.

Further, the compounds can be used in the treatment of sensory nerve dysfunction and congenital diseases or neurodegenerative diseases being associated with degenerative of retina.

In addition, the the compounds can be used in the treatment of inherited convulsive paraplegia associated with retina degeneration (Kjellin and Barnard-Scholz syndromes), retinitis pigmentosa, Stargardt disease, Usher syndromes (retinitis pigmentosa accompanied by congenital hearing loss) and Refsum syndrome (retinitis pigmentosa, congenital hearing loss, and polyneuropathy).

Further, the compounds can be used to treat obesity.

The compounds may also be used to treat cognitive impairment and/or attention deficit disorder, for example deficits and abnormalities in attention and vigilance, executive functions and memory (for instance working memory and episodic memory). Other disorders relating to cognitive dysfunction include sleep related breathing disorders (SRBD), behavioral impairments, information processing deficits and age-related disorders, Attention-deficit hyperactivity disorder (ADHD), childhood ADHD, adult ADHD, excess daytime somnolence, sleep apnea, traumatic brain injury, neurodegenerative disorders with associated memory and cognitive problems (such as Alzheimer's disease, Lewy body dementia, senile dementia, vascular dementia, Parkinson's disease), chronic fatigue syndrome, fatigue associated with sleep deprivation or prolonged wakefulness, age-related decline in memory and cognitive function (such as mild cognitive impairment), cognitive impairment associated with mood disorders (such as depression) and anxiety, schizophrenia, day time sleepiness associated with narcolepsy.

In addition, the compounds can be used to treat sleep disorders, e.g. narcolepsy, primary insomnia, sleep-awake rhythm disorders (e.g., work-shift syndrome, time-zone syndrome (jet-lag)).

In additions, the compounds can be used to treat depressive disorder, e.g. manic-depressive psychosis.

In a further use, the compounds can be useful in making patients feel better.

In a series of further specific or alternative embodiments, the present invention provides:

1.1 A method for preventing, inhibiting or treating a condition effected by BDNF production, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to XIb.

1.2 A method for alleviating or delaying progression of the symptoms of obesity, a sleep disorder or depressive disorder, in a subject in need thereof, in which method the BDNF-dependent factor associated with said disease is prevented or inhibited, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to XIb.

1.3 A method for inducing the production of BDNF, in a subject, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to XIb.

1.4 A method for slowing progression of obesity, a sleep disorder or depressive disorder, in a subject, in which method the BDNF-dependent factor associated with said disease is prevented or inhibited, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to XIb.

1.5 A method as indicated above, wherein the S1P receptor modulator is administered intermittently.

For example, the S1P receptor modulator may be administered to the subject every 2nd or 3rd day or once a week.

2. A pharmaceutical composition for use in any one of the methods 1.1 to 1.5, comprising an S1P receptor modulator, e.g. a compound of formulae I to XIb as defined hereinabove, together with one or more pharmaceutically acceptable diluents or carriers therefor.

3. An S1P receptor modulator, e.g. a compound of formula I to XIb as defined herein above, for use in any one of the methods 1.1 to 1.5.

4 An S1P receptor modulator, e.g. a compound of formulae I to XIb as defined herein above, for use in the preparation of a medicament for use in any one of the methods 1.1 to 1.5.

Utility of the S1P receptor modulators, e.g. the S1P receptor modulators comprising a group of formula Y, in preventing or treating a disease associated with BDNF as hereinabove specified, may be demonstrated in animal test methods as well as in clinic, for example in accordance with the methods hereinafter described.

Example 1: In vivo: S1P receptor modulator induced BDNF production

Female DA rats were treated for 9 days (5 days, 2 day pause, 4 days) with FTY720 p.o.

Expt 1: 0.3 mg/kg/d vs. vehicle.

N=3 rats/group

One day after the last treatment, the rats were perfused with ice-cold PBS and different CNS regions were isolated.

The results are shown in Figure 1.

Example 2: In vivo: S1P receptor modulator induced BDNF production

Female DA rats were treated for 9 days (5 days, 2 day pause, 4 days) with FTY720 p.o.

0.1; 0.3 or 1 mg/kg/d vs vehicle

N=3 rats/group

One day after the last treatment, the rats were perfused with ice-cold PBS and different CNS regions were isolated.

The results are shown in Figure 2.

Example 3: In vitro: S1P receptor modulator induced BDNF production

Effect of FTY720 on BDNF expression in cultured CTX, STR, and HIP neurons was investigated.

Neurons were treated with phosphorylated FTY720 (FTY-p) (1 and 10 nM) for the last 6 days.

Cell lysates were collected at 21 days in vitro.

Y axis indicates levels of BDNF normalized to control.

* $P<0.05$ vs DMSO

The results are shown in Figures 3A, B and C.

Example 4: In vitro: S1P receptor modulator induced BDNF production

Effect of FTY720 on BDNF expression in cultured CTX and HIP neurons was investigated.

Neurons were treated with FTY720 (FTY-p) (0.01, 0.1, 1 and 10 nM) for the last 6 days.

Cell lysates were collected at 21 days in vitro.

Y axis indicates levels of BDNF normalized to control.

The results are shown in Figure 4,

Example 5: Clinical Trial: S1P receptor modulator made people feel better

In a 6-month, placebo controlled, Phase II trial involving 281 patients with relapsing MS, FTY720 reduced gadolinium-enhanced magnetic resonance imaging (MRI) lesions by up to 80%, and the annualized relapse rate by more than 50%, compared with placebo, at doses of 1.25 and 5 mg once daily.[3] The resulting low disease activity on both MRI and relapses was sustained in patients treated with FTY720 for up to 24 months during a dose-blinded

extension phase. Patients who received placebo also had marked improvements after switching to FTY720 in the extension.

In this study, depressive symptoms were assessed by means of the Beck Depression Inventory second edition (BDI-II). These results are presented here.

Method

Patients with relapsing MS (relapsing-remitting or secondary progressive) were randomized to receive placebo or FTY720 1.25 or 5 mg/day, for 6 months (the core study). At the end of this period, placebo-treated patients were re-randomized to one of the two FTY720 doses, while those originally randomized to FTY720 continued treatment at the same doses. After approximately 18-24 months, patients receiving FTY720 5 mg, were switched to 1.25 mg in view of evidence that the higher dose conferred no efficacy benefit over the lower dose.

The BDI-II was administered at baseline, and at 3 and 6 months during the core study and at 12 and 24 months during the extension phase (i.e. 6 and 18 months after the start of the extension phase). This is a 21-item self-report scale measuring various symptoms and attitudes associated with depression. Respondents rate depressive symptoms experienced during the past two weeks on a 4-point scale, coded 0 to 3 by increasing order of severity.. A total score across all 21 items can be generated, with lower total scores indicating lower overall severity of depressive symptoms. BDI-II total scores of 14 or above are indicative of clinical depression. Ny reduction in the BDI-II score indicated an improvement in depression.

Results

Patients

Of the 281 patients originally randomized to treatment, 255 completed the core study. BDI-II scores at baseline and 6 months were available in 239 patients.

Changes in BDI-II scores during the core study

Mean BDI-II scores during the core study are shown in Figure 5, and changes in these scores from baseline during the core study are shown in Figure 6. BDI-II scores decreased from baseline in patients receiving FTY720 1.25 mg/day, remained consistent in patients receiving FTY720 5.0 mg/day, and increased in patients on placebo. At 6 months, the change in BDI-II scores from baseline in FTY720 1.25 mg/day treated patients was

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significantly greater than in placebo-treated patients. The difference in changes in BDI-II scores between the two doses of FTY720 was not significant at the 5% level.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for preventing, inhibiting or treating depression associated with multiple sclerosis effected by BDNF production, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator selected from the group consisting of 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-propane-1,3-diol, 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid and 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, or in each case a pharmaceutically acceptable salt thereof and/or a phosphoylated form thereof.

2. A method according to claim 1, wherein the S1P receptor modulator is 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, or a pharmaceutically acceptable salt thereof.

3. A method according to claim 1, wherein the S1P receptor modulator is 1-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol hydrochloride.

4. A method according to claim 1, wherein the S1P receptor modulator is 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-propane-1,3-diol, or a pharmaceutically acceptable salt thereof.

5. A method according to claim 1, wherein the S1P receptor modulator is 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

6. A method according to any one of claims 1 to 5, wherein the S1P receptor modulator is administered intermittently.

7. A method according to any one of claims 1 to 6 comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective non-toxic amount of a S1P receptor modulator as defined in any one of claims 1 to 5 and a second therapeutic substance.

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8. Use of an S1P receptor modulator selected from the group consisting of 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-propane-1,3-diol, 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid and 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, or in each case a pharmaceutically acceptable salt thereof and/or a phosphoylated form thereof, in the manufacture of a medicament for preventing, inhibiting or treating depression associated with multiple sclerosis effected by BDNF production.

9. Use according to claim 8, wherein the S1P receptor modulator is 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, or a pharmaceutically acceptable salt thereof.

10. Use according to claim 8, wherein the S1P receptor modulator is 1-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol hydrochloride.

11. Use according to claim 8, wherein the S1P receptor modulator is 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-propane-1,3-diol, or a pharmaceutically acceptable salt thereof.

12. Use according to claim 8, wherein the S1P receptor modulator is 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

13. A method or use according to any one of claims 1 to 12 substantially as hereinbefore described.

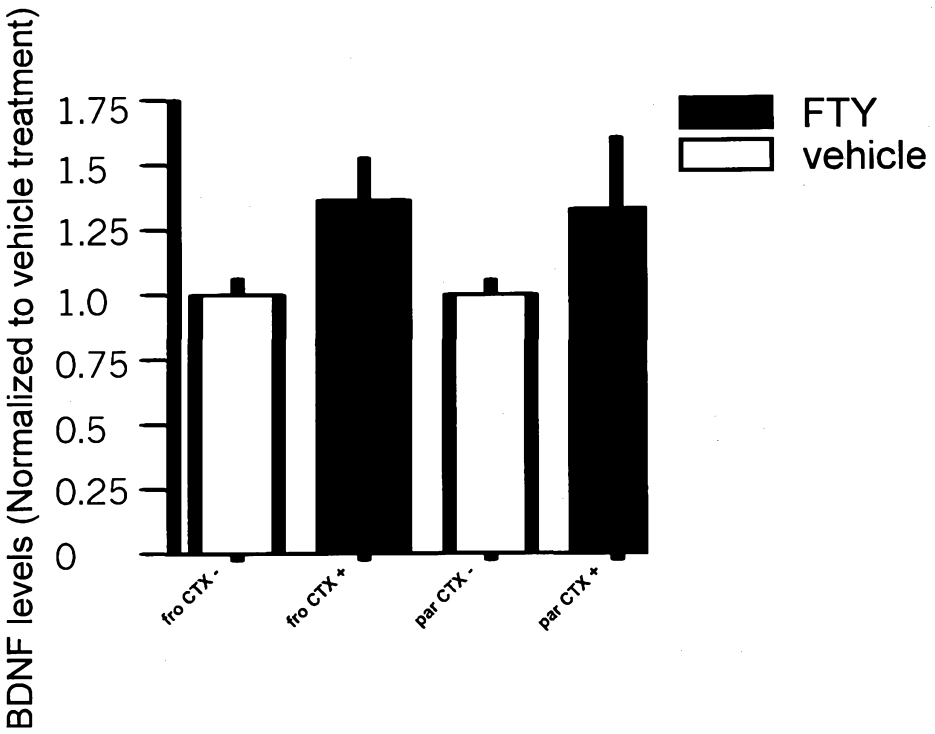
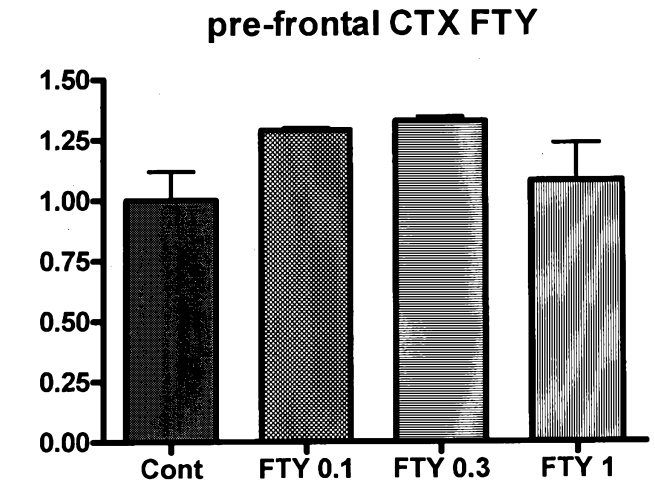

BDNF levels (Normalized to vehicle treatment)
1.75
1.5
1.25
1.0
0.75
0.5
0.25
0
fro CTX -
fro CTX +
par CTX -
par CTX +
FTY
vehicle

Figure 1


pre-frontal CTX FTY
1.50
1.25
1.00
0.75
0.50
0.25
0.00
Cont
FTY 0.1
FTY 0.3
FTY 1

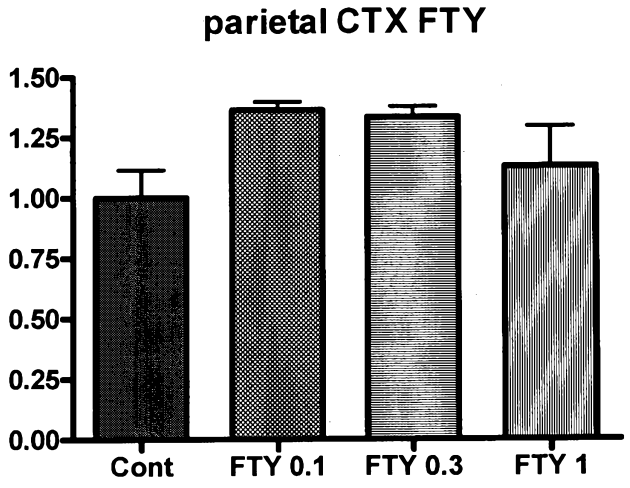

parietal CTX FTY
1.50
1.25
1.00
0.75
0.50
0.25
0.00
Cont
FTY 0.1
FTY 0.3
FTY 1

Figure 2

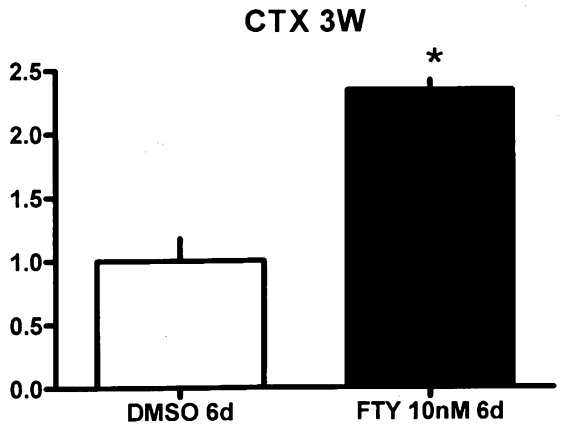


Figure 3A

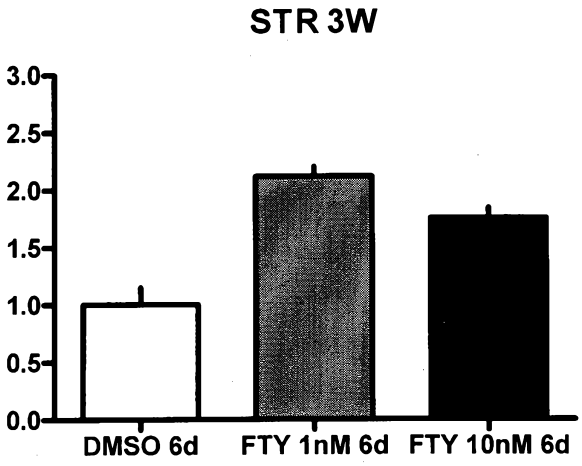


Figure 3B

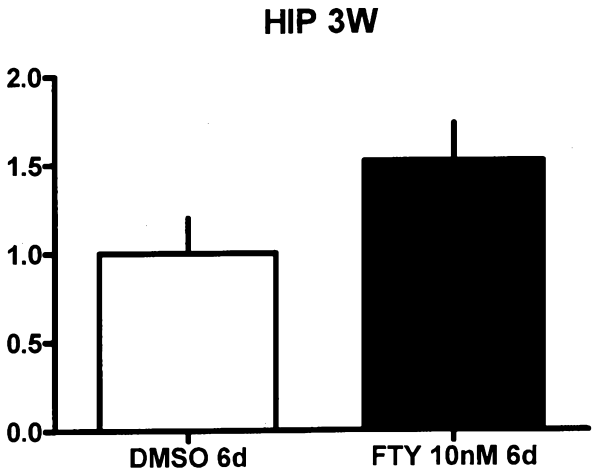
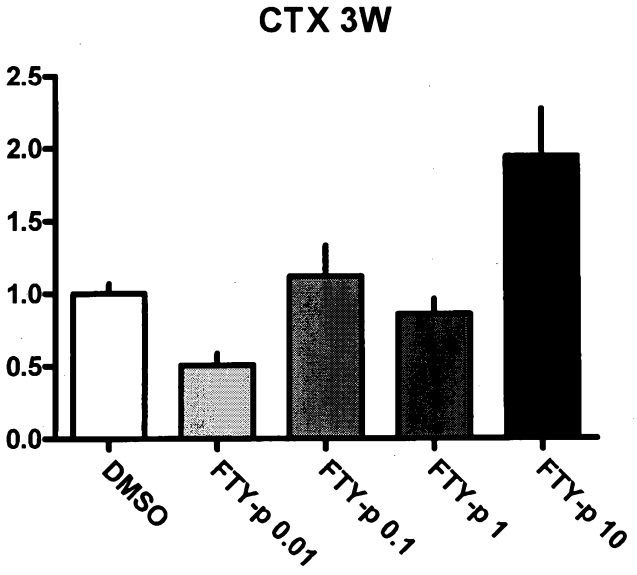


Figure 3C


CTX 3W
2.5
2.0
1.5
1.0
0.5
0.0
DMSO
FTY-p 0.01
FTY-p 0.1
FTY-p 1
FTY-p 10

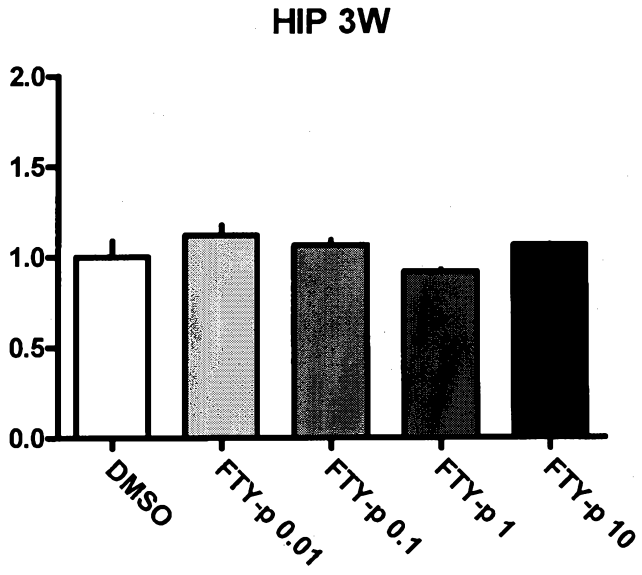

HIP 3W
2.0
1.5
1.0
0.5
0.0
DMSO
FTY-p 0.01
FTY-p 0.1
FTY-p 1
FTY-p 10

Figure 4

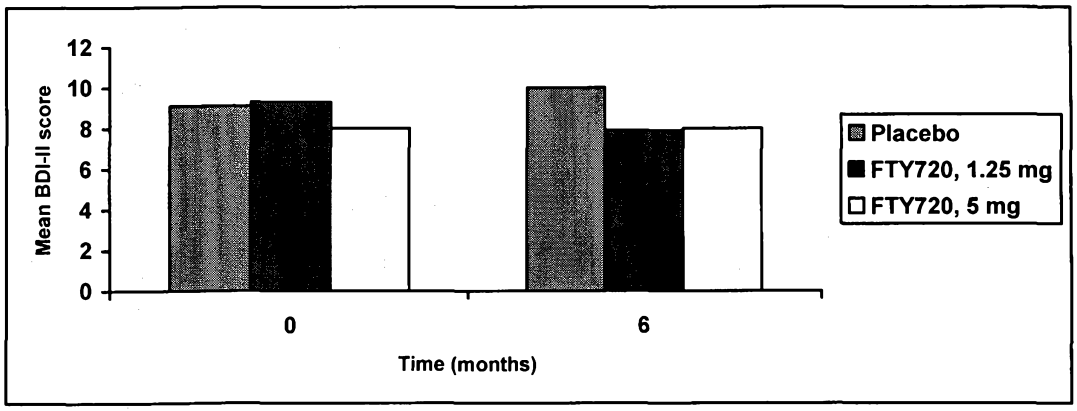


Figure 5. Mean BDI-II scores during the core study.

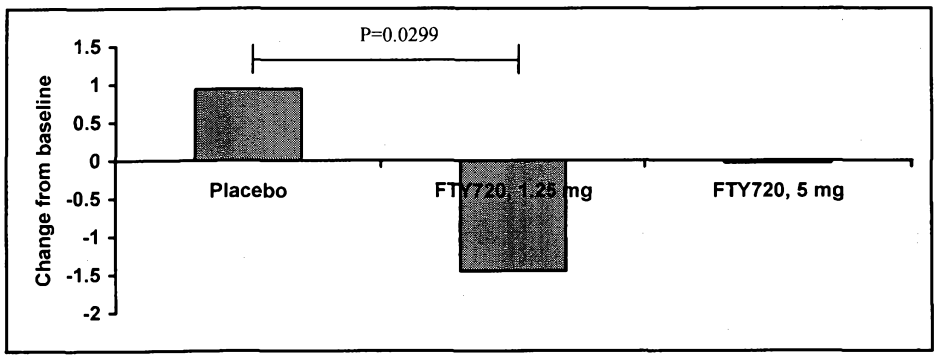


Figure 6. Changes in BDI-II scores from baseline during the core study.