A is selected from -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, -CCH_3-O- and the linking group –Y-$(CH_2)_n$-X- wherein

Y is attached to R1 and selected from a bond, -O-, -S-, -SO-, -SO_2-, -CH_2-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- and -C≡C- ;

n is an integer from 1 to 10; and

X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S-, -SO-, -SO_2-, -NH, -CO-, -C=C- and -C≡C-;

ring structure **B** optionally contains one nitrogen atom;

R2 is H, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, or halogen; and

R3 is (1-4C)alkylene-R5 wherein the alkylene group may be substituted with $(CH_2)_2$ to form a cyclopropyl moiety or one or two halogen atoms, or R3 is is (3-6C)cycloalkylene-R5 or -CO-CH_2-R5, wherein R5 is -OH, -PO_3H_2, -OPO_3H_2, -COOH, -COO(1-4C)alkyl or tetrazol-5-yl;

R4 is H or (1-4C)alkyl;

R6 is one or more substituents independently selected from H, (1-4C)alkyl or oxo;

W is -O-, -S-, -SO- or -SO_2-;

or a pharmaceutically acceptable salt, a solvate or hydrate thereof; with the proviso that the derivative of formula (**I**) is not

2-(4-ethylphenyl)-4-morpholinoethanol or

4-[4-(2-hydroxyethyl)-2-morpholinyl]benzeneacetonitrile.

display affinity for S1P receptors. In particular, compounds of the invention show selective affinity for the S1P5 receptor over the S1P1 and/or S1P3 receptor(s).

The use of the compound 2-(4-ethylphenyl)-4-morpholinoethanol as a reagent in the production of 2-(2-arylmorpholino)ethyl esters of naproxen is described in Database CA [Online] Chemical Abstracts Service, Columbus, OHIO, US; 2008, Hu, Ai-Xi et al, XP002558960 retrieved from STN database accession no. 2008:1527686; & Huaxue Xuebao, 66(22), 2553-2557 Coden: HHHPA4; ISSN: 0567-7351, 2008. No pharmacological activity of the compound is reported.

Similarly, in Farmatsiya (Sofia), Vol.45, no.1, 1998, pages 3-11, XP009126794 Yordanova, K. et al. describe the use of 4-[4-(2-hydroxyethyl)-2-morpholinyl]-benzeneacetonitrile as a reagent in the production of antidepressant phenylmorpholine derivatives. No pharmacological activity of the compound is reported.

Further, in an embodiment of the invention, A is selected from -CO-O-, -NH-CO-, -CO-NH, -C=C-, $-CCH_3-O-$ and the linking group $-Y-(CH_2)_n-X-$ wherein Y is attached to R1 and selected from a bond, -O-, $-SO_2-$, $-CH_2-O-$, -CO-, -CO-O-, -NH-CO-, -C=C- and -C≡C-; n is an integer from 1 to 7; and X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S- and -NH. Preferably, A selected from -CO-NH, -C=C-, $-CCH_3-O-$ and the linking groups $-(CH_2)_n-X-$ and $-O-(CH_2)_n-X-$. In preferred embodiments A is CH_2-O-.

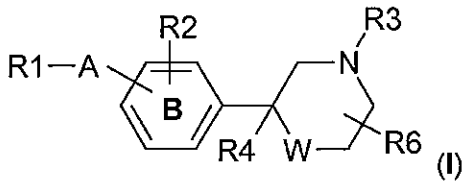
In further embodiments of the invention, R1 is selected from cyano, ethynyl, (1-4C)alkyl, cyclopentyl, cyclohexyl, cyclohexenyl, 6,6-dimethyl-bicyclo[3.1.1]hept-2-yl, indanyl optionally substituted with methyl, biphenyl, naphthyl, phenyl optionally substituted with one, two or three substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (2-4C)alkynyl, (1-4C)alkoxy, dimethylamino, trifluoromethyl, trifluoromethoxy and (3-6C)cycloalkyl, and R1 is further selected from phenyl monosubstituted with phenoxy, benzyl, benzyloxy, phenylethyl, pyrazolyl or triazolyl, and R1 is further selected from pyrazolyl, thiazolyl, oxadiazolyl, thienyl, tetrahydrofuranyl, pyridinyl, tetrahydropyranyl, each optionally substituted with chloro, (1-4C)alkyl or phenyl substituted with (1-4C)alkyl, and R1 is further selected from indolyl, imidazopyridinyl, dihydrobenzofuranyl and benzdioxanyl each optionally substituted with (1-4C)alkyl. In preferred embodiments, R1 is selected from ethynyl, (1-4C)alkyl, cyclopentyl, cyclohexyl, cyclohexenyl, biphenyl, naphthyl, phenyl optionally substituted with one, two or three substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (1-4C)alkoxy, dimethylamino, trifluoromethyl and trifluoromethoxy, and further selected from phenyl monosubstituted with phenoxy, benzyl, benzyloxy, phenylethyl, pyrazolyl or triazolyl, and further selected from thiazolyl, thienyl, tetrahydrofuranyl, pyridinyl, tetrahydropyranyl, each optionally substituted with chloro or (1-4C)alkyl, and benzdioxanyl. In particular, R1 is selected from (1-4C)alkyl, cyclopentyl, cyclohexyl, pyridinyl and phenyl, wherein the latter two groups are optionally substituted with one or two substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (1-4C)alkoxy and trifluoromethyl. In preferred embodiments, R1 is (1-4C)alkyl or dichlorophenyl.

In a highly preferred embodiment of the invention, R1 is 2,6-dichlorophenyl; A is the linking group $-Y-(CH_2)_n-X-$, wherein Y is attached to R1 and is a bond, n is 1 and X is attached to the phenylene group and is -O-; R2 is H; R3 is $-(CH_2)_2-COOH$; and R4 is H.

In further preferred embodiments of the invention, R1 is (1-4C)alkyl; A is the linking group $-Y-(CH_2)_n-X-$, wherein Y is attached to R1 and is a bond, n is an integer

CLAIMS

1. A (thio)morpholine derivative of the formula (I)



(I)

wherein
R1 is selected from
cyano,
(2-4C)alkynyl,
(1-4C)alkyl,
(3-6C)cycloalkyl,
(4-6C)cycloalkenyl,
(6-8C)bicycloalkyl, (8-10C)bicyclic group, each optionally substituted with (1-4C)alkyl,
phenyl, biphenyl, naphthyl, each optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (2-4C)alkynyl, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, amino, di(1-4C)alkylamino, $-SO_2$-(1-4C)alkyl, -CO-(1-4C)alkyl, -CO-O-(1-4C)alkyl, -NH-CO-(1-4C)alkyl and (3-6C)cycloalkyl,
phenyl substituted with phenoxy, benzyl, benzyloxy, phenylethyl or monocyclic heterocycle, each optionally substituted with (1-4C)alkyl,
monocyclic heterocycle optionally substituted with halogen, (1-4C)alkyl or with phenyl optionally substituted with (1-4C)alkyl,
and
bicyclic heterocycle optionally substituted with (1-4C)alkyl;
A is selected from -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, $-CCH_2$-O- and the linking group $-Y-(CH_2)_n-X-$ wherein
Y is attached to R1 and selected from a bond, -O-, -S-, -SO-, $-SO_2$-, $-CH_2$-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- and -C≡C- ;
n is an integer from 1 to 10; and
X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S-, -SO-, $-SO_2$-, -NH, -CO-, -C=C- and -C≡C-;
ring structure **B** optionally contains one nitrogen atom;

R2 is H, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, or halogen; and

R3 is (1-4C)alkylene-R5 wherein the alkylene group may be substituted with $(CH_2)_2$ to form a cyclopropyl moiety or one or two halogen atoms, or R3 is is (3-6C)cycloalkylene-R5 or -CO-CH_2-R5, wherein R5 is -OH, -PO_3H_2, -OPO_3H_2, -COOH, -COO(1-4C)alkyl or tetrazol-5-yl;

R4 is H or (1-4C)alkyl;

R6 is one or more substituents independently selected from H, (1-4C)alkyl or oxo;

W is -O-, -S-, -SO- or -SO_2-;

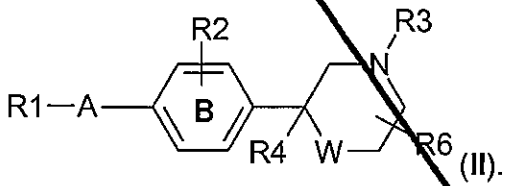
or a pharmaceutically acceptable salt, a solvate or hydrate thereof; with the proviso that the derivative of formula (**I**) is not

2-(4-ethylphenyl)-4-morpholinoethanol or

4-[4-(2-hydroxyethyl)-2-morpholinyl]benzeneacetonitrile.

2. The compound of claim 1, wherein the ring structure **B** is phenylene.

3. The compound of claim 1 or 2, having the structure (**II**)



(II).

4. The compound of any one of claims 1 to 3, wherein R3 is selected from -$(CH_2)_2$-OH, -CH_2-COOH, -$(CH_2)_2$-COOH, -$(CH_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH, -$CHCH_3$-CH_2-COOH, -CH_2-CF_2-COOH, -CO-CH_2-COOH, 1,3-cyclobutylene-COOH, -$(CH_2)_2$-PO_3H_2, -$(CH_2)_3$-PO_3H_2, -$(CH_2)_2$-OPO_3H_2, -$(CH_2)_3$-OPO_3H_2, -CH_2-tetrazol-5-yl, -$(CH_2)_2$-tetrazol-5-yl and -$(CH_2)_3$-tetrazol-5-yl; and W is -O- or -S-.

5. The compound of any one of claims 1 to 4, wherein R2 is H, methyl, methoxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, Cl or F, and R4 is H or methyl.

6. The compound of any one of claims 1 to 5, wherein A is selected from -CO-O-, -NH-CO-, -CO-NH, -C=C-, -CCH_3-O- and the linking group –Y-$(CH_2)_n$-X- wherein Y is attached to R1 and selected from a bond, -O-, -SO_2-, -CH_2-O-, -CO-, -CO-O-,

-NH-CO-, -C=C- and -C≡C-; n is an integer from 1 to 7; and X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S- and –NH.

7. The compound of any one of claims 1 to 6, wherein R1 is selected from cyano, ethynyl, (1-4C)alkyl, cyclopentyl, cyclohexyl, cyclohexenyl, 6,6-dimethyl-bicyclo[3.1.1]hept-2-yl, indanyl optionally substituted with methyl, biphenyl, naphthyl,
phenyl optionally substituted with one, two or three substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (2-4C)alkynyl, (1-4C)alkoxy, dimethylamino, trifluoromethyl, trifluoromethoxy and (3-6C)cycloalkyl,
phenyl monosubstituted with phenoxy, benzyl, benzyloxy, phenylethyl, pyrazolyl or triazolyl,
pyrazolyl, thiazolyl, oxadiazolyl, thienyl, tetrahydrofuranyl, pyridinyl, tetrahydro-pyranyl, each optionally substituted with chloro, (1-4C)alkyl or phenyl substituted with (1-4C)alkyl, and
indolyl, imidazopyridinyl, dihydrobenzofuranyl and benzdioxanyl, each optionally substituted with (1-4C)alkyl.

8. The compound of claim 7, wherein R1 is selected from (1-4C)alkyl, cyclopentyl, cyclohexyl, pyridinyl and phenyl, wherein the latter two groups are optionally substituted with one or two substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (1-4C)alkoxy and trifluoromethyl.

9. The compound of claim 8, wherein R1 is selected from (1-4C)alkyl and dichlorophenyl.

10. The compound of claim 1, having the structure (**II**), wherein R1 is 2,6-dichlorophenyl; A is the linking group -Y-$(CH_2)_n$-X-, wherein Y is attached to R1 and is a bond, n is 1 and X is attached to the phenylene group and is -O-; the ring structure **B** is phenylene; R2 is H; R3 is -$(CH_2)_2$-COOH and R4 is H.

11. The compound of claim 1, having the structure (**II**), wherein R1 is (1-4C)alkyl; A is the linking group -Y-$(CH_2)_n$-X-, wherein Y is attached to R1 and is a bond, n is an integer selected from 1 to 6 and X is attached to the phenylene group and is -O- or a bond; the ring structure **B** is phenylene; R2 is H; R3 is selected from -$(CH_2)_2$-COOH, -$(CH_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH,

-$CHCH_3$-CH_2-COOH, -$(CH_2)_2$-PO_3H_2, -$(CH_2)_3$-PO_3H_2 and -$(CH_2)_2$-OPO_3H_2; and R4 is H.

12. The compound of claim 11, wherein R1 and -$(CH_2)_n$- together are a linear octyl group, X is -O- and R3 is -$(CH_2)_2$-PO_3H_2.

13. The compound of claim 1, selected from
(3-{2-[4-(benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(6-Methyl-imidazo[1,2-a]pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid
3-(2-{4-[3-(2-Propyl-thiazol-5-yloxy)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(2-Benzyloxy-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Phenoxy-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Hex-5-ynyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(4-Acetoxy-butoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(4-Fluoro-phenoxy)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[2-(Naphthalen-2-yloxy)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-[2-(4-Phenylcarbamoylmethoxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(4-Pyrazol-1-yl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(1-Methyl-1H-pyrazol-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(6-Cyano-hexyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Phenethyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(3-Phenyl-propoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Benzyloxy-propoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(7-Methoxy-heptyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(4-tert-Butyl-phenyl)-[1,2,4]oxadiazol-5-ylmethoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(5-Oxo-hexyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Phenyl-butoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Cyclohexylmethoxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2-Benzenesulfonyl-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Phenoxy-propoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-[1,2,4]Triazol-1-yl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,3-Dihydro-benzofuran-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Biphenyl-4-yl-2-oxo-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Phenoxy-butoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Oxo-2-phenyl-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[2-(1H-Indol-3-yl)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
(+)-3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
(-)-3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-(4-Octyl-phenyl)-morpholin-4-yl)-propionic acid,
4-[2-(4-Octyl-phenyl)-morpholin-4-yl]-butyric acid,
3-[2-(4-Hexyloxy-phenyl)-morpholin-4-yl]-propionic acid,
4-[2-(4-Hexyloxy-phenyl)-morpholin-4-yl]-butyric acid,
3-[2-(4-Heptyloxy-phenyl)-morpholin-4-yl]-propionic acid,
4-[2-(4-Heptyloxy-phenyl)-morpholin-4-yl]-butyric acid,
3-(2-(4-Octyloxy-phenyl)-morpholin-4-yl)-propionic acid,
(+)-3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
(-)-3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
4-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-butyric acid,
2,2-Dimethyl-3-(2-(4-octyloxy-phenyl)-morpholin-4-yl)-propionic acid,
3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-butyric acid,
2-Methyl-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2-Chloro-6-fluorobenzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Difluoro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid ,
3-{2-[4-(2,6-Dimethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,5-Dichloro-pyridin-4-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4-Dichloro-pyridin-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-phenylcarbamoyl)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-phenoxymethyl)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[2-(2,6-Dichloro-phenyl)-vinyl]-phenyl}-morpholin-4-yl)-propionic acid,
3-[2-(4-Phenethyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,6-Dichloro-benzylamino)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzoylamino)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid,
3-[2-Methyl-2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
4-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-butyric acid,
3-(2-{4-[1-(2,6-Dichloro-phenyl)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[2-(2,6-Dichloro-phenyl)-ethyl]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[3-Methoxy-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-3-methoxy-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-3-methoxy-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(5-Bromo-2-methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Cyclopentylmethoxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,5-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(pyridin-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(naphthalen-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(6-methyl-pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,5-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Biphenyl-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,5-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(3-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Isopropyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(3-phenoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2-phenethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,4-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,5-Dimethyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Benzyloxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(thiophen-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Benzyloxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Biphenyl-4-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Butoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Cyclohexylmethoxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[2-Methyl-4-(tetrahydro-furan-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(3-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(4-trifluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(tetrahydro-pyran-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(4-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,4-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2,3,4-trimethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Cyclohex-3-enylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Butyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid
3-{2-[2-Methyl-4-(4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Dimethylamino-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(pyridin-4-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Iodo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,5-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2,4,5-trimethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-tert-Butyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,5-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(tetrahydro-furan-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-3-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-acetic acid,
3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-3-oxo-propionic acid,
2,2-Difluoro-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
2-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-ethanol,
2-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethanol,
{3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propyl}-phosphonic acid,
{2-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-ethyl}-phosphonic acid,
Phosphoric acid mono-{2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-ethyl} ester,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2-methyl-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-butyric acid,

Phosphoric acid mono-(2-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethyl) ester,
3-{2-[3-Methyl-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-3-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-3-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-5-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-3-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3,6-Trichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-5-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-5-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-5-propyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,.
3-{2-[4-(2-Chloro-5-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4,6-Trichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-iodo-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(2-Fluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(2,6-Dichloro-4-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Benzyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5-oxo-morpholin-4-yl}-propionic acid,
3-[2-(4-Octyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid·
3-(2-{4-[3-(2-Trifluoromethyl-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(2-Chloro-6-fluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(2,6-Dichloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(4-Chloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(2-Chloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[3-(2,3-Difluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[3-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[3-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[3-Chloro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-fluoro-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-2-fluoro-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Fluoro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-3-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-cyclopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-isobutyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5,5-dimethyl-morpholin-4-yl}-propionic acid,
3-[5,5-Dimethyl-2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Octyloxy-2-trifluoromethyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{6-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2,2-dimethyl-morpholin-4-yl}-propionic acid,
3-[2,2-Dimethyl-6-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,6-Dichloro-4-propyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-prop-1-ynyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-trifluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-3-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
2,6-Dichloro-benzoic acid 4-[4-(2-carboxy-ethyl)-morpholin-2-yl]-phenyl ester,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-cyclobutanecarboxylic acid,
3-{2-[4-(2,6-Dichloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Octylsulfanyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(4,4-Dimethyl-cyclohexyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Difluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Trifluoromethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-ethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-trifluoromethoxy-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-isopropyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-trifluoromethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-cyclopropyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Diethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyl)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-difluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-difluoromethoxy-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(3-Benzyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-[2-(3-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[3-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[3-(2-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Benzyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid,
3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-thiomorpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-thiomorpholin-4-yl}-propionic acid,
3-[2-(4-Octyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid,

3-{2-[5-(2,6-Dichloro-benzyloxy)-pyridin-2-yl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Indan-1-yloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(7-Methyl-indan-1-yloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Dihydro-benzofuran-3-yloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(4-Chloro-phenyl)-allyloxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(3-Phenyl-prop-2-ynyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-phenyl-allyloxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(4-Chloro-phenyl)-prop-2-ynyloxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(4-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-3-oxo-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-difluoro-propionic acid,
(3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propyl)-phosphonic acid,
2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4-(1(2)H-tetrazol-5-ylmethyl)-morpholine,
3-{2-[4-(2-Oxo-2-phenyl-ethyl)-phenyl]-morpholin-4-yl}-propionic acid
2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4-[2-(2H-tetrazol-5-yl)-ethyl]-morpholine
and
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-dimethyl-propionic acid
or a pharmaceutically acceptable salt, a solvate or hydrate thereof.

14. The compound of claim 1, being (-)-3-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid.

15. The compound of any one of claims 1 to 14 for use in therapy.

16. A pharmaceutical composition comprising the compound of any one of claims 1 to 14 and at least one pharmaceutically acceptable auxiliary.

17. Use of the compound of any one of claims 1 to 14 for the manufacture of a medicament for the treatment, alleviation or prevention of diseases and conditions in which any S1P receptor is involved or in which modulation of the endogenous S1P signaling system via any S1P receptor is involved.

18. The use of claim 17, wherein the disease is a CNS disorder, such as a neurodegenerative disorder, in particular selected from a cognitive disorder, Alzheimer's disease, (vascular) dementia, Nieman's Pick disease, and cognitive deficits in schizophrenia, obsessive-compulsive behavior, major depression, autism, multiple sclerosis and pain, and specifically the disease is a cognitive disorder, such as age-related cognitive decline.

19. Use of a S1P5 agonist for the manufacture of a medicament for the treatment, alleviation or prevention of a neurodegenerative disorder selected from a cognitive disorder, Alzheimer's disease, (vascular) dementia, Nieman's Pick disease, and cognitive deficits in schizophrenia, obsessive-compulsive behavior, major depression, autism, multiple sclerosis and pain, and specifically the disorder is a cognitive disorder, such as age-related cognitive decline.

A is selected from -CO-O-, -O-CO-, -NH-CO-, -CO-NH-, -C=C-, -CCH_3-O- and the linking group –Y-$(CH_2)_n$-X- wherein

Y is attached to R1 and selected from a bond, -O-, -S-, -SO-, -SO_2-, -CH_2-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- and -C≡C- ;

n is an integer from 1 to 10; and

X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S-, -SO-, -SO_2-,-NH-, -CO-, -C=C- and -C≡C-;

ring structure **B** optionally contains one nitrogen atom;

R2 is H, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, or halogen; and

R3 is (1-4C)alkylene-R5 wherein the alkylene group may be substituted with $(CH_2)_2$ to form a cyclopropyl moiety or one or two halogen atoms, or R3 is is (3-6C)cycloalkylene-R5 or -CO-CH_2-R5, wherein R5 is -OH, -PO_3H_2, -OPO_3H_2, -COOH, -COO(1-4C)alkyl or tetrazol-5-yl;

R4 is H or (1-4C)alkyl;

R6 is one or more substituents independently selected from H, (1-4C)alkyl or oxo;

W is -O-, -S-, -SO- or -SO_2-;

or a pharmaceutically acceptable salt, a solvate or hydrate thereof; with the proviso that the derivative of formula (I) is not

2-(4-ethylphenyl)-4-morpholinoethanol or

4-[4-(2-hydroxyethyl)-2-morpholinyl]benzeneacetonitrile.

display affinity for S1P receptors. In particular, compounds of the invention show selective affinity for the S1P5 receptor over the S1P1 and/or S1P3 receptor(s).

The use of the compound 2-(4-ethylphenyl)-4-morpholinoethanol as a reagent in the production of 2-(2-arylmorpholino)ethyl esters of naproxen is described in Database CA [Online] Chemical Abstracts Service, Columbus, OHIO, US; 2008, Hu, Ai-Xi et al, XP002558960 retrieved from STN database accession no. 2008:1527686; & Huaxue Xuebao, 66(22), 2553-2557 Coden: HHHPA4; ISSN: 0567-7351, 2008. No pharmacological activity of the compound is reported.

Similarly, in Farmatsiya (Sofia), Vol.45, no.1, 1998, pages 3-11, XP009126794 Yordanova, K. et al. describe the use of 4-[4-(2-hydroxyethyl)-2-morpholinyl]-benzeneacetonitrile as a reagent in the production of antidepressant phenylmorpholine derivatives. No pharmacological activity of the compound is reported.

Further, in an embodiment of the invention, A is selected from -CO-O-, -NH-CO-, -CO-NH-, -C=C-, $-CCH_3-O-$ and the linking group $-Y-(CH_2)_n-X-$ wherein Y is attached to R1 and selected from a bond, -O-, $-SO_2-$, $-CH_2-O-$, -CO-, -CO-O-, -NH-CO-, -C=C- and -C≡C-; n is an integer from 1 to 7; and X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S- and -NH. Preferably, A selected from -CO-NH-, -C=C-, $-CCH_3-O-$ and the linking groups $-(CH_2)_n-X-$ and $-O-(CH_2)_n-X-$. In preferred embodiments A is CH_2-O-.

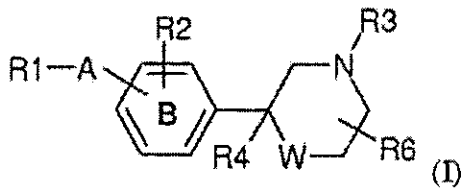
In further embodiments of the invention, R1 is selected from cyano, ethynyl, (1-4C)alkyl, cyclopentyl, cyclohexyl, cyclohexenyl, 6,6-dimethyl-bicyclo[3.1.1]hept-2-yl, indanyl optionally substituted with methyl, biphenyl, naphthyl, phenyl optionally substituted with one, two or three substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (2-4C)alkynyl, (1-4C)alkoxy, dimethylamino, trifluoromethyl, trifluoromethoxy and (3-6C)cycloalkyl, and R1 is further selected from phenyl monosubstituted with phenoxy, benzyl, benzyloxy, phenylethyl, pyrazolyl or triazolyl, and R1 is further selected from pyrazolyl, thiazolyl, oxadiazolyl, thienyl, tetrahydrofuranyl, pyridinyl, tetrahydropyranyl, each optionally substituted with chloro, (1-4C)alkyl or phenyl substituted with (1-4C)alkyl, and R1 is further selected from indolyl, imidazopyridinyl, dihydrobenzofuranyl and benzdioxanyl each optionally substituted with (1-4C)alkyl. In preferred embodiments, R1 is selected from ethynyl, (1-4C)alkyl, cyclopentyl, cyclohexyl, cyclohexenyl, biphenyl, naphthyl, phenyl optionally substituted with one, two or three substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (1-4C)alkoxy, dimethylamino, trifluoromethyl and trifluoromethoxy, and further selected from phenyl monosubstituted with phenoxy, benzyl, benzyloxy, phenylethyl, pyrazolyl or triazolyl, and further selected from thiazolyl, thienyl, tetrahydrofuranyl, pyridinyl, tetrahydropyranyl, each optionally substituted with chloro or (1-4C)alkyl, and benzdioxanyl. In particular, R1 is selected from (1-4C)alkyl, cyclopentyl, cyclohexyl, pyridinyl and phenyl, wherein the latter two groups are optionally substituted with one or two substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (1-4C)alkoxy and trifluoromethyl. In preferred embodiments, R1 is (1-4C)alkyl or dichlorophenyl.

In a highly preferred embodiment of the invention, R1 is 2,6-dichlorophenyl; A is the linking group $-Y-(CH_2)_n-X-$, wherein Y is attached to R1 and is a bond, n is 1 and X is attached to the phenylene group and is -O-; R2 is H; R3 is $-(CH_2)_2-COOH$; and R4 is H.

In further preferred embodiments of the invention, R1 is (1-4C)alkyl; A is the linking group $-Y-(CH_2)_n-X-$, wherein Y is attached to R1 and is a bond, n is an integer

Claims

1. A (thio)morpholine derivative of the formula (I)



(I)

wherein

R1 is selected from

cyano,
(2-4C)alkynyl,
(1-4C)alkyl,
(3-6C)cycloalkyl,
(4-6C)cycloalkenyl,
(6-8C)bicycloalkyl, (8-10C)bicyclic group, each optionally substituted with (1-4C)alkyl,
phenyl, biphenyl, naphthyl, each optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (2-4C)alkynyl, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, amino, di(1-4C)alkylamino, -SO_2-(1-4C)alkyl, -CO-(1-4C)alkyl, -CO-O-(1-4C)alkyl, -N H-CO-(1-4C)alkyl and (3-6C)cycloalkyl,
phenyl substituted with phenoxy, benzyl, benzyloxy, phenylethyl or monocyclic heterocycle, each optionally substituted with (1-4C)alkyl,
monocyclic heterocycle optionally substituted with halogen, (1-4C)alkyl or with phenyl optionally substituted with (1-4C)alkyl,
and
bicyclic heterocycle optionally substituted with (1-4C)alkyl;

A is selected from -CO-O-, -O-CO-, -NH-CO-, -CO-NH-, -C=C-, -CCH_3-O- and the linking group Y-$(CH_2)_n$-X- wherein

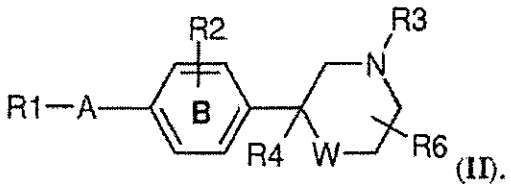
Y is attached to R1 and selected from a bond, -O-, -S-, -SO-, -SO_2-, -CH_2-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- and -C≡C-;
n is an integer from 1 to 10; and
X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S-, -SO-, -SO_2-, -NH-, -CO-, -C=C- and -C≡C-;

ring structure B optionally contains one nitrogen atom;
R2 is H, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted

with one or more fluoro atoms, or halogen; and
R3 is (1-4C)alkylene-R5 wherein the alkylene group may be substituted with $(CH_2)_2$ to form a cyclopropyl moiety or one or two halogen atoms, or R3 is is (3-6C)cycloalkylene-R5 or -CO-CH_2-R5, wherein R5 is -OH, -PO_3H_2, -OPO_3H_2, -COOH, -COO(1-4C)alkyl or tetrazol-5-yl;
R4 is H or (1-4C)alkyl;
R6 is one or more substituents independently selected from H, (1-4C)alkyl or oxo;
W is -O-, -S-, -SO- or -SO_2-;
or a pharmaceutically acceptable salt, a solvate or hydrate thereof; with the proviso that the derivative of formula (I) is not 2-(4-ethylphenyl)-4-morpholinoethanol, 4-[4-(2-hydroxyethyl)-2-morpholinyl]benzeneacetonitrile or 3-methyl-2-[4-(phenylmethoxy)phenyl]-4-morpholinoethanol hydrochloride.

2. The compound of claim 1, wherein the ring structure B is phenylene.

3. The compound of claim 1 or 2, having the structure (II)



(II).

4. The compound of any one of claims 1 to 3, wherein R3 is selected from -$(CH_2)_2$-OH, -CH_2-COOH, -$(CH_2)_2$-COOH, -$(CN_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH, -$CHCH_3$-CH_2-COOH, -CH_2-CF_2 -COOH, -CO-CH_2-COOH, 1,3-cyclobutylene-COOH, -$(CH_2)_2$-PO_3H_2, -$(CN_2)_3$-PO_3H_2, -$(CH_2)_2$-OPO_3H_2, -$(CH_2)_3$-OPO_3H_2, -CH_2-tetrazol-5-yl, -$(CH_2)_2$-tetrazol-5-yl and -$(CH_2)_3$-tetrazol-5-yl;
and W is -O- or -S-.

5. The compound of any one of claims 1 to 4, wherein R2 is H, methyl, methoxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, Cl or F; and R4 is H or methyl.

6. The compound of any one of claims 1 to 5, wherein A is selected from -CO-O-, -NH-CO-, -CO-NH-, -C=C-, -CCH_3-O- and the linking group -Y-$(CH_2)_n$-X- wherein Y is attached to R1 and selected from a bond, -O-, -SO_2-, -CH_2-O-, -CO-, -CO-O-, - NH-CO-, -C=C- and -C≡C-; n is an integer from 1 to 7; and X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S- and -NH.

7. The compound of any one of claims 1 to 6, wherein R1 is selected from cyano, ethynyl, (1-4C)alkyl, cyclopentyl, cyclohexyl, cyclohexenyl,
6,6-dimethyl-bicyclo[3.1.1]hept-2-yl, indanyl optionally substituted with methyl, biphenyl, naphthyl,
phenyl optionally substituted with one, two or three substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (2-4C)alkynyl, (1-4C)alkoxy, dimethylamino, trifluoromethyl, trifluoromethoxy and (3-6C)cycloalkyl,
phenyl monosubstituted with phenoxy, benzyl, benzyloxy, phenylethyl, pyrazolyl or triazolyl,
pyrazolyl, thiazolyl, oxadiazolyl, thienyl, tetrahydrofuranyl, pyridinyl, tetrahydro-pyranyl, each optionally substituted with chloro, (1-4C)alkyl or phenyl substituted with (1-4C)alkyl, and
indolyl, imidazopyridinyl, dihydrobenzofuranyl and benzdioxanyl, each optionally substituted with (1-4C)alkyl.

8. The compound of claim 7, wherein R1 is selected from (1-4C)alkyl, cyclopentyl, cyclohexyl, pyridinyl and phenyl, wherein the latter two groups are optionally substituted with one or two substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (1-4C)alkoxy and trifluoromethyl.

9. The compound of claim 8, wherein R1 is selected from (1-4C)alkyl and dichlorophenyl.

10. The compound of claim 1, having the structure (II), wherein R1 is 2,6-dichlorophenyl; A is the linking group -Y-$(CH_2)_n$-X-, wherein Y is attached to R1 and is a bond, n is 1 and X is attached to the phenylene group and is -O-; the ring structure B is phenylene; R2 is H; R3 is -$(CH_2)_2$-COOH and R4 is H.

11. The compound of claim 1, having the structure (II), wherein R1 is (1-4C)alkyl; A is the linking group -Y-$(CH_2)_n$-X-,

wherein Y is attached to R1 and is a bond, n is an integer selected from 1 to 6 and X is attached to the phenylene group and is -O- or a bond; the ring structure B is phenylene; R2 is H; R3 is selected from $-(CH_2)_2-COOH$, $-(CH_2)_3-COOH$, $-CH_2-CHCH_3-COOH$, $-CH_2-C(CH_3)_2-COOH$, $-CHCH_3-CH_2-C\ OOH$, $-(CH_2)_2-PO_3H_2$, $-(CH_2)_3-PO_3H_2$ and $-(CH_2)_2-OPO_3H_2$; and R4 is H.

12. The compound of claim 11, wherein R1 and $-(CH_2)_n-$ together are a linear octyl group, X is -O- and R3 is $-(CH_2)_2-PO_3H_2$.

13. The compound of claim 1, selected from
(3-{2-[4-(benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(6-Methyl-imidazo[1,2-a]pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid
3-(2-{4-[3-(2-Propyl-thiazol-5-yloxy)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(2-Benzyloxy-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Phenoxy-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Hex-5-ynyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(4-Acetoxy-butoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(4-Fluoro-phenoxy)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[2-(Naphthalen-2-yloxy)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-[2-(4-Phenylcarbamoylmethoxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(4-Pyrazol-1-yl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(1-Methyl-1H-pyrazol-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(6-Cyano-hexyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Phenethyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(3-Phenyl-propoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Benzyloxy-propoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(7-Methoxy-heptyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(4-tert-Butyl-phenyl)-[1,2,4]oxadiazol-5-ylmethoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(5-Oxo-hexyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Phenyl-butoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Cyclohexylmethoxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2-Benzenesulfonyl-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Phenoxy-propoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-[1,2,4]Triazol-1-yl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2- [4-(2,3-Dihydro-benzofuran-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Biphenyl-4-yl-2-oxo-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Phenoxy-butoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Oxo-2-phenyl-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-(2-{4-[2-(1H-Indol-3-yl)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
(+)-3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
(-)-3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-(4-Octyl-phenyl)-morpholin-4-yl)-propionic acid,
4-[2-(4-Octyl-phenyl)-morpholin-4-yl]-butyric acid,
3-[2-(4-Hexyloxy-phenyl)-morpholin-4-yl]-propionic acid,
4-[2-(4-Hexyloxy-phenyl)-morpholin-4-yl]-butyric acid,
3-[2-(4-Heptyloxy-phenyl)-morpholin-4-yl]-propionic acid,
4-[2-(4-Heptyloxy-phenyl)-morpholin-4-yl]-butyric acid,
3-(2-(4-Octyloxy-phenyl)-morpholin-4-yl)-propionic acid,
(+)-3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
(-)-3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
4-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-butyric acid,
2,2-Dimethyl-3-(2-(4-octyloxy-phenyl)-morpholin-4-yl)-propionic acid,
3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-butyric acid,
2-Methyl-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,

3-{2-[4-(2-Chloro-6-fluorobenzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Difluoro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid ,
3-{2-[4-(2.6-Dimethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid.
3-{2-[4-(3,5-Dichloro-pyridin-4-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4-Dichloro-pyridin-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-phenylcarbamoyl)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-phenoxymethyl)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[2-(2,6-Dichloro-phenyl)-vinyl]-phenyl}-morpholin-4-yl)-propionic acid,
3-[2-(4-Phenethyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,6-Dichloro-benzylamino)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzoylamino)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid,
3-[2-Methyl-2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
4-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-butyric acid,
3-(2-{4-[1-(2,6-Dichloro-phenyl)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[2-(2,6-Dichloro-phenyl)-ethyl]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[3-Methoxy-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-3-methoxy-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-3-methoxy-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(5-Bromo-2-methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Cyclopentylmethoxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,5-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(pyridin-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(naphthalen-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(6-methyl-pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,5-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Biphenyl-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,5-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(3-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Isopropyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(3-phenoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2-phenethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,4-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,5-Dimethyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Benzyloxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(thiophen-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Benzyloxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Biphenyl-4-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid.

3-{2-[2-Methyl-4-(pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Butoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Cyclohexylmethoxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[2-Methyl-4-(tetrahydro-furan-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(3-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(4-trifluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(tetrahydro-pyran-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(4-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,4-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2,3,4-trimethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Cyclohex-3-enylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Butyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid
3-{2-[2-Methyl-4-(4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Dimethylamino-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(pyridin-4-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Iodo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,5-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2,4,5-trimethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-tert-Butyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,5-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(tetrahydro-furan-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-3-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-acetic acid,
3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-3-oxo-propionic acid,
2,2-Difluoro-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
2-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-ethanol,
2-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethanol,
{3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propyl}-phosphonic acid,
{2-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-ethyl}-phosphonic acid,
Phosphoric acid mono-{2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-ethyl} ester,
3-{2-{4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2-methyl-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-butyric acid,
Phosphoric acid mono-(2-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethyl) ester,
3-{2-[3-Methyl-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-3-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-3-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-5-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-5-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-5-propyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,.
3-{2-[4-(2-Chloro-5-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4,6-Trichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-iodo-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(2-Fluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(2,6-Dichloro-4-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Benzyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5-oxo-morpholin-4-yl}-propionic acid,
3-[2-(4-Octyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid,
3-(2-{4-[3-(2-Trifluoromethyl-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(2-Chloro-6-fluoro-phenyl)-propoxy}-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(2,6-Dichloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(4-Chloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(2-Chloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(2,3-Difluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[3-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[3-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[3-Chloro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-fluoro-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-2-fluoro-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Fluoro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-3-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-cyclopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-isobutyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5,5-dimethyl-morpholin-4-yl}-propionic acid,
3-[5,5-Dimethyl-2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Octyloxy-2-trifluoromethyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{6-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2,2-dimethyl-morpholin-4-yl}-propionic acid,
3-[2,2-Dimethyl-6-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,6-Dichloro-4-propyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-prop-1-ynyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2- [4-(2-Chloro-6-trifluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-3-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
2,6-Dichloro-benzoic acid 4-[4-(2-carboxy-ethyl)-morpholin-2-yl]-phenyl ester,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-cyclobutanecarboxylic acid,
3-{2-[4-(2,6-Dichloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Octylsulfanyl-phenyl)-morpholin-4-yl]-propionic acid,

3-{2-[4-(4,4-Dimethyl-cyclohexyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Difluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Trifluoromethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-ethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-trifluoromethoxy-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-isopropyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-trifluoromethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-cyclopropyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Diethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid
3-{2-[2-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyl)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-difluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-difluoromethoxy-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(3-Benzyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-[2-(3-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[3-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[3-(2-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Benzyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid,
3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-thiomorpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-thiomorpholin-4-yl}-propionic acid.
3-[2-(4-Octyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid,
3-{2-[5-(2,6-Dichloro-benzyloxy)-pyridin-2-yl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Indan-1-yloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(7-Methyl-indan-1-yloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Dihydro-benzofuran-3-yloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(4-Chloro-phenyl)-allyloxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(3-Phenyl-prop-2-ynyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-phenyl-allyloxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(4-Chloro-phenyl)-prop-2-ynyloxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(4-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-3-oxo-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-difluoro-propionic acid,
(3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propyl)-phosphonic acid,
2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4-(1(2)H-tetrazol-5-ylmethyl)-morpholine,
3-{2-[4-(2-Oxo-2-phenyl-ethyl)-phenyl]-morpholin-4-yl}-propionic acid
2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4-[2-(2H-tetrazol-5-yl)-ethyl]-morpholine and
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-dimethyl-propionic acid
or a pharmaceutically acceptable salt, a solvate or hydrate thereof.

14. The compound of claim 1, being (-)-3-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid or a pharmaceutically acceptable salt, a solvate or hydrate thereof.

15. The compound of any one of claims 1 to 14 for use in therapy.

16. A pharmaceutical composition comprising the compound of any one of claims 1 to 14 and at least one pharmaceutically acceptable ingredient, excipient, carrier, adjuvant or vehicle.

17. Use of the compound of any one of claims 1 to 14 for the manufacture of a medicament for the treatment, alleviation or prevention of diseases, wherein the disease is a CNS disorder, such as a neurodegenerative disorder, in particular selected from a cognitive disorder, Alzheimer's disease, (vascular) dementia, Nieman's Pick disease, and cognitive deficits in schizophrenia, obsessive-compulsive behavior, major depression, autism, multiple sclerosis and pain, and specifically the disease is a cognitive disorder, such as age-related cognitive decline.