

NOVEL COMPOUNDS AS RECEPTOR MODULATORS WITH THERAPEUTIC UTILITY

By inventors: Todd M. Heidelbaugh and Phong X. Nguyen

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 61/264,038 filed on November 24, 2009, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to novel amine derivatives, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals as modulators of sphingosine-1-phosphate receptors. The invention relates specifically to the use of these compounds and their pharmaceutical compositions to treat disorders associated with sphingosine-1-phosphate (S1P) receptor modulation.

BACKGROUND OF THE INVENTION

Sphingosine-1 phosphate is stored in relatively high concentrations in human platelets, which lack the enzymes responsible for its catabolism, and it is released into the blood stream upon activation of physiological stimuli, such as growth factors, cytokines, and receptor agonists and antigens. It may also have a critical role in platelet aggregation and thrombosis and could aggravate cardiovascular diseases. On the other hand the relatively high concentration of the metabolite in high-density lipoproteins (HDL) may have beneficial implications for atherogenesis. For example, there are recent suggestions that sphingosine-1-phosphate, together with other lysolipids such as sphingosylphosphorylcholine and lysosulfatide, are responsible for the beneficial clinical effects of HDL by stimulating the production of the potent antiatherogenic signaling molecule nitric oxide by the vascular endothelium. In addition, like lysophosphatidic acid, it is a marker for certain types of cancer, and there is evidence that its role in cell division or proliferation may have an influence on the development of cancers. These are currently topics that are attracting great interest amongst medical researchers, and

the potential for therapeutic intervention in sphingosine-1-phosphate metabolism is under active investigation.

Journal of Medicinal Chemistry 2010, 53, 4412-4421 and Bioorganic & Medicinal Chemistry Letters 19 (2009) 5486-5489, describe phenyl-pyrazole derivatives as 5-HT_{2A} receptor antagonists.

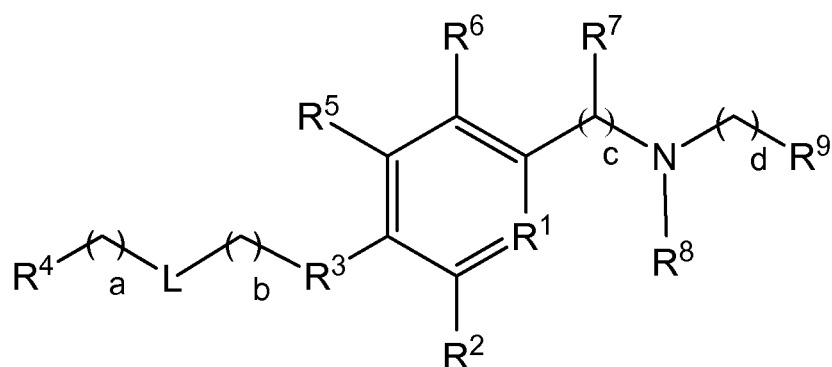
Patent Application US2009312315 describes phenyl-substituted carboxylic acid derivatives as PAI-1 inhibitors.

SUMMARY OF THE INVENTION

We have now discovered a group of novel compounds which are potent and selective sphingosine-1-phosphate modulators. As such, the compounds described herein are useful in treating a wide variety of disorders associated with modulation of sphingosine-1-phosphate receptors. The term "modulator" as used herein, includes but is not limited to: receptor agonist, antagonist, inverse agonist, inverse antagonist, partial agonist, partial antagonist.

This invention describes compounds of Formula I, which have sphingosine-1-phosphate receptor biological activity. The compounds in accordance with the present invention are thus of use in medicine, for example in the treatment of humans with diseases and conditions that are alleviated by S1P modulation.

In one aspect the invention provides a compound having Formula I or a pharmaceutically acceptable salt thereof or stereoisomeric forms thereof, or the geometrical isomers, enantiomers, diastereoisomers, tautomers, zwitterions and pharmaceutically acceptable salts thereof:



Formula I

wherein:

R¹ is N or C-R¹⁰;

R^2 is aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

R^3 is O, $N-R^{11}$, $CH-R^{12}$ or S, $-CR^{13}=CR^{14}-$, $-C(O)-$ or $-C\equiv C-$;

R^4 is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

5 R^5 is H, halogen, hydroxyl, $-OC_{1-3}$ alkyl, hydroxyl or C_{1-3} alkyl;

R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

R^7 is H or C_{1-6} alkyl;

R^8 is H or C_{1-6} alkyl;

R^9 is $-OPO_3H_2$, $-COOH$, $-P(O)(OH)_2$, $-C_{3-6}$ alkyl, $-S(O)_2OH$, $-P(O)MeOH$, $-P(O)(H)OH$

10 or $-OR^{15}$;

R^{10} is H, C_{1-6} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

R^{11} is H or C_{1-3} alkyl;

R^{12} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;

R^{13} is H or C_{1-3} alkyl;

15 R^{14} is H or C_{1-3} alkyl;

R^{15} is H or C_{1-3} alkyl;

L is CHR^{16} , O, S, NR^{17} or $-C(O)-$;

a is 0, 1, 2, 3, 4 or 5;

b is 0, 1, 2, 3, 4 or 5;

20 c is 0 or 1;

d is 0, 1, 2 or 3;

R^{16} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino, and

R^{17} is H or C_{1-3} alkyl;

with the provisos:

25 when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} ; and

when R^9 is $-OPO_3H_2$, $-COOH$, $-P(O)(OH)_2$, $-S(O)_2OH$, $-P(O)MeOH$ or $-P(O)(H)OH$ then d is not 0; and

when R^9 is $-OR^{15}$ then d is not 0 or 1.

30 The term "alkyl", as used herein, refers to saturated, monovalent or divalent hydrocarbon moieties having linear or branched moieties or combinations thereof and containing 1-6 carbon atom. One methylene ($-CH_2-$) group, of the alkyl can be replaced by oxygen, sulfur, sulfoxide, nitrogen, carbonyl, carboxyl, sulfonyl, or by a divalent C_{3-6} cycloalkyl. Alkyl groups can be substituted by halogen, hydroxyl,

cycloalkyl, amino, non-aromatic heterocycles, carboxylic acid, phosphonic acid groups, sulphonic acid groups, phosphoric acid.

The term "cycloalkyl", as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms, preferably 3 to 5 carbon atoms derived from a saturated cyclic hydrocarbon. Cycloalkyl groups can be monocyclic or polycyclic. Cycloalkyl can be substituted by 1 to 3 C₁₋₃ alkyl groups or 1 or 2 halogens. Cycloalkyl group in the present case is cyclopentane.

The term "cycloalkenyl", as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms, preferably 3 to 6 carbon atoms derived from a saturated cycloalkyl having one double bond. Cycloalkenyl groups can be monocyclic or polycyclic. Cycloalkenyl groups can be substituted by 1 to 3 C₁₋₃ alkyl groups or 1 or 2 halogens. Cycloalkenyl group in the present case is cyclopentene.

The term "halogen", as used herein, refers to an atom of chlorine, bromine, fluorine, iodine.

The term "alkenyl", as used herein, refers to a monovalent or divalent hydrocarbon radical having 2 to 6 carbon atoms, derived from a saturated alkyl, having at least one double bond. C₂₋₆ alkenyl can be in the E or Z configuration. Alkenyl groups can be substituted by 1 to 2 C₁₋₃ alkyl.

The term "alkynyl", as used herein, refers to a monovalent or divalent hydrocarbon radical having 2 to 6 carbon atoms, derived from a saturated alkyl, having at least one triple bond.

The term "heterocycle" as used herein, refers to a 3 to 10 membered ring, which can be aromatic or non-aromatic, saturated or non-saturated, containing at least one heteroatom selected from O or N or S or combinations of at least two thereof, interrupting the carbocyclic ring structure. The heterocyclic ring can be saturated or non-saturated. The heterocyclic ring can be interrupted by a C=O; the S heteroatom can be oxidized. Heterocycles can be monocyclic or polycyclic. Heterocyclic ring moieties can be substituted by hydroxyl, 1 to 2 C₁₋₃ alkyl or 1 to 2 halogens. Usually heterocyclic groups are 5 or 6 membered rings. Usually in the present case

heterocyclic groups are pyridine, pyrazol, pyrazolidine, pyrroline, pyrrolidine, imidazoline, pyrazoline, thiazoline, oxazoline, thiophene, dihydrothiophene, furan, dihydrofuran, pyrrole, pyrroline, oxazole, thiazole, imidazole, pyrazole, pyrazoline, isoxazole, isothiazole, tetrazole, oxadiazole, 1,2,5-oxadiazole, thiadiazole, 1,2,3-
5 triazole, 1,2,4-triazole, imidazole, imidazoline, pyrrolidinone, pyrrol-2(3H)-one, imidazolidin-2-one, or 1,2,4-triazol-5(4H)-one.

The term "aryl" as used herein, refers to an organic moiety derived from an aromatic hydrocarbon consisting of a ring containing 6 to 10 carbon atoms by removal of one
10 hydrogen, which can be substituted by 1 to 3 halogen atoms or by 1 to 2 C₁₋₃ alkyl groups. Usually aryl is phenyl.

The group of formula " $-\text{CR}^{13}=\text{CR}^{14}-$ ", as used herein, represents an alkenyl radical.

The group of formula " $-\text{C}\equiv\text{C}-$ ", as used herein, represents an alkynyl radical.

15 The term "hydroxyl" as used herein, represents a group of formula " $-\text{OH}$ ".

The term "carbonyl" as used herein, represents a group of formula " $-\text{C}=\text{O}$ ".

The term "carboxyl" as used herein, represents a group of formula " $-\text{C}(\text{O})\text{O}-$ ".

The term "sulfonyl" as used herein, represents a group of formula " $-\text{SO}_2$ ".

The term "sulfate" as used herein, represents a group of formula " $-\text{O}-\text{S}(\text{O})_2-\text{O}-$ ".

20 The term "carboxylic acid" as used herein, represents a group of formula " $-\text{C}(\text{O})\text{OH}$ ".

The term "sulfoxide" as used herein, represents a group of formula " $-\text{S}=\text{O}$ ".

The term "phosphonic acid" as used herein, represents a group of formula " $-\text{P}(\text{O})(\text{OH})_2$ ".

The term "phosphoric acid" as used herein, represents a group of formula " $-(\text{O})\text{P}(\text{O})(\text{OH})_2$ ".
25

The term "boronic acid", as used herein, represents a group of formula " $-\text{B}(\text{OH})_2$ ".

The term "sulphonic acid" as used herein, represents a group of formula " $-\text{S}(\text{O})_2\text{OH}$ ".

The formula " H ", as used herein, represents a hydrogen atom.

The formula " O ", as used herein, represents an oxygen atom.

30 The formula " N ", as used herein, represents a nitrogen atom.

The formula " S ", as used herein, represents a sulfur atom.

Generally R^1 is N or C- R^{10} .

Generally R^2 is aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl. Usually, in the present case, R^2 is aromatic heterocycle or cycloalkenyl. Usually aromatic heterocyclic rings are 5 membered rings. Preferred R^2 are pyrazol, pyrazolidine, pyrroline, pyrrolidine, imidazoline, pyrazoline, thiazoline, oxazoline, thiophene, dihydrothiophene, furan, dihydrofuran, pyrrole, pyrroline, oxazole, thiazole, imidazole, pyrazole, pyrazoline, isoxazole, isothiazole, tetrazole, oxadiazole, 1,2,5-oxadiazole, thiadiazole, 1,2,3-triazole, 1,2,4-triazole, imidazole, imidazoline, pyrrolidinone, pyrrol-2(3H)-one, imidazolidin-2-one, or 1,2,4-triazol-5(4H)-one.

Generally R^3 is O, N- R^{11} , CH- R^{12} , S, - $CR^{13}=CR^{14}$ -, -C(O) or - $C\equiv C$ -. Usually, in the present case, R^3 is O.

Generally R^4 is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl or aryl. Usually, in the present case, R^4 is aryl or H.

Generally R^5 is H, halogen, -OC₁₋₃ alkyl, hydroxyl or C₁₋₃ alky. Usually, in the present case, R^5 is H.

Generally R^6 is H, C₁₋₃ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl. Usually, in the present case, R^6 is H.

Generally R^7 is H or C₁₋₆ alkyl. Usually, in the present case, R^7 is H.

Generally R^8 is H or C₁₋₆ alkyl. Usually, in the present case, R^8 is H.

Generally R^9 is OPO₃H₂, COOH, P(O)(OH)₂, C₃₋₆ alkyl, -S(O)₂OH, -P(O)MeOH, -P(O)(H)OH or -OR¹⁵. Usually, in the present case, R^9 is P(O)(OH)₂.

Generally R^{10} is H, C₁₋₆ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl. Usually, in the present case, R^{10} is H.

Generally R^{11} is H or C₁₋₃ alkyl.

Generally R^{12} is H or C₁₋₃ alkyl

Generally R^{13} is H or C₁₋₃ alkyl.

Generally R^{14} is H or C₁₋₃ alkyl.

Generally R^{15} is H or C₁₋₃ alkyl.

Generally a is 0, 1, 2, 3, 4 or 5. Usually, in the present case, a is 1, 2, 3, 4 or 5.

Generally b is 0, 1, 2, 3, 4 or 5. Usually, in the present case, b is 1, 2, 3 or 4.

Generally c is 0 or 1. Usually, in the present case, c is 1.

Generally d is 0, 1, 2 or 3. Usually, in the present case, d is 3.

Generally L is CHR¹⁷, O, S or NR¹⁷. Usually, in the present case, L is CHR¹⁶.

Generally R^{16} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl, amino. Usually, in the present case, R^{16} is H.

Generally R^{17} is H or C_{1-3} alkyl.

5 In one embodiment of the invention

R^1 is N or $C-R^{10}$;

R^2 is aromatic heterocycle or cycloalkenyl;

R^3 is O, $N-R^{11}$, $CH-R^{12}$ or S, $-CR^{13}=CR^{14}-$, $-C(O)-$ or $-C\equiv C-$;

10 R^4 is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

R^5 is H, halogen, hydroxyl, $-OC_{1-3}$ alkyl, hydroxyl or C_{1-3} alkyl;

R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

R^7 is H or C_{1-6} alkyl;

R^8 is H or C_{1-6} alkyl;

15 R^9 is $-OPO_3H_2$, $-COOH$, $-P(O)(OH)_2$, $-C_{3-6}$ alkyl, $-S(O)_2OH$, $-P(O)MeOH$, $-P(O)(H)OH$ or $-OR^{15}$;

R^{10} is H, C_{1-6} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

R^{11} is H or C_{1-3} alkyl;

R^{12} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;

20 R^{13} is H or C_{1-3} alkyl;

R^{14} is H or C_{1-3} alkyl;

R^{15} is H or C_{1-3} alkyl;

L is CHR^{16} , O, S, NR^{17} or $-C(O)-$;

a is 0, 1, 2, 3, 4 or 5;

25 b is 0, 1, 2, 3, 4 or 5;

c is 0 or 1;

d is 0, 1, 2 or 3;

R^{16} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino; and

R^{17} is H or C_{1-3} alkyl;

30 with the provisos

when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} ; and

when R^9 is $-OPO_3H_2$, $-COOH$, $-P(O)(OH)_2$, $-S(O)_2OH$, $-P(O)MeOH$ or $-P(O)(H)OH$ then d is not 0; and

when R^9 is $-OR^{15}$ then d is not 0 or 1.

In another embodiment of the invention

R^1 is N or $C-R^{10}$;

R^2 is 5-member aromatic heterocycle or cycloalkenyl;

5 R^3 is O, $N-R^{11}$, $CH-R^{12}$ or S, $-CR^{13}=CR^{14}-$, $-C(O)-$ or $-C\equiv C-$;

R^4 is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

R^5 is H, halogen, hydroxyl, $-OC_{1-3}$ alkyl, hydroxyl or C_{1-3} alkyl;

R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

10 R^7 is H or C_{1-6} alkyl;

R^8 is H or C_{1-6} alkyl;

R^9 is $-OPO_3H_2$, $-COOH$, $-P(O)(OH)_2$, $-C_{3-6}$ alkyl, $-S(O)_2OH$, $-P(O)MeOH$, $-P(O)(H)OH$ or $-OR^{15}$;

R^{10} is H, C_{1-6} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

15 R^{11} is H or C_{1-3} alkyl;

R^{12} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;

R^{13} is H or C_{1-3} alkyl;

R^{14} is H or C_{1-3} alkyl;

R^{15} is H or C_{1-3} alkyl;

20 L is CHR^{16} , O, S, NR^{17} or $-C(O)-$;

a is 0, 1, 2, 3, 4 or 5;

b is 0, 1, 2, 3, 4 or 5;

c is 0 or 1;

d is 0, 1, 2 or 3;

25 R^{16} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino, and

R^{17} is H or C_{1-3} alkyl;

with the provisos:

when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} ; and

when R^9 is $-OPO_3H_2$, $-COOH$, $-P(O)(OH)_2$, $-S(O)_2OH$, $-P(O)MeOH$ or $-P(O)(H)OH$

30 then d is not 0; and

when R^9 is $-OR^{15}$ then d is not 0 or 1.

In another embodiment of the invention

R^1 is N or $C-R^{10}$;

R^2 is cyclopentane, cyclopentene, pyrazolidine, pyrroline, pyrrolidine, imidazoline, pyrazoline, thiazoline, oxazoline, thiophene, dihydrothiophene, furan, dihydrofuran, pyrrole, pyrroline, pyrrolidine, oxazole, oxazoline, thiazole, imidazole, pyrazole, pyrazoline, isoxazole, isothiazole, tetrazole, oxadiazole, 1,2,5-oxadiazole,

5 thiadiazole, 1,2,3-triazole, 1,2,4-triazole, imidazole, imidazoline, pyrrolidinone, pyrrol-2(3H)-one, imidazolidin-2-one, or 1,2,4-triazol-5(4H)-one;

R^3 is O, $N-R^{11}$, $CH-R^{12}$ or S, $-CR^{13}=CR^{14}-$, $-C(O)-$ or $-C\equiv C-$;

R^4 is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

10 R^5 is H, halogen, hydroxyl, $-OC_{1-3}$ alkyl, hydroxyl or C_{1-3} alkyl;

R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

R^7 is H or C_{1-6} alkyl;

R^8 is H or C_{1-6} alkyl;

R^9 is $-OPO_3H_2$, $-COOH$, $-P(O)(OH)_2$, $-C_{3-6}$ alkyl, $-S(O)_2OH$, $-P(O)MeOH$, $-P(O)(H)OH$
15 or $-OR^{15}$;

R^{10} is H, C_{1-6} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

R^{11} is H or C_{1-3} alkyl;

R^{12} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;

R^{13} is H or C_{1-3} alkyl;

20 R^{14} is H or C_{1-3} alkyl;

R^{15} is H or C_{1-3} alkyl;

L is CHR^{16} , O, S, NR^{17} or $-C(O)-$;

a is 0, 1, 2, 3, 4 or 5;

b is 0, 1, 2, 3, 4 or 5;

25 c is 0 or 1;

d is 0, 1, 2 or 3;

R^{16} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino, and

R^{17} is H or C_{1-3} alkyl;

with the provisos:

30 when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} ; and

when R^9 is $-OPO_3H_2$, $-COOH$, $-P(O)(OH)_2$, $-S(O)_2OH$, $-P(O)MeOH$ or $-P(O)(H)OH$ then d is not 0; and

when R^9 is $-OR^{15}$ then d is not 0 or 1.

In another embodiment of the invention

R^1 is N or $C-R^{10}$;

R^2 is 5-member aromatic heterocycle or cycloalkenyl;

R^3 is O, $N-R^{11}$, $CH-R^{12}$ or S, $-CR^{13}=CR^{14}-$, $-C(O)-$ or $-C\equiv C-$;

5 R^4 is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

R^5 is H, halogen, hydroxyl, $-OC_{1-3}$ alkyl, hydroxyl or C_{1-3} alkyl;

R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

R^7 is H or C_{1-6} alkyl;

10 R^8 is H or C_{1-6} alkyl;

R^9 is $-OPO_3H_2$, or $-OR^{15}$;

R^{10} is H, C_{1-6} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

R^{11} is H or C_{1-3} alkyl;

R^{12} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;

15 R^{13} is H or C_{1-3} alkyl;

R^{14} is H or C_{1-3} alkyl;

R^{15} is H or C_{1-3} alkyl;

L is CHR^{16} , O, S, NR^{17} or $-C(O)-$;

a is 0, 1, 2, 3, 4 or 5;

20 b is 0, 1, 2, 3, 4 or 5;

c is 0 or 1;

d is 1, 2 or 3;

R^{16} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino, and

R^{17} is H or C_{1-3} alkyl;

25 with the provisos :

when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} ; and

when R^9 is $-OR^{15}$ then d is not 1.

In another embodiment of the invention

30 R^1 is N or $C-R^{10}$;

R^2 is 5-member aromatic heterocycle or cycloalkenyl;

R^3 is O, $N-R^{11}$, $CH-R^{12}$ or S, $-CR^{13}=CR^{14}-$, $-C(O)-$ or $-C\equiv C-$;

R^4 is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

- R^5 is H, halogen, hydroxyl, $-OC_{1-3}$ alkyl, hydroxyl or C_{1-3} alkyl;
 R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;
 R^7 is H or C_{1-6} alkyl;
 R^8 is H or C_{1-6} alkyl;
5 R^9 is $-P(O)(OH)_2$, $-P(O)MeOH$, or $-P(O)(H)OH$;
 R^{10} is H, C_{1-6} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;
 R^{11} is H or C_{1-3} alkyl;
 R^{12} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;
 R^{13} is H or C_{1-3} alkyl;
10 R^{14} is H or C_{1-3} alkyl;
 R^{15} is H or C_{1-3} alkyl;
L is CHR^{16} , O, S, NR^{17} or $-C(O)-$;
a is 0, 1, 2, 3, 4 or 5;
b is 0, 1, 2, 3, 4 or 5;
15 c is 0 or 1;
d is 1, 2 or 3;
 R^{16} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino, and
 R^{17} is H or C_{1-3} alkyl;
with the proviso:
20 when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} .

In another embodiment of the invention

- R^1 is N or $C-R^{10}$;
 R^2 is 5-member aromatic heterocycle or cycloalkenyl;
25 R^3 is O, $N-R^{11}$, $CH-R^{12}$ or S, $-CR^{13}=CR^{14}-$, $-C(O)-$ or $-C\equiv C-$;
 R^4 is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;
 R^5 is H, halogen, hydroxyl, $-OC_{1-3}$ alkyl, hydroxyl or C_{1-3} alkyl;
 R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;
30 R^7 is H or C_{1-6} alkyl;
 R^8 is H or C_{1-6} alkyl;
 R^9 is $-COOH$, $-S(O)_2OH$;
 R^{10} is H, C_{1-6} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;
 R^{11} is H or C_{1-3} alkyl;

R^{12} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;

R^{13} is H or C_{1-3} alkyl;

R^{14} is H or C_{1-3} alkyl;

R^{15} is H or C_{1-3} alkyl;

5 L is CHR^{16} , O, S, NR^{17} or $-C(O)-$;

a is 0, 1, 2, 3, 4 or 5;

b is 0, 1, 2, 3, 4 or 5;

c is 0 or 1;

d is 1, 2 or 3;

10 R^{16} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino, and

R^{17} is H or C_{1-3} alkyl;

with the proviso:

when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} .

15 In another embodiment of the invention

R^1 is N or $C-R^{10}$; and

R^2 is aromatic heterocycle, non-aromatic heterocycle or cycloalkenyl; and

R^3 is O; and

R^4 is aryl or H; and

20 R^5 is H; and

R^6 is H; and

R^7 is H; and

R^8 is H; and

R^9 is $P(O)(OH)_2$; and

25 R^{10} is H; and

a is 1, 2, 4 or 5; and

b is 1, 2 or 4; and

c is 1; and

d is 3; and

30 L is CHR^{16} ; and

R^{16} is H.

In another embodiment of the invention

R^1 is N or $C-R^{10}$; and

R² is aromatic heterocycle, non-aromatic heterocycle or cycloalkenyl; and

R³ is O; and

R⁴ is aryl; and

R⁵ is H; and

5 R⁶ is H; and

R⁷ is H; and

R⁸ is H; and

R⁹ is P(O)(OH)₂; and

R¹⁰ is H; and

10 a is 1 or 2; and

b is 1 or 2; and

c is 1; and

d is 3; and

L is CHR¹⁶; and

15 R¹⁶ is H.

In another embodiment of the invention

R¹ is N; and

R² is aromatic heterocycle, non-aromatic heterocycle or cycloalkenyl; and

20 R³ is O; and

R⁴ is aryl; and

R⁵ is H; and

R⁶ is H; and

R⁷ is H; and

25 R⁸ is H; and

R⁹ is P(O)(OH)₂; and

a is 1 or 2; and

b is 1 or 2; and

c is 1; and

30 d is 3; and

L is CHR¹⁶; and

R¹⁶ is H.

In another embodiment of the invention

R¹ is C-R¹⁰; and

R² is aromatic heterocycle, non-aromatic heterocycle or cycloalkenyl; and

R³ is O; and

5 R⁴ is H; and

R⁵ is H; and

R⁶ is H; and

R⁷ is H; and

R⁸ is H; and

10 R⁹ is P(O)(OH)₂; and

R¹⁰ is H; and

a is 2, 3, 4 or 5; and

b is 2, 3, 4 or 5; and

c is 1; and

15 d is 3; and

L is CHR¹⁶; and

R¹⁶ is H.

Compounds of the invention are:

20 [3-({3-(2-furyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid;

[3-({3-(1,3-oxazol-2-yl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid;

[3-({4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-2-yl)benzyl}amino)propyl]phosphonic acid;

[3-({3-(3-furyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid;

[3-({4-[(5-phenylpentyl)oxy]-3-(3-thienyl)benzyl}amino)propyl]phosphonic acid;

25 [3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propyl]phosphonic acid;

[3-({4-[3-(4-isobutylphenyl)propoxy]-3-(2-thienyl)benzyl}amino)propyl]phosphonic acid;

[3-({3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid;

30 {3-[(6-(3-furyl)-5-[(5-phenylpentyl)oxy]pyridin-2-yl)methyl]amino}propyl}phosphonic acid;

{3-[(5-[(5-phenylpentyl)oxy]-6-(2-thienyl)pyridin-2-yl)methyl]amino}propyl}phosphonic acid;

(3-{[4-(nonyloxy)-3-(2-thienyl)benzyl]amino}propyl)phosphonic acid;

(3-([4-(decyloxy)-3-(2-thienyl)benzyl]amino)propyl)phosphonic acid;
3-({3-(5-fluoro-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid;
2-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)ethyl dihydrogen phosphate;
5 3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propane-1-sulfonic acid;

methyl[3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propyl]phosphinic acid;
2-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propan-1-ol;
2-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propane-1,3-diol.

10

Some compounds of Formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in an R or S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-13.

15

The term "pharmaceutically acceptable salts" refers to salts or complexes that retain the desired biological activity of the above identified compounds and exhibit minimal or no undesired toxicological effects. The "pharmaceutically acceptable salts" according to the invention include therapeutically active, non-toxic base or acid salt
20 forms, which the compounds of Formula I are able to form.

The acid addition salt form of a compound of Formula I that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, a hydrohalic acid such as hydrochloric acid, hydrobromic
25 acid, sulfuric acid, phosphoric acid, nitric acid and the like; or an organic acid such as for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, fumaric acid, maleic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, formic and the like (Handbook of Pharmaceutical Salts, P. Heinrich
30 Stahal & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta- Zürich, 2002, 329-345).

Compounds of Formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

With respect to the present invention reference to a compound or compounds, is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically.

- 5 Compounds according to the present invention may exist in different polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

10 The compounds of the invention are indicated for use in treating or preventing conditions in which there is likely to be a component involving the sphingosine-1-phosphate receptors.

In another embodiment, there are provided pharmaceutical compositions including at least one compound of the invention in a pharmaceutically acceptable carrier.

15

In a further embodiment of the invention, there are provided methods for treating disorders associated with modulation of sphingosine-1-phosphate receptors. Such methods can be performed, for example, by administering to a subject in need thereof a pharmaceutical composition containing a therapeutically effective amount of at least one compound of the invention.

20

These compounds are useful for the treatment of mammals, including humans, with a range of conditions and diseases that are alleviated by S1P modulation: not limited to the treatment of diabetic retinopathy, other retinal degenerative conditions, dry eye, angiogenesis and wounds.

25

Therapeutic utilities of S1P modulators are ocular diseases, such as but not limited to: wet and dry age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinal edema, geographic atrophy, glaucomatous optic neuropathy, chorioretinopathy, hypertensive retinopathy, ocular ischemic syndrome, prevention of inflammation-induced fibrosis in the back of the eye, various ocular inflammatory diseases including uveitis, scleritis, keratitis, and retinal vasculitis; or systemic vascular barrier related diseases such as but not limited to: various inflammatory diseases, including acute lung injury, its prevention, sepsis, tumor metastasis, atherosclerosis, pulmonary edemas, and ventilation-induced lung injury; or

35

autoimmune diseases and immunosuppression such as but not limited to: rheumatoid arthritis, Crohn's disease, Graves' disease, inflammatory bowel disease, multiple sclerosis, Myasthenia gravis, Psoriasis, ulcerative colitis, autoimmune uveitis, renal ischemia/perfusion injury, contact hypersensitivity, atopic dermatitis, and organ transplantation; or allergies and other inflammatory diseases such as but not limited to: urticaria, bronchial asthma, and other airway inflammations including pulmonary emphysema and chronic obstructive pulmonary diseases; or cardiac protection such as but not limited to: ischemia reperfusion injury and atherosclerosis; or wound healing such as but not limited to: scar-free healing of wounds from cosmetic skin surgery, ocular surgery, GI surgery, general surgery, oral injuries, various mechanical, heat and burn injuries, prevention and treatment of photoaging and skin ageing, and prevention of radiation-induced injuries; or bone formation such as but not limited to: treatment of osteoporosis and various bone fractures including hip and ankles; or anti-nociceptive activity such as but not limited to: visceral pain, pain associated with diabetic neuropathy, rheumatoid arthritis, chronic knee and joint pain, tendonitis, osteoarthritis, neuropathic pains; or central nervous system neuronal activity in Alzheimer's disease, age-related neuronal injuries; or in organ transplant such as renal, corneal, cardiac or adipose tissue transplant.

In still another embodiment of the invention, there are provided methods for treating disorders associated with modulation of sphingosine-1-phosphate receptors. Such methods can be performed, for example, by administering to a subject in need thereof a therapeutically effective amount of at least one compound of the invention, or any combination thereof, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual isomers, enantiomers, and diastereomers thereof.

The present invention concerns the use of a compound of Formula I or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of ocular disease, wet and dry age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinal edema, geographic atrophy, glaucomatous optic neuropathy, chorioretinopathy, hypertensive retinopathy, ocular ischemic syndrome, prevention of inflammation-induced fibrosis in the back of the eye, various ocular inflammatory diseases including uveitis, scleritis, keratitis, and retinal vasculitis; or systemic vascular barrier related diseases, various

inflammatory diseases, including acute lung injury, its prevention, sepsis, tumor metastasis, atherosclerosis, pulmonary edemas, and ventilation-induced lung injury; or autoimmune diseases and immunosuppression, rheumatoid arthritis, Crohn's disease, Graves' disease, inflammatory bowel disease, multiple sclerosis,

5 Myasthenia gravis, Psoriasis, ulcerative colitis, autoimmune uveitis, renal ischemia/perfusion injury, contact hypersensitivity, atopic dermatitis, and organ transplantation; or allergies and other inflammatory diseases, urticaria, bronchial asthma, and other airway inflammations including pulmonary emphysema and chronic obstructive pulmonary diseases; or cardiac protection, ischemia reperfusion
10 injury and atherosclerosis; or wound healing, scar-free healing of wounds from cosmetic skin surgery, ocular surgery, GI surgery, general surgery, oral injuries, various mechanical, heat and burn injuries, prevention and treatment of photoaging and skin ageing, and prevention of radiation-induced injuries; or bone formation, treatment of osteoporosis and various bone fractures including hip and ankles; or
15 anti-nociceptive activity, visceral pain, pain associated with diabetic neuropathy, rheumatoid arthritis, chronic knee and joint pain, tendonitis, osteoarthritis, neuropathic pains; or central nervous system neuronal activity in Alzheimer's disease, age-related neuronal injuries; or in organ transplant such as renal, corneal, cardiac or adipose tissue transplant.

20

The actual amount of the compound to be administered in any given case will be determined by a physician taking into account the relevant circumstances, such as the severity of the condition, the age and weight of the patient, the patient's general physical condition, the cause of the condition, and the route of administration.

25

The patient will be administered the compound orally in any acceptable form, such as a tablet, liquid, capsule, powder and the like, or other routes may be desirable or necessary, particularly if the patient suffers from nausea. Such other routes may include, without exception, transdermal, parenteral, subcutaneous, intranasal, via an
30 implant stent, intrathecal, intravitreal, topical to the eye, back to the eye, intramuscular, intravenous, and intrarectal modes of delivery. Additionally, the formulations may be designed to delay release of the active compound over a given period of time, or to carefully control the amount of drug released at a given time during the course of therapy.

In another embodiment of the invention, there are provided pharmaceutical compositions including at least one compound of the invention in a pharmaceutically acceptable carrier therefore. The phrase "pharmaceutically acceptable" means the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an emulsion, a dispersion, a micelle, a liposome, and the like, wherein the resulting composition contains one or more compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for enteral or parenteral applications. Invention compounds may be combined, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. Invention compounds are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

Pharmaceutical compositions containing invention compounds may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets containing invention compounds in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as

calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the invention compounds are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the invention compounds are mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Invention compounds may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the invention compounds with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of

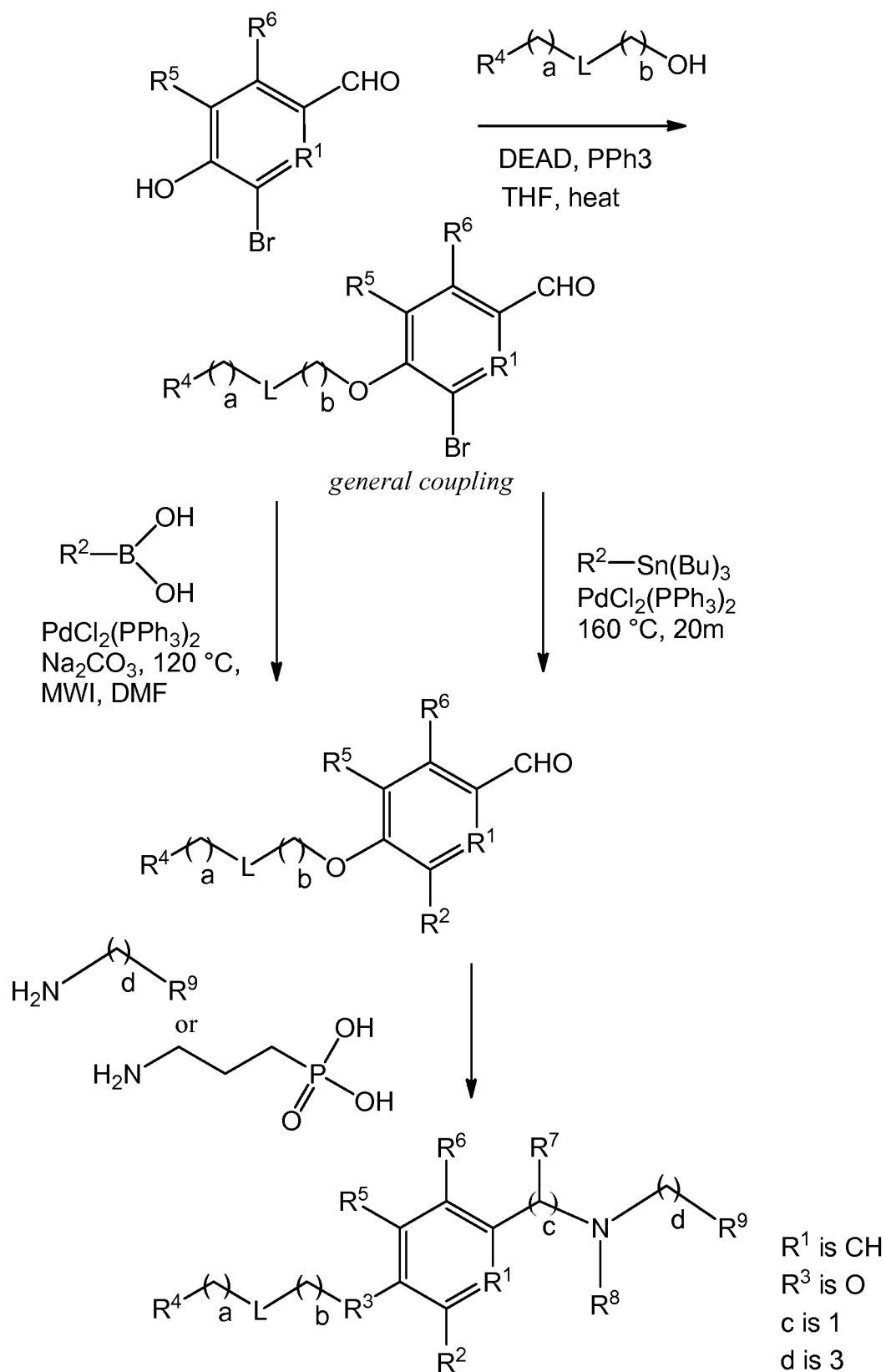
administration and dosage employed for each subject is left to the discretion of the practitioner.

The compounds and pharmaceutical compositions described herein are useful as medicaments in mammals, including humans, for treatment of diseases and or alleviations of conditions which are responsive to treatment by agonists or functional antagonists of sphingosine-1-phosphate receptors. Thus, in further embodiments of the invention, there are provided methods for treating a disorder associated with modulation of sphingosine-1-phosphate receptors. Such methods can be performed, for example, by administering to a subject in need thereof a pharmaceutical composition containing a therapeutically effective amount of at least one invention compound. As used herein, the term "therapeutically effective amount" means the amount of the pharmaceutical composition that will elicit the biological or medical response of a subject in need thereof that is being sought by the researcher, veterinarian, medical doctor or other clinician. In some embodiments, the subject in need thereof is a mammal. In some embodiments, the mammal is human.

The present invention concerns also processes for preparing the compounds of Formula I. The compounds of formula I according to the invention can be prepared analogously to conventional methods as understood by the person skilled in the art of synthetic organic chemistry. The synthetic schemes set forth below, illustrate how compounds according to the invention can be made. Those skilled in the art will be able to routinely modify and/or adapt the following scheme to synthesize any compounds of the invention covered by Formula I.

In **Scheme 1**, hydroxybenzaldehydes react with hydroxylated compounds in the presence of triphenylphosphine and diethyl azodicarboxylate to give the corresponding ether intermediate. This intermediate is coupled with the boronic acid or the stannate of the corresponding R^2 group to give the corresponding intermediate. This intermediate reacts with 3-aminopropylphosphonic acid to give a derivative of Formula I.

Scheme 1

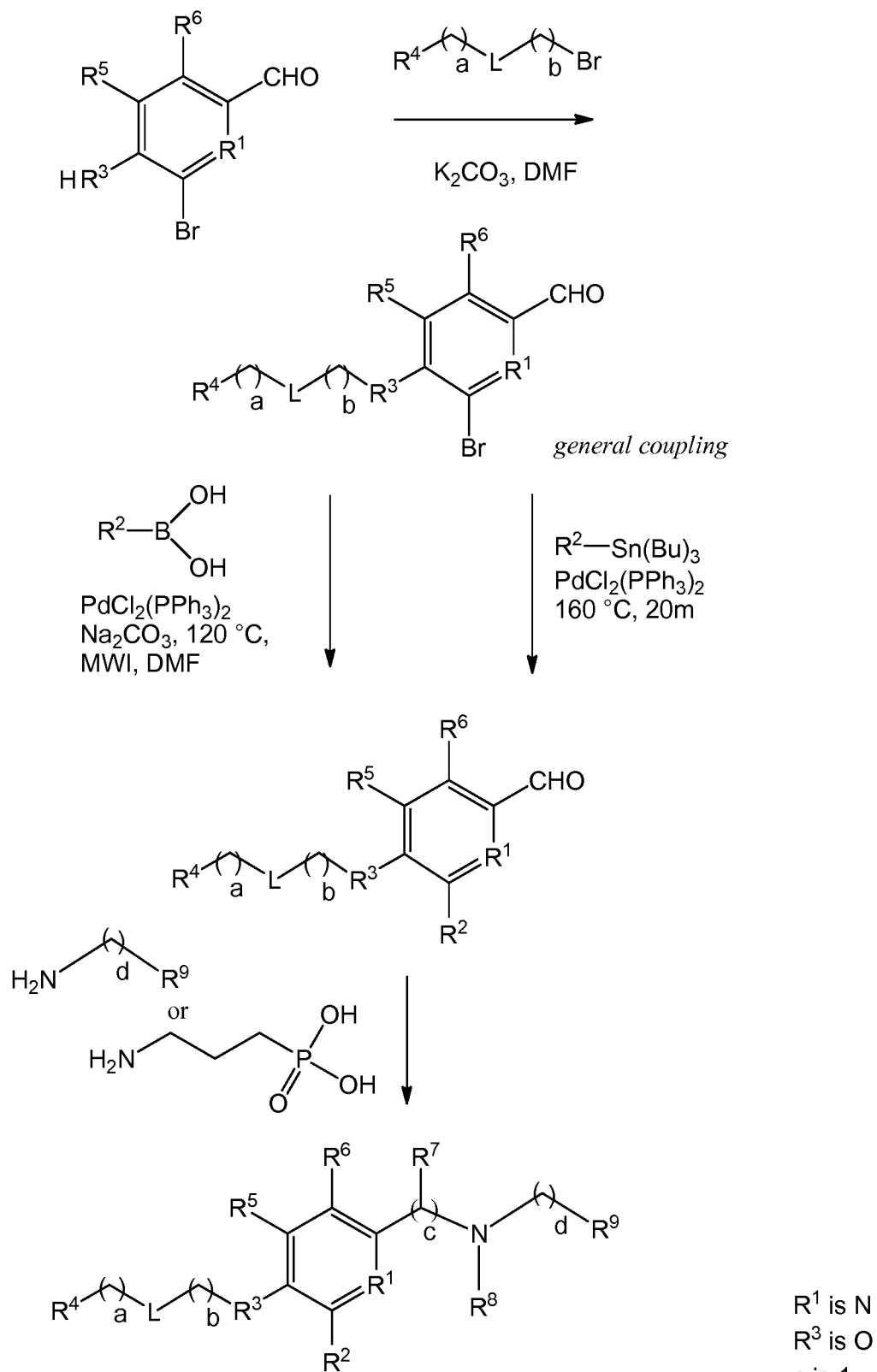


Formula I

In **Scheme 2**, picolinaldehydes react with brominated compounds in the presence of potassium carbonate to give the corresponding intermediate. This intermediate is

coupled with the boronic acid of the corresponding R^2 group to give the corresponding intermediate, which reacts with 3-aminopropylphosphonic acid to give a derivative of Formula I.

Scheme 2



Formula I

DETAILED DESCRIPTION OF THE INVENTION

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention claimed. As used herein, the use of the singular includes the plural unless specifically stated otherwise.

It will be readily apparent to those skilled in the art that some of the compounds of the invention may contain one or more asymmetric centers, such that the compounds may exist in enantiomeric as well as in diastereomeric forms. Unless it is specifically noted otherwise, the scope of the present invention includes all enantiomers, diastereomers and racemic mixtures. Some of the compounds of the invention may form salts with pharmaceutically acceptable acids or bases, and such pharmaceutically acceptable salts of the compounds described herein are also within the scope of the invention.

The present invention includes all pharmaceutically acceptable isotopically enriched compounds. Any compound of the invention may contain one or more isotopic atoms enriched or different than the natural ratio such as deuterium ^2H (or D) in place of protium ^1H (or H) or use of ^{13}C enriched material in place of ^{12}C and the like. Similar substitutions can be employed for N, O and S. The use of isotopes may assist in analytical as well as therapeutic aspects of the invention. For example, use of deuterium may increase the in vivo half-life by altering the metabolism (rate) of the compounds of the invention. These compounds can be prepared in accord with the preparations described by use of isotopically enriched reagents.

The following examples are for illustrative purposes only and are not intended, nor should they be construed as limiting the invention in any manner. Those skilled in the art will appreciate that variations and modifications of the following examples can be made without exceeding the spirit or scope of the invention.

As will be evident to those skilled in the art, individual isomeric forms can be obtained by separation of mixtures thereof in conventional manner. For example, in the case of diastereoisomeric isomers, chromatographic separation may be employed.

Compound names were generated with ACD version 8; and Intermediates and reagent names used in the examples were generated with software such as Chem Bio Draw Ultra version 12.0 or Auto Nom 2000 from MDL ISIS Draw 2.5 SP1.

- 5 In general, characterization of the compounds is performed according to the following methods:

NMR spectra are recorded on 300 and/or 600 MHz Varian and acquired at room temperature. Chemical shifts are given in ppm referenced either to internal TMS or to the solvent signal.

- 10 All the reagents, solvents, catalysts for which the synthesis is not described are purchased from chemical vendors such as Sigma Aldrich, Fluka, Bio-Blocks, Combi-blocks, TCI, VWR, Lancaster, Oakwood, Trans World Chemical, Alfa, AscentScientific LLC., Fisher, Maybridge, Frontier, Matrix, Ukrorgsynth, Toronto, Ryan Scientific, SiliCycle, Anaspec, Syn Chem, Chem-Impex, MIC-scientific, Ltd;
15 however some known intermediates, were prepared according to published procedures.

Usually the compounds of the invention were purified by column chromatography (Auto-column) on an Teledyne-ISCO CombiFlash with a silica column, unless noted otherwise.

20

The following abbreviations are used in the examples:

s, m, h, d second, minute, hour, day

NH₃ ammonia

CH₃CN acetonitrile

- 25 PSI pound per square inch

DCM dichloromethane

DMF *N,N*-dimethylformamide

NaOH sodium hydroxide

MeOH methanol

- 30 CD₃OD deuterated methanol

NH₃ ammonia

HCl hydrochloric acid

Na₂SO₄ sodium sulfate

rt room temperature

DMF dimethylformamide

MgSO₄ magnesium sulfate

EtOAc ethyl acetate

CDCl₃ deuterated chloroform

5 DMSO-d₆ deuterated dimethyl sulfoxide

Auto-column automated flash liquid chromatography

TFA trifluoroacetic acid

THF tetrahydrofuran

NaHB(OAc)₃ sodium triacetoxym borohydride

10 DEAD diethyl azodicarboxylate

Na₂CO₃ sodium carbonate

Cs₂CO₃ cesium carbonate

M molar

PdCl₂(PPh₃)₂ bis(triphenylphosphine)palladium(II) chloride

15 AcOH acetic acid

K₂CO₃ potassium carbonate

CuI copper iodide

MnO₂ magnesium oxide

MgCl₂ magnesium chloride

20 NaCl sodium chloride

Ti(OEt)₄ titanium ethoxide

MeMgBr methylmagnesium bromide

CHCl₃ chloroform

TBAH tetrabutylammonium hydroxide

25

The following synthetic schemes illustrate how compounds according to the invention can be made. Those skilled in the art will be routinely able to modify and/or adapt the following schemes to synthesize any compound of the invention covered by Formula I.

30 Some compounds of this invention can generally be prepared in one step from commercially available literature starting materials.

Example 1**Compound 1****[3-({3-(2-furyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid**

- 5 Step-1: A solution of 5-phenyl-pentan-1-ol [CAS 10521-91-2] (4.50 mL, 26.6 mmol), 3-bromo-4-hydroxybenzaldehyde [CAS 2973-78-6] (5.36 g, 26.7 mmol), triphenylphosphine (9.1 g, 34.6 mmol) and DEAD, (14.5 mL, 40% in toluene, ~1.2 eqv) in THF (100 mL) was reacted at rt for 1 h, followed by heating to 60 °C for 2 days. Silica gel was added and the solvents were removed under vacuum. Auto-
- 10 column: chromatography on an Teledyne-ISCO CombiFlash with a silica column with 9.5 hexane/0.5 EtOAc to 9 Hexanes/1 EtOAc gave **Intermediate 1** as a clear oil that solidified upon standing, 5.38 g (58%): **3-bromo-4-(5-phenyl-pentyloxy)-benzaldehyde**.
- ¹H NMR (300 MHz, CDCl₃): δ 9.83 (s, 1H), 8.07 (d, J = 2.1 Hz, 1H), 7.78 (dd, J = 8.7, 2.1 Hz, 1H), 7.28-7.18 (m, 5H), 6.96 (d, J = 8.4 Hz, 1H), 4.11 (t, J = 6.3 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 1.92-1.55 (m, 6H).

- Step-2: **Intermediate 1** (0.65 g, 1.87 mmol) in DMF (14 mL) was reacted with tributyl(furan-2-yl)stannane [CAS 118486-94-5] (1.2 mL, 3.70 mmol) and
- 20 PdCl₂(PPh₃)₂ (0.197 g, ~15 mol%) at 160 °C for 15m with MWI (microwave irradiation: Biotage Initiator 2.5). The reaction mixture was diluted with 2:1 EtOAc/Hexanes (~150 mL), washed with water (3x), and dried over MgSO₄, filtered and concentrated onto silica gel. Auto-column (9.5 hexane/0.5 EtOAc) gave **Intermediate 2: 3-furan-2-yl-4-(5-phenyl-pentyloxy)-benzaldehyde** as a white
- 25 solid, 0.44 g (70 %).
- ¹H NMR (300 MHz, CDCl₃): δ 9.94 (s, 1H), 8.37 (d, J = 2.1 Hz, 1H), 7.77-7.74 (m, 1H), 7.49 (d, J = 1.2 Hz, 1H), 7.30-7.10 (m, 5H), 7.04-6.90 (m, 2H), 6.50 (brs, 1H), 4.21-4.05 (m, 2H), 2.70-2.60 (m, 2H), 2.10-1.50 (series m, 6H).

- 30 Step 3: 3-Aminopropylphosphonic acid [CAS 13138-33-5](225 mg, 1.57 mmol) in MeOH (15 mL) followed by tetrabutylammonium hydroxide (TBAH) (12.8 mL, ~ 12.8 mmol, 1.0M in MeOH) at 50 °C for ~1 h. **Intermediate 2** (440 mg, 1.31 mmol) in THF (3 mL) and MeOH (6 mL) was added, and after 30 m at 50 °C the mixture was cooled to rt. Sodium borohydride (120 mg, 3.17 mmol) was added and the reaction

was continued until complete (1-2 h). [Alternative procedure: use of tetrabutylammonium hydroxide (3 eqv.) following with sodium borohydride (1.5 eqv.) at rt for ~16-18 h.] The solvent was removed under vacuum and water was added, followed by HCl (2M) until pH 2-4. The aqueous layer was extracted (two times) with chloroform:isopropanol (~3:1). The organic layers were dried over MgSO₄, filtered and concentrated onto amine-silica gel (ISCO). Auto-column (amine-silica gel column) (70% MeOH, 29.5% CH₂Cl₂, 0.5 % AcOH) gave the title compound **[3-({3-(2-furyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid** as a white solid. 310 mg, (52%)

¹H NMR (600 MHz, CF₃CO₂D): δ 7.58 (d, J = 1.8 Hz, 1H), 7.45 (brs, 2H), 7.39 (dd, J = 1.8, 8.4 Hz, 1H), 7.36 (s, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 4.41 (t, J = 4.8 Hz, 2H), 4.20 (t, J = 6.6 Hz, 2H), 3.55-3.48 (m, 2H), 2.70 (t, J = 7.8 Hz, 2H), 2.36-2.30 (m, 2H), 2.25-2.19 (m, 2H), 1.95-1.90 (m, 2H), 1.78-1.74 (m, 2H), 1.59-1.54 (m, 2H).

Compounds 2 and 3 were prepared from the corresponding benzaldehyde, stannate and 3-Aminopropylphosphonic acid in a similar manner to the procedure described in **Example 1** for **Compound 1**. The reagents used and the results are described below in **Table 1**.

Table 1

Compound number	IUPAC name	Reagent(s) used	¹ H NMR δ (ppm) for Compound
2	[3-({3-(1,3-oxazol-2-yl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid	2-(tributylstannyl)oxazole [CAS 145214-05-7]	¹ H NMR (600 MHz, CF ₃ CO ₂ D): δ 8.10 (d, J = 1.8 Hz, 1H), 7.94 (d, J = 1.8 Hz, 1H), 7.72 (d, J = 9.0 Hz, 1H), 7.47 (d, J = 1.8 Hz, 1H), 7.16 (d, J = 9.0 Hz, 1H), 7.01-6.98 (m, 2H), 6.93-6.90 (m, 3H), 4.26-4.24 (m, 4H), 3.30 (brs, 2H), 2.44 (t, J = 7.2 Hz, 2H), 2.11-2.07 (m, 2H), 1.98-1.94 (m, 2H), 1.81-1.76 (m, 2H), 1.56-1.51 (m, 2H), 1.31-1.27 (m, 2H).

3	[3-({4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-2-yl)benzyl}amino)propyl]phosphonic acid	2-(tributylstannyl)thiazole [CAS 121359-48-6]	¹ H NMR (600 MHz, CF ₃ CO ₂ D): δ 8.38 (brs, 1H), 8.19 (q, J = 1.8 Hz, 1H), 8.01-7.99 (m, 2H), 7.51 (dd, J = 1.8, 9.0 Hz, 1H), 7.41-7.38 (m, 2H), 7.34 (d, J = 7.8 Hz, 2H), 7.32-7.29 (m, 1H), 4.62 (brs, 2H), 4.58 (t, J = 6.0 Hz, 2H), 3.67 (brs, 2H), 2.86 (t, J = 6.61 Hz, 2H), 2.50-2.46 (m, 2H), 2.38-2.33 (m, 2H), 2.23-2.19 (m, 2H), 1.99-1.94 (m, 2H), 1.79-1.74 (m, 2H).

Example 2**Compound 4****[3-({3-(3-furyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid**

5

Step-1: A mixture of **Intermediate 1** (290 mg, 0.87 mmol) in DMF (12 mL) was reacted with furan-3-yl boronic acid [CAS 5552-70-0] (195 mg, 1.74 mmol) Na₂CO₃ (2.8 mL, 2M) and PdCl₂(PPh₃)₂ (69 mg, ~11 mol%) at 120 °C for 20 m with MWI (microwave irradiation: Biotage Initiator 2.5). The reaction mixture was diluted with water, and extracted (two times) with 1:1 EtOAc:Hexanes (200 mL). The organic layers were washed with water (three times), dried over MgSO₄, filtered and concentrated onto silica gel. Auto-column (9 hexane/1 EtOAc) gave **Intermediate 3: 3-(furan-3-yl)-4-((5-phenylpentyl)oxy)benzaldehyde** 230 mg (29%).

10

15

¹H NMR (300 MHz, CDCl₃): δ 9.92 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.75-7.72 (m, 1H), 7.48 (s, 15H), 7.30-7.16 (m, 3H), 7.19-7.16 (m, 3H), 7.02 (d, J = 8.7 Hz, 1H), 6.85 (d, J = 1.2 Hz, 1H), 4.14 (t, J = 6.3 Hz, 2H), 2.70-2.60 (m, 2H), 2.01-1.50 (series of m, 6H).

Step-2: Intermediate 3 (230 mg, 0.66 mmol) used in the appropriate steps of Example 1 produced the title compound: **[3-({3-(3-furyl)-4-[(5-phenylpentyl)oxy]benzyl}amino) propyl]phosphonic acid**

¹H NMR (600 MHz, CF₃CO₂D): δ 7.66 (d, J = 1.8 Hz, 1H), 7.56-7.50 (m, 2H), 7.40-7.35 (m, 3H), 7.30 (d, J = 7.8 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 6.85-6.83 (m, 1H), 4.47 (brs, 2H), 4.28 (t, J = 6.6 Hz, 2H), 3.56 (brs, 2H), 2.79 (t, J = 7.2 Hz, 2H), 2.42-2.36 (m, 2H), 2.31-2.25 (m, 2H), 2.09-2.05 (m, 2H), 1.88-1.84 (m, 2H), 1.71-1.68 (m, 2H).

Compounds 5, 6, 7 and 8 were prepared from the corresponding benzaldehyde, boronic acid and 3-aminopropylphosphonic acid in a similar manner to the procedure described in **Example 2** for **Compound 4**. The reagents used and the results are described below in **Table 2**.

Table 2

Compound number	IUPAC name	Reagent(s) used	¹ H NMR δ (ppm) for Compound
5	[3-({4-[(5-phenylpentyl)oxy]-3-(3-thienyl)benzyl}amino)propyl]phosphonic acid	thiophen-3-yl boronic acid [CAS 5552-70-0]	¹ H NMR (600 MHz, CF ₃ CO ₂ D): δ 7.58 (d, J = 1.8 Hz, 1H), 7.45 (brs, 2H), 7.39 (dd, J = 1.8, 8.4 Hz, 1H), 7.36 (s, 1H), 7.31 (t, J = 7.2 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 4.41 (t, J = 5.4 Hz, 2H), 4.20 (t, J = 6.0 HZ, 2H), 3.54-3.48 (m, 2H), 2.70 (t, J = 7.2 Hz, 2H), 2.35-2.30 (m, 2H), 2.25-2.20 (m, 2H), 1.94-1.91 (m, 2H), 1.77-1.74 (m, 2H), 1.58-1.55 (m, 2H).
6	[3-({4-[(5-phenylpentyl)oxy]-3-(2-	thiophen-2-yl boronic acid	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.59-7.56 (m, 1H), 7.40-7.35 (m, 2H), 7.26-

	thienyl)benzyl }amino)propyl]phosphonic acid	[CAS 13331-23-2]	7.20 (m, 2H), 7.17-7.05 (m, 5H), 4.14-4.10 (m, 4H), 3.10 (t, J = 6.6 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H) 2.06-1.88 (m, 4H), 1.76-1.56 (m, 6H).
7	[3-({4-[3-(4-isobutylphenyl)propoxy]-3-(2-thienyl)benzyl}amino)propyl]phosphonic acid	4-(2-methylpropyl)-benzenepropanol] [CAS 147598-21-8] thiophen-2-yl boronic acid [CAS 13331-23-2]	¹ H NMR (300 MHz, CD ₃ OD): δ 7.84 (d, J = 1.8 Hz, 1H), 7.64 (dd, J = 0.9, 3.6 Hz, 1H), 7.43 (d, J = 4.8 Hz, 1H), 7.35 (dd, J = 2.1, 8.4 Hz, 1H), 7.11-7.00 (m, 6H), 4.07-4.00 (m, 4H), 3.03 (t, J = 6.3 Hz, 2H), 2.81 (t, J = 7.8 Hz, 2H), 2.41 (d, J = 6.9 Hz, 2H), 2.18-2.10 (m, 2H), 2.10-2.19 (m, 2H), 1.85-1.75 (m, 1H), 1.71-1.61 (m, 2H), 0.87 (d, J = 6.6 Hz, 6H).
8	[3-({3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid	cyclopentenyl boronic acid [CAS 850036-28-1]	MS (M+H) ⁺ 457.35
9	2-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)ethyl dihydrogen phosphate	Intermediate 1 thiophen-2-yl boronic acid 2-aminoethyl	¹ H NMR (600 MHz, CF ₃ COOD): δ 7.70 (d, J = 2.4 Hz, 1H), 7.41 (brs, 2H), 7.33 (dd, J = 1.8, 8.4 Hz, 1H), 7.22-7.20 (m, 2H), 7.15 (d, J = 7.2 Hz, 2H), 7.12-7.09 (m, 2H), 7.03 (s, 1H), 4.51-4.48 (m,

		dihydrogen phosphate	2H), 4.40 (d, J = 4.2 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 3.58-3.52 (m, 2H), 2.63 (t, J = 7.8 Hz, 2H), 1.95-1.92 (m, 2H), 1.712-1.58 (m, 2H), 1.59-1.55 (m, 2H).
10	3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propane-1-sulfonic acid	Intermediate 1 thiophen-2-yl boronic acid 3-aminopropane-1-sulfonic acid	¹ H NMR (600 MHz, CF ₃ COOD): δ 7.65 (brs, 1H), 7.36 (brs, 2H), 7.25 (d, J = 7.8 Hz, 1H), 7.20-7.18 (m, 2H), 7.13-7.12 (m, 2H), 7.10-7.05 (m, 2H), 7.01 (s, 1H), 4.30 (t, J = 5.4 Hz, 2H), 4.13 (t, J = 6.6, 2H), 3.52-3.50 (m, 2H), 3.42 (t, J = 6.6 Hz, 2H), 2.61 (t, J = 7.8 Hz, 2H), 2.46-2.40 (m, 2H), 1.84-1.89 (m, 2H), 1.72-1.67 (m, 2H), 1.58-1.53 (m, 2H).
11	methyl[3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propyl]phosphinic acid	Intermediate 1 thiophen-2-yl boronic acid (3-aminopropyl)(methyl)phosphinic acid	¹ H NMR (600 MHz, CF ₃ COOD): δ 7.67 (d, J = 2.4 Hz, 1H), 7.45 (brs, 2H), 7.28 (dd, J = 2.4, 8.4 Hz, 1H), 7.23-7.21 (m, 2H), 7.16-7.15 (m, 2H), 7.13-7.08 (m, 2H), 7.04 (s, 1H), 4.26-4.33 (m, 2H), 4.17 (t, J = 6.0 Hz, 2H), 3.46-3.39 (m, 2H), 2.64 (t, J = 7.2 Hz, 2H), 3.00-2.24 (m, 2H), 2.13-2.08 (m, 2H), 1.97-1.92 (m, 2H), 1.75-1.69 (m, 5H), 1.61-1.56 (m, 2H).
12	2-({4-[(5-phenylpentyl)oxy]-3-(2-	Intermediate 1 thiophen-2-yl	¹ H NMR (600 MHz, CDCl ₃): δ 7.60 (d, J = 1.8 Hz, 1H), 7.50 (dd, J = 1.2, 4.2 Hz, 1H), 7.31

	thienyl)benzyl }amino)propa n-1-ol	boronic acid 2-aminopropan-1- ol	(dd, J = 1.2, 5.4 Hz, 1H), 7.27 (t, J = 7.8 Hz, 2H), 7.20-7.17 (m, 4H), 7.07 (dd, J = 3.6, 4.8 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 4.06 (t, J = 6.6 Hz, 2H), 3.86 (d, J = 12.6 Hz, 1H), 3.72 (d, J = 12.6 Hz, 1H), 3.63-3.61 (m, 1H), 3.49 (s, 2H), 3.31- 3.28 (m, 1H), 2.89-2.86 (m, 1H), 2.65 (t, J = 7.8 Hz, 2H), 1.94-1.89 (m, 2H), 1.74- 1.69 (m, 2H), 1.60-1.55 (m, 2H), 1.11 (d, J = 6.6 Hz, 3H)
13	2-({4-[(5- phenylpentyl) oxy]-3-(2- thienyl)benzyl }amino)propa ne-1,3-diol	Intermediate 1 thiophen-2-yl boronic acid 2-aminopropane- 1,3-diol	¹ H NMR (600 MHz, CDCl ₃): δ 7.62 (d, J = 2.1 Hz, 1H), 7.51 (dd, J = 1.2, 3.6 Hz, 1H), 7.31 (dd, J = 1.2, 5.4 Hz, 1H), 7.28- 7.25 (m, 2H), 7.22-7.17 (m, 4H), 7.07 (dd, J = 3.6, 5.1 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 4.06 (t, J = 6.3 Hz, 2H), 3.84 (s, 2H), 3.78-3.73 (m, 2H), 3.65-3.60 (m, 2H), 2.88-2.83 (m, 1H), 2.65 (t, J = 7.2 Hz, 2H), 2.19 (brs, 3H), 1.96-1.87 (m, 2H), 1.75-1.66 (m, 2H), 1.62-1.54 (m, 2H).

Example 3**Compound 14**

{3-[(6-(3-furyl)-5-[(5-phenylpentyl)oxy]pyridin-2-yl)methyl]amino}propyl}phosphonic acid

5

Step-1: A solution of 2-bromo-6-(hydroxymethyl)pyridin-3-ol [CAS 168015-04-1] (~1g, ~5 mmol) in dioxane (100 mL) was treated with MnO₂ (3.0 g, 29.3 mmol, 85%) at 100 °C for 16-18 h. The mixture was filtered, and concentrated onto silica gel. Auto-column (7:3 hexane/EtOAc gave **Intermediate 4: 6-bromo-5-**

10 **hydroxypicolinaldehyde** as a solid 0.6 g (60%). ¹H NMR (300 MHz, CDCl₃): δ 9.91 (s, 1H), 7.92 (d, 4.2 Hz, 1H), 7.43 (d, 4.2 Hz, 1H)

Step-2: Reaction of **Intermediate 4** (0.59 g, 2.92 mmol) and (5-bromopentyl)benzene [CAS14469-83-1] (0.80 g, 3.52 mmol) and K₂CO₃ (0.8 g, 5.79 mmol) in DMF (15 mL) at 100 °C for 4 h followed by a standard aqueous work-up and auto-column purification gave the product **Intermediate 5: 6-bromo-5-(5-phenylpentyl)oxy)picolinaldehyde** as a clear oil (0.67 g (66%). ¹H NMR (300 MHz, CDCl₃): δ 9.93 (s, 1H), 7.92 9s, J = 8.1 Hz, 1H), 7.28-7.18 (m, 6H), 4.12 (t, J = 6.0 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 1.93-1.55 (series of m, 6H).

20

Step-3: **Intermediate 5** (0.335 g, 0.96 mmol) and furan-3-yl boronic acid [CAS 5552-70-0] (0.215 g, 1.92 mmol), Na₂CO₃ (2.8 mL, 2M) in DMF (12 mL) with PdCl₂(PPh₃)₂ (74mg, ~11 mol%) at 120 °C for 20 m with MWI (microwave irradiation: Biotage Initiator 2.5). The reaction mixture was diluted with water, and extracted (three times) with 1:1 EtOAc:Hexanes. The organic layers were dried over MgSO₄, filtered and concentrated onto silica gel. Auto-column (9 hexane/1 EtOAc) gave **Intermediate 6: 6-(furan-3-yl)-5-((5-phenylpentyl)oxy)picolinaldehyde**. ¹H NMR (300 MHz, CDCl₃): δ 10.0 (s, 1H), 8.21 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.50 (brs, 1H), 7.28-7.17 (series of m, 7H), 4.16 (t, J = 6.3 Hz, 2H), 2.67 (t, J = 9.0 Hz, 2H), 1.99-1.55 (series of m, 6H).

30

Use of **Intermediate 6** in the appropriate steps of **Example 1** produced the title compound; **{3-[(6-(3-furyl)-5-[(5-phenylpentyl)oxy]pyridin-2-yl)methyl]amino}propyl} phosphonic acid** 0.17 g (53 %)

¹H NMR (600 MHz, CF₃CO₂D): δ 8.57 (s, 1H), 8.60-8.30 (m, 2H), 7.73 (s, 1H), 7.30 (t, J = 7.2 Hz, 2H), 7.21-7.18 (m, 2H), 4.95 (s, 2H), 4.46 (t, J = 6.0 Hz, 2H), 3.68 (t, J = 6.6 Hz, 2H), 2.75 (t, J = 7.8 Hz, 2H), 2.45-2.40 (m, 2H), 2.31-2.27 (m, 2H), 2.15-2.12 (m, 2H), 1.87-1.84 (m, 2H), 1.69-1.65 (m, 2H).

5

Compounds 15, 16 and 17 were prepared from the corresponding starting materials and 3-aminopropylphosphonic acid in a similar manner to the procedure described in **Example 3** for **Compound 14**. The reagents used and the results are described below in **Table 3**.

10

Table 3

Compound number	IUPAC name	Reagent(s) used	¹ H NMR δ (ppm) for Compound
15	{3-[(5-phenylpentyl)oxy]-6-(2-thienyl)pyridin-2-yl}methylamino]propyl}phosphonic acid	thiophen-2-yl boronic acid [CAS 13331-23-2]	¹ H NMR (600 MHz, CF ₃ CO ₂ D): δ 8.29 (d, J = 3.6 Hz, 1H), 8.14-8.09 (m, 3H), 7.50 (t, J = 4.81 Hz, 1H), 7.42-7.38 (m, 2H), 7.35-7.30 (m, 3H), 5.06 (s, 2H), 4.57 (t, J = 6.0 Hz, 2H), 3.79 (t, 6.6 Hz, 2H), 2.86 (t, J = 6.6 Hz, 2H), 2.55-2.50 (m, 2H), 2.41-2.36 (m, 2H), 2.55-2.23 (m, 2H), 1.98-1.94 (m, 2H), 1.70-1.60 (m, 2H).
16	(3-{[4-(nonyloxy)-3-(2-thienyl)benzyl]amino}propyl)phosphonic acid	3-bromo-4-hydroxybenzaldehyde [CAS 2973-78-6] 1-bromononane [CAS 693-58-3] tributyl(thiophen-2-yl)stannane	¹ H NMR (600 MHz, CF ₃ CO ₂ D): δ 7.68 (s, 1H), 7.51-7.38 (m, 2H), 7.29 (d, J = 3.9 Hz, 1H), 7.13 (dd, J = 1.2, 8.4 Hz, 1H), 7.07 (d, J = 1.8 Hz, 1H), 4.35 (s, 2H), 4.20-4.18 (m, 2H), 3.44 (s, 2H), 2.30-2.22 (m, 2H), 2.20-2.10 (m, 2H), 1.93 (t, J = 6.0 Hz, 2H), 1.56-1.53 (m, 2H), 1.40-1.29 (m, 10H), 0.87-

		[CAS 54663-78-4]	0.85 (m, 3H).
17	(3-{[4-(decyloxy)-3-(2-thienyl)benzyl]amino}propyl)phosphonic acid	3-bromo-4-hydroxybenzaldehyde [CAS 2973-78-6] 1-bromodecane [CAS 112-29-8] tributyl(thiophen-2-yl)stannane [CAS 54663-78-4]	¹ H NMR (600 MHz, CF ₃ CO ₂ D): δ 7.74 (s, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.13 (s, 1H), 4.40 (s, 2H), 4.25 (t, J = 6.6 Hz, 2H), 3.49 (t, J = 6.6 Hz, 2H), 2.35-2.29 (m, 2H), 2.23-2.18 (m, 2H), 2.01-1.97 (m, 2H), 1.62-1.58 (m, 2H), 1.47-1.34 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H).

Example 4**Compound 18 3-({3-(5-fluoro-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid**

The following experimental describes methods used for preparation of **3-(5-fluorothiophen-2-yl)-4-((5-phenylpentyl)oxy)benzaldehyde (Intermediate 10)**

Proton NMR (nuclear magnetic resonance) spectra were taken either at 60 MHz on a Varian T-60 spectrometer or at 300 MHz on a Varian Inova system.

The spectra of all products were consistent with their structures. Reverse-phase HPLC analyses of products were performed on an Agilent 1100 instrument using an Zorbax SB-phenyl column (250 X 4.6 mm), with a flow rate at 1.0 mL/min. The elution was isocratic at 40 °C using a mixture of A1 (700 mL of water, 300 mL of methanol, and 3 mL of Et₃N adjusted to pH 3.4 with H₃PO₄), and methanol.

Conditions: A1:CH₃OH (10:90). The retention times were as follows: 4,4,5,5-tetramethyl-2-(4-((5-phenylpentyl)oxy)-3-(thiophen-2-yl)phenyl)-1,3-dioxolane, 5.36 min; 2-(3-(5-fluorothiophen-2-yl)-4-((5-phenylpentyl)oxy)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane, 5.54 min; and for 3-(5-fluorothiophen-2-yl)-4-((5-phenylpentyl)oxy)benzaldehyde, 5.0 min. Thin layer chromatography (TLC) made use of E. Merck Kieselgel PF60 plates. TLC solvent systems are indicated in the text.

Intermediate-1 and thiophen-2-yl boronic acid, [CAS 13331-23-2] were used in the appropriate procedural steps of **Example 2** for **Compound 6** to produce **4-((5-phenylpentyl)oxy)-3-(thiophen-2-yl)benzaldehyde (Intermediate 7)**.

5

Step-1: In a 500 mL 3-necked flask equipped with a stir-bar and condenser was placed **4-((5-phenylpentyl)oxy)-3-(thiophen-2-yl)benzaldehyde (Intermediate 7)** (4.9 g, 1.4 mmol), pinacol (6.6 g, 5.6 mol) and p-toluenesulfonic acid (0.8 g, 4.2 mmol) in benzene (125 mL). The resulting mixture was refluxed for 1 h. TLC analysis (EtOAc: hexane; 1:1) showed the reaction was complete. The reaction was cooled to room temperature, washed with saturated NaHCO₃ (2x75 mL), brine (1x75 mL), filtered through 1PS filter paper and concentrated under reduced pressure to give a brown oil. The oil was flash chromatographed over silica gel (100 g) with anhydrous sodium sulfate (20 g) on top packed with hexane. The column was eluted with 12x50 mL of 15% EtOAc in hexane. The product was eluted to give 5.1 g (81%) **4,4,5,5-tetramethyl-2-(4-((5-phenylpentyl)oxy)-3-(thiophen-2-yl)phenyl)-1,3-dioxolane (Intermediate 8)** as a yellow oil. HPLC analysis showed a purity of ~97%. NMR (CDCl₃) δ 7.8(s, 1H), 7.55(d, 1H), 7.1-7.4(m, 8H), 6.95(d, 1H), 6.0(s, 1H), 4.1(t, 2H), 2.7(t, 2H), 1.95(m, 2H), 1.7(m, 2H), 1.6(m, 2H), 1.35(d, 12H).

10

15

20

Step-2: In a 500 mL 3-necked flask equipped with a stir-bar, dropping funnel, and thermometer was placed **4,4,5,5-tetramethyl-2-(4-((5-phenylpentyl)oxy)-3-(thiophen-2-yl)phenyl)-1,3-dioxolane (Intermediate 8)** (4.95 g, 1.1 mmol) in tetrahydrofuran (100 mL) under argon. The resulting solution was cooled to -78 °C. n-BuLi (8.8 mL, 2.2 mmol of 2.5 M in hexane) was added over 30 min. The mixture was stirred for 90 m and then N-fluorobenzenesulfonimide (7.5 g, 2.4 mmol) was added as powder in one portion. To the reaction mixture was added saturated ammonium chloride (75 mL), water (25 mL) and ethyl acetate (100 mL) after stirring for 90 m at -78 °C. The reaction mixture was warmed to room temperature. The organic layer was separated, washed with brine (1x75 mL), filtered through 1PS filter paper and concentrated under reduced pressure to give 11.5 g of a green residue. The residue was triturated with 10% EtOAc in hexane (50 mL). The insoluble material was filtered and filtrate concentrated under reduced pressure to give 6.5 g of a green residue. The residue was flash chromatographed repeatedly over silica gel with anhydrous sodium sulfate on top; the columns were eluted with either

25

30

EtOAc:hexanes and/or hexanes:CH₂Cl₂ to give 2.9 g (57%) of **2-(3-(5-fluorothiophen-2-yl)-4-((5-phenylpentyl)oxy)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (Intermediate 9)** as colorless oil. HPLC analysis showed a purity of ~98%.

5 NMR (CDCl₃) δ 7.75(s, 1H), 7.2-7.4(m, 6H), 7.15(t, 1H), 6.95(d, 1H), 6.45(t, 1H), 6.0(s, 1H), 4.15(t, 2H), 2.7(t, 2H), 1.95(m, 2H), 1.75(m, 2H), 1.6(m, 2H), 1.35(d, 12H).

Step-3: A solution of **2-(3-(5-fluorothiophen-2-yl)-4-((5-phenylpentyl)oxy)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (Intermediate 9)**

10 (2.01 g, 4.3 mmol) in tetrahydrofuran (50 mL) and 3 M HCl (50 mL) was stirred at rt, overnight. To the reaction mixture was diluted with ethyl acetate (50 mL) and water (50 mL). The organic layer was separated, washed with brine (1x50 mL), filtered through 1PS filter paper and concentrated under reduced pressure to give 1.6 g of an oil. The oil was dissolved in boiling hexane (20 mL) and after standing for 2 h, a
15 white crystalline solid was collected; and dried under vacuum to give 1.15 g (73%) of **Intermediate 10: 3-(5-fluorothiophen-2-yl)-4-((5-phenylpentyl)oxy)benzaldehyde**, HPLC analysis showed a purity of ~99%.

¹⁹F NMR showed a quartet at -131.201, -131.209, -131.215 and -131.223.

Use of **Intermediate 10** in the procedure of **Example 1** produced the title compound

20 **[3-({3-(5-fluoro-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid**.

¹H NMR (600 MHz, CF₃CO₂D): δ 7.57 (d, J = 1.8 Hz, 1H), 7.23-7.18 (m, 3H), 7.14 (d, J = 6.6 Hz, 2H), 7.08 (t, J = 7.2 Hz, 1H), 7.03-7.01 (m, 2H), 6.38-6.37 (m, 1H), 4.30 (t, J = 5.4 Hz, 2H), 4.13 (t, J = 6.6 Hz, 2H), 3.44-3.36 (m, 2H), 2.63 (t, J = 7.8
25 Hz, 2H), 2.25-2.22 (m, 2H), 2.15-2.10 (m, 2H), 1.95-1.92 (m, 2H), 1.74-1.68 (m, 2H), 1.58-1.55 (m, 2H).

Example 5

Biological Data

30 Compounds were synthesized and tested for S1P1 activity using the GTP γ³⁵S binding assay. These compounds may be assessed for their ability to activate or block activation of the human S1P1 receptor in cells stably expressing the S1P1 receptor.

GTP $\gamma^{35}\text{S}$ binding was measured in the medium containing (mM) HEPES 25, pH 7.4, MgCl_2 10, NaCl 100, dithiothreitol 0.5, digitonin 0.003%, 0.2 nM GTP $\gamma^{35}\text{S}$, and 5 μg membrane protein in a volume of 150 μl . Test compounds were included in the concentration range from 0.08 to 5,000 nM unless indicated otherwise. Membranes were incubated with 100 μM 5'-adenylylimidodiphosphate for 30 min, and subsequently with 10 μM GDP for 10 min on ice. Drug solutions and membrane were mixed, and then reactions were initiated by adding GTP $\gamma^{35}\text{S}$ and continued for 30 min at 25 °C. Reaction mixtures were filtered over Whatman GF/B filters under vacuum, and washed three times with 3 mL of ice-cold buffer (HEPES 25, pH7.4, MgCl_2 10 and NaCl 100). Filters were dried and mixed with scintillant, and counted for ^{35}S activity using a β -counter. Agonist-induced GTP $\gamma^{35}\text{S}$ binding was obtained by subtracting that in the absence of agonist. Binding data were analyzed using a non-linear regression method. In case of antagonist assay, the reaction mixture contained 10 nM S1P in the presence of test antagonist at concentrations ranging from 0.08 to 5000 nM.

Table 1 shows activity potency: S1P1 receptor from GTP $\gamma^{35}\text{S}$: nM, (EC_{50}), % stimulation.

Activity potency: S1P1 receptor from GTP $\gamma^{35}\text{S}$: nM, (EC_{50}),

Table 2

Compound number	IUPAC name	S1P1 EC_{50} (nM)
6	[3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propyl]phosphonic acid	1
7	[3-({4-[3-(4-isobutylphenyl)propoxy]-3-(2-thienyl)benzyl}amino)propyl]phosphonic acid	15
8	[3-({3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid	3
10	{3-[(5-[(5-phenylpentyl)oxy]-6-(2-thienyl)pyridin-2-yl)methyl]amino}propyl}phosphonic acid	1
12	(3-{[4-(decyloxy)-3-(2-thienyl)benzyl]amino}propyl)phosphonic acid	294

Example 6

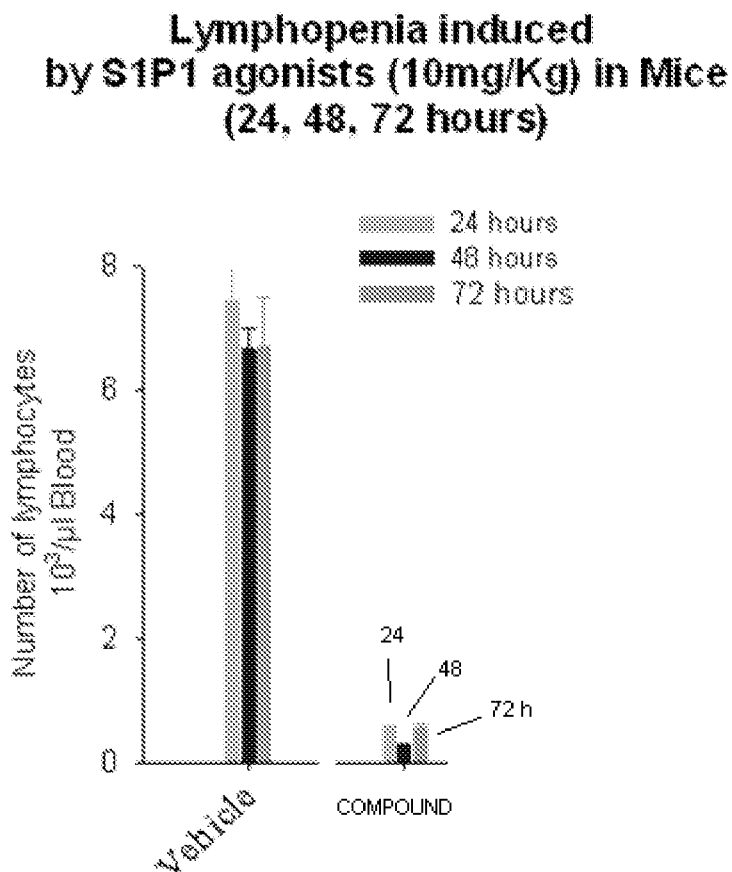
5

Lymphopenia Assay in Mice

Test drugs are prepared in a solution containing 3% (w/v) 2-hydroxy propyl β -cyclodextrin (HPBCD) and 1% DMSO to a final concentration of 1 mg/ml, and subcutaneously injected to female C57BL6 mice (CHARLES RIVERS) weighing 20-25 g at the dose of 10 mg/Kg. Blood samples are obtained by puncturing the submandibular skin with a Goldenrod animal lancet at 5, 24, 48, 72, and 96 hrs post drug application. Blood is collected into microvettes (SARSTEDT) containing EDTA tripotassium salt. Lymphocytes in blood samples are counted using a HEMAVET Multispecies Hematology System, HEMAVET HV950FS (Drew Scientific Inc.).

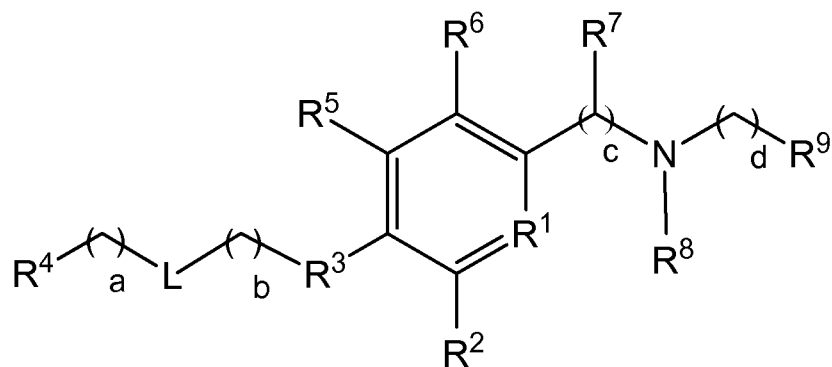
(Hale, J. et al Bioorg. & Med. Chem. Lett. 14 (2004) 3351).

Lymphopenia induced by S1P1 agonists in mice: Time course (10 mg/Kg)
[3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propyl]phosphonic acid



What is claimed is:

1. A compound having Formula I, its enantiomers, diastereoisomers, hydrates, solvates, crystal forms and individual isomers, tautomers or a pharmaceutically acceptable salt thereof,



Formula I

wherein:

R¹ is N or C-R¹⁰;

R² is aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

10 R³ is O, N-R¹¹, CH-R¹² or S, -CR¹³=CR¹⁴-, -C(O) or -C≡C-;

R⁴ is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

R⁵ is H, halogen, hydroxyl, -OC₁₋₃ alkyl, hydroxyl or C₁₋₃ alkyl;

R⁶ is H, C₁₋₃ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;

15 R⁷ is H or C₁₋₆ alkyl;

R⁸ is H or C₁₋₆ alkyl;

R⁹ is -OPO₃H₂, -COOH, -P(O)(OH)₂, -C₃₋₆ alkyl, -S(O)₂OH, -P(O)MeOH, -P(O)(H)OH or -OR¹⁵;

R¹⁰ is H, C₁₋₆ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;

20 R¹¹ is H or C₁₋₃ alkyl;

R¹² is H, C₁₋₃ alkyl, halogen, hydroxyl, -OC₁₋₃alkyl or amino;

R¹³ is H or C₁₋₃ alkyl;

R¹⁴ is H or C₁₋₃ alkyl;

R¹⁵ is H or C₁₋₃ alkyl;

25 L is CHR¹⁶, O, S, NR¹⁷ or -C(O)-;

a is 0, 1, 2, 3, 4 or 5;

b is 0, 1, 2, 3, 4 or 5;

c is 0 or 1;

d is 0, 1, 2 or 3;

R¹⁶ is H, C₁₋₃ alkyl, -OC₁₋₃ alkyl, halogen, hydroxyl or amino, and

R¹⁷ is H or C₁₋₃ alkyl;

with the provisos:

- 5 when R³ is O, N-R¹², or S, and b is 0 or 1 then L is not O, S, or NR¹⁷; and
 when R⁹ is -OPO₃H₂, -COOH, -P(O)(OH)₂, -S(O)₂OH, -P(O)MeOH or -P(O)(H)OH
 then d is not 0; and
 when R⁹ is OR¹⁵ then d is not 0 or 1.

10 2. A compound according to claim 1, wherein:

R¹ is N or C-R¹⁰;

R² is aromatic heterocycle or cycloalkenyl;

R³ is O, N-R¹¹, CH-R¹² or S, -CR¹³=CR¹⁴-, -C(O) or -C≡C-;

R⁴ is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or
 15 aryl;

R⁵ is H, halogen, hydroxyl, -OC₁₋₃ alkyl, hydroxyl or C₁₋₃ alkyl;

R⁶ is H, C₁₋₃ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;

R⁷ is H or C₁₋₆ alkyl;

R⁸ is H or C₁₋₆ alkyl;

20 R⁹ is -OPO₃H₂, -COOH, -P(O)(OH)₂, -C₃₋₆ alkyl, -S(O)₂OH, -P(O)MeOH, -P(O)(H)OH
 or -OR¹⁵;

R¹⁰ is H, C₁₋₆ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;

R¹¹ is H or C₁₋₃ alkyl;

R¹² is H, C₁₋₃ alkyl, halogen, hydroxyl, -OC₁₋₃alkyl or amino;

25 R¹³ is H or C₁₋₃ alkyl;

R¹⁴ is H or C₁₋₃ alkyl;

R¹⁵ is H or C₁₋₃ alkyl;

L is CHR¹⁶, O, S, NR¹⁷ or -C(O)-;

a is 0, 1, 2, 3, 4 or 5;

30 b is 0, 1, 2, 3, 4 or 5;

c is 0 or 1;

d is 0, 1, 2 or 3;

R¹⁶ is H, C₁₋₃ alkyl, -OC₁₋₃ alkyl, halogen, hydroxyl or amino, and

R¹⁷ is H or C₁₋₃ alkyl;

with the provisos:

when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} ; and

when R^9 is $-OPO_3H_2$, $-COOH$, $-P(O)(OH)_2$, $-S(O)_2OH$, $-P(O)MeOH$ or $-P(O)(H)OH$

then d is not 0; and

5 when R^9 is $-OR^{15}$ then d is not 0 or 1.

3. A compound according to claim 1, wherein:

R^1 is N or $C-R^{10}$;

R^2 is 5-member aromatic heterocycle or cycloalkenyl;

10 R^3 is O, $N-R^{11}$, $CH-R^{12}$ or S, $-CR^{13}=CR^{14}-$, $-C(O)-$ or $-C\equiv C-$;

R^4 is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

R^5 is H, halogen, hydroxyl, $-OC_{1-3}$ alkyl, hydroxyl or C_{1-3} alkyl;

R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

15 R^7 is H or C_{1-6} alkyl;

R^8 is H or C_{1-6} alkyl;

R^9 is $-OPO_3H_2$, $-COOH$, $-P(O)(OH)_2$, $-C_{3-6}$ alkyl, $-S(O)_2OH$, $-P(O)MeOH$, $-P(O)(H)OH$ or $-OR^{15}$;

R^{10} is H, C_{1-6} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

20 R^{11} is H or C_{1-3} alkyl;

R^{12} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;

R^{13} is H or C_{1-3} alkyl;

R^{14} is H or C_{1-3} alkyl;

R^{15} is H or C_{1-3} alkyl;

25 L is CHR^{16} , O, S, NR^{17} or $-C(O)-$;

a is 0, 1, 2, 3, 4 or 5;

b is 0, 1, 2, 3, 4 or 5;

c is 0 or 1;

d is 0, 1, 2 or 3;

30 R^{16} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino, and

R^{17} is H or C_{1-3} alkyl;

with the provisos:

when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} ; and

when R⁹ is -OPO₃H₂, -COOH, -P(O)(OH)₂, -S(O)₂OH, -P(O)MeOH or -P(O)(H)OH
 then d is not 0; and
 when R⁹ is -OR¹⁵ then d is not 0 or 1.

- 5 4. A compound according to claim 1, wherein:
 R¹ is N or C-R¹⁰;
 R² is cyclopentane, cyclopentene, pyrazolidine, pyrroline, pyrrolidine, imidazoline,
 pyrazoline, thiazoline, oxazoline, thiophene, dihydrothiophene, furan, dihydrofuran,
 pyrrole, pyrroline, pyrrolidine, oxazole, oxazoline, thiazole, imidazole, pyrazole,
 10 pyrazoline, isoxazole, isothiazole, tetrazole, oxadiazole, 1,2,5-oxadiazole,
 thiadiazole, 1,2,3-triazole, 1,2,4-triazole, imidazole, imidazoline, pyrrolidinone, pyrrol-
 2(3H)-one, imidazolidin-2-one, or 1,2,4-triazol-5(4H)-one;
 R³ is O, N-R¹¹, CH-R¹² or S, -CR¹³=CR¹⁴-, -C(O) or -C≡C- ;
 R⁴ is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or
 15 aryl;
 R⁵ is H, halogen, hydroxyl, -OC₁₋₃ alkyl, hydroxyl or C₁₋₃ alkyl;
 R⁶ is H, C₁₋₃ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;
 R⁷ is H or C₁₋₆ alkyl;
 R⁸ is H or C₁₋₆ alkyl;
 20 R⁹ is -OPO₃H₂, -COOH, -P(O)(OH)₂, -C₃₋₆ alkyl, -S(O)₂OH, -P(O)MeOH, -P(O)(H)OH
 or -OR¹⁵;
 R¹⁰ is H, C₁₋₆ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;
 R¹¹ is H or C₁₋₃ alkyl;
 R¹² is H, C₁₋₃ alkyl, halogen, hydroxyl, -OC₁₋₃alkyl or amino;
 25 R¹³ is H or C₁₋₃ alkyl;
 R¹⁴ is H or C₁₋₃ alkyl;
 R¹⁵ is H or C₁₋₃ alkyl;
 L is CHR¹⁶, O, S, NR¹⁷ or -C(O)- ;
 a is 0, 1, 2, 3, 4 or 5;
 30 b is 0, 1, 2, 3, 4 or 5;
 c is 0 or 1;
 d is 0, 1, 2 or 3;
 R¹⁶ is H, C₁₋₃ alkyl, -OC₁₋₃ alkyl, halogen, hydroxyl or amino, and
 R¹⁷ is H or C₁₋₃ alkyl;

with the provisos:

when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} ; and

when R^9 is $-OPO_3H_2$, $-COOH$, $-P(O)(OH)_2$, $-S(O)_2OH$, $-P(O)MeOH$ or $-P(O)(H)OH$

then d is not 0; and

5 when R^9 is $-OR^{15}$ then d is not 0 or 1.

5. A compound according to claim 1, wherein:

R^1 is N or $C-R^{10}$;

R^2 is 5-member aromatic heterocycle or cycloalkenyl;

10 R^3 is O, $N-R^{11}$, $CH-R^{12}$ or S, $-CR^{13}=CR^{14}-$, $-C(O)-$ or $-C\equiv C-$;

R^4 is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

R^5 is H, halogen, hydroxyl, $-OC_{1-3}$ alkyl, hydroxyl or C_{1-3} alkyl;

R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

15 R^7 is H or C_{1-6} alkyl;

R^8 is H or C_{1-6} alkyl;

R^9 is $-OPO_3H_2$, or $-OR^{15}$;

R^{10} is H, C_{1-6} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

R^{11} is H or C_{1-3} alkyl;

20 R^{12} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;

R^{13} is H or C_{1-3} alkyl;

R^{14} is H or C_{1-3} alkyl;

R^{15} is H or C_{1-3} alkyl;

L is CHR^{16} , O, S, NR^{17} or $-C(O)-$;

25 a is 0, 1, 2, 3, 4 or 5;

b is 0, 1, 2, 3, 4 or 5;

c is 0 or 1;

d is 1, 2 or 3;

R^{16} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino, and

30 R^{17} is H or C_{1-3} alkyl;

with the provisos:

when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} ; and

when R^9 is $-OR^{15}$ then d is not 1.

6. A compound according to claim 1, wherein:

R¹ is N or C-R¹⁰;

R² is 5-member aromatic heterocycle or cycloalkenyl;

R³ is O, N-R¹¹, CH-R¹² or S, -CR¹³=CR¹⁴-, -C(O) or -C≡C- ;

5 R⁴ is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

R⁵ is H, halogen, hydroxyl, -OC₁₋₃ alkyl, hydroxyl or C₁₋₃ alkyl;

R⁶ is H, C₁₋₃ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;

R⁷ is H or C₁₋₆ alkyl;

10 R⁸ is H or C₁₋₆ alkyl;

R⁹ is -P(O)(OH)₂, -P(O)MeOH, or -P(O)(H)OH;

R¹⁰ is H, C₁₋₆ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;

R¹¹ is H or C₁₋₃ alkyl;

R¹² is H, C₁₋₃ alkyl, halogen, hydroxyl, -OC₁₋₃alkyl or amino;

15 R¹³ is H or C₁₋₃ alkyl;

R¹⁴ is H or C₁₋₃ alkyl;

R¹⁵ is H or C₁₋₃ alkyl;

L is CHR¹⁶, O, S, NR¹⁷ or -C(O)- ;

a is 0, 1, 2, 3, 4 or 5;

20 b is 0, 1, 2, 3, 4 or 5;

c is 0 or 1;

d is 1, 2 or 3;

R¹⁶ is H, C₁₋₃ alkyl, -OC₁₋₃ alkyl, halogen, hydroxyl or amino, and

R¹⁷ is H or C₁₋₃ alkyl;

25 with the proviso that when R³ is O, N-R¹², or S, and b is 0 or 1 then L is not O, S, or NR¹⁷.

7. A compound according to claim 1, wherein:

R¹ is N or C-R¹⁰;

30 R² is 5-member aromatic heterocycle or cycloalkenyl;

R³ is O, N-R¹¹, CH-R¹² or S, -CR¹³=CR¹⁴-, -C(O) or -C≡C- ;

R⁴ is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

R⁵ is H, halogen, hydroxyl, -OC₁₋₃ alkyl, hydroxyl or C₁₋₃ alkyl;

R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

R^7 is H or C_{1-6} alkyl;

R^8 is H or C_{1-6} alkyl;

R^9 is $-COOH$, $-S(O)_2OH$;

5 R^{10} is H, C_{1-6} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

R^{11} is H or C_{1-3} alkyl;

R^{12} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;

R^{13} is H or C_{1-3} alkyl;

R^{14} is H or C_{1-3} alkyl;

10 R^{15} is H or C_{1-3} alkyl;

L is CHR^{16} , O, S, NR^{17} or $-C(O)-$;

a is 0, 1, 2, 3, 4 or 5;

b is 0, 1, 2, 3, 4 or 5;

c is 0 or 1;

15 d is 1, 2 or 3;

R^{16} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino, and

R^{17} is H or C_{1-3} alkyl;

with the proviso that when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} .

20

8. A compound according to claim 1, wherein:

R^1 is N or $C-R^{10}$; and

R^2 is aromatic heterocycle, non-aromatic heterocycle or cycloalkenyl; and

R^3 is O; and

25 R^4 is aryl or H; and

R^5 is H; and

R^6 is H; and

R^7 is H; and

R^8 is H; and

30 R^9 is $P(O)(OH)_2$; and

R^{10} is H; and

a is 1, 2, 4 or 5; and

b is 1, 2 or 4; and

c is 1; and

d is 3; and
L is CHR^{16} ; and
 R^{16} is H.

9. A compound according to claim 1, wherein:

- 5 R^1 is N or C-R^{10} ; and
 R^2 is aromatic heterocycle, non-aromatic heterocycle or cycloalkenyl; and
 R^3 is O; and
 R^4 is aryl; and
 R^5 is H; and
10 R^6 is H; and
 R^7 is H; and
 R^8 is H; and
 R^9 is P(O)(OH)_2 ; and
 R^{10} is H; and
15 a is 1 or 2; and
b is 1 or 2; and
c is 1; and
d is 3; and
L is CHR^{16} ; and
20 R^{16} is H.

10. A compound according to claim 1, wherein:

- R^1 is N; and
 R^2 is aromatic heterocycle, non-aromatic heterocycle or cycloalkenyl; and
 R^3 is O; and
25 R^4 is aryl; and
 R^5 is H; and
 R^6 is H; and
 R^7 is H; and
 R^8 is H; and
30 R^9 is P(O)(OH)_2 ; and
a is 1 or 2; and
b is 1 or 2; and
c is 1; and

d is 3; and
 L is CHR¹⁶; and
 R¹⁶ is H.

11. A compound according to claim 1, wherein:

- 5 R¹ is C-R¹⁰; and
 R² is aromatic heterocycle, non-aromatic heterocycle or cycloalkenyl; and
 R³ is O; and
 R⁴ is H; and
 R⁵ is H; and
 10 R⁶ is H; and
 R⁷ is H; and
 R⁸ is H; and
 R⁹ is P(O)(OH)₂; and
 R¹⁰ is H; and
 15 a is 2, 3, 4 or 5; and
 b is 2, 3, 4 or 5; and
 c is 1; and
 d is 3; and
 L is CHR¹⁶; and
 20 R¹⁶ is H.

12. A compound according to claim 1 selected from:

- [3-({3-(2-furyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid;
 [3-({3-(1,3-oxazol-2-yl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid;
 [3-({4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-2-yl)benzyl}amino)propyl]phosphonic acid;
 25 [3-({3-(3-furyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid;
 [3-({4-[(5-phenylpentyl)oxy]-3-(3-thienyl)benzyl}amino)propyl]phosphonic acid;
 [3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propyl]phosphonic acid;
 [3-({4-[3-(4-isobutylphenyl)propoxy]-3-(2-thienyl)benzyl}amino)propyl]phosphonic
 acid;
 30 [3-({3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic
 acid;
 {3-[(6-(3-furyl)-5-[(5-phenylpentyl)oxy]pyridin-2-yl)methyl]amino}propyl]phosphonic
 acid;

{3-[(5-phenylpentyl)oxy]-6-(2-thienyl)pyridin-2-yl)methyl)amino]propyl}phosphonic acid;

(3-{[4-(nonyloxy)-3-(2-thienyl)benzyl]amino}propyl)phosphonic acid;

(3-{[4-(decyloxy)-3-(2-thienyl)benzyl]amino}propyl)phosphonic acid;

5 3-({3-(5-fluoro-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl}phosphonic acid

2-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)ethyl dihydrogen phosphate;

3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propane-1-sulfonic acid;

methyl[3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propyl]phosphinic acid;

10 2-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propan-1-ol;

2-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propane-1,3-diol.

13. A pharmaceutical composition comprising as active ingredient a
15 therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable adjuvant, diluents or carrier.

14. A pharmaceutical composition according to claim 7 wherein the compound is selected from

20 [3-({3-(2-furyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid;

[3-({3-(1,3-oxazol-2-yl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid;

[3-({4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-2-yl)benzyl}amino)propyl]phosphonic acid;

[3-({3-(3-furyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid;

[3-({4-[(5-phenylpentyl)oxy]-3-(3-thienyl)benzyl}amino)propyl]phosphonic acid;

25 [3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propyl]phosphonic acid;

[3-({4-[3-(4-isobutylphenyl)propoxy]-3-(2-thienyl)benzyl}amino)propyl]phosphonic acid;

[3-({3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid;

30 {3-[(6-(3-furyl)-5-[(5-phenylpentyl)oxy]pyridin-2-yl)methyl)amino]propyl}phosphonic acid;

{3-[(5-phenylpentyl)oxy]-6-(2-thienyl)pyridin-2-yl)methyl)amino]propyl}phosphonic acid;

(3-{[4-(nonyloxy)-3-(2-thienyl)benzyl]amino}propyl)phosphonic acid;

35 (3-{[4-(decyloxy)-3-(2-thienyl)benzyl]amino}propyl)phosphonic acid;

3-({3-(5-fluoro-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}amino)propyl]phosphonic acid

2-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)ethyl dihydrogen phosphate;

3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propane-1-sulfonic acid;

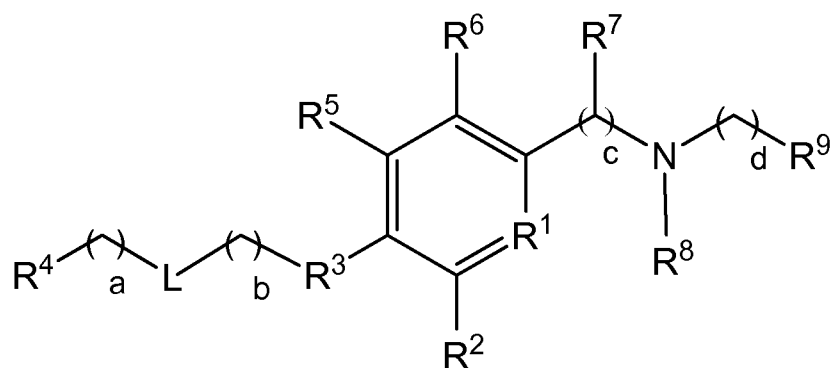
5 methyl[3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propyl]phosphinic acid;

2-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propan-1-ol;

2-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)propane-1,3-diol.

15. A method of treating a disorder associated with sphingosine-1-

10 phosphate (S1P) receptor modulation, which comprises administering to a mammal in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of Formula I



Formula I

15 wherein:

R¹ is N or C-R¹⁰;

R² is aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;

R³ is O, N-R¹¹, CH-R¹² or S, -CR¹³=CR¹⁴-, -C(O) or -C≡C-;

R⁴ is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or

20 aryl;

R⁵ is H, halogen, hydroxyl, -OC₁₋₃ alkyl, hydroxyl or C₁₋₃ alkyl;

R⁶ is H, C₁₋₃ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;

R⁷ is H or C₁₋₆ alkyl;

R⁸ is H or C₁₋₆ alkyl;

25 R⁹ is -OPO₃H₂, -COOH, -P(O)(OH)₂, -C₃₋₆ alkyl, -S(O)₂OH, -P(O)MeOH, -P(O)(H)OH or -OR¹⁵;

R¹⁰ is H, C₁₋₆ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;

R¹¹ is H or C₁₋₃ alkyl;

R^{12} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;

R^{13} is H or C_{1-3} alkyl;

R^{14} is H or C_{1-3} alkyl;

R^{15} is H or C_{1-3} alkyl;

5 L is CHR^{16} , O, S, NR^{17} or $-C(O)-$;

a is 0, 1, 2, 3, 4 or 5;

b is 0, 1, 2, 3, 4 or 5;

c is 0 or 1;

d is 0, 1, 2 or 3;

10 R^{16} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino, and

R^{17} is H or C_{1-3} alkyl;

with the proviso:

when R^3 is O, $N-R^{12}$, or S, and b is 0 or 1 then L is not O, S, or NR^{17} ; and

when R^9 is $-OPO_3H_2$, $-COOH$, $-P(O)(OH)_2$, $-S(O)_2OH$, $-P(O)MeOH$ or $-P(O)(H)OH$

15 then d is not 0; and

when R^9 is OR^{15} then d is not 0 or 1.

16. A method of claim 9, wherein the pharmaceutical composition is administered to the mammal to treat ocular disease, wet and dry age-related
 20 macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinal edema, geographic atrophy, glaucomatous optic neuropathy, chorioretinopathy, hypertensive retinopathy, ocular ischemic syndrome, prevention of inflammation-induced fibrosis in the back of the eye, various ocular inflammatory diseases including uveitis, scleritis, keratitis, and retinal vasculitis; or systemic vascular barrier
 25 related diseases, various inflammatory diseases, including acute lung injury, its prevention, sepsis, tumor metastasis, atherosclerosis, pulmonary edemas, and ventilation-induced lung injury; or autoimmune diseases and immunosuppression, rheumatoid arthritis, Crohn's disease, Graves' disease, inflammatory bowel disease, multiple sclerosis, Myasthenia gravis, Psoriasis, ulcerative colitis, autoimmune
 30 uveitis, renal ischemia/perfusion injury, contact hypersensitivity, atopic dermatitis, and organ transplantation; or allergies and other inflammatory diseases, urticaria, bronchial asthma, and other airway inflammations including pulmonary emphysema and chronic obstructive pulmonary diseases; or cardiac protection, ischemia reperfusion injury and atherosclerosis; or wound healing, scar-free healing of

wounds from cosmetic skin surgery, ocular surgery, GI surgery, general surgery, oral injuries, various mechanical, heat and burn injuries, prevention and treatment of photoaging and skin ageing, and prevention of radiation-induced injuries; or bone formation, treatment of osteoporosis and various bone fractures including hip and ankles; or anti-nociceptive activity, visceral pain, pain associated with diabetic neuropathy, rheumatoid arthritis, chronic knee and joint pain, tendonitis, osteoarthritis, neuropathic pains.

17. A method of claim 10, wherein the mammal is a human.