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(54) Title: NOVEL COMPOUNDS AS RECEPTOR MODULATORS WITH THERAPEUTIC UTILITY

(57) Abstract: The present invention relates to novel cyclic amine and cycloalkyl derivatives, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals as modulators of sphingosine-1-phosphate receptors.

**NOVEL COMPOUNDS AS RECEPTOR MODULATORS
WITH THERAPEUTIC UTILITY**

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

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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.

10

FIELD OF THE INVENTION

The present invention relates to novel cyclic amine and cycloalkyl 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.

SUMMARY OF THE INVENTION

We have now discovered a group of novel compounds which are potent and

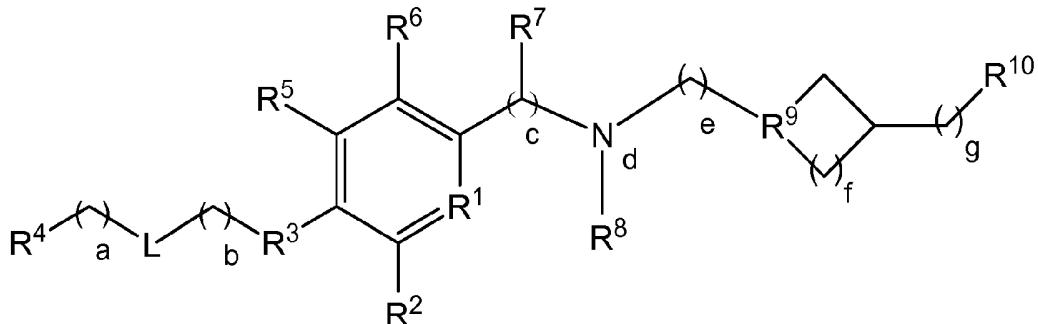
selective sphingosine-1-phosphate modulators. As such, the compounds described

5 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.

10 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

15 pharmaceutically acceptable salt thereof or stereoisomeric forms thereof, or the geometrical isomers, enantiomers, diastereoisomers, tautomers, zwitterions and pharmaceutically acceptable salts thereof:



Formula I

20 wherein:

R¹ is N or C-R¹¹;

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

R³ is O, N-R¹², CH-R¹³, S, -CR¹⁴=CR¹⁵-, -C≡C- or -C(O)-;

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

25 aryl;

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

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;

R⁹ is CH or N;

R¹⁰ is OPO₃H₂, carboxylic acid, PO₃H₂, C₁₋₆ alkyl, -S(O)₂OH, -P(O)MeOH, -P(O)(H)OH or OR¹⁶;

5 R¹¹ is H, C₁₋₆ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;

R¹² is H or C₁₋₃ alkyl;

R¹³ is H, C₁₋₃ alkyl, halogen, hydroxyl, -OC₁₋₃ alkyl or amino;

R¹⁴ is H or C₁₋₃ alkyl;

R¹⁵ is H or C₁₋₃ alkyl;

10 R¹⁶ is H or C₁₋₆ alkyl;

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

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

c is 0 or 1;

d is 0 or 1;

15 e is 0, 1, 2 or 3;

f is 0, 1, 2 or 3;

g is 0, 1, 2 or 3;

L is CHR¹⁷, O, S, NR¹⁸ or -C(O)-;

R¹⁷ is H, C₁₋₃ alkyl, -OC₁₋₃ alkyl, halogen, hydroxyl or amino; and

20 R¹⁸ is H or C₁₋₃ alkyl;

with the proviso that when R³ is O, N-R¹², or S, and b is 0 or 1 then L is not O, S, NR¹⁸.

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 to 6 carbon atoms. One methylene (-CH₂-) group, of the alkyl can be replaced by oxygen, sulfur, sulfoxide, nitrogen, carbonyl, carboxyl, sulfonyl, or by a divalent C₃₋₆ 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. Usually, in the present case, cycloalkyl group is cyclopentane.

The term "cycloalkenyl", as used herein, refers to a monovalent or divalent group of 5 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. Usually, in the present case, cycloalkenyl group is cyclopentene.

10 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 15 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.

20 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 25 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, in the present case, heterocyclic groups are 5 or 6 membered rings. Usually, in the present case, heterocyclic groups are pyridine, azetidine, pyrazolidine, pyrrolidine, 30 pyrrolidine, imidazoline, pyrazoline, thiazoline, oxazoline, thiophene, dihydrothiophene, furan, dihydrofuran, pyrrole, pyrrolidine, pyrrolidine, oxazole, oxazoline, 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.

5 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 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 "-CR¹⁴=CR¹⁵-", as used herein, represents an alkenyl radical.

10 The group of formula "-C≡C-", as used herein, represents an alkynyl radical.

The term "hydroxyl" as used herein, represents a group of formula "-OH".

The term "carbonyl" as used herein, represents a group of formula "-C(O)".

The term "carboxyl" as used herein, represents a group of formula "-C(O)O-".

The term "sulfonyl" as used herein, represents a group of formula "-SO₂".

15 The term "sulfate" as used herein, represents a group of formula "-O-S(O)₂-O-".

The term "carboxylic acid" as used herein, represents a group of formula "-C(O)OH".

The term "sulfoxide" as used herein, represents a group of formula "-S=O".

The term "phosphonic acid" as used herein, represents a group of formula "-P(O)(OH)₂".

20 The term "phosphoric acid" as used herein, represents a group of formula "-(O)P(O)(OH)₂".

The term "boronic acid", as used herein, represents a group of formula "-B(OH)₂".

The term "sulphonic acid" as used herein, represents a group of formula "-S(O)₂OH".

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

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

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

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

Generally R¹ is N or C-R¹¹. Usually, in the present case, R¹ is C-R¹¹.

30 Generally R² is aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl. Usually, in the present case, R² is aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl. Preferred R² groups are cyclopentane, cyclopentene, pyrazolidine, pyrrolidine, pyrrolidine, imidazoline, pyrazoline, thiazoline, oxazoline, thiophene, dihydrothiophene, furan, dihydrofuran, pyrrole, pyrrolidine, pyrrolidine,

oxazole, oxazoline, 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.

5

Generally R^3 is O, $N-R^{12}$, $CH-R^{13}$ or S; $-CR^{14}=CR^{15}-$; $-C\equiv C-$. Usually, in the present case, R^3 is O or S.

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

10 Generally R^5 is H, halogen, $-OC_{1-3}$ alkyl or C_{1-6} alky. Usually, in the present case, R^5 is H, halogen or $-OC_{1-3}$ alkyl.

Generally R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl. Usually, in the present case, R^6 is H.

Generally R^7 is H or C_{1-6} alky.

15 Generally R^8 is H or C_{1-6} alky. Usually, in the present case, R^8 is H.

Generally R^9 is CH or N.

Generally R^{10} is $OP(O)H_2$, $COOH$, PO_3H_2 , C_{1-6} alkyl, $-S(O)_2OH$, $-P(O)MeOH$, $-P(O)(H)OH$ or OR^{16} . Usually, in the present case, R^{10} is $COOH$.

20 Generally R^{11} is H, C_{1-3} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl. Usually, in the present case, R^{11} is H.

Generally R^{12} is H or C_{1-3} alkyl

Generally R^{13} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino.

Generally R^{14} is H or C_{1-3} alky.

Generally R^{15} is H or C_{1-3} alky.

25 Generally R^{16} is H or C_{1-6} alky.

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

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

Generally c is 0 or 1.

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

30 Generally e is 0 to 3. Usually, in the present case, e is 0 or 1.

Generally f is 0 to 3. Usually, in the present case, f is 1.

Generally g is 0 to 3. Usually g is 0.

Generally L is CHR^{17} , O, S, $-C(O)$ or NR^{18} . Usually, in the present case, L is CHR^{17} or O.

Generally R^{17} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino. Usually, in the present case, R^{17} is H or C_{1-3} alkyl.

Generally R^{18} is H or C_{1-3} alkyl.

5 In one embodiment of the invention

R^1 is N or $C-R^{11}$;

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

R^3 is O, $N-R^{12}$, $CH-R^{13}$, S, $-CR^{14}=CR^{15}-$, $-C\equiv C-$ or $-C(O)-$;

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

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

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 CH or N;

R^{10} is OPO_3H_2 , carboxylic acid, $-PO_3H_2$, C_{1-6} alkyl, $-S(O)_2OH$, $-P(O)MeOH$, $-P(O)(H)OH$ or $-OR^{16}$;

R^{11} is H, C_{1-6} alkyl, halogen, hydroxyl or $-OC_{1-3}$ alkyl;

R^{12} is H or C_{1-3} alkyl;

20 R^{13} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;

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

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

R^{16} is H or C_{1-6} alkyl;

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

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

c is 0 or 1;

d is 0 or 1;

e is 0, 1, 2 or 3;

f is 0, 1, 2 or 3;

30 g is 0, 1, 2 or 3;

L is CHR^{17} , O, S, NR^{18} or $-C(O)-$;

R^{17} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino, and

R^{18} is H or C_{1-3} alkyl;

with the proviso that when R^3 is O, $N-R^{12}$, S and b is 0 or 1 then L is not O, S, NR^{18} .

In another embodiment of the invention

R¹ is N or C-R¹¹;

R² is a cyclopentane, cyclopentene, pyrazolidine, pyrrolidine, imidazoline, 5 pyrazoline, thiazoline, oxazoline, thiophene, dihydrothiophene, furan, dihydrofuran, pyrrole, pyrrolidine, oxazole, oxazoline, 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;

10 R³ is O, N-R¹², CH-R¹³, S, -CR¹⁴=CR¹⁵-, -C≡C- or -C(O)-;

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

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

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 CH or N;

R¹⁰ is OPO₃H₂, carboxylic acid, -PO₃H₂, C₁₋₆ alkyl, -S(O)₂OH, -P(O)MeOH, -P(O)(H)OH or -OR¹⁶;

20 R¹¹ is H, C₁₋₆ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;

R¹² is H or C₁₋₃ alkyl;

R¹³ is H, C₁₋₃ alkyl, halogen, hydroxyl, -OC₁₋₃ alkyl or amino;

R¹⁴ is H or C₁₋₃ alkyl;

R¹⁵ is H or C₁₋₃ alkyl;

25 R¹⁶ is H or C₁₋₆ alkyl;

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

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

c is 0 or 1;

d is 0 or 1;

30 e is 0, 1, 2 or 3;

f is 0, 1, 2 or 3;

g is 0, 1, 2 or 3;

L is CHR¹⁷, O, S, NR¹⁸ or -C(O)-;

R¹⁷ is H, C₁₋₃ alkyl, -OC₁₋₃ alkyl, halogen, hydroxyl or amino, and

R^{18} is H or C_{1-3} alkyl;

with the proviso that when R^3 is O, $N-R^{12}$, S and b is 0 or 1 then L is not O, S, NR^{18} .

In another embodiment of the invention

5 R^1 is N;

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

R^3 is O, $N-R^{12}$, $CH-R^{13}$, S, $-CR^{14}=CR^{15}-$, $-C\equiv C-$ or $-C(O)-$;

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

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

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 CH or N;

15 R^{10} is $OP_3O_2H_2$, carboxylic acid, $-PO_3H_2$, C_{1-6} alkyl, $-S(O)_2OH$, $-P(O)MeOH$, $-P(O)(H)OH$ or $-OR^{16}$;

R^{12} is H or C_{1-3} alkyl;

R^{13} is H, C_{1-3} alkyl, halogen, hydroxyl, $-OC_{1-3}$ alkyl or amino;

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

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

R^{16} is H or C_{1-6} alkyl;

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

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

c is 0 or 1;

25 d is 0 or 1;

e is 0, 1, 2 or 3;

f is 0, 1, 2 or 3;

g is 0, 1, 2 or 3;

L is CHR^{17} , O, S, NR^{18} or $-C(O)-$;

30 R^{17} is H, C_{1-3} alkyl, $-OC_{1-3}$ alkyl, halogen, hydroxyl or amino, and

R^{18} is H or C_{1-3} alkyl;

with the proviso that when R^3 is O, $N-R^{12}$, S and b is 0 or 1 then L is not O, S, NR^{18} .

In another embodiment of the invention

R¹ is C-R¹¹; and

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

R³ is O or S; and

5 R⁴ is aryl; and

R⁵ is H, -OC₁₋₃ alkyl or halogen; and

R⁶ is H; and

R⁷ is H or C₁₋₆ alkyl; and

R⁸ is H; and

10 R⁹ is CH or N; and

R¹⁰ is COOH; and

R¹¹ is H; and

a is 0, 1, 2 or 3; and

b is 1, 2 or 3; and

15 c is 0 or 1; and

d is 0 or 1; and

e is 0 or 1; and

f is 1; and

g is 0; and

20 L is CHR¹⁷ or O; and

R¹⁷ is H or C₁₋₃ alkyl;

with the proviso that when R³ is O or S and b is 1 then L is not O.

In another embodiment of the invention

25 R¹ is C-R¹¹; and

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

R³ is O; and

R⁴ is aryl; and

R⁵ is H, -OC₁₋₃ alkyl or halogen; and

30 R⁶ is H; and

R⁷ is H or C₁₋₆ alkyl; and

R⁸ is H; and

R⁹ is CH; and

R¹⁰ is COOH; and

R¹¹ is H; and
a is 0, 1, 2 or 3; and
b is 1, 2 or 3; and
c is 1; and
5 d is 1; and
e is 0 or 1; and
f is 1; and
g is 0; and
L is CHR¹⁷; and
10 R¹⁷ is H.

In another embodiment of the invention

R¹ is C-R¹¹; and
R² is aromatic heterocycle, non-aromatic heterocycle or cycloalkenyl; and
15 R³ is S; and
R⁴ is aryl; and
R⁵ is H, -OC₁₋₃ alkyl or halogen; and
R⁶ is H; and
R⁷ is H or C₁₋₆ alkyl; and
20 R⁸ is H; and
R⁹ is CH or N; and
R¹⁰ is COOH; and
R¹¹ is H; and
a is 0, 1, 2 or 3; and
25 b is 1, 2 or 3; and
c is 0 or 1; and
d is 0 or 1; and
e is 0 or 1; and
f is 1; and
30 g is 0; and
L is CHR¹⁷ or O; and
R¹⁷ is H or C₁₋₃ alkyl;
with the provisio that when R³ is S and b is 1 then L is not O.

In another embodiment of the invention

R¹ is C-R¹¹; and

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

5 R³ is O; and

R⁴ is aryl; and

R⁵ is H, -OC₁₋₃ alkyl or halogen; and

R⁶ is H; and

R⁷ is H or C₁₋₆ alkyl; and

10 R⁸ is H; and

R⁹ is CH or N; and

R¹⁰ is COOH; and

R¹¹ is H; and

a is 0, 1, 2 or 3; and

15 b is 1, 2 or 3; and

c is 0 or 1; and

d is 0 or 1; and

e is 0 or 1; and

f is 1; and

20 g is 0; and

L is CHR¹⁷ or O; and

R¹⁷ is H or C₁₋₃ alkyl;

with the proviso that when R³ is O and b is 1 then L is not O.

25 In another embodiment of the invention

R¹ is C-R¹¹; and

R² is aromatic heterocycle, aryl or cycloalkenyl; and

R³ is O; and

R⁴ is aryl; and

30 R⁵ is H, or halogen; and

R⁶ is H; and

R⁷ is H or C₁₋₆ alkyl; and

R⁸ is H; and

R⁹ is CH or N; and

R¹⁰ is COOH; and
R¹¹ is H; and
a is 0, 1, 2 or 3; and
b is 1, 2 or 3; and
5 c is 0 or 1; and
d is 0 or 1; and
e is 0 or 1; and
f is 1; and
g is 0; and
10 L is CHR¹⁷; and
R¹⁷ is H.

In another embodiment of the invention

R¹ is C-R¹¹; and
15 R² is aromatic heterocycle or cycloalkenyl; and
R³ is O or S; and
R⁴ is aryl; and
R⁵ is H, -OC₁₋₃ alkyl or halogen; and
R⁶ is H; and
20 R⁹ is N; and
R¹⁰ is COOH; and
R¹¹ is H; and
a is 0, 1, 2 or 3; and
b is 1, 2 or 3; and
25 c is 0; and
d is 0; and
e is 1; and
f is 1; and
g is 0; and
30 L is CHR¹⁷ or O; and
R¹⁷ is H or C₁₋₃ alkyl;
with the proviso that when R³ is O or S and b is 1 then L is not O.

Compounds of the invention are:

1-{3-(3-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 1-{3-methoxy-4-[(5-phenylpentyl)oxy]-5-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
 1-{4-[(6-phenylhexyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
 5 1-{4-[3-(benzyloxy)propoxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
 1-{4-[3-(4-isobutylphenyl)propoxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
 1-[4-(2-biphenyl-4-yethoxy)-3-(2-thienyl)benzyl]azetidine-3-carboxylic acid;
 1-{3-chloro-4-[(5-phenylpentyl)oxy]-5-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
 1-{3-chloro-4-[(5-phenylpentyl)oxy]-5-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
 10 1-{4-[(3-methyl-5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
 1-{3-(5-methyl-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 1-{3-(4-methyl-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 1-{3-(3-methyl-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-5-yl)benzyl}azetidine-3-carboxylic acid;
 15 1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-4-yl)benzyl}azetidine-3-carboxylic acid;
 1-{3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-5-yl)benzyl}azetidine-3-carboxylic acid;
 20 1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-4-yl)benzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-pyridin-4-ylbenzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-(3-thienyl)benzyl}azetidine-3-carboxylic acid;
 1-{6-[(5-phenylpentyl)oxy]biphenyl-3-yl}methyl)azetidine-3-carboxylic acid;
 25 1-{3-(2-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-2-yl)benzyl}azetidine-3-carboxylic acid;
 1-{3-(1,3-oxazol-2-yl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-1-yl)benzyl}azetidine-3-carboxylic acid;
 30 1-{4-[(5-phenylpentyl)thio]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
 1-{3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)thio]benzyl}azetidine-3-carboxylic acid;
 3-[(4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl]amino)cyclobutanecarboxylic acid;
 3-[(1-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)phenyl}ethyl)amino]cyclobutanecarboxylic acid.

Preferred compounds of the invention are:

35 1-{3-(3-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;

1-{3-chloro-4-[(5-phenylpentyl)oxy]-5-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-5-yl)benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-4-yl)benzyl}azetidine-3-carboxylic acid;
1-{3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
5 1-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-5-yl)benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-4-yl)benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(3-thienyl)benzyl}azetidine-3-carboxylic acid;
1-{3-(2-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
10 1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-2-yl)benzyl}azetidine-3-carboxylic acid;
1-{3-(1,3-oxazol-2-yl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-1-yl)benzyl}azetidine-3-carboxylic acid;
3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)cyclobutanecarboxylic acid;
3-[(1-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)phenyl}ethyl)amino]cyclobutanecarboxylic
15 acid.

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
20 described in Pure Appl. Chem. (1976), 45, 11-13.

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”
25 according to the invention include therapeutically active, non-toxic base or acid salt 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,
30 hydrobromic 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, methylsulfonic, ethanesulfonic,

benzenesulfonic, formic and the like (Handbook of Pharmaceutical Salts, P.Heinrich Stahal& Camille G. Wermuth (Eds), Verlag Helvetica Chemica Acta- Zürich, 2002, 329-345).

5 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 10 mixtures thereof unless the particular isomeric form is referred to specifically.

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.

15 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.

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

In a further embodiment of the invention, there are provided methods for treating 25 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.

These compounds are useful for the treatment of mammals, including humans, with 30 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.

Therapeutic utilities related to the S1P receptors are ocular diseases, such as but 35 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 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, 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 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; 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.

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.

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 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 5 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 10 compositions including at least one compound of the invention in a pharmaceutically acceptable carrier thereof. 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 15 solid, a solution, an emulsion, a dispersion, a patch, 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, 20 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 25 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 30 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 in 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.

5 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.

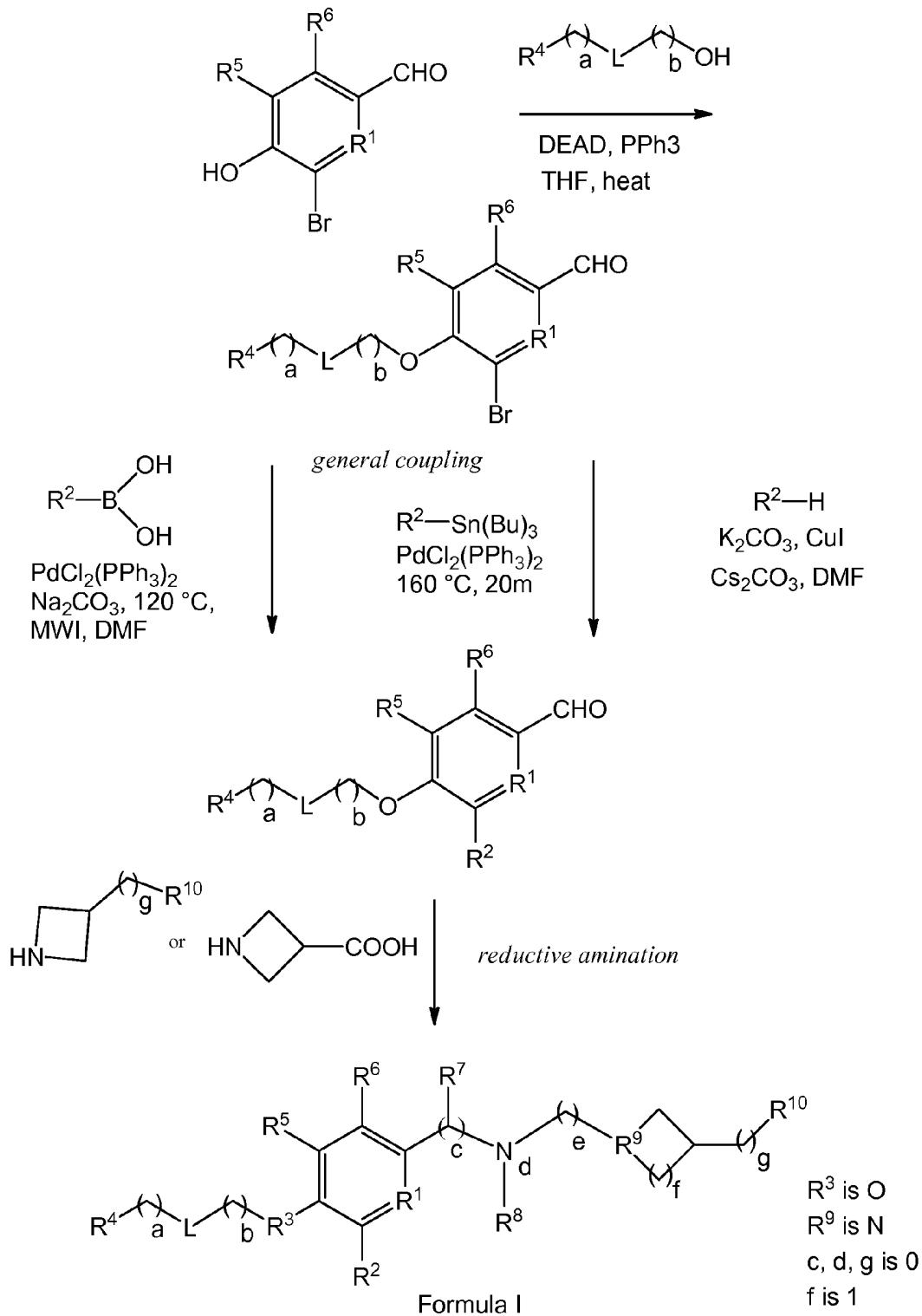
10 The compounds and pharmaceutical compositions described herein are useful as medicaments in mammals, including humans, for treatment of diseases and/or alleviations of conditions which are responsive to treatment by agonists or functional antagonists of sphingosine-1-phosphate receptors. Thus, in 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 15 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 20 need thereof is a mammal. In some embodiments, the mammal is human.

25 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 30 compounds of the invention covered by Formula I.

30 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 R² group to give the corresponding

intermediate. This intermediate reacts with azetidine-3-carboxylic acid in reductive amination conditions to give a derivative of Formula I.

Scheme 1



In **Scheme 2**, mercaptobenzaldehydes react with brominated compounds in the presence of triethylamine to give the corresponding thio intermediate. This intermediate is coupled with the boronic acid or the stannate of the corresponding R² group to give the corresponding intermediate. This intermediate reacts with 5 azetidine-3-carboxylic acid in reductive amination conditions to give a derivative of Formula I.

10

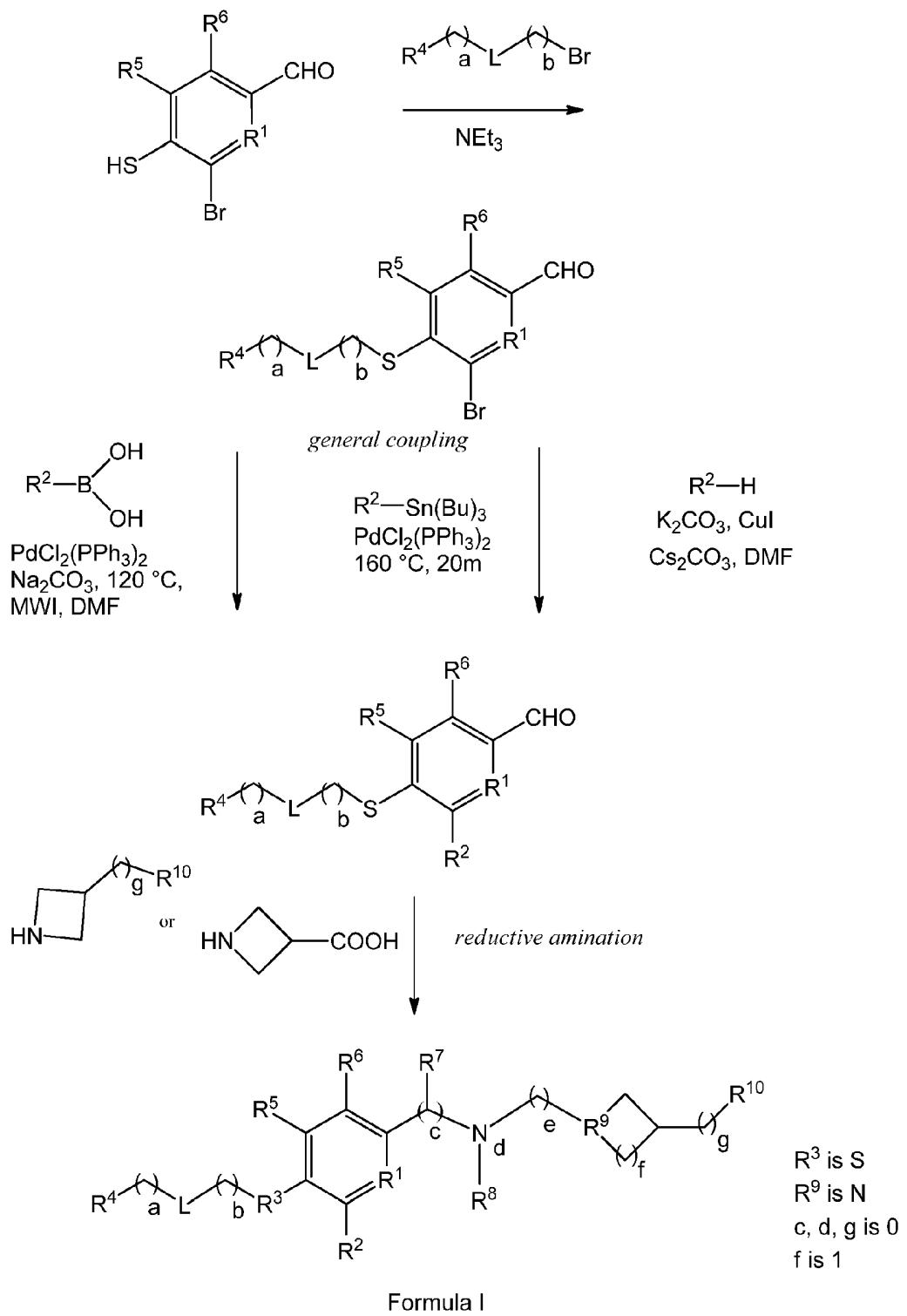
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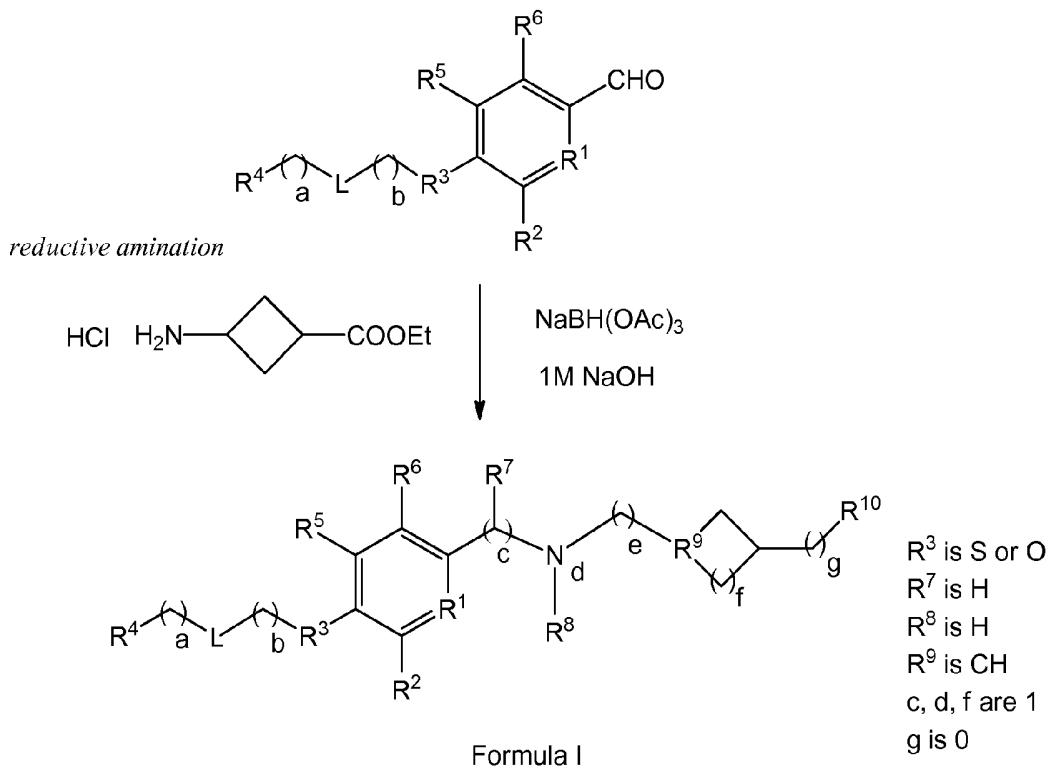
Scheme 2



In **Scheme 3**, ether or thio intermediates, obtained as described in Schemes 1 or 2 react with ethyl 3-aminocyclobutanecarboxylate–HCl salt in the presence of Sodium triacetoxyborohydride to give a derivative of Formula I.

5

Scheme 3



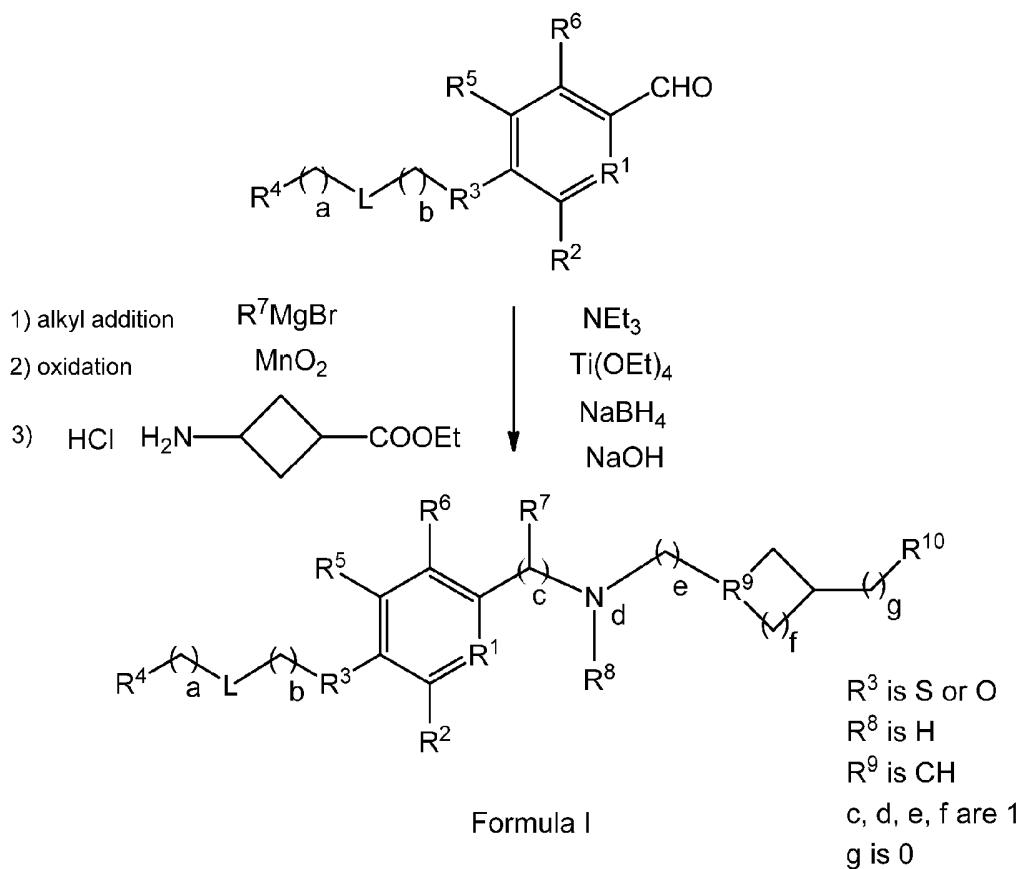
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15

In **Scheme 4**, ether or thio intermediates, obtained as described in Schemes 1 or 2 react with an alkylmagnesium bromide derivative and ethyl 3-aminocyclobutanecarboxylate–HCl salt in the presence of magnesium oxide to give a derivative of Formula I.

5

Scheme 4



DETAILED DESCRIPTION OF THE INVENTION

10 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.

15 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.

5

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.

10

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.

15

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.

20

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.

25

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.

30

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.

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, Fisher, Maybridge, Frontier, Matrix, Ukrorgsynth, Toronto, Ryan Scientific, SiliCycle, 5 Anaspec, Syn Chem, Chem-Impex, MIC-scientific, Ltd; 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.

10

The following abbreviations are used in the examples:

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

NH₃ ammonia

CH₃CN acetonitrile

15 PSI pound per square inch

DCM dichloromethane

DMF *N,N*-dimethylformamide

NaOH sodium hydroxide

MeOH methanol

20 CD₃OD deuterated methanol

NH₃ ammonia

HCl hydrochloric acid

Na₂SO₄ sodium sulfate

Si-CBH Silica bonded cyanoborohydride

25 rt room temperature

MgSO₄ magnesium sulfate

EtOAc ethyl acetate

CDCl₃ deuterated chloroform

DMSO-d₆ deuterated dimethyl sulfoxide

30 Auto-column automated flash liquid chromatography

TFA trifluoroacetic acid

THF tetrahydrofuran

NaHB(OAc)₃ sodium triacetoxyborohydride

DEAD diethyl azodicarboxylate

Na₂CO₃ sodium carbonate
Cs₂CO₃ cesium carbonate
M molar
PdCl₂(PPh₃)₂ bis(triphenylphosphine)palladium(II) chloride
5 AcOH acetic acid
K₂CO₃ potassium carbonate
CuI copper iodide
MnO₂ magnesium oxide
MgCl₂ magnesium chloride
10 NaCl sodium chloride
Ti(OEt)₄ titanium ethoxide
MeMgBr methylmagnesium bromide
CHCl₃ chloroform

15 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.

20 **Example 1**

Compound 1

1-{3-(3-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid

Step-1: A solution of 5-phenyl-pentan-1-ol [CAS 10521-91-2] (4.50 mL, 26.6 mmol),
25 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.
Chromatography on an Teledyne-ISCO CombiFlash with a silica column (auto-
30 column) with 9.5 Hexanes/0.5 EtOAc to 9 Hexanes/1 EtOAc gave **Intermediate1:**
3-bromo-4-(5-phenyl-pentyloxy)-benzaldehyde as a clear oil that solidified upon
standing, 5.38 g (58%).

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).

5 Step-2: 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 10 washed with water (three times), dried over MgSO₄, filtered and concentrated onto silica gel. Auto-column (9 Hexanes/1 EtOAc) gave **Intermediate 2: 3-(furan-3-yl)-4-((5-phenylpentyl)oxy)benzaldehyde** 230 mg (29%).

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).

20 Step-3: A solution of **Intermediate 2** (230 mg, 0.66 mmol) and azetidine-3-carboxylic acid [CAS 36476-78-5] (66 mg, 0.65 mmol) in AcOH (0.2 mL), THF (2 mL) and MeOH (10 mL) was treated with Si-CBH, silica bonded cyanoborohydride (0.71 g, 0.93 mmol/g on silica gel support) and the mixture was reacted at rt for ~16-18 h. The mixture was concentrated onto silica gel and the solvent was removed under vacuum. Auto-column (25→40% MeOH: CH₂Cl₂) gave a white solid of the title compound: **1-{3-(3-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid** 189 mg (69%).

25 ¹H NMR (300 MHz, CD₃OD): δ 8.02 (s, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.53 (t, J = 1.8 Hz, 1H), 7.30-7.20 (m, 3H), 7.16-7.0 (m, 3H), 7.06 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 1.2 Hz, 1H), 4.26 (s, 2H), 4.14-4.07 (m, 6H), 3.40-3.33 (m, 1H), 2.63 (t, J = 7.8 Hz, 2H), 1.94-1.84 (m, 2H), 1.75-1.65 (m, 2H), 1.58-1.48 (m, 2H).

30

Compounds 2-21 were prepared from the corresponding benzaldehyde, and azetidine-3-carboxylic acid in a similar manner to the procedure described in **Example 1 for Compound 1**. The reagents used and the results are described 35 below in **Table 1**.

Table 1

Compound number	IUPAC name	Reagent(s) used	¹ H NMR δ (ppm) for Compound
2	1-{3-methoxy-4-[(5-phenylpentyl)oxy]-5-(2-thienyl)benzyl}azetidine-3-carboxylic acid	5-phenyl-pantan-1-ol [CAS 10521-91-2] 3-bromo-4-hydroxy-5-methoxybenzaldehyde [CAS 2973-76-4] thiophen-2-yl boronic acid [CAS 13331-23-2]	(300 MHz, CD ₃ OD): δ 7.52 (dd, J = 0.9, 3.6 Hz, 1H), 7.43 (dd, J = 0.6, 4.8 Hz, 1H), 7.37 (d, J = 0.9 Hz, 1H), 7.26-7.21 (m, 2H), 7.15-7.13 (m, 3H), 7.08 (dd, J = 3.6, 4.8 Hz, 1H), 7.04 (d, J = 1.8 Hz, 1H), 4.28 (s, 2H), 4.17 (d, J = 8.4 Hz, 4H), 3.96-3.83 (m, 2H), 3.8 (s, 3H), 3.44-3.34 (m, 1H), 2.58 (t, J = 7.8 Hz, 1H), 1.81-1.72 (m, 2H), 1.67-1.57 (m, 2H), 1.49-1.39 (m, 2H)
3	1-{4-[(6-phenylhexyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid	3-bromo-4-hydroxybenzaldehyde [CAS 2973-78-6] 6-phenylhexan-1-ol [CAS 2430-16-2] thiophen-2-yl boronic acid [CAS 13331-23-2]	(300 MHz, CDCl ₃): δ 7.72 (d, J = 1.8 Hz, 1H), 7.50 (d, J = 2.7 Hz, 1H), 7.28-7.24 (m, 4H), 7.18-7.15 (m, 3H), 7.01 (dd, J = 3.9, 5.1 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 4.05-3.96 (m, 8H), 3.40-3.35 (m, 1H), 2.60 (t, J = 7.8 Hz, 2H), 1.90-1.80 (m, 2H), 1.69-1.59 (m, 2H), 1.56-1.48 (m, 2H), 1.44-1.37 (m, 2H).
4	1-{4-[3-(benzyloxy)propoxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic	3-bromo-4-hydroxybenzaldehyde [CAS 2973-78-6] 3-	(300 MHz, CDCl ₃): δ 7.73 (s, 1H), 7.47 (d, J = 3.0 Hz, 1H), 7.30-7.24 (m, 7H), 7.01-6.98 (m, 1H), 6.91 (d, J = 8.4 Hz, 1H), 4.49 (s, 2H), 4.16 (t, J = 6.3 Hz, 2H), 4.08-3.97 (m,

	acid	(benzyloxy)propan-1-ol [CAS 4799-68-2]	6H), 3.70 (t, J = 6.0 Hz, 2H), 3.44-3.36 (m, 1H), 2.20-2.13 (m, 2H)
5	1-[4-[3-(4-isobutylphenyl)propoxy]-3-(2-thienyl)benzyl]azetidine-3-carboxylic acid	3-bromo-4-hydroxybenzaldehyde [CAS 2973-78-6]	(300 MHz, CDCl_3): δ 7.74 (s, 1H), 7.52 (d, J = 2.7 Hz, 1H), 7.29-7.22 (m, 2H), 7.11-7.01 (m, 5H), 6.86 (d, J = 8.7 Hz, 1H), 4.06-4.01 (m, 8H), 3.42-3.36 (m, 1H), 2.82 (t, J = 7.8 Hz, 2H), 2.43 (d, J = 6.9 Hz, 2H), 2.22-2.14 (m, 2H), 1.90-1.76 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).
6	1-[4-(2-biphenyl-4-yloxy)-3-(2-thienyl)benzyl]azetidine-3-carboxylic acid	3-bromo-4-hydroxybenzaldehyde [CAS 2973-78-6]	(300 MHz, CDCl_3 - CD_3OD): δ 7.67 (d, J = 1.8 Hz, 1H), 7.59-7.53 (m, 4H), 7.47-7.41 (m, 3H), 7.38-7.32 (m, 4H), 7.27 (d, J = 8.7 Hz, 1H), 7.07-7.04 (m, 1H), 6.99 (d, J = 8.1 Hz, 1H), 4.34 (t, J = 6.9 Hz, 2H), 4.15-4.10 (m, 4H), 3.95 (t, J = 9.3 Hz, 2H), 3.30-3.24 (m, 3H).
7	1-[3-chloro-4-[(5-	3-bromo-5-chloro-4-hydroxy-	(300 MHz, CDCl_3): δ 7.66 (d, J = 2.1 Hz, 1H), 7.54 (d, J =

	phenylpentyl) oxy]-5-(2- thienyl)benzyl }azetidine-3- carboxylic acid	benzaldehyde [CAS 2973-78-6] 5-phenyl-pantan-1- ol [CAS 10521-91-2] thiophen-2-yl boronic acid [CAS 13331-23-2]	2.7 Hz, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 1.8 Hz, 1H), 7.26-7.21 (m, 2H), 7.16- 7.10 (m, 4H), 4.17 (s, 2H), 4.09-3.98 (m, 14H), 3.82 (t, J = 6.3 Hz, 2H), 3.42-3.34 (m, 1H), 2.61 (t, J = 7.8 Hz, 2H), 1.85-1.76 (m, 2H), 1.68-1.58 (m, 2H), 1.53-1.45 (m, 2H).
8	1-{3-chloro-4- [(5- phenylpentyl) oxy]-5-(2- thienyl)benzyl }azetidine-3- carboxylic acid	3-bromo-5-chloro- 4-hydroxy- benzaldehyde, [CAS 2973-78-6] 2-(4- isobutylphenyl)eth anol [CAS 36039-35-7] thiophen-2-yl boronic acid [CAS 13331-23-2]	(300 MHz, CD ₃ OD): δ 7.74 (d, J = 1.8 Hz, 1H), 7.45 (d, J = 3.6 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.7 Hz, 1H), 7.07-7.03 (m, 3H), 4.35 (t, J = 6.9 Hz, 2H), 4.27 (s, 2H), 4.13 (d, J = 8.4 Hz, 4H), 3.45-3.34 (m, 1H), 3.15 (t, J = 6.9 Hz, 2H), 2.43 (d, J = 7.2 Hz, 2H), 1.87-1.77 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H).
9	1-{4-[(3- methyl-5- phenylpentyl) oxy]-3-(2- thienyl)benzyl }azetidine-3- carboxylic acid	3-bromo-5-chloro- 4-hydroxy- benzaldehyde, [CAS 2973-78-6] 3-methyl-5- phenylpentan-1-ol [CAS 55066-48-3] thiophen-2-yl boronic acid	(300 MHz, CD ₃ OD): δ 7.77 (d, J = 2.1 Hz, 1H) 7.54 (dd, J = 0.9, 3.6 Hz, 1H), 7.38 (d, J = 5.1 Hz, 1H), 7.32 (dd, J = 2.1, 8.4 Hz, 1H), 7.23-7.18 (m, 2H), 7.14-7.04 (m, 5H), 4.26 (s, 2H), 4.17-4.11 (m, 6H), 3.42-3.33 (m, 1H), 2.72-2.52 (m, 2H), 2.04-1.91 (m, 1H), 1.85-1.63 (m, 3H), 1.56-1.44 (m, 1H), 1.00 (d, J = 6.6 Hz,

		[CAS 13331-23-2]	3H).
10	1-{3-(5-methyl-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid	Intermediate 1 (5-methylthiophen-2-yl)boronic acid [CAS 162607-20-7]	(300 MHz, CD ₃ OD): δ 7.70 (d, J = 2.1 Hz, 1H), 7.34 (d, J = 3.3 Hz, 1H), 7.29-7.20 9m, 3H), 7.16-7.12 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 4.25 (s, 2H), 4.14-4.08 (m, 6H), 3.42-3.33 (m, 1H), 2.63 (t, J = 7.5 Hz, 2H), 2.47 (s, 3H), 1.94-1.86 (m, 2H), 1.76-1.66 (m, 2H), 1.62-1.52 (m, 2H)
11	1-{3-(4-methyl-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid	Intermediate 1 (4-methylthiophen-2-yl)boronic acid [CAS 162607-15-0]	(300 MHz, CD ₃ OD): δ 7.74 (d, J = 2.1 Hz, 1H), 7.39 (s, 1H), 7.29 (dd, J = 2.1, 8.4 Hz, 1H), 7.25-7.20 (m, 2H), 7.16-7.12 (m, 3H), 7.08 (d, J = 8.7 Hz, 1H), 6.97 (s, 1H), 4.26 (s, 2H), 4.14-4.08 (m, 6H), 3.37 (t, J = 7.8 Hz, 2H), 2.26 (s, 3H), 1.94-1.85 (m, 2H), 1.72-1.65 (m, 2H), 1.62-1.57 9m, 2H).
12	1-{3-(3-methyl-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid	Intermediate 1 (3-methylthiophen-2-yl)boronic acid [CAS 177735-09-0]	(300 MHz, CD ₃ OD): δ 7.41(dd, J = 1.8, 8.1 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.28 (d, J = 5.1 Hz, 1H), 7.24-7.20 (m, 2H), 7.14-7.08 (m, 4H), 6.88 (d, J = 5.1 Hz, 1H), 4.28 (s, 2H), 4.14 (d, J = 8.1 Hz, 4H) 3.98 (t, J = 6.0 Hz, 2H), 3.42-3.36 (m, 1H), 2.54 (t, J = 7.8 Hz, 2H), 2.08 (s, 3H), 1.76-1.67 (m, 2H), 1.63-1.53 (m,

			2H), 1.44-1.36 (m, 2H).
13	1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-5-yl)benzyl}azetidine-3-carboxylic acid	Intermediate 1 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole [CAS 1086111-09-2]	(300 MHz, CD ₃ OD): δ 8.93 (s, 1H), 8.33 (s, 1H), 7.80 (d, J = 1.8 Hz, 1H), 7.37 (dd, J = 2.1, 8.4 Hz, 1H), 7.25-7.20 (m, 2H), 7.16-7.11 (m, 4H), 4.14 (t, J = 6.3 Hz, 2H), 4.06 (s, 2H), 3.98-3.84 (m, 4H), 3.38-3.30 (m, 1H), 2.63 (t, J = 7.5 Hz, 2H), 1.95-1.86 (m, 3H), 1.76-1.86 (m, 2H), 1.76-1.66 (m, 2H), 1.61-1.53 (m, 2H).
14	1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-4-yl)benzyl}azetidine-3-carboxylic acid	Intermediate 1 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole [CAS 1083180-00-0]	(300 MHz, CD ₃ OD): δ 8.98 (d, J = 1.5 Hz, 1H), 8.23 (d, J = 1.8 Hz, 1H), 7.99 (d, J = 1.8, 1H), 7.39 (dd, J = 2.1, 8.4 Hz, 1H), 7.26-7.20 (m, 2H), 7.15-7.09 (m, 4H), 4.27 (s, 2H), 4.16-4.10 (m, 6H), 3.42-3.33 (m, 1H), 2.62 (t, J = 7.5 Hz, 2H), 1.95-1.85 (m, 2H), 1.74-1.65 (m, 2H), 1.56-1.46 (m, 2H).
15	1-{3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid	Intermediate 1 cyclopent-1-en-1-ylboronic acid [CAS 850036-28-1]	(300 MHz, CD ₃ OD): δ 7.33 (d, J = 2.1 Hz, 1H), 7.26-7.20 (m, 3H), 7.16-7.10 (m, 3H), 6.98 (d, J = 8.7 Hz, 1H), 6.40 (brs, 1H), 4.23 (s, 2H), 4.12 (d, J = 8.4 Hz, 4H), 4.01 (t, J = 6.3 Hz, 2H), 3.42-3.33 (m, 1H), 2.75-2.69 (m, 2H), 2.62 (t, J =

			7.8 Hz, 2H), 2.51-2.45 (m, 2H), 1.97-1.79 (m, 4H), 1.74-1.64 (m, 2H), 1.56-1.46 (m, 2H).
16	1-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid	Intermediate 1 thiophen-2-ylboronic acid [CAS 13331-23-2]	(300 MHz, CD ₃ OD): δ 7.77 (d, J = 2.1 Hz, 1H), 7.54 (d, J = 3.3 Hz, 1H), 7.38 (d, J = 4.5 Hz, 1H), 7.30 (dd, J = 2.1, 8.7 Hz, 1H), 7.24-7.19 (m, 2H), 7.15-7.12 9m, 3H), 7.08-7.04 (m, 2H), 4.24 (s, 3H), 4.13-4.06 (m, 6H), 3.43-3.33 (m, 1H), 2.60 (t, J = 7.2 Hz, 2H), 1.94-1.82 (m, 2H), 1.73-1.63 (m, 2H), 1.62-1.51 (m, 2H).
17	1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-5-yl)benzyl}azetidine-3-carboxylic acid	Intermediate 1 (1H-pyrazol-5-yl)boronic acid [CAS 1239363-47-3]	(300 MHz, CD ₃ OD): δ 7.79 (d, J = 2.1 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.37 (dd, J = 2.1, 8.7 Hz, 1H), 7.24-7.20 (m, 2H), 7.15-7.09 (m, 4H), 6.73 (d, J = 2.1 Hz, 1H), 4.23 (s, 2H), 4.12-4.07 9m, 6H), 3.43-3.33 (m, 1H), 2.60 (t, J = 7.5 Hz, 2H), 1.92-1.82 (m, 2H), 1.73-1.62 (m, 2H), 1.55-1.44 (m, 2H).
18	1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-4-yl)benzyl}azetidine-3-	Intermediate 1 (1H-pyrazol-4-yl)boronic acid [CAS 763120-58-7]	(300 MHz, CD ₃ OD): δ 8.07 (s, 2H), 7.69 (d, J = 2.4 Hz, 1H), 7.24-7.04 (m, 7H), 4.23 (s, 2H), 4.12-4.06 (m, 6H), 3.42-3.30 (m, 1H), 2.62 (t, J = 7.2, 2H), 1.95-1.85 (m, 2H), 1.75-

	carboxylic acid		1.64 (m, 2H), 1.60-1.50 9m, 2H).
19	1-{4-[(5-phenylpentyl)oxy]-3-pyridin-4-ylbenzyl}azetidine-3-carboxylic acid	Intermediate 1 pyridin-4-ylboronic acid [CAS 1692-15-5]	(300 MHz, CD ₃ OD): δ 8.48 (dd, J = 1.5, 4.5 Hz, 2H), 7.55 (dd, J = 1.8, 4.5 Hz, 2H), 7.50-7.48 (m, 2H), 7.26-7.19 (m, 2H), 7.15-7.10 (m, 4H), 4.26 (s, 2H), 4.13-4.10 (m, 4H), 4.03 (t, J = 6.3 Hz, 2H), 3.49-3.33 (m, 2H), 2.56 (t, J = 7.2 Hz, 2H), 1.79-1.69 (m, 2H), 1.66-1.56 (m, 2H), 1.45-1.35 (m, 2H).
20	1-{4-[(5-phenylpentyl)oxy]-3-(3-thienyl)benzyl}azetidine-3-carboxylic acid	Intermediate 1 thiophen-3-ylboronic acid [CAS 5552-70-0]	(300 MHz, CD ₃ OD): δ 7.66 (dd, J = 1.2, 3.0 Hz, 1H), 7.60 (d, J = 1.2 Hz, 1H), 7.44 (dd, J = 1.2, 5.1 Hz, 1H), 7.38 (dd, J = 3.0, 4.8 Hz, 1H), 7.32 (dd, J = 2.1, 8.4 Hz, 1H), 7.25-7.20 (m, 2H), 7.14 (d, J = 6.9 Hz, 3H), 7.08 (d, J = 8.7 Hz, 1H), 4.23 (s, 2H), 4.13 (d, J = 8.4 Hz, 4H), 4.05 (t, J = 6.6 Hz, 2H), 3.42-3.33 (m, 1H), 2.60 (t, J = 7.5 Hz, 2H), 2.60 (t, J = 7.5 Hz, 2H), 1.87-1.78 (m, 2H), 1.71-1.61 (m, 2H), 1.53-1.43 (m, 2H).
21	1-{6-[(5-phenylpentyl)oxy]biphenyl-	Intermediate 1 phenylboronic acid	(300 MHz, CD ₃ OD): δ 7.46 (dd, J = 1.8, 8.1 Hz, 2H), 7.34-7.28 (m, 5H), 7.25-7.19 (m,

	3-(2-furyl)methyl)azetidine-3-carboxylic acid	[CAS 98-80-6]	2H), 7.14-7.06 (m, 4H), 4.28 (s, 2H), 4.14 (d, J = 8.1 Hz, 4H), 3.98 (t, J = 6.0 Hz, 2H), 3.36 (pentet, J = 7.8 Hz, 1H), 2.54 (t, J = 7.8 Hz, 2H), 1.76-1.68 (m, 2H), 1.61-1.53 (m, 2H), 1.43-1.36 (m, 2H).
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Example 2**Compound 22****1-{3-(2-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid**

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Step-1: 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 $\text{PdCl}_2(\text{PPh}_3)_2$ (0.197 g, ~15 mol%) at 160 °C for 15 m with MWI (microwave irradiation: Biotage Initiator 2.5). The reaction mixture was diluted with 2:1 EtOAc/Hexanes (~150 mL), washed with water (three times), and dried over MgSO_4 , filtered and concentrated onto silica gel. Auto-column (9.5 Hexanes/0.5 EtOAc) gave **Intermediate 3: 3-furan-2-yl-4-(5-phenyl-pentyloxy)-benzaldehyde** as a white solid, 0.44 g (70 %).

15 ^1H NMR (300 MHz, CD_3OD): 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).

20 Step 2: Intermediate 3 reacted with azetidine-3-carboxylic acid as described in the procedure for Example 1 to produce the title compound: **1-{3-(2-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid**.

25 ^1H NMR (300 MHz, CD_3OD): δ 7.90 (s, 1H), 7.53 (s, 1H), 7.28 (t, J = 8.1 Hz, 1H), 7.21 (d, J = 6.9 Hz, 2H), 7.16-7.12 (m, 3H), 7.06 (d, J = 8.7 Hz, 1H), 6.92 (d, J = 3.3 Hz, 1H), 6.48 (s, 1H), 4.28 (s, 2H), 4.15-4.07 (s, 2H), 3.40-3.33 (m, 1H), 2.62 (t, J = 7.2 Hz, 2H), 1.93-1.84 (m, 2H), 1.75-1.65 (m, 2H), 1.58-1.48 (m, 2H).

Compounds 23 and 24 were prepared from the corresponding stannate, and azetidine-3-carboxylic acid in a similar manner to the procedure described in **Example 2 for Compound 22**. The reagents used and the results are described below in **Table 2**.

5

Table 2

23	1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-2-yl)benzyl}azetidine-3-carboxylic acid	Intermediate 1 2-(tributylstannyloxy)thiazole [CAS 121359-48-6]	(300 MHz, CD ₃ OD): δ 8.36 (d, J = 2.1 Hz, 1H), 7.88 (d, J = 3.3 Hz, 1H), 7.58 (d, J = 3.3 Hz, 1H), 7.49 (dd, J = 1.8, 8.4 Hz, 1H), 7.25-7.10 (m, 6H), 4.32 (s, 2H), 4.23 (t, J = 8.4 Hz, 4H), 3.34-3.42 (m, 1H), 2.64 (t, J = 7.2 Hz, 2H), 2.02-1.93 (m, 2H), 1.76-1.68 (m, 2H), 1.65-1.58 (m, 2H).
24	1-{3-(1,3-oxazol-2-yl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid	Intermediate 1 2-(tributylstannyloxy)oxazole [CAS 145214-05-7]	(300 MHz, CD ₃ OD): δ 7.91-7.90 (m, 2H), 7.56 (dd, J = 2.1, 8.4 Hz, 1H), 7.28 (s, 1H), 7.24-7.10 (m, 6H), 4.29 (s, 2H), 4.19-4.09 (m, 6H), 3.42-3.33 (m, 1H), 2.60 (t, J = 7.5 Hz, 2H), 1.88-1.79 (m, 2H), 1.71-1.62 (m, 2H), 1.55-1.45 (m, 2H).

10 **Example 3****Compound 25****1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-1-yl)benzyl}azetidine-3-carboxylic acid**

15 Step 1: A solution of **Intermediate 1** (0.41 g, 1.18 mmol), K₂CO₃ (0.49 g, 3.54 mmol), CuI (0.23 g, 2.39 mmol), pyrazole [CAS 288-13-1] (0.18 g, 2.64 mmol) and

N,N-dimethylethane-1,2-diamine (0.1 mL, 0.93 mmol) in dioxane was heated to 105 °C for 16-18 h. To the mixture was added Cs₂CO₃ (1.0 g, 3.07 mmol) Cu-Sn alloy (500 mg, 200 mesh) and DMF (~15 mL) and heating at 160 °C was continued for 16-18 h. The mixture was cooled to rt and subjected to a standard aqueous work-up.

5 The crude material was purified on auto-column (8:2 Hexanes/EtOAc) to give

Intermediate 4 as a white solid, **4-(5-phenylpentyloxy)-3-(1H-pyrazol-1-yl)benzaldehyde** 120 mg (51%).

¹H NMR (300 MHz, CD₃OD): δ 9.94 (s, 1H), 8.31 (d, J = 1.8 Hz, 1H), 8.05 (d, J = 1.8 Hz, 1H), 7.84-7.80 (m, 1H), 7.79 (s, 1H), 7.29-7.24 (m, 2H), 7.78-7.11 (m, 4H), 6.42 (s, 1H), 4.14 (t, J = 6.3 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H), 1.83-1.39 (series of m, 6H).

Step 2: **Intermediate 4** reacted with azetidine-3-carboxylic acid as described in the procedure for **Example 1** to produce the title compound: **1-{4-[(5-phenylpentyloxy)-3-(1H-pyrazol-1-yl)benzyl}azetidine-3-carboxylic acid**.

15 ¹H NMR (300 MHz, CD₃OD): δ 8.01 (d, J = 2.1 Hz, 1H), 7.68 (dd, J = 2.1, 7.8 Hz, 2H), 7.43 (dd, J = 2.1, 8.4 Hz, 1H), 7.25-7.20 (m, 3H), 6.44 (t, J = 2.4 Hz, 1H), 4.26 (s, 2H), 4.16-4.04 (m, 6H), 3.40-3.32 (m, 1H), 2.58 (t, J = 7.5 Hz, 2H), 1.83-1.74 (m, 2H), 1.68-1.58 (m, 2H), 1.47-1.39 (m, 2H).

20 **Example 4**

Compound 26

1-{4-[(5-phenylpentyloxy)-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid

Step-1: A mixture of 3-bromo-4-fluorobenzaldehyde [CAS 77771-02-9] (5.1 g, 24.6 mmol) in DMF (25 mL) was treated with sodium sulfide Na₂S·9H₂O (6.80 g, 27.7 mmol) and the mixture was stirred at rt for 9 d. After an acidic workup and extraction with Hexanes/EtOAc (1:1) the pooled organic layers were washed with water (three times) and dried over MgSO₄, filtered and concentrated onto silica gel. Auto-column (9:1 hexane/EtOAc) gave **Intermediate 5** as a solid 3.07 g (58%) **3-bromo-4-mercaptopbenzaldehyde**.

30 ¹H NMR (300 MHz, CD₃OD): δ 9.86 (s, 1H), 7.98 (d, J = 1.5 Hz, 1H), 7.64 (d, J = 1.8 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 4.31 (s, 1H).

Step-2: A solution of **Intermediate 5** (2.80 g, 11.3 mmol) and (5-bromopentyl)benzene [CAS 14469-83-1] (2.61 g, 11.5 mol) with triethylamine (3.1 mL) in THF (30 mL) was stirred at rt for 18 hr. The solvent was removed under vacuum and the residue was dissolved in EtOAc/Hexanes (200 mL, 1:1), washed with water, dried over MgSO₄, filtered and concentrated onto silica gel. Auto-column (9.5 Hexanes/0.5 EtOAc) gave **Intermediate 6** an oil, 1.74 g (42%) **3-bromo-4-((5-phenylpentyl)thio)benzaldehyde**.

¹H NMR (300 MHz, CDCl₃): δ 9.86 (s, 1H), 7.98 (d, J = 1.8 Hz, 1H), 7.72 (dd, J = 8.4, 1.2 Hz, 1H), 7.28-7.15 (m, 6H), 2.97 (t, J = 7.5 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 1.79-1.54 (series of m, 6H).

Step-3: Intermediate **6** and thiophen-2-ylboronic acid reacted with azetidine-3-carboxylic acid as described in the procedure for Example 1 to produce the title compound: **1-{4-[(5-phenylpentyl)thio]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid.**

15 ^1H NMR (600 MHz, CD_3OD): δ 7.48-7.47 (m, 1H), 7.46-7.45 (m, 2H), 7.36 (dd, J = 2.4, 8.4 Hz, 1H), 7.26-7.25 (m, 1H), 7.23-7.21 (m, 2H), 7.13-7.11 (m, 3H), 7.10 (dd, J = 4.2, 5.4 Hz, 1H), 4.26 (s, 2H), 4.14-4.08 (m, 4H), 3.39-3.34 (m, 1H), 2.86 (9t, J = 7.8 Hz, 2H), 2.56 (t, J = 7.8 Hz, 2H), 1.64-1.56 (m, 4H), 1.44-1.39 (m, 2H).

20 Example 5

Compound 27

1-{3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)thio]benzyl}azetidine-3-carboxylic acid

25 The title compound was synthesized according to the procedure described in
Example 4; wherein **Intermediate 6** reacted with cyclopent-1-en-1-ylboronic acid in
Step 3.

¹H NMR (600 MHz, CD₃OD): δ 7.34 (d, J = 8.4, 1H), 7.26-7.21 (m, 4H), 7.14-7.11 (m, 3H), 5.91 (pentet, J = 2.4 Hz, 1H), 4.23 (s, 2H), 4.13-4.08 (m, 4H), 3.39-3.33 (m, 1H), 2.90 (t, J = 7.8 Hz, 2H), 2.73-2.70 (m, 2H), 2.58 (t, J = 7.2 Hz, 2H), 2.54-2.50 (m, 2H), 2.03-1.98 (m, 2H), 1.66-1.59 (m, 4H), 1.48-1.43 (m, 2H).

Example 6**Compound 28****3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)cyclobutanecarboxylic acid**

5

Step-1: A solution of **Intermediate 7: 4-((5-phenylpentyl)oxy)-3-(thiophen-2-yl)benzaldehyde** [as produced during the synthesis of **Compound 16**, from **Intermediate 1** and thiophen-2-yl boronic acid] (230 mg, 0.66 mmol) and ethyl 3-aminocyclobutanecarboxylate-HCl salt [CAS 957793-35-0] (150 mg, 0.84 mmol) in

10 THF (11 mL), acetic acid (1.2 mL) and EtOH (6 mL) was stirred at rt for 1 h.

Intermediate 7: ^1H NMR (300 MHz, CDCl_3): δ 9.92 (s, 1H), 8.17 (d, J = 2.1 Hz, 1H), 7.75 (dd, J = 9.9, 2.1 Hz, 1H), 7.56 (dd, J = 3.6, 1.2 Hz, 1H), 7.37-7.02 (series of m, 8H), 4.16 (t, J = 6.6 Hz, 2H), 2.66 (t, J = 7.2 Hz, 2H), 2.01-1.54 (series of m, 6H).

15 $\text{NaBH}(\text{OAc})_3$ (320 mg, 1.43 mmol) was added and the mixture was stirred at rt for 18 h. Solvents were removed under vacuum and the mixture was treated with NaOH (1 M) to adjust pH > 7. The mixture was extracted with EtOAc, and the organic layers were combined, dried over MgSO_4 , filtered and concentrated onto silica gel. Auto column (EtOAc) gave **Intermediate 8** as a clear oil, **ethyl 3-((4-((5-phenylpentyl)oxy)-3-(thiophen-2-yl)benzyl)amino)cyclobutanecarboxylate**.

20 ^1H NMR (300 MHz, CDCl_3): δ 7.57 (d, J = 1.8 Hz, 1H), 7.50 (dd, J = 0.9, 2.7 Hz, 1H), 7.31-7.14 (m, 7H), 7.06 (dd, J = 3.9, 1.5 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.15-4.03 (m, 4H), 3.69 (s, 2H), 3.29-3.18 (m, 1H), 2.78-2.46 (m, 5H), 2.01-1.49 (series of m, 8H), 1.24 (t, J = 6.9 Hz, 3H).

25 Step-2: **Intermediate 8** (200 mg, 0.42 mmol) in dioxane (10 mL) was treated with NaOH (3.5 mL, 1M) at rt for 1h. Solvent was removed under vacuum and the pH was adjusted to 3-4 with HCl (1M). The solution was extracted with CHCl_3 : isopropanol (3:1). The organic solvent was removed under vacuum to give the title compound: **3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)cyclobutanecarboxylic acid**.

30 ^1H NMR (300 MHz, CD_3OD): δ 7.83 (d, J = 2.1 Hz, 1H), 7.58 (dd, J = 0.9, 3.9 Hz, 1H), 7.41 (d, J = 5.4 Hz, 1H), 7.35 (dd, J = 2.1, 8.4 Hz, 1H), 7.25-7.20 (m, 2H), 7.16-7.13 (m, 3H), 7.10-7.06 (m, 2H), 4.15-4.09 (m, 4H), 3.77 (pentet, J = 8.4 Hz, 1H),

3.02 (pentet, J = 9.0 Hz, 1H), 2.65-2.56 (m, 4H), 2.45-2.35 (m, 2H), 1.95-1.86 (m, 2H), 1.75-1.65 (m, 2H), 1.62-1.52 (m, 2H).

Example 7

5

Compound 29

3-[(1-{4-[(5-phenylpentyl)oxy]-3-thienyl}phenyl}ethyl)amino] cyclobutanecarboxylic acid

Step-1: A mixture of **Intermediate 7** (600 mg, 1.71 mmol) in THF (15 mL) at -78 °C was reacted with MeMgBr (2.0 mL, 3.0 M in diethyl ether) and warmed to 0 °C for 3 h. The mixture was quenched with water, and THF removed under vacuum. The aqueous layer was extracted with EtOAc. The pooled organic extracts were dried over MgSO₄, filtered, and concentrated onto silica gel. Auto-column (8.5 hexane/1.5 EtOAc) gave **Intermediate 9**, as an oil, 450 mg (72%): **1-(4-((5-phenylpentyl)oxy)-3-(thiophen-2-yl)phenyl) ethanol**.

20

¹H NMR (600 MHz, CDCl₃): δ 7.63 (d, J = 4.2 Hz, 1H), 7.49 (dd, J = 1.2, 4.2 Hz, 1H), 7.29-7.16 (series of m, 7H), 7.05 (dd, J = 3.6, 4.8 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 4.83 (q, J = 6.0 Hz, 1H), 4.02 (d, J = 6.0 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H), 1.91-1.54 (series of m, 6H), 1.48 (d, J = 6.6 Hz, 3H).

25

Step-2: A mixture of **Intermediate 9** (450 mg, 1.23 mmol) and MnO₂ (1.1 g, 10.7 mmol (85%)) in dioxane (20 mL) was heated at 100 °C for 18 h. The mixture was filtered and solvent removed under vacuum. The residue was dissolved in chloroform and concentrated onto silica gel under reduced pressure. Auto-column (9 hexane: 1 EtOAc) gave **Intermediate 10**, as a white solid 350 mg (78%) **1-(4-((5-phenylpentyl)oxy)-3-(thiophen-2-yl)phenyl)ethanone**. MS [M+23]⁺ 387.19

30

Step-3: 3-Aminocyclobutanecarboxylate-HCl salt (260 mg, 1.45 mmol) in THF (8 mL) was treated with triethylamine (0.185 mL, 1.33 mmol) for 1 h at rt. Ti(OEt)₄ (0.32 mL) was added followed by **Intermediate 10** (350 mg, 0.96 mmol) in THF (6mL) at rt for 2.5 h. Sodium borohydride (190 mg) was added and the mixture was stirred at rt for ~18 h. Aqueous ammonium hydroxide (2.5 mL) was added and the mixture stirred for 1 h at rt. The solvent was removed and the mixture was diluted with EtOAc, water, and filtered through celite. The organic layer was separated and the

aqueous layer was extracted with EtOAc. The organic was combined, dried over MgSO₄, filtered and concentrated onto silica gel. Auto-column (8 EtOAc: 2 Hexanes) gave **Intermediate 11** as a clear oil 100 mg, (21%) **ethyl 3-((1-(4-((5-phenylpentyl)oxy)-3-(thiophen-2-yl)phenyl) ethyl) amino)cyclobutanecarboxylate**.

5

¹H NMR (600 MHz, CDCl₃): δ 7.56 (d, J = 2.4 Hz, 1H), 7.51-7.50 (m, 1H), 7.31-7.25 (m, 3H), 7.19-7.15 (m, 4H), 7.06 (dd, J = 3.6, 5.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.11-4.05 (m, 4H), 3.08 (m, 1H), 2.66-2.62 (m, 3H), 2.60-2.30 (series of m, 2H), 1.94-1.22 (series of m, 12H)

10

Step-4: A mixture of **Intermediate 11** was hydrolyzed according to the procedure described in **Example 6 Step 2** and gave 81 mg of the title compound **3-[(1-(4-[(5-phenylpentyl)oxy]-3-(2-thienyl)phenyl)ethyl) amino] cyclobutanecarboxylic acid**

15

¹H NMR (600 MHz, CD₃OD): δ 7.76 (d, J = 2.4 Hz, 1H), 7.56 (dd, J = 1.2, 4.2 Hz, 1H), 7.41 (dd, J = 1.2, 5.4 Hz, 1H), 7.31 (dd, J = 2.4, 9.0 Hz, 1H), 7.23 (t, J = 7.8 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 7.14-7.12 (m, 2H), 7.08 (dd, J = 3.6, 5.4 Hz, 1H), 4.32 (q, J = 7.2 Hz, 1H), 4.14 (t, J = 6.0 Hz, 2H), 3.50 (t, J = 7.8 Hz, 1H), 2.81-2.75 (m, 1H), 2.64 (t, J = 7.8 Hz, 2H), 2.56-2.53 (m, 1H), 2.35-2.27 (m, 2H), 2.14-2.11 (m, 1H), 1.93-1.89 (m, 2H), 1.74-1.66 (m, 2H), 1.65 (d, J = 6.6 Hz, 3H), 1.61-1.57 (m, 2H).

20

Example 8

Biological Data

25

Compounds were synthesized and tested for S1P1 activity using the GTP γ^{35} S 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.

30

GTP γ^{35} S binding was measured in the medium containing (mM) HEPES 25, pH 7.4, MgCl₂ 10, NaCl 100, dithiothreitol 0.5, digitonin 0.003%, 0.2 nM GTP γ^{35} S, and 5 μ g membrane protein in a volume of 150 μ l. Test compounds were included in the concentration range from 0.08 to 5,000 nM unless indicated otherwise. Membranes were incubated with 100 μ M 5'-adenylylimmidodiphosphate for 30 min, and subsequently with 10 μ M 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, MgCl₂ 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.

10 Table 3 shows activity potency: S1P1 receptor from GTP $\gamma^{35}\text{S}$: nM, (EC₅₀), % stimulation.

Activity potency: S1P1 receptor from GTP $\gamma^{35}\text{S}$: nM, (EC₅₀),

15

Table 3

Compound number	IUPAC name	S1P1 EC ₅₀ (nM)
16	1-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid	15
28	3-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)cyclobutanecarboxylic acid	15
26	1-{4-[(5-phenylpentyl)thio]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid	182
15	1-{3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid	13
25	1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-1-yl)benzyl}azetidine-3-carboxylic acid	22

Example 9**Lymphopenia Assay in Mice**

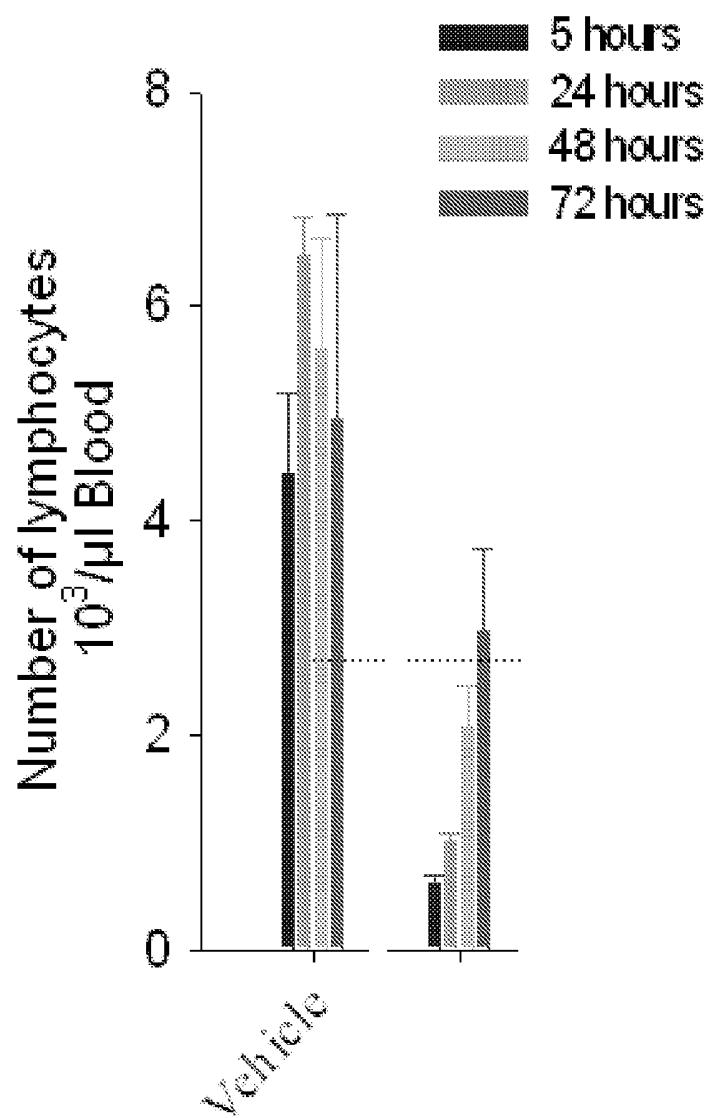
5

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 10 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).

15

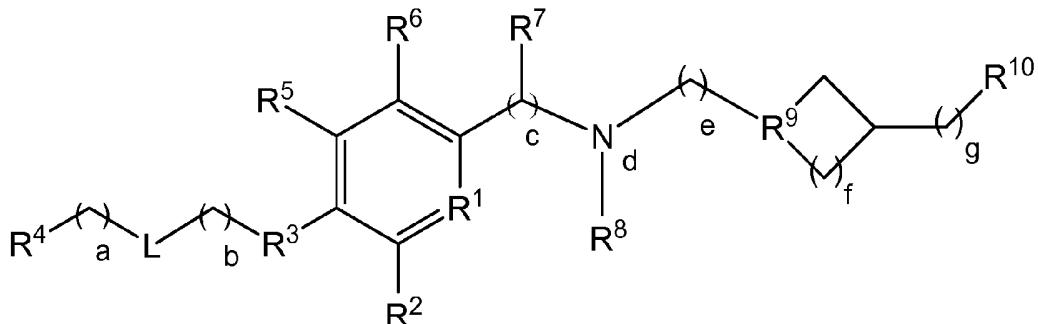
Lymphopenia induced by S1P1 agonists in mice: Time course (10 mg/Kg ip)

1-{4-[(5-phenylpentyloxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic 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,



5

Formula I

wherein:

R^1 is N or C- R^{11} ;

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

10 R³ is O, N-R¹², CH-R¹³, S, -CR¹⁴=CR¹⁵-, -C≡C- or -C(O)-;

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

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

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

15 R⁷ is H or C₁₋₆ alkyl;

R⁸ is H or C₁₋₆ alkyl;

R^9 is CH or N;

R^{10} is OPO_3H_2 , carboxylic acid, $-\text{PO}_3\text{H}_2$, C_{1-6} alkyl, $-\text{S}(\text{O})_2\text{OH}$, $-\text{P}(\text{O})\text{MeOH}$, -

P(O)(H)OH or -OR¹⁶;

20 R¹¹ is H, C₁₋₆ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;

R^{12} is H or C_{1-3} alkyl;

R^{13} is H, C₁₋₃ alkyl, halogen, hydroxyl, -OC₁₋₃alkyl or amino;

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

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

25 R¹⁶ is H or C₁₋₆ alkyl;

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

b is 0, 1, 2, 3 or 4:

c is 0 or 1:

d is 0 or 1;
e is 0, 1, 2 or 3;
f is 0, 1, 2 or 3;
g is 0, 1, 2 or 3;
5 L is CHR^{17} , O, S, NR^{18} or $-\text{C}(\text{O})-$;
 R^{17} is H, C_{1-3} alkyl, $-\text{OC}_{1-3}$ alkyl, halogen, hydroxyl or amino, and
 R^{18} is H or C_{1-3} alkyl;
with the proviso that when R^3 is O, $\text{N}-\text{R}^{12}$, S and b is 0 or 1 then L is not O, S, NR^{18} .

10 2. A compound according to claim 1, wherein:
 R^1 is N or $\text{C}-\text{R}^{11}$;
 R^2 is a 5-member aromatic heterocycle, or 5-member cycloalkenyl;
 R^3 is O, $\text{N}-\text{R}^{12}$, $\text{CH}-\text{R}^{13}$, S, $-\text{CR}^{14}=\text{CR}^{15}-$, $-\text{C}\equiv\text{C}-$ or $-\text{C}(\text{O})-$;
15 R^4 is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or
aryl;
 R^5 is H, halogen, $-\text{OC}_{1-3}$ alkyl, C_{1-3} alkyl or hydroxyl;
 R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-\text{OC}_{1-3}$ alkyl;
 R^7 is H or C_{1-6} alkyl;
20 R^8 is H or C_{1-6} alkyl;
 R^9 is CH or N;
 R^{10} is OPO_3H_2 , carboxylic acid, $-\text{PO}_3\text{H}_2$, C_{1-6} alkyl, $-\text{S}(\text{O})_2\text{OH}$, $-\text{P}(\text{O})\text{MeOH}$, $-\text{P}(\text{O})(\text{H})\text{OH}$ or $-\text{OR}^{16}$;
25 R^{11} is H, C_{1-6} alkyl, halogen, hydroxyl or $-\text{OC}_{1-3}$ alkyl;
 R^{12} is H or C_{1-3} alkyl;
 R^{13} is H, C_{1-3} alkyl, halogen, hydroxyl, $-\text{OC}_{1-3}$ alkyl or amino;
30 R^{14} is H or C_{1-3} alkyl;
 R^{15} is H or C_{1-3} alkyl;
 R^{16} is H or C_{1-6} alkyl;
a is 0, 1, 2, 3 or 4;
b is 0, 1, 2, 3 or 4;
c is 0 or 1;
d is 0 or 1;
e is 0, 1, 2 or 3;
f is 0, 1, 2 or 3;

g is 0, 1, 2 or 3;

L is CHR^{17} , O, S, NR^{18} or $-\text{C}(\text{O})-$;

R^{17} is H, C_{1-3} alkyl, $-\text{OC}_{1-3}$ alkyl, halogen, hydroxyl or amino, and

R^{18} is H or C_{1-3} alkyl;

5 with the proviso that when R^3 is O, $\text{N}-\text{R}^{12}$, S and b is 0 or 1 then L is not O, S, NR^{18} .

3. A compound according to claim 1, wherein:

R^1 is N or $\text{C}-\text{R}^{11}$;

R^2 is a cyclopentane, cyclopentene, pyrazolidine, pyrrolidine, imidazoline, 10 pyrazoline, thiazoline, oxazoline, thiophene, dihydrothiophene, furan, dihydrofuran, pyrrole, pyrrolidine, oxazole, oxazoline, 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;

15 R^3 is O, $\text{N}-\text{R}^{12}$, $\text{CH}-\text{R}^{13}$, S, $-\text{CR}^{14}=\text{CR}^{15}-$, $-\text{C}\equiv\text{C}-$ or $-\text{C}(\text{O})-$;

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

R^5 is H, halogen, $-\text{OC}_{1-3}$ alkyl, C_{1-3} alkyl or hydroxyl;

R^6 is H, C_{1-3} alkyl, halogen, hydroxyl or $-\text{OC}_{1-3}$ alkyl;

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

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

R^9 is CH or N;

R^{10} is OPO_3H_2 , carboxylic acid, $-\text{PO}_3\text{H}_2$, C_{1-6} alkyl, $-\text{S}(\text{O})_2\text{OH}$, $-\text{P}(\text{O})\text{MeOH}$, $-\text{P}(\text{O})(\text{H})\text{OH}$ or $-\text{OR}^{16}$;

25 R^{11} is H, C_{1-6} alkyl, halogen, hydroxyl or $-\text{OC}_{1-3}$ alkyl;

R^{12} is H or C_{1-3} alkyl;

R^{13} is H, C_{1-3} alkyl, halogen, hydroxyl, $-\text{OC}_{1-3}$ alkyl or amino;

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

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

30 R^{16} is H or C_{1-6} alkyl;

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

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

c is 0 or 1;

d is 0 or 1;

e is 0, 1, 2 or 3;
 f is 0, 1, 2 or 3;
 g is 0, 1, 2 or 3;
 L is CHR^{17} , O, S, NR^{18} or $-\text{C}(\text{O})-$;
 5 R¹⁷ is H, C₁₋₃ alkyl, $-\text{OC}_{1-3}$ alkyl, halogen, hydroxyl or amino, and
 R¹⁸ is H or C₁₋₃ alkyl;
 with the proviso that when R³ is O, N-R¹², S and b is 0 or 1 then L is not O, S, NR^{18} .

4. A compound according to claim 1, wherein:

10 R¹ is N;
 R² is aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;
 R³ is O, N-R¹², CH-R^{13} , S, $-\text{CR}^{14}=\text{CR}^{15}-$, $-\text{C}\equiv\text{C}-$ or $-\text{C}(\text{O})-$;
 R⁴ is H, aromatic heterocycle, non-aromatic heterocycle, cycloalkyl, cycloalkenyl or aryl;
 15 R⁵ is H, halogen, $-\text{OC}_{1-3}$ alkyl, C₁₋₃ alkyl or hydroxyl;
 R⁶ is H, C₁₋₃ alkyl, halogen, hydroxyl or $-\text{OC}_{1-3}$ alkyl;
 R⁷ is H or C₁₋₆ alkyl;
 R⁸ is H or C₁₋₆ alkyl;
 R⁹ is CH or N;
 20 R¹⁰ is OPO_3H_2 , carboxylic acid, $-\text{PO}_3\text{H}_2$, C₁₋₆ alkyl, $-\text{S}(\text{O})_2\text{OH}$, $-\text{P}(\text{O})\text{MeOH}$, $-\text{P}(\text{O})(\text{H})\text{OH}$ or $-\text{OR}^{16}$;
 R¹² is H or C₁₋₃ alkyl;
 25 R¹³ is H, C₁₋₃ alkyl, halogen, hydroxyl, $-\text{OC}_{1-3}$ alkyl or amino;
 R¹⁴ is H or C₁₋₃ alkyl;
 R¹⁵ is H or C₁₋₃ alkyl;
 R¹⁶ is H or C₁₋₆ alkyl;
 a is 0, 1, 2, 3 or 4;
 b is 0, 1, 2, 3 or 4;
 c is 0 or 1;
 30 d is 0 or 1;
 e is 0, 1, 2 or 3;
 f is 0, 1, 2 or 3;
 g is 0, 1, 2 or 3;
 L is CHR^{17} , O, S, NR^{18} or $-\text{C}(\text{O})-$;

R¹⁷ is H, C₁₋₃ alkyl, -OC₁₋₃ alkyl, halogen, hydroxyl or amino, and

R¹⁸ is H or C₁₋₃ alkyl;

with the proviso that when R³ is O, N-R¹², S and b is 0 or 1 then L is not O, S, NR¹⁸.

5

5. A compound according to claim 1, wherein:

R¹ is C-R¹¹; and

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

R³ is O or S; and

10 R⁴ is aryl; and

R⁵ is H, -OC₁₋₃ alkyl or halogen; and

R⁶ is H; and

R⁷ is H or C₁₋₆ alkyl; and

R⁸ is H; and

15 R⁹ is CH or N; and

R¹⁰ is COOH; and

R¹¹ is H; and

a is 0, 1, 2 or 3; and

b is 1, 2 or 3; and

20 c is 0 or 1; and

d is 0 or 1; and

e is 0 or 1; and

f is 1; and

g is 0; and

25 L is CHR¹⁷ or O; and

R¹⁷ is H or C₁₋₃ alkyl;

with the provisio that when R³ is O or S and b is 1 then L is not O.

6. A compound according to claim 1, wherein:

R¹ is C-R¹¹; and

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

R³ is O; and

R⁴ is aryl; and

R⁵ is H, -OC₁₋₃ alkyl or halogen; and

R⁶ is H; and
R⁷ is H or C₁₋₆ alkyl; and
R⁸ is H; and
R⁹ is CH; and
5 R¹⁰ is COOH; and
R¹¹ is H; and
a is 0, 1, 2 or 3; and
b is 1, 2 or 3; and
c is 1; and
10 d is 1; and
e is 0 or 1; and
f is 1; and
g is 0; and
L is CHR¹⁷; and
15 R¹⁷ is H.

7. A compound according to claim 1, wherein:
R¹ is C-R¹¹; and
R² is aromatic heterocycle, non-aromatic heterocycle or cycloalkenyl; and
20 R³ is S; and
R⁴ is aryl; and
R⁵ is H, -OC₁₋₃ alkyl or halogen; and
R⁶ is H; and
R⁷ is H or C₁₋₆ alkyl; and
25 R⁸ is H; and
R⁹ is CH or N; and
R¹⁰ is COOH; and
R¹¹ is H; and
a is 0, 1, 2 or 3; and
30 b is 1, 2 or 3; and
c is 0 or 1; and
d is 0 or 1; and
e is 0 or 1; and

f is 1; and
g is 0; and
L is CHR^{17} or O; and
 R^{17} is H or C_{1-3} alkyl;
5 with the provisio that when R^3 is S and b is 1 then L is not O.

8. A compound according to claim 1, wherein:

R^1 is C-R^{11} ; and
 R^2 is aromatic heterocycle, non-aromatic heterocycle or cycloalkenyl; and
10 R^3 is O; and
 R^4 is aryl; and
 R^5 is H, $-\text{OC}_{1-3}$ alkyl or halogen; and
 R^6 is H; and
 R^7 is H or C_{1-6} alkyl; and
15 R^8 is H; and
 R^9 is CH or N; and
 R^{10} is COOH; and
 R^{11} is H; and
a is 0, 1, 2 or 3; and
20 b is 1, 2 or 3; and
c is 0 or 1; and
d is 0 or 1; and
e is 0 or 1; and
f is 1; and
25 g is 0; and
L is CHR^{17} or O; and
 R^{17} is H or C_{1-3} alkyl;
with the provisio that when R^3 is O and b is 1 then L is not O.

30 9. A compound according to claim 1, wherein:
 R^1 is C-R^{11} ; and
 R^2 is aromatic heterocycle, aryl or cycloalkenyl; and
 R^3 is O; and

R⁴ is aryl; and
R⁵ is H, or halogen; and
R⁶ is H; and
R⁷ is H or C₁₋₆ alkyl; and
5 R⁸ is H; and
R⁹ is CH or N; and
R¹⁰ is COOH; and
R¹¹ is H; and
a is 0, 1, 2 or 3; and
10 b is 1, 2 or 3; and
c is 0 or 1; and
d is 0 or 1; and
e is 0 or 1; and
f is 1; and
15 g is 0; and
L is CHR¹⁷; and
R¹⁷ is H.

10. A compound according to claim 1, wherein:
R¹ is C-R¹¹; and
20 R² is aromatic heterocycle or cycloalkenyl; and
R³ is O or S; and
R⁴ is aryl; and
R⁵ is H, -OC₁₋₃ alkyl or halogen; and
R⁶ is H; and
25 R⁹ is N; and
R¹⁰ is COOH; and
a is 0, 1, 2 or 3; and
b is 1, 2 or 3; and
c is 0; and
30 d is 0; and
e is 1; and
f is 1; and
g is 0; and
L is CHR¹⁷ or O; and

R¹⁷ is H or C₁₋₃ alkyl;

with the provisio that when R³ is O or S and b is 1 then L is not O.

11. A compound according to claim 1 selected from:

5 1-{3-(3-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
1-{3-methoxy-4-[(5-phenylpentyl)oxy]-5-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
1-{4-[(6-phenylhexyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
1-{4-[3-(benzyloxy)propoxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
1-{4-[3-(4-isobutylphenyl)propoxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
10 1-[4-(2-biphenyl-4-yloxy)-3-(2-thienyl)benzyl]azetidine-3-carboxylic acid;
1-{3-chloro-4-[(5-phenylpentyl)oxy]-5-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
1-{3-chloro-4-[(5-phenylpentyl)oxy]-5-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
1-{4-[(3-methyl-5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
1-{3-(5-methyl-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
15 1-{3-(4-methyl-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
1-{3-(3-methyl-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-5-yl)benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-4-yl)benzyl}azetidine-3-carboxylic acid;
1-{3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
20 1-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-5-yl)benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-4-yl)benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-pyridin-4-ylbenzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(3-thienyl)benzyl}azetidine-3-carboxylic acid;
25 1-{6-[(5-phenylpentyl)oxy]biphenyl-3-yl}methyl)azetidine-3-carboxylic acid;
1-{3-(2-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-2-yl)benzyl}azetidine-3-carboxylic acid;
1-{3-(1,3-oxazol-2-yl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-1-yl)benzyl}azetidine-3-carboxylic acid;
30 1-{4-[(5-phenylpentyl)thio]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
1-{3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)thio]benzyl}azetidine-3-carboxylic acid;
3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)cyclobutanecarboxylic acid;
3-[(1-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)phenyl}ethyl)amino]cyclobutanecarboxylic acid.

12. A compound according to claim 1 selected from:

1-{3-(3-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;

5 1-{3-chloro-4-[(5-phenylpentyl)oxy]-5-(2-thienyl)benzyl}azetidine-3-carboxylic acid;

1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-5-yl)benzyl}azetidine-3-carboxylic acid;

1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-4-yl)benzyl}azetidine-3-carboxylic acid;

1-{3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;

1-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;

10 1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-5-yl)benzyl}azetidine-3-carboxylic acid;

1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-4-yl)benzyl}azetidine-3-carboxylic acid;

1-{4-[(5-phenylpentyl)oxy]-3-(3-thienyl)benzyl}azetidine-3-carboxylic acid;

1-{3-(2-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;

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

15 1-{3-(1,3-oxazol-2-yl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;

1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-1-yl)benzyl}azetidine-3-carboxylic acid;

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

3-[(1-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)phenyl}ethyl)amino]cyclobutanecarboxylic acid.

20

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

25

14. A pharmaceutical composition according to claim 10 wherein the compound is selected from:

1-{3-(3-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;

1-{3-methoxy-4-[(5-phenylpentyl)oxy]-5-(2-thienyl)benzyl}azetidine-3-carboxylic acid;

30 1-{4-[(6-phenylhexyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;

1-{4-[3-(benzyloxy)propoxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;

1-{4-[3-(4-isobutylphenyl)propoxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;

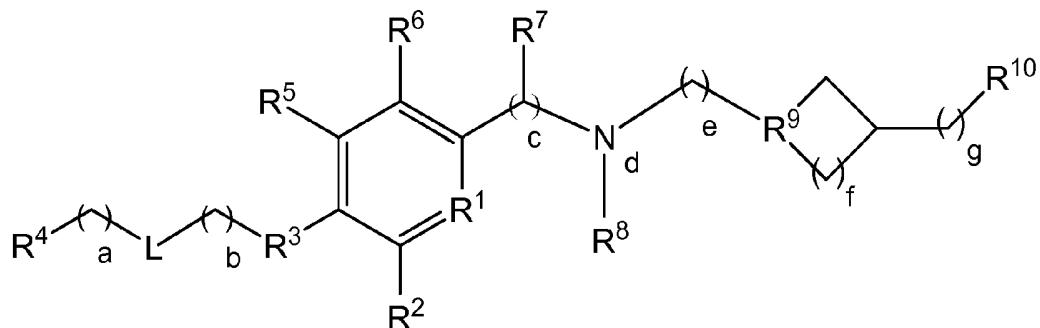
1-[4-(2-biphenyl-4-yloxy)-3-(2-thienyl)benzyl]azetidine-3-carboxylic acid;

1-{3-chloro-4-[(5-phenylpentyl)oxy]-5-(2-thienyl)benzyl}azetidine-3-carboxylic acid;

35 1-{3-chloro-4-[(5-phenylpentyl)oxy]-5-(2-thienyl)benzyl}azetidine-3-carboxylic acid;

1-{4-[(3-methyl-5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
 1-{3-(5-methyl-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 1-{3-(4-methyl-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 1-{3-(3-methyl-2-thienyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 5 1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-5-yl)benzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-4-yl)benzyl}azetidine-3-carboxylic acid;
 1-{3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-5-yl)benzyl}azetidine-3-carboxylic acid;
 10 1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-4-yl)benzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-pyridin-4-ylbenzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-(3-thienyl)benzyl}azetidine-3-carboxylic acid;
 1-({6-[(5-phenylpentyl)oxy]biphenyl-3-yl}methyl)azetidine-3-carboxylic acid;
 1-{3-(2-furyl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 15 1-{4-[(5-phenylpentyl)oxy]-3-(1,3-thiazol-2-yl)benzyl}azetidine-3-carboxylic acid;
 1-{3-(1,3-oxazol-2-yl)-4-[(5-phenylpentyl)oxy]benzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)oxy]-3-(1H-pyrazol-1-yl)benzyl}azetidine-3-carboxylic acid;
 1-{4-[(5-phenylpentyl)thio]-3-(2-thienyl)benzyl}azetidine-3-carboxylic acid;
 20 1-{3-cyclopent-1-en-1-yl-4-[(5-phenylpentyl)thio]benzyl}azetidine-3-carboxylic acid;
 3-({4-[(5-phenylpentyl)oxy]-3-(2-thienyl)benzyl}amino)cyclobutanecarboxylic acid;
 3-[(1-{4-[(5-phenylpentyl)oxy]-3-(2-thienyl)phenyl}ethyl)amino]cyclobutanecarboxylic acid.

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

wherein:

R^1 is N or C- R^{11} ;

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

5 R^3 is O, N- R^{12} , CH- R^{13} , S, -CR¹⁴=CR¹⁵-, -C≡C- or -C(O)-;

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

R^5 is H, halogen, -OC₁₋₃ alkyl, C₁₋₃ alkyl or hydroxyl;

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

10 R^7 is H or C₁₋₆ alkyl;

R^8 is H or C₁₋₆ alkyl;

R^9 is CH or N;

R^{10} is OPO₃H₂, carboxylic acid, PO₃H₂, C₁₋₆ alkyl, -S(O)₂OH, -P(O)MeOH, -

P(O)(H)OH or OR¹⁶;

15 R^{11} is H, C₁₋₆ alkyl, halogen, hydroxyl or -OC₁₋₃ alkyl;

R^{12} is H or C₁₋₃ alkyl;

R^{13} is H, C₁₋₃ alkyl, halogen, hydroxyl, -OC₁₋₃ alkyl or amino;

R^{14} is H or C₁₋₃ alkyl;

R^{15} is H or C₁₋₃ alkyl;

20 R^{16} is H or C₁₋₆ alkyl;

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

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

c is 0 or 1;

d is 0 or 1;

25 e is 0, 1, 2 or 3;

f is 0, 1, 2 or 3;

g is 0, 1, 2 or 3;

L is CHR¹⁷, O, S, NR¹⁸ or -C(O)-;

R^{17} is H, C₁₋₃ alkyl, -OC₁₋₃ alkyl, halogen, hydroxyl or amino, and

30 R^{18} is H or C₁₋₃ 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,

NR¹⁸.

16. A method of claim 12, wherein the pharmaceutical composition is administered to the mammal to treat ocular disease, wet and dry age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinal edema, geographic atrophy, glaucomatous optic neuropathy, chorioretinopathy, 5 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 10 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 uveitis, renal ischemia/perfusion injury, contact hypersensitivity, atopic dermatitis, and organ transplantation; or allergies and other inflammatory diseases , urticaria, 15 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 20 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.

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17. The method of claim 13 wherein the mammal is a human.