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(54) **Title**: BICYCLIC DERIVATIVES AS SPHINGOSINE-1 -PHOSPHATE RECEPTORS MODULATORS

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

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BICYCLIC DERIVATIVES AS SPHINGOSINE-1-PHOSPHATE RECEPTORS MODULATORS

RELATED APPLICATIONS

This application claims the benefit of United States Provisional Patent Application Serial No. 61/983,918 filed April 24, 2014, and the benefit of United States Provisional Patent Application Serial No. 61/983,927 filed April 24, 2014, the disclosure of which are hereby incorporated in their entirety by reference.

FIELD OF THE INVENTION

The present invention relates to novel bicyclic 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

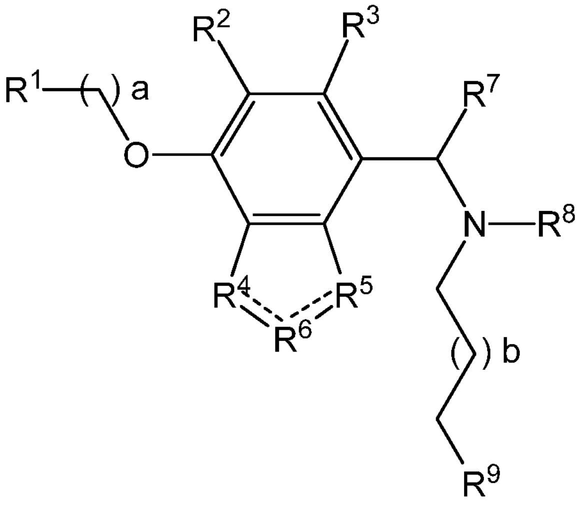
Sphingosine-1-phosphate is stored in relatively high concentrations in human platelets, which lack the enzymes responsible for its catabolism, and it is released into the blood stream upon activation of physiological stimuli, such as growth factors, cytokines, and receptor agonists and antigens. It may 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 herein are useful in treating a wide variety of disorders associated with modulation of sphingosine-1-phosphate receptors. The term “modulator” as used herein, includes but is not limited to: receptor agonist, antagonist, inverse agonist, inverse antagonist, partial agonist, partial antagonist.

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

In one aspect, the invention provides a compound having **Formula I,** its enantiomers, its diastereoisomers, its tautomers, or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

R^1 is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted $_{5\text{-}8}$ cycloalkyl, substituted or unsubstituted $C_{5\text{-}8}$ cycloalkenyl or hydrogen;

R^2 is hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, $C(O)R^{10}$ or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, $C(O)R^{10}$ or hydroxyl;

R^4 is CH, S, O, N, NH or CH_2;

R^5 is CH, S, O, N, NH or CH_2;

R^6 is CH, S, O, NH or CH_2;

R^7 is H, halogen, $-OC_{1-6}$ alkyl, substituted or unsubstituted C_{1-6} alkyl;

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

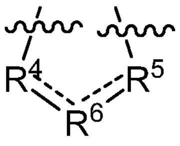
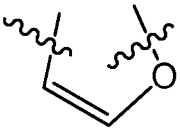
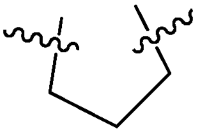
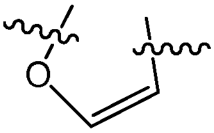
R^9 is OPO_3H_2, carboxylic acid, PO_3H_2, -P(O)MeOH, -P(O)(H)OH or OR^{11};

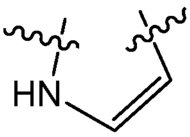
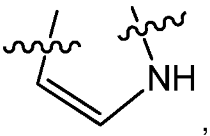
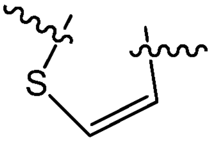
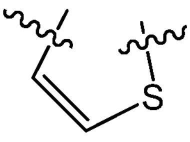
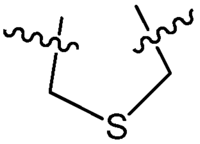
R^{10} is hydroxyl or substituted or unsubstituted C_{1-6} alkyl;

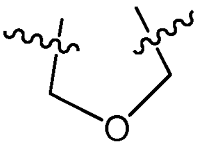
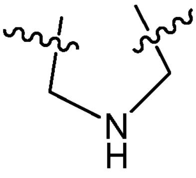
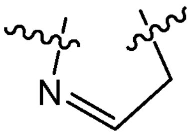
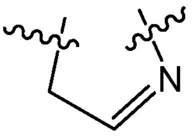
R^{11} is H or substituted or unsubstituted C_{1-6} alkyl;

a is 5, 6, 7 or 8;

b is 0 or 1; and

with the proviso that  is , , ,

, , , , ,

, ,  or .

In another aspect, the invention provides a compound having **Formula I,** wherein:

R^1 is substituted or unsubstituted aryl;

R^2 is hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl;

R^4 is CH, O or CH_2;

R^5 is CH, O or CH_2;

R^6 is CH or CH_2;

R^7 is H;

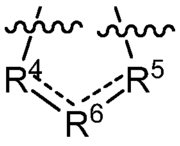
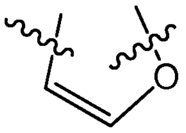
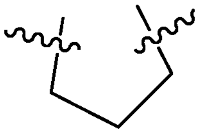
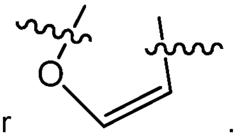
R^8 is H or C_{1-6} alkyl;

R^9 is OPO_3H_2, PO_3H_2 or OR^{11};

R^{11} is H;

a is 5, 6, 7 or 8;

b is 0 or 1; and

with the proviso that  is ,  or .

In another aspect, the invention provides a compound having **Formula I,** wherein:

R^1 is substituted or unsubstituted aryl;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is CH_2;

R^5 is CH_2;

R^6 is CH_2;

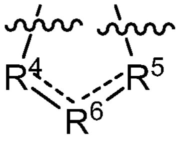
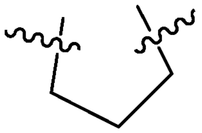
R^7 is H;

R^8 is H;

R^9 is PO_3H_2;

a is 5;

b is 1; and

with the proviso that  is .

In another aspect, the invention provides a compound having **Formula I,** wherein:

R^1 is substituted or unsubstituted aryl;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is CH, O;

R^5 is CH, O;

R^6 is CH;

R^7 is H;

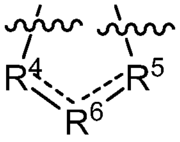
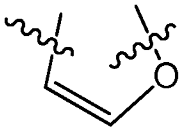
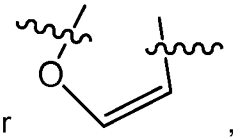
R^8 is H;

R^9 is OPO_3H_2, PO_3H_2 or OR^{11};

R^{11} is H;

a is 5;

b is 0 or 1; and

with the proviso that  is , or ,

In another aspect, the invention provides a compound having **Formula I,** wherein:

R^1 is substituted or unsubstituted aryl;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is CH, O;

R^5 is CH, O;

R^6 is CH;

R^7 is H;

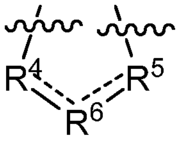
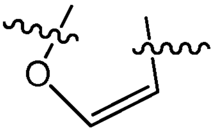
R^8 is H;

R^9 is PO_3H_2;

R^{11} is H;

a is 5;

b is 1; and

with the proviso that  is ,

In another aspect, the invention provides a compound having **Formula I,** wherein:

R^1 is substituted or unsubstituted aryl;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is CH, O;

R^5 is CH, O;

R^6 is CH;

R^7 is H;

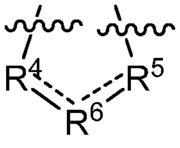
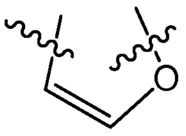
R^8 is H;

R^9 is OPO_3H_2, PO_3H_2 or OR^{11};

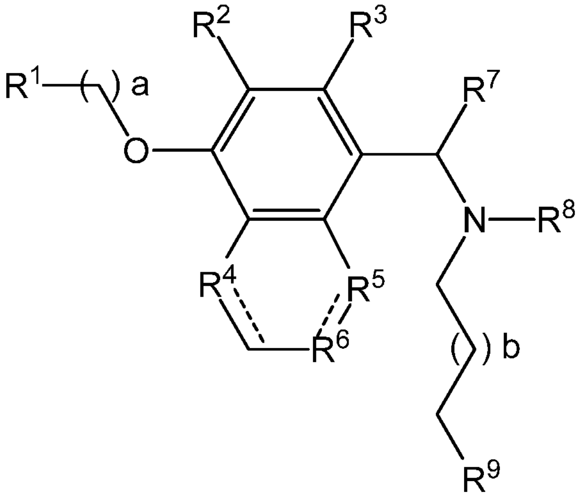
R^{11} is H;

a is 5;

b is 0 or 1; and

with the proviso that  is  .

In another aspect, the invention provides a compound having **Formula II,** its enantiomers, its diastereoisomers, its tautomers, or a pharmaceutically acceptable salt thereof:



Formula II

wherein:

R^1 is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{5\text{-}8}$ cycloalkyl, substituted or unsubstituted C $_{5\text{-}8}$ cycloalkenyl or hydrogen;

R^2 is hydrogen, halogen, substituted or unsubstituted $C_{1\text{-}3}$ alkyl, $C(O)R^{10}$ or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted $C_{1\text{-}3}$ alkyl, $C(O)R^{10}$ or hydroxyl;

R^4 is CH, S, O, N, NH or CH_2;

R^5 is CH, S, O, N, NH or CH_2;

R^6 is CH or CH_2;

R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl;

R^8 is H or C_{1-3} alkyl;

R^9 is OPO_3H_2, carboxylic acid, PO_3H_2, -P(O)MeOH, -P(O)(H)OH or OR^{11};

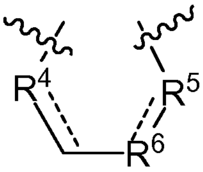
R^{10} is hydroxyl or substituted or unsubstituted C_{1-3} alkyl;

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

a is 5, 6, 7 or 8;

b is 0 or 1; and

with the proviso that



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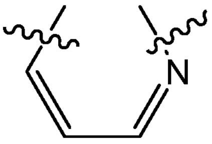
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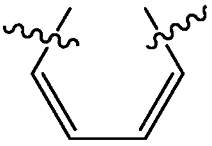
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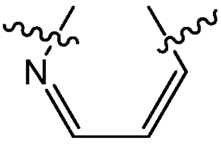
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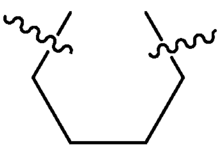
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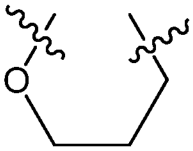
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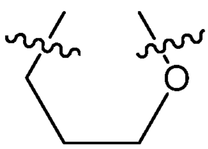
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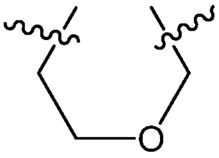
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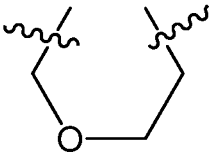
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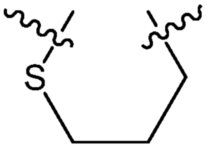
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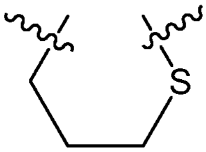
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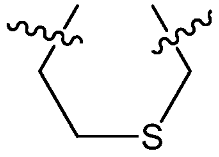
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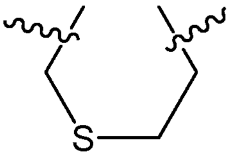
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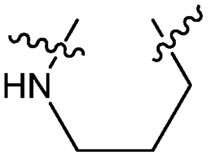
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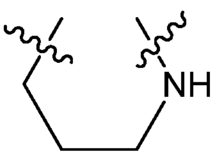
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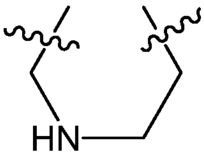
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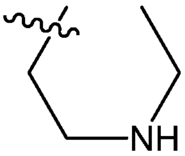
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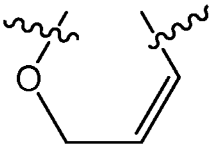
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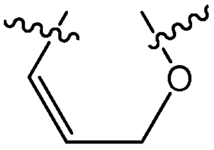
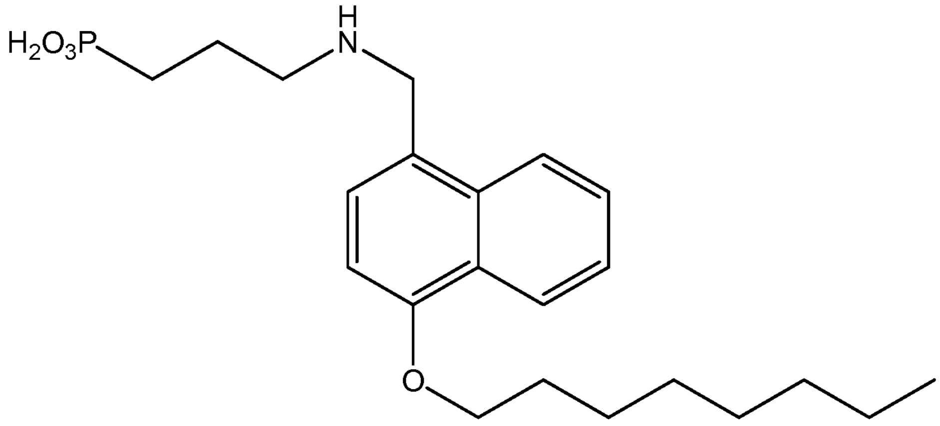

;

with the proviso that the compound of Formula II is not of structure:



.

In another aspect the invention provides a compound of Formula II, wherein:

R^1 is substituted or unsubstituted aryl, or hydrogen;

R^2 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl;

R^4 is CH, N;

R^5 is CH or N;

R^6 is CH;

R^7 is H, substituted or unsubstituted C_{1-3} alkyl;

R^8 is H;

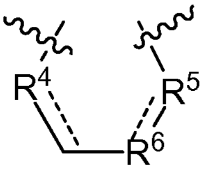
R^9 is OPO_3H_2, carboxylic acid, PO_3H_2 or OR^{11};

R^{11} is H;

a is 5, 6, 7 or 8;

b is 0 or 1; and

with the proviso that



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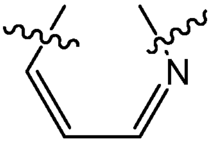

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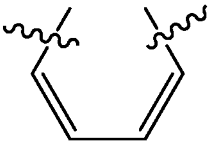
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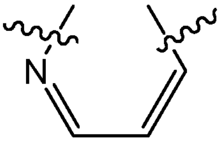
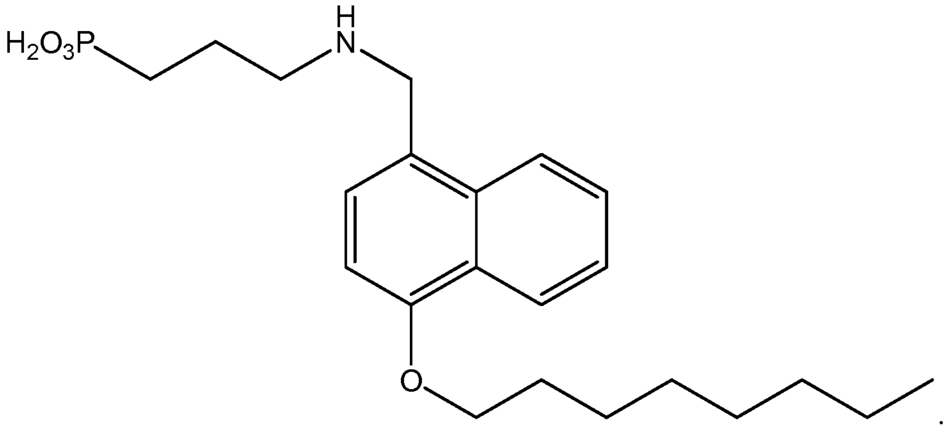


;

with the proviso that the compound of Formula I is not of structure:



In another aspect the invention provides a compound of Formula II, wherein:

R^1 is substituted or unsubstituted aryl;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is CH;

R^5 is N;

R^6 is CH;

R^7 is H;

R^8 is H;

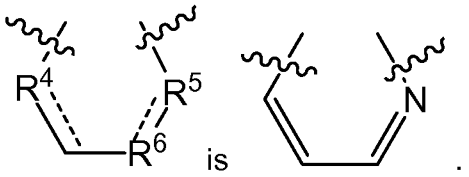
R^9 is OPO_3H_2, carboxylic acid, PO_3H_2 or OR^{11};

R^{11} is H;

a is 5, 6, 7 or 8;

b is 0 or 1; and

with the proviso that



In another aspect the invention provides a compound of Formula II, wherein:

R^1 is substituted or unsubstituted aryl, or hydrogen;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is CH;

R^5 is CH;

R^6 is CH;

R^7 is H;

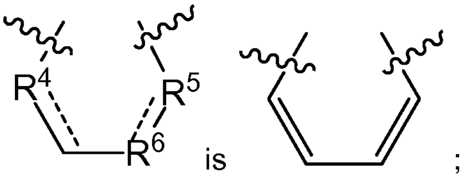
R^8 is H;

R^9 is PO_3H_2;

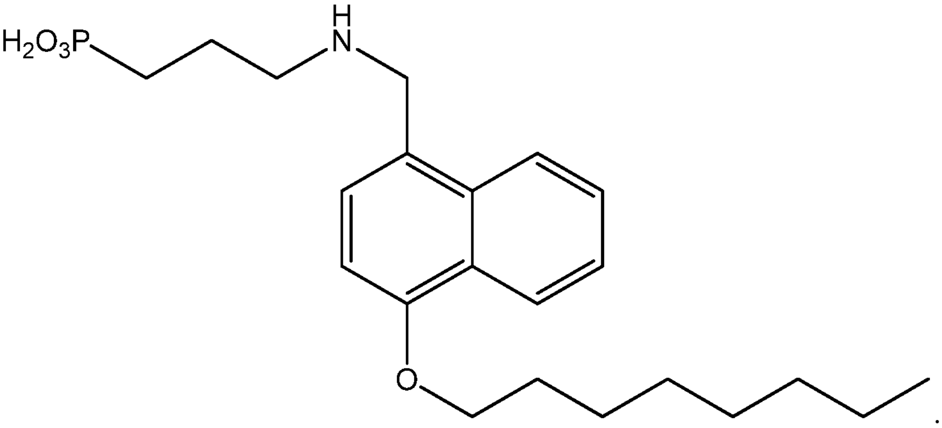
a is 5, 6, 7 or 8;

b is 0 or 1; and

with the proviso that



with the proviso that the compound of Formula I is not of structure:



In another aspect the invention provides a compound of Formula II, wherein:

R^1 is substituted or unsubstituted aryl, or hydrogen;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is N;

R^5 is CH;

R^6 is CH;

R^7 is H;

R^8 is H;

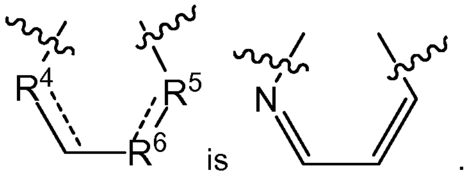
R^9 is PO_3H_2;

R^{11} is H;

a is 5, 6, 7 or 8;

b is 0 or 1; and

with the proviso that



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 ($-CH_2-$) group, of the alkyl can be replaced by oxygen, sulfur, sulfoxide, nitrogen, carbonyl, carboxyl, sulfonyl, or by a divalent C_{3-6} cycloalkyl. Alkyl groups can be substituted by halogen, hydroxyl, cycloalkyl, amino, non-aromatic heterocycles, carboxylic acid, phosphonic acid groups, sulphonic acid groups, phosphoric acid.

The term “cycloalkyl”, as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms, preferably 3 to 5 carbon atoms derived from a saturated cyclic hydrocarbon. Cycloalkyl groups can be monocyclic or polycyclic. Cycloalkyl can be substituted by 1 to 3 C_{1-3} alkyl groups or 1 or 2 halogens.

The term “cycloalkenyl”, as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms, preferably 3 to 6 carbon atoms derived from a saturated cycloalkyl having one double bond. Cycloalkenyl groups can be monocyclic or polycyclic. Cycloalkenyl groups can be substituted by alkyl groups or halogens.

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 moiety having 2 to 6 carbon atoms, derived from a saturated alkyl, having at least one double bond. C_{2-6} alkenyl can be in the E or Z configuration. Alkenyl groups can be substituted by alkyl groups.

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

The term “heterocycle” as used herein, refers to a 3 to 10 membered ring, which can be aromatic or non-aromatic, saturated or non-saturated, containing at least one heteroatom selected form O or N or S or combinations of at least two thereof, interrupting the carbocyclic ring structure. 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, alkyl or halogens. Usually, in the present case, heterocyclic groups are 5 or 6 membered rings.

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 halogen atoms or by alkyl groups.

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 “-SO_2”.

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 “-$P(O)(OH)_2$”.

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.

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.

Compounds of the invention are:

(3-{[(7-{[5-(3-methoxyphenyl)pentyl]oxy}-2,3-dihydro-1H-inden-4-yl)methyl]amino}propyl)phosphonic acid;

2-{[(4-{[5-(3-methoxyphenyl)pentyl]oxy}-1-benzofuran-7-yl)methyl]amino}ethanol;

2-{[(4-{[5-(3-methoxyphenyl)pentyl]oxy}-1-benzofuran-7-yl)methyl]amino}ethyl dihydrogen phosphate;

(3-{[(4-{[5-(3-methoxyphenyl)pentyl]oxy}-1-benzofuran-7-yl)methyl]amino}propyl)phosphonic acid;

{3-[({7-[(5-phenylpentyl)oxy]-2,3-dihydro-1H-inden-4-yl}methyl)amino]propyl}phosphonic acid;

{3-[({4-[(5-phenylpentyl)oxy]-1-benzofuran-7-yl}methyl)amino]propyl}phosphonic acid;

{3-[({7-[(5-phenylpentyl)oxy]-1-benzofuran-4-yl}methyl)amino]propyl}phosphonic acid;

2-{[(5-{[5-(3-methoxyphenyl)pentyl]oxy}quinolin-8-yl)methyl]amino}ethanol;

2-{[(5-{[5-(3-methoxyphenyl)pentyl]oxy}quinolin-8-yl)methyl]amino}ethyl dihydrogen phosphate;

(3-{[(5-{[5-(3-methoxyphenyl)pentyl]oxy}quinolin-8-yl)methyl]amino}propyl)phosphonic acid;

(3-{[(4-{[5-(3-methoxyphenyl)pentyl]oxy}naphthalen-1-yl)methyl]amino}propyl)phosphonic acid;

{3-[({5-[(5-phenylpentyl)oxy]quinolin-8-yl}methyl)amino]propyl}phosphonic acid;

[3-({[8-(nonyloxy)quinolin-5-yl]methyl}amino)propyl]phosphonic acid;

[3-({[4-(nonyloxy)naphthalen-1-yl]methyl}amino)propyl]phosphonic acid;

[3-({[4-(heptyloxy)naphthalen-1-yl]methyl}amino)propyl]phosphonic acid;

{3-[({4-[(5-phenylpentyl)oxy]naphthalen-1-yl}methyl)amino]propyl}phosphonic acid;

{3-[({8-[(5-phenylpentyl)oxy]quinolin-5-yl}methyl)amino]propyl}phosphonic acid.

Some compounds of Formula I or of Formula II and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in an R or S configuration, said R and S notation is used in correspondence with the rules described in Pure Appli. 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” 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 or of Formula II 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, such as for example, hydrochloric acid, 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 Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta- Zürich, 2002, 329-345).

The base addition salt form of a compound of Formula I or of Formula II that occurs in its acid form can be obtained by treating the acid with an appropriate base such as an inorganic base, for example, sodium hydroxide, magnesium hydroxide, potassium hydroxide, calcium hydroxide, ammonia and the like; or an organic base such as for example, L-Arginine, ethanolamine, betaine, benzathine, morpholine and the like. (Handbook of Pharmaceutical Salts, P. Heinrich Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta- Zürich, 2002, 329-345).

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

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.

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

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

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

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

Therapeutic utilities of S1P modulators are ocular diseases, such as but not limited to: wet and dry age-related macular degeneration, diabetic retinopathy, angiogenesis inhibition, 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 diastereoisomers thereof.

The present invention concerns the use of a compound of Formula I or Formula II 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, angiogenesis inhibition, 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 period of time, or to carefully control the amount of drug released at a given time during the course of therapy.

In another embodiment of the invention, there are provided pharmaceutical compositions including at least one compound of the invention in a pharmaceutically acceptable carrier 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 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, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. Invention compounds are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

Pharmaceutical compositions containing invention compounds may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known 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.

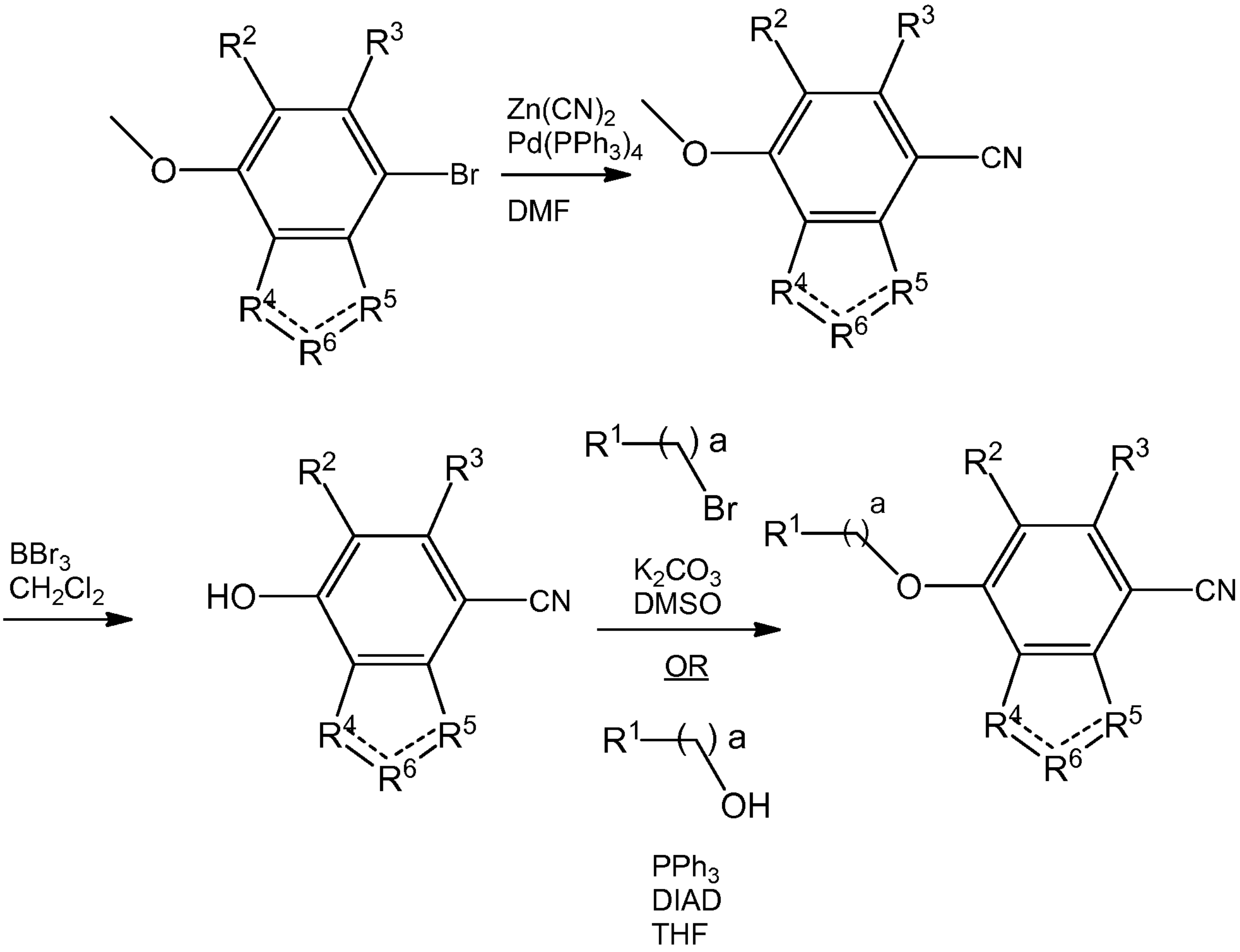
Invention compounds may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the invention compounds with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which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

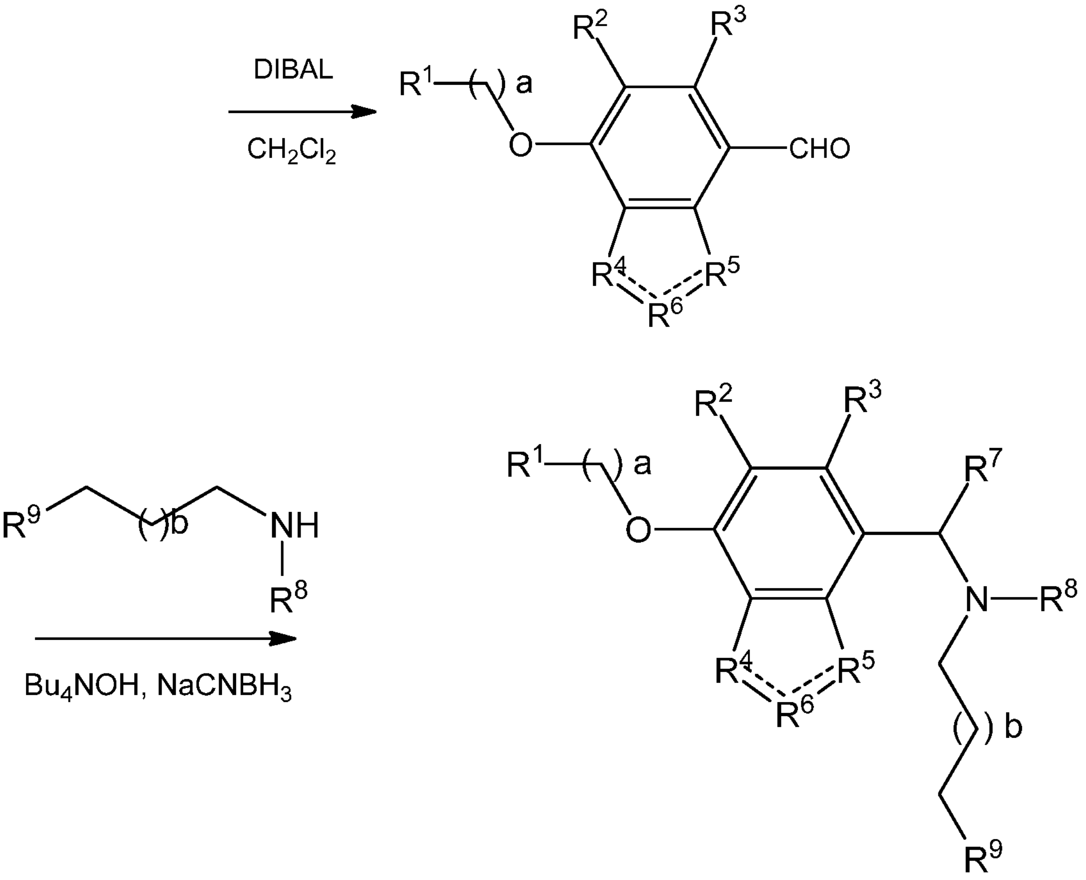
Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner.

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

The present invention concerns also processes for preparing the compounds of Formula I. The compounds of Formula I according to the invention can be prepared analogously to conventional methods as understood by the person skilled in the art of synthetic organic chemistry. The synthetic scheme set forth below, illustrates how compounds according to the invention can be made.

Scheme 1





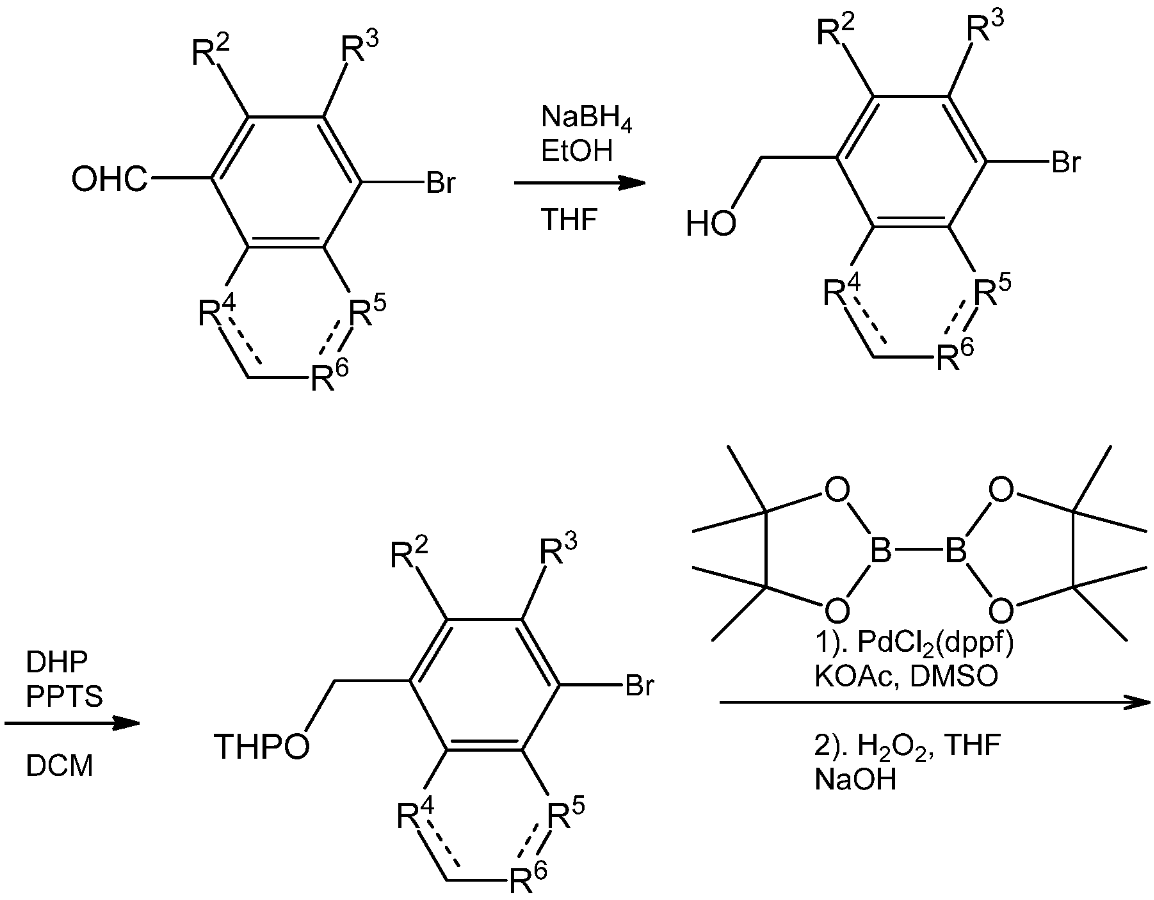
The following abbreviations are used in the general scheme and in the examples:

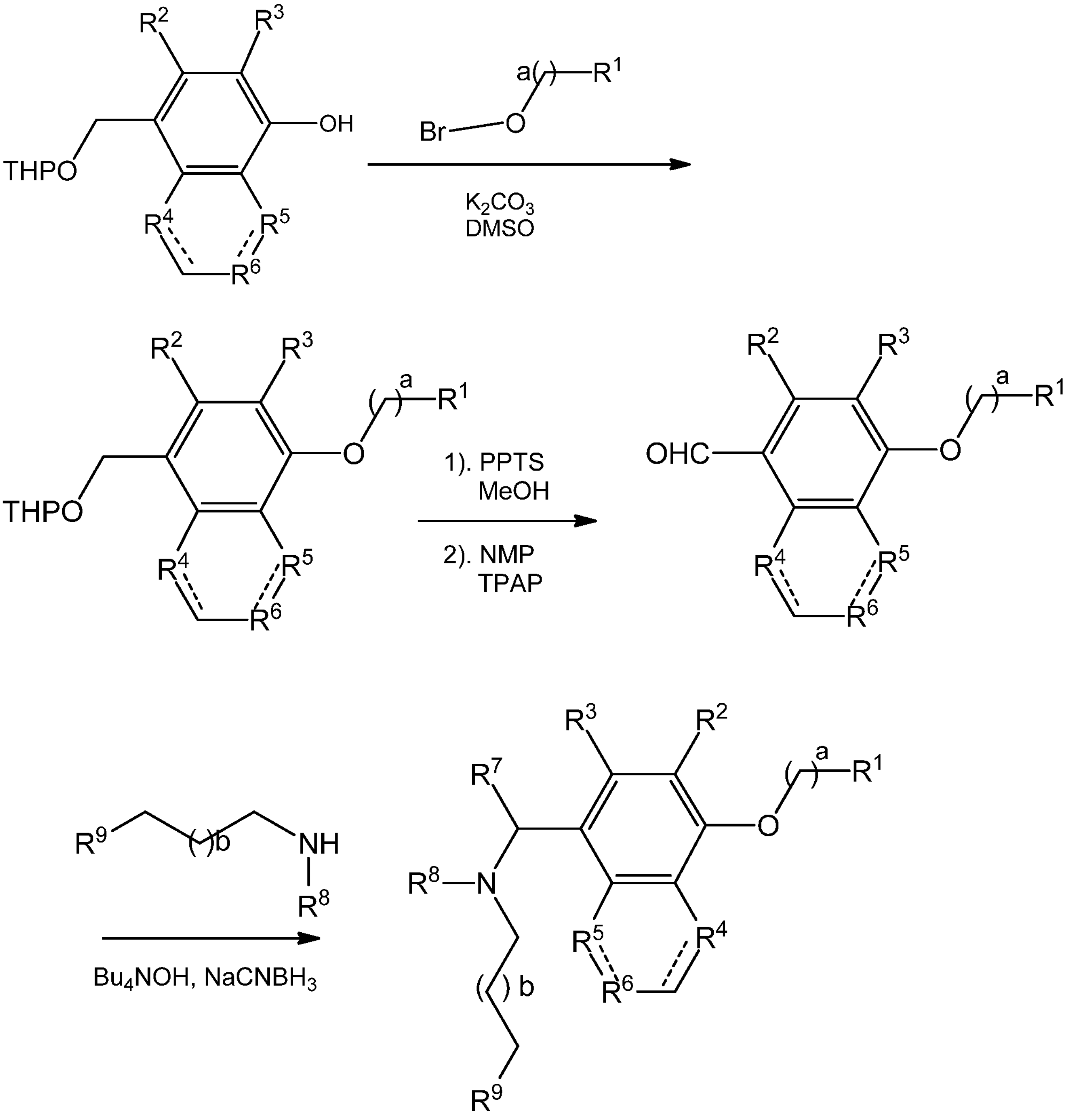
DMF	dimethylformamide
RT	room temperature
MPLC	medium pressure liquid chromatography
$CDCl_3$	deuterated chloroform
DMSO	dimethylsulfonoxide
K_2CO_3	potassium carbonate
DIBAL	diisobutylaluminium hydride
$MgSO_4$	magnesium sulfate
HCl	hydrochloric acid
MeOH	methanol
$Zn(CN)_2$	zinc cyanide
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
PPh_3	triphenylphosphine
DIAD	diisopropyl azodicarboxylate

CH_2Cl_2	dichloromethane
THF	tetrahydrofuran
Bu_4NOH	tetrabutylammonium hydroxide
$NaCNBH_3$	sodium cyanoborohydride
BBr_3	boron tribromide
CH_2Cl_2	dichloromethane

The present invention concerns also processes for preparing the compounds of Formula II. The compounds of Formula II 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 scheme set forth below, illustrates how compounds according to the invention can be made.

Scheme 2





The following abbreviations are used in the general scheme and in the examples:

DMF	dimethylformamide
RT	room temperature
MPLC	medium pressure liquid chromatography
$CDCl_3$	deuterated chloroform
DMSO	dimethylsulfonoxide

K_2CO_3	potassium carbonate
DIBAL	diisobutylaluminium hydride
$MgSO_4$	magnesium sulfate
HCl	hydrochloric acid
MeOH	methanol
$Zn(CN)_2$	zinc cyanide
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
PPh_3	triphenylphosphine
DIAD	diisopropyl azodicarboxylate
CH_2Cl_2	dichloromethane
THF	tetrahydrofuran
Bu_4NOH	tetrabutylammonium hydroxide
$NaCNBH_3$	sodium cyanoborohydride
PPTS	pyridinium p-toluenesulfonate
NMP	1-methyl-2-pyrrolidinone
TPAP	tetrapropylammonium perruthenate

Those skilled in the art will be able to routinely modify and/or adapt the following schemes to synthesize any compound of the invention covered by Formula I or by Formula II.

DETAILED DESCRIPTION OF THE INVENTION

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

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

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

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

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

Compound names were generated with ACDLabs version 12.5; 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.

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, AK Scientific, AmFine Com, Carbocore, Maybridge, Frontier, Matrix, Ukrorgsynth, Toronto, Ryan Scientific, SiliCycle, Anaspec, Syn Chem, Chem-Impex, MIC-scientific, Ltd; however some known intermediates, were prepared according to published procedures.

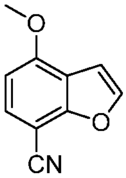
Usually the compounds of the invention were purified by column chromatography (Auto-column) on an Teledyne-ISCO CombiFlash with a silica column, unless noted otherwise.

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

Example 1

Intermediate 1

4-methoxybenzofuran-7-carbonitrile



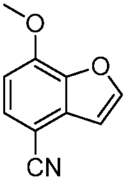
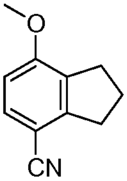
To a solution of 7-bromo-4-methoxybenzofuran (CAS 286836-01-9) (3.55g, 15.6 mmol) in DMF (110 mL) were added zinc cyanide (6.88 g, 58.8 mmol) and tetrakis(triphenylphosphine)palladium(0) (3.2 g, 2.8 mmol). After heating to 50°C with stirring for 16h, the reaction mixture was cooled to RT and filtered. The filtrate was concentrated and purified by MPLC (10% ethyl acetate in hexanes) to give rise to 2.36 g of **Intermediate 1** as colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57-7.62 (m, 1H), 7.35 (d, *J*=8.50 Hz, 1H), 6.90-6.94 (m, 1H), 6.54-6.60 (m, 1H), 3.92 (s, 3H)

Intermediates 2 and **3** were prepared from 4-bromo-7-methoxybenzofuran (CAS 1258960-00-7) and 4-bromo-7-methoxy-2,3-dihydro-1H-indene (CAS 872785-

24-5) in a similar manner to the procedure described in **Example 1** for **Intermediate 1**. The results are tabulated below in **Table 1**.

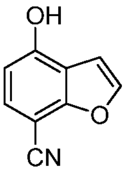
Table 1

Interm. No.	**Structure IUPAC Name**	**^{1}H NMR δ (ppm)**
2	 **7-methoxybenzofuran-4-carbonitrile**	^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, J=2.05 Hz, 1H), 7.53 (d, J=8.22 Hz, 1H), 6.95 (d, J=2.05 Hz, 1H), 6.78-6.86 (m, 1H), 4.07 (s, 3H)
3	 **7-methoxyindane-4-carbonitrile**	^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, J=7.91 Hz, 1H), 6.71 (d, J=8.20 Hz, 1H), 3.87 (s, 3H), 3.02-3.15 (m, 2H), 2.83-2.95 (m, 2H), 2.06-2.23 (m, 2H)

Example 2

Intermediate 4

4-hydroxybenzofuran-7-carbonitrile

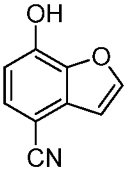
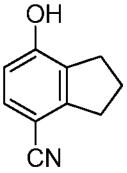


To a solution of **Intermediate 1**(2.36g, 13.6mmol) in methylene chloride (200 mL) at -78°C was added boron tribromide (1M solution in methylene chloride, 28 mL) slowly dropwise. After stirring at RT for 16h, more boron tribromide(1M solution in methylene chloride, 28mL) was added and continued to stir for another day. This was repeated another two times after which time, the reaction mixture was quenched with water at -78°C. The reaction mixture was further diluted with water and extracted with methylene chloride. The organic layers were combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude material was purified by MPLC (20% ethyl acetate in hexanes) to afford 1.6g of **Intermediate 4** as colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J*=2.35 Hz, 1H), 7.49 (d, *J*=8.22 Hz, 1H), 6.93 (d, *J*=2.35 Hz, 1H), 6.70 (d, *J*=8.22 Hz, 1H)

Intermediates 5 and **6** were prepared from **Intermediate 2** and **3**, in a similar manner to the procedure described in **Example 2** for **Intermediate 4**. The results are tabulated below in **Table 2**.

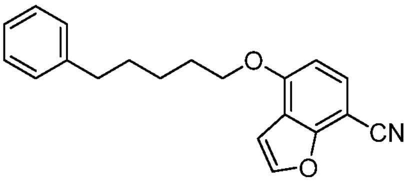
Table 2

Interm. No.	**Structure IUPAC Name**	**Interm. No.**	**^{1}H NMR δ (ppm)**
5	 **7-hydroxybenzofuran-4-carbonitrile**	**2**	^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J*=2.05 Hz, 1H), 7.50 (d, *J*=8.22 Hz, 1H), 7.00 (d, *J*=2.05 Hz, 1H), 6.86-6.92 (m, 1H)
6	 **7-hydroxyindane-4-carbonitrile**	**3**	^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.22 Hz, 1H), 6.68 (dd, *J* = 1.76, 8.22 Hz, 1H), 5.30 (br. s, 1H), 3.11 (t, *J* = 7.63 Hz, 2H), 2.90 (t, *J* = 7.34 Hz, 2H), 2.19 (quin, *J* = 7.56 Hz, 2H).

Example 3

Intermediate 7

4-((5-phenylpentyl)oxy)benzofuran-7-carbonitrile

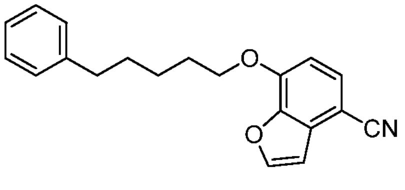
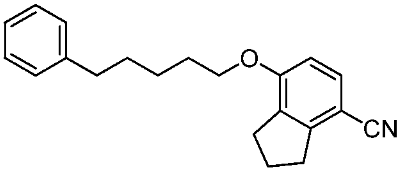


To the solution of **intermediate 4 (**427mg, 2.68mmol) and 5-bromopentyl) benzene (914mg, 4.02mmol) (CAS 14469-83-1) in DMSO (10mL) was added K_2CO_3 (1.48g, 10.7mmol). After stirring at rt for 16 h the mixture was diluted with water, extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude material was purified by MPLC (10% ethyl acetate in hexanes) to afford 604mg of **Intermediate 7** as colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.64 (d, *J*=2.05 Hz, 1H), 7.53 (d, *J*=8.50 Hz, 1H), 7.27-7.31 (m, 2H), 7.15-7.22 (m, 3H), 6.90 (d, *J*=2.05 Hz, 1H), 6.69 (s, 1H), 4.15 (s, 2H), 2.61-2.72 (m, 2H), 1.82-2.04 (m, 2H), 1.65-1.79 (m, 2H), 1.45-1.62 (m, 2H).

Intermediates 8 and **9** were prepared from **Intermediate 5** and **6**, in a similar manner to the procedure described in **Example 3** for **Intermediate 7**. The results are tabulated below in **Table 3**.

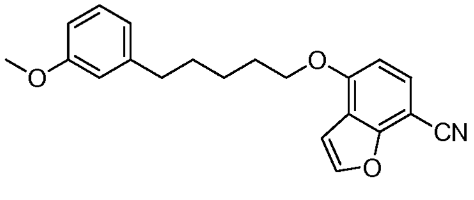
Table 3

Interm. No.	**Structure IUPAC Name**	**Interm. No.**	**^{1}H NMR δ (ppm)**
8	 **7-((5-phenylpentyl)oxy)benzofuran-4-carbonitrile**	**5**	^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J*=2.05 Hz, 1H), 7.52 (d, *J*=8.20 Hz, 1H), 7.23-7.32 (m, 2H), 7.13-7.22 (m, 3H), 6.97 (d, *J*=2.34 Hz, 1H), 6.77-6.85 (m, 1H), 4.23 (t, *J*=6.59 Hz, 2H), 2.60-2.74 (m, 2H), 1.87-2.01 (m, 2H), 1.72 (d, *J*=8.20 Hz, 2H), 1.51-1.56 (m, 2H)
9	 **7-((5-phenylpentyl)oxy)-2,3-dihydro-1H-indene-4-carbonitrile**	**6**	^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38-7.44 (m, 1H), 7.24-7.33 (m, 2H), 7.19 (s, 3H), 6.63-6.69 (m, 1H), 4.00 (s, 2H), 3.01-3.15 (m, 2H), 2.79-2.92 (m, 2H), 2.59-2.71 (m, 2H), 2.06-2.19 (m, 2H), 1.77-1.90 (m, 2H), 1.64-1.76 (m, 2H), 1.51 (d, *J*=7.03 Hz, 2H)

Example 4

Intermediate 10

4-((5-(3-methoxyphenyl)pentyl)oxy)benzofuran-7-carbonitrile

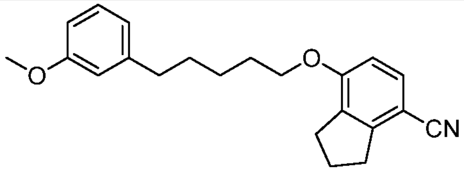


To a solution of **intermediate 4** (263mg, 1.65mmol), 5-(3-methoxyphenyl) pentan-1-ol (CAS 66004-20-4) (321mg, 1.65mmom) and triphenylphosphine (477mg, 1.82mmol) in THF(8)mL was added diisopropyl azodicarboxylate (0.36mL, 1.82mmol). The mixture was stirred at rt for 16 hr before concentration. Purification by MPLC (10% ethyl acetate in hexanes) to afford 499mg of **Intermediate 10** as colorless solid.

^{1}H NMR (600 MHz, CDCl$_3$) δ: 7.59-7.63 (m, 1H), 7.48-7.53 (m, 1H), 7.15-7.22 (m, 1H), 6.87-6.91 (m, 1H), 6.76-6.80 (m, 1H), 6.71-6.75 (m, 2H), 6.63-6.68 (m, 1H), 4.13 (t, J=6.46 Hz, 2H), 3.78 (s, 3H), 2.62-2.65 (m, 2H), 1.83-1.95 (m, 2H), 1.68-1.77 (m, 2H), 1.48-1.59 (m, 2H).

Intermediate 11 was prepared from **Intermediate 6**, in a similar manner to the procedure described in **Example 4** for **Intermediate 10**. The results are tabulated below in **Table 4**.

Table 4

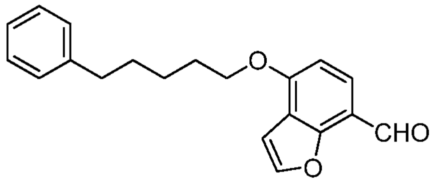
Interm. No.	Structure IUPAC Name	Interm. No.	^{1}H NMR δ (ppm)
			^{1}H NMR (600 MHz, CDCl$_3$) δ: 7.40 (d, J=8.51 Hz, 1H), 7.15-7.23 (m, 1H), 6.77 (d, J=7.34 Hz, 1H), 6.71-6.74 (m, 2H), 6.65 (d, J=8.51 Hz,

11	**7-((5-(3-methoxyphenyl)pentyl)oxy)-2,3-dihydro-1H-indene-4-carbonitrile**	**6**	1H), 4.00 (t, *J*=6.46 Hz, 2H), 3.79 (s, 3H), 3.07 (t, *J*=7.48 Hz, 2H), 2.86 (t, *J*=7.78 Hz, 2H), 2.62 (t, *J*=7.63 Hz, 2H), 2.12 (quin, *J*=7.56 Hz, 2H), 1.77-1.88 (m, 2H), 1.65-1.73 (m, 2H), 1.47-1.54 (m, 2H)

Example 5

Intermediate 12

4-((5-phenylpentyl)oxy)benzofuran-7-carbaldehyde

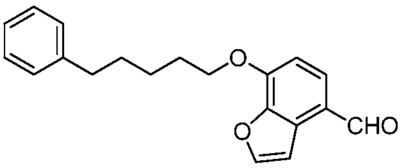
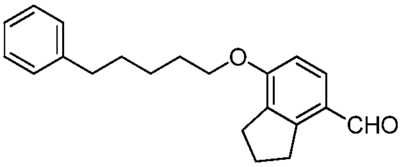
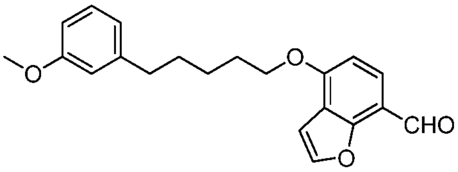


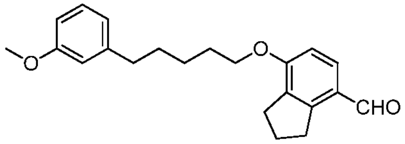
To a solution of **Intermediate 7** (604mg 1.98mmol) in dichloromethane (20mL) at -78°C was added DIBAL (1M solution in dichloromethane, 2.4mL, 2.4mmol). After stirring at -78°C for 8h, the reaction mixture was quenched with methanol then warmed to 0 °C. A 10% HCl solution was then added and warmed to RT. The mixture was diluted with water and the aqueous layer was extracted with dichloromethane The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by MPLC (5% ethyl acetate in hexanes) gave 296mg of **Intermediate 12** as white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 10.23 (s, 1H), 7.71-7.81 (m, 1H), 7.63-7.69 (m, 1H), 7.25-7.33 (m, 2H), 7.14-7.22 (m, 3H), 6.90 (d, *J*=2.05 Hz, 1H), 6.75 (d, *J*=8.20 Hz, 1H), 4.19 (t, *J*=6.59 Hz, 2H), 2.64-2.69 (m, 2H), 1.86-1.99 (m, 2H), 1.67-1.81 (m, 2H), 1.48-1.64 (m, 2H).

Intermediates 13 through 1**6** were prepared from **Intermediate 8** through **11**, in a similar manner to the procedure described in **Example 5** for **Intermediate 12**. The results are tabulated below in **Table 5**.

Table 5

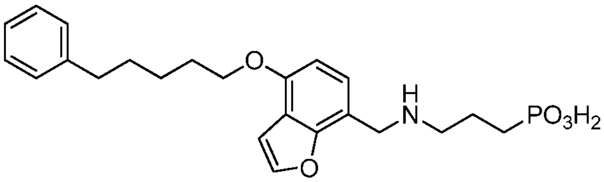
Interm. No.	**Structure IUPAC Name**	**Interm. No.**	**^{1}H NMR δ (ppm)**
13	 **7-((5-phenylpentyl)oxy)benzofuran-4-carbaldehyde**	**8**	^{1}H NMR (600 MHz, $CDCl_3$) δ: 10.04 (s, 1H), 7.77 (d, *J*=2.34 Hz, 1H), 7.66 (d, *J*=8.20 Hz, 1H), 7.53 (d, *J*=2.05 Hz, 1H), 7.24-7.33 (m, 2H), 7.13-7.23 (m, 3H), 6.88 (d, *J*=8.20 Hz, 1H), 4.28 (t, *J*=6.59 Hz, 2H), 2.65 (d, *J*=7.62 Hz, 2H), 1.90-2.02 (m, 2H), 1.67-1.80 (m, 2H), 1.54-1.65 (m, 2H)
14	 **7-((5-phenylpentyl)oxy)-2,3-dihydro-1H-indene-4-carbaldehyde**	**9**	^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.99 (s, 1H), 7.61 (s, 1H), 7.24-7.33 (m, 2H), 7.19 (s, 3H), 6.77 (s, 1H), 4.06 (t, *J*=6.45 Hz, 2H), 3.29 (t, *J*=7.62 Hz, 2H), 2.78-2.87 (m, 2H), 2.60-2.71 (m, 2H), 2.05-2.20 (m, 2H), 1.78-1.94 (m, 2H), 1.65-1.78 (m, 2H), 1.47-1.59 (m, 2H)
15	 **4-((5-(3-methoxyphenyl)pentyl)oxy)ben**	**10**	^{1}H NMR (600 MHz, $CDCl_3$) δ: 10.21 (s, 1H), 7.73 (d, *J*=8.51 Hz, 1H), 7.66 (d, *J*=2.35 Hz, 1H), 7.16-7.22 (m, 1H), 6.90 (d, *J*=2.35 Hz, 1H), 6.76-6.81 (m, 1H), 6.69-6.75 (m, 3H), 4.17 (s, 2H), 3.78 (s, 3H), 2.58-2.68 (m, 2H), 1.84-1.95 (m, 2H),

	zofuran-7-carbaldehyde		1.67-1.79 (m, 2H), 1.49-1.62 (m, 2H)
16	 **7-((5-(3-methoxyphenyl)pentyl)oxy)-2,3-dihydro-1H-indene-4-carbaldehyde**	**11**	^{1}H NMR (600 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.62 (d, *J*=8.51 Hz, 1H), 7.19 (dd, *J*=7.63, 8.80 Hz, 1H), 6.70-6.80 (m, 4H), 4.05 (t, *J*=6.46 Hz, 2H), 3.79 (s, 3H), 3.29 (t, *J*=7.48 Hz, 2H), 2.83 (t, *J*=7.63 Hz, 2H), 2.59-2.66 (m, 2H), 2.09-2.16 (m, 2H), 1.81-1.88 (m, 2H), 1.66-1.74 (m, 2H), 1.48-1.56 (m, 2H)

Example 6

Compound 1

{3-[({4-[(5-phenylpentyl)oxy]-1-benzofuran-7-yl}methyl)amino]propyl} phosphonic acid

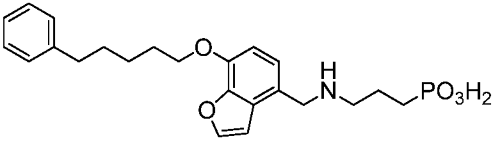
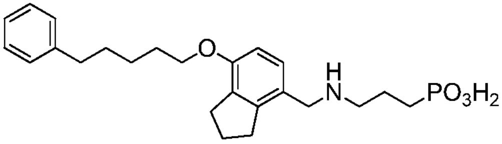
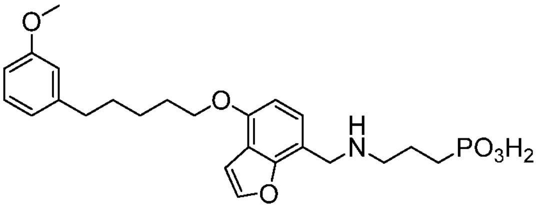


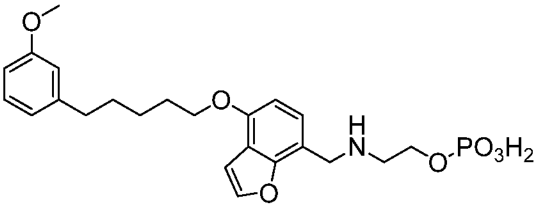
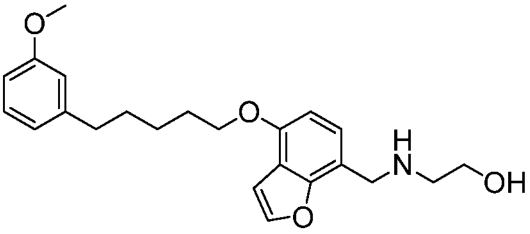
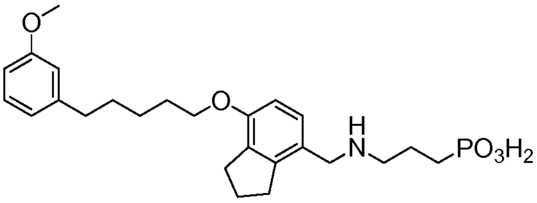
To a solution of **Intermediate 12** (296mg, 0.96mmol) and (3-aminopropyl) phosphonic acid (134mg, 0.96mmol) in methanol (10mL) was added tetrabutyl ammonium hydroxide (1M in MeOH, 0.96mL, 1.2mmol). The reaction mixture was heated at 50°C for 1h with stirring, then sodium borohydride (55mg, 1.44mmol) was added. The reaction mixture was stirred at rt for 3h. The mixture was concentrated and purified by MPLC (100% methanol) to give 278mg of **Compound 1** as colorless solid.

^{1}H NMR (600 MHz, CD_3OD) δ: 7.73-7.77 (m, 1H), 7.31-7.37 (m, 1H), 7.09-7.28 (m, 5H), 6.90-6.94 (m, 1H), 6.77-6.84 (m, 1H), 4.44 (s, 2H), 4.15 (s, 2H), 3.10-3.25 (m, 2H), 2.58-2.72 (m, 2H), 1.95-2.13 (m, 2H), 1.66-1.95 (m, 6H), 1.49-1.62 (m, 2H).

Compound 2 through **7** were prepared from **intermediates 13** through **16**, in a similar manner to the procedure described in **Example 6** for **Compound 1**. The results are tabulated below in **Table 6**.

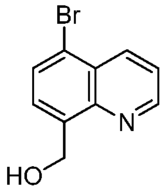
Table 6

Cmpd No.	Structure IUPAC Name	Interm. No.	^{1}H NMR δ (ppm)
2	 **{3-[({7-[(5-phenylpentyl)oxy]-1-benzofuran-4-yl}methyl)amino]propyl} phosphonic acid**	13	^{1}H NMR (600 MHz, CD_3OD) δ 7.85 (d, *J*=2.05 Hz, 1H), 7.10-7.32 (m, 6H), 7.08 (d, *J*=2.05 Hz, 1H), 6.93 (d, *J*=8.50 Hz, 1H), 4.39 (s, 2H), 4.15-4.26 (m, 2H), 3.12-3.24 (m, 2H), 2.58-2.72 (m, 2H), 2.01 (d, *J*=7.62 Hz, 2H), 1.65-1.96 (m, 6H), 1.50-1.64 (m, 2H)
3	 **{3-[({7-[(5-phenylpentyl)oxy]-2,3-dihydro-1H-inden-4-yl}methyl)amino] propyl}phosphonic acid**	14	^{1}H NMR (600 MHz, CD_3OD) δ 7.07-7.28 (m, 6H), 6.74-6.82 (m, 1H), 4.07-4.15 (m, 2H), 3.95-4.04 (m, 2H), 3.09-3.22 (m, 2H), 2.93-3.04 (m, 2H), 2.77-2.90 (m, 2H), 2.57-2.68 (m, 2H), 1.91-2.20 (m, 4H), 1.60-1.88 (m, 6H), 1.40-1.59 (m, 2H)
4	 **(3-{[(4-{[5-(3-methoxyphenyl)pentyl] oxy}-1-benzofuran-7-yl)methyl]amino} propyl)phosphonic acid**	15	^{1}H NMR (600 MHz, CD_3OD) δ 7.75 (d, *J*=2.35 Hz, 1H), 7.31-7.36 (m, 1H), 7.12-7.18 (m, 1H), 6.92 (d, *J*=2.35 Hz, 1H), 6.80 (d, *J*=8.22 Hz, 1H), 6.73-6.77 (m, 2H), 6.70-6.73 (m, 1H), 4.45 (s, 2H), 4.15 (t, *J*=6.31 Hz, 2H), 3.76 (s, 3H), 3.14-3.22 (m, 2H), 2.58-2.69 (m, 2H), 2.0-2.07 (m, 2H), 1.86-1.93 (m, 2H), 1.82 (td, *J*=7.74, 18.56 Hz, 2H), 1.72 (t, *J*=7.78 Hz, 2H), 1.52-

			1.60 (m, 2H)
5	 **2-{[(4-{[5-(3-methoxyphenyl)pentyl] oxy}-1-benzofuran-7-yl)methyl]amino} ethyl dihydrogen phosphate**	**15**	^{1}H NMR (600 MHz, CD_3OD) δ 7.75-7.77 (m, 1H), 7.34-7.38 (m, 1H), 7.12-7.18 (m, 1H), 6.92 (d, J=2.05 Hz, 1H), 6.79-6.84 (m, 1H), 6.73-6.77 (m, 2H), 6.70-6.73 (m, 1H), 4.51 (s, 2H), 4.27 (dd, J=2.20, 5.14 Hz, 2H), 4.16 (t, J=6.46 Hz, 2H), 3.76 (s, 3H), 3.36 (dd, J=4.70, 5.58 Hz, 2H), 2.63 (t, J=7.63 Hz, 2H), 1.85-1.93 (m, 2H), 1.72 (td, J=7.56, 15.41 Hz, 2H), 1.52-1.60 (m, 2H)
6	 **2-{[(4-{[5-(3-methoxyphenyl)pentyl] oxy}-1-benzofuran-7-yl)methyl] amino}ethanol**	**15**	^{1}H NMR (600 MHz, CD_3OD) δ 7.66 (d, J=2.35 Hz, 1H), 7.12-7.18 (m, 2H), 6.83 (d, J=2.35 Hz, 1H), 6.73-6.76 (m, 2H), 6.69-6.72 (m, 1H), 6.67 (d, J=8.22 Hz, 1H), 4.07-4.10 (m, 2H), 4.00 (s, 2H), 3.75 (s, 3H), 3.60-3.69 (m, 2H), 2.69-2.78 (m, 2H), 2.55-2.66 (m, 2H), 1.79-1.90 (m, 2H), 1.65-1.74 (m, 2H), 1.47-1.60 (m, 2H)
7	 **(3-{[(7-{[5-(3-methoxyphenyl)pentyl] oxy}-2,3-dihydro-1H-inden-4-yl) methyl]amino}propyl)phosphonic acid**	**16**	^{1}H NMR (600 MHz, CD_3OD) δ 7.18-7.23 (m, 1H), 7.12-7.17 (m, 1H), 6.77-6.83 (m, 1H), 6.69-6.77 (m, 3H), 4.11 (s, 2H), 4.01 (t, J=6.31 Hz, 2H), 3.76 (s, 3H), 3.12-3.19 (m, 2H), 2.95-3.05 (m, 2H), 2.80-2.88 (m, 2H), 2.55-2.67 (m, 2H), 2.08-2.16 (m, 2H), 1.97-2.07 (m, 2H), 1.76-1.87 (m, 4H), 1.65-1.73 (m, 2H), 1.47-1.55 (m, 2H)

Example 7

Intermediate 17



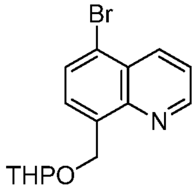
(5-bromoquinolin-8-yl)methanol

To a suspension of 5-bromoquinoline-8-carbaldehyde (CAS 885267-41-4) (10g, 42.4 mmol) in MeOH(50 mL) and THF (150 mL) at 0°C was added $NaBH_4$ (1.61g, 42.4 mmol). It became a clear solution after strring at 0°C for 30 min. The reaction mixture was quenched with NH_4Cl(sat) at 0°C, warmed up to rt and extracted with ethyl acetate. The organic layers were combined, washed with water, brine, dried over magnesium sulfate, and concentrated under reduced pressure to give 10g of **Intermediate 17** as yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.88-9.01 (m, 1H), 8.56-8.71 (m, 1H), 7.75-7.88 (m, 1H), 7.56-7.66 (m, 1H), 7.45-7.55 (m, 1H), 5.09-5.27 (m, 2H)

Example 8

Intermediate 18



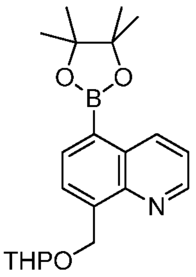
5-bromo-8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)quinolone

To **Intermediate 17** (4.67g, 19.6mmol) in methylene chloride (70mL) at rt was added Pyridinium p-Toluenesulfonate (492mg, 1.9mmol) and 3,4-Dihydropyran (3.6mL, 39.2mmol). The reaction mixture was stirred at rt for 16 hr. The mixture was diluted with water, extracted with methylene chloride. The organic layers were combined, washed with water, brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude material was purified by MPLC (20% ethyl acetate in hexanes) to afford 6.1 g of **Intermediate 18** as yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.90-9.00 (m, 1H), 8.50-8.60 (m, 1H), 7.81-7.89 (m, 1H), 7.71-7.81 (m, 1H), 7.48-7.57 (m, 1H), 5.36-5.51 (m, 1H), 5.18-5.33 (m, 1H), 4.83-4.98 (m, 1H), 3.90-4.03 (m, 1H), 3.51-3.64 (m, 1H), 1.88-1.99 (m, 1H), 1.79-1.86 (m, 1H), 1.71-1.78 (m, 1H), 1.53-1.69 (m, 3H)

Example 9

Intermediate 19



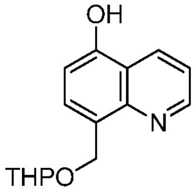
8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolineol

To a solution of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.45g, 13.6mmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (991mg, 1.21mmol) and potassium acetate(3.57g, 36.42mmol) in DMSO (80mL) was added **Intermediate 18** (3.91g, 12.1mmol). The mixture was stirred at 80°C for 16 hr. The reaction mixture was cooled to rt, diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with water, brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude material was purified by MPLC (20% ethyl acetate in hexanes) to afford 4.11 g of **Intermediate 19** as yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.04-9.18 (m, 1H), 8.82-8.92 (m, 1H), 8.10-8.19 (m, 1H), 7.85-7.92 (m, 1H), 7.40-7.50 (m, 1H), 5.47-5.53 (m, 1H), 5.31-5.40 (m, 1H), 4.85-4.92 (m, 1H), 3.93-4.02 (m, 1H), 3.51-3.60 (m, 1H), 1.91-2.01 (m, 1H), 1.71-1.86 (m, 2H), 1.53-1.67 (m, 3H), 1.42 (s, 12H).

Example 10

Intermediate 20



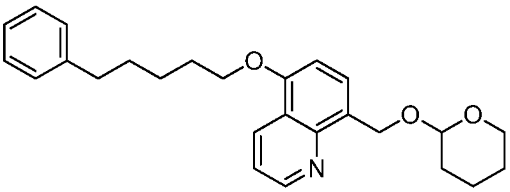
8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)quinolin-5-ol

To a solution of **Intermediate 19** (4.11g, 11.1mmol) in THF (80mL) at 0°C was added sodium hydroxide (3M, 10mL, 30mmol) and hydrogen peroxide (30%, 4.8mL). The mixture was stirred at at 0°C for 1 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with water, brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude material was purified by MPLC (25% ethyl acetate in hexanes) to afford 1.68 g of **Intermediate 20** as yellow solid.

^{1}H NMR (600 MHz, CDCl$_3$) δ 8.87-8.97 (m, 1H), 8.53-8.63 (m, 1H), 7.58-7.64 (m, 1H), 7.35-7.41 (m, 1H), 6.83 (d, *J*=7.92 Hz, 1H), 5.31-5.38 (m, 1H), 5.17-5.25 (m, 1H), 4.83-4.89 (m, 1H), 3.97-4.03 (m, 1H), 3.52-3.60 (m, 1H), 1.83-1.93 (m, 1H), 1.73-1.82 (m, 1H), 1.48-1.71 (m, 4H)

Example 11

Intermediate 21



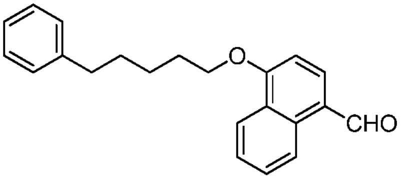
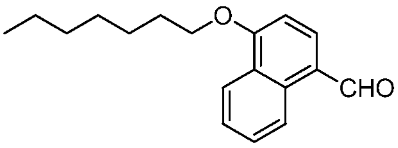
5-((5-phenylpentyl)oxy)-8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)quinoline

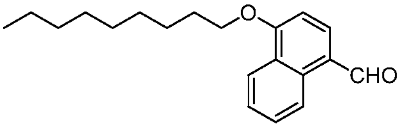
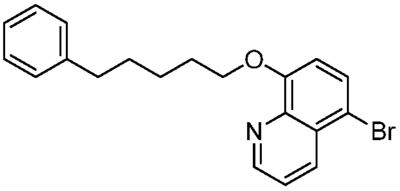
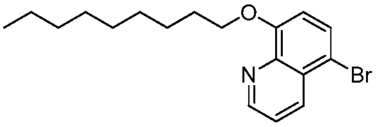
To the solution of **intermediate 20 (**440mg, 1.7mmol) and (5-bromopentyl)benzene (579mg, 2.55mmol) (CAS 14469-83-1) in DMSO (15mL) was added K_2CO_3 (938g, 6.8mmol). After stirring at rt for 16 h the mixture was diluted with water, extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude material was purified by MPLC (30% ethyl acetate in hexanes) to afford 506mg of **Intermediate 21** as colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.87-8.99 (m, 1H), 8.50-8.62 (m, 1H), 7.65-7.78 (m, 1H), 7.34-7.41 (m, 1H), 7.24-7.32 (m, 2H), 7.15-7.23 (m, 3H), 6.80-6.85 (m, 1H), 5.30-5.40 (m, 1H), 5.15-5.26 (m, 1H), 4.83-4.91 (m, 1H), 4.06-4.19 (m, 2H), 3.93-4.05 (m, 1H), 3.50-3.64 (m, 1H), 2.62-2.74 (m, 2H), 1.88-2.02 (m, 3H), 1.68-1.85 (m, 4H), 1.48-1.66 (m, 5H)

Intermediates 22 through **26** were prepared from 4-hydroxy-1-naphthaldehyde(CAS 7770-45-8) and 5-bromoquinolin-8-ol (CAS 1198-14-7) , in a similar manner to the procedure described in **Example 11** for **Intermediate 21**. The results are tabulated below in **Table 7**.

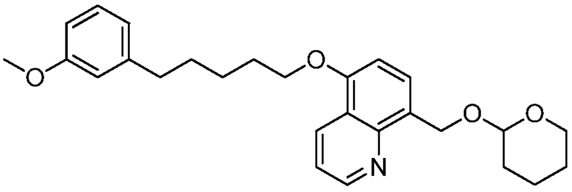
Table 7

Interm. No.	**Structure IUPAC Name**	**^{1}H NMR δ (ppm)**
22	 **4-((5-phenylpentyl)oxy)-1-naphthaldehyde**	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.11 (s, 1H), 9.20-9.36 (m, 1H), 8.19-8.33 (m, 1H), 7.70-7.81 (m, 1H), 7.59-7.67 (m, 1H), 7.46-7.53 (m, 1H), 7.22-7.29 (m, 2H), 7.12-7.20 (m, 3H), 6.69-6.75 (m, 1H), 4.00-4.17 (m, 2H), 2.55-2.72 (m, 2H), 1.83-1.96 (m, 2H), 1.64-1.77 (m, 2H), 1.47-1.61 (m, 2H)
23	 **4-(heptyloxy)-1-naphthaldehyde**	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.17 (s, 1H), 9.23-9.38 (m, 1H), 8.26-8.42 (m, 1H), 7.80-7.92 (m, 1H), 7.64-7.71 (m, 1H), 7.52-7.58 (m, 1H), 6.82-6.89 (m, 1H), 4.13-4.26 (m, 2H), 1.87-2.03 (m, 2H), 1.52-1.60 (m, 2H), 1.37-1.45 (m, 2H), 1.23-1.36 (m, 4H), 0.89 (s, 3H)

24	 **4-(nonyloxy)-1-naphthaldehyde**	^{1}H NMR (600 MHz, CDCl$_3$) δ 10.19 (s, 1H), 9.21-9.38 (m, 1H), 8.32-8.37 (m, 1H), 7.86-7.90 (m, 1H), 7.65-7.71 (m, 1H), 7.53-7.59 (m, 1H), 6.84-6.91 (m, 1H), 4.18-4.28 (m, 2H), 3.32-3.46 (m, 2H), 1.92-2.00 (m, 2H), 1.79-1.87 (m, 2H), 1.52-1.61 (m, 2H), 1.37-1.46 (m, 4H), 1.22-1.36 (m, 2H), 0.84-0.92 (m, 3H)
25	 **5-bromo-8-((5-phenylpentyl)oxy)quinoline**	^{1}H NMR (600 MHz, CDCl$_3$) δ 8.94-9.04 (m, 1H), 8.44-8.58 (m, 1H), 7.66-7.77 (m, 1H), 7.48-7.60 (m, 1H), 7.23-7.31 (m, 2H), 7.13-7.21 (m, 3H), 6.90-6.96 (m, 1H), 4.10-4.29 (m, 2H), 2.59-2.74 (m, 2H), 1.92-2.15 (m, 2H), 1.67-1.81 (m, 2H), 1.51-1.64 (m, 2H)
26	 **5-bromo-8-(nonyloxy)quinoline**	^{1}H NMR (600 MHz, CDCl$_3$) δ 8.92-9.07 (m, 1H), 8.44-8.57 (m, 1H), 7.65-7.76 (m, 1H), 7.48-7.59 (m, 1H), 6.88-7.01 (m, 1H), 4.15-4.29 (m, 2H), 1.96-2.11 (m, 2H), 1.46-1.58 (m, 2H), 1.19-1.42 (m, 10H), 0.77-0.94 (m, 3H)

Example 12

Intermediate 27



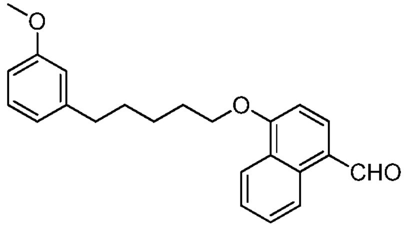
5-((5-(3-methoxyphenyl)pentyl)oxy)-8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)quinolone

To a solution of **intermediate 20** (865mg, 3.3mmol), 5-(3-methoxyphenyl)pentan-1-ol (CAS 66004-20-4) (648mg, 3.3mmom) and triphenylphosphine (964mg, 3.7mmol) in THF(15mL) was added diisopropyl azodicarboxylate (0.73mL, 3.7mmol). The mixture was stirred at rt for 16 hr before concentration. Purification by MPLC (30% ethyl acetate in hexanes) to afford 487mg of **Intermediate 27** as colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.88-8.98 (m, 1H), 8.52-8.62 (m, 1H), 7.72 (d, *J*=7.92 Hz, 1H), 7.31-7.44 (m, 1H), 7.15-7.22 (m, 1H), 6.81-6.84 (m, 1H), 6.77-6.80 (m, 1H), 6.72-6.76 (m, 2H), 5.32-5.40 (m, 1H), 5.16-5.25 (m, 1H), 4.84-4.91 (m, 1H), 4.09-4.18 (m, 2H), 3.97-4.05 (m, 1H), 3.79 (s, 3H), 3.53-3.61 (m, 1H), 2.61-2.70 (m, 2H), 1.87-1.99 (m, 3H), 1.67-1.81 (m, 4H), 1.50-1.66 (m, 5H)

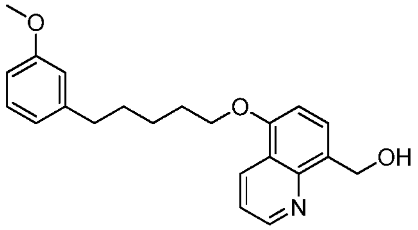
Intermediates 28 was prepared from 4-hydroxy-1-naphthaldehyde(CAS 7770-45-8) in a similar manner to the procedure described in **Example 12** for **Intermediate 27**. The results are tabulated below in **Table 8**.

Table 8

Interm. No.	**Structure IUPAC Name**	**^{1}H NMR δ (ppm)**
28	 **4-((5-(3-methoxyphenyl)pentyl)oxy)-1-naphthaldehyde**	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.16 (s, 1H), 9.23-9.35 (m, 1H), 8.22-8.35 (m, 1H), 7.79-7.88 (m, 1H), 7.61-7.72 (m, 1H), 7.47-7.59 (m, 1H), 7.12-7.25 (m, 1H), 6.68-6.87 (m, 4H), 4.17 (s, 2H), 3.77 (s, 3H), 2.59-2.72 (m, 2H), 1.88-2.06 (m, 2H), 1.67-1.83 (m, 2H), 1.52-1.67 (m, 2H)

Example 13

Intermediate 29



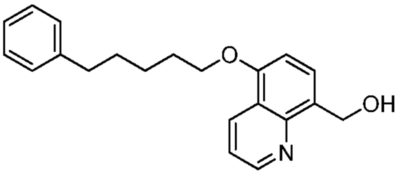
(5-((5-(3-methoxyphenyl)pentyl)oxy)quinolin-8-yl)methanol

To **Intermediate 28** (1.19g, 2.73mmol) in MeOH (26mL) was added Pyridinium p-Toluenesulfonate (69mg, 0.27mmol). The mixture was stirred at 50 °C for 24 hr. The reaction mixture was cooled to rt and concentrated. Purification by MPLC (20% ethyl acetate in hexanes)to afford 355mg of **Intermediate 29** as yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78-8.86 (m, 1H), 8.52-8.60 (m, 1H), 7.42-7.45 (m, 1H), 7.34-7.38 (m, 1H), 7.16-7.21 (m, 1H), 6.76-6.80 (m, 1H), 6.69-6.75 (m, 3H), 5.03-5.16 (m, 2H), 4.02-4.15 (m, 2H), 3.76 (s, 3H), 2.56-2.70 (m, 2H), 1.85-1.98 (m, 2H), 1.67-1.79 (m, 2H), 1.49-1.64 (m, 2H).

Intermediate 30 was prepared from **Intermediate 21**, in a similar manner to the procedure described in **Example 13** for **Intermediate 29**. The results are tabulated below in **Table 9**.

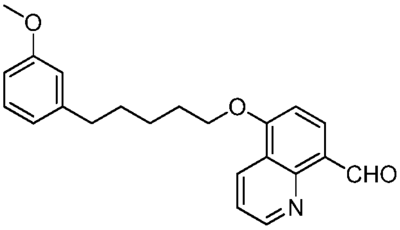
Table 9

Interm. No.	Structure IUPAC Name	^{1}H NMR δ (ppm)
30	 **(5-((5-phenylpentyl)oxy)**	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.82-8.92 (m, 1H), 8.53-8.65 (m, 1H), 7.36-7.53 (m, 2H), 7.24-7.33 (m, 2H), 7.15-7.22 (m, 3H), 6.72-6.79 (m, 1H), 5.10 (s, 2H), 4.05-4.23 (m, 2H), 2.60-2.77 (m, 2H), 1.86-2.02 (m, 2H),

	quinolin-8-yl)methanol	1.69-1.83 (m, 2H), 1.53-1.67 (m, 2H)

Example 14

Intermediate 31



5-((5-(3-methoxyphenyl)pentyl)oxy)quinoline-8-carbaldehyde

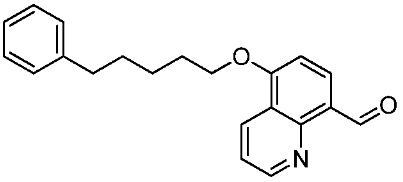
To a solution of **Intermediate 29** (355mg , 1.01mmol) in methylene chloride at rt under argon was added MnO_2 (1.8g, 20.8mmol). The mixture was stirred at rt for 4 hr and then filtered through a pad of celite and washed with methylene chloride. The mixture was concentrated. Purification by MPLC (20% ethyl acetate in hexanes)to afford 298mg of **Intermediate 31** as white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 11.26 (s, 1H), 8.96-9.06 (m, 1H), 8.53-8.64 (m, 1H), 8.26-8.36 (m, 1H), 7.38-7.51 (m, 1H), 7.16-7.23 (m, 1H), 6.89-6.97 (m, 1H), 6.77-6.81 (m, 1H), 6.72-6.76 (m, 2H), 4.18-4.27 (m, 2H), 3.79 (s, 3H), 2.61-2.70 (m, 2H), 1.94-2.03 (m, 2H), 1.71-1.81 (m, 2H), 1.55-1.65 (m, 2H).

Intermediate 32 was prepared from **Intermediate 30**, in a similar manner to the procedure described in **Example 14** for **Intermediate 31**. The results are tabulated below in **Table 10**.

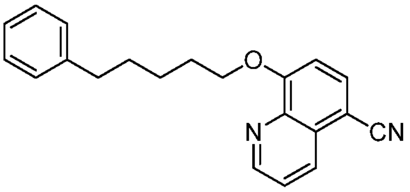
Table 10

Interm.	Structure	^{1}H NMR δ (ppm)

No.	IUPAC Name	
32	 **5-((5-phenylpentyl)oxy) quinoline-8-carbaldehyde**	^{1}H NMR (600 MHz, $CDCl_3$) δ 11.26 (s, 1H), 8.97-9.10 (m, 1H), 8.53-8.69 (m, 1H), 8.25-8.40 (m, 1H), 7.41-7.55 (m, 1H), 7.25-7.33 (m, 2H), 7.15-7.23 (m, 3H), 6.93-6.98 (m, 1H), 4.19-4.31 (m, 2H), 2.61-2.77 (m, 2H), 1.92-2.03 (m, 2H), 1.70-1.84 (m, 2H), 1.54-1.68 (m, 2H)

Example 15

Intermediate 33



8-((5-phenylpentyl)oxy)quinoline-5-carbonitrile

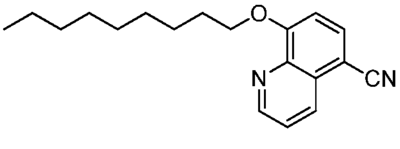
To **Intermediate 25** (825mg, 2.22mmol), sodium cyanide(219mg, 4.46mmol) and 1,5-Bis(diphenylphosphino)pentane (196mg, 0.44mmol) in mesitylene (12mL) was added tetramethylethylenediamine(0.5mL, 3.34mmol) and Palladium(**II**) acetate (25mg, 0.11mmol). The mixture was bubbled for 10 min with argon and heated at 170 °C for 16 hrs. The mixture was cooled to rt and degased water was added and the resulting mixture was stirred for 10 min. Phases were separated and aqueous phase was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude material was purified by MPLC (40% ethyl acetate in hexanes) to afford 418mg of **Intermediate 33** as colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.98-9.09 (m, 1H), 8.44-8.52 (m, 1H), 7.83-7.95 (m, 1H), 7.56-7.66 (m, 1H), 7.22-7.32 (m, 2H), 7.18 (s, 3H), 7.03-7.07 (m, 1H), 4.19-

4.35 (m, 2H), 2.59-2.74 (m, 2H), 2.00-2.16 (m, 2H), 1.68-1.85 (m, 2H), 1.51-1.66 (m, 2H)

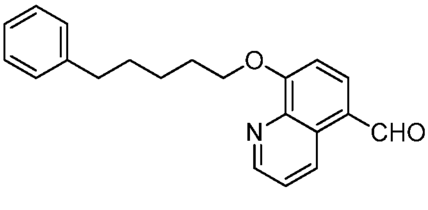
Intermediates 34 was prepared from **Intermediate 26**, in a similar manner to the procedure described in **Example 15** for **Intermediate 33**. The results are tabulated below in **Table 11**.

Table 11

Interm. No.	**Structure IUPAC Name**	**^{1}H NMR δ (ppm)**
34	 **8-(nonyloxy)quinoline-5-carbonitrile**	^{1}H NMR (600 MHz, $CDCl_3$) δ 9.01-9.11 (m, 1H), 8.45-8.58 (m, 1H), 7.86-7.99 (m, 1H), 7.58-7.70 (m, 1H), 7.00-7.13 (m, 1H), 4.25-4.38 (m, 2H), 1.99-2.11 (m, 2H), 1.48-1.61 (m, 2H), 1.19-1.45 (m, 10H), 0.81-0.93 (m, 3H)

Example 16

Intermediate 35



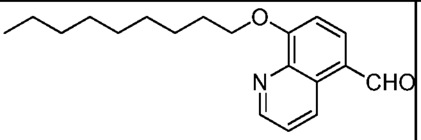
8-((5-phenylpentyl)oxy)quinoline-5-carbaldehyde

To **Intermediate 33** (418mg, 1.32mmol) in methylene chloride (10mL)at -78°C was added DiBAL(1.6mL, 1.6mmol) and stirred at -78°C for 2 hrs. The reaction was quenched with methanol at -78°C and warmed up to rt. HCl(10%) was added and stirred ar rt for 10 min. Phases were separated and aqueous phase was extracted with methylene chloride. The organic layers were combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude material was purified by MPLC (40% ethyl acetate in hexanes) to afford 113mg of **Intermediate 35** as colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.16 (s, 1H), 9.65-9.71 (m, 1H), 9.00-9.04 (m, 1H), 7.93-7.99 (m, 1H), 7.58-7.63 (m, 1H), 7.24-7.30 (m, 2H), 7.15-7.21 (m, 3H), 7.10-7.15 (m, 1H), 4.31-4.37 (m, 2H), 2.62-2.72 (m, 2H), 2.05-2.15 (m, 2H), 1.69-1.80 (m, 2H), 1.53-1.65 (m, 2H)

Intermediate 36 was prepared from **Intermediate 34**, in a similar manner to the procedure described in **Example 16** for **Intermediate 35**. The results are tabulated below in **Table 12**.

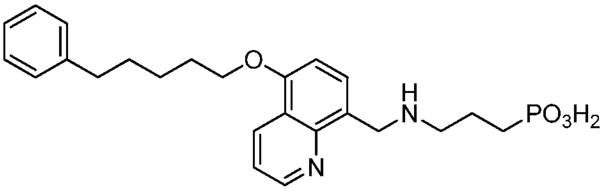
Table 12

Interm. No.	**Structure** **IUPAC Name**	**^{1}H NMR δ (ppm)**
36	 **8-(nonyloxy)quinoline-5-carbaldehyde**	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.16 (s, 1H), 9.62-9.74 (m, 1H), 9.01-9.04 (m, 1H), 7.97 (d, *J*=7.92 Hz, 1H), 7.58-7.63 (m, 1H), 7.13-7.18 (m, 1H), 4.31-4.40 (m, 2H), 1.99-2.13 (m, 2H), 1.48-1.61 (m, 2H), 1.20-1.45 (m, 10H), 0.80-0.94 (m, 3H)

Example 17

Compound 8

{3-[({5-[(5-phenylpentyl)oxy]quinolin-8-yl}methyl)amino]propyl}phosphonic acid

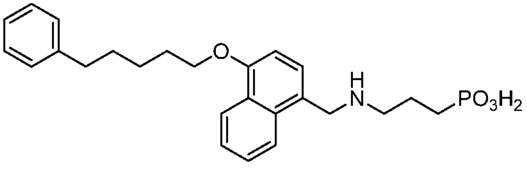


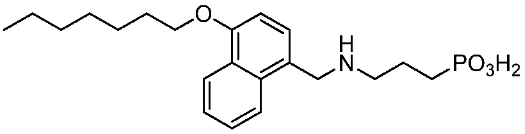
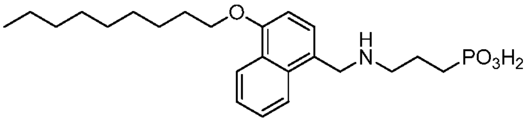
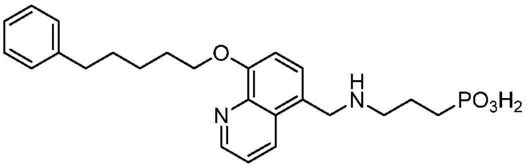
To a solution of **Intermediate 32** (90mg, 0.28mmol) and (3-aminopropyl)phosphonic acid (39mg, 0.28mmol) in methanol (10mL) was added tetrabutylammonium hydroxide (1M in MeOH, 0.28mL, 0.28mmol). The reaction mixture was heated at 50°C for 1h with stirring, then sodium cyanoborohydride (16mg, 0.42mmol) was added. The reaction mixture was stirred at rt for 3h. The mixture was concentrated and purified by MPLC (100% methanol) to give 103mg of **Compound 8** as colorless solid.

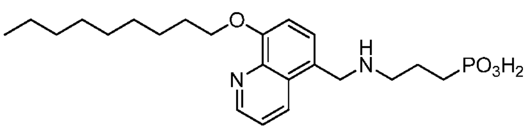
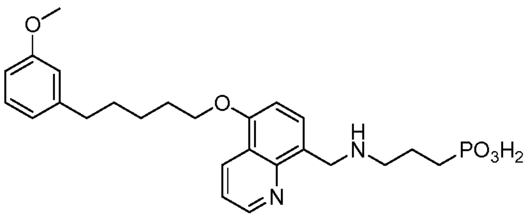
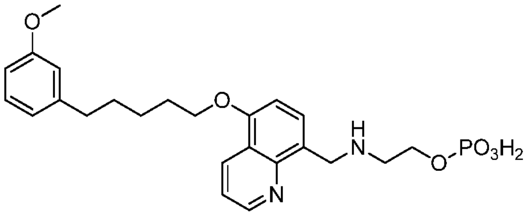
^{1}H NMR (600 MHz, CD_3OD) δ 9.06-9.14 (m, 1H), 8.85-8.94 (m, 1H), 7.90-7.97 (m, 1H), 7.70-7.78 (m, 1H), 7.21-7.25 (m, 2H), 7.16-7.20 (m, 2H), 7.11-7.16 (m, 2H), 4.72 (s, 2H), 4.21-4.29 (m, 2H), 3.26-3.31 (m, 2H), 2.62-2.71 (m, 2H), 2.04-2.16 (m, 2H), 1.94-2.02 (m, 2H), 1.82-1.92 (m, 2H), 1.71-1.81 (m, 2H), 1.55-1.67 (m, 2H)

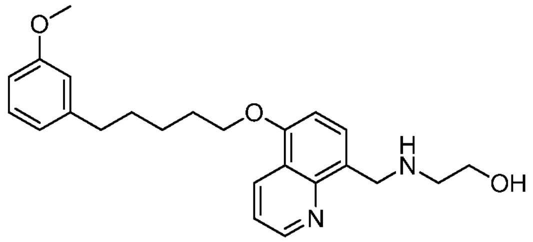
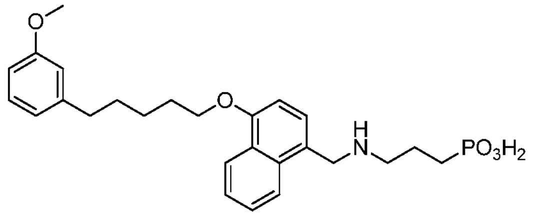
Compounds 9 through **17** were prepared from the corresponding intermediates, in a similar manner to the procedure described in **Example 17** for **Compound 8**. The results are tabulated below in **Table 13**.

Table 13

Cmpd No.	**Structure IUPAC Name**	**Interm. No.**	**^{1}H NMR δ (ppm)**
9	 **{3-[({4-[(5-phenylpentyl)oxy] naphthalen-1-yl}methyl) amino]propyl}phosphonic acid**	**22**	^{1}H NMR (600 MHz, CD_3OD) δ 8.29-8.35 (m, 1H), 8.04-8.10 (m, 1H), 7.65-7.72 (m, 1H), 7.52-7.61 (m, 2H), 7.21-7.27 (m, 2H), 7.17-7.20 (m, 2H), 7.12-7.16 (m, 1H), 6.92-6.96 (m, 1H), 4.62 (s, 2H), 4.14-4.28 (m, 2H), 3.21-

			3.30 (m, 2H), 2.64-2.71 (m, 2H), 2.01-2.11 (m, 2H), 1.95-2.01 (m, 2H), 1.80-1.88 (m, 2H), 1.73-1.80 (m, 2H), 1.59-1.67 (m, 2H)
10	 **[3-({[4-(heptyloxy)naphthalen-1-yl]methyl}amino)propyl]phosphonic acid**	23	^{1}H NMR (600 MHz, CD_3OD) δ 8.34-8.40 (m, 1H), 8.03-8.12 (m, 1H), 7.64-7.73 (m, 1H), 7.53-7.62 (m, 2H), 6.91-6.99 (m, 1H), 4.62 (s, 2H), 4.14-4.28 (m, 2H), 3.22-3.30 (m, 2H), 2.00-2.11 (m, 2H), 1.92-1.99 (m, 2H), 1.78-1.90 (m, 2H), 1.55-1.64 (m, 2H), 1.42-1.50 (m, 2H), 1.32-1.40 (m, 4H), 0.88-0.96 (m, 3H)
11	 **[3-({[4-(nonyloxy)naphthalen-1-yl]methyl}amino)propyl]phosphonic acid**	23	^{1}H NMR (600 MHz, CD_3OD) δ 8.31-8.45 (m, 1H), 8.01-8.13 (m, 1H), 7.63-7.71 (m, 1H), 7.53-7.62 (m, 2H), 6.88-6.99 (m, 1H), 4.62 (s, 2H), 4.12-4.30 (m, 2H), 3.19-3.31 (m, 2H), 2.01-2.16 (m, 2H), 1.91-2.00 (m, 2H), 1.80-1.90 (m, 2H), 1.54-1.66 (m, 2H), 1.42-1.51 (m, 2H), 1.25-1.40 (m, 8H), 0.85-0.95 (m, 3H)
12	 **{3-[({8-[(5-phenylpentyl)oxy] quinolin-5-yl}methyl) amino]propyl}phosphonic acid**	35	^{1}H NMR (600 MHz, CD_3OD) δ 8.84-8.91 (m, 1H), 8.61-8.69 (m, 1H), 7.64-7.75 (m, 2H), 7.05-7.32 (m, 6H), 4.47-4.56 (m, 2H), 4.18-4.31 (m, 2H), 3.10-3.21 (m, 2H), 2.60-2.70 (m, 2H), 1.92-2.06 (m, 4H), 1.65-1.79 (m, 4H), 1.56-1.64 (m, 2H)

13	 **[3-({[8-(nonyloxy)quinolin-5-yl] methyl}amino)propyl]phosphonic acid**	36	^{1}H NMR (600 MHz, CD_3OD) δ 9.48-9.59 (m, 1H), 9.14-9.24 (m, 1H), 8.21-8.31 (m, 1H), 8.05-8.15 (m, 1H), 7.64-7.76 (m, 1H), 4.80 (s, 2H), 4.41-4.51 (m, 2H), 3.34-3.38 (m, 2H), 2.01-2.16 (m, 4H), 1.84-1.94 (m, 2H), 1.56-1.66 (m, 2H), 1.42-1.50 (m, 2H), 1.25-1.41 (m, 8H), 0.86-0.93 (m, 3H)
14	 **(3-{[(5-{[5-(3-methoxyphenyl)pentyl] oxy}quinolin-8-yl)methyl]amino} propyl) phosphonic acid**	31	^{1}H NMR (600 MHz, CD_3OD) δ 8.95-9.02 (m, 1H), 8.61-8.71 (m, 1H), 7.74-7.83 (m, 1H), 7.55-7.64 (m, 1H), 7.09-7.20 (m, 1H), 6.98-7.06 (m, 1H), 6.65-6.80 (m, 3H), 4.67 (s, 2H), 4.18-4.29 (m, 2H), 3.74 (s, 3H), 3.16-3.24 (m, 2H), 2.60-2.70 (m, 2H), 2.02-2.11 (m, 2H), 1.94-2.01 (m, 2H), 1.79-1.87 (m, 2H), 1.72-1.79 (m, 2H), 1.57-1.64 (m, 2H)
15	 **2-{[(5-{[5-(3-methoxyphenyl)pentyl] oxy} quinolin-8-yl)methyl]amino} ethyl dihydrogen phosphate**	31	^{1}H NMR (600 MHz, CD_3OD) δ 8.90-9.03 (m, 1H), 8.57-8.65 (m, 1H), 7.74-7.84 (m, 1H), 7.50-7.59 (m, 1H), 7.09-7.19 (m, 1H), 6.95-7.04 (m, 1H), 6.67-6.81 (m, 3H), 4.68 (s, 2H), 4.17-4.24 (m, 2H), 4.06-4.16 (m, 2H), 3.74 (s, 3H), 3.23-3.28 (m, 2H), 2.60-2.68 (m, 2H), 1.92-2.01 (m, 2H), 1.71-1.80 (m, 2H), 1.56-1.66 (m, 2H)

16	 **2-{[(5-{[5-(3-methoxyphenyl)pentyl] oxy}quinolin-8-yl)methyl]amino} ethanol**	**31**	^{1}H NMR (600 MHz, CD_3OD) δ 8.83-8.89 (m, 1H), 8.50-8.59 (m, 1H), 7.54-7.62 (m, 1H), 7.40-7.48 (m, 1H), 7.09-7.18 (m, 1H), 6.86-6.94 (m, 1H), 6.66-6.80 (m, 3H), 4.20-4.25 (m, 2H), 4.12-4.19 (m, 2H), 3.74 (s, 3H), 3.63-3.69 (m, 2H), 2.70-2.77 (m, 2H), 2.60-2.67 (m, 2H), 1.89-1.99 (m, 2H), 1.69-1.78 (m, 2H), 1.53-1.65 (m, 2H)
17	 **(3-{[(4-{[5-(3-methoxyphenyl)pentyl] oxy}naphthalen-1-yl)methyl]amino} propyl) phosphonic acid**	**28**	^{1}H NMR (600 MHz, CD_3OD) δ 8.27-8.37 (m, 1H), 8.03-8.11 (m, 1H), 7.64-7.72 (m, 1H), 7.52-7.61 (m, 2H), 7.11-7.20 (m, 1H), 6.89-6.97 (m, 1H), 6.67-6.80 (m, 3H), 4.62 (s, 2H), 4.15-4.25 (m, 2H), 3.75 (s, 3H), 3.22-3.29 (m, 2H), 2.62-2.69 (m, 2H), 2.01-2.11 (m, 2H), 1.94-2.01 (m, 2H), 1.80-1.87 (m, 2H), 1.73-1.80 (m, 2H), 1.59-1.67 (m, 2H)

Example 18

Biological Data

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.

GTP γ^{35}S binding was measured in the medium containing (mM) HEPES 25, pH 7.4, $MgCl_2$ 10, NaCl 100, dithiothreitol 0.5, digitonin 0.003%, 0.2 nM GTP γ^{35}S, and

5 µg membrane protein in a volume of 150 µl. Test compounds were included in the concentration range from 0.08 to 5,000 nM unless indicated otherwise. Membranes were incubated with 100 µM 5'-adenylyl immido diphosphate for 30 min, and subsequently with 10 µM GDP for 10 min on ice. Drug solutions and membrane were mixed, and then reactions were initiated by adding GTP $\gamma^{35}S$ and continued for 30 min at 25 °C. Reaction mixtures were filtered over Whatman GF/B filters under vacuum, and washed three times with 3 mL of ice-cold buffer (HEPES 25, pH7.4, $MgCl_2$ 10 and NaCl 100). Filters were dried and mixed with scintillant, and counted for ^{35}S activity using a β-counter. Agonist-induced GTP $\gamma^{35}S$ 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 S1P1 in the presence of test antagonist at concentrations ranging from 0.08 to 5000 nM.

Table 14 shows activity potency: S1P1 receptor from GTP $\gamma^{35}S$: nM, (EC_{50})

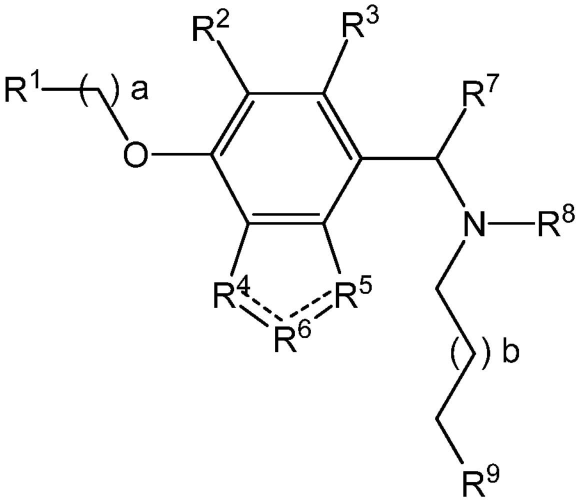
Table 14

IUPAC name	**S1P1 EC_{50} (nM)**
{3-[({4-[(5-phenylpentyl)oxy]-1-benzofuran-7-yl}methyl)amino]propyl} phosphonic acid	2.96
{3-[({7-[(5-phenylpentyl)oxy]-1-benzofuran-4-yl}methyl)amino]propyl} phosphonic acid	2.58
{3-[({7-[(5-phenylpentyl)oxy]-2,3-dihydro-1H-inden-4-yl}methyl)amino] propyl}phosphonic acid	2.45
(3-{[(4-{[5-(3-methoxyphenyl)pentyl] oxy}-1-benzofuran-7-yl)methyl]amino} propyl)phosphonic acid	210.77
2-{[(4-{[5-(3-methoxyphenyl)pentyl] oxy}-1-benzofuran-7-yl)methyl]amino} ethyl dihydrogen phosphate	976.53
(3-{[(7-{[5-(3-methoxyphenyl)pentyl] oxy}-2,3-dihydro-1H-inden-4-yl) methyl]amino}propyl)phosphonic acid	113.14
{3-[({4-[(5-phenylpentyl)oxy]-1-naphthyl}methyl)amino]propyl}phosphonic acid	3.66

[3-({[4-(heptyloxy)-1-naphthyl]methyl}amino)propyl] phosphonic acid	771.34
[3-({[4-(nonyloxy)-1-naphthyl]methyl}amino)propyl] phosphonic acid	63.38
[3-({[8-(nonyloxy)quinolin-5-yl]methyl}amino)propyl]phosphonic acid	1216.09
{3-[({5-[(5-phenylpentyl)oxy]quinolin-8-yl}methyl)amino]propyl}phosphonic acid	0.76
(3-{[(4-{[5-(3-methoxyphenyl)pentyl]oxy}-1-naphthyl)methyl]amino}propyl)phosphonic acid	34.44
(3-{[(5-{[5-(3-methoxyphenyl)pentyl]oxy}quinolin-8-yl)methyl]amino}propyl)phosphonic acid	7.09
2-{[(5-{[5-(3-methoxyphenyl)pentyl]oxy}quinolin-8-yl)methyl]amino}ethyl dihydrogen phosphate	84.82
2-{[(5-{[5-(3-methoxyphenyl)pentyl]oxy}quinolin-8-yl)methyl]amino}ethanol	627.03

What is claimed is:

1. A compound having represented by **Formula I,** its enantiomers, its diastereoisomers, its tautomers, or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

R^1 is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted $_{5\text{-}8}$ cycloalkyl, substituted or unsubstituted $C_{5\text{-}8}$ cycloalkenyl or hydrogen;

R^2 is hydrogen, halogen, substituted or unsubstituted $C_{1\text{-}6}$ alkyl, $C(O)R^{10}$ or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted $C_{1\text{-}6}$ alkyl, $C(O)R^{10}$ or hydroxyl;

R^4 is CH, S, O, N, NH or CH_2;

R^5 is CH, S, O, N, NH or CH_2;

R^6 is CH, S, O, NH or CH_2;

R^7 is H, halogen, $-OC_{1\text{-}6}$ alkyl, substituted or unsubstituted $C_{1\text{-}6}$ alkyl;

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

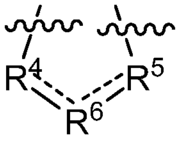
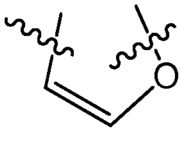
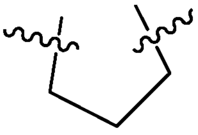
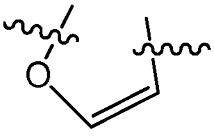
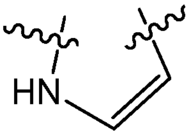
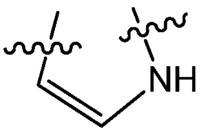
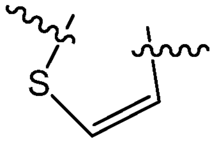
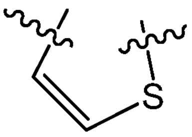
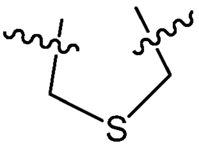
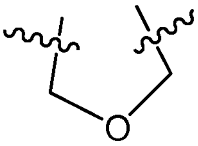
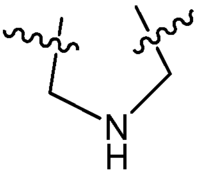
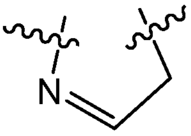
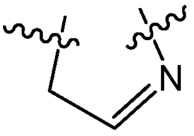
R^9 is OPO_3H_2, carboxylic acid, PO_3H_2, -P(O)MeOH, -P(O)(H)OH or OR^{11};

R^{10} is hydroxyl or substituted or unsubstituted $C_{1\text{-}6}$ alkyl;

R^{11} is H or substituted or unsubstituted $C_{1\text{-}6}$ alkyl;

a is 5, 6, 7 or 8;

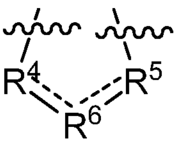
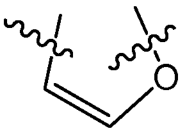
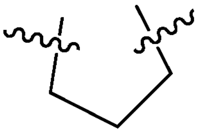
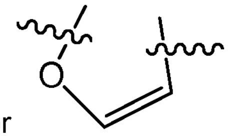
b is 0 or 1; and

with the proviso that  is , , , , , , , , , ,  or .

2. A compound according to claim 1, wherein:
R^7 is H.

3. A compound according to claim 1, wherein:
R^8 is H .

4. A compound according to claim 1, wherein:
R^9 is OPO_3H_2, PO_3H_2, or OR^{11}; and
R^{11} is H.

5. A compound according to claim 1, wherein:
 is ,  or .

6. A compound according to claim 1, selected from:
(3-{[(7-{[5-(3-methoxyphenyl)pentyl]oxy}-2,3-dihydro-1H-inden-4-yl)methyl] amino}propyl)phosphonic acid;
2-{[(4-{[5-(3-methoxyphenyl)pentyl]oxy}-1-benzofuran-7-yl)methyl]amino}ethanol;
2-{[(4-{[5-(3-methoxyphenyl)pentyl]oxy}-1-benzofuran-7-yl)methyl]amino}ethyl dihydrogen phosphate;
(3-{[(4-{[5-(3-methoxyphenyl)pentyl]oxy}-1-benzofuran-7-yl)methyl]amino} propyl)phosphonic acid;

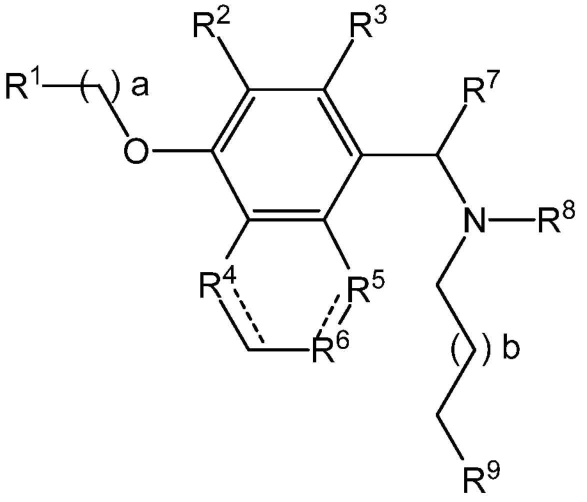
{3-[({7-[(5-phenylpentyl)oxy]-2,3-dihydro-1H-inden-4-yl}methyl)amino] propyl}phosphonic acid;

{3-[({4-[(5-phenylpentyl)oxy]-1-benzofuran-7-yl}methyl)amino]propyl}phosphonic acid; and

{3-[({7-[(5-phenylpentyl)oxy]-1-benzofuran-4-yl}methyl)amino]propyl}phosphonic acid.

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

8. A compound having represented by **Formula II**, its enantiomers, its diastereoisomers, its tautomers, or a pharmaceutically acceptable salt thereof:



Formula II

wherein:

R^1 is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted C $_{5-8}$ cycloalkyl, substituted or unsubstituted C $_{5-8}$ cycloalkenyl or hydrogen;

R^2 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl, $C(O)R^{10}$ or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl, $C(O)R^{10}$ or hydroxyl;

R^4 is CH, S, O, N, NH or CH_2;

R^5 is CH, S, O, N, NH or CH_2;

R^6 is CH or CH_2;

R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl;

R^8 is H or C_{1-3} alkyl;

R^9 is OPO_3H_2, carboxylic acid, PO_3H_2, -P(O)MeOH, -P(O)(H)OH or OR^{11};

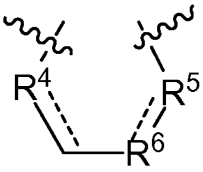
R^{10} is hydroxyl or substituted or unsubstituted C_{1-3} alkyl;

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

a is 5, 6, 7 or 8;

b is 0 or 1; and

with the proviso that



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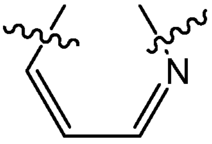

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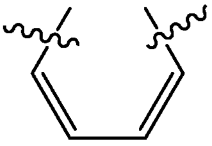
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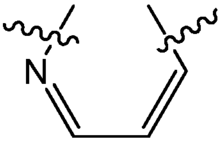

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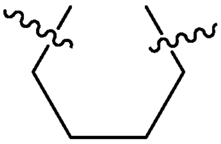
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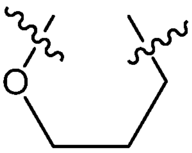

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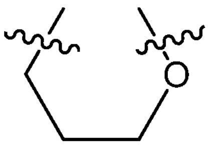

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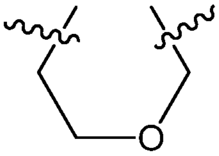

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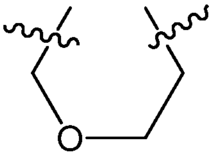

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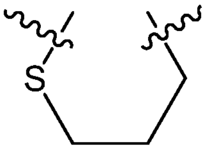

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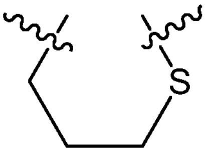

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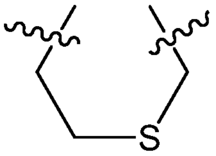

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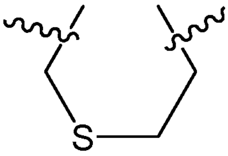

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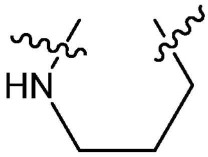

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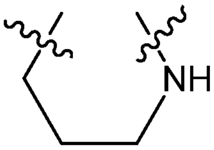

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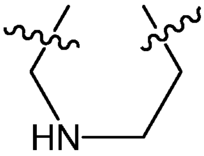

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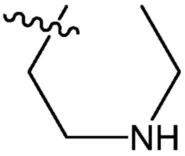

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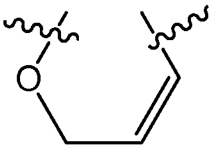

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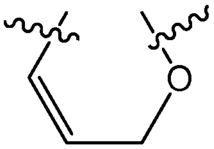
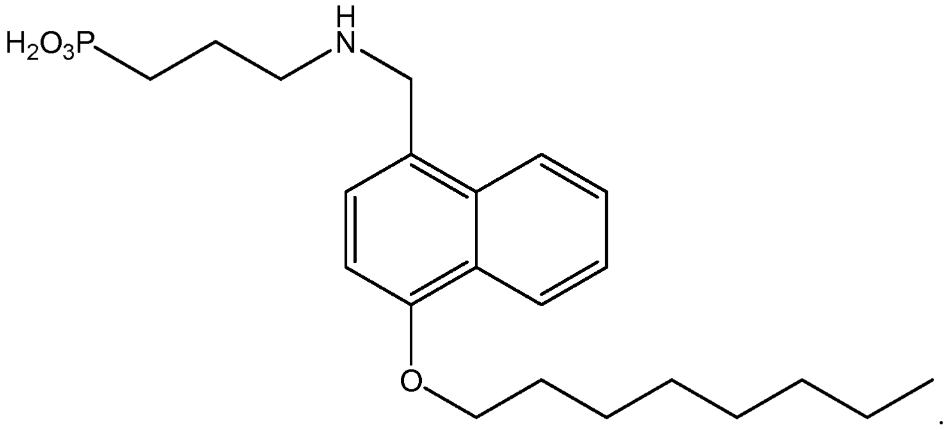


;

with the proviso that the compound of Formula I is not of structure:

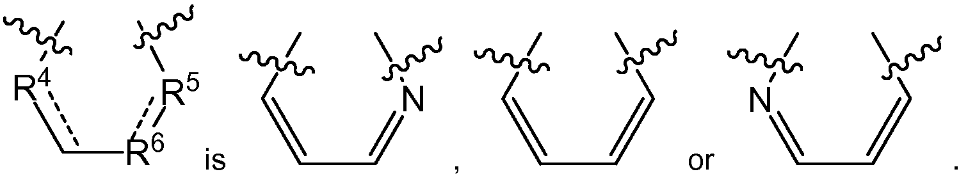


9. A compound according to claim 8, wherein:
R^7 is H.

10. A compound according to claim 8, wherein:
R^8 is H .

11. A compound according to claim 8, wherein:
R^9 is OPO_3H_2, PO_3H_2, or OR^{11}; and
R^{11} is H.

12. A compound according to claim 8, wherein:



13. A compound according to claim 8, selected from:
2-{[(5-{[5-(3-methoxyphenyl)pentyl]oxy}quinolin-8-yl)methyl]amino}ethanol;
2-{[(5-{[5-(3-methoxyphenyl)pentyl]oxy}quinolin-8-yl)methyl]amino}ethyl dihydrogen phosphate;
(3-{[(5-{[5-(3-methoxyphenyl)pentyl]oxy}quinolin-8-yl)methyl]amino}propyl)phosphonic acid;

(3-{[(4-{[5-(3-methoxyphenyl)pentyl]oxy}naphthalen-1-yl)methyl]amino}propyl) phosphonic acid;
{3-[({5-[(5-phenylpentyl)oxy]quinolin-8-yl}methyl)amino]propyl}phosphonic acid;
[3-({[8-(nonyloxy)quinolin-5-yl]methyl}amino)propyl]phosphonic acid;
[3-({[4-(nonyloxy)naphthalen-1-yl]methyl}amino)propyl]phosphonic acid;
[3-({[4-(heptyloxy)naphthalen-1-yl]methyl}amino)propyl]phosphonic acid;
{3-[({4-[(5-phenylpentyl)oxy]naphthalen-1-yl}methyl)amino]propyl}phosphonic acid; and
{3-[({8-[(5-phenylpentyl)oxy]quinolin-5-yl}methyl)amino]propyl}phosphonic acid.

14. A pharmaceutical composition comprising as active ingredient a therapeutically effective amount of a compound according to claim 8 and a pharmaceutically acceptable adjuvant, diluent or carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/059769

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/20 C07D307/79 C07F9/38 A61K31/662
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US 2005/033055 A1 (BUGIANESI ROBERT L [US] ET AL) 10 February 2005 (2005-02-10) page 11; claims 1,34,47; example 24	8-14 1-7
X	US 2005/020837 A1 (DOHERTY GEORGE A [US] ET AL) 27 January 2005 (2005-01-27) page 10 - page 13; claims 1,22,34,35; examples 28,43	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 12 January 2015	Date of mailing of the international search report 21/01/2015
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Voyiazoglou, D

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/059769

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005033055 A1	10-02-2005	AT 441654 T	15-09-2009
		CA 2472715 A1	31-07-2003
		EP 1470137 A1	27-10-2004
		JP 4430941 B2	10-03-2010
		JP 2005515259 A	26-05-2005
		US 2005033055 A1	10-02-2005
		WO 03062252 A1	31-07-2003
US 2005020837 A1	27-01-2005	AT 448193 T	15-11-2009
		CA 2472713 A1	31-07-2003
		EP 1575964 A2	21-09-2005
		JP 4709488 B2	22-06-2011
		JP 2005527494 A	15-09-2005
		US 2005020837 A1	27-01-2005
		WO 03062248 A2	31-07-2003