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(54) Title: ALKENE AZETIDINE DERIVATIVES AS SPHINGOSINE 1-PHOSPHATE (S1P) RECEPTOR MODULATORS

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

ALKENE AZETIDINE DERIVATIVES AS SPHINGOSINE 1-PHOSPHATE (S1P) RECEPTOR MODULATORS

By inventors: Wenkui K. Fang, Evelyn G. Corpuz, and Ken Chow

RELATED APPLICATIONS

This application claims the benefit of United States Provisional Patent Application Serial No. 61/763,599 filed February 12, 2013, the disclosure of which is hereby incorporated in its entirety herein by reference.

FIELD OF THE INVENTION

The present invention relates to alkene azetidine derivatives, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals, as modulators of the sphingosine-1-phosphate receptors. The invention relates 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

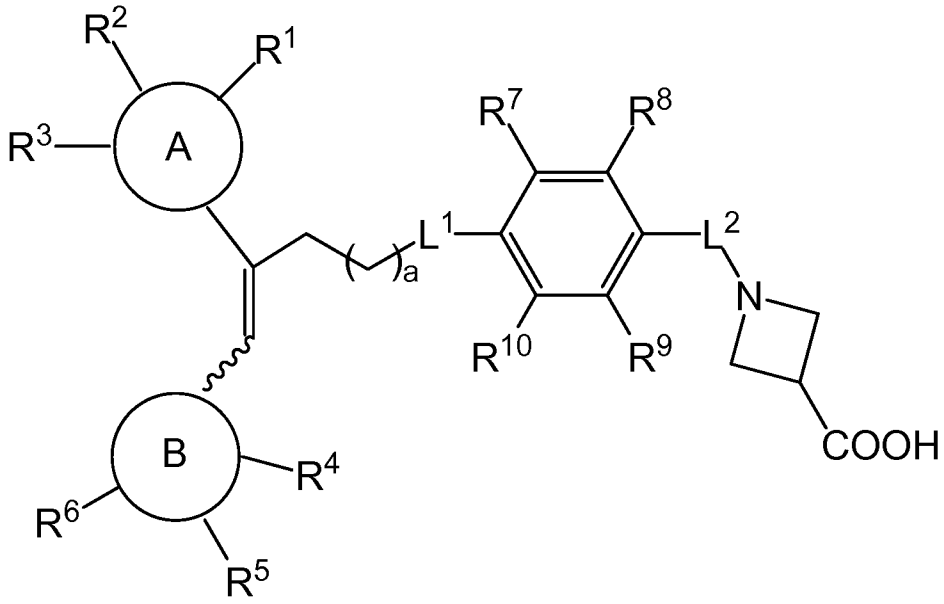
influence on the development of cancers. These are currently topics that are attracting great interest amongst medical researchers, and the potential for therapeutic intervention in sphingosine-1-phosphate metabolism is under active investigation.

SUMMARY OF THE INVENTION

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

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

In one aspect, the invention provides a compound having **Formula I,** or an E geometric isomer, or a Z geometric isomer, or a mixture of an E and a Z geometric isomers, or an enantiomer, or a diastereoisomer, or a tautomer, or a zwitterion, or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

A is optionally substituted C_{6-10} aryl, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl or optionally substituted C_{3-8} cycloalkenyl;

B is optionally substituted C_{6-10} aryl, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl or optionally substituted C_{3-8} cycloalkenyl;

R^1 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, $NR^{12}R^{13}$ or hydroxyl;

R^2 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, $NR^{12}R^{13}$ or hydroxyl;

R^3 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, $NR^{12}R^{13}$ or hydroxyl;

R^4 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, $NR^{12}R^{13}$ or hydroxyl;

R^5 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, $NR^{12}R^{13}$ or hydroxyl;

R^6 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, $NR^{12}R^{13}$ or hydroxyl;

R^7 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, optionally substituted C_{6-10} aryl, optionally substituted heterocycle,

optionally substituted C $_{3-8}$ cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, $NR^{12}R^{13}$ or hydroxyl;

R^8 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, optionally substituted C_{6-10} aryl, optionally substituted heterocycle, optionally substituted C $_{3-8}$ cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, $NR^{12}R^{13}$ or hydroxyl;

R^9 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, optionally substituted C_{6-10} aryl, optionally substituted heterocycle, optionally substituted C $_{3-8}$ cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, $NR^{12}R^{13}$ or hydroxyl;

R^{10} is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, optionally substituted C_{6-10} aryl, optionally substituted heterocycle, optionally substituted C $_{3-8}$ cyclolalkyl, optionally substituted C_{3-8} cycloalkenyl, $NR^{12}R^{13}$ or hydroxyl;

L^1 is O, S, S(O), NH or CH_2;

L^2 is O, S or CHR^{12};

R^{11} is OH or optionally substituted C_{1-8} alkyl;

a is 1, 2, 3, 4, 5 or 6; and

R^{12} is H or optionally substituted C_{1-8} alkyl;

R^{13} is H or optionally substituted C_{1-8} alkyl.

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

the double bond is in the E configuration.

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

the double bond is in the Z configuration.

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

the double bond is in a mixture of E and Z geometric isomers.

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

L^1 is S.

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

L^1 is O.

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

L^1 is S(O).

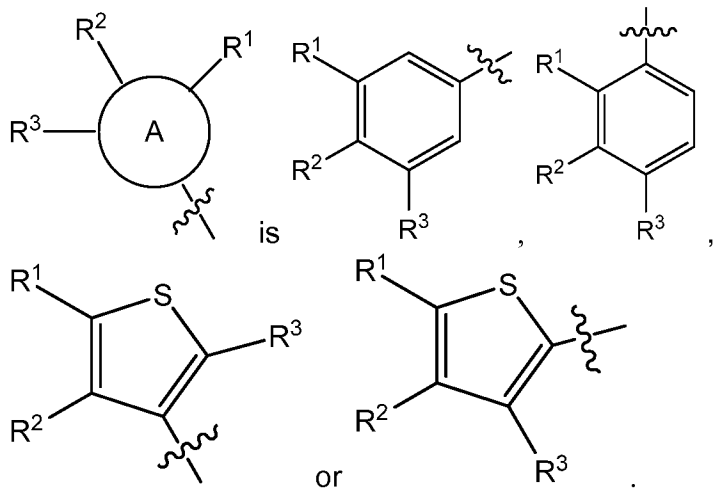
In another aspect, the invention provides a compound having **Formula I** wherein

L^2 is CH_2.

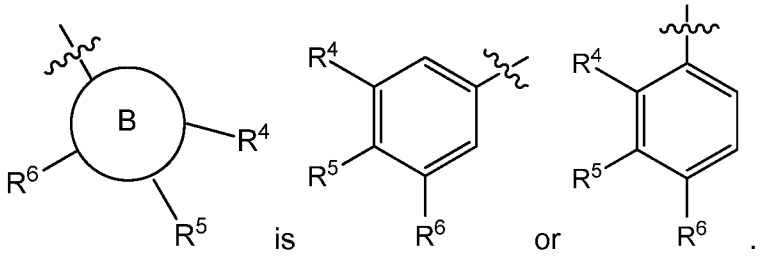
In another aspect, the invention provides a compound having **Formula I** wherein

a is 1, 2 or 3.

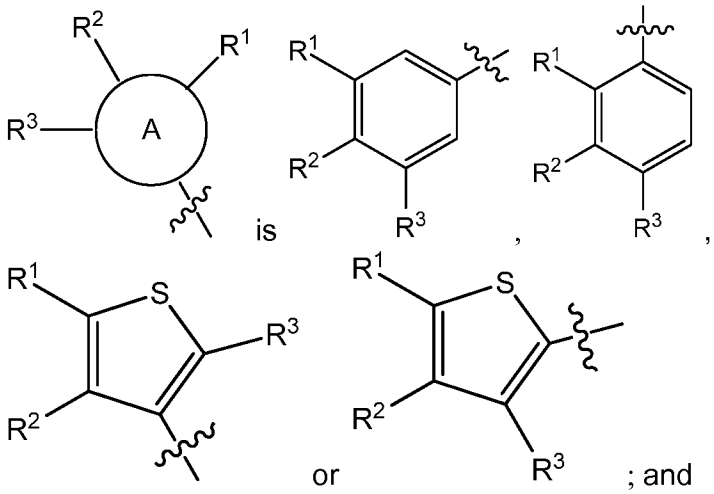
In another aspect, the invention provides a compound having **Formula I** wherein

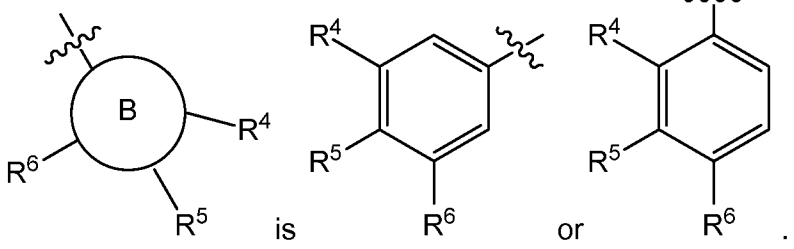


In another aspect, the invention provides a compound having **Formula I** wherein

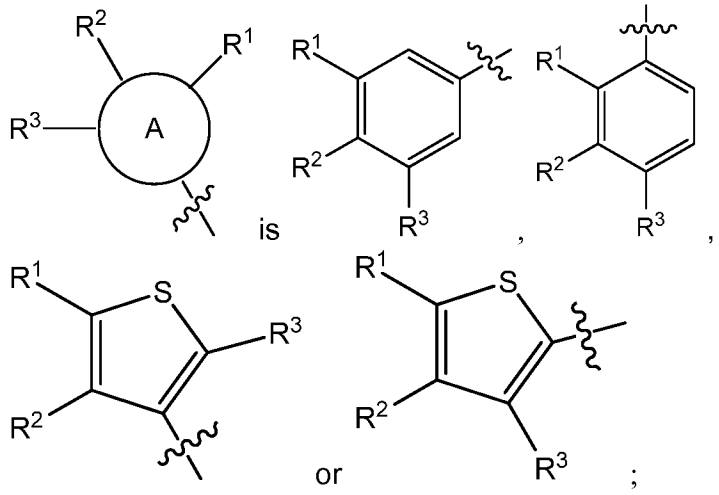


In another aspect, the invention provides a compound having **Formula I** wherein

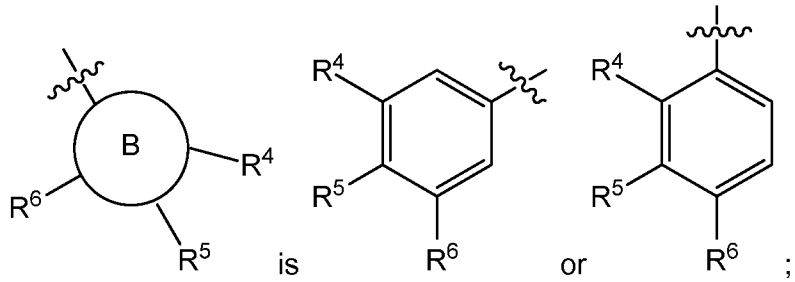




In another aspect, the invention provides a compound having **Formula I** wherein



is , , , or ;



is or ;

R^1 is H, halogen or optionally substituted C_{1-8} alkyl;

R^2 is H, halogen or optionally substituted C_{1-8} alkyl;

R^3 is H, halogen or optionally substituted C_{1-8} alkyl;

R^4 is H, halogen or optionally substituted C_{1-8} alkyl;

R^5 is H, halogen or optionally substituted C_{1-8} alkyl;

R^6 is H, halogen or optionally substituted C_{1-8} alkyl;

R^7 is H, halogen or optionally substituted C_{1-8} alkyl;

R^8 is H, halogen or optionally substituted C_{1-8} alkyl;

R^9 is H, halogen or optionally substituted C_{1-8} alkyl;

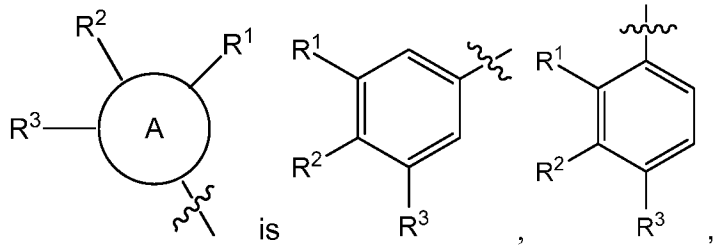
R^{10} is H, halogen or optionally substituted C_{1-8} alkyl;

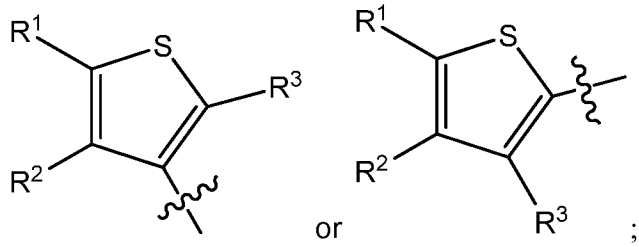
L^1 is O, NH, CH_2, S or S(O);

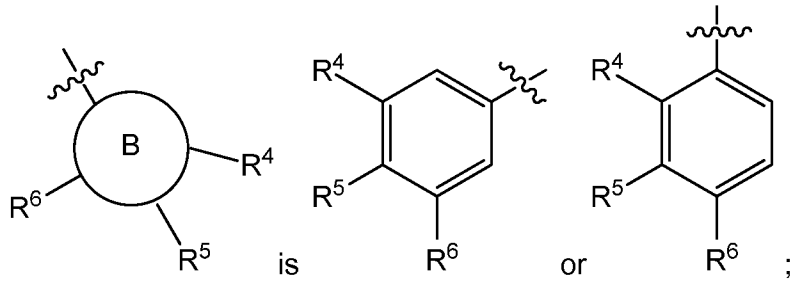
L^2 is CH_2; and

a is 1, 2 or 3.

In another aspect, the invention provides a compound having **Formula I** in the E geometrical configuration, wherein:







R^1 is H, halogen or optionally substituted C_{1-8} alkyl;

R^2 is H, halogen or optionally substituted C_{1-8} alkyl;

R^3 is H, halogen or optionally substituted C_{1-8} alkyl;

R^4 is H, halogen or optionally substituted C_{1-8} alkyl;

R^5 is H, halogen or optionally substituted C_{1-8} alkyl;

R^6 is H, halogen or optionally substituted C_{1-8} alkyl;

R^7 is H, halogen or optionally substituted C_{1-8} alkyl;

R^8 is H, halogen or optionally substituted C_{1-8} alkyl;

R^9 is H, halogen or optionally substituted C_{1-8} alkyl;

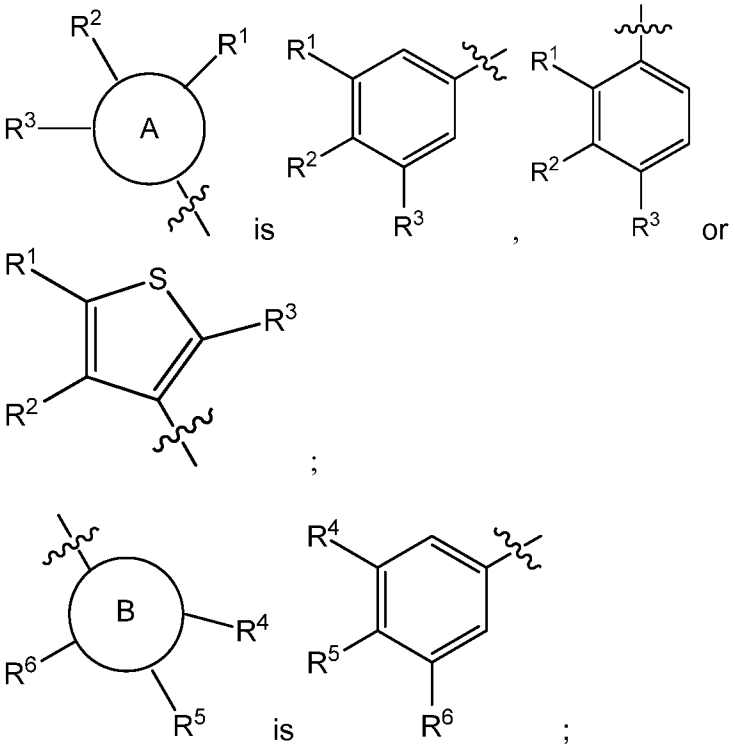
R^{10} is H, halogen or optionally substituted C_{1-8} alkyl;

L^1 is O, NH, CH_2, S or S(O);

L^2 is CH_2; and

a is 1, 2 or 3.

In another aspect, the invention provides a compound having **Formula I** in the E geometrical configuration, wherein:



is , or ;

is ;

R^1 is H, halogen or optionally substituted C_{1-8} alkyl;

R^2 is H, halogen or optionally substituted C_{1-8} alkyl;

R^3 is H, halogen or optionally substituted C_{1-8} alkyl;

R^4 is H, halogen or optionally substituted C_{1-8} alkyl;

R^5 is H, halogen or optionally substituted C_{1-8} alkyl;

R^6 is H, halogen or optionally substituted C_{1-8} alkyl;

R^7 is H, halogen or optionally substituted C_{1-8} alkyl;

R^8 is H, halogen or optionally substituted C_{1-8} alkyl;

R^9 is H, halogen or optionally substituted C_{1-8} alkyl;

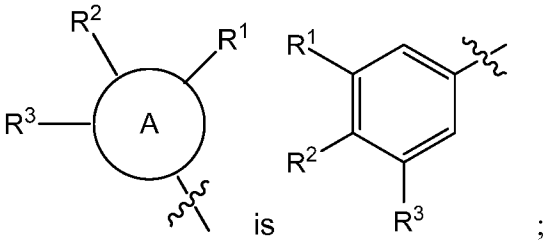
R^{10} is H, halogen or optionally substituted C_{1-8} alkyl;

L^1 is O, S or S(O);

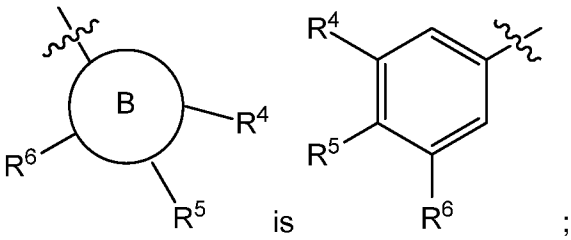
L^2 is CH_2; and

a is 1, 2 or 3.

In another aspect, the invention provides a compound having **Formula I** in the E geometrical configuration, wherein:



is ;



is ;

R^1 is H, halogen or optionally substituted C_{1-8} alkyl;

R^2 is H, halogen or optionally substituted C_{1-8} alkyl;

R^3 is H, halogen or optionally substituted C_{1-8} alkyl;

R^4 is H, halogen or optionally substituted C_{1-8} alkyl;

R^5 is H, halogen or optionally substituted C_{1-8} alkyl;

R^6 is H, halogen or optionally substituted C_{1-8} alkyl;

R^7 is H, halogen or optionally substituted C_{1-8} alkyl;

R^8 is H, halogen or optionally substituted C_{1-8} alkyl;

R^9 is H, halogen or optionally substituted C_{1-8} alkyl;

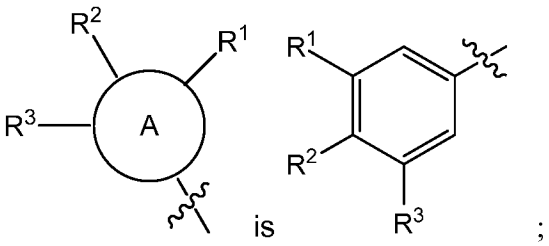
R^{10} is H, halogen or optionally substituted C_{1-8} alkyl;

L^1 is S;

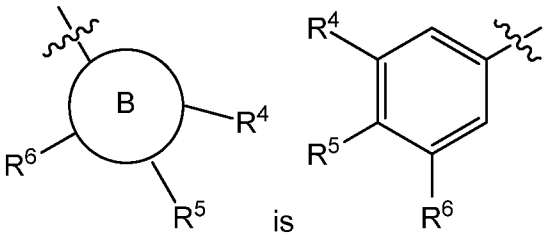
L^2 is CH_2; and

a is 1, 2 or 3.

In another aspect, the invention provides a compound having **Formula I** in the E geometrical configuration, wherein:



is ;



;

R^1 is H, halogen or optionally substituted C_{1-8} alkyl;

R^2 is H, halogen or optionally substituted C_{1-8} alkyl;

R^3 is H, halogen or optionally substituted C_{1-8} alkyl;

R^4 is H, halogen or optionally substituted C_{1-8} alkyl;

R^5 is H, halogen or optionally substituted C_{1-8} alkyl;

R^6 is H, halogen or optionally substituted C_{1-8} alkyl;

R^7 is H, halogen or optionally substituted C_{1-8} alkyl;

R^8 is H, halogen or optionally substituted C_{1-8} alkyl;

R^9 is H, halogen or optionally substituted C_{1-8} alkyl;

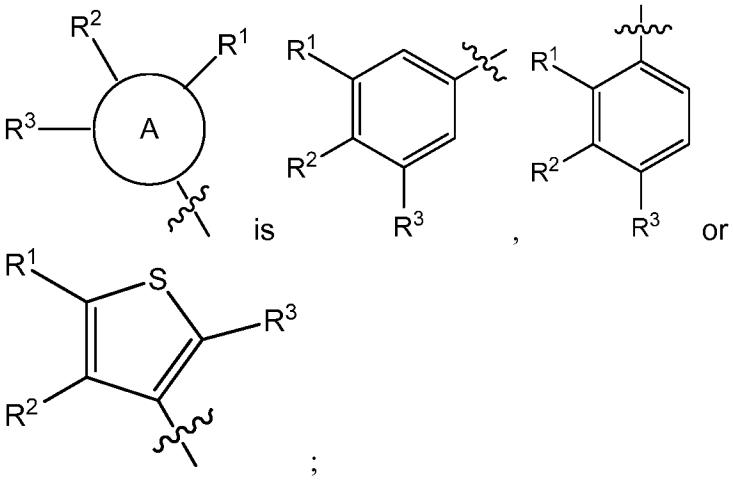
R^{10} is H, halogen or optionally substituted C_{1-8} alkyl;

L^1 is S(O);

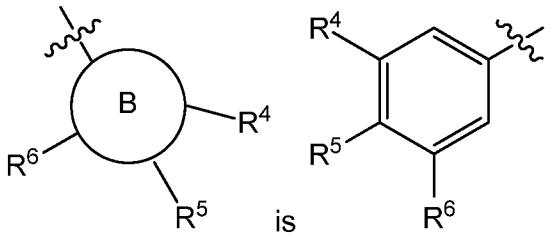
L^2 is CH_2; and

a is 1, 2 or 3.

In another aspect, the invention provides a compound having **Formula I** in the E geometrical configuration, wherein:



;



;

R^1 is H, halogen or optionally substituted C_{1-8} alkyl;

R^2 is H, halogen or optionally substituted C_{1-8} alkyl;

R^3 is H, halogen or optionally substituted C_{1-8} alkyl;

R^4 is H, halogen or optionally substituted C_{1-8} alkyl;

R^5 is H, halogen or optionally substituted C_{1-8} alkyl;

R^6 is H, halogen or optionally substituted C_{1-8} alkyl;

R^7 is H, halogen or optionally substituted C_{1-8} alkyl;

R^8 is H, halogen or optionally substituted C_{1-8} alkyl;

R^9 is H, halogen or optionally substituted C_{1-8} alkyl;

R^{10} is H, halogen or optionally substituted C_{1-8} alkyl;

L^1 is O;

L^2 is CH_2; and

a is 1, 2 or 3.

The term ”alkyl”, as used herein, refers to saturated, monovalent hydrocarbon moieties having linear or branched moieties or combinations thereof and containing 1 to 8 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_{3-8} cycloalkyl. Alkyl groups can be independently substituted by halogen atoms, hydroxyl groups, cycloalkyl groups, amine groups, heterocyclic groups, carboxylic acid groups, phosphonic acid groups, sulphonic acid groups, phosphoric acid groups, nitro groups, amide groups, sulfonamides groups.

The term “cycloalkyl”, as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms, derived from a saturated cyclic hydrocarbon. Cycloalkyl groups can be monocyclic or polycyclic. Cycloalkyl can be

independently substituted by halogen, nitro groups, cyano groups, -OC_{1-6} alkyl groups, -SC_{1-6} alkyl groups, -C_{1-6} alkyl groups, -C_{2-6} alkenyl groups, - C_{2-6} alkynyl groups , C_{3-8} cycloalkyl groups, carboxylic acid groups, ester groups, ketone groups, aldehyde groups, amide groups, amine groups, sulfonamide groups or hydroxyl groups.

The term “cycloalkenyl”, as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms, derived from a saturated cycloalkyl having one double bond. Cycloalkenyl groups can be monocyclic or polycyclic. Cycloalkenyl groups can be independently substituted by halogen atoms, nitro groups, cyano groups, -OC_{1-6} alkyl groups, -SC_{1-6} alkyl groups, -C_{1-6} alkyl groups, -C_{2-6} alkenyl groups, - C_{2-6} alkynyl groups, carboxylic acid groups, ester groups, ketone groups, aldehyde groups, amide groups, amine groups, sulfonamide groups, C_{3-8} cycloalkyl groups or hydroxyl groups.

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

The term “alkenyl”, as used herein, refers to a monovalent or divalent hydrocarbon radical having 2 to 6 carbon atoms, derived from a saturated alkyl, having at least one double bond. C_{2-6} alkenyl can be in the E or Z configuration. Alkenyl groups can be substituted by C_{1-8} alkyl.

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

The term “heterocycle” as used herein, refers to a 3 to 10 membered ring, which can be aromatic or non-aromatic, saturated or non-saturated, monocyclic or polycyclic, 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 halogen, nitro groups, cyano groups, -OC_{1-}

$_6$ alkyl groups, -SC_{1-6} alkyl groups, -C_{1-6} alkyl groups, -C_{2-6} alkenyl groups, - C_{2-6} alkynyl groups, carboxylic acid groups, ester groups, ketone groups, aldehyde groups, amide groups, amine groups, sulfonamide groups, C_{3-8} cycloalkyl groups or hydroxyl groups.

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. Aryl can be monocyclic or polycyclic. Aryl can be substituted by halogen atoms, nitro groups, cyano groups, -OC_{1-6} alkyl groups, -SC_{1-6} alkyl groups, -C_{1-6} alkyl groups, -C_{2-6} alkenyl groups, - C_{2-6} alkynyl groups , carboxylic acid groups, ester groups, ketone groups, aldehyde groups, amide groups, amine groups, sulfonamide groups, C_{3-8} cycloalkyl groups or hydroxyl groups. Usually aryl is phenyl. Preferred substitution site on aryl are meta and para positions.

The term "cyano" as used herein, represents a group of formula "-CN".

The term "nitro" as used herein, represents a group of formula "–NO_2".

The term "amide" as used herein, represents a group of formula "-$C(O)NR^xR^y$," wherein R^x and R^y can be the same or independently H, alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

The term "amine" as used herein, represents a group of formula "-NR^xR^y ",wherein R^x and R^y can be the same or independently H, alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

The term "ketone" as used herein, represents an organic compound having a carbonyl group linked to a carbon atom such as -$(CO)R^x$ wherein R^x can be alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

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

The term "ester" as used herein, represents a group of formula "-$C(O)OR^x$", wherein R^x can be alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

The term "sulfonamide" as used herein, represents a group of formula "-$S(O)_2NR^xR^y$" wherein R^x and R^y can be the same or independently H, alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

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 “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:

1-(4-{[(5E)-5-(3,5-difluorophenyl)-6-(3,4-dimethylphenyl)hex-5-en-1-yl]sulfanyl}benzyl) azetidine-3-carboxylic acid;

1-(4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]sulfinyl}benzyl) azetidine-3-carboxylic acid;

1-(4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzyl) azetidine-3-carboxylic acid;

1-(4-{[(4E)-4-(3-chlorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid;

1-(4-{[(4E)-4-(2,3-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzyl) azetidine-3-carboxylic acid;

1-(4-{[5-(3,4-dimethylphenyl)-4-(3-thienyl)pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid;

1-(4-{[3-(3,5-difluorophenyl)-4-(3,4-dimethylphenyl)but-3-en-1-yl]thio}benzyl)azetidine-3-carboxylic acid.

Some compounds of Formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in an R or S configuration, said R and S notation is used in correspondence with the rules 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 that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; or an organic acid such as for example, acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, malonic acid, fumaric acid, maleic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, citric acid, methylsulfonic acid, ethanesulfonic acid, benzenesulfonic acid, 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 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).

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

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

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.

Therapeutic utilities of S1P modulators are: Ocular Diseases: wet and dry age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinal edema, dry eye, 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;
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;
Autoimmune and immunosuppression diseases: 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;
Allergies and other inflammatory diseases: urticaria, bronchial asthma, airway inflammations, pulmonary emphysema and chronic obstructive pulmonary diseases;
Cardiac functions: bradycardia, congestional heart failure, cardiac arrhythmia, prevention and treatment of atherosclerosis, and ischemia/reperfusion injury;
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, skin ageing, and prevention of radiation-induced injuries;

Bone formation: treatment of osteoporosis and various bone fractures including hip and ankles;
Anti-nociceptive activity: visceral pain, pain associated with diabetic neuropathy, rheumatoid arthritis, chronic knee and joint pain, tendonitis, osteoarthritis, neuropathic pains;
Anti-fibrosis: ocular, cardiac, hepatic and pulmonary fibrosis, proliferative vitreoretinopathy, cicatricial pemphigoid, surgically induced fibrosis in cornea, conjunctiva and tenon;
Pains and anti-inflammation: acute pain, flare-up of chronic pain, musculo-skeletal pains, visceral pain, pain associated with diabetic neuropathy, rheumatoid arthritis, chronic knee and joint pain, tendonitis, osteoarthritis, bursitis, neuropathic pains;
CNS neuronal injuries: Alzheimer's disease, age-related neuronal injuries;
Organ transplants: renal, corneal, cardiac and adipose tissue transplants.

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

The present invention concerns the use of a compound of Formula I or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of Ocular Diseases: wet and dry age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinal edema, dry eye, 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;

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;

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 ;

Allergies and other inflammatory diseases: urticaria, bronchial asthma, and other airway inflammations including pulmonary emphysema and chronic obstructive pulmonary diseases; Cardiac functions: bradycardia, congestional heart failure, cardiac arrhythmia, prevention and treatment of atherosclerosis, and ischemia/reperfusion injury; 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; Bone formation: treatment of osteoporosis and various bone fractures including hip and ankles; Anti-nociceptive activity: visceral pain, pain associated with diabetic neuropathy, rheumatoid arthritis, chronic knee and joint pain, tendonitis, osteoarthritis, neuropathic pains; Anti-fibrosis: ocular, cardiac, hepatic and pulmonary fibrosis, proliferative vitreoretinopathy, cicatricial pemphigoid, surgically induced fibrosis in cornea, conjunctiva and tenon; Pains and anti-inflammation: acute pain, flare-up of chronic pain, musculo-skeletal pains, visceral pain, pain associated with diabetic neuropathy, rheumatoid arthritis, chronic knee and joint pain, tendonitis, osteoarthritis, bursitis, neuropathic pains; CNS neuronal injuries: Alzheimer's disease, age-related neuronal injuries; Organ transplants: renal, corneal, cardiac and adipose tissue transplants.

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.

Pharmaceutical compositions containing invention compounds may be in a form suitable for topical use, for example, as oily suspensions, as solutions or suspensions in aqueous liquids or nonaqueous liquids, or as oil-in-water or water-in-oil liquid emulsions. Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable salt thereof, as an active ingredient with conventional ophthalmically acceptable pharmaceutical excipients and by preparation of unit dosage suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 2.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 4.5 and 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. The formulations may also contain conventional pharmaceutically acceptable preservatives, stabilizers and surfactants. Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is,

for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose cyclodextrin and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar manner an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place of or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	0-10
buffer	0.01-10
pH adjustor	q .s. pH 4.5-7.8
antioxidant	as needed
surfactant	as needed

purified water to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate application to the eye. Containers suitable for drop wise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution. One package may contain one or more unit doses. Especially preservative-free solutions are often formulated in non-resalable containers containing up to about ten, preferably up to about five units doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop usually is about 20-35 µl.

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.

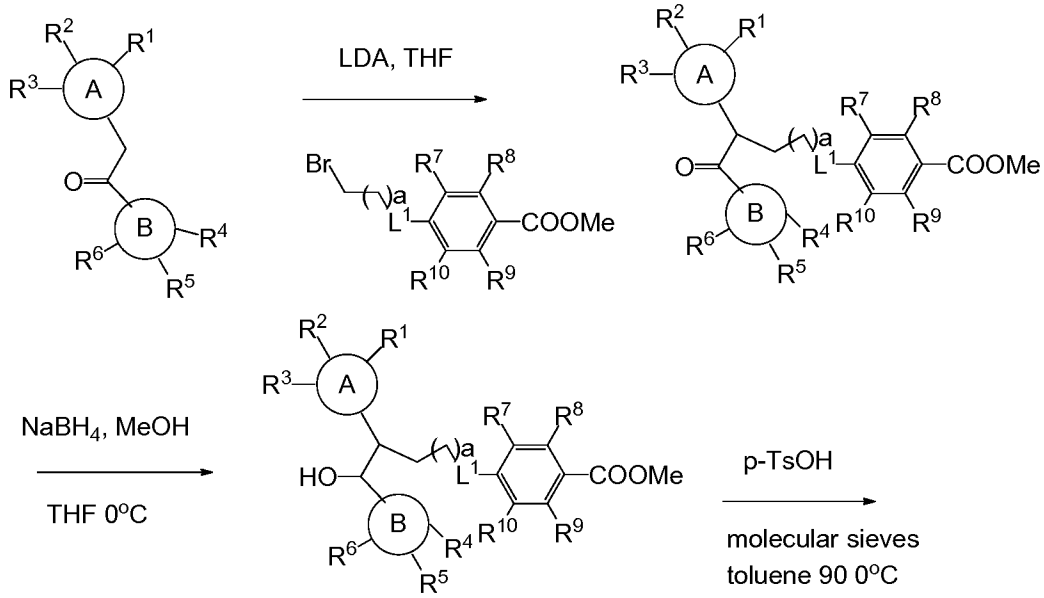
Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner.

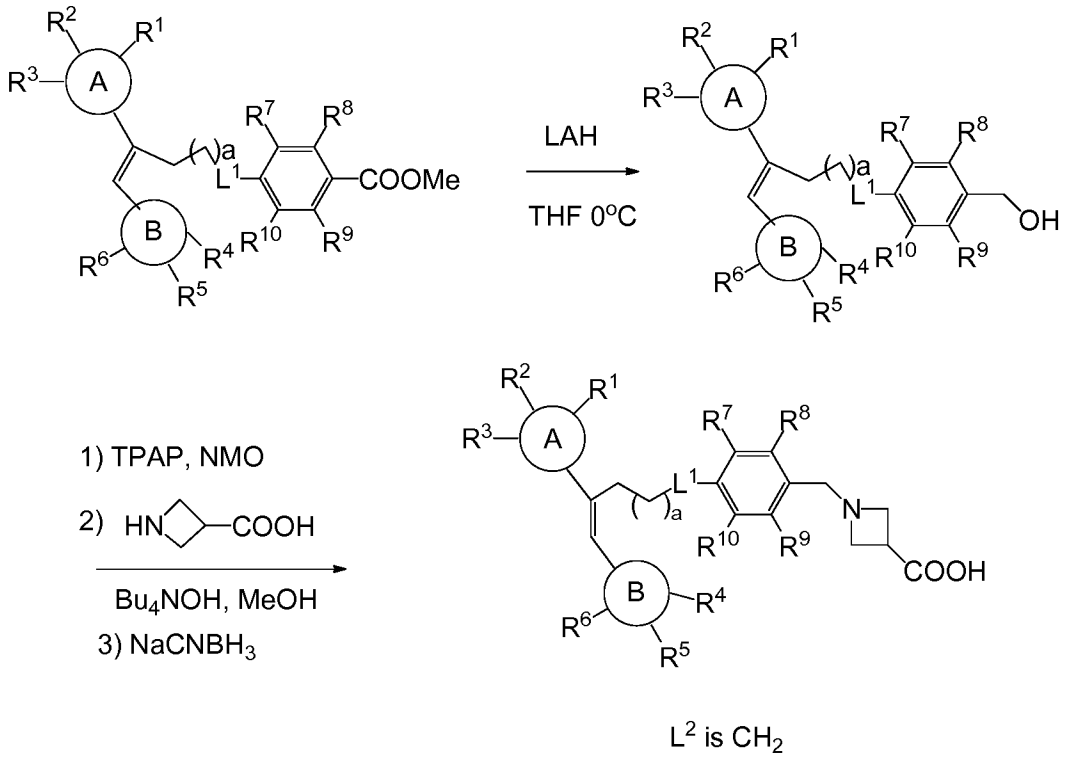
The compounds and pharmaceutical compositions described herein are useful as medicaments in mammals, including humans, for treatment of diseases and/or alleviations of conditions which are responsive to treatment by agonists or functional antagonists of sphingosine-1-phosphate receptors.

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





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

The following abbreviations are used in **Scheme 1** and in the examples:

CD_3OD	deuterated methanol
RT	room temperature
$CDCl_3$	deuterated chloroform
MPLC	medium pressure liquid chromatography
$NaHCO_3$	sodium bicarbonate
EtOAc	ethyl acetate
$Na_2S_2O_3$	sodium thiosulfate
$MgSO_4$	magnesium sulfate
NaCl	sodium chloride
$NaBH_4$	Sodium borohydride
Et_2O	ether

p-TsOH	p-Toluenesulfonic acid
LAH	Lithium aluminium hydride
NMO	N-Methylmorpholine-N-Oxide
TPAP	tetrapropylammonium perruthenate
DMSO-d_6	deuterated dimeythylsulfonamide
THF	tetrahydrofuran
MeOH	methanol
LDA	lithium diisopropylamide
HCl	hydrochloric acid
DMSO	dimeythylsulfonamide
$NaCNBH_3$	sodium cyanoborohydride
HOAc	acetic acid

DETAILED DESCRIPTION OF THE INVENTION

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

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

The present invention includes all pharmaceutically acceptable isotopically enriched compounds. Any compound of the invention may contain one or more isotopic atoms enriched or different than the natural ratio such as deuterium ^{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.

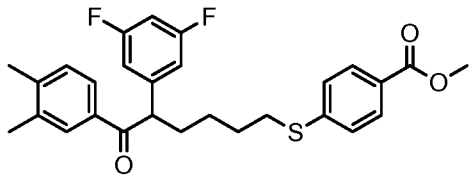
As will be evident to those skilled in the art, individual isomeric forms can be obtained by separation of mixtures thereof in conventional manner. For example, in the case of diasteroisomeric isomers, chromatographic separation may be employed.

Compound names were generated with ACDLab 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.

Example 1

Intermediate 1

Methyl 4-{[5-(3,5-difluorophenyl)-6-(3,4-dimethylphenyl)-6-oxohexyl]thio}benzoate



A sample of 2-(3,5-difluorophenyl)-1-(3,4-dimethylphenyl)ethanone [CAS 1450736-61-4] (5.0 g, 19.2 mmole) was dissolved in THF and set to -78 °C. Lithium diisopropyl amide (10.6 mL, 1.1 eq.) was added dropwise and the

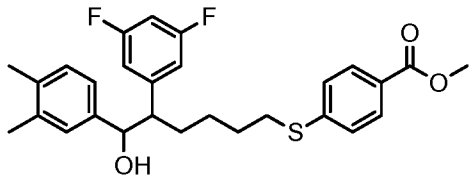
resulting mixture was stirred for 30 minutes. A solution of methyl 4-[(4-bromobutyl)thio]benzoate [CAS 1456736-45-4] (6.4 g, 1.1 eq) in THF was then added dropwise and the reaction mixture was allowed to stir overnight. It was then refluxed at 90 °C for overnight. The reaction mixture was cooled to room temperature, then to 0 °C after which it was quenched with 1M HCl to pH 2. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with saturated NaCl, dried with $MgSO_4$, filtered, concentrated and purified by MPLC to give 3.76 g (40%) of **Intermediate 1**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 - 1.54 (m, 2 H) 1.63 - 1.91 (m, 3 H) 2.09 - 2.24 (m, 1 H) 2.28 (s, 6 H) 2.94 (t, *J*=7.33 Hz, 2 H) 3.89 (s, 3 H) 4.50 (t, *J*=7.18 Hz, 1 H) 6.57 - 6.70 (m, 1 H) 6.79 - 6.88 (m, 2 H) 7.17 (d, *J*=7.62 Hz, 1 H) 7.24 (d, *J*=8.79 Hz, 2 H) 7.60 - 7.68 (m, 1 H) 7.71 (s, 1 H) 7.90 (d, *J*=8.50 Hz, 2 H).

Example 2

Intermediate 2

Methyl 4-{[5-(3,5-difluorophenyl)-6-(3,4-dimethylphenyl)-6-hydroxyhexyl]thio}benzoate



A sample of **Intermediate 1** (3.76 g, 7.8 mmoles) was dissolved in 2 mL of THF and diluted with MeOH. The resulting solution was cooled to 0 °C and $NaBH_4$ (295 mg, 1.0 eq) was added. The reaction mixture was stirred at 0 °C for 2 hours. It was then quenched with 1M HCl and the solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated NaCl, dried with $MgSO_4$, filtered, concentrated and purified by MPLC to give 3.48 g (92%) of **Intermediate 2.**

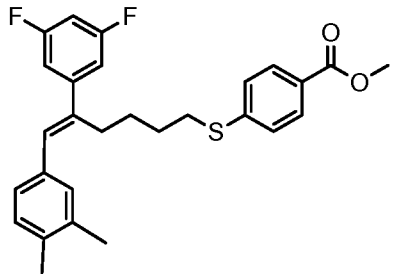
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.01 - 1.27 (m, 2 H) 1.32 - 1.66 (m, 4 H) 2.25 (s, 6 H) 2.68 - 2.91 (m, 3 H) 3.89 (s, 3 H) 4.63 (d, *J*=8.20 Hz, 1 H) 6.58 -

6.82 (m, 3 H) 6.95 - 7.13 (m, 3 H) 7.19 (d, *J*=8.79 Hz, 2 H) 7.89 (d, *J*=8.50 Hz, 2 H).

Example 3

Intermediate 3

Methyl 4-{[(5E)-5-(3,5-difluorophenyl)-6-(3,4-dimethylphenyl)hex-5-en-1-yl]thio}benzoate



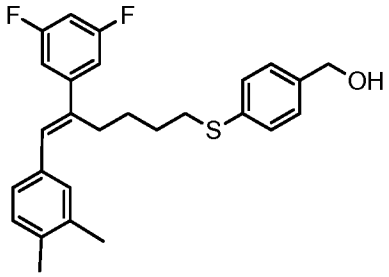
A sample of **Intermediate 2** (3.48 g, 7.2 mmoles) was dissolved in toluene. Molecular sieves (200 mg) were added followed by p-TsOH (1.5 g, 1.1 eq). The resulting mixture was refluxed at 110 °C for 3 hours after which it was cooled to room temperature. The solvent was evaporated and the residue was dissolved in Et_2O. The solution was washed with saturated $NaHCO_3$ (2 x 20 mL), H_2O (1 x 20 mL) and brine. It was then dried over $MgSO_4$, filtered, concentrated and purified by MPLC to give 2.9 g (87%) of **Intermediate 3**.

^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.39 - 1.61 (m, 2 H) 1.64 - 1.84 (m, 2 H) 2.10 (s, 3 H) 2.17 (s, 3 H) 2.46 (t, *J*=7.30 Hz, 2 H) 2.97 (t, *J*=7.18 Hz, 2 H) 3.89 (s, 3 H) 6.40 (s, 1 H) 6.55 - 6.74 (m, 5 H) 6.86 (d, *J*=7.91 Hz, 1 H) 7.26 (d, *J*=8.79 Hz, 2 H) 7.91 (d, *J*=8.79 Hz, 2 H).

Example 4

Intermediate 4

(4-{[(5E)-5-(3,5-Difluorophenyl)-6-(3,4-dimethylphenyl)hex-5-en-1-yl]thio}phenyl)methanol



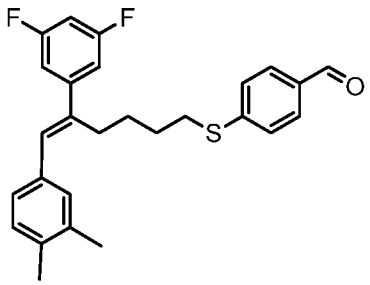
A sample of **Intermediate 3** (2.9 g, 6.22 mmoles) was dissolved in THF and cooled to –30 °C. Lithium aluminum hydride (1.0 M, 6.8mL, 1.1 eq) was added dropwise and the resulting mixture was stirred at –30 °C for 1 hour. Ether and celite were added to the reaction mixture followed by 1M HCl until pH 2-3. The resulting solution was filtered over celite and the filtrate was concentrated and purified by MPLC to give 2.25 g (83%) of **Intermediate 4**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.43 - 1.79 (m, 4 H) 2.10 (s, 3 H) 2.17 (s, 3 H) 2.38 - 2.51 (m, 2 H) 2.90 (t, *J*=7.18 Hz, 2 H) 4.64 (s, 2 H) 6.38 (s, 1 H) 6.50 - 6.75 (m, 5 H) 6.86 (d, *J*=7.91 Hz, 1 H) 7.14 - 7.40 (m, 4 H).

Example 5

Intermediate 5

4-{[(5E)-5-(3,5-Difluorophenyl)-6-(3,4-dimethylphenyl)hex-5-en-1-yl]thio}benzaldehyde



A solution of oxalyl chloride (240 µL, 1.1 eq) in 5.0 mL of CH_2Cl_2 was cooled to -78 °C. Dimethylsulfoxide (401 µL, 2.2 eq) was added and the resulting mixture was stirred for 30 minutes. A solution of **Intermediate 4** (1.125 g, 2.6 mmoles) in 5 mL CH_2Cl_2 was added and the reaction mixture was stirred at -78

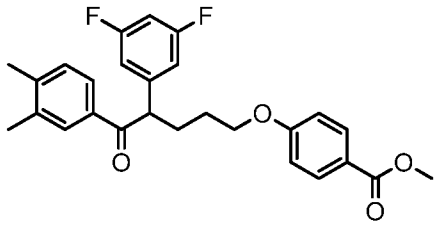
°C for 2 hours. Triethylamine (1.8 mL, 5.0 eq) was added and the resulting mixture was stirred for 30 minutes. Water was added to quench the reaction mixture and stirring was continued until the solution is at room temperature. The layers were isolated and the organic layer was washed with brine, dried with $MgSO_4$, filtered, concentrated and purified by MPLC to give **Intermediate 5** (866 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.46 - 1.62 (m, 2 H) 1.68 - 1.85 (m, 2 H) 2.10 (s, 3 H) 2.17 (s, 3 H) 2.48 (t, *J*=7.03 Hz, 2 H) 3.00 (t, *J*=7.33 Hz, 2 H) 6.41 (s, 1 H) 6.54 - 6.75 (m, 5 H) 6.86 (d, *J*=7.91 Hz, 1 H) 7.33 (d, *J*=8.50 Hz, 2 H) 7.75 (d, *J*=8.79 Hz, 2 H) 9.91 (s, 1 H).

Example 6

Intermediate 6

Methyl 4-{[4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)-5-oxopentyl]oxy}benzoate



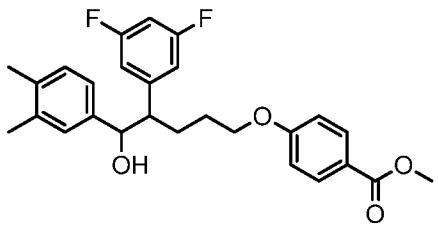
A mixture of 2-(3,5-difluorophenyl)-1-(3,4-dimethylphenyl)ethanone [CAS 1450736-61-4] (2.3 g, 8.8 mmoles), LDA (6.6 mL, 1.5 eq), and methyl 4-(3-iodopropoxy) benzoate [CAS 152936-91-9] (4.25 g, 1.5 eq) were reacted to give 3.7 g (93%) of **Intermediate 6**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.65 - 1.90 (m, 2 H) 1.91 - 2.04 (m, 1 H) 2.25 - 2.32 (m, 6 H) 2.30 - 2.43 (m, 1 H) 3.88 (s, 3 H) 4.01 (t, *J*=6.15 Hz, 2 H) 4.61 (t, *J*=7.18 Hz, 1 H) 6.52 - 6.73 (m, 1 H) 6.82 - 6.90 (m, 4 H) 7.17 (d, *J*=7.91 Hz, 1 H) 7.55 - 7.77 (m, 2 H) 7.93 - 7.98 (m, 2 H).

Example 7

Intermediate 7

Methyl 4-{[4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)-5-hydroxypentyl]oxy}benzoate



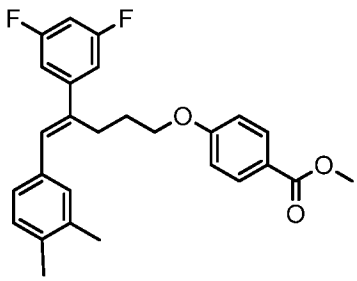
A mixture of **Intermediate 6** (4.06 g, 9.0 mmoles), and $NaBH_4$ (340 mg, 1.0 eq) were reacted to give 3.17 g (78%) of **Intermediate 7**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.48 - 1.64 (m, 4 H) 2.25 (s, 3 H) 2.26 (s, 3 H) 3.79 - 3.86 (m, 2 H) 3.87 (s, 3 H) 4.59 - 4.73 (m, 2 H) 6.65 - 6.92 (m, 4 H) 6.97 - 7.14 (m, 4 H) 7.91 - 8.03 (m, 2 H).

Example 8

Intermediate 8

Methyl 4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzoate



A mixture of **Intermediate 7** (3.17 g, 7.0 mmoles), molecular sieves (200 mg) and p-TsOH (1.6 g, 1.2 eq) were reacted to give quantitative yield of **Intermediate 8**.

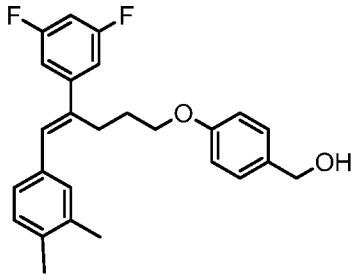
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.78 - 2.00 (m, 2 H) 2.10 (s, 3 H) 2.17 (s, 3 H) 2.52 - 2.73 (m, 2 H) 3.89 (s, 3 H) 4.03 (t, *J*=6.20 Hz, 2 H) 6.45 (s, 1 H)

6.53 - 6.64 (m, 1 H) 6.67 - 6.76 (m, 4 H) 6.80 - 6.97 (m, 3 H) 7.99 (d, *J*=8.79 Hz, 2 H).

Example 9

Intermediate 9

(4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}phenyl)methanol



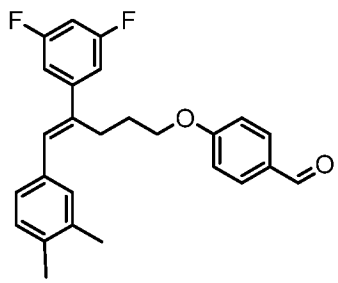
A mixture of **Intermediate 8** (3.32 g, 7.6 mmoles) and LAH (1.0 M, 8.4 mL, 1.1 eq) were reacted to give 2.6 g (84%) of **Intermediate 9**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.82 - 1.92 (m, 2 H) 2.10 (s, 3 H) 2.16 (s, 3 H) 2.51 - 2.72 (m, 2 H) 3.98 (t, *J*=6.30 Hz, 2 H) 4.59 - 4.63 (m, 2 H) 6.46 (s, 1 H) 6.54 - 6.65 (m, 1 H) 6.66 - 6.75 (m, 4 H) 6.83 - 6.90 (m, 3 H) 7.24 - 7.30 (m, 2 H).

Example 10

Intermediate 10

4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzaldehyde



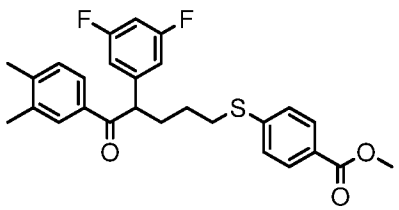
A mixture of **Intermediate 9** (2.6 g, 6.4 mmoles), 2.0 g of molecular sieves, NMO (1.5 g, 2.0 eq) and TPAP (100 mg) were reacted to give 2.0 g (77%) of **Intermediate 10.**

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.76 - 2.01 (m, 2 H) 2.10 (s, 3 H) 2.17 (s, 3 H) 2.65 (t, *J*=7.30 Hz, 2 H) 4.06 (t, *J*=6.15 Hz, 2 H) 6.46 (s, 1 H) 6.54 - 6.64 (m, 1 H) 6.67 - 6.77 (m, 4 H) 6.87 (d, *J*=8.20 Hz, 1 H) 6.99 (d, *J*=8.80 Hz, 2 H) 7.83 (d, *J*=8.80 Hz, 2 H) 9.89 (s, *J*=3.22 Hz, 1 H).

Example 11

Intermediate11

Methyl 4-{[4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)-5-oxopentyl]thio}benzoate



A sample of 2-(3,5-difluorophenyl)-1-(3,4-dimethylphenyl)ethanone [CAS 1450736-61-4] (5.0 g, 19.2 mmole) was dissolved in THF and cooled to -78 °C. Lithium diisopropyl amide (10.6 mL, 1.1 eq.) was added dropwise and the resulting mixture was stirred for 30 minutes. A solution of methyl 4-[(3-bromopropyl)thio]benzoate [CAS 134520-57-3] (6.1 g, 1.1 eq) in THF was then added dropwise and the reaction mixture was allowed to stir overnight. It was then refluxed at 90 °C overnight. The reaction mixture was cooled to room temperature, then to 0 °C after which it was quenched with 1M HCl to pH 2. The resulting mixture was extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with saturated NaCl, dried with $MgSO_4$, filtered, concentrated and purified by MPLC to give 4.28 g (48%) of **Intermediate 11**.

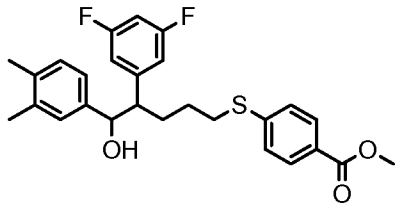
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.53 - 1.78 (m, 2 H) 1.86 - 2.11 (m, 1 H) 2.28 (s, 6 H) 2.31 - 2.38 (m, 1 H) 2.89 - 3.06 (m, 2 H) 3.89 (s, 3 H) 4.51 (t,

J=7.33 Hz, 1 H) 6.57 - 6.71 (m, 1 H) 6.78 - 6.88 (m, 2 H) 7.14 - 7.29 (m, 3 H) 7.62 - 7.66 (m, 1 H) 7.69 - 7.72 (m, 1 H) 7.90 (d, *J*=7.66 Hz, 2 H).

Example 12

Intermediate 12

Methyl 4-{[4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)-5-hydroxypentyl]thio}benzoate



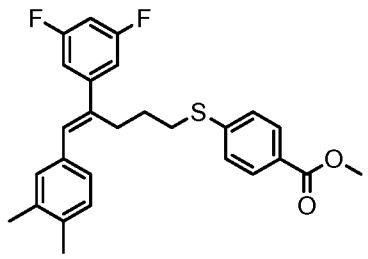
A sample of **Intermediate 11** (4.28 g, 9.1 mmoles) was dissolved in 5 mL of THF and diluted with MeOH. The resulting solution was cooled to 0 °C and $NaBH_4$ (346 mg, 1.0 eq) was added. The reaction mixture was stirred at 0 °C for 2 hours. It was then quenched with 1M HCl and the solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated NaCl, dried with $MgSO_4$, filtered, concentrated and purified by MPLC to give 3.73 g (87%) of **Intermediate 12.**

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 - 1.50 (m, 2 H) 1.53 - 1.72 (m, 2 H) 2.26 (s, 6 H) 2.70 - 2.90 (m, 3 H) 3.89 (s, 3 H) 4.63 (d, *J*=8.20 Hz, 1 H) 6.56 - 6.85 (m, 3 H) 6.90 - 7.05 (m, 2 H) 7.07 - 7.21 (m, 3 H) 7.83 - 7.89 (m, 2 H).

Example 13

Intermediate 13

Methyl 4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]thio}benzoate



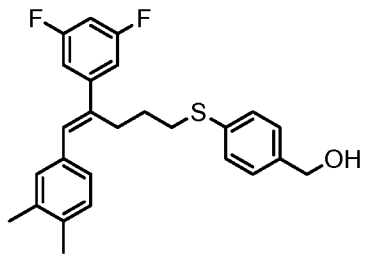
A mixture of **Intermediate 12** (880 mg, 1.9 mmoles), molecular sieve (50 mg) and p-TsOH (392 mg, 1.1 eq) were reacted to give 685 mg (81%) of **Intermediate 13**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.62 - 1.86 (m, 2 H) 2.10 (s, 3 H) 2.17 (s, 3 H) 2.55 - 2.73 (m, 2 H) 3.00 (t, *J*=7.18 Hz, 2 H) 3.90 (s, 3 H) 6.44 (s, 1 H) 6.53 - 6.77 (m, 5 H) 6.87 (d, *J*=7.91 Hz, 1 H) 7.26 (d, *J*=8.50 Hz, 2 H) 7.91 (d, *J*=8.50 Hz, 2 H).

Example 14

Intermediate 14

(4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]thio}phenyl)methanol



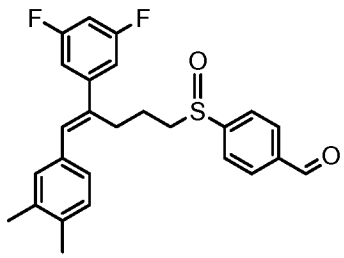
A mixture of **Intermediate 13** (685 mg, 1.5 mmoles) and LAH (1.0 M, 1.7 mL, 1.1 eq) were reacted to give 550 mg (86%) of **Intermediate 14**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.61 - 1.80 (m, 2 H) 2.10 (s, 3 H) 2.16 (s, 3 H) 2.58 (t, *J*=7.30 Hz, 2 H) 2.92 (t, *J*=7.18 Hz, 2 H) 4.55 - 4.72 (m, 2 H) 6.42 (s, 1 H) 6.48 - 6.77 (m, 5 H) 6.86 (d, *J*=7.91 Hz, 1 H) 7.17 - 7.38 (m, 4 H).

Example 15

Intermediate 15

4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]sulfinyl}benzaldehyde



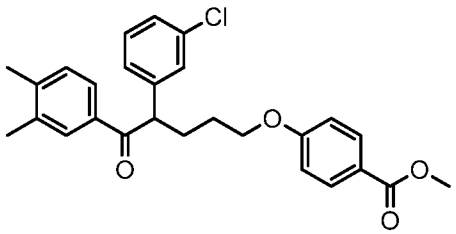
A mixture of **Intermediate 14** (440 mg, 1.03 mmoles), oxalyl-Cl (96 µL, 1.1 eq), DMSO (162 µL, 2.2 eq) and triethylamine (720 µL, 5.0 eq) were reacted to give 286 mg (65%) of **Intermediate 15**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.59 - 1.89 (m, 2 H) 2.10 (s, 3 H) 2.17 (s, 3 H) 2.62 (t, *J*=7.00 Hz, 2 H) 3.02 (t, *J*=7.33 Hz, 2 H) 6.46 (s, 1 H) 6.54 - 6.76 (m, 5 H) 6.87 (d, *J*=7.91 Hz, 1 H) 7.32 (d, *J*=8.50 Hz, 2 H) 7.74 (d, *J*=8.79 Hz, 2 H) 9.92 (s, 1 H).

Example 16

Intermediate 16

Methyl4-{[4-(3-chlorophenyl)-5-(3,4-dimethylphenyl)-5-oxopentyl]oxy}benzoate



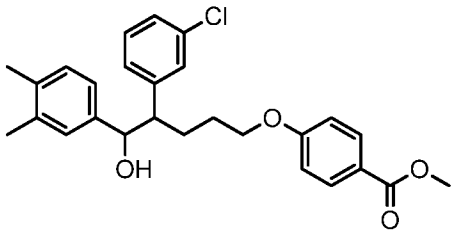
A mixture of 2-(3-chlorophenyl)-1-(3,4-dimethylphenyl)ethanone [CAS 1275947-05-1] (2.0 g, 7.7 moles), LDA (7.8 mL, 1.5 eq), and 4-(3-iodopropoxylbenzoate) [CAS 152936-91-9] (3.2 g, 1.5 eq) were reacted to give 1.64 g (47%) of **Intermediate 16**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.66 - 1.88 (m, 2 H) 1.90 - 2.10 (m, 1 H) 2.27 (s, 6 H) 2.29 - 2.41 (m, 1 H) 3.87 (s, 3 H) 4.00 (t, *J*=6.30 Hz, 2 H) 4.60 (t, *J*=7.33 Hz, 1 H) 6.84 (d, *J*=9.08 Hz, 2 H) 7.13 - 7.24 (m, 4 H) 7.32 (br. s, 1 H) 7.68 (d, *J*=7.70 Hz, 1 H) 7.73 (s, 1 H) 7.95 (d, *J*=9.08 Hz, 2 H).

Example 17

Intermediate 17

Methyl 4-{[4-(3-chlorophenyl)-5-(3,4-dimethylphenyl)-5-hydroxypentyl]oxy}benzoate



A mixture of **Intermediate 16** (1.96 g, 4.35 mmoles), $NaBH_4$ (164 mg, 1.0 eq) were reacted to give quantitative yield of **Intermediate 17**.

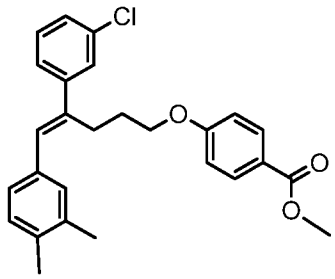
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.42 - 1.71 (m, 4 H) 2.20 - 2.26 (m, 6 H) 2.83 - 2.92 (m, 1 H) 3.76 - 3.83 (m, 2 H) 3.86 (s, 3 H) 4.65 (d, *J*=8.20 Hz, 1 H)

6.75 (d, *J*=8.79 Hz, 2 H) 6.93 - 7.18 (m, 5 H) 7.19 - 7.32 (m, 2 H) 7.92 (d, *J*=8.79 Hz, 2 H).

Example 18

Intermediate 18

Methyl 4-{[(4E)-4-(3-chlorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzoate



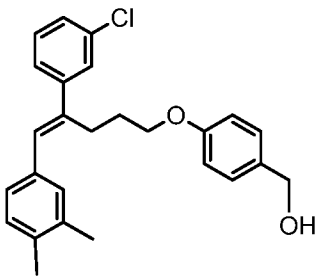
A mixture of **Intermediate 17** (2.25 g, 5.0 mmoles), molecular sieves (100 mg) and p-TsOH (1.1 g, 1.2 eq) were reacted to give 2.0 g (86%) of **Intermediate 18**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.83 - 1.93 (m, 2 H) 2.07 (s, 3 H) 2.14 (s, 3 H) 2.65 (t, *J*=7.18 Hz, 2 H) 3.87 (s, 3 H) 4.01 (t, *J*=6.30 Hz, 2 H) 6.43 (s, 1 H) 6.56 - 6.60 (m, 1 H) 6.69 (s, *J*=5.89, 5.89 Hz, 1 H) 6.78 - 6.91 (m, 3 H) 7.02 - 7.09 (m, 1 H) 7.17 - 7.26 (m, 3 H) 7.93 - 8.00 (m, 2 H).

Example 19

Intermediate 19

(4-{[(4E)-4-(3-chlorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}phenyl)methanol



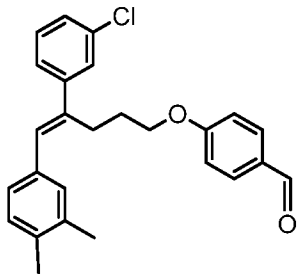
A mixture of **Intermediate 18** (1.6 g, 3.7 mmoles) and LAH (1.0 M, 4.0 mL, 1.1 eq) were reacted to give 1.15 g (77%) of **Intermediate 19**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.84 - 1.91 (m, 2 H) 2.08 (s, 3 H) 2.15 (s, 3 H) 2.61 - 2.67 (m, 2 H) 3.97 (t, *J*=6.30 Hz, 2 H) 4.60 (d, *J*=5.27 Hz, 2 H) 6.43 (s, 1 H) 6.57 - 6.60 (m, 1 H) 6.69 - 6.71 (m, 1 H) 6.82 - 6.90 (m, 3 H) 7.02 - 7.06 (m, 1 H) 7.17 - 7.29 (m, 5 H).

Example 20

Intermediate 20

4-{[(4E)-4-(3-chlorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzaldehyde



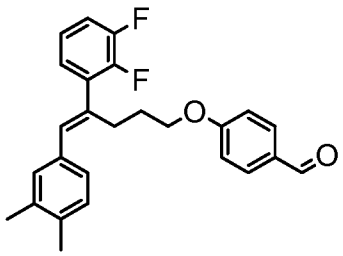
A mixture of **Intermediate 19** (1.24 g, 3.0 mmoles), 1.0 g of molecular sieves, NMO (714 mg, 2.0 eq) and TPAP (50 mg) were reacted to give 857 mg (70%) of **Intermediate 20.**

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.86 - 1.95 (m, 2 H) 2.08 (s, 3 H) 2.15 (s, 3 H) 2.66 (t, *J*=7.60 Hz, 2 H) 4.06 (t, *J*=6.30 Hz, 2 H) 6.44 (s, 1 H) 6.54 - 6.63 (m, 1 H) 6.69 (s, 1 H) 6.84 (d, *J*=6.28 Hz, 1 H) 6.94 - 7.01 (m, 2 H) 7.03 - 7.09 (m, 1 H) 7.18 - 7.27 (m, 3 H) 7.83 (d, *J*=7.98 Hz, 2 H) 9.88 (s, *J*=3.23 Hz, 1 H).

Example 21

Intermediate 21

(E)-4-((4-(2,3-Difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl)oxy)benzaldehyde



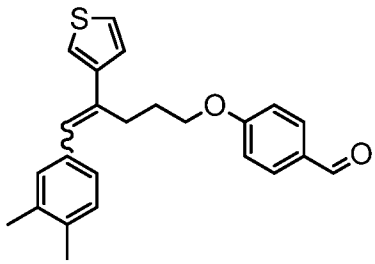
A mixture of (E)-(4-((4-(2,3-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl)oxy)phenyl)methanol (1.2 g, 2.9 mmoles), 1.0 g of molecular sieve, NMO (690 mg, 2.0 eq) and TPAP (50 mg) were reacted to give 980 mg (82 %) of **Intermediate 21.**

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.81 - 1.99 (m, 2 H) 2.08 (s, 3 H) 2.15 (s, 3 H) 2.69 (t, *J*=7.62 Hz, 2 H) 4.08 (t, *J*=6.30 Hz, 2 H) 6.50 - 6.64 (m, 2 H) 6.69 (s, 1 H) 6.79 - 6.93 (m, 2 H) 6.94 - 7.18 (m, 4 H) 7.83 (d, *J*=8.50 Hz, 2 H) 9.89 (s, 1 H).

Example 22

Intermediate 22

4-((5-(3,4-dimethylphenyl)-4-(thiophen-3-yl)pent-4-en-1-yl)oxy)benzaldehyde



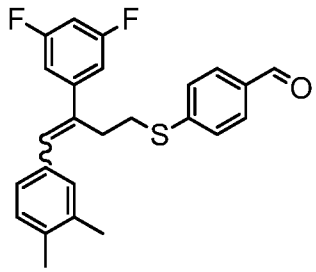
A mixture of (E)-(4-((5-(3,4-dimethylphenyl)-4-(thiophen-3-yl)pent-4-en-1-yl)oxy)phenyl)methanol (1.64 g, 4.3 mmoles), 1.0 g of molecular sieve, NMO (1.0 g, 2.0 eq) and TPAP (60 mg) were reacted to give 324 mg of **Intermediate 22.**

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.84 - 1.99 (m, 2 H) 2.11 (s, 3 H) 2.18 (s, 3 H) 2.24 (d, *J*=3.22 Hz, 4 H) 2.58 - 2.73 (m, 2 H) 2.89 (t, *J*=7.62 Hz, 1 H) 3.93 - 4.10 (m, 3 H) 6.42 (s, 1 H) 6.72 (d, *J*=12.89 Hz, 2 H) 6.84 - 6.93 (m, 3 H) 6.98 (d, *J*=8.50 Hz, 2 H) 7.07 (s, 2 H) 7.19 - 7.27 (m, 1 H) 7.27 - 7.36 (m, 2 H) 7.75 - 7.88 (m, 3 H) 9.88 (s, 1 H).

Example 23

Intermediate 23

4-((3-(3,5-Difluorophenyl)-4-(3,4-dimethylphenyl)but-3-en-1-yl)thio)benzaldehyde



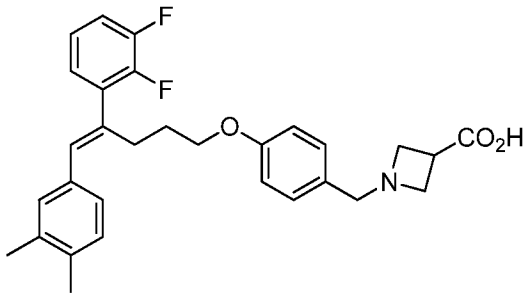
A mixture of (E)-(4-((3-(3,5-difluorophenyl)-4-(3,4-dimethylphenyl)but-3-en-1-yl)thio)phenyl)methanol (987 mg, 2.4 mmoles), 500 mg of molecular sieve, NMO (562 mg, 2.0 eq) and TPAP (40 mg) were reacted to give **Intermediate 23.**

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.23 (s, 3 H) 2.28 (s, 3 H) 2.96 - 3.09 (m, 4 H) 6.70 - 6.80 (m, 1 H) 6.81 (s, 1 H) 6.92 - 7.01 (m, 2 H) 7.03 (d, *J*=5.57 Hz, 2 H) 7.07 - 7.13 (m, 1 H) 7.20 (d, *J*=8.50 Hz, 2 H) 7.66 (d, *J*=8.20 Hz, 2 H) 9.91 (s, 1 H). (mixture of isomers)

Example 24

Compound 1

1-(4-{[(4E)-4-(2,3-Difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid



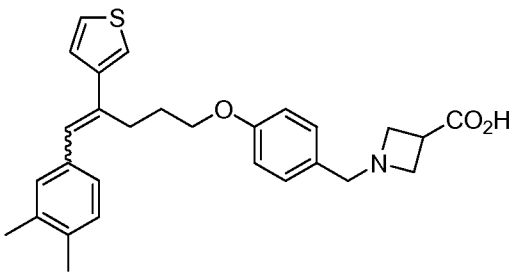
A mixture of **Intermediate 21** (156 mg, 0.38 mmoles), azetidine carboxylic acid (39 mg, 1.0 eq), HOAc (5 drops) and $NaCNBH_3$ (24.2 mg, 1.0 eq) were reacted to give **Compound 1**.

^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.73 - 1.95 (m, 2 H) 2.07 (s, 3 H) 2.14 (s, 3 H) 2.65 (t, *J*=7.18 Hz, 2 H) 3.20 - 3.42 (m, 1 H) 3.82 - 4.02 (m, 4 H) 4.07 (s, 2 H) 4.12 - 4.28 (m, 2 H) 6.52 - 6.64 (m, 2 H) 6.70 (s, 1 H) 6.78 - 6.94 (m, 4 H) 6.96 - 7.14 (m, 2 H) 7.34 (d, *J*=8.50 Hz, 2 H).

Example 25

Compound 2

1-(4-{[5-(3,4-dimethylphenyl)-4-(3-thienyl)pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid



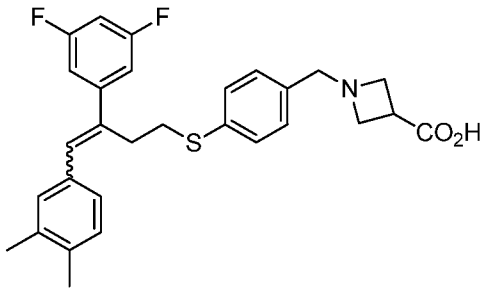
A mixture of **Intermediate 22** (162 mg, 0.43 mmoles), azetidine carboxylic acid (43.5 mg, 1.0 eq), HOAc (5 drops) and $NaCNBH_3$ (27.0 mg, 1.0 eq) were reacted to give **Compound 2**.

(mixture of isomers): ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.79 - 1.96 (m, 2 H) 1.97 - 2.06 (m, 1 H) 2.10 (s, 3 H) 2.17 (s, 3 H) 2.25 (s, 4 H) 2.53 - 2.69 (m, 2 H) 2.77 - 2.94 (m, 1 H) 3.23 - 3.42 (m, 2 H) 3.80 - 4.02 (m, 7 H) 4.02 - 4.23 (m, 6 H) 6.30 - 6.49 (m, 1 H) 6.69 (d, *J*=6.74 Hz, 1 H) 6.76 (s, 1 H) 6.78 - 6.93 (m, 6 H) 7.00 - 7.05 (m, 1 H) 7.08 (br. s, 2 H) 7.16 - 7.24 (m, 1 H) 7.25 - 7.37 (m, 5 H).

Example 26

Compound 3

1-(4-{[3-(3,5-difluorophenyl)-4-(3,4-dimethylphenyl)but-3-en-1-yl]thio}benzyl)azetidine-3-carboxylic acid



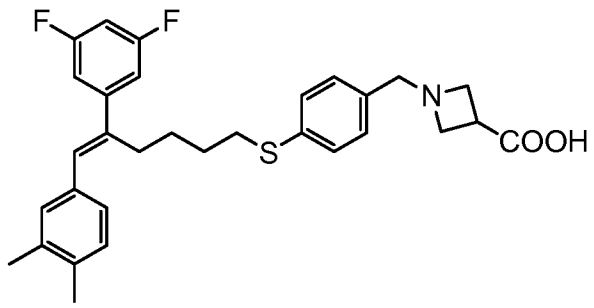
A mixture of **Intermediate 23** (265 mg, 0.65 mmoles), azetidine carboxylic acid (65.0 mg, 1.0 eq), HOAc (5 drops) and $NaCNBH_3$ (41.0 mg, 1.0 eq) were reacted to give **Compound 3**.

(mixture of isomers): ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.04 (s, 3 H) 2.09 (s, 3 H) 2.15 (s, 3 H) 2.20 (s, 3 H) 2.67 - 2.78 (m, 1 H) 2.85 - 2.97 (m, 3 H) 3.13 (d, *J*=2.93 Hz, 3 H) 3.32 (br. s., 2 H) 3.46 (s, 2 H) 6.47 (s, 1 H) 6.50 - 6.58 (m, 1 H) 6.71 (s, 1 H) 6.78 - 6.91 (m, 2 H) 6.94 - 7.11 (m, 1 H) 7.10 - 7.27 (m, 5 H).

Example 27

Compound 4

1-(4-{[(5E)-5-(3,5-difluorophenyl)-6-(3,4-dimethylphenyl)hex-5-en-1-yl]sulfanyl}benzyl)azetidine-3-carboxylic acid



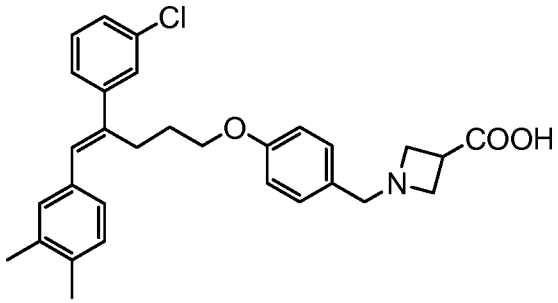
A sample of **Intermediate 5** (100 mg, 0.23 mmoles) was dissolved in minimum THF. Methanol (5mL) was then added followed by 5 drops of HOAc. Azetidine-3-carboxylic acid (23 mg, 1.0 eq) was added and the resulting mixture was stirred at room temperature for 30 minutes. $NaCNBH_3$ (14.4 mg, 1.0 eq) was dissolved in 0.5 mL MeOH and added to the reaction. The resulting mixture was stirred at room temperature for 3 hours. It was then quenched with water and concentrated on the rotary evaporator. The crude mixture was purified by MPLC to give **Compound 4**.

^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.46-1.58 (m, 2 H) 1.62-1.74 (m, 2 H) 2.08 (s, 3 H) 2.15 (s, 3 H) 2.51 (t, *J*=7.18 Hz, 2 H) 2.96 (t, *J*=7.03 Hz, 2 H) 3.36 (t, *J*=8.20 Hz, 1 H) 4.00 - 4.15 (m, 4 H) 4.24 (s, 2 H) 6.45 (s, 1 H) 6.60 (d, *J*=7.90 Hz, 1 H) 6.63 - 6.73 (m, 3 H) 6.84 (m, 2 H) 7.33 (br. s, 4 H).

Example 28

Compound 5

1-(4-{[(4E)-4-(3-Chlorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid



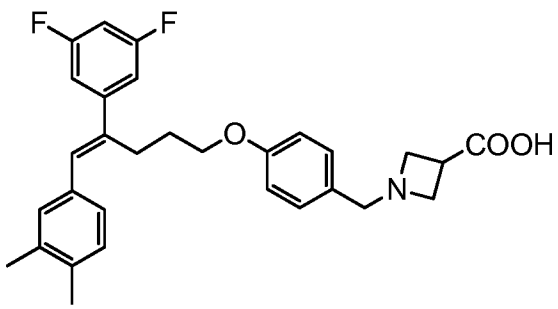
A mixture of **Intermediate 20** (236 mg, 0.58 mmoles), azetidine carboxylic acid (59 mg, 1.0 eq), HOAc (10 drops) and $NaCNBH_3$ (36.7 mg, 1 eq) were reacted to give **Compound 5**.

^1H NMR (300 MHz, CD_3OD) δ ppm 1.78 - 1.88 (m, 2 H) 2.05 (s, 3 H) 2.14 (s, 3 H) 2.69 (t, *J*=7.03 Hz, 2 H) 3.33 - 3.43 (m, 1 H) 4.02 (t, *J*=6.15 Hz, 2 H) 4.12 (d, *J*=8.20 Hz, 4 H) 4.24 (s, 2 H) 6.47 (s, 1 H) 6.54 - 6.58 (m, 1 H) 6.65 (s, 1 H) 6.81 (d, *J*=7.91 Hz, 1 H) 6.94 - 7.00 (m, 2 H) 7.06-7.11 (m, 1 H) 7.15 - 7.18 (m, 1 H) 7.23 - 7.29 (m, 2 H) 7.35 (d, *J*=8.79 Hz, 2 H).

Example 29

Compound 6

1-(4-{[(4E)-4-(3,5-Difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid



A mixture of **Intermediate 10** (200 mg, 0.5 mmoles), azetidine carboxylic acid (49.75 mg, 1.0 eq), HOAc (10 drops) and $NaCNBH_3$ (31 mg, 1 eq) were reacted to give **Compound 6**.

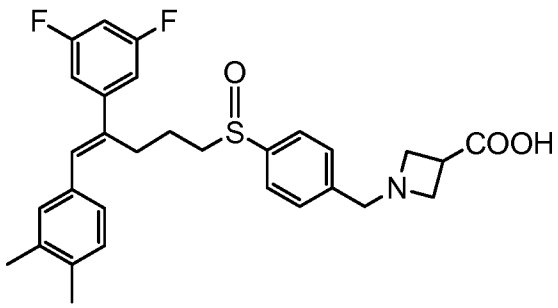
^1H NMR (300 MHz, CD_3OD) δ ppm 1.79 - 1.91 (m, 2 H) 2.07 (s, 3 H) 2.15 (s, 3 H) 2.68 (t, *J*=7.03 Hz, 2 H) 3.36 (t, *J*=8.50 Hz, 1 H) 4.02 (t, *J*=6.15 Hz, 2 H)

4.11 (d, *J*=8.50 Hz, 4 H) 4.23 (s, 2 H) 6.50 (s, 1 H) 6.55 - 6.61 (m, 1 H) 6.68 (s, 1 H) 6.71 - 6.88 (m, 4 H) 6.94 - 7.00 (m, 2 H) 7.36 (d, *J*=8.50 Hz, 2 H).

Example 30

Compound 7

1-(4-{[(4E)-4-(3,5-Difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]sulfinyl}benzyl)azetidine-3-carboxylic acid



A mixture of **Intermediate 15** (143 mg, 0.34 mmoles), azetidine carboxylic acid (34 mg, 1.0 eq), HOAc (7 drops) and $NaCNBH_3$ (21.2 mg, 1 eq) were reacted to give **Compound 7**.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.28 - 1.57 (m, 2 H) 1.76 - 1.95 (m, 1 H) 1.97 - 2.14 (m, 1 H) 2.23 (s, 6 H) 2.85 - 3.02 (m, 2 H) 3.06 - 3.19 (m, 2 H) 3.23 - 3.34 (m, 2 H) 3.44 (s, 2 H) 4.91 (t, *J*=7.90 Hz, 1 H) 6.97 - 7.19 (m, 8 H) 7.23 (d, *J*=7.91 Hz, 1 H) 7.73 - 7.81 (m, 2 H).

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, dithitothreitol 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'-adenylylimmidodiphosphate 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 S1P in the presence of test antagonist at concentrations ranging from 0.08 to 5000 nM.

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

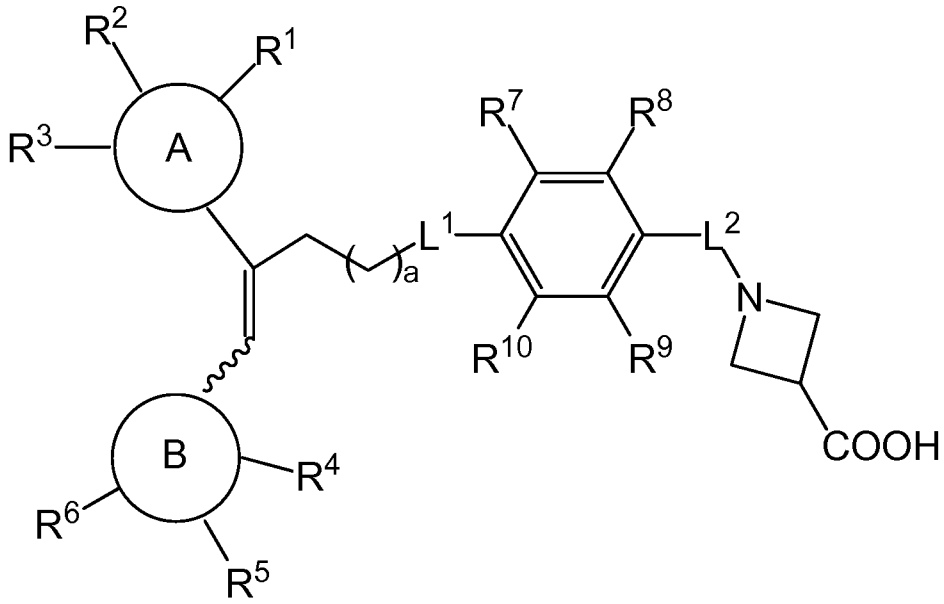
Activity potency: S1P1 receptor from GTP $\gamma^{35}S$: nM, (EC_{50}).

Table 1

IUPAC name	**S1P1 EC_{50} (nM)**
1-(4-{[(5E)-5-(3,5-difluorophenyl)-6-(3,4-dimethyl phenyl) hex-5-en-1-yl]sulfanyl}benzyl)azetidine-3-carboxylic acid	652.36
1-(4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl) pent-4-en-1-yl]sulfinyl}benzyl)azetidine-3-carboxylic acid	157.75
1-(4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl) pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid	4.21
1-(4-{[(4E)-4-(3-chlorophenyl)-5-(3,4-dimethylphenyl) pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid	27.90
1-(4-{[(4E)-4-(2,3-difluorophenyl)-5-(3,4-dimethylphenyl) pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid	479.84
1-(4-{[5-(3,4-dimethylphenyl)-4-(3-thienyl)pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid	36.03

What is claimed is:

1. A compound represented by Formula I, or an E geometric isomer, or a Z geometric isomer, or a mixture of an E and a Z geometric isomers, or an enantiomer, or a diastereoisomer, or a tautomer, or a zwitterion, or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

A is optionally substituted C_{6-10} aryl, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl or optionally substituted C_{3-8} cycloalkenyl;

B is optionally substituted C_{6-10} aryl, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl or optionally substituted C_{3-8} cycloalkenyl;

R^1 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, C(O)R^{11}, $NR^{12}R^{13}$ or hydroxyl;

R^2 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, C(O)R^{11}, $NR^{12}R^{13}$ or hydroxyl;

R^3 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, $NR^{12}R^{13}$ or hydroxyl;

R^4 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, $NR^{12}R^{13}$ or hydroxyl;

R^5 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, $NR^{12}R^{13}$ or hydroxyl;

R^6 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, $NR^{12}R^{13}$ or hydroxyl;

R^7 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, optionally substituted C_{6-10} aryl, optionally substituted heterocycle, optionally substituted C $_{3-8}$ cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, $NR^{12}R^{13}$ or hydroxyl;

R^8 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, optionally substituted C_{6-10} aryl, optionally substituted heterocycle, optionally substituted C $_{3-8}$ cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, $NR^{12}R^{13}$ or hydroxyl;

R^9 is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, optionally substituted C_{6-10} aryl, optionally substituted heterocycle, optionally substituted C $_{3-8}$ cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, $NR^{12}R^{13}$ or hydroxyl;

R^{10} is H, halogen, -OC_{1-8} alkyl, optionally substituted C_{1-8} alkyl, CN, $C(O)R^{11}$, optionally substituted C_{6-10} aryl, optionally substituted heterocycle, optionally substituted C $_{3-8}$ cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, $NR^{12}R^{13}$ or hydroxyl;

L^1 is O, S, S(O), NH or CH_2;

L^2 is O, S or CHR^{12};

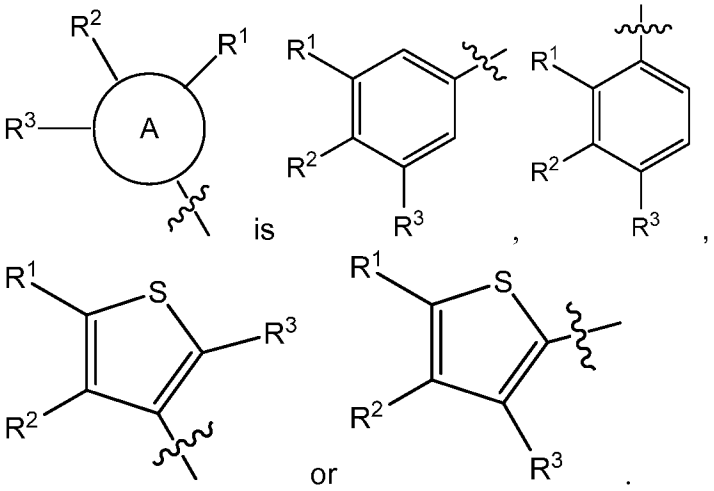
R^{11} is OH or optionally substituted C_{1-8} alkyl;

a is 1, 2, 3, 4, 5 or 6;

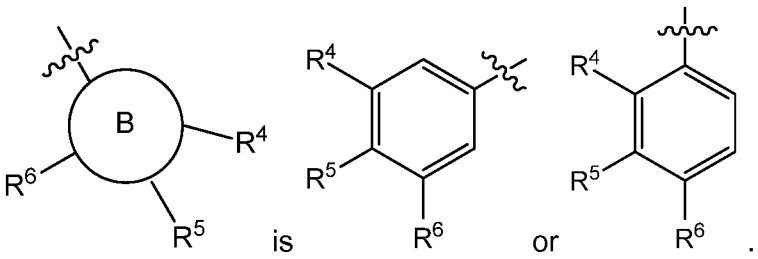
R^{12} is H or optionally substituted C_{1-8} alkyl; and

R^{13} is H or optionally substituted C_{1-8} alkyl.

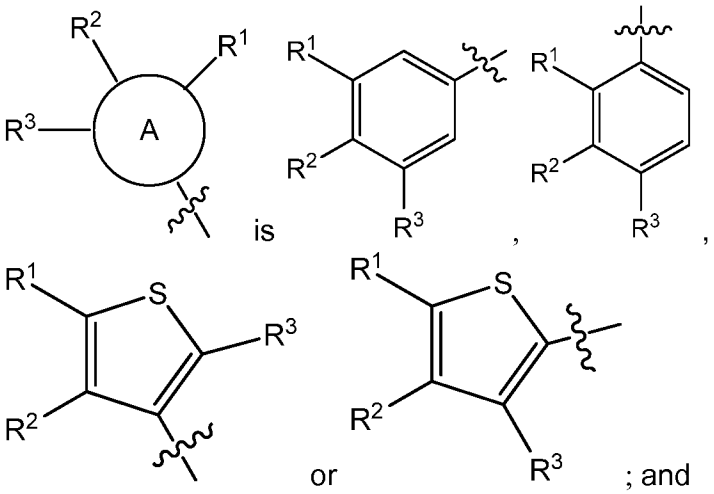
2. A compound according to claim 1 wherein

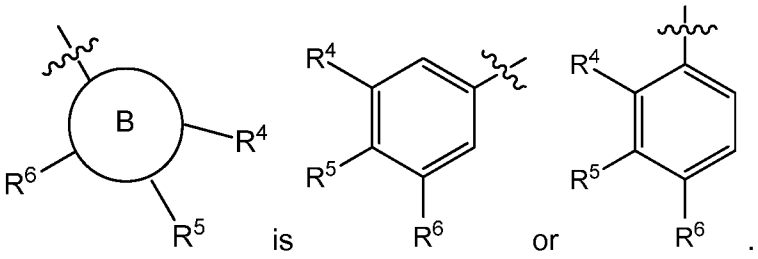


3. A compound according to claim 1 wherein

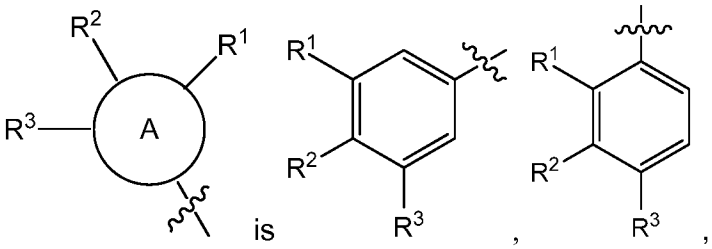


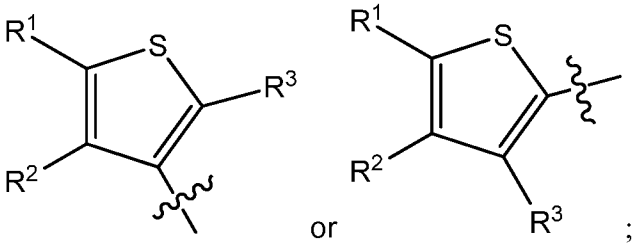
4. A compound according to claim 1, wherein

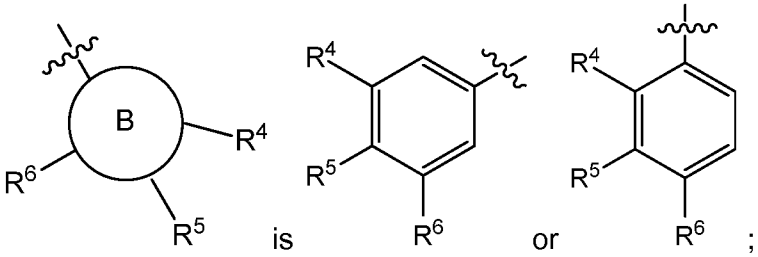




5. A compound according to claim 1, wherein







R^1 is H, halogen or optionally substituted C_{1-8} alkyl;

R^2 is H, halogen or optionally substituted C_{1-8} alkyl;

R^3 is H, halogen or optionally substituted C_{1-8} alkyl;

R^4 is H, halogen or optionally substituted C_{1-8} alkyl;

R^5 is H, halogen or optionally substituted C_{1-8} alkyl;

R^6 is H, halogen or optionally substituted C_{1-8} alkyl;

R^7 is H, halogen or optionally substituted C_{1-8} alkyl;

R^8 is H, halogen or optionally substituted C_{1-8} alkyl;

R^9 is H, halogen or optionally substituted C_{1-8} alkyl;
R^{10} is H, halogen or optionally substituted C_{1-8} alkyl;
L^1 is O, NH, CH_2, S or S(O);
L^2 is CH_2; and
a is 1, 2 or 3.

6. The compound of claim 5 in an E geometrical configuration.

7. The compound of claim 5 in an mixture of E and Z geometrical configuration.

8. A compound according to claim 5 wherein L^1 is S(O).

9. A compound according to claim 5 wherein L^1 is S.

10. A compound according to claim 5 wherein L^1 is O.

11. A compound according to claim 1, selected from:
1-(4-{[(5E)-5-(3,5-difluorophenyl)-6-(3,4-dimethylphenyl)hex-5-en-1-yl]sulfanyl}benzyl) azetidine-3-carboxylic acid;
1-(4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]sulfinyl}benzyl) azetidine-3-carboxylic acid;
1-(4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzyl) azetidine-3-carboxylic acid;
1-(4-{[(4E)-4-(3-chlorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid;
1-(4-{[(4E)-4-(2,3-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzyl) azetidine-3-carboxylic acid;
1-(4-{[5-(3,4-dimethylphenyl)-4-(3-thienyl)pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid; and
1-(4-{[3-(3,5-difluorophenyl)-4-(3,4-dimethylphenyl)but-3-en-1-yl]thio}benzyl)azetidine-3-carboxylic acid.

12. 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.

13. A pharmaceutical composition according to claim 12 wherein the compound is selected from:

1-(4-{[(5E)-5-(3,5-difluorophenyl)-6-(3,4-dimethylphenyl)hex-5-en-1-yl]sulfanyl}benzyl) azetidine-3-carboxylic acid;

1-(4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]sulfinyl}benzyl) azetidine-3-carboxylic acid;

1-(4-{[(4E)-4-(3,5-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzyl) azetidine-3-carboxylic acid;

1-(4-{[(4E)-4-(3-chlorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid;

1-(4-{[(4E)-4-(2,3-difluorophenyl)-5-(3,4-dimethylphenyl)pent-4-en-1-yl]oxy}benzyl) azetidine-3-carboxylic acid;

1-(4-{[5-(3,4-dimethylphenyl)-4-(3-thienyl)pent-4-en-1-yl]oxy}benzyl)azetidine-3-carboxylic acid; and

1-(4-{[3-(3,5-difluorophenyl)-4-(3,4-dimethylphenyl)but-3-en-1-yl]thio}benzyl)azetidine-3-carboxylic acid.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/015291

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D409/12 A61K31/397 C07D205/04
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 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, BIOSIS, CHEM ABS Data, EMBASE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/093704 A1 (ABBOTT LAB [US]; HARRIS CHRISTOPHER M [US]; HOBSON ADRIAN D [US]; WILS) 19 August 2010 (2010-08-19) Formula 1; Formula on page 16; page 16, line 11 - page 17, line 18; claims 5,7,8,18; compound F.10 -----	1-13
A	WO 2012/074926 A1 (ALLERGAN INC [US]; SINHA SANTOSH C [US]; BHAT SMITA S [US]; CORPUZ EVE) 7 June 2012 (2012-06-07) Formula I; page 2, lines 5-20; claims 1,12; compound 6 -----	1-13

☐ 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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"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	Date of mailing of the international search report
28 March 2014	10/04/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rudolf, Manfred

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/015291

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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