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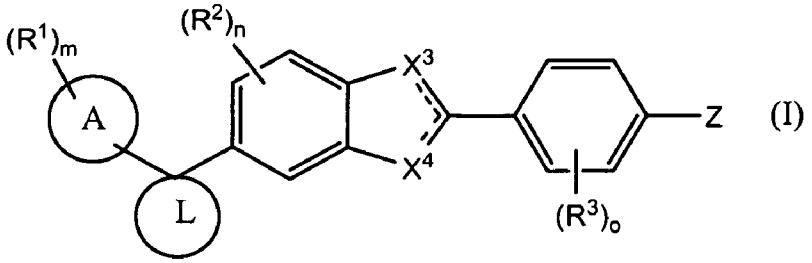

(57) Abstract: The present invention relates to compounds of Formula (I) that are have activity as S1P receptor modulating agents, more specifically to specifically compounds that are S1P1 receptor agonists. The invention also related to the use of such compounds to treat diseases associated with inappropriate S1P1 receptor activity such as autoimmune diseases.

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S1P1 RECEPTOR AGONISTS AND USE THEREOF

CROSS-REFERENCE

This application claims priority under 35 U.S.C. 119(e) to US provisional application No. 61/074,476 filed on June 20, 2008, the disclosures of which are incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to compounds that are have activity as S1P receptor modulating agents, more specifically to specifically compounds that are S1P1 receptor agonists. The invention also related to the use of such compounds to treat diseases associated with inappropriate S1P1 receptor activity such as autoimmune diseases.

BACKGROUND

Sphingosine-1-phosphate (S1P) has been demonstrated to induce many cellular effects, including those that result in platelet aggregation, cell proliferation, cell morphology changes, tumor cell invasion, endothelial cell chemotaxis and endothelial cell *in vitro* angiogenesis. S1P receptors are therefore good targets for therapeutic applications such as wound healing and tumor growth inhibition. S1P signals cells in part via a set of G protein-coupled receptors named S1P1, S1P2, S1P3, S1P4, and S1P5 (formerly called EDG-1, EDG-5, EDG-3, EDG-6, and EDG-8, respectively). These receptors share 50-55% amino acid and cluster identity with three other receptors (LPA1, LPA2, and LPA3 (formerly EDG-2, EDG-4 and EDG-7)) for the structurally-related lysophosphatidic acid (LPA).

A conformational shift is induced in the G-Protein Coupled Receptor (GPCR) when the ligand binds to that receptor, causing GDP to be replaced by GTP on the α-subunit of the associated G-proteins and subsequent release of the G-proteins into the cytoplasm. The α-subunit then dissociates from the βγ-subunit, and each subunit can then associate with effector proteins, which activate second messengers leading to a cellular response. Eventually the GTP on the G-proteins is hydrolyzed to GDP, and the subunits of the G-proteins re-associate with each other and then with the receptor. Amplification plays a major role in the general GPCR pathway. The binding of one ligand to one receptor leads to the activation of many G-proteins, each capable of associating with many effector proteins, leading to an amplified cellular response.

S1P receptors make good drug targets, because individual receptors are both tissue- and response-specific. Tissue specificity of the S1P receptors is important, because development of an agonist or antagonist selective for one receptor localizes the cellular response to tissues containing that receptor, limiting unwanted side effects. Response specificity of the S1P receptors is also important because it allows for development of agonists or antagonists that initiate or suppress certain cellular responses without affecting other things.

For example, the S1P1 receptor subtype plays a key role in lymphocyte trafficking, and it is well established that synthetic small molecule S1P1 receptor agonists can suppress the peripheral immune response by inducing lymphocyte sequestration in secondary lymph organs (Cooke, N.; Zecri, F. Sphingosine 1-phosphate type 1 receptor modulators: recent advances and therapeutic potential. *Ann. Reports Med. Chem.* 2007;42: 245-263).

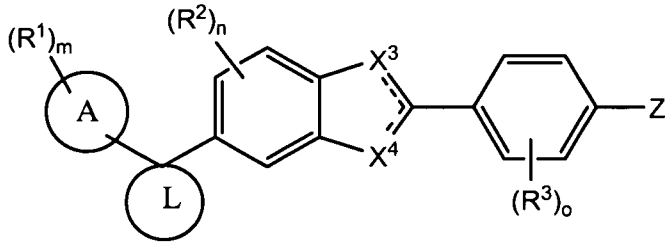
Identification of the importance of this axis in modulating immune function was primarily accomplished via reverse pharmacology with the small molecule FTY720 (fingolimod). FTY720 is a prodrug that is phosphorylated *in vivo* to generate FTY720-P, an agonist of all known S1P receptors with the exception of $S1P_2$ (Mandala S, Hajdu R, Bergstrom J, et al. Alteration of lymphocyte trafficking by sphingosine-1-phosphate receptor agonists. *Science.* 2002;296:346-349). Preclinical studies established that FTY720 administration resulted in peripheral lymphopenia that was associated with beneficial outcomes in animal models of transplantation (Brinkmann V and Lynch KR. FTY720: targeting G-protein-coupled receptors for spingosine-1-phosphate in transplantation and autoimmunity. *Curr. Op. Immunol.* 2002; 14:569-575 and references therein) and autoimmune diseases (e.g. arthritis; Matsuura M, Imayoshi T and Okumoto T. Effect of FTY720, a novel immunosuppressant, on adjuvant-and collagen-induced arthritis in rats. *Int. J of Immunopharm.* 2000;22:323-331), including experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS); (Kataoka H, Sugahara K, Shimano K, et al. FTY720, sphingosine 1-phosphate receptor modulator, ameliorates experimental autoimmune encephalomyelitis by inhibition of T cell infiltration. *Cell. and Mol. Immunol.* 2005; 2(6):439-448; MRL-lpr/lpr mice, an animal model of systemic lupus erythematosus (SLE) (Okazaki H, Hirata D, Kamimura T et al. Effects of FTY720 in MRL-lpr/lpr Mice: Therapeutic Potential in Systemic Lupus Erythematosus. *J. Rheumatol.* 2002; 29:707-716) and development of diabetes in NOD mice (Yang Z., Chen M. Fialkow LB et al. Immune modulator FTY720 prevents autoimmune diabetes in non obese diabetic mice. *Clin Imunol.* 2003; 107:30-35). In addition, results from a recently completed clinical trial of FTY720 (Phase 2) in MS patients highlight the potential of S1P receptor agonism as an effective therapeutic approach for treating human autoimmune diseases (Kappos

L, Antel J, Comi G, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl. J. Med.* 2006; 355(11):1124-1140).

The current therapies for the treatment of immune diseases usually suppress the whole immune system of the patient and hence the body's ability to react to infections is also severely compromised. Typical drugs in this class include azathioprine, chlorambucil, cyclophosphamide, cyclosporin, or methotrexate. Corticosteroids which reduce inflammation and suppress the immune response, cause side effects when used in long term treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce pain and inflammation, however, they exhibit considerable side effects such as gastrointestinal bleeding. Accordingly, there is a need for treatments that do not suffer from these side effects. The present invention fulfills this and related needs.

SUMMARY

In one aspect, provided is a compound of Formula (I):



wherein:

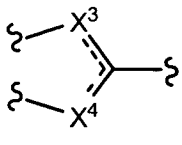
m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

o is 0, 1, 2 or 3;

A is a phenyl, heterocyclyl, three to six membered cycloalkyl, or a five or six membered heteroaryl ring;

L is a saturated 3, 4, 5, 6 or 7-member ring containing 0, 1 or 2 atoms selected from N, O and S and optionally containing a double bond, the ring being substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;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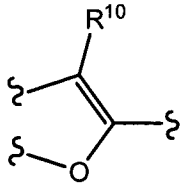
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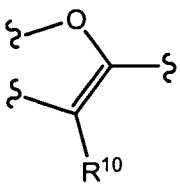
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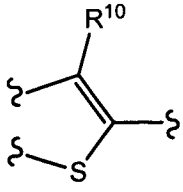
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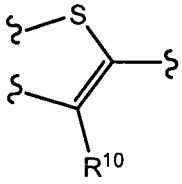

;

R^1 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, CN, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;

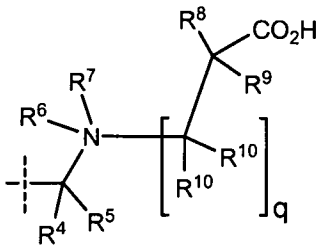
R^2 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;

R^3 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, amino, and -OC_{1-4}haloalkyl;

Z is:

(i) a cycloalkyl substituted with amino, monoalkylamino or dialkylamino group; a cycloalkylalkyl substituted with one or two carboxy groups; a monosubstituted amino, disubstituted amino, carboxyalkylamino, hydroxyalkyl, substituted hydroxyalkyl, hydroxyalkoxy, substituted hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, substituted carboxyalkyl, carboxyalkyloxy, substituted carboxyalkyloxy, carboxyalkylthio, substituted carboxyalkylthio, carboxyalkylsulfonyl, substituted carboxyalkylsulfonyl, carboxyalkoxyalkyl, substituted carboxyalkoxyalkyl, aminocarbonyl, acylamino, sulfonylamino, heterocycloamino, heterocycloaminoalkyl, heterocycloaminocarbonyl, heterocycloaminooxy, or heteroaralkyl group;

(ii) a group of formula (b):


(b)

where:

q is 0, 1 or 2;

R^4 is selected from H, C_{1-3}haloalkyl, C_{1-6}alkyl;

R^5 is selected from H, C_{1-3}haloalkyl, C_{1-4}alkyl; or

R^4 and R^5 together with the carbon atom to which they are attached form a 3, 4, 5, 6 or 7-member carbocyclic ring substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;

R^6 is a lone pair of electrons or O;

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

R^8 is selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; or

R^7 and R^8, when taken together, form a group that is selected from -$(CR^{10}R^{10})$-, -$(CR^{10}R^{10})$O-, -O$(CR^{10}R^{10})$-, -$(CR^{10}R^{10})(CR^{10}R^{10})$-, and -$(CR^{10}R^{10})_3$-;

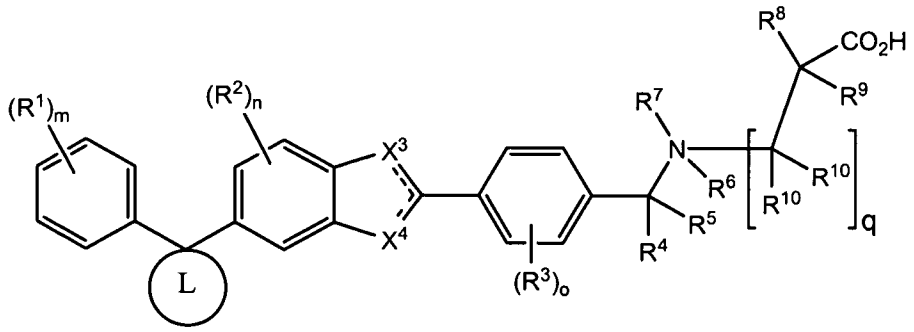
R^9 is selected from H, F, C_{1-3}haloalkyl, C_{1-4}alkyl, OH and OC_{1-4}alkyl; or R^8 and R^9 together with the carbon atom to which they are attached from cycloalkyl; and

each R^{10} is independently in each instance selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; or

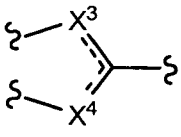
(iii) when R^3 is on a carbon atom of the phenyl ring that is adjacent to the carbon of the phenyl ring that is bonded to Z, then R^3 and Z can combine to form -CH=CH-NR^{11}-, –$(CH_2)_2NR^{11}$-, –$CH_2NR^{11}CH_2$-, –$(CH_2)_2NR^{11}CH_2$-, -N=CR^{11}-NH-, or -N=CH-NR^{11}-, where R^{11} is selected from hydrogen, hydroxyalkyl, aminoalkyl, carboxyalkyl, substituted hydroxyalkyl or substituted carboxyalkyl; or aminocarbonyl; or

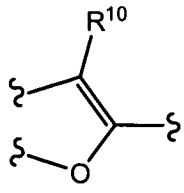
a pharmaceutically acceptable thereof.

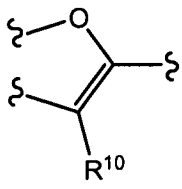
In one embodiment, the compound of Formula (I) has the Formula (Ia):

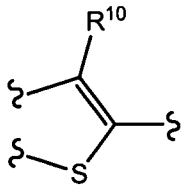


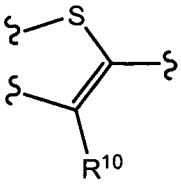
(Ia)



is selected from 

, 

, 

and 

;

L is a saturated 3, 4, 5, 6 or 7-member ring containing 0, 1 or 2 atoms selected from N, O and S, the ring being substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

o is 0, 1, 2 or 3;

q is 1 or 2;

R^1 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;

R^2 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;

R^3 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;

R^4 is selected from H, C_{1-3}haloalkyl, C_{1-6}alkyl;

R^5 is selected from H, C_{1-3}haloalkyl, C_{1-4}alkyl; or R^4 and R^5 together with the carbon atom to which they are attached form a 3, 4, 5, 6 or 7-member carbocyclic ring substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;

R^6 is a lone pair of electrons or O;

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

R^8 is selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, OC_{1-4}alkyl, and OC_{1-4}haloalkyl; or R^7 and R^8, when taken together, form a group that is selected from -($CR^{10}R^{10}$)-, -($CR^{10}R^{10}$)O-, -O($CR^{10}R^{10}$)- and -($CR^{10}R^{10}$)($CR^{10}R^{10}$)-;

R^9 is selected from H, F, C_{1-3}haloalkyl, C_{1-4}alkyl, OH and OC_{1-4}alkyl; and

R^{10} is independently in each instance selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; and

R^{10} is independently in each instance selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; or

a pharmaceutically-acceptable salt thereof.

In a second aspect, the present invention provides a method for treating an S1P1 receptor mediated condition in a patient. In such a method, an amount of a compound effective to modulate an S1P1 receptor-mediated biological activity is administered to the patient. The S1P1 receptor mediated condition may be, *e.g.,* transplant rejection (solid organ transplant and islet cells); transplant rejection (tissue); cancer; autoimmune/inflammatory diseases; rheumatoid arthritis; lupus; insulin dependent diabetes (Type I); non-insulin dependent diabetes (Type II); multiple sclerosis; psoriasis; ulcerative colitis; inflammatory bowel disease; Crohn's disease; acute and chronic lymphocytic leukemias and lymphomas.

In a third aspect, the present invention provides methods for modulating S1P1 receptor mediated biological activity. The present invention also provides methods for using S1P1 modulators (*i.e.,* agonists) in treating or preventing diseases such as ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer and prostrate cancer; acute lung diseases, adult respiratory distress syndrome ("ARDS"), acute inflammatory exacerbation of chronic lung diseases such as asthma, surface epithelial cell injury such as transcorneal freezing or cutaneous burns, and cardiovascular diseases such as ischemia in a patient in need of such treatment or prevention.

In a fourth aspect, the invention provides methods for using S1P1 modulators in treating disorders such as, but not limited to, vasoconstriction in cerebral arteries, autoimmune and related immune disorders including systemic lupus erythematosus, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, type I diabetes, uveitis, psoriasis, myasthenia gravis, rheumatoid arthritis, non-glomerular nephrosis, hepatitis, Behçet's disease, glomerulonephritis, chronic thrombocytopenic purpura, hemolytic anemia, hepatitis and Wegner's granuloma.

In a fifth aspect, the invention provides methods for using S1P1 modulators to treat a disease or disorder in a patient, comprising administering to a subject in need of such treatment a therapeutically effective amount of an S1P-1 modulator, *e.g.,* an agonist, that stimulates the immune system. In certain embodiments, the patient is afflicted by an infectious agent. In other embodiments, the subject is immunocompromised.

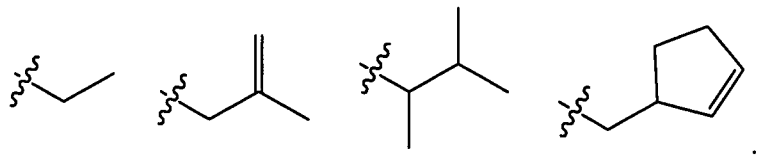
In a sixth aspect, the invention provides a pharmaceutical composition comprising a compound of Formula (I) or (Ia) and a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

DETAILED DESCRIPTION

Definitions

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

"$C_{\alpha-\beta}$alkyl" means an alkyl group comprising a minimum of α and a maximum of β carbon atoms in a branched, cyclical or linear relationship or any combination of the three, wherein α and β represent whole numbers. The alkyl groups described in this section may also contain one or two double or triple bonds. Examples of C_{1-6}alkyl include, but are not limited to the following:



"-$OC_{\alpha-\beta}$alkyl" means a radical where $C_{\alpha-\beta}$alkyl is as defined above.

"Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, unless otherwise stated, e.g., methyl, ethyl, propyl, 2-propyl, butyl, and the like. Alkyl is independent of "$C_{\alpha-\beta}$alkyl" group defined above and is referred to when the alkyl group is not written in $C_{\alpha-\beta}$alkyl format.

"Alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms unless otherwise stated e.g., methylene, ethylene, propylene, 1-methylpropylene, 2-methylpropylene, butylene, pentylene, and the like.

"Amino" means a -NH_2.

"Alkylcarbonyl" means a -COR radical where R is alkyl as defined above e.g., methylcarbonyl, and the like.

"Alkoxyalkyl" means a linear saturated hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbons substituted with

one or two -OR groups where R is alkyl as defined above, e.g., 2-methoxyethyl, 1-, 2-, or 3-methoxypropyl, 2-ethoxyethyl, and the like.

"Aminoalkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbons substituted with one or two, -NRR' where R is hydrogen or alkyl and R' is selected from hydrogen, alkyl, carboxyalkyl, alkylcarbonyl, aralkyl, heterocycloaminoalkyl, alkylcarbonyl, alkylsulfonyl, or –C(O)COOH and/or one to three fluoro, each as defined herein, e.g., aminomethyl, methylaminoethyl, 2-ethylamino-2-methylethyl, 1,3-diaminopropyl, acetylaminopropyl, and the like; provided that when the Z group in (i) is aminoalkyl then the aminoalkyl group is not -CR^aR^b-NRR' where each R, R^a and R^b is independently H or alkyl and R' is carboxyalkyl.

"Aminoalkoxy" means a -OR radical where R is a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent saturated hydrocarbon radical of three to six carbons substituted with one or two, -NRR' where R is hydrogen or alkyl and R' is selected from hydrogen, alkyl, carboxyalkyl, alkylcarbonyl, aralkyl, heterocycloaminoalkyl, alkylsulfonyl, or –C(O)COOH, each as defined herein, e.g., 2-aminoethoxy, 2-dimethylaminopropoxy, and the like.

"Aminocarbonyl" means a –CONRR' radical where R is hydrogen or alkyl and R' is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl or cycloalkyl, each as defined herein, e.g., -CONH-(3-hydroxypropyl), cyclopropylaminocarbonyl, and the like.

"Acyl" means a -COR radical where R is alkyl or haloalkyl as defined herein.

"Acylamino" means a -NHCOR radical where R is haloalkyl, alkoxy, hydroxyalkyl, substituted hydroxyalkyl, carboxyalkyl, or substituted carboxyalkyl, each as defined herein, e.g., 2,2,2-trifluoroethylcarbonylamino, 3-carboxypropionylamino, -NHCO-$CH(NH_2)CH_2COOH$, and the like.

"Aralkyl" means a –(alkylene)-R radical where R is phenyl.

"Carbocyclic" means a cyclic ring that has only carbon ring atoms.

"Cycloalkyl" means a cyclic saturated monovalent hydrocarbon radical of three to ten carbon atoms, unless otherwise stated e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, and the like. The cycloalkyl group is optionally substituted with amino, alkylamino, dialkylamino or carboxy unless otherwise stated.

"Cycloalkylalkyl" means –(alkylene)-R radical where R is cycloalkyl as defined above.

"Carboxy" means –COOH.

"Carboxyalkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbons substituted with a carboxy group e.g., 2-carboxyethyl, carboxymethyl, and the like.

"Substituted carboxyalkyl" means carboxyalkyl as defined above which is substituted with one or two amino.

"Carboxyalkyloxy" means –O-R radical where R is carboxyalkyl as defined above.

"Substituted carboxyalkyloxy" means –O-R radical where R is substituted carboxyalkyl as defined above.

"Carboxyalkylthio" means –S-R radical where R is carboxyalkyl as defined above.

"Substituted carboxyalkylthio" means –S-R radical where R is substituted carboxyalkyl as defined above.

"Carboxyalkylsulfonyl" means $-SO_2$-R radical where R is carboxyalkyl as defined above.

"Substituted carboxyalkylsulfonyl" means $-SO_2$-R radical where R is substituted carboxyalkyl as defined above.

"Carboxyalkoxyalkyl" means –(alkylene)-O-R radical where R is carboxyalkyl as defined above.

"Substituted carboxyalkoxyalkyl" means –(alkylene)-O-R radical where R is substituted carboxyalkyl as defined above.

"Carboxyalkylamino" means –NHR where R is carboxyalkyl group as defined above.

"Disubstituted amino" means a –NRR' radical where R and R' are independently alkyl or alkylsulfonyl, each as defined herein, e.g., dimethylamino, methylethylamino, and the like. When R and R' are alkyl, it is also referred to herein as dialkylamino.

"Halo" or "halogen" means a halogen atom selected from F, Cl, Br and I.

"C_{v-w}haloalkyl" means an alkyl group comprising a minimum of v and a maximum of w carbon atoms in a branched, cyclical or linear relationship or any combination of the three, wherein v and w represent whole numbers. The alkyl groups described in this section may also contain one or two double or triple bonds and wherein any number, at least one, of the hydrogen atoms attached to the alkyl chain are replaced by F, Cl, Br or I.

"-OC_{v-w}haloalkyl" means a radical where C_{v-w}haloalkyl is as defined above.

"Hydroxy" means –OH.

"Haloalkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, unless otherwise stated, that has one to three hydrogen atoms replaced by a halo group

e.g., trifluoromethyl, and the like. Haloalkyl is independent of "C_{v-w}haloalkyl" group defined above and is referred to when the alkyl group is not written in C_{v-w}haloalkyl format.

"Hydroxyalkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbons substituted with one or two hydroxy groups, provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl.

"Hydroxyalkoxy" or "hydroxyalkyloxy" means a –OR radical where R is hydroxyalkyl as defined above.

"Substituted hydroxyalkyl" means hydroxyalkyl as defined above that is substituted with one or two substituents independently selected from amino, mono or disubstituted amino, carboxyalkylamino, carboxy, or -$P(O)(OR)_3$ where R is hydrogen or alkyl; and/or one to three fluoro.

"Substituted hydroxyalkyloxy" means –O-R where R is substituted hydroxyalkyl as defined above.

"Five or six membered heteroaryl" means a monovalent monocyclic aromatic radical of 5 or 6 ring atoms where one, two, or three, ring atoms are heteroatom independently selected from N, O, or S, the remaining ring atoms being carbon. Representative examples include, but are not limited to, pyrrolyl, thienyl, thiazolyl, imidazolyl, furanyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, and the like.

"Heteroaralkyl" means –(alkylene)-R where R is a heteroaryl ring which is a monovalent monocyclic aromatic radical of 5 or 6 ring atoms where one, two, or three, ring atoms are heteroatom independently selected from N, O, or S, the remaining ring atoms being carbon provided that at least one ring atom is N. The heteroaryl ring can be optionally substituted with carboxy.

"Heterocyclyl" means a saturated monovalent monocyclic group of 5 to 8 ring atoms in which one or two ring atoms are heteroatom independently selected from N, O, or $S(O)_n$, where n is an integer from 0 to 2, the remaining ring atoms being C.

"Heterocycloamino" means a saturated monovalent monocyclic group of 5 to 8 ring atoms in which one or two ring atoms are heteroatom independently selected from N, O, or

$S(O)_n$, C(O) where n is an integer from 0 to 2, the remaining ring atoms being C provided at least one ring atom is nitrogen e.g., pyrrolidinyl, piperidinyl, azetidinyl, aziridinyl, and the like. The heterocycloamino group can optionally be substituted with one to two substituents independently selected from hydroxyl, carboxy, fluoro, carboxyalkyl, or alkyl.

"Heterocycloaminocarbonyl" means a –C(O)-R radical where R is heterocycloamino group as defined above e.g., pyrrolidinylcarbonyl, azetidinylcarbonyl, and the like.

"Heterocycloaminooxy" means a –O-R radical where R is heterocycloamino group as defined above e.g., pyrrolidinyloxy, azetidinyloxy, and the like.

"Heterocycloaminoalkyl" means a -alkylene-R radical where R is heterocycloamino group as defined above e.g., pyrrolidinylethyl, azetidinylpropyl, and the like; provided that when the Z group in (i) is heterocycloamino group that is substituted with a (one) carboxy group, then the alkylene chain is not $–CR^aR^b-$ where R^a and R^b are independently H or alkyl.

"Monosubstituted amino" means a –NHR radical where R is alkyl or cycloalkyl substituted with carboxy, each as defined herein, e.g., methylamino, cyclopropylamino, and the like. When R is alkyl, it is also referred to herein as monoalkylamino.

The terms "oxo" and "thioxo" represent the groups =O (as in carbonyl) and =S (as in thiocarbonyl), respectively.

"Halo" or "halogen" means a halogen atoms selected from F, Cl, Br and I.

"Sulfonylamino" means a $–NHSO_2R$ radical where R is alkyl or carboxalkyl, each as defined herein. When R is alkyl it is also referred to herein as alkylsulfonyl.

The specification and claims contain listing of species using the language "selected from . . . and . . ." and "is . . . or . . ." (sometimes referred to as Markush groups). When this language is used in this application, unless otherwise stated it is meant to include the group as a whole, or any single members thereof, or any subgroups thereof. The use of this language is merely for shorthand purposes and is not meant in any way to limit the removal of individual elements or subgroups as needed.

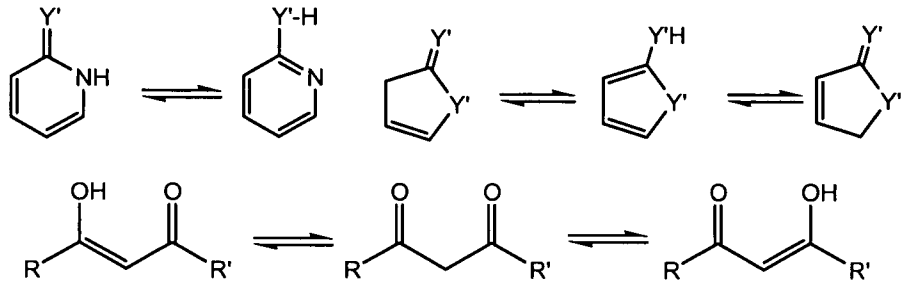
"Treating" and "Treatment", includes any effect, *e.g.,* lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder, etc. and includes preventative and reactive treatment.

"Pharmaceutically-acceptable salt" means a salt prepared by conventional means, and are well known by those skilled in the art. The "pharmaceutically acceptable salts" include basic salts of inorganic and organic acids, including but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, malic acid, acetic acid, oxalic acid, tartaric acid, citric acid, lactic acid, fumaric acid, succinic

acid, maleic acid, salicylic acid, benzoic acid, phenylacetic acid, mandelic acid and the like. When compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. For additional examples of "pharmacologically acceptable salts," *see infra* and Berge et al., *J. Pharm. Sci.* 66:1 (1977).

It will be noted that the structure of some of the compounds of the invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (*e.g.*, all enantiomers and diastereomers) are included within the scope of the invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Alkenes can include either the E- or Z-geometry, where appropriate.

It should be noted that compounds of the invention may contain groups that may exist in tautomeric forms, such as heteroatom substituted heterocycloamino groups (Y' = O, S, NR), and the like, which are illustrated in the following examples:



and though one form is named, described, displayed and/or claimed herein, all the tautomeric forms are intended to be inherently included in such name, description, display and/or claim.

Prodrugs of the compounds of this invention are also contemplated by this invention. A prodrug is an active or inactive compound that is modified chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a patient. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyl-oxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives, which are cleaved by esterases in vivo releasing

the free drug and formaldehyde (Bungaard *J. Med. Chem.* 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

"EC_{50} of an agent" included that concentration of an agent at which a given activity, including binding of sphingosine or other ligand of an S1P receptor and/or a functional activity of a S1P receptor (*e.g.*, a signaling activity), is 50% maximal for that S1P receptor. Stated differently, the EC_{50} is the concentration of agent that gives 50% activation, when 100% activation is set at the amount of activity of the S1P receptor which does not increase with the addition of more ligand/agonist and 0% activation is set at the amount of activity in the assay in the absence of added ligand/agonist.

"Purified" and like terms relate to the isolation of a molecule or compound in a form that is substantially free of contaminants normally associated with the molecule or compound in a native or natural environment.

"Immunomodulation" includes effects on the functioning of the immune system, and includes both the enhancement of an immune response as well as suppression of the immune response.

An "effective amount" includes an amount sufficient to produce a selected effect. For example, an effective amount of an S1P1 receptor agonist is an amount that decreases the cell signaling activity of the S1P1 receptor.

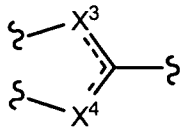
"Pharmaceutically acceptable" include molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate.

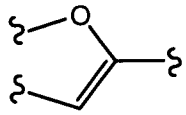
"Pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

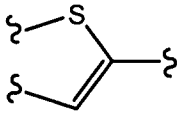
The term "L is a saturated 3, 4, 5, 6 or 7-member ring containing 0, 1 or 2 atoms selected from N, O and S" means that L is saturated carbocyclic ring (ring with only carbon ring atoms) having 3, 4, 5, 6 or 7 carbon atoms wherein 0, 1, or 2 carbon ring atoms can be replaced by N, O, or S.

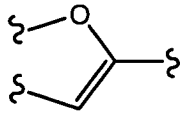
Embodiments

I. In one embodiment, the compounds of Formula (I) are those wherein:



is 

or 

, preferably 

. Within embodiment (I) and groups contained therein, in one group of compounds n is 0.

(a) Within the above embodiment (I) and groups contained therein, in one group of compounds L is a saturated 3, 4, 5, 6 or 7-member ring the ring being substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl. Within this group, in one group of compounds, L is cyclopropyl, cyclopentyl, cyclohexyl, preferably cyclopropyl.

(b) Within the above embodiment (I) and groups contained therein, in another group of compounds L is a saturated 3, 4, 5, 6 or 7-member ring containing 1 or 2 atoms selected from N, O, or S and the ring being substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl. Within this group, in one group of compounds, L is piperidinyl, tetrahydropyranyl or oxetanyl.

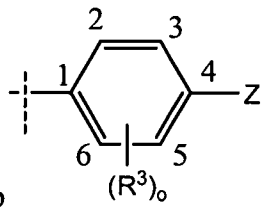
II. In another embodiment, the compounds of Formula (I) are those wherein L is a saturated 3, 4, 5, 6 or 7-member ring the ring being substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl. Within this group, in one group of compounds, L is cyclopropyl, cyclopentyl, cyclohexyl, preferably cyclopropyl.

(i) Within embodiments I, I(a), I(b), and II, and groups contained therein, in one embodiment, A is phenyl substituted with R^1 group as defined in the Summary. Within these groups, in another group of compounds R^1 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl where the alkyl group is above listed groups is linear or branched and saturated. Within these groups, in another group of compounds R^1 is methyl, fluoro, or hydroxyl.

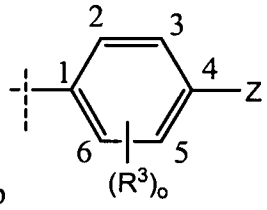
(ii) Within embodiments I, I(a), I(b), and II, and groups contained therein, in another embodiment, the compounds of Formula (I) are those wherein A is cycloalkyl substituted with R^1 group as defined in the Summary. Within these groups, in one group of compounds, A is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl and R^1 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl where the alkyl group is above groups is linear or branched and saturated, preferably R^1 is fluoro.

(iii) Within embodiments I, I(a), I(b), and II, and groups contained therein, in another group of compounds, A is five or six membered heterocyclyl, preferably, A is tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, substituted with R^1 group as defined in the Summary. Within this group in one group of compounds R^1 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl where the alkyl group is above groups is linear or branched and saturated.

(iv) Within embodiments I, I(a), I(b), and II, and groups contained therein, in another group of compounds, A is five or six membered heteroaryl substituted with R^1 group as defined in the Summary. Within this group, in one group of compounds R^1 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl where the alkyl group is above groups is linear or branched and saturated.

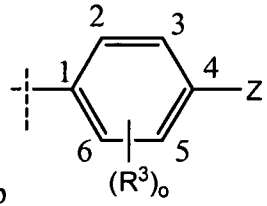
(A) Within embodiments I, I(a), I(b), I(a)(i), I(a)(ii), I(a)(iii), I(a)(iv), I(b)(i), I(b)(ii), I(b)(iii), I(b)(iv), II, I(i), I(ii), I(iii), I(iv), II(i), II(ii), II(iii), and II(iv), and groups contained therein, in one group of compounds, in group 

, Z is cycloalkyl substituted with amino, monoalkylamino or dialkylamino; or cycloalkylalkyl substituted with one or two carboxy. Within this group, in one group of compounds n is 0 and R^3 is fluoro, amino, or methyl and o is 1 or 2, preferably R^3 is fluoro and attached to the 2-position of the phenyl ring.

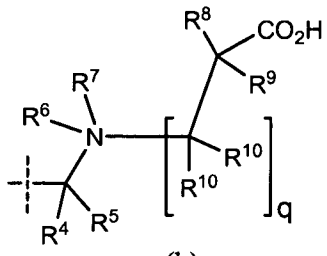
(B) Within embodiments I, I(a), I(b), I(a)(i), I(a)(ii), I(a)(iii), I(a)(iv), I(b)(i), I(b)(ii), I(b)(iii), I(b)(iv), II, I(i), I(ii), I(iii), I(iv), II(i), II(ii), II(iii), and II(iv), and groups contained therein, in another group of compounds, in group 

, Z is monosubstituted amino, disubstituted amino, or sulfonylamino. Within this group, in one group of compounds n is 0 and R^3 is fluoro, amino, or methyl and o is 1 or 2, preferably R^3 is fluoro and attached to the 2-position of the phenyl ring.

(C) Within embodiments I, I(a), I(b), I(a)(i), I(a)(ii), I(a)(iii), I(a)(iv), I(b)(i), I(b)(ii), I(b)(iii), I(b)(iv), II, I(i), I(ii), I(iii), I(iv), II(i), II(ii), II(iii), and II(iv), and groups contained



therein, in another group of compounds, in group , Z is a group of formula (b):



(b)

where:

q is 0, 1 or 2;

R^4 is selected from H, C_{1-3}haloalkyl, C_{1-6}alkyl; preferably H or linear or branched C_{1-6}alkyl; preferably R^4 is H or methyl;

R^5 is selected from H, C_{1-3}haloalkyl, C_{1-4}alkyl; preferably H or linear or branched C_{1-6}alkyl; preferably R^5 is H or methyl; or

R^4 and R^5 together form a 3, 4, 5, 6 or 7-member carbocyclic ring substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; preferably R^4 and R^5 together form cyclopropyl;

R^6 is a lone pair of electrons or O;

R^7 is H or C_{1-6}alkyl; preferably H or linear or branched C_{1-6}alkyl; preferably R^7 is H or methyl;

R^8 is selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; preferably H or linear or branched C_{1-6}alkyl; preferably R^8 is H or methyl; or

R^7 and R^8 together is selected from -$(CR^{10}R^{10})$-, -$(CR^{10}R^{10})$O-, -O$(CR^{10}R^{10})$-, -$(CR^{10}R^{10})(CR^{10}R^{10})$-, and -$(CR^{10}R^{10})_3$-; preferably R^7 and R^8 together is –CH_2-, -$(CH_2)_2$- or –$(CH_2)_3$-;

R^9 is selected from H, F, C_{1-3}haloalkyl, C_{1-4}alkyl, OH and OC_{1-4}alkyl; or R^8 and R^9 together with the carbon atom to which they are attached form cycloalkyl; preferably R^9 is H; and

each R^{10} is independently in each instance selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl.; preferably H or linear or branched C_{1-6}alkyl; preferably R^{10} is H or methyl.

Within this group of compounds, in one group of compounds:

q is 0, 1 or 2;

R^4 is selected from H, C_{1-3}haloalkyl, C_{1-6}alkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^4 is H or methyl;

R^5 is selected from H, C_{1-3}haloalkyl, C_{1-4}alkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^5 is H or methyl;

R^6 is a lone pair of electrons or O;

R^7 is H or C_{1-6}alkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^7 is H or methyl;

R^8 is selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^8 is H or methyl;

R^9 is selected from H, F, C_{1-3}haloalkyl, C_{1-4}alkyl, OH and OC_{1-4}alkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^9 is H or methyl; and

each R^{10} is independently in each instance selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^{10} is H or methyl.

Within this group of compounds, in another group of compounds:

q is 0, 1 or 2;

R^4 and R^5 together form a 3, 4, 5, 6 or 7-member carbocyclic ring substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; preferably R^4 and R^5 together form cyclopropyl;

R^6 is a lone pair of electrons or O;

R^7 is H or C_{1-6}alkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^7 is H or methyl;

R^8 is selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^8 is H or methyl;

R^9 is selected from H, F, C_{1-3}haloalkyl, C_{1-4}alkyl, OH and OC_{1-4}alkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^9 is H or methyl; and

each R^{10} is independently in each instance selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^{10} is H or methyl.

Within this group of compounds, in yet another group of compounds:

q is 0, 1 or 2;

R^4 is selected from H, C_{1-3}haloalkyl, C_{1-6}alkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^4 is H or methyl;

R^5 is selected from H, C_{1-3}haloalkyl, C_{1-4}alkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^5 is H or methyl;

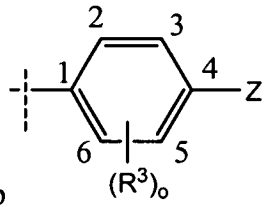
R^6 is a lone pair of electrons or O;

R^7 and R^8 together is selected from -($CR^{10}R^{10}$)-, -($CR^{10}R^{10}$)O-, -O($CR^{10}R^{10}$)-, -($CR^{10}R^{10}$)($CR^{10}R^{10}$)-, and -($CR^{10}R^{10}$)$_3$-; preferably R^7 and R^8 together is –CH_2-, -$(CH_2)_2$- or –$(CH_2)_3$-;

R^9 is selected from H, F, C_{1-3}haloalkyl, C_{1-4}alkyl, OH and OC_{1-4}alkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^9 is H or methyl; and

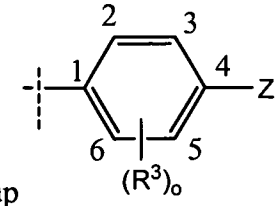
each R^{10} is independently in each instance selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; preferably or linear or branched C_{1-6}alkyl; preferably R^{10} is H or methyl..

Within this group, and group contained therein, in one group of compounds, n is 0 and R^3 is fluoro, amino, or methyl and o is 1 or 2 and Z is 3-carboxyazetidin-1-ylmethyl.

(D) Within embodiments I, I(a), I(b), I(a)(i), I(a)(ii), I(a)(iii), I(a)(iv), I(b)(i), I(b)(ii), I(b)(iii), I(b)(iv), II, I(i), I(ii), I(iii), I(iv), II(i), II(ii), II(iii), and II(iv), and groups contained therein, in another group of compounds, in group 

, Z is where R^3 is on carbon atom on the phenyl ring that is adjacent to carbon carrying Z, and R^3 and Z can combine to form -CH=CH-NR^{11}-, –$(CH_2)_2NR^{11}$-, –$CH_2NR^{11}CH_2$-, –$(CH_2)_2NR^{11}CH_2$-, -N=CR^{11}-NH-, or -N=CH-NR^{11}-, where R^{11} is selected from hydrogen, hydroxyalkyl, aminoalkyl, carboxyalkyl, substituted hydroxyalkyl or substituted carboxyalkyl; or aminocarbonyl. Within this group, and group contained therein, in one group of compounds, n is 0 and R^3 is fluoro, amino, or methyl and o is 1 or 2, preferably R^3 is fluoro and attached to the 2-position of the phenyl ring.

(E) Within embodiments I, I(a), I(b), I(a)(i), I(a)(ii), I(a)(iii), I(a)(iv), I(b)(i), I(b)(ii), I(b)(iii), I(b)(iv), II, I(i), I(ii), I(iii), I(iv), II(i), II(ii), II(iii), and II(iv), and groups contained



therein, in another group of compounds, in group , Z is carboxyalkylamino, hydroxyalkyl, substituted hydroxyalkyl, hydroxyalkoxy, substituted hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, substituted carboxyalkyl, carboxyalkyloxy, substituted carboxyalkyloxy, carboxyalkoxyalkyl, substituted carboxyalkoxyalkyl, aminocarbonyl, acylamino, sulfonylamino, heterocycloamino, heterocycloaminoalkyl, heterocycloaminocarbonyl, heterocycloaminooxy, or heteroaralkyl.

(IV). Within compounds of Formula (Ia):

Inone embodiment, in conjunction with any w embodiments below, L is a saturated 3, 4 or 5-member ring substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, OC_{1-4}alkyl, and OC_{1-4}haloalkyl.

In another embodiment, in conjunction with any above or below embodiments, L is an unsubstituted saturated 3, 4 or 5-member ring.

In another embodiment, in conjunction with any above or below embodiments, L is a saturated 3, 4 or 5-member ring substituted by 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, OC_{1-4}alkyl, and OC_{1-4}haloalkyl.

In another embodiment, in conjunction with any above or below embodiments, L is cyclopropyl substituted by 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, OC_{1-4}alkyl, and OC_{1-4}haloalkyl.

In another embodiment, in conjunction with any above or below embodiments, L is cyclopropyl.

In another embodiment, in conjunction with any above or below embodiments, m is 0 or 1; n is 0 or 1; and o is 1 or 2.

In another embodiment, in conjunction with any above or below embodiments, m is 0.

In another embodiment, in conjunction with any above or below embodiments, n is 0.

In another embodiment, in conjunction with any above or below embodiments, o is 1 or 2.

In another embodiment, in conjunction with any above or below embodiments, R^7 and R^8, when taken together, form a group that is selected from -($CR^{10}R^{10}$)-, -($CR^{10}R^{10}$)O-, -O($CR^{10}R^{10}$)- and -($CR^{10}R^{10}$)($CR^{10}R^{10}$)-.

In another embodiment, in conjunction with any above or below embodiments, R^7 and R^8, when taken together, form a group that is selected from -($CR^{10}R^{10}$)- and -($CR^{10}R^{10}$)($CR^{10}R^{10}$)-.

In another embodiment, in conjunction with any above or below embodiments, R^7 and R^8, when taken together, form a group that is -($CR^{10}R^{10}$)-.

In another embodiment, in conjunction with any above or below embodiments, R^7 and R^8, when taken together, form a group that is CH_2; q is 1; R^9 is H; and R^{10} is H.

In another embodiment, in conjunction with any above or below embodiments, R^1 is F; R^2 is F; R^3 is F; R^4 is H; R^5 is H; and R^6 is a lone pair of electrons.

In another embodiment, in conjunction with any above or below embodiments, R^1 is F; and m is 1.

In another embodiment, in conjunction with any above or below embodiments, R^2 is F; and n is 1.

In another embodiment, in conjunction with any above or below embodiments, R^3 is F; and o is 1.

In another embodiment, in conjunction with any above or below embodiments, R^4 is selected from C_{1-3}haloalkyl and C_{1-4}alkyl; and R^5 is H.

In another embodiment, in conjunction with any above or below embodiments, R^4 and R^5 together form a 3, 4, 5, 6 or 7-member carbocyclic ring substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, OC_{1-4}alkyl, and OC_{1-4}haloalkyl.

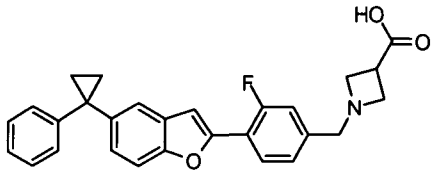
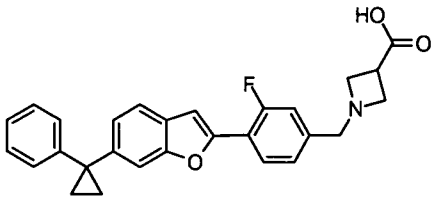
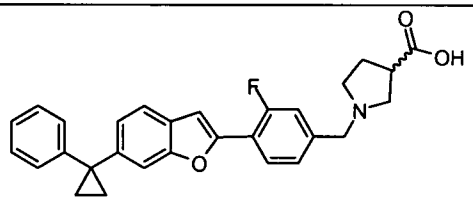
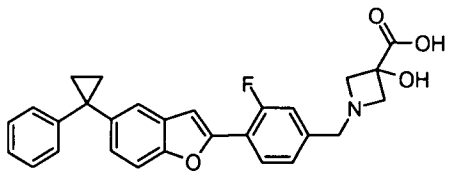
In another embodiment, in conjunction with any above or below embodiments, R^4 and R^5 together form a 3-member carbocyclic ring substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, OC_{1-4}alkyl, and OC_{1-4}haloalkyl.

In another embodiment, in conjunction with any above or below embodiments, R^4 and R^5 together form cyclopropyl.

In another embodiment, in conjunction with any above or below embodiments, R^6 is a lone pair of electrons.

In another embodiment, in conjunction with any above or below embodiments, R^6 is O.

Representative compounds of Formula (I) are and can be prepared by the procedures in Schemes indicated:

Cpd No.	Structure	Name	Synthetic Examples
1		1-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzofuran-2-yl)-benzyl)azetidine-3-carboxylic acid	Example 1
2		1-(3-fluoro-4-(6-(1-phenylcyclopropyl)benzofuran-2-yl)benzyl)-azetidine-3-carboxylic acid	Example 1
3		1-(3-fluoro-4-(6-(1-phenylcyclopropyl)benzofuran-2-yl)benzyl)-pyrrolidine-3-carboxylic acid	Example 1
4		1-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzofuran-2-yl)benzyl)-3-hydroxyazetidine-3-carboxylic acid	General scheme

Cpd No.	Structure	Name	Synthetic Examples
5		3-fluoro-1-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzofuran-2-yl)-benzyl)azetidine-3-carboxylic acid	General scheme
6		3-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzofuran-2-yl)benzyl-amino)propylphosphonic acid	General scheme
7		1-(3-fluoro-4-(5-(1-(pyridin-2-yl)cyclopropyl)benzofuran-2-yl)-benzyl)azetidine-3-carboxylic acid	Example 1
8		1-(3-fluoro-4-(6-(1-(pyridin-2-yl)cyclopropyl)benzofuran-2-yl)-benzyl)azetidine-3-carboxylic acid	Example 1

Cpd No.	Structure	Name	Synthetic Examples
9		1-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzo[b]thiophen-2-yl)-benzyl)azetidine-3-carboxylic acid	Example 1
10		1-(3-fluoro-4-(5-(1-(3-fluorophenyl)cyclopropyl)benzofuran-2-yl)-benzyl)azetidine-3-carboxylic acid	Example 1
11		1-(4-(5-(1-(3-cyanophenyl)cyclopropyl)benzofuran-2-yl)-3-fluorobenzyl)azetidine-3-carboxylic acid	Example 1
12		1-(3-fluoro-4-(6-(1-(3-fluorophenyl)cyclopropyl)benzofuran-2-yl)-benzyl)azetidine-3-carboxylic acid	Example 1

Cpd No.	Structure	Name	Synthetic Examples
13		1-(4-(6-(1-cyclohexylcyclopropyl)benzofuran-2-yl)-3-fluoro-benzyl)azetidine-3-carboxylic acid	Example 1 & 2
14		1-(4-(6-(1-cyclopentylcyclopropyl)benzofuran-2-yl)-3-fluoro-benzyl)azetidine-3-carboxylic acid	Example 1 & 2
15		1-(3-fluoro-4-(6-(1-(tetrahydro-2H-pyran-4-yl)cyclopropyl)-benzofuran-2-yl)benzyl)azetidine-3-carboxylic acid	Example 1 & 2
16		1-(4-(6-(1-(4,4-difluorocyclohexyl)cyclopropyl)benzofuran-2-yl)-3-fluorobenzyl)azetidine-3-carboxylic acid	Example 1 & 2

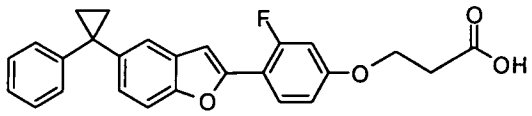
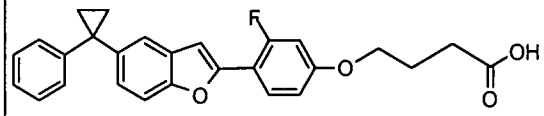
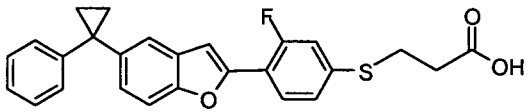
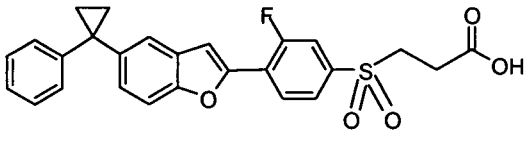
Cpd No.	Structure	Name	Synthetic Examples
17		1-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzo[b]thiophen-2-yl)-benzyl)azetidine-3-carboxylic acid	Example 1
18		1-(3-fluoro-4-(6-(1-phenylcyclopropyl)benzo[b]thiophen-2-yl)-benzyl)azetidine-3-carboxylic acid	Example 1
19		1-(3-fluoro-4-(6-(1-(piperidin-1-yl)cyclopropyl)benzofuran-2-yl)-benzyl)azetidine-3-carboxylic acid	Example 3 or 4
20		1-(3-fluoro-4-(6-(1-(piperidin-1-yl)-cyclopropyl)benzo[b]thiophen-2-yl)benzyl)azetidine-3-carboxylic acid	Example 3 or 4

Cpd No.	Structure	Name	Synthetic Examples
21		1-(4-(6-(1-(azepan-1-yl)cyclopropyl)benzofuran-2-yl)-3-fluoro-benzyl)azetidine-3-carboxylic acid	Example 3 or 4
22		1-(3-fluoro-4-(6-(1-(pyrrolidin-1-yl)cyclopropyl)benzofuran-2-yl)-benzyl)azetidine-3-carboxylic acid	Example 3 or 4
23		1-(3-fluoro-4-(5-(1-(piperidin-1-yl)cyclopropyl)benzofuran-2-yl)-benzyl)azetidine-3-carboxylic acid	Example 3 or 4
24		1-(3-fluoro-4-(5-(1-(piperidin-1-yl)cyclopropyl)benzo[b]-thiophen-2-yl)benzyl)azetidine-3-carboxylic acid	Example 3 or 4

Cpd No.	Structure	Name	Synthetic Examples
25		1-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzo[b]thiophen-2-yl)-benzyl)azetidine-3-carboxylic acid	Example 1
26		1-(3-fluoro-4-(6-(1-(1-methyl-1H-imidazol-5-yl)cyclopropyl)-benzofuran-2-yl)benzyl)azetidine-3-carboxylic acid	Example 5
27		1-(3-fluoro-4-(5-(1-(1-methyl-1H-imidazol-2-yl)cyclopropyl)-benzofuran-2-yl)benzyl)azetidine-3-carboxylic acid	Example 5
28		1-(3-fluoro-4-(5-(1-(5-methylthiophen-2-yl)cyclopropyl)-benzo[b]thiophen-2-yl)benzyl)azetidine-3-carboxylic acid	Example 6

Cpd No.	Structure	Name	Synthetic Examples
29		1-(chlorothiophen-2-yl)cyclopropyl)benzo[b]thiophen-2-yl)-3-fluorobenzyl)azetidine-3-carboxylic acid	Example 6
30		1-(3-fluoro-4-(5-(1-(5-methylfuran-2-yl)cyclopropyl)-benzo[b]thiophen-2-yl)benzyl)azetidine-3-carboxylic acid	Example 6
31		1-(3-fluoro-4-(5-(1-(thiazol-2-yl)cyclopropyl)benzo[b]thiophen-2-yl)benzyl)azetidine-3-carboxylic acid	Example 6
32		1-(3-fluoro-4-(5-(1-(1-methyl-1H-imidazol-2-yl)cyclopropyl)-benzo[b]thiophen-2-yl)benzyl)azetidine-3-carboxylic acid	Example 6

Cpd No.	Structure	Name	Synthetic Examples
33		1-(3-fluoro-4-(6-(1-(5-methylthiophen-2-yl)cyclopropyl)-benzofuran-2-yl)benzyl)azetidine-3-carboxylic acid	Example 6
34		1-(3-fluoro-4-(5-(1-(5-methylthiophen-2-yl)cyclopropyl)-benzofuran-2-yl)benzyl)azetidine-3-carboxylic acid	Example 6
35		1-(4-(5-(1-(5-chlorothiophen-2-yl)cyclopropyl)benzofuran-2-yl)-3-fluorobenzyl)azetidine-3-carboxylic acid	Example 6
36		3-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzofuran-2-yl)phenoxy)-propanoic acid	Example 7

Cpd No.	Structure	Name	Synthetic Examples
37		3-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzofuran-2-yl)phenoxy)-propanoic acid	Example 7
38		4-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzofuran-2-yl)phenoxy)-butanoic acid	Example 7
39		3-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzofuran-2-yl)phenyl-thio)propanoic acid	Example 7
40		3-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzofuran-2-yl)phenyl-sulfonyl)propanoic acid	Example 8

Cpd No.	Structure	Name	Synthetic Examples
41		2-(6-fluoro-5-(5-(1-phenylcyclopropyl)benzofuran-2-yl)indolin-1-yl)acetic acid	
42		2-(4-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzofuran-2-yl-)phenyl)-1H-imidazol-2-yl)acetic acid	Example 9
43		2-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzofuran-2-yl)phenyl)-cyclopropanecarboxylic acid	Example 10
44		2-(1-(3-fluoro-4-(5-(1-phenylcyclopropyl)benzofuran-2-yl)-phenyl)-1H-pyrazol-3-yl)acetic acid	Example 9

General Synthetic Scheme

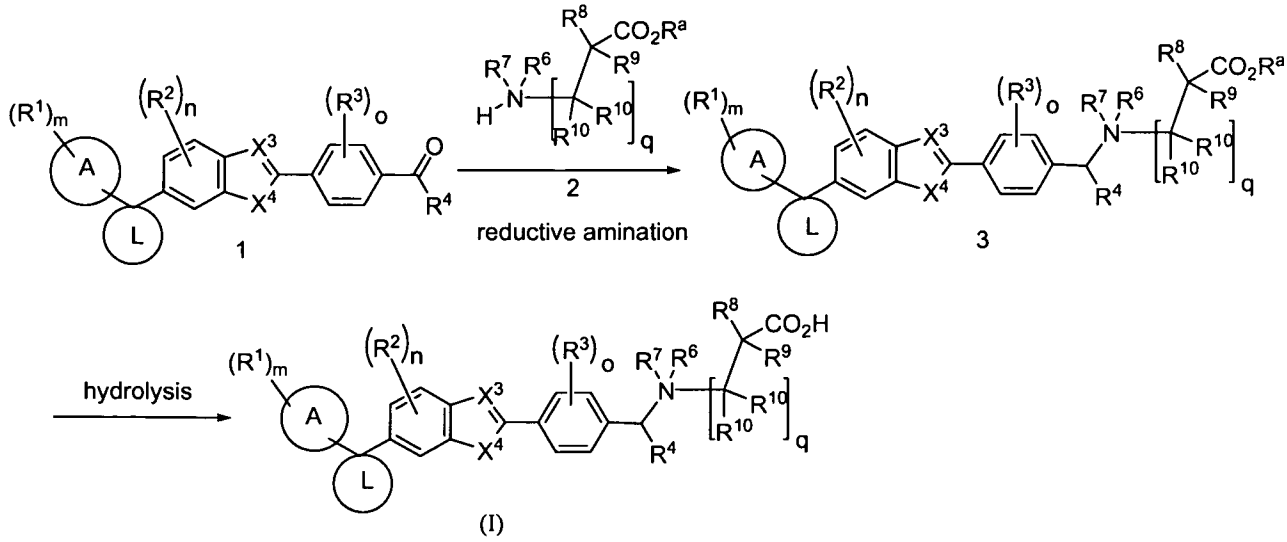
Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure. The starting materials and the intermediates, and the final products of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about –78 °C to about 260 °C, more preferably from about 0 °C to about 125 °C and most preferably at about room (or ambient) temperature, e.g., about 20 °C.

Compounds of Formula (I) where A, L, X^1, X^2, R^1, R^2, R^3 are as defined in the Summary and Z is a group of formula (b) can be prepared as described in Scheme 1 below.

Scheme 1

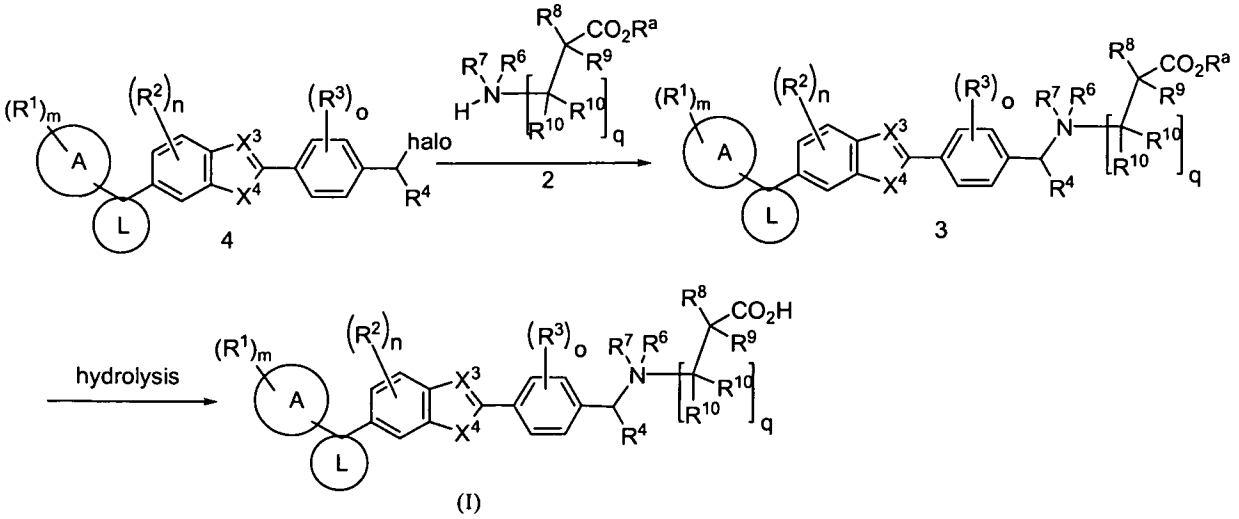


(I)

Reaction of a compound of formula 1 where R^4 is hydrogen or as defined in the Summary, with an amino compound of formula 2 under reductive amination reaction conditions provides a compound of formula 3. The reaction is typically carried out in in the presence of a suitable reducing agent (e.g., sodium cyanoborohydride, sodium triacetoxyborohydride, and the like) and an organic acid (e.g., glacial acetic acid, trifluoroacetic acid, and the like) at ambient temperature. Suitable solvents for the reaction are halogenated hydrocarbons (e.g., 1,2-dichloroethane, chloroform, and the like) or MeOH or mixtures thereof.

Hydrolysis of the ester group in 3 under basic hydrolysis reaction conditions, followed by acidic workup then provides a compound of Formula (I). Following the reductive amination procedure compounds of Formula (I) where Z is aminoalkyl can also be prepared. Detailed syntheses of compounds of formula 1 and 2 and compounds of Formula (I) using the above procedure are provided in working examples below.

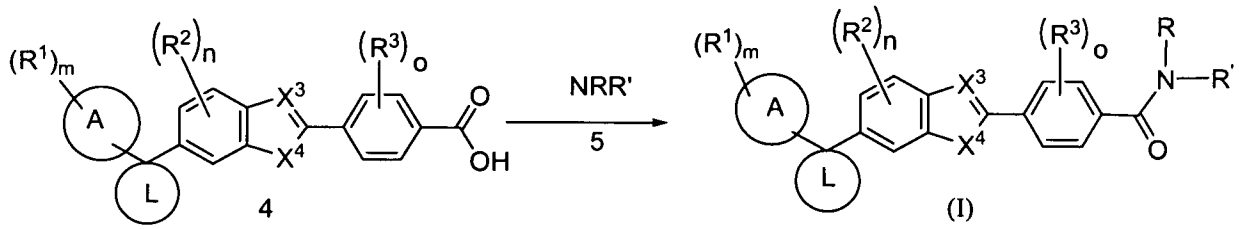
Alternatively, the above compounds can be prepared by reacting a halide of formula 4 with an amine of formula 2 as shown below.



The reaction is carried out in the presence of a non-nucleophilic amine such as triethylamine, pyridine, DIPEA, and the like.

Compounds of Formula (I) where A, L, X^1, X^5, R^1, R^2, R^3 are as defined in the Summary and Z is an aminocarbonyl (-CONRR' where R and R' are as defined in the definition section) can be prepared as described in Scheme 2 below.

Scheme 2

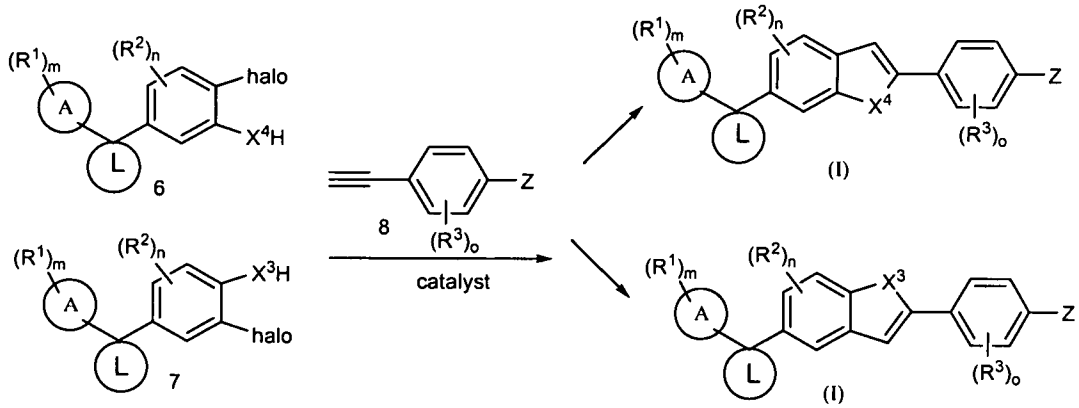


Compounds of Formula (I) where A, Y, X^1, X^2, R^1, R^2, R^3 are as defined in the Summary and Z is an aminocarbonyl (-CONRR' where R and R' are as defined in the definition of aminocarbonyl group) can be prepared by reacting a compound of formula 4 with an amine of formula 5. The reaction is carried out in the presence of coupling reagents known to one skilled in the art of organic synthesis such as EDCI/HOBT, O-(7-azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate (HATU) and chlorodipyrrolidinocarbenium hexafluorophosphate (PyCIU) (see for example, Han, S-Y.; Kim, Y-A. Tetrahedron 2005, 60 (11), 2447-67), in the presence of an amine such as diisopropylethylamine and in a suitable organic solvent such as dimethylformamide.

Alternatively, the acid 4 can be converted to an acid halide and then reacted with an amine of formula 5. The reaction is carried out in the presence of a non-nucleophilic amine such as triethylamine, pyridine, and the like. The acid chloride can be prepared in situ from the acid 4 using either oxalyl chloride or thionyl chloride.

Compounds of Formula (X) where one X^3 and X^4 is –CH- and other is –O- or –S-, and A, L, R^1, R^2, R^3 are as defined in the Summary and Z is a group of formula (b) can be prepared as described in Scheme 3 below.

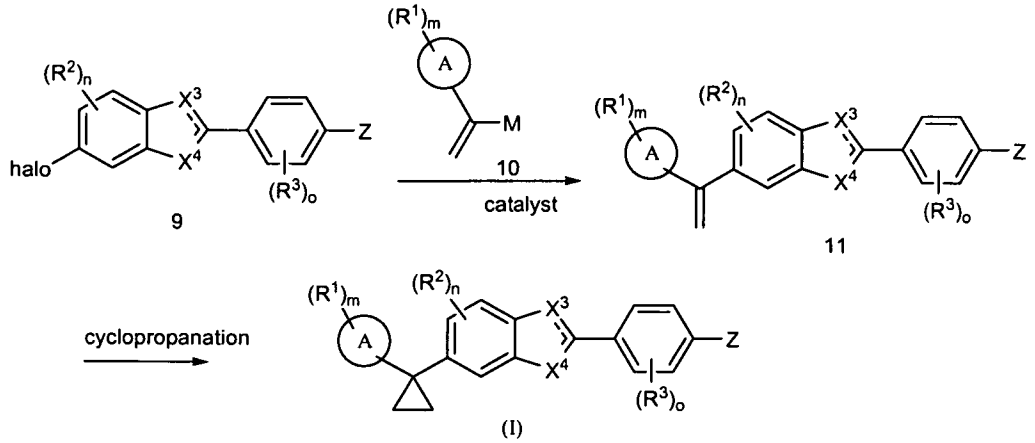
Scheme 3



Reaction of a compound of formula 6 or 7, where X^3 or X^4 is –CH- and A, Y, R^1, R^2, R^3 are as defined in the Summary and Z is a group of formula (b), with an alkyne of formula 8 provides a compound of Formula (I). The reaction is typically carried out in in the presence of transition metal catalysts (e.g., tetrakis(triphenylphosphine) palladium (0), copper (I) iodide, and the like) and at elevated temperature. Suitable solvents for the reaction are organic solvents (e.g., tetrahydrofuran, dimethylformamide, and the like).

Compounds of Formula (I) where L is cyclopropyl and A, X^1, X^2, R^1, R^2, R^3 are as defined in the Summary and Z is a group of formula (b) can be prepared as described in Scheme 4 below.

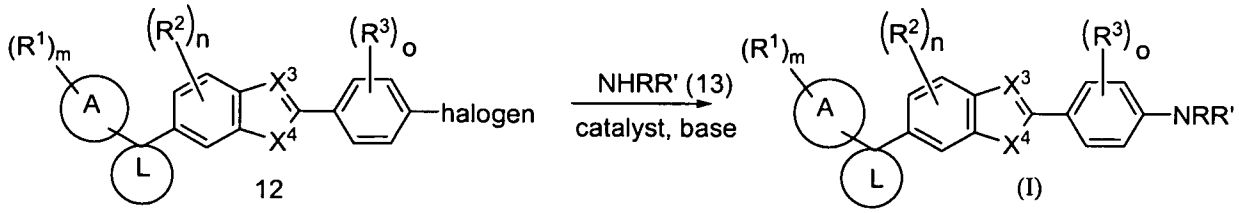
Scheme 4



Reaction of halogenated compound 9 with a vinylmetal compound 10 (where M is typically $B(OH)_2$ or trialkylstannane) provides an intermediate compound 11. The reaction is typically carried out in the presence of a transition metal catalyst (e.g., tetrakis(triphenylphosphine) palladium (0), and the like) at elevated temperature in organic solvents (e.g., ethanol, methanol, toluene, tetrahydrofuran, dioxane, and the like). When M = $B(OH)_2$, the reaction typically also requires a base (e.g., sodium carbonate, sodium acetate, and the like), and water as a co-solvent. Compound 11 is then reacted with suitable cyclopropanating reagents (e.g., trimethylsulfoxonium iodide and potassium tert-butoxide, diethylzinc and diiodomethane, zinc amalgam and diiodomethane) to give a compound of Formula (I). Suitable solvents for the reaction are organic solvents (e.g., hexanes, tetrahydrofuran, dioxane, toluene, dimethylsulfoxide, and the like).

Compounds of Formula (I) where A, L, X^1, X^2, R^1, R^2, R^3 are as defined in the Summary and Z is an aminoalkyl (-NRR' where R and R' are as defined in the definition section) can be prepared as described in Scheme 5 below.

Scheme 5

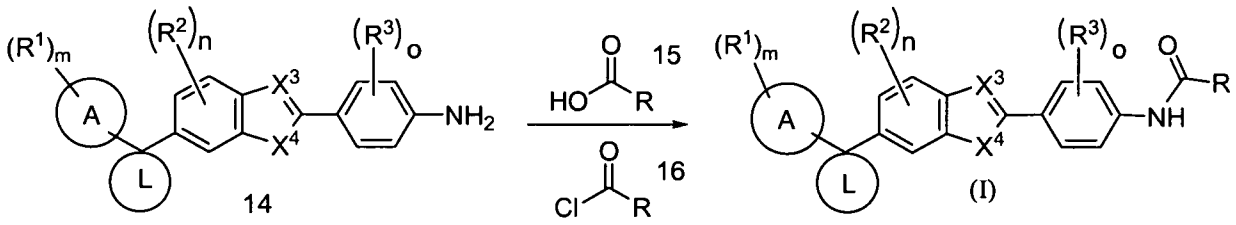


Compounds of Formula (I) can be prepared by reacting a compound of formula 12 with an amine of formula 13. The reaction is carried out in the presence of a transition metal catalyst (e.g., $Pd_2(dba)_3$, palladium (II) acetate, and the like), a suitable ligand (e.g., Xantphos,

and the like), in the presence of a base such as sodium tert-butoxide and in a suitable organic solvent such as toluene.

Compounds of Formula (I) where A, L, X^1, X^2, R^1, R^2, R^3 are as defined in the Summary and Z is an acylamino (-NHCOR where R is as defined in the definition section) can be prepared as described in Scheme 6 below.

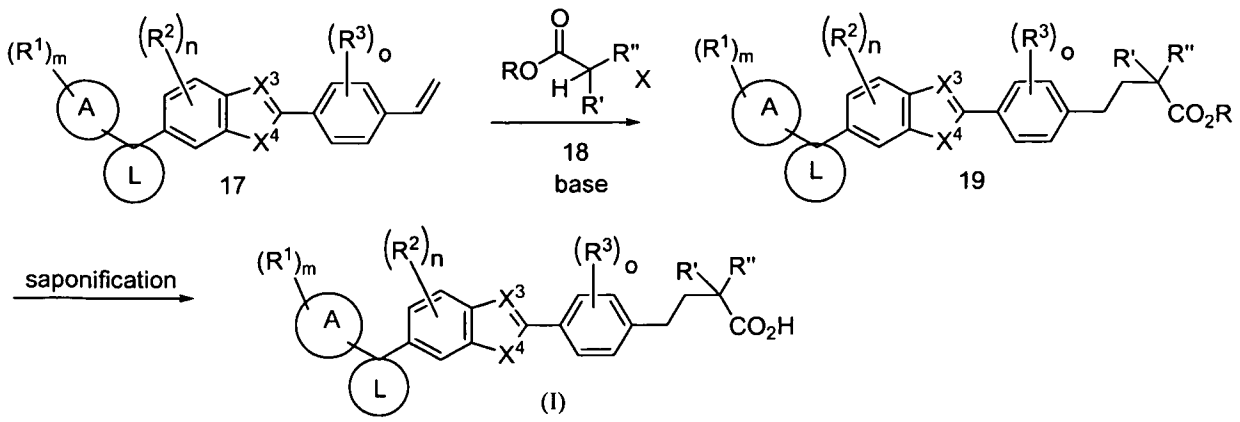
Scheme 6



Compounds of Formula (I) where Z is acylamino can be prepared by reacting a compound of formula 14 with an acid of formula 15. The reaction is carried out in the presence of coupling reagents known to one skilled in the art of organic synthesis such as EDCI/HOBT, O-(7-azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluoro-phosphate (HATU) and chlorodipyrrolidinocarbenium hexafluorophosphate (PyCIU) (see for example, Han, S-Y.; Kim, Y-A. T*etrahedron* 2005, 60 (11), 2447-67), in the presence of an amine such as diisopropylethylamine and in a suitable organic solvent such as dimethylformamide. Alternatively, the acid 15 can be converted to an acid halide and then reacted with an amine of formula 14. The reaction is carried out in the presence of a non-nucleophilic amine such as triethylamine, pyridine, and the like. The acid chloride can be prepared in situ from the acid 15 using either oxalyl chloride or thionyl chloride.

Compounds of Formula ((I)) where A, L, X^1, X^2, R^1, R^2, R^3 are as defined in the Summary and Z is an carboxyalkyl or substituted carboxyalkyl can be prepared as described in Scheme 7 below.

Scheme 7



Compounds of Formula (I) where Z is carboxyalkyl or substituted carboxyalkyl can be prepared by reacting a compound of formula 17 with an ester of formula 18 in the presence of a base such as cesium carbonate in a suitable solvent such as dimethylformamide to give compound 19. Compound 19 is then saponified with a base such as sodium hydroxide in a solvent mixture such as tetrahydrofuran/water to give a compound of Formula (I).

Utility

The compounds of the invention are high affinity agonists (or antagonists) at various S1P receptors, in particular the compounds of this invention are SIP1 agonists, and hence are useful in the treatment of a variety of S1P, in particular S1P1, receptor-mediated clinical conditions. Such conditions include transplant rejection (solid organ transplant and islet cells); transplant rejection (tissue); cancer; autoimmune/inflammatory diseases; rheumatoid arthritis; lupus; insulin dependent diabetes (Type I); non-insulin dependent diabetes (Type II); multiple sclerosis; psoriasis; ulcerative colitis; inflammatory bowel disease; Crohn's disease; acute and chronic lymphocytic leukemias and lymphomas where immunosuppression is central.

Specifically, S1P1 receptor agonists suppress the peripheral immune response by inducing lymphocyte sequestration in secondary lymph organs thereby resulting in lymphopenia. Thus the compounds of the invention can be used as immune modulators, and are useful in treating or preventing pathologies mediated by lymphocyte actions, including acute or chronic rejection of tissue grafts such as organ transplants, and autoimmune diseases. Autoimmune diseases that may be treated with compounds of the invention include: systemic lupus erythematosus, multiple sclerosis, Behçet's disease, glomerulonephritis, rheumatoid arthritis, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, type I diabetes, uveitis, psoriasis, myasthenia gravis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, hepatitis and Wegner's granuloma. The

compounds of the invention are useful also in treating inflammatory disorders, including atopic asthma, inflammatory glomerular injury and ischemia-reperfusion injury.

Lysophospholipids, S1P and lysophosphatidic acid (LPA), stimulate cellular proliferation and affect numerous cellular functions by signaling through G protein-coupled endothelial differentiation gene-encoded (S1P) receptors. Accordingly, the compounds of this invention are anticipated to have utility in immunomodulation, *e.g.,* in anti-angiogenesis therapy, such as in neoplastic disease treatment.

It has also been reported that S1P inhibits fibrosis in various organs. Accordingly, the compounds of this invention can be used to prevent/treat diseases associated with organ fibrosis, such as pulmonary fibrosis, interstitial pneumonia, chronic hepatitis, hepatic cirrhosis, chronic renal insufficiency or kidney glomerular sclerosis. In addition, S1P compounds of the invention can inhibit exit of lymphocytes from secondary lymphoid tissues. Thus the present compounds can be used to reduce lymphocyte infiltration of transplanted organs, *e.g.,* allografts, or healthy cells, *e.g.,* pancreatic islets as in type I diabetes, myelin sheathing (multiple sclerosis), kidney, heart and lung transplantations or other tissues that may be subjected to an undesirable immunoresponse, and thus decrease damage to such tissues from the immune system.

In addition the compounds of this invention can be used to treat a disorder of abnormal cell growth and differentiation. These disorders include Alzheimer's disease, aberrant corpus luteum formation, osteoporosis, anovulation, Parkinson's disease, and cancer. S1P also acts as a survival factor in many cell types. Hence, the compounds of the invention are expected to be useful in protecting cells and tissues from hypoxic conditions, including injury sustained as a result of ischemia such as ischemia reperfusion type injury.

In particular, the compounds can be administered to patients as part of the treatment associated with organ transplantation, including pancreas, pancreatic islets, kidney, heart and lung transplantations.

Testing

The SIP1 agonistic activity of the compounds of the present invention can be tested using the *in vitro* and *in vivo* assays described in Biological Examples 1 and 2 below.

Administration and Pharmaceutical Composition

The compounds of the invention may be administered to patients in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. An appropriate dosage level will generally be about 0.001 to 500 mg, preferably 0.001 to 50 mg per kg patient body

weight per day, which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.005 to about 250 mg/kg per day; more preferably about 0.005 to about 100 mg/kg per day, or about 0.005 to about 50 mg/kg per day; or 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. For example, in the treatment or prevention of a disorder of the central nervous system, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially about 0.01 to 1 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the dose required for use in any particular application will vary from patient to patient, not only with the particular compound or composition selected, but also with the route of administration, the nature of the condition being treated, the age and condition of the patient, concurrent medication or special diets then being followed by the patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician.

The compounds of the invention can be used in combination with other pharmacological agents (e.g., in combination with known immunosuppressants such as cyclosporine, tacrolimus, rapamycin, azathioprine, cyclophosphamide, methotrexate and corticosteroids such as cortisone, des-oxymetasone, betametasone, desametasone, flunisolide, prednisolone, prednisone, amcinomide, desonide, methylprednisolone, triamcinolone, and alclometasone). The compounds of the invention and the other pharmacologically active agent may be administered to a patient simultaneously, sequentially or in combination. It will be appreciated that when using a combination of the invention, the compound of the invention and the other pharmacologically active agent may be in the same pharmaceutically acceptable carrier and therefore administered simultaneously. They may be in separate pharmaceutical carriers such as conventional oral dosage forms which are taken simultaneously. The term "combination" further refers to the case where the compounds are provided in separate dosage forms and are administered sequentially.

"Combination therapy" (or "co-therapy") includes the administration of a S1P receptor modulator of the invention and at least a second agent as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination

selected). "Combination therapy" may, but generally is not, intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention.

"Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical.

"Combination therapy" also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies (*e.g.*, surgery or radiation treatment.) Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non-drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

The compositions and combination therapies of the invention may be administered in combination with a variety of pharmaceutical excipients, including stabilizing agents, carriers and/or encapsulation formulations as described herein.

The compositions and combination therapies of the invention can generally be formulated for parenteral administration, *e.g.*, formulated for injection via the intravenous, intramuscular, subcutaneous, intralesional, or even intraperitoneal routes. The preparation of an aqueous composition that contains a composition of the invention or an active component or ingredient will be known to those of skill in the art in light of the present disclosure. Typically,

such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The preparation of more, or highly, concentrated solutions for intramuscular injection is also contemplated. In this regard, the use of DMSO as solvent is preferred as this will result in extremely rapid penetration, delivering high concentrations of the active compound(s) or agent(s) to a small area.

Solutions of active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Therapeutic or pharmacological compositions of the present invention will generally comprise an effective amount of the component(s) of the combination therapy, dissolved or dispersed in a pharmaceutically acceptable medium. Pharmaceutically acceptable media or carriers include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents

for pharmaceutical active substances is well known in the art. Supplementary active ingredients can also be incorporated into the therapeutic compositions of the present invention.

Suitable preservatives for use in such a solution include benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal and the like. Suitable buffers include boric acid, sodium and potassium bicarbonate, sodium and potassium borates, sodium and potassium carbonate, sodium acetate, sodium biphosphate and the like, in amounts sufficient to maintain the pH at between about pH 6 and pH 8, and preferably, between about pH 7 and pH 7.5. Suitable tonicity agents are dextran 40, dextran 70, dextrose, glycerin, potassium chloride, propylene glycol, sodium chloride, and the like, such that the sodium chloride equivalent of the ophthalmic solution is in the range 0.9 plus or minus 0.2%. Suitable antioxidants and stabilizers include sodium bisulfite, sodium metabisulfite, sodium thiosulfite, thiourea and the like. Suitable wetting and clarifying agents include polysorbate 80, polysorbate 20, poloxamer 282 and tyloxapol. Suitable viscosity-increasing agents include dextran 40, dextran 70, gelatin, glycerin, hydroxyethylcellulose, hydroxmethylpropylcellulose, lanolin, methylcellulose, petrolatum, polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose and the like.

A minimal volume of a composition required to disperse the active compounds is typically utilized. Suitable regimes for administration are also variable, but would be typified by initially administering the compound and monitoring the results and then giving further controlled doses at further intervals. For example, for parenteral administration, a suitably buffered, and if necessary, isotonic aqueous solution would be prepared and used for intravenous, intramuscular, subcutaneous or even intraperitoneal administration. One dosage could be dissolved in 1 mL of isotonic NaCl solution and either added to 1000 mL of hypodermolysis fluid or injected at the proposed site of infusion, (see for example, *Remington's Pharmaceutical Sciences* 15th Edition, pages 1035-1038 and 1570-1580).

The carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Upon formulation, therapeutics will be administered in a manner compatible with the dosage formulation, and in such amount as is pharmacologically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above, but drug release capsules and the like can also be employed.

In this context, the quantity of active ingredient and volume of composition to be administered depends on the host animal to be treated. Precise amounts of active compound required for administration depend on the judgment of the practitioner and are peculiar to each individual.

In certain embodiments, active compounds may be administered orally. This is contemplated for agents which are generally resistant, or have been rendered resistant, to proteolysis by digestive enzymes. Such compounds are contemplated to include chemically designed or modified agents; dextrorotatory peptides; and peptide and liposomal formulations in time release capsules to avoid peptidase and lipase degradation.

Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders.

In certain defined embodiments, oral pharmaceutical compositions will comprise an inert diluent or assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 75% of the weight of the unit, or preferably between 25-60%. The amount of active compounds in such therapeutically useful compositions is such that a suitable dosage will be obtained.

The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or

saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup of elixir may contain the active compounds sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, *e.g.,* conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.,* water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.005 to 500, preferably, 0.1 to about 500 mg of the active ingredient of the invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the compositions of the invention may be incorporated for administration orally include aqueous solution, suitably flavored syrups, aqueous or oil suspensions, and emulsions with acceptable oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, or with a solubilizing or emulsifying agent suitable for intravenous use, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

Additional formulations suitable for other modes of administration include suppositories. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%.

Examples

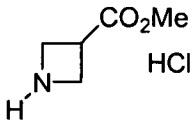
Synthetic Examples

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All parts are by weight and temperatures are in degrees centigrade unless otherwise indicated. Microwave assisted reactions were conducted with a Discover™ model microwave reactor (CEM, Matthews, North Carolina) or a Smith Synthesizer™ (Personal Chemistry, Uppsala, Sweden). All compounds showed NMR spectra consistent with their assigned structures. Melting points were determined on a Buchi apparatus and are uncorrected. Mass spectral data was determined by electrospray ionization technique. All examples were purified to >90% purity as determined by high-performance liquid chromatography (HPLC).

The features and other details of the invention are more particularly described below. It will be understood that particular embodiments described herein are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various embodiments without departing from the scope of the invention. All parts and percentages are by weight unless otherwise specified.

Reference A

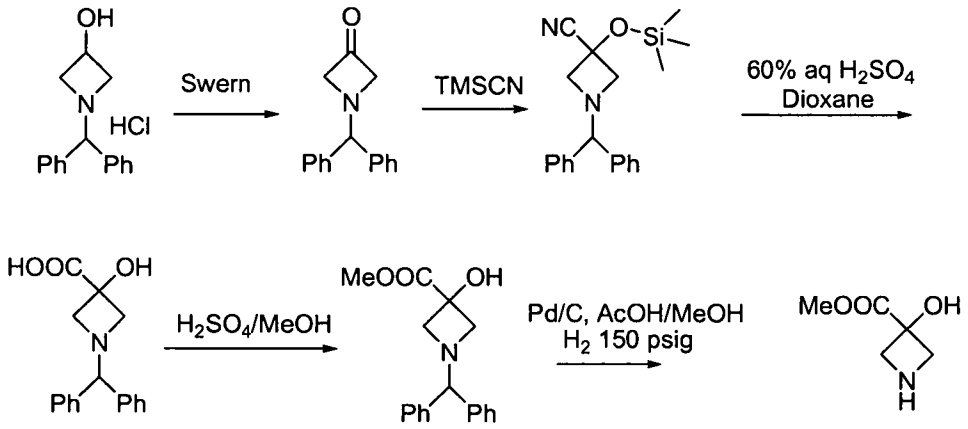
Synthesis of methyl azetidine-3-carboxylate hydrochloride



To a slurry of azetidine-3-carboxylic acid (20 g, 198 mmol) in 500 mL anhyd. MeOH under nitrogen at 0 °C was added slowly dropwise thionyl chloride (36 mL, 495 mmol) over 4 h. The resulting clear, light yellow solution was sealed and placed in a 0 °C freezer overnight. In the morning the reaction mixture was concentrated in vacuo, and the resulting oil was treated with 100 mL anhydrous benzene and concentrated in vacuo to give a solid. This was repeated anhydrous benzene. The resulting light yellow solid was dried in vacuo to give methyl azetidine-3-carboxylate hydrochloride. ^{1}H NMR (400 MHz, MeOH-d_4) δ ppm 4.21-4.30 (m, 4H), 3.78 (s, 3H), 3.71-3.78 (m, 1H).

Reference B

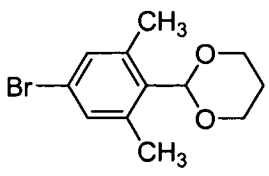
Synthesis of methyl 3-hydroxyazetidine-3-carboxylate



Experimental procedures can be found in patent publication WO 02/7109334.

Reference C

Synthesis of 2-(4-Bromo-2,6-dimethylphenyl)-1,3-dioxane



Step 1

A mixture of 4-bromo-2,6-dimethylbenzenamine (20 g, 100 mmol) and conc. HCl (100 mL) in water (100 mL) was sonicated for 5 min and then cooled to 0 °C. A solution of sodium nitrite (6.9 g, 100 mmol) in water (25 mL) was added, and the resulting mixture was stirred at 0 °C for 30 min, then neutralized by the addition of solid sodium bicarbonate. The resulting mixture was slowly poured (in portions) into a solution of potassium cyanide (6.5 g, 100 mmol) and copper(I) cyanide (9.0 g, 100 mmol) in water (50 mL). The resulting mixture was heated at 70 °C for 30 min, then cooled to 25 °C and extracted with EtOAc (3×150 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide 4-bromo-2,6-dimethylbenzonitrile as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.56 (s, 2 H), 2.45 (s, 6 H).

Step 2

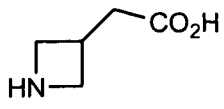
DIBAL-H (1.0M in hexanes; 22.0 mL, 22.0 mmol) was added to a solution of 4-bromo-2,6-dimethylbenzonitrile (3.87 g, 18 mmol) in CH_2Cl_2 (50 mL) at 0 °C, and the resulting mixture stirred at 25 °C for 3 h. Saturated aqueous sodium potassium tartrate solution (75 mL) was then slowly added, and the resulting mixture was stirred vigorously for 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0–20% EtOAc/hexanes) furnished 4-bromo-2,6-dimethylbenzaldehyde as a light brown solid.

Step 3

A mixture of 4-bromo-2,6-dimethylbenzaldehyde (2.51 g, 12 mmol), 4-methyl-benzenesulfonic acid (0.20 g, 1.2 mmol), and propane-1,3-diol (1.2 mL, 16 mmol) in toluene (200 mL) was heated under nitrogen at 140 °C for 16 h, using a Dean–Stark trap to remove water. The reaction solution was then cooled to 25 °C, diluted with EtOAc (200 mL), and sequentially washed with saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide a yellow- brown oil. Hexane (200 mL) was added to the oil, and the resulting mixture was stirred vigorously for 10 min, resulting in the precipitation of a solid. This solid was collected by vacuum filtration, washed with hexanes (100 mL), and dried in vacuo to provide 2-(4-bromo-2,6-dimethylphenyl)-1,3-dioxane as a tan solid.

Reference D

Synthesis of 2-(azetidin-3-yl)acetic acid trifluoroacetic acid salt



Step 1

To a solution of 1-benzhydrylazetidin-3-ol (20 g, 0.835 mol) in pyridine (167 mL) was added DMAP (12.24 g, 0.1 mM) and p-toluene sulphonylchloride at – 40 °C. The reaction mixture was stirred overnight. The reaction mixture was partitioned between dichloromethane (200 mL) and water. Solvent was evaporated off, purified by column chromatography using silica gel, 100-200mesh) and 10% ethyl acetate hexane as eluent to obtain 1-benzhydryl-3-(toluene-4-sulfonyl)-azetidine. ^{1}H-NMR (400 MHz, $CDCl_3$,), δ ppm 7.76-7.74(m, 2H), 7.34-7.15(m, 12H), 4.89-4.85(m, 1H), 4.32(s,1H), 3.47-3.43(m, 2H), 3.06-3.03(m,2H), 2.43(s, 3H).

Step 2

To a suspension of sodium hydride (4.97 g, 0.129 mol) in 130 mL of anhydrous dimethyl formamide was added diethyl malonate (22.7 mL, 0.142mol) dropwise at 0 °C and this reaction mixturewas stirred at room temperature for 2 h . 1-Benzhydryl-3-(toluene-4-sulfonyl)-azetidine was added to it dropwise at 0 °C and reaction mixture was refluxed at 110 °C for 20 h. Excess sodium hydride was quenched with ammonium chloride, DMF was removed, and the reaction mixture was partitioned between chloroform and water; the aqueous layer was extracted with chloroform, the solvent was removed in vacuo, and purification by (neutral alumina) chromatography and 30% ethyl acetate/hexanes as eluent provided 2-(1-benzhydryl-azetidin-3-yl)-malonic acid diethyl ester. ^{1}H-NMR (400 MHz, $CDCl_3$), δ ppm 7.41-7.17(m, 10H), 4.34(s, 1H), 4.25-4.09(m, 3H), 3.66(d, 1H, J=3.66Hz), 3.41-3.37(m, 2H), 3.07-2.99(m, 1H), 2.93-2.90 (m, 2H), 1.25-1.23(m,6H)

Step 3

To a solution of 2-(1-benzhydryl-azetidin-3-yl)-malonic acid diethyl ester (20.2 g, 0.053 mol) in 159 mL of ethyl acetate, palladium hydroxide (0.741g, 5.3 mmol) was added under nitrogen, followed by Boc_2O (15.01mL, 68.8 mmol). The reaction was performed under hydrogen atmosphere. The reaction mixturewas passed through celite, washed with ethyl acetate, concentrated, purified by column chromatography (neutral alumina) using 4% ethyl acetate/hexanes as eluent to give 2-(1-tert-butoxycarbonyl-azetidin-3-yl)-malonic acid diethyl ester. ^{1}H-NMR (400 MHz, $CDCl_3$,), δ ppm 4.23-4.17 (m, 4H), 4.16-4.06 (m, 2H), 3.73-3.69 (m, 2H), 3.62-3.59 (m, 1H), 3.12-3.10 (m, 1H), 1.42 (s,9H), 1.28-1.24 (m, 6H).

Step 4

To a solution of 2-(1-tert-butoxycarbonyl-azetidin-3-yl)-malonic acid diethyl ester (3g, 0.0952 mol) in 95 mL toluene was added (2.514g , 0.0952 mol) of 18-crown-6. A solution of sodium hydroxide (0.1047 mol, 1.1 M) in ethanol was added dropwise. The reaction mixturewas stirred at 25 °C for 5 h and then heated to reflux overnight. The reaction mixture was cooled, concentrated in vacuo, and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, solvent was evaporated off, and the residue purified by column chromatography (neutral alumina) using ethyl acetate/hexanes as eluent to give 3-ethoxycarbonyl-methyl-azetidine-1-carboxylic acid tert-butyl ester.

Step 5

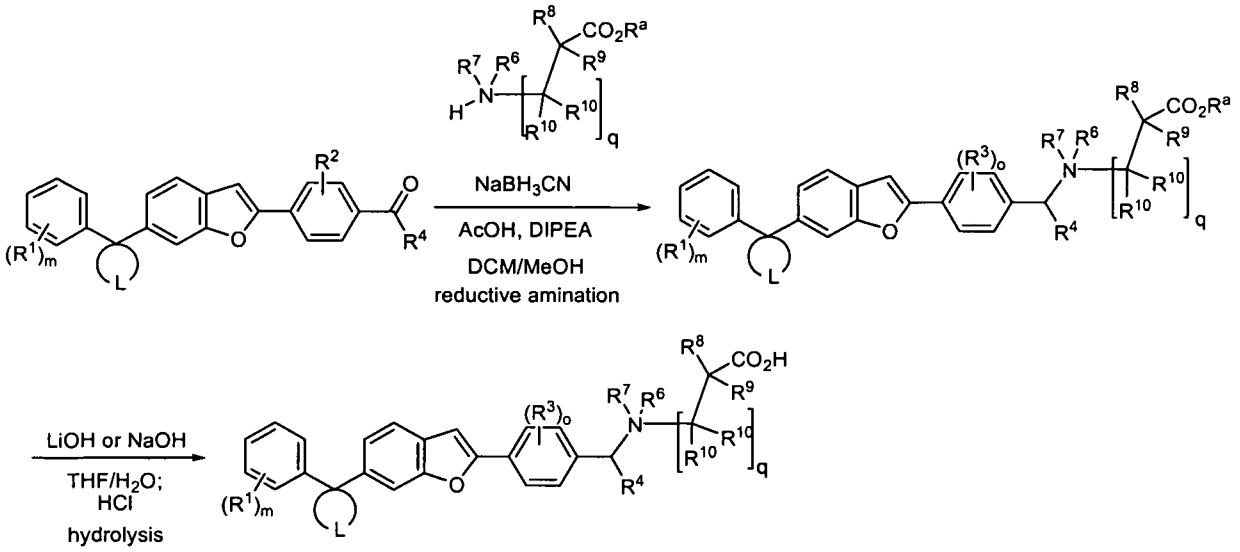
To a solution of 3-ethoxycarbonylmethyl-azetidine-1-carboxylic acid tert-butyl ester (2.3 g, 0.095 mol) in 30 mL THF/MeOH/water (3:2:1) was added (0.477 g, 11.35 mmol) of $LiOH*H_2O$ at 0 °C. The reaction mixturewas stirred for 3 h at 25 °C. Methanol and THF were removed in vacuo, and the reaction mixture was diluted with 50 mL water, and extracted with ethyl acetate. The aqueous layer was acidified with 2N HCl, extracted with ethyl acetate, and the organic layer was dried over Na_2SO_4, and concentrated to give 2-(1-(tert-butoxycarbonyl)-azetidin-3-yl)acetic acid. ^{1}H-NMR (400 MHz, $CDCl_3$), δ ppm 4.12-4.07 (m, 2H), 3.66-3.60 (m, 2H), 2.91-2.84 (m, 1H), 2.68-2.66 (m, 2H), 1.43 (s, 9H).

Step 6

2-(1-(tert-Butoxycarbonyl)azetidin-3-yl)acetic acid (0.308g, 1.43 mmol) was dissolved in 5 mL dichloromethane and was stirred at room temperature. Trifluoroacetic acid (1.47 mL) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 h. Trifluoroacetic acid was removed in vacuo to give 2-(azetidin-3-yl)acetic acid trifluoroacetic acid salt. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 4.18-4.13 (m, 2H), 3.93-3.88 (m, 2H), 3.25-3.19 (m, 1H), 2.71 (d, 2H, J=7.6Hz).

Reference F

General Reductive Amination and Hydrolysis Procedures



General procedure for reductive amination of aldehydes:

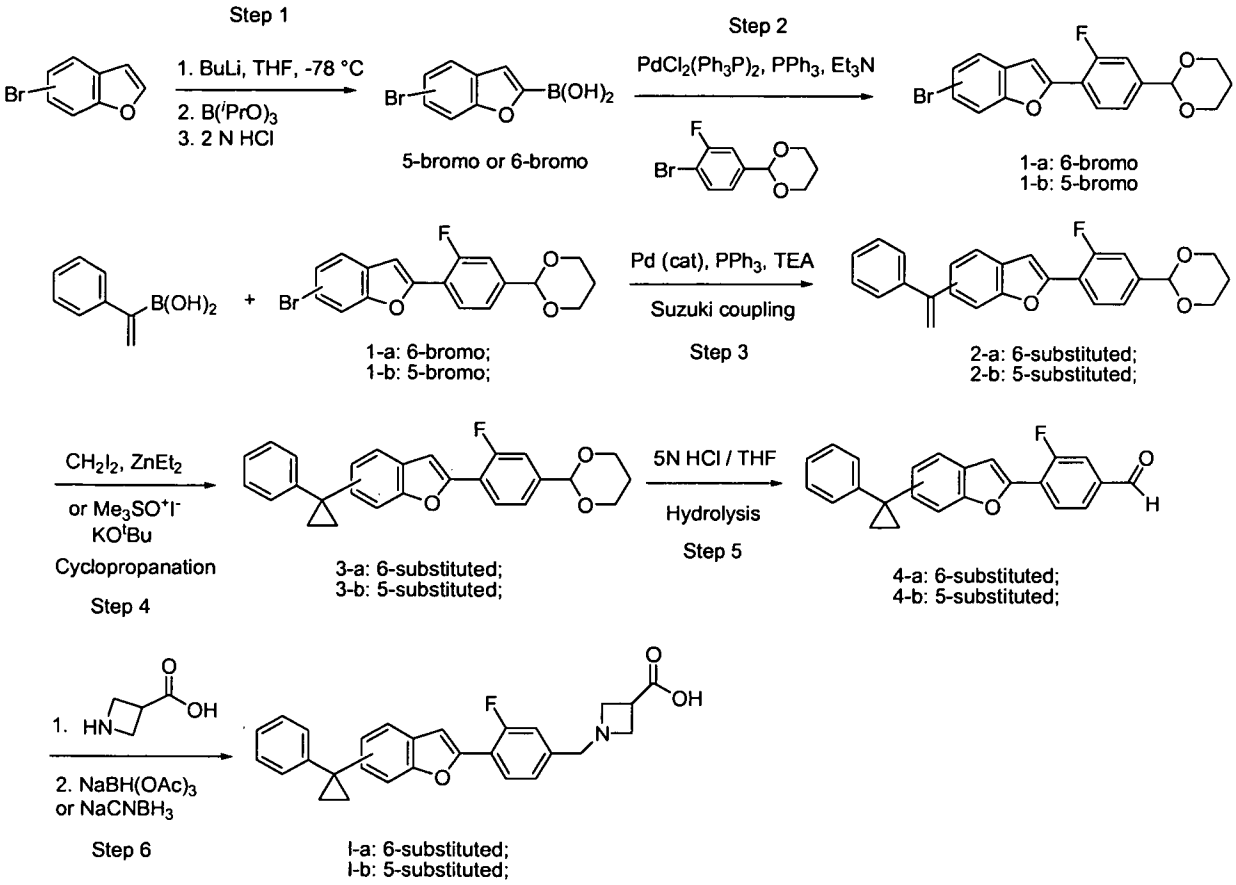
A mixture of aldehyde (1.0 mmol), acetic acid (1.5-5 mmol), amine (1.5-5 mmol), and DIPEA (0-5 mmol, used in 1:1 ratio with amine*HCl salts) in DCM/MeOH (1:1, 5 mL) was stirred at room temperature for 1 h. Sodium cyanoborohydride (0.5-1.0 mmol) was added and the reaction mixture was stirred for 2-3 h at room temperature. The reaction mixture was concentrated in vacuo, diluted with DCM, and the acid was quenched by addition of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with DCM, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Purification by silica gel chromatography provided the desired products.

General procedure for hydrolysis of esters:

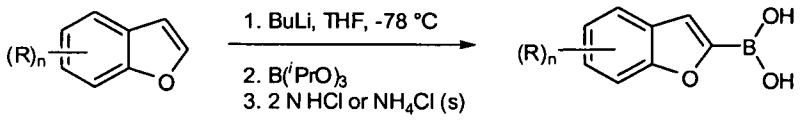
To a solution of ester (0.5 mmol) in 2 mL THF was added sodium hydroxide (1.0M in water, 1.5 mmol). The reaction was stirred until completion. The THF was removed in vacuo, and the solid was suspended in 2 mL water. HCl (1.0N in water, 1.5 mmol) was added to neutralize the base, and the mixture was sonicated. Phosphate buffer (4 mL, 1M, pH 6) was added and the reaction was sonicated. The slurry was filtered and the solid rinsed with water and EtOH and dried in vacuo to give the desired product. Occasionally compounds were isolated as HCl salts. In these cases, the THF was removed in vacuo, and the reaction acidified with HCl until approximately pH 1-2. The solids were collected by filtration, rinsing with water and ether, and dried in vacuo to give the desired products as HCl salts.

Example 1

Synthesis of compounds of Formula (I) where X is O or S, L is cyclopropyl, Z is 3-carboxyazetidin-1-ylmethyl, m and n are 0, o is 1, A is phenyl and R^3 is fluoro



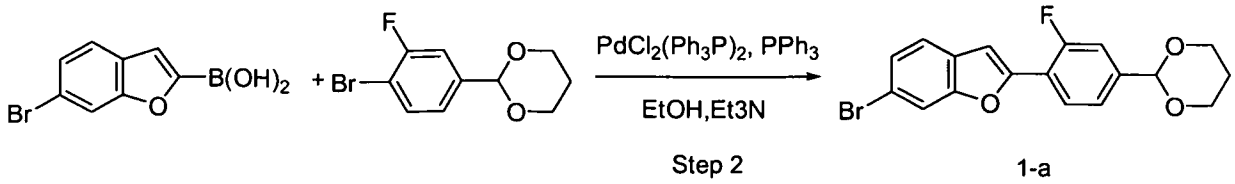
Step 1



Step 1

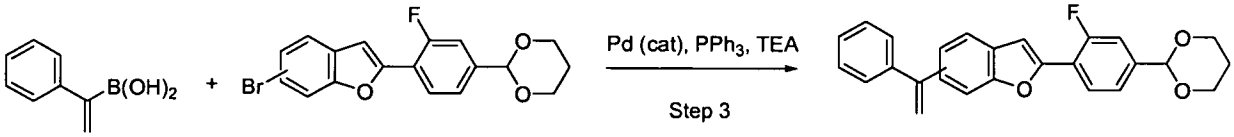
A solution of *n*-BuLi (1.2 mmol, 2.5M solution in hexanes) is added dropwise to a solution of benzofuran compounds (1.0 mmol) in anhydrous THF (20 mL) at -78 °C. The resulting mixture is stirred at -78 °C for 20 min, and treated with $B(^iPrO)_3$ (1.5 mmol). The reaction mixture is allowed to warm up slowly to room temperature and stirred for 1 h. The reaction is cooled in ice-bath and quenched with 2N HCl or saturate NH_4Cl and extracted with Et_2O. The combined organic extracts are washed with brine, dried and concentrated under reduced pressure to yield a desired benzofuran boronic acid without further purification for next step.

Step 2



A mixture of benzofuran boronic acid (1.1 mmol), aryl halide (1.0 mmol), triethylamine (20 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.05 mmol) in ethanol (30 mL) is irradiated in a Microwave instrument at 100 °C for 20 min. The reaction mixture is cooled, and the solvent is removed. The residue is treated with water and extracted with ethyl acetate. The organic layer is dried and concentrated *in vacuo* (the aqueous work-up is optional). Purification by silica gel chromatography gives the desired product 1-a.

Step 3

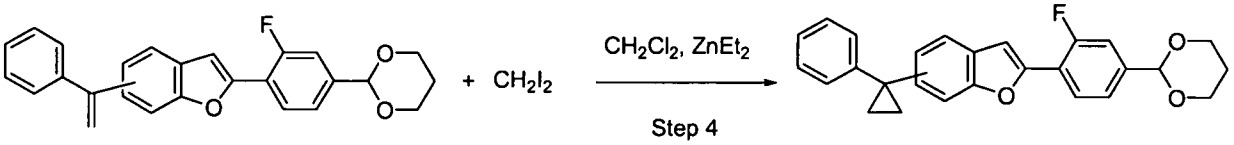


1-a: 6-bromo
1-b: 5-bromo

2-a: 6-substituted;
2-b: 5-substituted;

A mixture of 1-Phenylvinylboronic acid (1.1 mmol, Aldrich), 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-bromobenzofuran (1.0 mmol), triethylamine (20 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.05 mmol) in ethanol (30 mL) is irradiated in a Microwave instrument at 100 °C for 20 min. The reaction mixture is cooled, and the solvent is removed. The residue is treated with water and extracted with ethyl acetate. The organic layer is dried and concentrated *in vacuo* (the aqueous work-up is optional). Purification by silica gel chromatography gives the desired product 2-a or 2-b.

Step 4



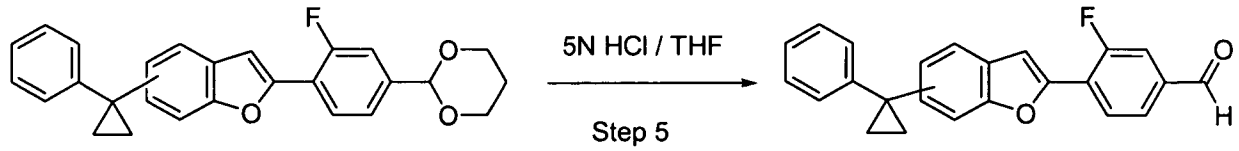
2-a: 6-substituted;
2-b: 5-substituted

3-a: 6-substituted;
3-b: 5-substituted

Diiodomethane (10 mmol) is added slowly to a solution of the alkene (1.0mmol) and diethyl zinc (1.0 M in hexane, 5.0 mmol) in dry dichloromethane. The cloudy solution is heated under reflux overnight. After cooling the solution is poured into water, extracted into dichloromethane. The organics are washed with water then dried over magnesium sulfate. After the solvents are removed under reduced pressure, the resulting residue is dissolved in

methanol and water, purified by reverse phase preparative HPLC or silica gel chromatography to yield the desired final product 3-a or 3-b. (See a) Organic Letters, 9(18), 3499-3502; 2007. b) WO 9412880; C) Encyclopedia of Reagents for Organic Synthesis, 2001).

Step 5

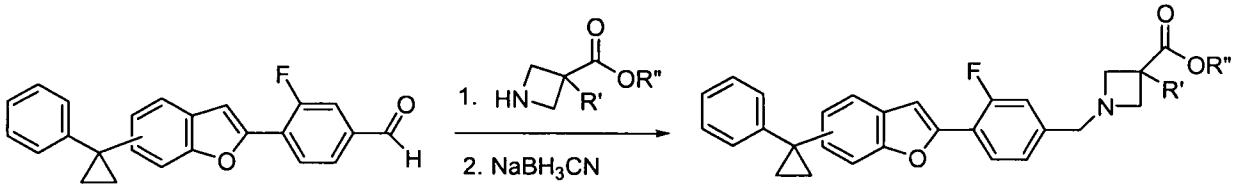


3-a: 6-substituted;
3-b: 5-substituted

4-a: 6-substituted;
4-b: 5-substituted

To a solution of acetal (1.0 mmol) in THF (4 mL) is added 7~8 mL of aquesous solution of hydrogen chloride (5 *N*, 37~40 mmol) at 0 °C. The mixture is allowed to warm up slowly and stirred at room temperature overnight. After the hydrolysis is completed, the mixture is extracted with diethyl ether. The organics are washed with water then dried over magnesium sulfate. After the solvents are removed under reduced pressure, the resulting residue is purified by reverse phase preparative HPLC to yield the desired product 4-a or 4-b.

Step 6



4-a: 6-substituted;
4-b: 5-substituted

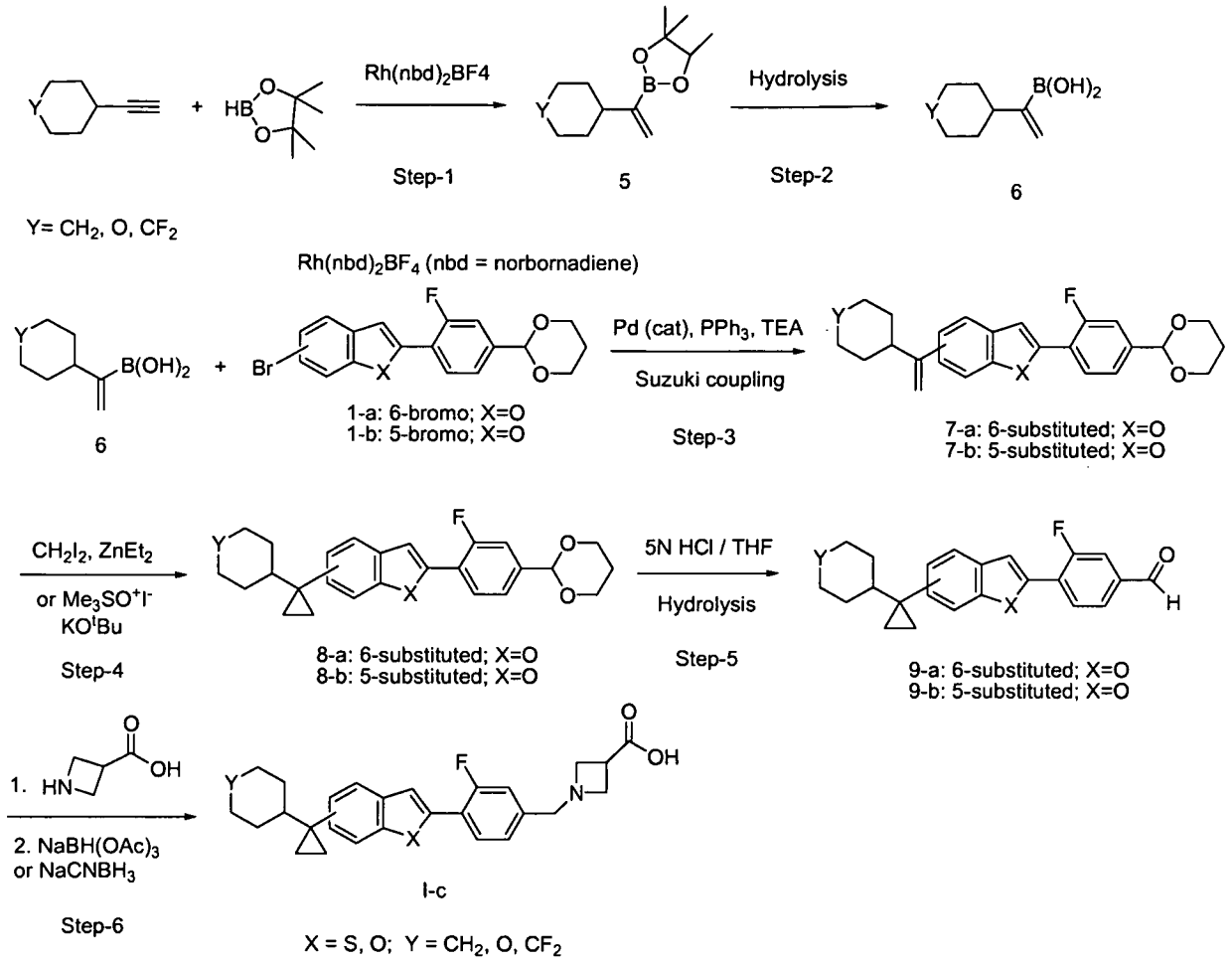
I

R' = H, OH, F: R"= H, Me, Et

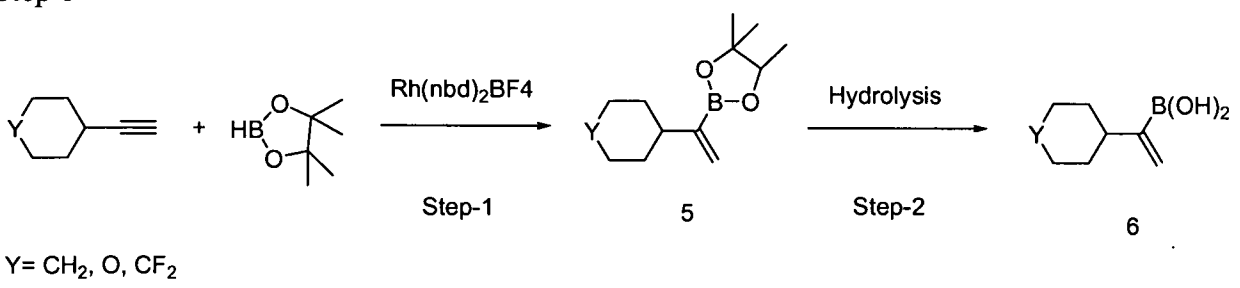
A mixture of aldehyde (1.0 mmol), acetic acid (1.5 mmol) and azetidine-3-carboxylic acid or ester (1.2-1.5 mmol) in DCM/MeOH (1:1, 10 mL) is stirred at room temperature for 1 h. Sodium cyanoborohydride (0.5 mmol) is added and the reaction mixture is stirred for 2-3 h at room temperature. After concentration of solvent under reduced pressure, the resulting residue is dissolved in DMSO, filtered and purified by reverse phase preparative HPLC to yield the desired final product (I) with puritiy greater than 95%.

Example 2

Synthesis of compounds of Formula (I) where X is O or S, L is cyclopropyl, Z is 3-carboxyazetidin-1-ylmethyl, n is 0, o is 1, A is cyclohexyl, 4,4-difluorocyclohexyl or tetrahydropyran-4-yl, and R^3 is fluoro



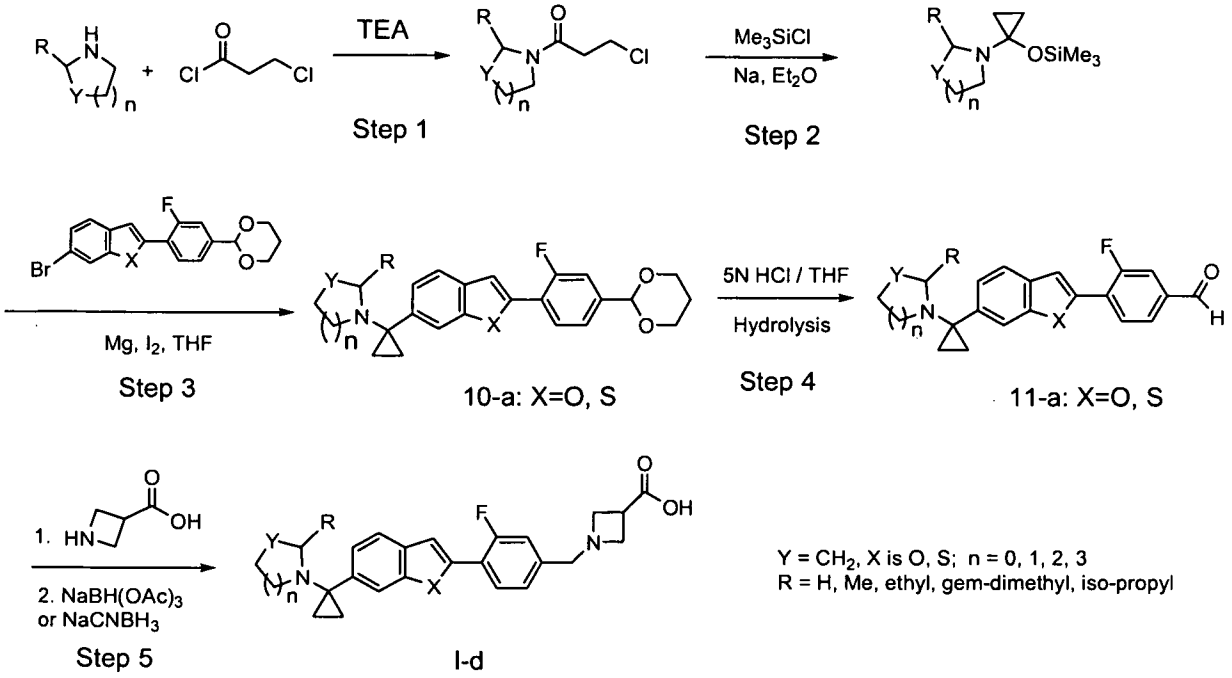
Step 1



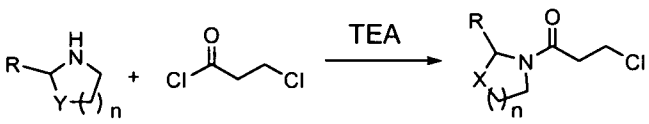
Compound 5 can be prepared by the synthetic procedure described in *Tetrahedron*, 64(29), 6853-6862; 2008. Hydrolyisis of the boron protecting group, followed by the Steps 3-6, described in Scheme 1 above then provides compound of formula I-c.

Example 3

Synthesis of compounds of Formula (I) where X is O or S, L is cyclopropyl, Z is 3-carboxyazetidin-1-ylmethyl, m and n are 0, o is 1, A is pyrrolidin-1-yl azetidin-1-yl, piperidin-1-yl, homopiperidin-1-yl or alkylated derivatives thereof, and R^3 is fluoro

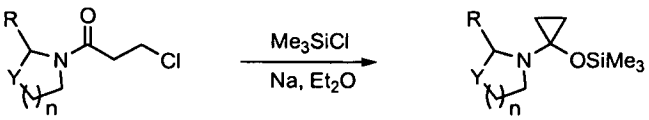


Step 1



To freshly distiiled dichloromethane, cyclic amine (1.0 mmol) and N,N-dimethylaniline (1.8 mmol) are added. The solution is cooled to 0 °C under a nitrogen atmosphere, and 3-chloropropionyl chloride (0.82 mmol) in dichloromethane is added dropwise at 0 °C in 30 min. The solution is allowed to warm to room temperature and stirred for 12 h. The reaction mixture is washed with 1N aqueous hydrochloric acid, water, and saturated aqueous sodium bicarbonate. The organic layer is dried over magnesium sulfate, and solvent is removed under reduced pressure. The reaction mixture is purified by distillation or by silica gel column chromatography (hexane/ethyl acetate) to give the product.

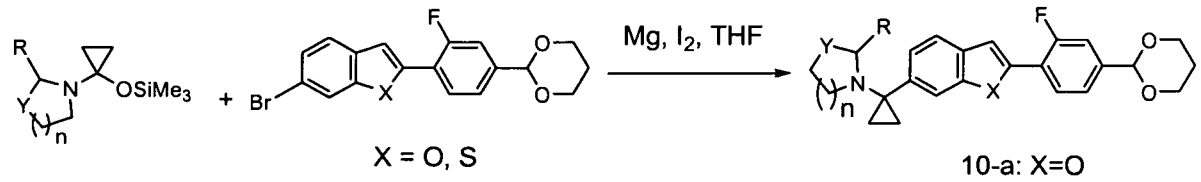
Step 2



To finely divided sodium (3.83 mmol) in ether is added trimethylsilyl chloride (3.35 mmol) under nitrogen atmosphere. To this mixture, the chloroamide (1.0 mmol) in ether is added dropwise with constant vigorous stirring during 5 h. The solution is stirred for 24 h at

room temperature and the solvent is carefully decanted. The residual solid is washed with ether, the organic layers combined, and excess trimethylsilyl chloride and ether are removed by distillation to give the product.

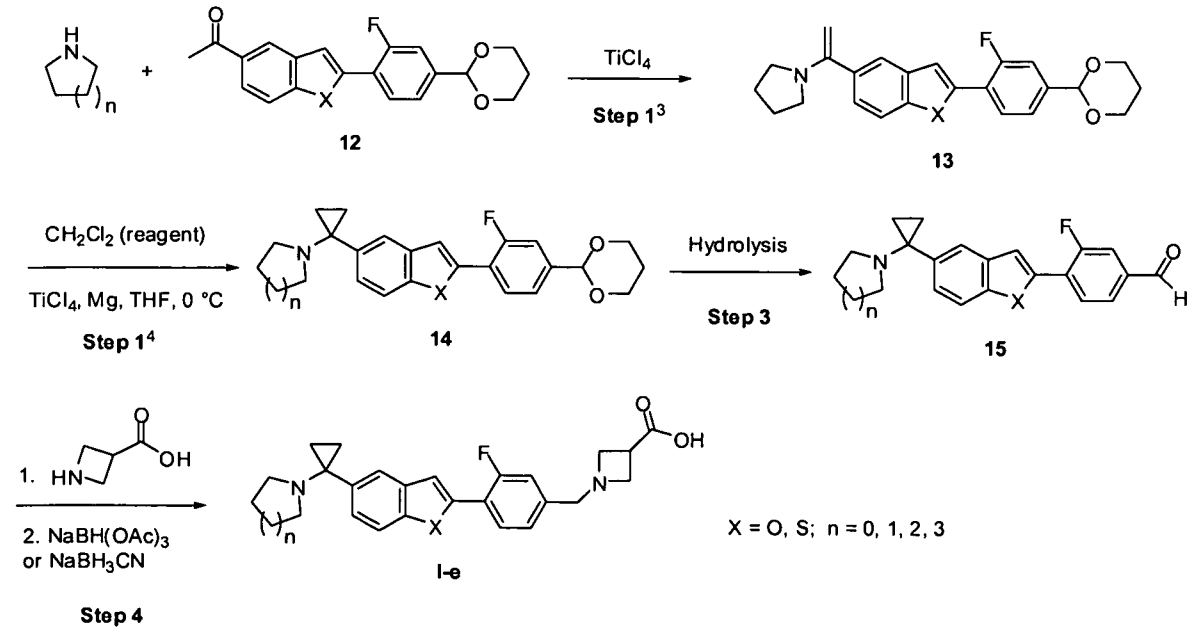
Step 3



To solution of tetrahydrofuran containing magnesium turning (1.28 mmol), a solution of tetrahydrofuran containing bromobenzofuran derivative (1.02 mmol) is added in several portions. The reaction is stirred at room temperature for 16 h. To this mixture, TMS-cyclopropane derivative is added neat in two portions. The reaction is stirred for 3 h. The excess Grinard reagent is quenched with 10% aqueous sodium hydrogen phosphate. The aqueous mixture is washed with ether. The organic layers are combined and dried over magnesium sulfate. The mixture is filtered and solvent is removed under reduced pressure at lower than 30 °C. The mixture is purified by silica gel chromatography (hexane/ethyl acetate) to give the desired product 10. Compound 10 can then be converted to compound I-d by following the procedures described in Scheme 1, Steps 5 and 6 above.

Example 4

Synthesis of compounds of Formula (I) where X is O or S, L is cyclopropyl, Z is 3-carboxyazetidin-1-ylmethyl, m and n are 0, o is 1, A is pyrrolidin-1-yl azetidin-1-yl, piperidin-1-yl, homopiperidin-1-yl, and R^3 is fluoro

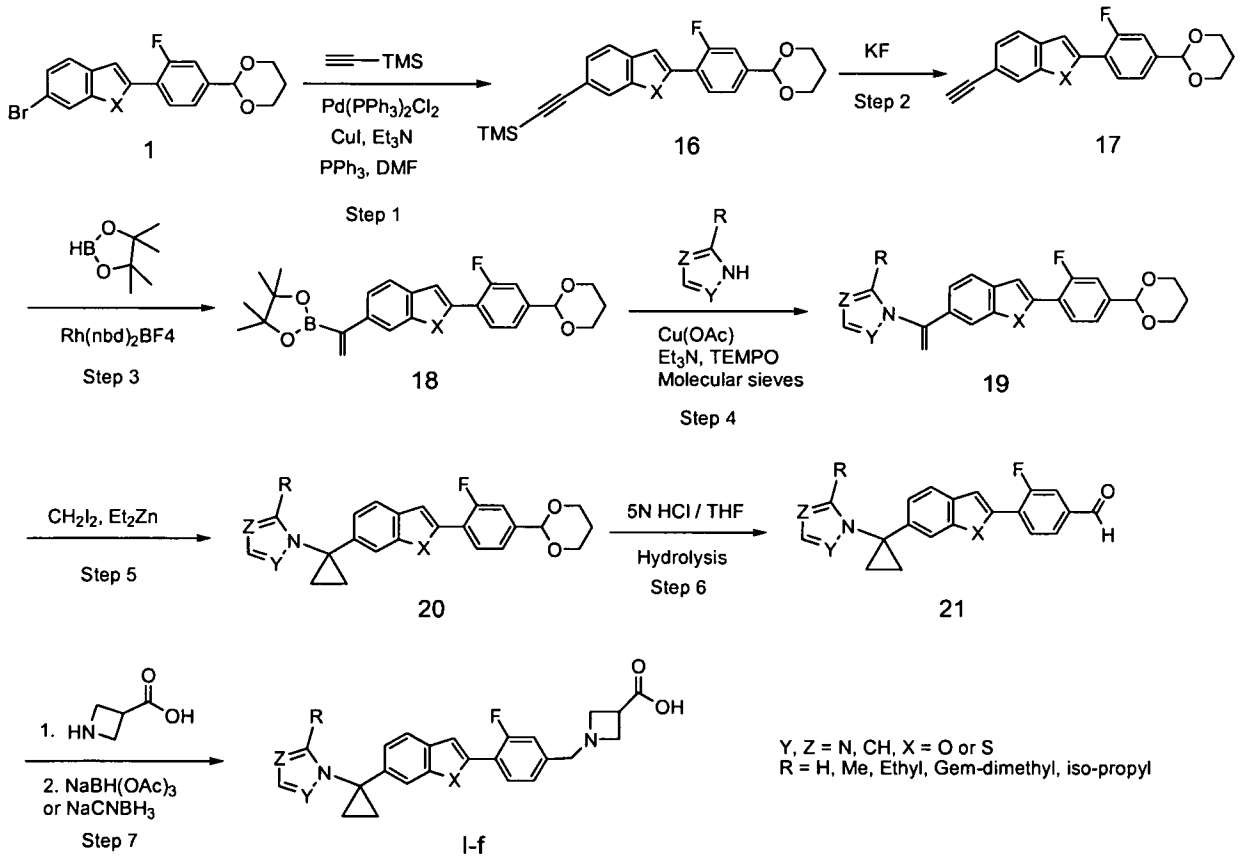


Compound of formula 13 can be prepared by the procedure described in a)*Tetrahedron Letters*, 49(51), 7290-7293; 2008. b) Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999), (8), 1957-60; 1979

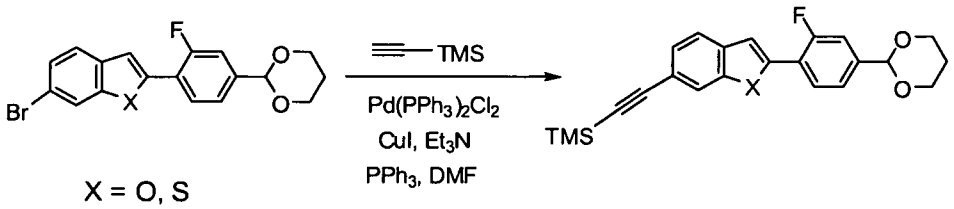
Compound of formula 14 can be prepared by the procedure described in Organic Letters, 8(11), 2261-2263; 2006. Compound 14 is then convered to a compound of formula I-e as described in Example 1, steps 5 and 6.

Example 5

Synthesis of compounds of Formula (I) where X is O or S, L is cyclopropyl, Z is 3-carboxyazetidin-1-ylmethyl, m and n are 0, o is 1, A is heteroaryl, and R^3 is fluoro

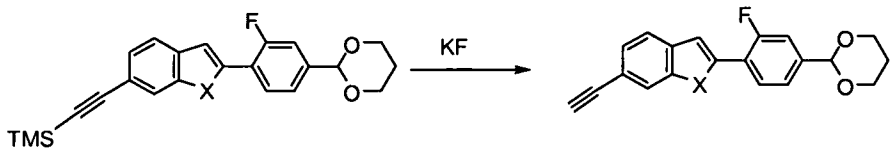


Step 1



In an oven-dried microwave vial, benzofuran bromide or benzothiophen bromide (1.0 mmol), alkyne (1.1 mmol), $Pd(PPh_3)_2Cl_2$ (0.1 mmol), PPh_3 (0.2 mmol), and CuI (0.5 mmol) are mixed and purged under nitrogen. To the mixture is added DMF (0.6 mL) then Et_3N (15.0 mmol). The mixture is irradiated in a microwave (Personal Chemistry Emrys™ Optimizer microwave reactor) for 35 min at 120 °C. The reaction mixture is diluted with EtOAc, washed with sat. NH_4Cl and then with sat. NaCl. The organic layers are dried over Na_2SO_4 and concentrated *in vccuo*. The product is purified by column chromatography on an ISCO system, or is purified by reverse phase preparative HPLC to yield the desired final product.

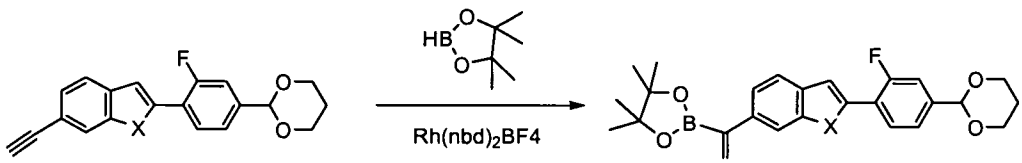
Step 2



X = O, S

Benzofuran (trimethylsilyl)ethynyl derivative (1.0 mmol) and KF (1.5 mmol) are dissolved in dry methanol. The reaction mixture is stirred at room temperature for 18 h. The reaction mixture is concentrated *in vacuo* to remove methanol. Diethyl ether is added and the organic phase is washed with water, brine and dried over magnesium sulfate then filtered. After concentration *in vacuo* the crude product is purified by column chromatography on silica gel using ethyl acetate/dichloromethane as eluent to afford the product.

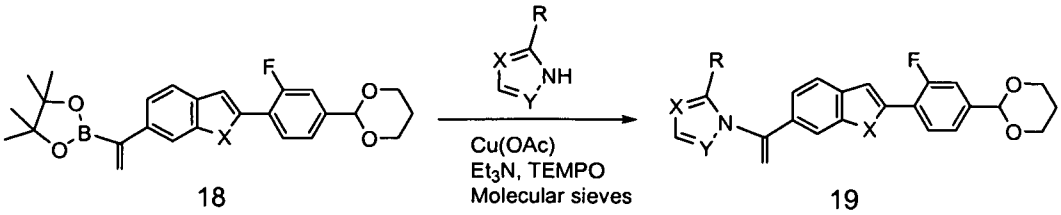
Step 3



17 18

A Rh complex ($Rh(nbd)_2BF_4$, 0.03 mmol) is first weighed into a glass vial containing a stir bar and then sealed with a 20:400 TFE/silicone (Alltech) septum followed by a plastic open-centered cap. Tetrafuran, triethylamine (5 mmol) and pinacolborane (1.0 mmol) are added. After stirring at ambient temperature for 30 min, benzofuranetylene derivative 17 (1.2 eq.) is then added. After stirring the resulting mixture for an additional 14 h at 25 °C, any residual borane is quenched through the addition of excess MeOH. The product 18 is isolated by column chromatography on silica gel (hexanes/ethyl acetate as eluent).

Step 4

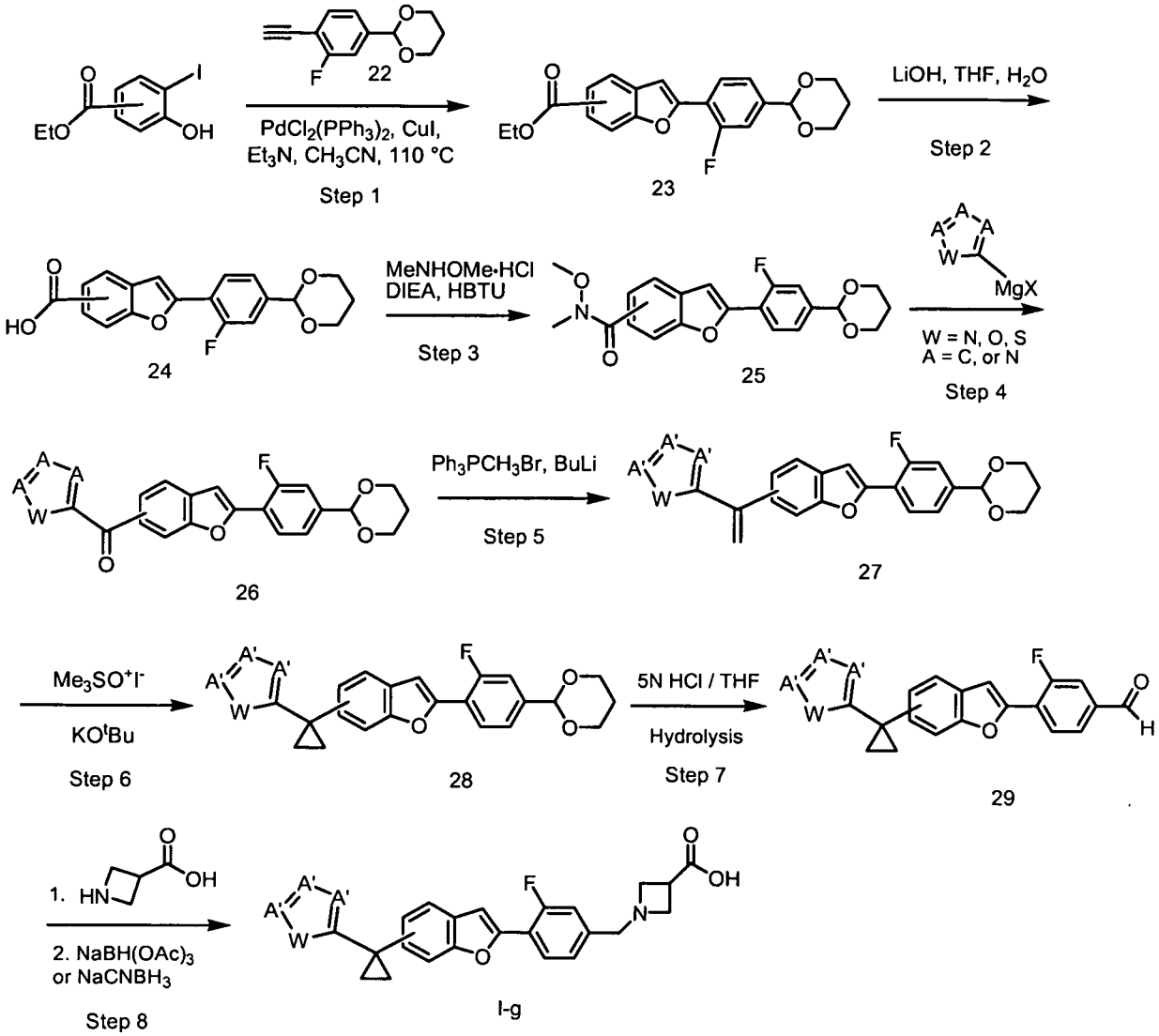


18 19

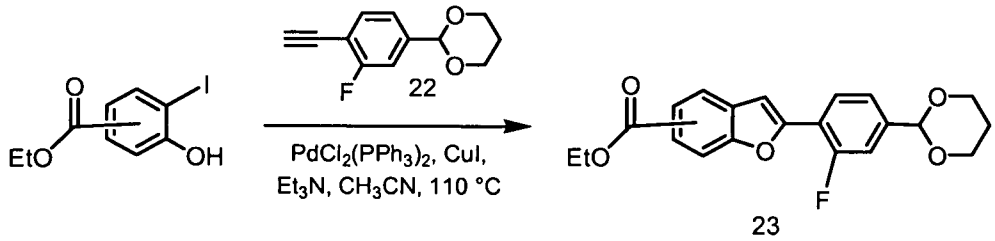
To a vial is added in sequence 4 A molecular sieves, boronic ester (2.0 eq.), dry dichloromethane, triethylamine (2.0 eq.), pyrazole or imidazole (1.0 eq.), cupric acetate (0.1 equiv.) and TEMPO (1.1 equiv.). The progress of the reaction is monitored by TLC (eluent: 15% ethyl acetate/hexane). The reaction is allowed to stir under air at room temperature for 4 days. The reaction is quenched by a solution of NH_3 in methanol (2 M). The solvent is evaporated under reduced pressure and the residue is purified by silica gel chromatography (eluent: 15% ethyl acetate/hexane) to give the product 19. Compound 19 can then be converted to a compound of I-f by following the procedure described in Scheme 1, steps 4, 5, and 6.

Example 6

Synthesis of compounds of Formula (I) where X is O, L is cyclopropyl, Z is 3-carboxyazetidin-1-ylmethyl, m and n are 0, o is 1, A is heteroaryl, and R^3 is fluoro

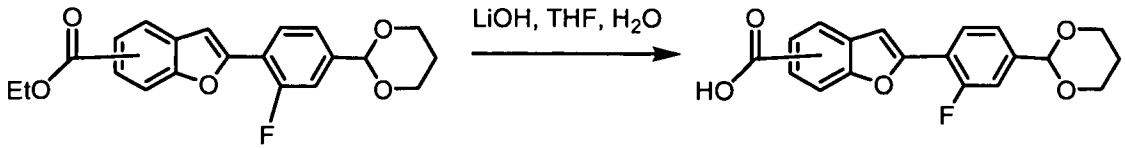


Step 1



$PdCl_2(PPh_3)_2$ (1.29 mmol), copper(I) iodide (1.29 mmol), ethyl 4-hydroxy-3-iodobenzoate or ethyl 3-hydroxy-4-iodobenzoate (12.9 mmol) and 2-(4-ethynyl-3-fluorophenyl)-1,3-dioxane (15.4 mmol) are combined in a sealable tube and 15 mL DMF and 15 mL TEA is added. Argon is bubbled through the solvent for 3 min, and homogeneous reaction is sealed and heated to 100 ^{0}C. After completion of the reaction, the mixture is concentrated *in vacuo* and the residue is purified by ISCO to give the desired product 23.

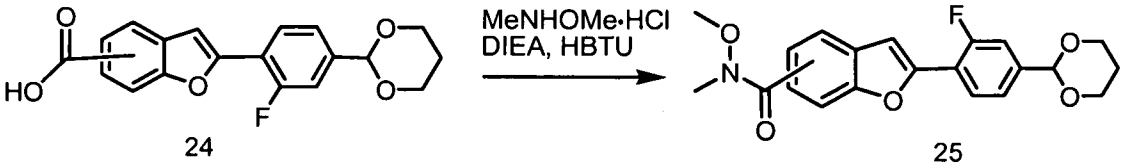
Step 2



23 24

To a solution of ester (7 mmol) in 10 mL of THF is added lithium hydroxide hydrate (21 mmol) in 5 mL of water. The reaction is stirred until completion. THF is removed and the solid is suspended in water. HCl (2 N) is added to neutralize the base to PH = 3 to 4. The mixture is extracted with EtOAc. Removal of the solvents give the residue which was purified by ISCO system.

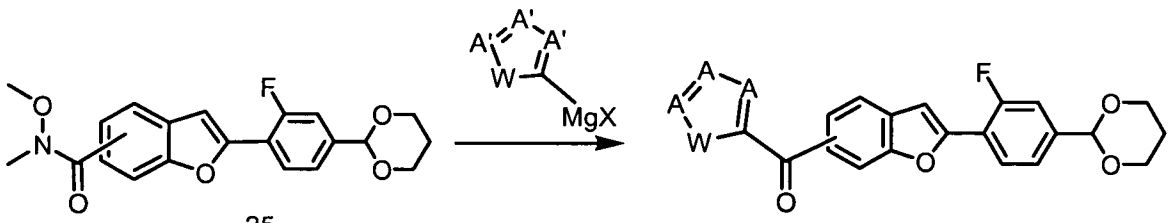
Step 3



24 25

To a solution of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)benzofuran carboxylic acid (5 mmol), MeNHOMe.HCl (7.5 mmol), DIEA (15 mmol) in THF (10 mL) at 0 ^{0}C is added HBTU (7.5 mmol). The resulting mixture is stirred 24 h at room temperature. The reaction is diluted with EtOAc and washed with brine. The mixture is extracted with ethyl acetate. The ethyl acetate fraction is dried (MgSO4), filtered and concentrated. The product is purified on ISCO system.

Step 4

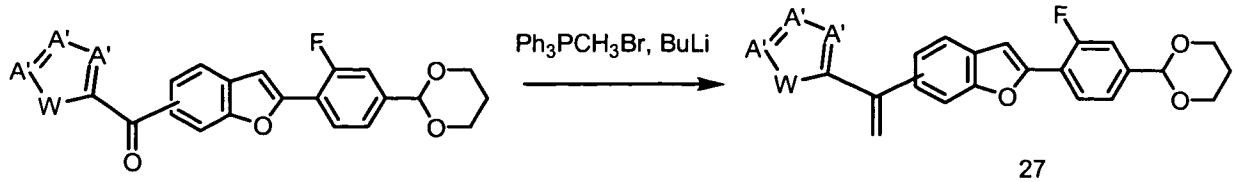


25 26

W = N, O, S
A' = C, or N

To a solution of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-N-methoxy-N-methylbenzofuran carboxamide (3 mmol) in THF (10 mL) at 0 ^{0}C is added a solution of heteroarylmagnesium bromide (6 mmol) dropwise. The resulting mixture is stirred 3 h at 0 ^{0}C. The reaction is quenched with 0.2 N HCl. The mixture is extracted with ethyl acetate. The ethyl acetate fraction is dried ($MgSO_4$), filtered and concentrated. The product is purified on ISCO system.

Step 5

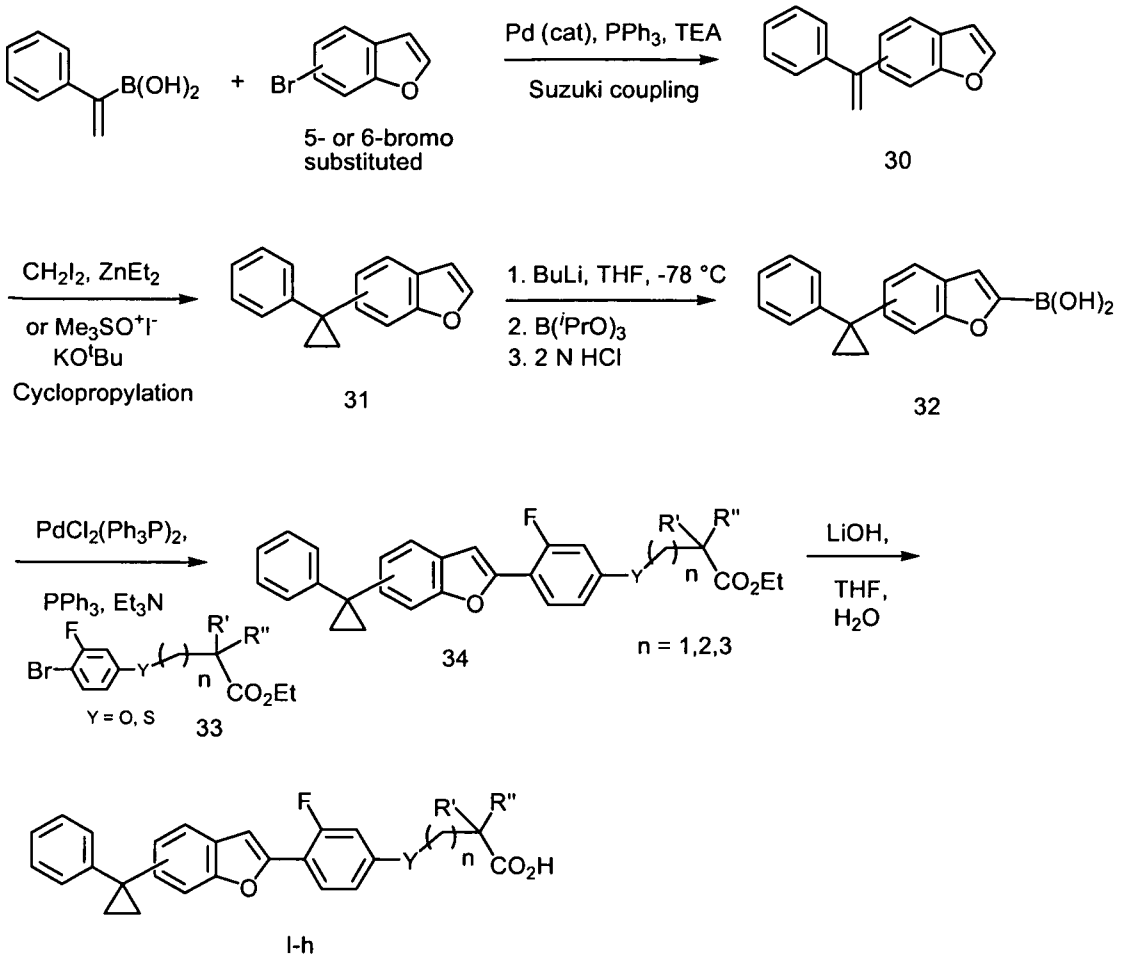


26 27

A 50 ml round bottom flask is filled with argon and the solution of CH_3PPh_3Br (2 mmol) in THF is put into the flask and then cooled to 0 ^{0}C. To the solution is added n-BuLi (1.8 mmol). After the reaction mixture is stirred for 2 hours at the same temperature, a solution of the ketone (1.5 mmol) in THF is added. The temperature of the reaction is raised to room temperature. After the reaction goes the completion, the solution is quenched by NH_4Cl and stirred for 10 minutes. The resulting solution is concentrated, extracted with EtOAc, washed with brine and dried over $MgSO_4$. The product is purified on ISCO system. Compound 27 is then converted to compound I-g following the procedure described in Scheme 1, steps 4, 5 and 6.

Example 7

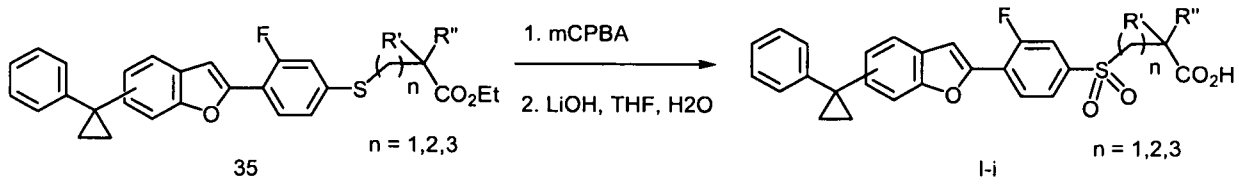
Synthesis of compounds of Formula (I) where X is O, L is cyclopropyl, Z is carboxyalkoxy or carboxyalkylthiol, m and n are 0, o is 1, A is phenyl, and R^3 is fluoro



Compound 30, 31, 32 and 34 can be prepared by the synthetic procedures described in the Step 3 (Suzuki coupling), Step 1 (formation of benzofuran boronic acid), Step 2 (Suzuki coupling) of Scheme 1. Hydrolyisis of the ester group of compound 34, followed by the general protocol F described above, then provides compound of formula I-h.

Example 8

Synthesis of compounds of Formula (I) where X is O, L is cyclopropyl, Z is carboxyalkoxy or carboxyalkylsulfonyl, m and n are 0, o is 1, A is phenyl, and R^3 is fluoro

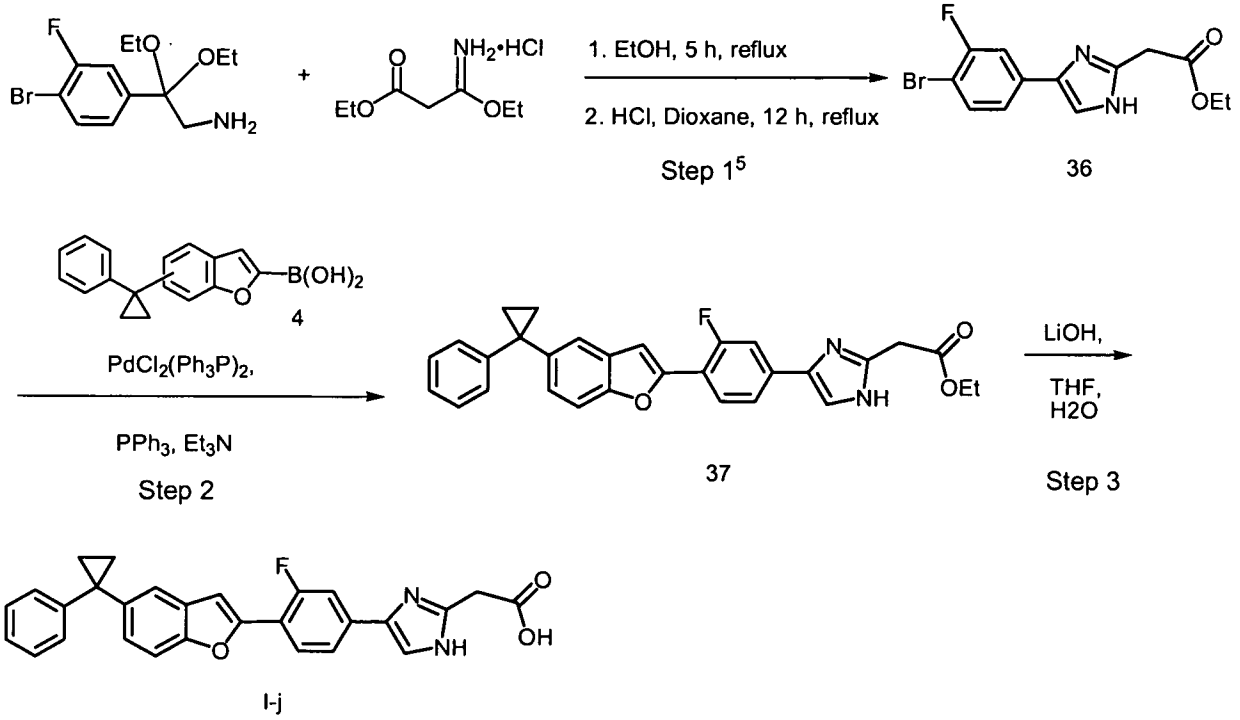


A mixture of compound 35 (1.2 mmol) and m-chloroperbenzoic acid (3.0 mmol) in chloroform and MeOH (9:1) is stirred at 0 ^{0}C for 1 hour. Concentration of the solvent under

reduced pressure affords the residue is purified by ISCO. The desired product is hydrolyzed according to the general procedure F above to give the desired product.

Example 9

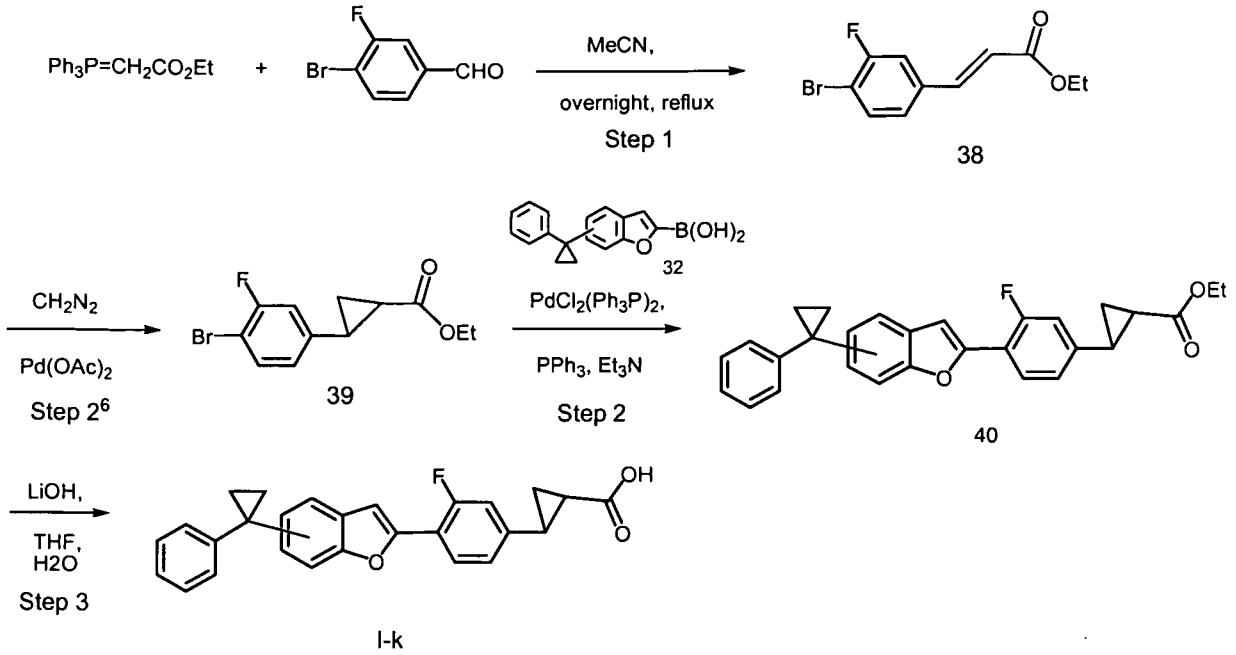
Synthesis of compounds of Formula (I) where X is O, L is cyclopropyl, Z is carboxyalkoxy or carboxyalkylsulfonyl, m and n are 0, o is 1, A is phenyl, and R^3 is fluoro



Compound 36 can be prepared by the procedure described in a)*Tetrahedron Letters*, 47(35), 6201-6204; 2006; b) WO0801155. Compound 36 can be converted to a compound of formula I-j as described in Example 1 above.

Example 10

Synthesis of compounds of Formula (I) where X is O, L is cyclopropyl, Z is carboxyalkoxy or carboxyalkylsulfonyl, m and n are 0, o is 1, A is phenyl, and R^3 is fluoro



(*E*)-Ethyl 3-(4-bromo-3-fluorophenyl)acrylate, 38, can be prepared by using the well-established Wittig methodology described in *J. of Med. Chem.* 33(3), 1990, 908-18.

Compound 38 is reacted with diazomethane under the reaction conditions described in a) *J. of Med. Chem.*, 48(13), 2005, 4254-4265, b) WO05058848 to give compound 39. Compound 39 is the converted to compound I-k as described in Example 1 above

Biological Examples

Example 1

In vitro assay

The activity of compounds of the invention can be determined by a cell imaging-based assay measuring the degree of hS1P1 receptor internalization and a Ca^{2+} mobilization assay measuring the level of S1P receptor activation. The receptor internalization assay can be employed to determine the potency and efficacy of compounds on hS1P1 receptor, while Ca^{2+} mobilization assay can be used to determine selectivity among different S1P receptors and activity on S1P receptors from species such as rat, dog, and cyno.

The hS1P1 receptor internalization assay is performed using a U2OS cell line expressing hS1P1-eGFP chimeric protein (Thermo Scientific, Soeborg, Denmark). Upon compound treatment, the hS1P1 receptor is internalized in cytoplasma and formed GFP-containing-endosomes. This event is detected by an automated microscope, ArrayScan

(Thermo Scientific Cellomics, Pittsburg), and the degree of receptor internalization is quantitated by counting green fluorescent GFP-containing endosomes per cell. In this assay, hS1P1-eGFP expressing U2OS cells are starved in serum free media for two hours prior to compound treatment. Then compounds are incubated with the starved cells at 37 °C for one hour. Subsequently, compound-treated cells are fixed using 4% formaldehyde, and the nuclei are stained using Hoechst. Then the cells are imaged in ArrayScan. The potency and efficacy of the compounds are determined by plotting the number of green fluorescent GFP-containing endosomes per cell against corresponding compound concentration.

The Ca^{2+} mobilization assay is performed using CHO cell lines co-expressing target S1P receptor and a chimeric $G_{q/i5}$ G-protein. Agonist, S1P and compounds, treatment of these cell lines activated PLC-β and IP3 pathway, and triggered release of Ca^{2+} from intracellular storarage, such as ER. Since these cells are loaded with Ca^{2+} sensitive fluorescent dye prior to compound treatment, when the intracellular Ca^{2+} is elevated it bound to the Ca^{2+} sensitive dye and makes the dye emit fluorescence signal upon excitation. The level of receptor activiation is quantitated by measuring fluorescence intensity upon compound treatment. In this assay, the cells are starved in medium contain charcoal/dextran stripped serum for 16-20 hours. Compounds are added on cells loaded with Ca^{2+} sensitive dye inside FLIPR (Molecular Devices, Sunnyvale, CA), and the fluorescence signal is measured simultaneously. CHO cells expressing only the chimeric $G_{q/i5}$ G-protein are tesed as the negative control. The potency and efficacy of the compounds are determined by plotting fluorescence intensity against corresponding compound concentration.

Example 2

Rat Lymphopenia Model ...*in vivo assay*

Female Lewis rats (150-175 gms, 6-8 wks) are received from Charles River Laboratories and allowed to acclimatize for at least one week before being placed on study. Rats (n = 4/group) are administered compound or vehicle (12.5% captisol in water orally (PO, 10 mL/kg) at time 0. At various time points following dosing (1, 4, 8, or 24 h), animals are sacrificed by CO_2 inhalation. Using a 20G needle and 1cc syringe, blood is collected by cardiac puncture. Approximately 500 uL of blood is placed in a microtainer tube containing EDTA (BD #365973), and the sample iss mixed thoroughly. Differential cell counts are perfomed using an Advia 120 hematology system by Bayer.

Formulation Examples

The following are representative pharmaceutical formulations containing a compound of Formula (I).

Tablet Formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet mg
compound of this invention	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

Capsule Formulation

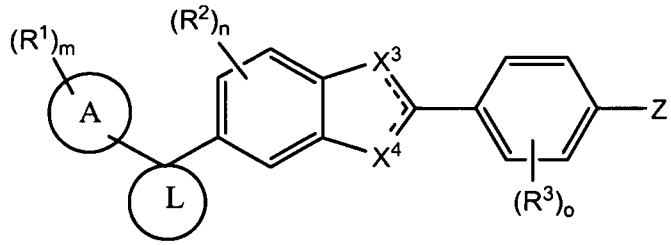
The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule mg
compound of this invention	200
lactose spray dried	148
magnesium stearate	2

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of the invention. Various substitutions, alterations, and modifications may be made to the invention without departing from the spirit and scope of the invention. Other aspects, advantages, and modifications are within the scope of the invention. The contents of all references, issued patents, and published patent applications cited throughout this application are hereby incorporated by reference. The appropriate components, processes, and methods of those patents, applications and other documents may be selected for the invention and embodiments thereof.

What is claimed is:

1. A compound of Formula (I):



wherein:

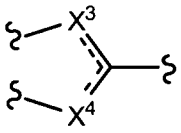
m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

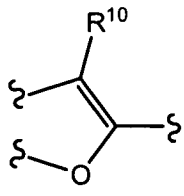
o is 0, 1, 2 or 3;

A is a phenyl, heterocyclyl, three to six membered cycloalkyl, or a five or six membered heteroaryl ring;

L is a saturated 3, 4, 5, 6 or 7-member ring containing 0, 1 or 2 atoms selected from N, O and S and optionally containing a double bond, the ring being substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;



is selected from



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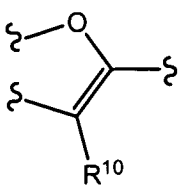

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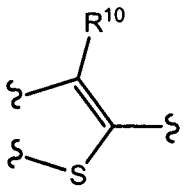
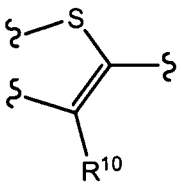


and



;

R^1 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, CN, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;

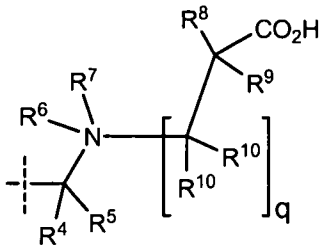
R^2 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;

R^3 is selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, amino, and -OC_{1-4}haloalkyl;

Z is:

(i) a cycloalkyl substituted with amino, monoalkylamino or dialkylamino group; a cycloalkylalkyl substituted with one or two carboxy groups; a monosubstituted amino, disubstituted amino, carboxyalkylamino, hydroxyalkyl, substituted hydroxyalkyl, hydroxyalkoxy, substituted hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, substituted carboxyalkyl, carboxyalkyloxy, substituted carboxyalkyloxy, carboxyalkylthio, substituted carboxyalkylthio, carboxyalkylsulfonyl, substituted carboxyalkylsulfonyl, carboxyalkoxyalkyl, substituted carboxyalkoxyalkyl, aminocarbonyl, acylamino, sulfonylamino, heterocycloamino, heterocycloaminoalkyl, heterocycloaminocarbonyl, heterocycloaminooxy, or heteroaralkyl group;

(ii) a group of formula (b):



(b)

where:

q is 0, 1 or 2;

R^4 is selected from H, C_{1-3}haloalkyl, C_{1-6}alkyl;

R^5 is selected from H, C_{1-3}haloalkyl, C_{1-4}alkyl; or

R^4 and R^5 together with the carbon atom to which they are attached form a 3, 4, 5, 6 or 7-member carbocyclic ring substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl;

R^6 is a lone pair of electrons or O;

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

R^8 is selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; or

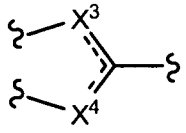
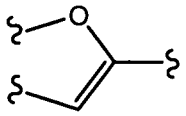
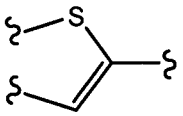
R^7 and R^8, when taken together, form a group that is selected from -$(CR^{10}R^{10})$-, -$(CR^{10}R^{10})$O-, -O$(CR^{10}R^{10})$-, -$(CR^{10}R^{10})(CR^{10}R^{10})$-, and -$(CR^{10}R^{10})_3$-;

R^9 is selected from H, F, C_{1-3}haloalkyl, C_{1-4}alkyl, OH and OC_{1-4}alkyl; or R^8 and R^9 together with the carbon atom to which they are attached from cycloalkyl; and

each R^{10} is independently in each instance selected from H, F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl; or

(iii) when R^3 is on a carbon atom of the phenyl ring that is adjacent to the carbon of the phenyl ring that is bonded to Z, then R^3 and Z can combine to form -CH=CH-NR^{11}-, –$(CH_2)_2NR^{11}$-, –$CH_2NR^{11}CH_2$-, –$(CH_2)_2NR^{11}CH_2$-, -N=CR^{11}-NH-, or -N=CH-NR^{11}-, where R^{11} is selected from hydrogen, hydroxyalkyl, aminoalkyl, carboxyalkyl, substituted hydroxyalkyl or substituted carboxyalkyl; or aminocarbonyl; or

a pharmaceutically acceptable thereof.

2. The compound of Claim 1 wherein  is  or  .

3. The compound of Claim 1 or 2 wherein L is a saturated 3, 4, 5, 6 or 7-member ring the ring being substituted by 0, 1 or 2 groups selected from F, Cl, C_{1-4}alkyl, C_{1-4}haloalkyl, OH, -OC_{1-4}alkyl, and -OC_{1-4}haloalkyl.

4. The compound of any of the Claims 1-3 wherein A is phenyl.

5. The compound of any of the Claims 1-3 wherein A is cycloalkyl.

6. The compound of any of the Claims 1-3 wherein A is five or six membered heterocyclyl.

7. The compound of any of the Claims 1-3 wherein A is five or six membered heteroaryl.

8. The compound of any of the Claims 1-7 wherein Z is a group of formula (b).

9. The compound of any of the Claims 1-7 wherein Z is 3-carboxyazetidin-1-ylmethyl.

10. The compound of any of the Claims 1-7 wherein Z is carboxyalkylamino, hydroxyalkyl, substituted hydroxyalkyl, hydroxyalkoxy, substituted hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, substituted carboxyalkyl, carboxyalkyloxy, substituted carboxyalkyloxy, carboxyalkoxyalkyl, substituted carboxyalkoxyalkyl, aminocarbonyl, acylamino, sulfonylamino, heterocycloamino, heterocycloaminoalkyl, heterocycloaminocarbonyl, heterocycloaminooxy, or heteroaralkyl.

11. The compound of any of the Claims 1-10 wherein n is 0.

12. The compound of any of the Claims 1-11 wherein m is 0, o is 1 and R^3 is fluoro.

13. A pharmaceutical composition a compound of any of the Claim 1-12 and a pharmaceutically acceptable excipient.

14. A method for treating an S1P1 receptor mediated condition in a patient comprising administering to the patient a therapeurically effective amount of a compound of any of the claim 1-12.

15. The method of Claim 25 wherein the disease is multiple sclerosis.

16. Compound of any of the Claims 1-12 for use in the treatment of multiple sclerosis.

17. Use of a compound of any of the Claims 1-12 for the manufacture of a medicament fo the treatment of multiple sclerosis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/003673

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D307/78 C07D405/04 C07D405/10 C07D409/10 A61K31/343
A61K31/397 A61P25/00

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)
A61K C07D

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 practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS 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 2007/109334 A (EPIX DELAWARE INC [US]; SAHA ASHIS [US]; YU XIANG Y [US]; LOBERA MERCE) 27 September 2007 (2007-09-27) Examples 1, 4, 6, 7, 9, 12, 14, 15, 17, 18, 27-31, 33, 34, 36, 40-43, 47, 48, 51, 53, 54, 59- 61 claims 1-3,5-18,20-26,29-31	1-17
X	WO 2007/061458 A (PREDIX PHARMACEUTICALS HOLDING [US]; SAHA ASHIS K [US]; SHARADENDU ANU) 31 May 2007 (2007-05-31) Examples 1, 4, 6, 7, 9, 12, 14, 15, 17, 18, 27-31, 33, 34, 36, 40-43, 47, 48, 51, 53, 54, 59- 61claims 1-3,5-18,20-26,29-31	1-17

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[X] Further documents are listed in the continuation of Box C.

[X] 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
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"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
4 September 2009	23/09/2009

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	Sotoca Usina, E

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/003673

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/000833 A (IRM LLC [US]; MI YUAN [US]; PAN SHIFENG [US]; GRAY NATHANAEL S [US]; G) 6 January 2005 (2005-01-06) claims 1-12; examples 1,2,4,8,10; compounds 1-43, 45-49	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/003673

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007109334 A	27-09-2007	NONE	
WO 2007061458 A	31-05-2007	AU 2006317689 A1	31-05-2007
		CA 2630714 A1	31-05-2007
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		JP 2006528698 T	21-12-2006
		MX PA05012461 A	22-02-2006
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