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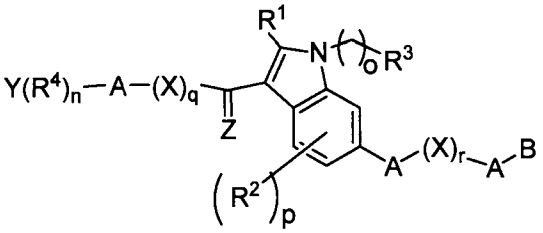
(54) **Title:** 6-SUBSTITUTED INDOLE-3-CARBOXYLIC ACID AMIDE COMPOUNDS HAVING SPHINGOSINE-1-PHOSPHATE (S1P) RECEPTOR ANTAGONIST BIOLOGICAL ACTIVITY



Formula I

(57) **Abstract:** The invention provides compounds represented by the formula I, each of which compounds may have sphingosine-1 -phosphate receptor agonist and or antagonist biological activity; Formula (I) and wherein the variables Y, R^4, n, o, A, A^1, A^2, X, Z, R^1, R^3, R^2, p, q and r are as defined in the specification. These compounds are useful for treating a disease or condition selected from the group consisting of glaucoma, dry eye, angiogenesis, cardiovascular conditions and diseases, and wound healing

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6-SUBSTITUTED INDOLE-3-CARBOXYLIC ACID AMIDE COMPOUNDS HAVING SPHINGOSINE-1-PHOSPHATE (S1P) RECEPTOR ANTAGONIST BIOLOGICAL ACTIVITY

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CROSS REFERENCE

This application claims the benefit of U.S. Provisional Application serial number 60/884,470, filed January 11, 2007 which is hereby incorporated by reference in its entirety.

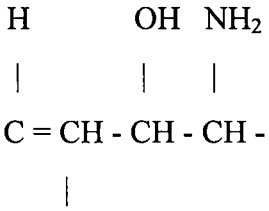
BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to derivatives and/or analogues of sphingosine and pharmaceutical compositions, including such derivatives and/or analogues, which are useful as drugs for the treatment of fungal infections, allergic diseases, immune disorders, etc.

2. Summary of the Art

Sphingosine is a compound having the chemical structure shown in the general formula described below, in which Y^1 is hydrogen. It is known that various sphingolipids, having sphingosine as a constituent, are widely distributed in the living body including on the surface of cell membranes of cells in the nervous system.



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A sphingolipid is one of the lipids having important roles in the living body. A disease called lipidosis is caused by accumulation of a specified sphingolipid in the body. Sphingolipids present on cell membranes function to regulate cell growth; participate in the development and differentiation of cells; function in nerves; are involved in the infection and malignancy of cells; etc. Many of the physiological roles of sphingolipids remain to be solved. Recently the possibility that ceramide, a derivative of sphingosine, has an important role in the mechanism of cell signal transduction has been indicated, and studies about its effect on apoptosis and cell cycle have been reported.

Sphingosine-1-phosphate is an important cellular metabolite, derived from ceramide that is synthesized de novo or as part of the sphingomeyeline cycle (in animals cells). It has also been found in insects, yeasts and plants.

The enzyme, ceramidase, acts upon ceramides to release sphingosine, which is phosphorylated by spingosine kinase, a ubiquitous enzyme in the cytosol and endoplasmic reticulum, to form sphingosine-1-phosphate. The reverse reaction can occur also by the action of sphingosine phosphatases, and the enzymes act in concert to control the cellular concentrations of the metabolite, which concentrations are always low. In plasma, such concentration can reach 0.2 to 0.9 μM, and the metabolite is found in association with the lipoproteins, especially the HDL. It should also be noted that sphingosine-1-phosphate formation is an essential step in the catabolism of sphingoid bases.

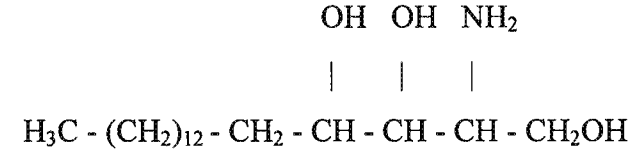
Like its precursors, sphingosine-1-phosphate is a potent messenger molecule that perhaps uniquely operates both intra- and inter-cellularly, but with very different functions from ceramides and sphingosine. The balance between these various sphingolipid metabolites may be important for health. For example, within the cell, sphingosine-1-phosphate promotes cellular division (mitosis) as opposed to cell death (apoptosis), which it inhibits. Intracellularly, it also

functions to regulate calcium mobilization and cell growth in response to a variety of extracellular stimuli. Current opinion appears to suggest that the balance between sphingosine-1-phosphate and ceramide and/or spingosine levels in cells is critical for their viability. In common with the lysophospholipids, especially lysophosphatidic acid, with which it has some structural similarities, sphingosine-1-phosphate exerts many of its extra-cellular effects through interaction with five specific G protein-coupled receptors on cell surfaces. These are important for the growth of new blood vessels, vascular maturation, cardiac development and immunity, and for directed cell movement.

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

Fungi and plants have sphingolipids and the major sphingosine contained in these organisms has the formula described below. It is known that these lipids

have important roles in the cell growth of fungi and plants, but details of the roles remain to be solved.



Recently it has been known that derivatives of sphingolipids and their related compounds exhibit a variety of biological activities through inhibition or stimulation of the metabolism pathways. These compounds include inhibitors of protein kinase C, inducers of apoptosis, immuno-suppressive compounds, antifungal compounds, and the like. Substances having these biological activities are expected to be useful compounds for various diseases.

Derivatives of sphingosine have been prepared in various patents. For example, see U.S. Patents 4,952,683; 5,110,987; 6,235,912 B1 and 6,239,297 B1.

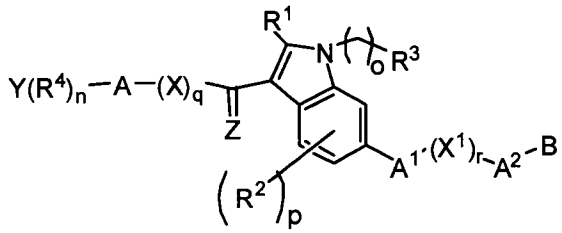
Also, compounds which are similar to certain spingosine derivatives, but which are not reported as being ligands for the spingosine receptors are reported in various patents and published patent applications. See for example, U.S. Patents 5,294,722; 5,102,901; 5,403,851 and 5,580,878. U.S. Patent Application Publication No. U.S. 2003/0125371 A2. While certain of the compounds reported in the above patents are indoles, it does not appear that indole compounds have been reported as being ligands for sphingosine receptor or having activity as sphingosine agonists or antagonists.

SUMMARY OF THE INVENTION

The present invention provides a derivative or analogue of sphingosine that is able to regulate the functions of sphingolipid, and pharmaceutical compositions

comprising said derivative or analogue.

Compounds represented by the formula I having sphingosine-1-phosphate receptor agonist and or antagonist biological activity:



Formula I

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wherein:

R^1 R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, straight or branched chain alkyl having 1 to 12 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, carbocyclic hydrocarbon groups having from 3 to 20 carbon atoms, heterocyclic groups having up to 20 carbon atoms and at least one of oxygen, nitrogen and/or sulfur in the ring, halo, C_1 to C_{12} haloalkyl, hydroxyl, C_1 to C_{12} alkoxy, C_3 to C_{20} arylalkyloxy, C_1 to C_{12} alkylcarbonyl, formyl, oxycarbonyl, carboxy, C_1 to C_{12} alkyl carboxylate, C_1 to C_{12} alkyl amide, aminocarbonyl, amino, cyano, diazo, nitro, thio, sulfoxyl, and sulfonyl groups;

X and X^1 are independently selected from the group consisting of NR^5, O and S;

R^5 is hydrogen, an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons, phenyl or lower alkylphenyl; Y is a carbocyclic aryl or heterocyclic aryl group wherein said carbocylic aryl comprises from 6 to 20 atoms and said heterocyclic aryl comprises from 2 to 20 carbon atoms and from 1 to 5 heteroatoms selected from the group consisting of

nitrogen, oxygen and sulfur, and wherein said aryl may be bonded to A at any position;

Z is O or S;

n is 0 or an integer of from 1 to 5;

o is 0 or an integer of from 1 to 3;

p is 0 or an integer of from 1 to 3;

q is 0 or 1;

r is 0 or 1;

A, A^1 and A^2 are independently selected from the group consisting of $(CH_2)_v$ wherein v is 0 or an integer of from 1 to 12, branched chain alkyl having 3 to 12 carbons, cycloalkyl having 3 to 12 carbons, alkenyl having 2 to 10 carbons and 1–3 double bonds and alkynyl having 2 to 10 carbons and 1 to 3 triple bonds;

B is selected from the group consisting of hydrogen, OR^6, $COOR^7$, NR^8R^9, $CONR^8R^9$, COR^{10}, $CH=NOR^{11}$, $CH=NNR^{12}R^{13}$ wherein R^6, R^7, R^{10} and R^{11} are independently selected from the group consisting of hydrogen, straight or branched chain alkyl having 1 to 12 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, a carbocyclic hydrocarbon group having from 3 to 20 carbon atoms, a heterocyclic group having up to 20 carbon atoms and at least one of oxygen, nitrogen and/or sulfur in the ring, R^8, R^9, R^{12} and R^{13} are independently selected from the group consisting of hydrogen, straight or branched chain alkyl having 1 to 12 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, a carbocyclic hydrocarbon group having from 3 to 20 carbon atoms, a heterocyclic group having up to 20 carbon

atoms and at least one of oxygen, nitrogen and/or sulfur in the ring, or R^8 and R^9 and/or R^{12} and R^{13}, together, can form a divalent carbon radical of 2 to 5 carbons to form a heterocyclic ring with nitrogen, wherein any of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} or R^{13} may be substituted with one or more halogen, hydroxy, alkyloxy, cyano, nitro, mercapto or thiol radical; provided however, when v is 0, and r is 0, B is not hydrogen; or B is a carbocyclic hydrocarbon group having from 3 to 20 carbon atoms, or a heterocyclic group having up to 20 carbon atoms and at least one of oxygen, nitrogen and/or sulfur in the ring, and wherein when said B is a carbocyclic or heterocyclic group B may be bonded to A^2 at any position, or a pharmaceutically acceptable salt of said compound.

The aryl group is a carbocyclic aryl or heterocyclic aryl group wherein said carbocylic aryl comprises from 6 to 20 atoms and said heterocyclic aryl comprise from 2 to 20 carbon atoms and from 1 to 5 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and preferably said aryl group is selected from the group consisting of benzene, pyridine, pyrazine, pyridazine, pyrimidine, triazine, thiophene, furan, thiazole, thiadiazole, isothiazole, oxazole,oxadiazole, isooxazole, naphthalene, quinoline, tetralin, chroman, thiochroman, tetrahydroquinoline, dihydronaphthalene, tetrahydronaphthalen, chromene, thiochromene, dihydroquinoline, indan, dihydrobenzofuran, dihydrobenzothiophene, indene, benzofuran, benzothiophene, coumarin and coumarinone. Said aryl groups can be bonded to

the above moiety at any position. Said aryl group may itself be substituted with any common organic functional group including but not limited to C_1 to C_{12} alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, halo, C_1 to C_{12} haloalkyl, hydroxyl, C_1 to C_{12} alkoxyl, C_1 to C_{12} alkylcarbonyl, formyl, oxycarbonyl, carboxyl, C_1 to C_{12} alkyl carboxylate, C_1 to C_{12} alkyl amide, aminocarbonyl, amino, cyano, diazo, nitro, thio, sulfoxyl, or sulfonyl groups.

Preferably Z is O.

Preferably, the carbocyclic aryl group will comprise from 6 to 14 carbon atoms, e.g. from 6 to 10 carbon atoms. Preferably the heterocyclic aryl group will comprise from 2 to 14 carbon atoms and one or more, e.g. from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur.

Preferably, A is CH_2.

Preferably, X is NH.

Preferably, n is 0 or an integer of 1 or 2 and R^4 is fluoro.

Preferably, R^1 is i-propyl.

Preferably, R^3 is selected from the group consisting of phenyl, which may be substituted with one or two flouro groups, and pyridyl.

Preferably, p is 0.

Preferably, A^1 and A^2 are absent.

Preferably, B is OR^6 or $COOR^7$.

Preferably, X is O, r is 1, A^1 is absent, A^2 is $(CH_2)_v$, wherein v is 1 or 2, and B is OR^6 or NR^8R^9

and R^6, R^8 and R^9 are methyl.

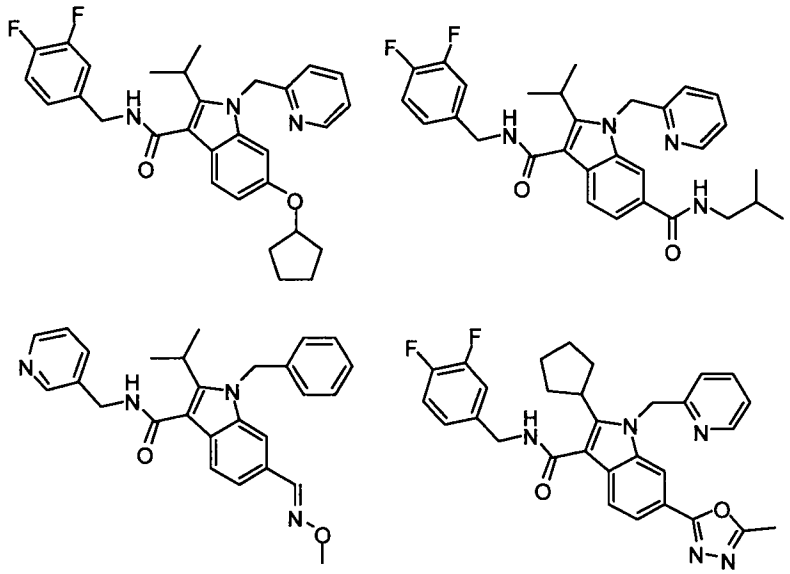
Preferably, B is CR^{10}=$NOR^{11}R^{10}$ wherein R^{10} is H and R^{11} is methyl or i-butyl

or

B is $CONR^8R^9$ wherein R^8 and R^9 are selected from the group consisting of H, methyl, ethyl and propyl, or R^8 and R^9, together with N, form a 5-member ring.

Preferably, A^1 is absent, r is 0, A^2 is CH_2 and B is OR^6, wherein R^6 is H, or X is O, r is 1 and B is COR^{10} ,wherein R^{10} is methyl.

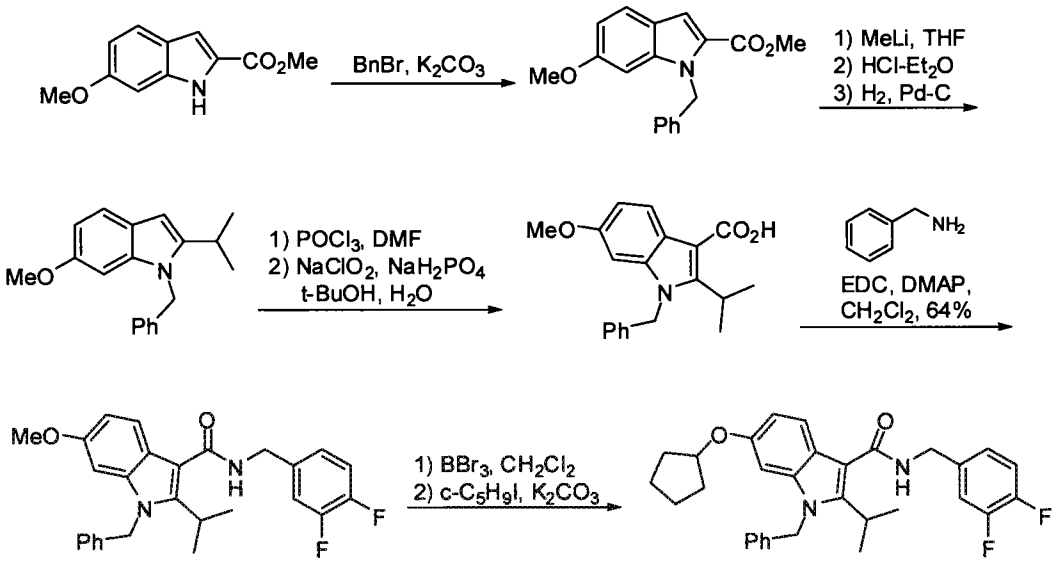
Specific Examples of the compounds of formula I include



Some compounds within the scope of the invention may be prepared as depicted in Scheme 1. Thus, methyl 6-methoxyindole-2-carboxylate is treated with an electrophilic compound (e.g. benzyl bromide) in the presence of an weak base (e.g. potassium carbonate) to produce an N-alkylated indole (e.g. methyl 1-benzyl-6-methoxyindole-2-carboxylate). The 2-carboxylate group is converted to an alkyl group by a three-step process: Grignard reaction, elimination, and hydrogenation. The resulting 2-alkyl indole is carboxylated in the 3-position by treatment with dimethylformamide and phosphorus oxychloride followed by sodium hypochlorite oxidation of the resulting aldehyde. The carboxylic acid may be further functionalized by treatment with an amine in the presence of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodimide (EDC) to produce a 6-methoxyindole-3-carboxamide derivative (e.g. 3,4-difluorophenylmethyl 6-

methoxy-2-isopropyl-1-benzylindole-3-carboxamide). The carboxylic acid may also be treated with an alcohol or thiol in the presence of EDC to produce an ester and thiol ester derivatives, respectively. The 6-methoxy group may then be deprotected using boron tribromide and the resulting hydroxide subjected to alkylating (e.g. cyclopentyl iodide/potassium carbonate) or acylating (e.g. pivaloyl chloride/ pyridine) reagents to produce a large variety of 6-substituted indole homologs and derivatives within the scope of the invention.

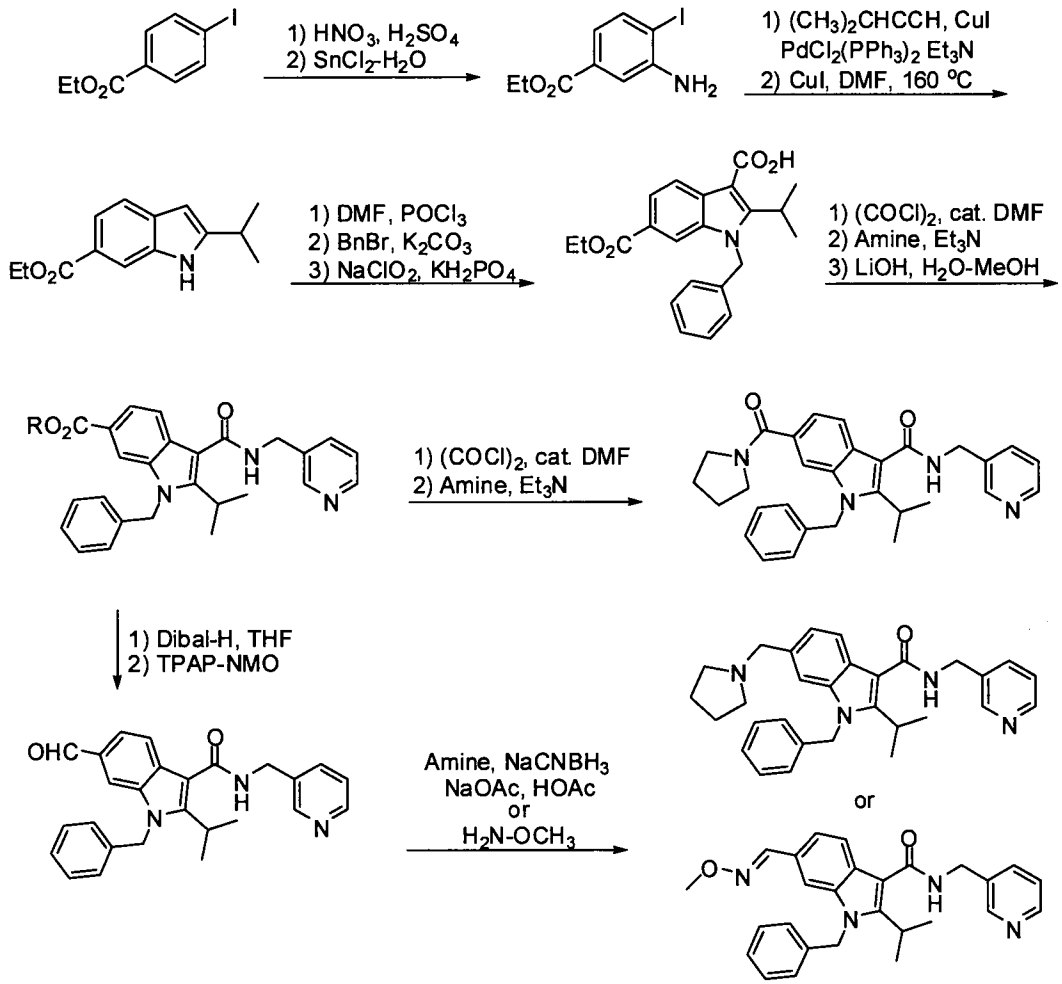
Scheme 1



Many other compounds within the scope of the invention may be prepared as depicted in Scheme 2. Thus, ethyl 4-iodobenzoate may be nitrated in the 3-position with fuming nitric acid and the resulting nitro compound reduced under mild conditions (e.g. $SnCl_2$-H_2O) to produce ethyl 3-amino-4-iodobenzoate. This compound may be converted to the indole by treatment with a terminal alkyne (e.g. 3-methylbutyne) in the presence of a palladium catalyst and copper iodide followed by heating the aryl alkyne in the presence copper iodide. The resulting 2-alkyl indole may then be carbonylated in the 3-position by treatment with dimethylformamide and phosphorus oxychloride and N-alkylated as described above (benzyl bromide, potassium carbonate), followed by sodium hypochlorite oxidation to produce an N-alkylindole-3-carboxylic

acid. The carboxylic acid may be further functionalized by treatment with an amine in the presence of EDC to

Scheme 2



produce a 6-methoxyindole-3-carboxamide derivative (e.g. 3-pyridylmethyl 1-benzyl-6-carboethoxy-2-isopropylindole-3-carboxamide). The carboxylic acid may also be treated with an alcohol or thiol in the presence of EDC to produce an ester and thiol ester derivatives, respectively. The 6-carboethoxy group may be further functionalized to produce a large variety of 6-substituted indole homologs and derivatives within the scope of the invention. For example, the 6-carboethoxy group be hydrolyzed with strong base and the resulting carboxylic acid converted to the carboxylic acid chloride, which could be reacted with

various alcohols or amines in the presence of base to produce ester or amide derivatives, respectively, such as 3-pyridylmethyl1-benzyl-2-isopropyl-6-(1-pyrrolidinylcarbamoyl)indole-3-carboxamide. Alternatively, the 6-carboethoxy group could be reduced to an alcohol and re-oxidized to an aldehyde intermediate, which may then be treated with an amine under reducing conditions to give amine derivatives such as 3-pyridylmethyl 1-benzyl-2-isopropyl-6-(1-pyrrolidinylmethyl)-indole-3-carboxamide. The aldehyde may also be treated with oxime or hydrazine compounds to produce oxime and hydrazone derivatives, respectively. Thus, many compounds within the scope of the invention may be produced by the general route depicted in Scheme 2.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise indicated, the following terms as used throughout this specification have the following meanings:

"Me" refers to methyl.

"Et" refers to ethyl.

"tBu" refers to t-butyl.

"iPr" refers to i-propyl.

"Ph" refers to phenyl.

"Pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are obtained by reaction with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

"Alkyl" refers to a straight-chain, branched or cyclic saturated aliphatic hydrocarbon. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from 1 to 7 carbons, most preferably 1 to 4 carbons. Typical alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl and the like. The alkyl group may be optionally substituted with one or more substituents are selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethyl amino and SH.

"Alkenyl" refers to a straight-chain, branched or cyclic unsaturated hydrocarbon group containing at least one carbon--carbon double bond. Preferably, the alkenyl group has 2 to 12 carbons. More preferably it is a lower alkenyl of from 2 to 7 carbons, most preferably 2 to 4 carbons. The alkenyl group may be optionally substituted with one or more substituents selected from the group consisting of hydroxyl, cyano, alkoxy, O, S, NO_2, halogen, dimethyl amino and SH.

"Alkynyl" refers to a straight-chain, branched or cyclic unsaturated hydrocarbon containing at least one carbon--carbon triple bond. Preferably, the alkynyl group has 2 to 12 carbons. More preferably it is a lower alkynyl of from 2 to 7 carbons, most preferably 2 to 4 carbons. The alkynyl group may be optionally substituted with one or more substituents selected from the group consisting of hydroxyl, cyano, alkoxy, O, S, NO_2, halogen, dimethyl amino and SH.

"Alkoxy" refers to an "O-alkyl" group.

"Aryl" refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups. The aryl group may be optionally substituted with one or more substituents selected from the group consisting of halogen, trihalomethyl, hydroxyl, SH, OH, NO_2, amine, thioether, cyano, alkoxy, alkyl, and amino.

"Alkaryl" refers to an alkyl that is covalently joined to an aryl group. Preferably, the alkyl is a lower alkyl.

"Aryloxy" refers to an "O-aryl" group.

"Arylalkyloxy" refers to an "O-alkaryl" group.

"Carbocyclic" refers to cyclic saturated or unsaturated aliphatic hydrocarbon and aryl hydrocarbon groups wherein the ring atoms are exclusively carbons, and comprises from 6 to 20 carbon atoms, including said ring atoms.

"Carbocyclic aryl" refers to an aryl group wherein the ring atoms are carbon.

"Heterocyclic" refers to cyclic groups wherein the ring atoms comprise carbon atoms and at least one oxygen, nitrogen, and/or sulfur atom and may be saturated, unsaturated, i.e. have one or more double bonds, or aryl, and comprises up to 20 carbon atoms and from 1 to 5 of the above heteroatoms.

"Heterocyclic aryl" refers to an aryl group having from 1 to 3 heteroatoms as ring atoms, the remainder of the ring atoms being carbon. Heteroatoms include oxygen, sulfur, and nitrogen.

"Hydrocarbyl" refers to a hydrocarbon radical having only carbon and hydrogen atoms. Preferably, the hydrocarbyl radical has from 1 to 20 carbon atoms, more preferably from 1 to 12 carbon atoms and most preferably from 1 to 7 carbon atoms.

"Substituted hydrocarbyl" refers to a hydrocarbyl radical wherein one or more, but not all, of the hydrogen and/or the carbon atoms are replaced by a halogen, nitrogen, oxygen, sulfur or phosphorus atom or a radical including a halogen, nitrogen, oxygen, sulfur or phosphorus atom, e.g. fluoro, chloro, cyano, nitro,

hydroxyl, phosphate, thiol, etc.

"Amide" refers to --C(O)--NH--R', wherein R' is alkyl, aryl, alkylaryl or hydrogen.

"Ester" refers to --C(O)--O--R', wherein R' is alkyl, aryl or alkylaryl.

"Thioamide" refers to --C(S)--NH--R', wherein R' is alkyl, aryl, alkylaryl or hydrogen.

"Thiol ester" refers to --C(O)--S--R', wherein R' is alkyl, aryl, alkylaryl or hydrogen.

"Amine" refers to a --N(R")R'" group, wherein R" and R'" are independently selected from the group consisting of alkyl, aryl, and alkylaryl.

"Thioether" refers to --S--R", wherein R" is alkyl, aryl, or alkylaryl.

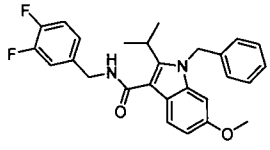
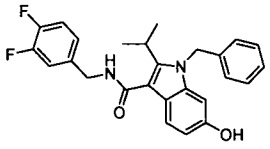
"Sulfonyl" refers to --$S(O)_2$ --R"", where R"" is aryl, C(CN)=C-aryl, CH_2 CN, alkyaryl, sulfonamide, NH-alkyl, NH-alkylaryl, or NH-aryl.

Also, alternatively the substituent on the phenyl moiety, as shown below, is referred to as an o, m or p substituent or a 2, 3 or 4 substituent, respectively. (Obviously, the 5 substituent is also a m substituent and the 6 substituent is an o substituent.)

Specific compounds of the invention, that are prepared according to Example 2 through 29 and/or Schemes 1 through 3, are able to inhibit the activity of sphingosine-1-phosphate receptors reported in Table I, below. Compounds were assessed for their ability to activate or block activation of the human S1P3 receptor in T24 cells stably expressing the human S1P3 receptor. Ten thousand

cells/well were plated into 384-well poly-D-lysine coated plates one day prior to use. The growth media for the S1P3 receptor expressing cell line was McCoy's 5A medium supplemented with 10% charcoal-treated fetal bovine serum (FBS), 1% antibiotic-antimycotic and 400 μg/ml geneticin. On the day of the experiment, the cells were washed twice with Hank's Balanced Salt Solution supplemented with 20 mM HEPES (HBSS/Hepes buffer). The cells were then dye loaded with 2 uM Fluo-4 diluted in the HBSS/Hepes buffer with 1.25 mM Probenecid and incubated at 37°C for 40 minutes. Extracellular dye was removed by washing the cell plates four times prior to placing the plates in the FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices). Ligands were diluted in HBSS/Hepes buffer and prepared in 384-well microplates. The positive control, Sphingosine-1-Phosphate (S1P), was diluted in HBSS/Hepes buffer with 4 mg/ml fatty acid free bovine serum albumin. The FLIPR transferred 12.5 μl from the ligand microplate to the cell plate and took fluorescent measurements for 75 seconds, taking readings every second, and then for 2.5 minutes, taking readings every 10 seconds. Drugs were tested over the concentration range of 0.61 nM to 10,000 nM. Data for Ca^{+2} responses were obtained in arbitrary fluorescence units and not translated into Ca^{+2} concentrations. IC_{50} values were determined through a linear regression analysis using the Levenburg Marquardt algorithm.

Table 1

Compound Number	Structure	S1P3 IC_{50} (% inh) Kb
7		560 nM (98)
8		3.1 μM (71)

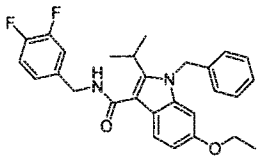
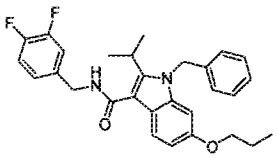
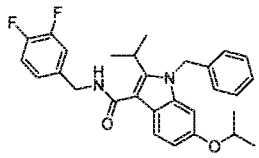
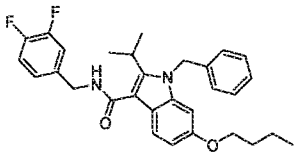
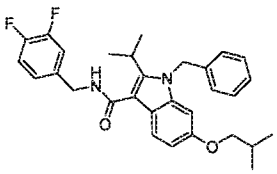
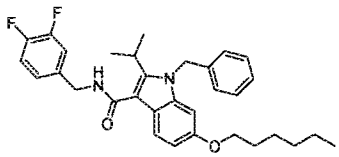
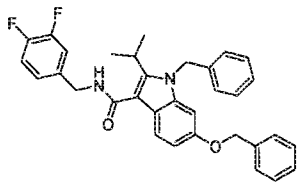
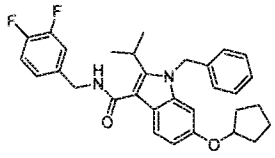
9		19 nM (100)
10		5 nM (100) 2 nM
11		6 nM (100) 2 nM
12		3 nM (100) ND
13		1.2 nM (100) 1.6 nM

Table 1

Compound Number	Structure	S1P3 IC_{50} (% inh) Kb
14		3.1 μM (96)
15		260 nM (100)
16		3 nM (100) 1.2 nM

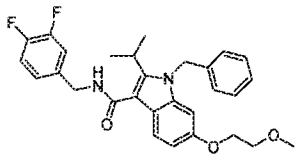
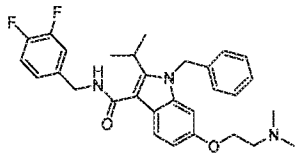
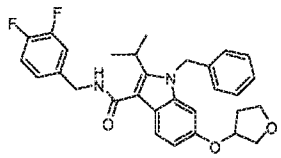
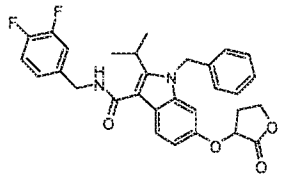
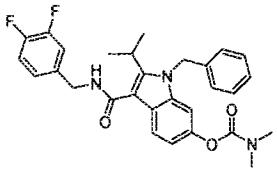
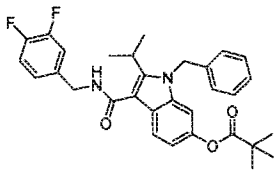
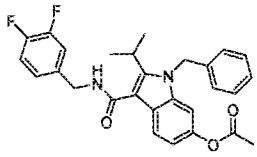
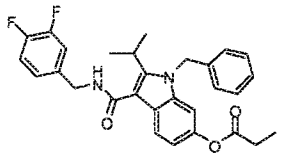
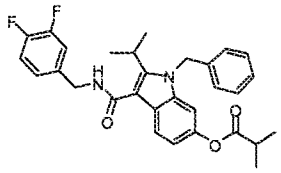
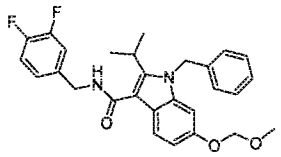
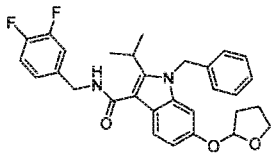
17		6.5 nM (99)
18		242 nM (94)
19		6 nM (100)
20		81 nM (100)

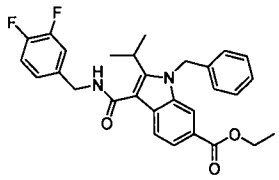
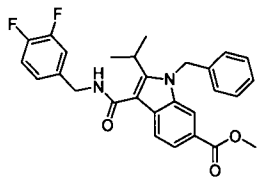
Table 1

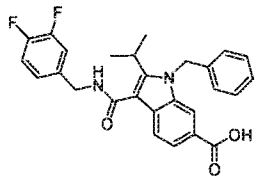
Compound Number	Structure	S1P3 IC_{50} (% inh) Kb
21		24 nM (99)
22		4 nM (99)
23		14 nM (100)

24		**20 nM (100)**
25		**14 nM (100)**
26		**39 nM (100) 13 nM**
27		**6 nM (100) 11 nM**

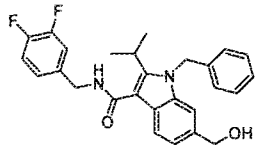
The compounds of Table 1B are prepared according to procedures analogous to the procedures of Schemes 1 through 3 and/or Examples 2 through 29. These compounds are also tested for ability to inhibit the activity of the S1P3 receptor.

Table 1B

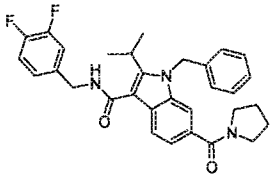
Compound Number	Structure	S1P3 IC_{50} (% inh) Kb
		**7 nM (100) 8 nM**
		**12 nM (100)**



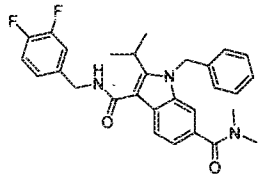
>10 μM
(40)



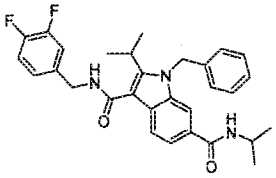
2.0 μM
(85)



170 nM
(100)

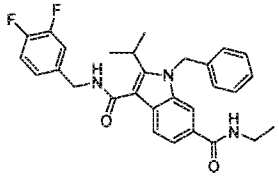
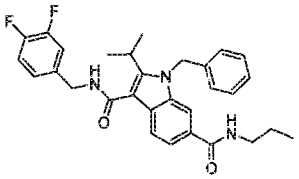


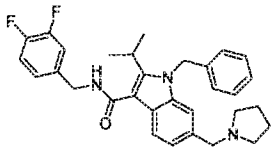
197 nM
(100)



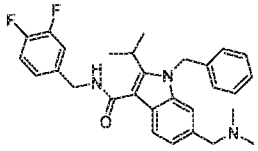
634 nM
(100)

Table 1B

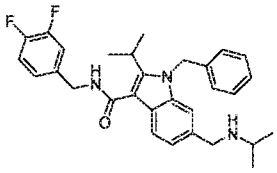
Compound Number	Structure	S1P3 IC_{50} (% inh) Kb
		346 nM (99)
		146 nM (99)



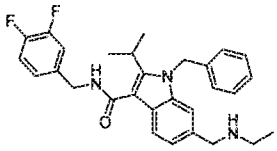
362 nM
(93)



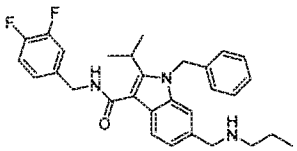
990 nM
(98)



2.3 μM
(84)

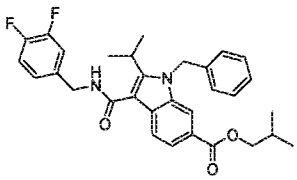
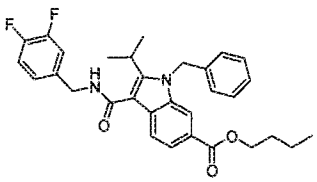
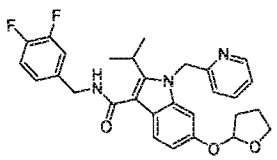


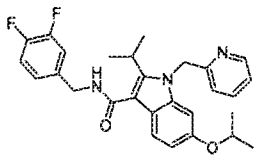
2.5 μM
(87)



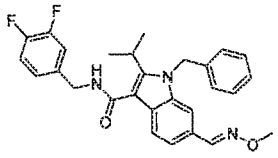
2.6 μM
(77)

Table 1B

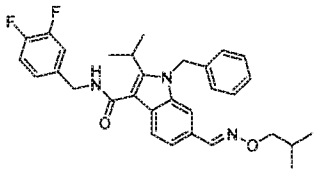
Compound Number	Structure	S1P3 IC_{50} (% inh) Kb
		12 nM (97)
		4 nM (97)
		9 nM (100)



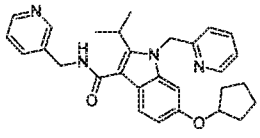
0.9 nM
(100)



21 nM
(99)

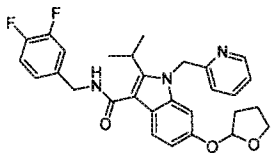
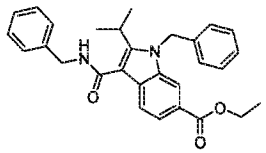
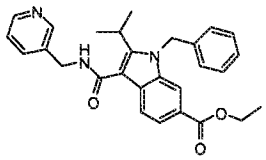
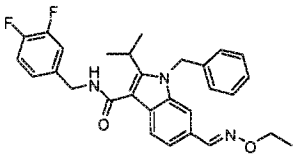


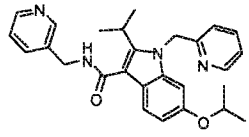
88 nM
(100)



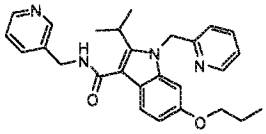
86 nM
(95)

Table 1B

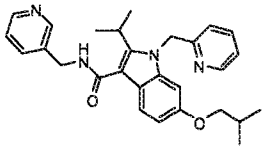
Compound Number	Structure	S1P3 IC_{50} (% inh) Kb
		9 nM (100)
		9 nM (96)
		187 nM (95)
		145 nM (99)



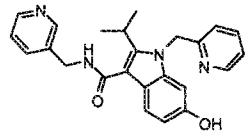
ND
(98)



1.2 μM
(99)



124 nM
(99)



ND
(54)

Table 1B

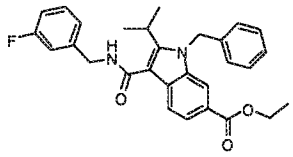
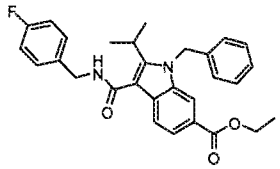
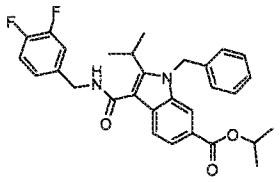
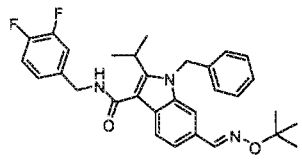
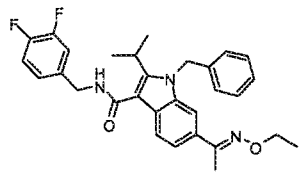
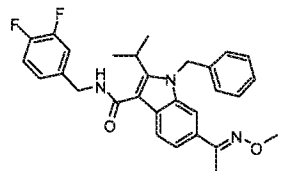
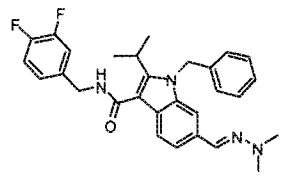
Compound Number	Structure	S1P3 IC_{50} (% inh) Kb
		42 nM (99)
		43 nM (99)
		45 nM (99)
		145 nM (99)
		262 nM (98)
		147 nM (100)
		33 nM (100) 7 nM

Table 1B

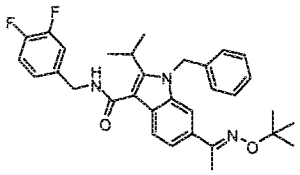
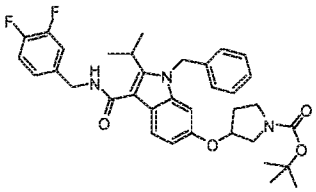
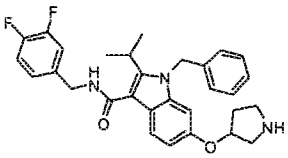
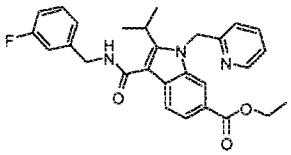
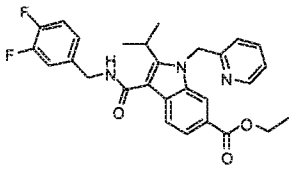
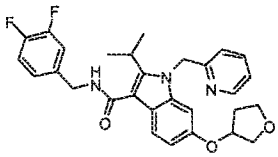
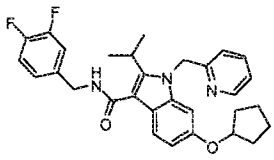
Compound Number	Structure	S1P3 IC_{50} (% inh) Kb
		NA
		673 nM (100)
		2.4 μM (80)
		174 nM (100)
		58 nM (100)
		19 nM (100) 21 nM
		3 nM (100) 4 nM

Table 1B

Compound Number	Structure	S1P3 IC_{50} (% inh)

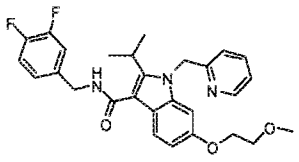
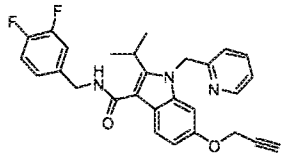
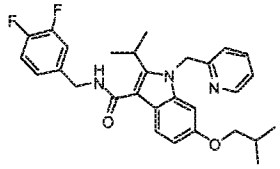
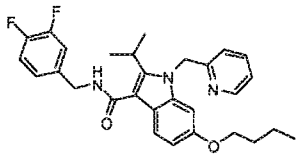
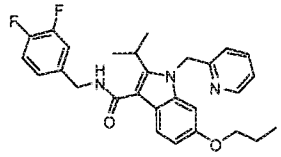
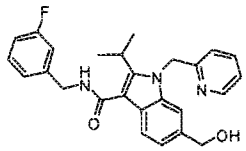
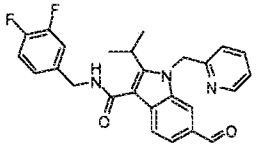
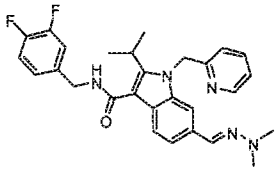
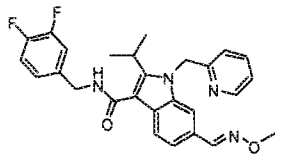
	Kb
	288 nM (100)
	324 nM (99)
	5 nM (100) 9 nM
	8 nM (100)
	15 nM (100) 13 nM
	NA
	ND (65)
	93 nM (100)

Table 1B

Compound Number	Structure	S1P3 IC_{50} (% inh) Kb



137 nM
(100)

As a result of the above activity of the compounds utilized in the method of the present invention, it is clear that such compounds may be used in treating the following diseases and conditions for the following reasons.

Glaucoma

S1P3 subtypes are expressed in primary human trabecular meshwork cells and S1P decreases outflow facility >30% in perfused porcine eyes (See IOVS 45, 2263; 2004) by altering paracellular permeability.

Dry Eye/Immunology

Induces lymphocyte sequestration without affecting T cell proliferation.

Angiogenesis disorders

S1P3 receptor subtype is expressed in vascular endothelial cells and siRNA knockdown of S1P1 and S1P3 inhibits angiogenesis. S1P also promotes vascular endothelial cell migration and promotes barrier assembly and integrity.

Cardiovascular (S1P3)

S1P3 "knock out" mice lack S1P induced pulmonary edema.

The invention is further illustrated by the following examples which are illustrative of a specific mode of practicing the invention and are not intended as limiting the scope of the claims.

Unless otherwise indicated, the following Chemical Abbreviations are used in the examples:

BBr_3: boron tribromide

HCl: hydrogen chloride or hydrochloric acid

KOH: potassium hydroxide

K_2CO_3: potassium carbonate

KH_2PO_4: potassium dihydrogenphosphate

NaOH: sodium hydroxide

$NaHCO_3$: sodium bicarbonate

$NaClO_2$: sodium hypochlorite

NaI: sodium iodide

Na_2SO_4: sodium sulfate

$MgSO_4$: magnesium sulfate

$POCl_3$: phosphorus oxychloride

t-BuOH: *tert*-butyl alcohol

MeOH: methanol

EtOH: ethanol

i-PrOH: isopropanol

EtOAc: ethyl acetate

Et_2O: diethyl ether

CH_2Cl_2: methylene chloride

CH_3CN: acetonitrile

DHP: dihydropyran

DMAP: 4-(dimethylamino)pyridine

DMF: *N,N*-dimethylformamide

DMSO: dimethylsulfoxide

EDC : 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide

LDA: lithium diisopropylamide

$LiAlH_4$: lithium aluminum hydride

MOMCl: methyl chloromethyl ether

MeLi: methyllithium

MeMgBr: Methylmagnesium bromide

$NaBH_3CN$: sodium cyanoborohydride

NMO: 4-methylmorpholine, N-oxide

Pd-C: palladium on activated carbon

PhCHO: benzaldehyde

THF: tetrahydrofuran

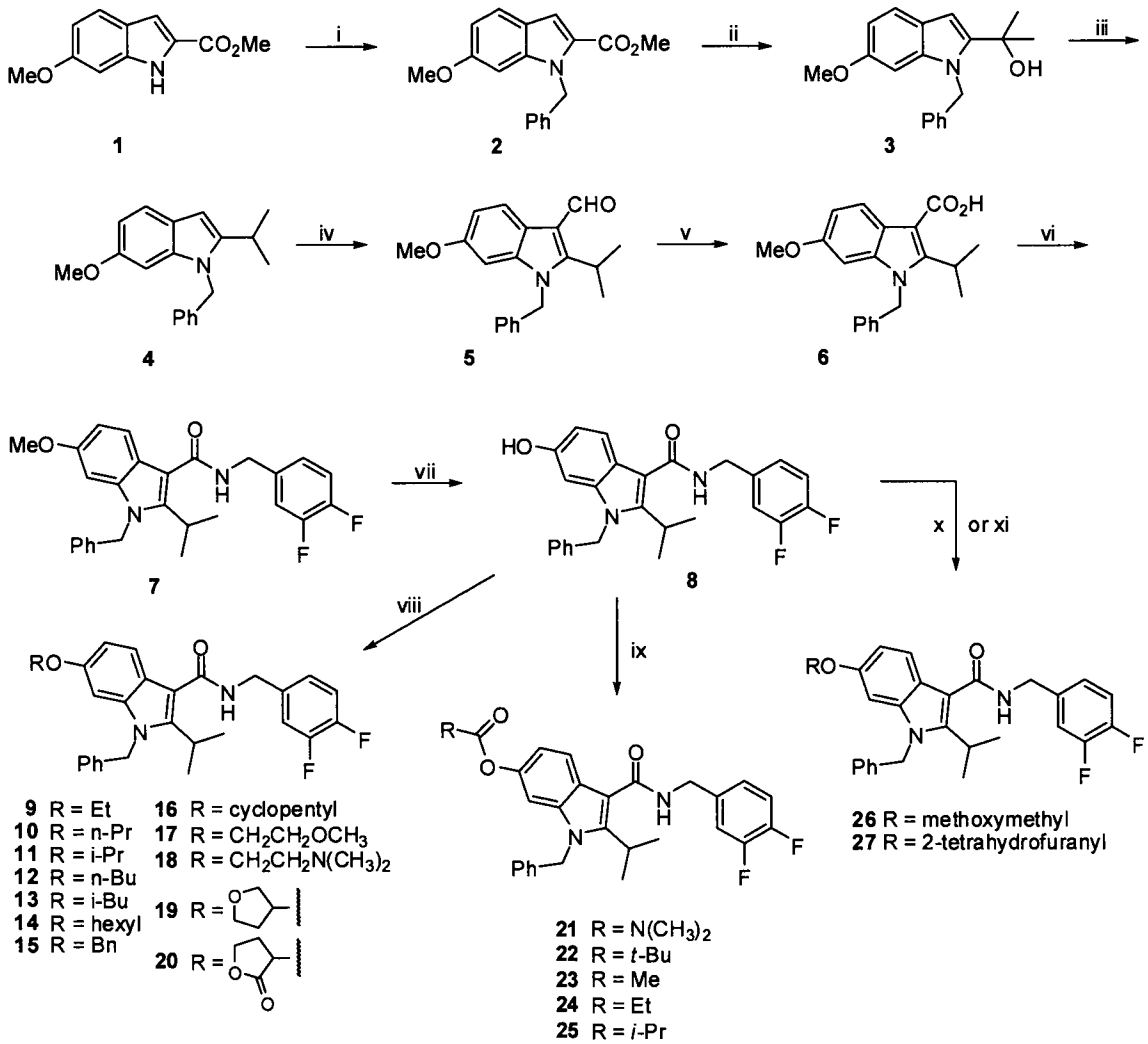
THP: tetrahydropyran

TPAP: tetrapropylammonium perruthenate

PTLC: preparative thin layer chromatography

Acetyl chloride, benzyl bromide, 2-bromoethyl methyl ether, cyclopentyl iodide, diisopropylethylamine, 2-dimethylaminoethyl chloride hydrochloride, dimethylcarbamyl chloride, 1-iodobutane, 2-iodobutane, iodoethane, 1-iodohexane, 1-iodopropane, 2-iodopropane, 4-methylbenzene-1sulfonyl chloride, pivaloyl chloride, pyridinium p-toluenesufonate and tetrahydrofuran-3-ol were purchased from Aldrich Chemical Company.

Scheme 3[a]



[a] Reagents and conditions: (i) BnBr, K_2CO_3, DMF; (ii) MeLi, THF; (iii) H_2, Pd-C, EtOAc, EtOH, HCl-Et_2O; (iv) $POCl_3$, DMF; (v) $NaClO_2$, KH_2PO_4, isobutene, *t*-BuOH, CH_3CN, H_2O; (vi) 3,4-difluorobenzylamine, EDC, DMAP, CH_2Cl_2; (vii) BBr_3, CH_2Cl_2; (viii) RX, K_2CO_3, DMF; (ix) RCOCl, pyridine; (x) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (xi) 2,3-dihydrofuran, PPTS, CH_2Cl_2.

Example 2

Methyl 1-Benzyl-6-methoxy-1H-indole-2-carboxylate (Compound 2). To a solution of methyl 6-methoxy-1H-indole-2-carboxylate (**Compound 1**, 1.0 g, 4.9 mmol) in DMF (10 ml) was added K_2CO_3 (2.0 g, 14.6 mmol) and benzyl bromide (0.87 ml, 7.3 mmol). The mixture was stirred at room temperature for 40 h and was diluted with EtOAc, washed with H_2O, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by crystallization from Et_2O to yield the title compound as an off-white solid.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 3.81 (s, 3 H), 3.85 (s, 3 H), 5.81 (s, 2 H), 6.73 (d, *J* = 2.0 Hz, 1 H), 6.84 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.07 (d, *J* = 6.8 Hz, 2 H), 7.19 - 7.29 (m, 3 H), 7.33 (s, 1 H), 7.58 (d, *J* = 8.8 Hz, 1 H).

Example 3

2-(1-Benzyl-6-methoxy-1H-indol-2-yl)propan-2-ol (Compound 3). To a solution of methyl 1-benzyl-6-methoxy-1H-indole-2-carboxylate (**Compound 2**, 4.33 g, 14.7 mmol) in THF (50 ml) at 0 °C under argon was added MeLi (3.0 M in diethoxymethane, 19.6 ml, 58.7 mmol) slowly. After 1 h, the ice-water bath was removed and the reaction was stirred at room temperature for 1h, cooled to -78 °C, quenched with dry ice, diluted with EtOAc, washed with H_2O, brine, dried over Na_2SO_4, concentrated *in vacuo* to yield the crude title compound as a yellow solid.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.69 (s, 6 H), 3.73 (s, 3 H), 5.76 (s, 2 H), 6.42 (s, 1 H), 6.55 (d, *J* = 2.4 Hz, 1 H), 6.75 - 6.81 (m, 1 H), 6.96 (d, *J* = 7.3 Hz, 2 H), 7.22 (d, *J* = 7.3 Hz, 1 H), 7.25 - 7.30 (m, 2 H), 7.49 (d, *J* = 8.8 Hz, 1 H).

Example 4

1-Benzyl-2-isopropyl-6-methoxy-1H-indole (Compound 4). To a solution of 2-(1-benzyl-6-methoxy-1H-indol-2-yl)propan-2-ol (**Compound 3**, 1.05 g, 3.57 mmol) in EtOAc (35 ml) and EtOH (15 ml) was added 10% Pd-C (190 mg, 0.18 mmol) and HCl-Et_2O (1.0 M, 1.25 ml, 1.25 mmol). The mixture was stirred under hydrogen gas (atmospheric pressure) for 1h and was filtered. To the filtrate was added $NaHCO_3$ (0.5 g) and H_2O (0.5 ml), followed by Na_2SO_4 and $MgSO_4$. This was then filtered and concentrated *in vacuo* to yield the crude title compound as a yellow solid.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.31 (d, *J* = 6.7 Hz, 6 H), 2.90 - 3.10 (m, 1 H), 3.79 (s, 3 H), 5.33 (s, 2 H), 6.33 (s, 1 H), 6.68 (d, *J* = 2.1 Hz, 1 H), 6.79 (dd, *J* = 8.5, 2.3 Hz, 1 H), 6.94 - 7.04 (m, 2 H), 7.20 - 7.37 (m, 2 H), 7.49 (d, *J* = 8.5 Hz, 1 H).

Example 5

1-Benzyl-2-isopropyl-6-methoxy-1H-indole-3-carbaldehyde (Compound 5). $POCl_3$ (0.48 ml, 5.23 mmol) was added dropwise to anhydrous DMF (2 ml) at 0 °C under argon. After stirred for 30 min, this solution was added dropwise to a solution of 1-benzyl-2-isopropyl-6-methoxy-1H-indole (**Compound 4**, 583 mg, 2.09 mmol) in anhydrous DMF (8 ml) at 0 °C under argon. The reaction was stirred for 1 h at 0 °C and 30 min at room temperature, diluted with EtOAc, washed with aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (0→30% EtOAc-hexanes) to yield the title compound as a light yellow syrup.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.45 (d, *J* = 7.3 Hz, 6 H), 3.40 - 3.52 (m, 1 H), 3.79 (s, 3 H), 5.40 (s, 2 H), 6.69 (d, *J* = 2.4 Hz, 1 H), 6.94 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.01 (d, *J* = 7.3 Hz, 2 H), 7.25 - 7.35 (m, 3 H), 8.28 (d, *J* = 8.8 Hz, 1 H), 10.45 (s, 1 H).

Example 6

1-Benzyl-2-isopropyl-6-methoxy-1H-indole-3-carboxylic Acid (Compound 6). To a solution of 1-benzyl-2-isopropyl-6-methoxy-1H-indole-3-carbaldehyde

(**Compound 5**, 608 mg, 1.98 mmol) in t-BuOH (15 ml), CH_3CN (15 ml), and 2-methyl-2-butene (10 ml) was added a solution of KH_2PO_4 (5.4 g, 39.6 mmol) and $NaClO_2$ (80%, 4.5 g, 39.6 mmol) in H_2O (50 ml). The mixture was stirred at room temperature and additional 2-methyl-2-butene, KH_2PO_4, and $NaClO_2$ were added at the above ratio every 16-24 h until the starting material was consumed. The reaction mixture was extracted with EtOAc (×3) and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (0→25% EtOAc-hexanes) to yield the title compound as a yellow solid.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.39 (d, *J* = 7.3 Hz, 6 H), 3.75 (s, 3 H), 3.99 - 4.17 (m, 1 H), 5.45 (s, 2 H), 6.62 (d, *J* = 2.4 Hz, 1 H), 6.90 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.99 (d, *J* = 7.3 Hz, 2 H), 7.22 - 7.34 (m, 3 H), 8.18 (d, *J* = 8.8 Hz, 1 H).

Example 7

1-Benzyl-N-(3,4-difluorobenzyl)-2-isopropyl-6-methoxy-1H-indole-3-carboxamide (Compound 7). To a solution of 1-benzyl-2-isopropyl-6-methoxy-1H-indole-3-carboxylic acid (**Compound 6**, 226 mg, 0.70 mmol) in CH_2Cl_2 (7.0 ml) was added EDC (202 mg, 1.05 mmol) and DMAP (128 mg, 1.05 mmol) followed by 3,4-difluorobenzylamine (0.25 ml, 2.1 mmol). The reaction was stirred at room temperature for 18 h, diluted with EtOAc, washed with H_2O, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (0→30% EtOAc-hexanes) to yield the title compound as a yellow solid.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.37 (d, *J* = 7.3 Hz, 6 H), 3.65 - 3.73 (m, 1 H), 3.74 (s, 3 H), 4.66 (d, *J* = 5.9 Hz, 2 H), 5.40 (s, 2 H), 6.30 (t, *J* = 6.3 Hz, 1 H), 6.63 (d, *J* = 2.0 Hz, 1 H), 6.82 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.96 (d, *J* = 6.8 Hz, 2 H), 7.11 - 7.17 (m, 2 H), 7.21 - 7.31 (m, 4 H), 7.51 (d, *J* = 8.3 Hz, 1 H).

Example 8

1-Benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (Compound 8). To a solution of 1-benzyl-N-(3,4-difluorobenzyl)-2-isopropyl-6-methoxy-1H-indole-3-carboxamide (**Compound 7**, 452 mg, 1.0 mmol) in CH_2Cl_2 (20 ml) at 0 °C was added BBr_3 (1.0 M in CH_2Cl_2, 3.0 ml, 3.0 mmol) dropwise. The reaction was stirred for 1 h at 0 °C and 1 h at room temperature, quenched with ice, extracted with EtOAc, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (0→50% EtOAc-hexanes) to yield the title compound as a yellow solid.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.37 (d, *J* = 7.3 Hz, 6 H), 3.65 - 3.74 (m, 1 H), 4.66 (d, *J* = 5.9 Hz, 2 H), 4.78 (s, 1 H), 5.37 (s, 2 H), 6.27 (t, *J* = 5.6 Hz, 1 H), 6.60 (d, *J* = 2.4 Hz, 1 H), 6.71 (dd, *J* = 8.5, 2.2 Hz, 1 H), 6.95 (d, *J* = 6.8 Hz, 2 H), 7.11 - 7.17 (m, 2 H), 7.21 - 7.32 (m, 4 H), 7.46 (d, *J* = 8.8 Hz, 1 H).

Example 9

1-benzyl-N-(3,4-difluorobenzyl)-6-ethoxy-2-isopropyl-1H-indole-3-carboxamide (Compound 9). General Procedure A. To a solution of 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 40 mg, 0.092 mmol) in DMF (2.0 ml) was added K_2CO_3 (39 mg, 0.28 mmol) and iodoethane (22 µl, 0.28 mmol). The reaction was stirred at room temperature for 48 h, diluted with EtOAc, washed with H_2O, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by PTLC on silica gel (30% EtOAc-hexanes) to yield the title compound as an off-white solid.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.37 (t, *J* = 7.0 Hz, 3 H), 1.38 (d, *J* = 7.3 Hz, 6 H), 3.68 - 3.75 (m, 1 H), 3.96 (q, *J* = 7.0 Hz, 2 H), 4.67 (d, *J* = 6.3 Hz, 2 H), 5.40 (s, 2 H), 6.31 (t, *J* = 5.4 Hz, 1 H), 6.64 (d, *J* = 2.4 Hz, 1 H), 6.82 (dd, *J* = 8.8, 2.0 Hz, 1 H), 6.97 (d, *J* = 6.8 Hz, 2 H), 7.13 - 7.17 (m, 2 H), 7.23 - 7.31 (m, 4 H), 7.52 (d, *J* = 8.3 Hz, 1 H)

Example 10

1-Benzyl-N-(3,4-difluorobenzyl)-2-isopropyl-6-propoxy-1H-indole-3-carboxamide (Compound 10). Following General Procedure A, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 8.0 mg, 0.018 mmol) in DMF (1.0 ml) was reacted with K_2CO_3 (8.0 mg, 0.055 mmol) and 1-iodopropane (9.0 µl, 0.092 mmol) to yield the title compound as a white solid.

^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 0.99 (t, J = 7.6 Hz, 3 H), 1.32 (d, J = 7.3 Hz, 6 H), 1.67 - 1.77 (m, 2 H), 3.42 - 3.53 (m, 1 H), 3.84 (t, J = 6.6 Hz, 2 H), 4.57 (s, 2 H), 5.46 (s, 2 H), 6.73 (d, J = 2.0 Hz, 1 H), 6.78 (dd, J = 8.8, 2.4 Hz, 1 H), 6.95 (d, J = 6.8 Hz, 2 H), 7.19 - 7.29 (m, 5 H), 7.30 - 7.36 (m, 1 H), 7.49 (d, J = 8.3 Hz, 1 H).

Example 11

1-Benzyl-N-(3,4-difluorobenzyl)-6-isopropoxy-2-isopropyl-1H-indole-3-carboxamide (Compound 11). Following General Procedure A, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 8.0 mg, 0.018 mmol) in DMF (1.0 ml) was reacted with K_2CO_3 (8.0 mg, 0.055 mmol) and 2-iodopropane (9.0 µl, 0.092 mmol) to yield the title compound as a white solid.

^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 1.21 (d, J = 5.9 Hz, 6 H), 1.33 (d, J = 7.3 Hz, 6 H), 3.45 - 3.55 (m, 1 H), 4.41 - 4.50 (m, 1 H), 4.57 (s, 2 H), 5.46 (s, 2 H), 6.72 (d, J = 2.0 Hz, 1 H), 6.74 - 6.79 (m, 1 H), 6.96 (d, J = 7.3 Hz, 2 H), 7.18 - 7.29 (m, 5 H), 7.30 - 7.37 (m, 1 H), 7.49 (d, J = 8.8 Hz, 1 H).

Example 12

1-Benzyl-6-butoxy-N-(3,4-difluorobenzyl)-2-isopropyl-1H-indole-3-carboxamide (Compound 12). Following General Procedure A, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 10.7 mg, 0.025 mmol) in DMF (1.0 ml) was reacted with K_2CO_3

(10.0 mg, 0.074 mmol) and 1-iodobutane (14.0 µl, 0.12 mmol) to yield the title compound as a white solid.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 0.93 (t, *J* = 7.3 Hz, 3 H), 1.37 (d, *J* = 7.3 Hz, 6 H), 1.40 - 1.50 (m, 2 H), 1.66 - 1.74 (m, 2 H), 3.61 - 3.75 (m, 1 H), 3.88 (t, *J* = 6.6 Hz, 2 H), 4.66 (d, *J* = 6.3 Hz, 2 H), 5.39 (s, 2 H), 6.30 (t, *J* = 5.9 Hz, 1 H), 6.63 (d, *J* = 2.0 Hz, 1 H), 6.81 (dd, *J* = 8.5, 2.2 Hz, 1 H), 6.96 (d, *J* = 6.8 Hz, 2 H), 7.10 - 7.17 (m, 2 H), 7.21 - 7.32 (m, 4 H), 7.50 (d, *J* = 8.8 Hz, 1 H).

Example 13

1-Benzyl-N-(3,4-difluorobenzyl)-6-isobutoxy-2-isopropyl-1H-indole-3-carboxamide (Compound 13). Following General Procedure A, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 10.7 mg, 0.025 mmol) in DMF (1.0 ml) was reacted with K_2CO_3 (10.0 mg, 0.074 mmol) and 2-iodobutane (14.0 µl, 0.12 mmol) to yield the title compound as a white solid.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 0.98 (d, *J* = 6.8 Hz, 6 H), 1.36 (d, *J* = 7.3 Hz, 6 H), 1.96 - 2.08 (m, 1 H), 3.65 (d, *J* = 6.8 Hz, 2 H), 3.65 - 3.72 (m, 1 H), 4.66 (d, *J* = 6.3 Hz, 2 H), 5.39 (s, 2 H), 6.29 (t, *J* = 5.6 Hz, 1 H), 6.63 (d, *J* = 2.0 Hz, 1 H), 6.82 (dd, *J* = 8.8, 2.0 Hz, 1 H), 6.96 (d, *J* = 6.8 Hz, 2 H), 7.11 - 7.16 (m, 2 H), 7.21 - 7.31 (m, 4 H), 7.50 (d, *J* = 8.8 Hz, 1 H).

Example 14

1-Benzyl-N-(3,4-difluorobenzyl)-6-(hexoxy)-2-isopropyl-1H-indole-3-carboxamide (Compound 14). Following General Procedure A, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 10.7 mg, 0.025 mmol) in DMF (1.0 ml) was reacted with K_2CO_3 (10.0 mg, 0.074 mmol) and 1-iodohexane (18.0 µl, 0.12 mmol) to yield the title compound as a white solid.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 0.85 - 0.93 (m, 3 H), 1.24 - 1.33 (m, 4 H), 1.37 (d, *J* = 6.8 Hz, 6 H), 1.38 - 1.46 (m, 2 H), 1.66 - 1.77 (m, 2

H), 3.63 - 3.75 (m, 1 H), 3.87 (t, *J* = 6.6 Hz, 2 H), 4.66 (d, *J* = 5.9 Hz, 2 H), 5.39 (s, 2 H), 6.30 (t, *J* = 5.6 Hz, 1 H), 6.63 (d, *J* = 2.4 Hz, 1 H), 6.81 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.96 (d, *J* = 6.8 Hz, 2 H), 7.10 - 7.16 (m, 2 H), 7.21 - 7.31 (m, 4 H), 7.50 (d, *J* = 8.8 Hz, 1 H).

Example 15

1-Benzyl-6-(benzyloxy)-N-(3,4-difluorobenzyl)-2-isopropyl-1H-indole-3-carboxamide (Compound 15). Following General Procedure A, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 10.7 mg, 0.025 mmol) in DMF (1.0 ml) and acetone (1.0 ml) was reacted with K_2CO_3 (10.0 mg, 0.074 mmol), benzyl bromide (14.0 µl, 0.12 mmol), and catalytic amount of NaI to yield the title compound as an off-white solid.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.37 (d, *J* = 7.3 Hz, 6 H), 3.65 - 3.75 (m, 1 H), 4.66 (d, *J* = 6.3 Hz, 2 H), 4.99 (s, 2 H), 5.37 (s, 2 H), 6.28 (t, *J* = 6.3 Hz, 1 H), 6.71 (d, *J* = 2.0 Hz, 1 H), 6.89 (dd, *J* = 8.8, 2.0 Hz, 1 H), 6.95 (d, *J* = 6.8 Hz, 2 H), 7.11 - 7.18 (m, 2 H), 7.22 - 7.30 (m, 5 H), 7.31 - 7.39 (m, 4 H), 7.51 (d, *J* = 8.8 Hz, 1 H).

Example 16

1-Benzyl-6-(cyclopentoxy)-N-(3,4-difluorobenzyl)-2-isopropyl-1H-indole-3-carboxamide (Compound 16). Following General Procedure A, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 40 mg, 0.092 mmol) in DMF (1.0 ml) was reacted with K_2CO_3 (38 mg, 0.28 mmol), cyclopentyl iodide (53 µl, 0.46 mmol) to yield the title compound as a white solid.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.37 (d, *J* = 7.0 Hz, 6 H), 1.48 - 1.60 (m, 2 H), 1.66 - 1.86 (m, 6 H), 3.62 - 3.83 (m, 1 H), 4.56 - 4.77 (m, 3 H), 5.38 (s, 2 H), 6.32 (t, *J* = 5.9 Hz, 1 H), 6.61 (d, *J* = 2.1 Hz, 1 H), 6.78 (dd, *J* = 8.8, 2.1 Hz, 1 H), 6.91 - 7.02 (m, 2 H), 7.08 - 7.17 (m, 2 H), 7.17 - 7.36 (m, 4 H), 7.49 (d, *J* = 8.5 Hz, 1 H).

Example 17

1-Benzyl-N-(3,4-difluorobenzyl)-2-isopropyl-6-(2-methoxyethoxy)-1H-indole-3-carboxamide (Compound 17). Following General Procedure A, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 17 mg, 0.039 mmol) in DMF (1.0 ml) was reacted with K_2CO_3 (28 mg, 0.20 mmol), 2-bromoethyl methyl ether (18 μl, 0.20 mmol) to yield the title compound (9 mg, 49%).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.37 (d, J = 7.04 Hz, 6 H), 3.40 (s, 3 H), 3.60 - 3.78 (m, 3 H), 4.04 (dd, J = 5.42, 3.96 Hz, 2 H), 4.66 (d, J = 5.86 Hz, 2 H), 5.39 (s, 2 H), 6.30 (t, J = 5.86 Hz, 1 H), 6.68 (d, J = 2.35 Hz, 1 H), 6.85 (dd, J = 8.65, 2.20 Hz, 1 H), 6.89 - 7.01 (m, 2 H), 7.10 - 7.18 (m, 2 H), 7.17 - 7.35 (m, 4 H), 7.51 (d, J = 8.79 Hz, 1 H).

Example 18

1-Benzyl-N-(3,4-difluorobenzyl)-6-(2-(dimethylamino)ethoxy)-2-isopropyl-1H-indole-3-carboxamide (Compound 18). Following General Procedure A, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 17 mg, 0.039 mmol) in DMF (1.0 ml) was reacted with K_2CO_3 (28 mg, 0.20 mmol), 2-dimehtylamino ethyl chloride hydrochloride (20 mg, 0.20 mmol) to yield the title compound (10 mg, 53%).

^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.32 (d, J = 7.04 Hz, 6 H), 2.30 (s, 6 H), 2.71 (t, J = 5.42 Hz, 2 H), 3.37 - 3.59 (m, 1 H), 4.02 (t, J = 5.42 Hz, 2 H), 4.57 (s, 2 H), 5.48 (s, 2 H), 6.73 - 6.88 (m, 2 H), 6.89 - 7.02 (m, 2 H), 7.12 - 7.40 (m, 6 H), 7.50 (d, J = 8.50 Hz, 1 H).

Example 19

1-Benzyl-N-(3,4-difluorobenzyl)-2-isopropyl-6-(tetrahydrofuran-3-yloxy)-1H-indole-3-carboxamide (Compound 19). To a solution of 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 8 mg, 0.039 mmol) in DMF (1.0 ml) was added K_2CO_3 (13 mg, 0.092 mmol)

and catalytic amount of NaOH, 3-iodotetrahydrofuran (**Compound 29,** 120 mg, crude). The reaction was stirred at room temperature for 2 days, and purified by a short silica gel column to yield the title compound (8 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.38 (d, J = 7.04 Hz, 6 H), 1.95 - 2.14 (m, 2 H), 3.59 - 4.01 (m, 5 H), 4.66 (d, J = 6.16 Hz, 2 H), 4.74 - 4.88 (m, 1 H), 5.39 (s, 2 H), 6.29 (t, J = 4.40 Hz, 1 H), 6.57 (d, J = 2.05 Hz, 1 H), 6.69 - 6.83 (m, 1 H), 6.96 (d, J = 7.62 Hz, 2 H), 7.08 - 7.19 (m, 2 H), 7.18 - 7.35 (m, 4 H), 7.51 (d, J = 8.79 Hz, 1 H).

Example 20

1-Benzyl-N-(3,4-difluorobenzyl)-2-isopropyl-6-(2-oxotetrahydrofuran-3-yloxy)-1H-indole-3-carboxamide (Compound 20). Following General Procedure A, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 19mg, 0.044mol) in DMF (1.0 ml) was reacted with K_2CO_3 (30 g, 0.22 mmol), 3-bromodihydrofuran-2(3H)-one (20 mg, 0.22mmol) to yield the title compound (16mg, 71%).

^{1}H NMR (300 MHz, acetone-d_6) δ ppm 1.33 (d, J = 5.57 Hz, 6 H), 2.21 - 2.42 (m, 1 H), 2.68 - 2.88 (m, 1 H), 3.43 - 3.65 (m, 1 H), 4.21 - 4.53 (m, 2 H), 4.66 (d, J = 6.16 Hz, 2 H), 5.10 - 5.24 (m, 1 H), 5.54 (s, 2 H), 6.90 (dd, J = 8.65, 2.20 Hz, 1 H), 6.97 - 7.08 (m, 2 H), 7.11 (d, J = 2.35 Hz, 1 H), 7.17 - 7.35 (m, 5 H), 7.42 (dd, J = 12.31, 8.50 Hz, 1 H), 7.62 (d, J = 8.79 Hz, 1 H), 7.68 - 7.78 (m, 1 H).

Example 21

1-benzyl-3-(3,4-difluorobenzylcarbamoyl)-2-isopropyl-1H-indol-6-yl Dimethylcarbamate (Compound 21). General Procedure B. To a solution of 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 18mg, 0.041mol) in pyridine (1 ml) was added dimethylcarbamyl chloride (40 μl, 0.41 mmol) and stirred at room temperature overnight. The reaction was quenched with water, extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over Na_2SO_4,

and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (0→50% EtOAc-hexanes) to yield the title compound as a white solid (17 mg, 82%).

^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.32 (d, J = 7.04 Hz, 6 H), 2.96 (s, 3 H), 3.09 (s, 3 H), 3.37 - 3.55 (m, 1 H), 4.58 (s, 2 H), 5.48 (s, 2 H), 6.87 (dd, J = 8.65, 1.91 Hz, 1 H), 6.91 - 6.99 (m, 2 H),7.02 (d, J = 2.05 Hz, 1 H), 7.16 - 7.39 (m, 6 H), 7.58 (d, J = 8.79 Hz, 1 H).

Example 22

1-Benzyl-3-(3,4-difluorobenzylcarbamoyl)-2-isopropyl-1H-indol-6-yl Pivalate (Compound 22). Following General Procedure B, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 18mg, 0.041mol) in pyridine (1 ml) was reacted with pivaloyl chloride (5.1 µl, 0.41 mmol) to yield the title compound (16 mg, 74%).

^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.25 - 1.40 (m, 15 H), 3.34 - 3.55 (m, 1 H), 4.58 (d, J = 5.86 Hz, 2 H), 5.49 (s, 2 H), 6.73 - 6.88 (m, 1 H), 6.89 - 6.99 (m, 2 H), 7.00 (d, J = 1.76 Hz, 1 H), 7.14 - 7.41 (m, 6 H), 7.60 (d, J = 8.50 Hz, 1 H).

Example 23

1-Benzyl-3-(3,4-difluorobenzylcarbamoyl)-2-isopropyl-1H-indol-6-yl Acetate (Compound 23). Following General Procedure B, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 7mg, 0.016mol) in pyridine (1 ml) was reacted with acetyl chloride (1.0 µl, 0.16 mmol) to yield the title compound (8 mg, 100%).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.37 (d, J = 7.04 Hz, 6 H), 2.26 (s, 3 H), 3.54 - 3.76 (m, 1 H), 4.66 (d, J = 6.16 Hz, 2 H), 5.41 (s, 2 H), 6.28 (t, J = 6.01 Hz, 1 H), 6.81 - 7.01 (m, 4 H), 7.06 - 7.19 (m, 2 H), 7.18 - 7.35 (m, 4 H), 7.61 (d, J = 9.09 Hz, 1 H).

Example 24

1-Benzyl-3-(3,4-difluorobenzylcarbamoyl)-2-isopropyl-1H-indol-6-yl Propionate (Compound 24). Following General Procedure B, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 7mg, 0.016mol) in pyridine (1 ml) was reacted with propionyl chloride (1.4 μl, 0.16 mmol) to yield the title compound (8 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 (t, J = 7.48 Hz, 3 H), 1.37 (d, J = 7.33 Hz, 6 H), 2.55 (q, J = 7.43 Hz, 2 H), 3.53 - 3.73 (m, 1 H), 4.66 (d, J = 5.86 Hz, 2 H), 5.41 (s, 2 H), 6.30 (t, J = 5.72 Hz, 1 H), 6.83 - 7.00 (m, 4 H), 7.06 - 7.18 (m, 2 H), 7.18 - 7.35 (m, 4 H), 7.60 (d, J = 8.50 Hz, 1 H).

Example 25

1-Benzyl-3-(3,4-difluorobenzylcarbamoyl)-2-isopropyl-1H-indol-6-yl Isobutyrate (Compound 25). Following General Procedure B, 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 9mg, 0.021mol) in pyridine (1 ml) was reacted with isobutyryl chloride (4.1 μl, 0.21 mmol) to yield the title compound (8 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.13 - 1.42 (m, 12 H), 2.47 - 2.85 (m, 1 H), 3.50 - 3.74 (m, 1 H), 4.66 (d, J = 6.16 Hz, 2 H), 5.41 (s, 2 H), 6.20 - 6.44 (m, 1 H), 6.74 - 7.00 (m, 4 H), 7.07 - 7.18 (m, 2 H), 7.17 - 7.35 (m, 4 H), 7.60 (d, J = 8.50 Hz, 1 H).

Example 26

1-Benzyl-N-(3,4-difluorobenzyl)-2-isopropyl-6-(methoxymethoxy)-1H-indole-3-carboxamide (Compound 26). To a solution of 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 39 mg, 0.090 mmol) in CH_2Cl_2 (2.0 ml) was added i-Pr_2NEt (47 μl, 0.27 mmol) and MOMCl (35 μl, 0.45 mmol). The reaction was stirred at room temperature for 4 h, and was purified directly by PTLC on silica gel (30% EtOAc-hexanes) to yield the title compound as a white solid. ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.37 (d, J = 7.0 Hz, 6 H), 3.42 (s, 3 H), 3.59 - 3.78 (m, 1 H), 4.66 (d, J = 5.9 Hz, 2 H), 5.10 (s, 2 H), 5.40 (s, 2

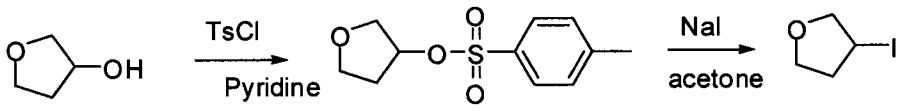
H), 6.29 (t, J = 5.7 Hz, 1 H), 6.85 (d, J = 2.1 Hz, 1 H), 6.89 - 7.01 (m, 3 H), 7.10 - 7.17 (m, 2 H), 7.20 - 7.34 (m, 4 H), 7.52 (d, J = 8.5 Hz, 1 H).

Example 27

1-Benzyl-N-(3,4-difluorobenzyl)-2-isopropyl-6-(tetrahydrofuran-2-yloxy)-1H-indole-3-carboxamide (Compound 27). To a solution of 1-benzyl-N-(3,4-difluorobenzyl)-6-hydroxy-2-isopropyl-1H-indole-3-carboxamide (**Compound 8**, 39 mg, 0.090 mmol) in CH_2Cl_2 (2.0 ml) was added 2,3-dihydrofuran (68 µl, 0.90 mmol) and catalytic amount of PPTS. The reaction was stirred at room temperature for 4 h, and was purified directly by PTLC on silica gel (30% EtOAc-hexanes) to yield the title compound as a white solid.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.36 (d, J = 7.3 Hz, 6 H), 1.85 - 1.98 (m, 1 H), 2.01 - 2.19 (m, 3 H), 3.58 - 3.73 (m, 1 H), 3.85 - 3.95 (m, 1 H), 3.96 - 4.07 (m, 1 H), 4.66 (d, J = 5.9 Hz, 2 H), 5.40 (s, 2 H), 5.70 (d, J = 4.7 Hz, 1 H), 6.29 (t, J = 5.7 Hz, 1 H), 6.86 (d, J = 2.1 Hz, 1 H), 6.89 - 6.99 (m, 3 H), 7.11 - 7.17 (m, 2 H), 7.19 - 7.32 (m, 4 H), 7.51 (d, J = 8.5 Hz, 1 H).

Scheme 4



28 **29**

Example 28

Tetrahydrofuran-3-yl 4-methylbenzenesulfonate (Compound 28). To a solution of tetrahydrofuran-3-ol (500 mg, 5.67 mmol) in pyridine (10 ml) at 0 °C was added 4-methylbenzene-1-sulfonyl chloride (1.08 g, 5.67 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with water, extracted with ethyl acetate. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo to yield crude oil (1.2 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.91 - 2.23 (m, 2 H), 3.61 - 4.05 (m, 4 H), 4.95 - 5.24 (m, 1 H), 7.36 (d, *J* = 7.92 Hz, 2 H), 7.80 (d, *J* = 8.50 Hz, 2 H).

Example 29

3-Iodotetrahydrofuran (Compound 29). To a solution of crude tetrahydrofuran-3-yl 4-methylbenzenesulfonate (**Compound 28**, 1.2 g, 4.96 mmol) in dry acetone (50 ml) was added NaI (1.1 g, 7.44 mmol). The reacted was heated at 60 °C for 2 days. The mixture was diluted with water and extracted with diethyl ether. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo to yield crude oil which was used directly without purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.23 - 2.55 (m, 2 H), 3.81 - 4.08 (m, 3 H), 4.08 - 4.43 (m, 2 H).

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention was to be governed only by the lawful construction of the appended claims. In particular, the present invention includes a 6-substituted indole-3-carboxylic acid-N- arylmethyl amide having sphingosine-1-phosphate antagonist activity wherein the 6-substituent is represented by the formula

$$-A^1-(X^1)_r-A^2-B$$

wherein X_1 is O;

r is 0 or 1;

A^2 is absent or is $(CH_2)_v$, wherein v is 1 or 2;

B is OR^6 or NR^8R^9, wherein R^6, R^8 and R^9 are methyl; or

B is CR^{10}=NO $R^{11}R^{10}$ wherein R^{10} is H and

R^{11} is methyl or i-butyl; or B is $CONR^8R^9$, wherein R^8 and R^9 are selected from the group consisting of H, methyl, ethyl and propyl or R^8 and R^9, together with N, form a 5-membered ring; or B is OR^6, wherein R^6 is H; or

B is COR^{10}, wherein R^{10} is methyl.

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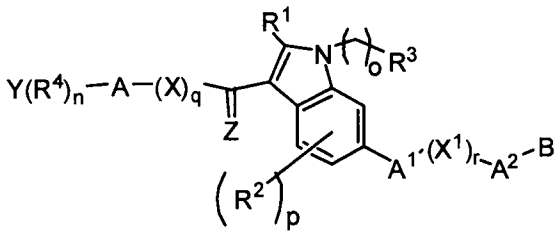
What is claimed is:

1. Compounds represented by the formula I having sphingosine-1-phosphate receptor agonist and or antagonist biological activity:



Formula I

wherein:

R^1 R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, straight or branched chain alkyl having 1 to 12 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, carbocyclic hydrocarbon groups having from 3 to 20 carbon atoms, heterocyclic groups having up to 20 carbon atoms and at least one of oxygen, nitrogen and/or sulfur in the ring, halo, C_1 to C_{12} haloalkyl, hydroxyl, C_1 to C_{12} alkoxy, C_3 to C_{20} arylalkyloxy, C_1 to C_{12} alkylcarbonyl, formyl, oxycarbonyl, carboxy, C_1 to C_{12} alkyl carboxylate, C_1 to C_{12} alkyl amide, aminocarbonyl, amino, cyano, diazo, nitro, thio, sulfoxyl, and sulfonyl groups;

X and X^1 are independently selected from the group consisting of NR^5, O and S;

R^5 is hydrogen, an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons, phenyl or lower alkylphenyl;

Y is a carbocyclic aryl or heterocyclic aryl group wherein said carbocyclic aryl comprises from 6 to 20 atoms and said heterocyclic aryl comprises from 2 to 20 carbon atoms and from 1 to 5 heteroatoms selected from the

group consisting of nitrogen, oxygen and sulfur, and wherein said aryl may be bonded to A at any position;

Z is O or S;

n is 0 or an integer of from 1 to 5;

o is 0 or an integer of from 1 to 3;

p is 0 or an integer of from 1 to 3;

q is 0 or 1;

r is 0 or 1;

A, A^1 and A^2 are independently selected from the group consisting of $(CH_2)_v$ wherein v is 0 or an integer of from 1 to 12, branched chain alkyl having 3 to 12 carbons, cycloalkyl having 3 to 12 carbons, alkenyl having 2 to 10 carbons and 1–3 double bonds and alkynyl having 2 to 10 carbons and 1 to 3 triple bonds;

B is selected from the group consisting of hydrogen, OR^6, $COOR^7$, NR^8R^9, $CONR^8R^9$, COR^{10}, $CH{=}NOR^{11}$, $CH{=}NNR^{12}R^{13}$

wherein R^6, R^7, R^{10} and R^{11} are independently selected from the group consisting of hydrogen, straight or branched chain alkyl having 1 to 12 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, a carbocyclic hydrocarbon group having from 3 to 20 carbon atoms, a heterocyclic group having up to 20 carbon atoms and at least one of oxygen, nitrogen and/or sulfur in the ring, R^8, R^9 , R^{12} and R^{13} are independently selected from the group consisting of hydrogen, straight or branched chain alkyl having 1 to 12 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, a carbocyclic hydrocarbon group having from 3 to 20 carbon atoms, a heterocyclic group having up to

20 carbon atoms and at least one of oxygen, nitrogen and/or sulfur in the ring, or R^8 and R^9 and/or R^{12} and R^{13}, together, can form a divalent carbon radical of 2 to 5 carbons to form a heterocyclic ring with nitrogen, wherein any of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} or R^{13} may be substituted with one or more halogen, hydroxy, alkyloxy, cyano, nitro, mercapto or thiol radical; provided however, when v is 0, and r is 0, B is not hydrogen; or B is a carbocyclic hydrocarbon group having from 3 to 20 carbon atoms, or a heterocyclic group having up to 20 carbon atoms and at least one of oxygen, nitrogen and/or sulfur in the ring, and wherein when said B is a carbocyclic or heterocyclic group B may be bonded to A^2 at any position, or a pharmaceutically acceptable salt of said compound.

2. The compound of claim 1 wherein Z is O.

3. The compound of claim 2 wherein Y is a phenyl group or a pyridyl group.

4. The compound of claim 3 wherein A is CH_2.

5. The compound of claim 4 wherein X is NH.

6. The compound of claim 5 wherein n is 0 or an integer of 1 or 2 and R^4 is fluoro.

7. The compound of claim 6 wherein R^1 is i-propyl.

8. The compound of claim 7 wherein R^3 is selected from the group consisting of phenyl, which may be substituted with one or two flouro groups, and pyridyl.

9. The compound of claim 8 wherein p is 0.

10. The compound of claim 9 wherein A^1 and A^2 are absent.

11. The compound of claim 10 wherein B is OR^6.

12. The compound of claim 10 wherein B is $COOR^7$.

13. The compound of claim 10 wherein X^1 is O, r is 1, A^1 is absent, A^2 is $(CH_2)_v$, wherein v is 1 or 2, and B is OR^6 or NR^8R^9.

14. The compound of claim 13 wherien R^6, R^8 and R^9 are methyl.

15. The compound of claim 10 wherein B is CR^{10}=$NOR^{11}R^{10}$ wherein R^{10} is H and R^{11} is methyl or i-butyl.

16. The compound of claim 10 wherein B is $CONR^8R^9$ wherein R^8 and R^9 are selected from the group consisting of H, methyl, ethyl and propyl, or R^8 and R^9, together with N, form a 5-member ring.

17. The compound of claim 10 wherein A^1 is absent, r is 0, A^2 is CH_2 and B is OR^6, wherein R^6 is H.

18. The compound of claim 10 wherein A^1 is absent, X is O, r is 1 and B is COR^{10} wherein R^{10} is methyl.

19. A 6-substituted indole-3-carboxylic acid-N- arylmethyl amide having spingosine-1-phosphate antagonist activity wherein the 6-substituent is represented by the formula

$(X^1)_r$-A^2-B

wherein X^1 is O;

r is 0 or 1;

A^2 is absent or is $(CH_2)_v$, wherein v is 1 or 2;

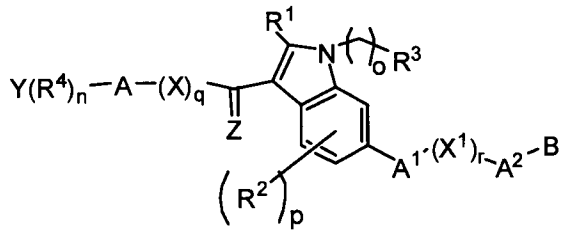
B is OR^6 or NR^8R^9, wherein R^6, R^8 and R^9 are methyl; or

B is CR^{10}=NO $R^{11}R^{10}$ wherein R^{10} is H and

R^{11} is methyl or i-butyl; or

B is $CONR^8R^9$, wherein R^8 and R^9 are selected from the group consisting of H, methyl, ethyl and propyl or R^8 and R^9, together with N, form a 5-membered ring; or B is OR^6, wherein R^6 is H; or
B is COR^{10}, wherein R^{10} is methyl.

20. A method of treating a disease or condition selected from the group consisting of glaucoma, dry eye, angiogenesis, cardiovascular conditions and diseases, and wound healing, which comprises administering to a patient in need thereof a compound having sphingosine-1-phosphate receptor agonist and or antagonist biological activity represented by the general formula I:



Formula I

wherein:
R^1 R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, straight or branched chain alkyl having 1 to 12 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, carbocyclic hydrocarbon groups having from 3 to 20 carbon atoms, heterocyclic groups having up to 20 carbon atoms and at least one of oxygen, nitrogen and/or sulfur in the ring, halo, C_1 to C_{12} haloalkyl, hydroxyl, C_1 to C_{12} alkoxy, C_3 to C_{20} arylalkyloxy, C_1 to C_{12} alkylcarbonyl, formyl, oxycarbonyl, carboxy, C_1 to C_{12} alkyl carboxylate, C_1 to C_{12} alkyl amide, aminocarbonyl, amino, cyano, diazo, nitro, thio, sulfoxyl, and sulfonyl groups;

X and X^1 are independently selected from the group consisting of NR^5, O and S;

R^5 is hydrogen, an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons, phenyl or lower alkylphenyl;

Y is a carbocyclic aryl or heterocyclic aryl group wherein said carbocylic aryl comprises from 6 to 20 atoms and said heterocyclic aryl comprises from 2 to 20 carbon atoms and from 1 to 5 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and wherein said aryl may be bonded to A at any position;

Z is O or S;

n is 0 or an integer of from 1 to 5;

o is 0 or an integer of from 1 to 3;

p is 0 or an integer of from 1 to 3;

q is 0 or 1;

r is 0 or 1;

A, A^1 and A^2 are independently selected from the group consisting of $(CH_2)_v$ wherein v is 0 or an integer of from 1 to 12, branched chain alkyl having 3 to 12 carbons, cycloalkyl having 3 to 12 carbons, alkenyl having 2 to 10 carbons and 1–3 double bonds and alkynyl having 2 to 10 carbons and 1 to 3 triple bonds;

B is selected from the group consisting of hydrogen, OR^6, $COOR^7$, NR^8R^9, $CONR^8R^9$, COR^{10}, $CH{=}NOR^{11}$, $CH{=}NNR^{12}R^{13}$

wherein R^6, R^7, R^{10} and R^{11} are independently selected from the group consisting of hydrogen, straight or branched chain alkyl having 1 to 12 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, a carbocyclic hydrocarbon group having from 3 to 20 carbon atoms, a heterocyclic group having up to

20 carbon atoms and at least one of oxygen, nitrogen and/or sulfur in the ring, R^8, R^9 , R^{12} and R^{13} are are independently selected from the group consisting of hydrogen, straight or branched chain alkyl having 1 to 12 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, a carbocyclic hydrocarbon group having from 3 to 20 carbon atoms, a heterocyclic group having up to 20 carbon atoms and at least one of oxygen, nitrogen and/or sulfur in the ring, or R^8 and R^9 and/or R^{12} and R^{13} , together, can form a divalent carbon radical of 2 to 5 carbons to form a heterocyclic ring with nitrogen, wherein any of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} or R^{13} may be substituted with one or more halogen, hydroxy, alkyloxy, cyano, nitro, mercapto or thiol radical; provided however, when v is 0, and r is 0, B is not hydrogen; or B is a carbocyclic hydrocarbon group having from 3 to 20 carbon atoms, or a heterocyclic group having up to 20 carbon atoms and at least one of oxygen, nitrogen and/or sulfur in the ring, and wherein when said B is a carbocyclic or heterocyclic group B may be bonded to A^2 at any position, or a pharmaceutically acceptable salt of said compound.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/050695

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/42 C07D405/12 C07D405/14 A61K31/404 A61P27/00
C07D401/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAGASHIMA ET AL: "Fluorous 2-chloropyridinium salt (Mukaiyama condensation reagent) for amide formation reactions" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 46, no. 38, 19 September 2005 (2005-09-19), pages 6585-6588, XP005034771 ISSN: 0040-4039 entry 7	1-5

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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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2008	19/06/2008

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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Diederen, Jeroen

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/050695

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DARYL R. SAUER ET AL.: "Microwave-assisted synthesis utilizing supported reagents: a rapid and efficient acylation procedure" ORGANIC LETTERS, vol. 5, no. 24, 2003, pages 4721-4724, XP002444821 synthesis of benzyl-(1-methyl-3-carboxamide-indole)	1-6
X	WO 03/070691 A (OSAKA IND PROMOTION ORG [JP]; UESATO SHINICHI [JP]; NAGAOKA YASUO [JP]) 28 August 2003 (2003-08-28) abstract -& DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002444827 retrieved from STN Database accession no. 2003:678775 RN: 591218-03-0, 591218-02-9 abstract	1-5
X	WO 00/42045 A (WARNER LAMBERT CO [US]; HARRIMAN GERALDINE C [US]; KOLZ CHRISTINE NYLU) 20 July 2000 (2000-07-20) page 58, 5-hydroxy-2-methyl-1H-indole-3-carboxylic acid benyl amide	1-6
X	DOMSCHKE G ET AL: "N-SUBSTITUIERTE 1-BENZYL-2-METHYL-3-AMINOMETHYL-5-METHOXY-INDOLE UND VERWANDTE VERBINDUNGEN" CHEMISCHE BERICHTE, VERLAG CHEMIE GMBH. WEINHEIM, DE, vol. 93, 1960, pages 2097-2106, XP000961036 ISSN: 0009-2940 compound XII	1-6
X	FR 2 121 394 A1 (ANVAR ANVAR [FR]) 25 August 1972 (1972-08-25) examples 9,10	1-6
X	KUTSCHY P ET AL: "Synthesis of some analogs of indole phytoalexins brassinin and methoxybras sinin B and their postional isomers" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, INSTITUTE OF ORGANIC CHEMISTRY & BIOCHEMISTRY, PRAGUE, CZ, vol. 64, no. 2, February 1999 (1999-02), pages 348-362, XP002276545 ISSN: 0010-0765 compound 26c	1-6

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/050695

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 197 53 522 A1 (BOEHRINGER INGELHEIM PHARMA [DE]) 10 June 1999 (1999-06-10) examples 124,a,b	1-5
X	DI SANTO R ET AL: "N-(1-naphthylmethyl)-n-(1-alkyl-4-aryl-1h -pyrrol-3-ylmethyl)methylam ines related to naftifine. Synthesis and antifungal activity" MEDICINAL CHEMISTRY RESEARCH, BIRKHAEUSER, BOSTON, US, vol. 7, no. 2, 1997, pages 98-108, XP002958012 ISSN: 1054-2523 compound 7b	1,2
X	US 5 994 378 A (MATSUO MASAAKI [JP] ET AL) 30 November 1999 (1999-11-30) example 55	1-6
X	DATABASE CHEMCATS CHEMICAL ASBTRACTS SERVICE, COLUMBUS, OHIOS, USA; XP002444828 order number: 9T-1488, 7T-1489, 7T-1483, 7T-1482, 7T-1481, A3356/0142417 & "Interchim Intermediates" 18 January 2005 (2005-01-18), INTERCHIM , 211 BIS AV JF KENNEDY, BP 1140, MONTLUCON, 03103, FRANCE	1-6
X	JOGINDER S. BAJWA: "Chemoselective deprotection of benzyl esters in the presence of benzyl ethers, benzyloxymethyl ether and N-benzyl groups by catalytic transfer hydrogenation" TETRAHEDRON LETTERS, vol. 33, no. 17, 1992, pages 2299-2302, XP002444822 compound 3	1-6
X	JONATHAN CLAYDEN ET AL.: "Nucleophilic addition to electron-rich heteroaromatics: dearomatizing anionic cyclizations of pyrrolecarboxamides" ORGANIC LETTERS, vol. 6, no. 4, 2004, pages 609-611, XP002444823 compound 12	1-6

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/050695

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOHN T. CARLOCK ET AL.: "3-diazo-4-oxo-3,4-dihydroquinoline. A novel synthon for indole-3-carboxamides" JOURNAL OF ORGANIC CHEMISTRY, vol. 42, no. 11, 1977, pages 1883-1885, XP002444824 products 2-9	1-6
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002481307 retrieved from STN Database accession no. 131:31874 226901-36-6 abstract	19
A	WO 01/98301 A (JAPAN TOBACCO INC [JP]; KAWASAKI HISASHI [JP]; OZAWA KOICHI [JP]; YAMA) 27 December 2001 (2001-12-27) the whole document	1-48
P,X	WO 2007/095561 A (ALLERGAN INC [US]; BEARD RICHARD L [US]; DONELLO JOHN E [US]; YUAN HAI) 23 August 2007 (2007-08-23) examples claims	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/050695

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 20 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/050695

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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WO 2007095561	A	23-08-2007	NONE		