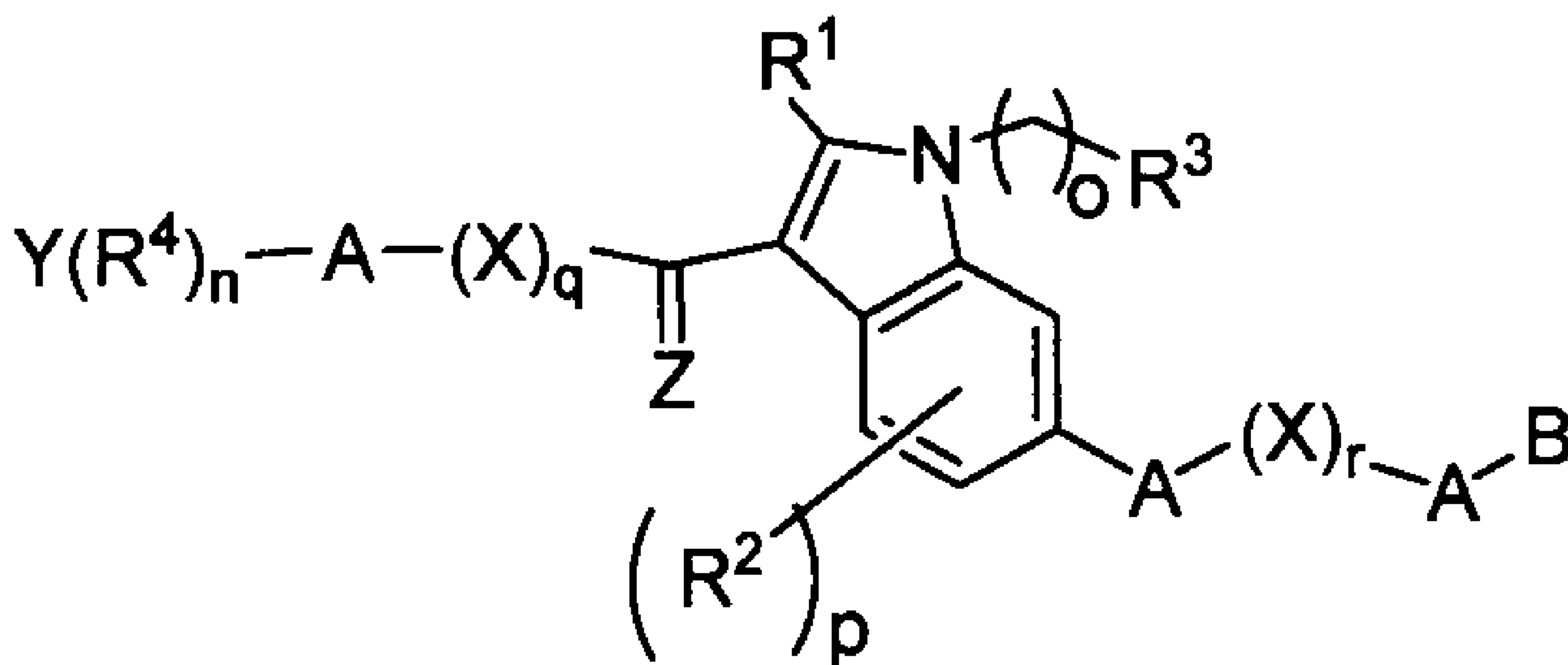




(86) Date de dépôt PCT/PCT Filing Date: 2008/01/10
(87) Date publication PCT/PCT Publication Date: 2008/07/24
(85) Entrée phase nationale/National Entry: 2009/07/08
(86) N° demande PCT/PCT Application No.: US 2008/050695
(87) N° publication PCT/PCT Publication No.: 2008/089015
(30) Priorité/Priority: 2007/01/11 (US60/884,470)

(51) Cl.Int./Int.Cl. *C07D 209/42* (2006.01),
A61K 31/404 (2006.01), *A61P 27/00* (2006.01),
C07D 401/06 (2006.01), *C07D 405/12* (2006.01),
C07D 405/14 (2006.01)
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(54) Titre : COMPOSE AMIDE D'ACIDE INDOLE-3-CARBOXYLIQUE 6-SUBSTITUE AYANT UNE ACTIVITE
BIOLOGIQUE D'ANTAGONISTE DU RECEPTEUR DE SPHINGOSINE-1-PHOSPHATE (S1P)
(54) Title: 6-SUBSTITUTED INDOLE-3-CARBOXYLIC ACID AMIDE COMPOUNDS HAVING SPHINGOSINE-1-
PHOSPHATE (S1P) RECEPTOR ANTAGONIST BIOLOGICAL ACTIVITY



Formula I

(57) **Abrégé/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, R⁴, n, o, A, A¹, A², X, Z, R¹, R³, R², 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



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 July 2008 (24.07.2008)

PCT

(10) International Publication Number
WO 2008/089015 A1

(51) International Patent Classification:

C07D 209/42 (2006.01) *A61K 31/404* (2006.01)
C07D 405/12 (2006.01) *A61P 27/00* (2006.01)
C07D 405/14 (2006.01) *C07D 401/06* (2006.01)

(21) International Application Number:

PCT/US2008/050695

(22) International Filing Date: 10 January 2008 (10.01.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/884,470 11 January 2007 (11.01.2007) US

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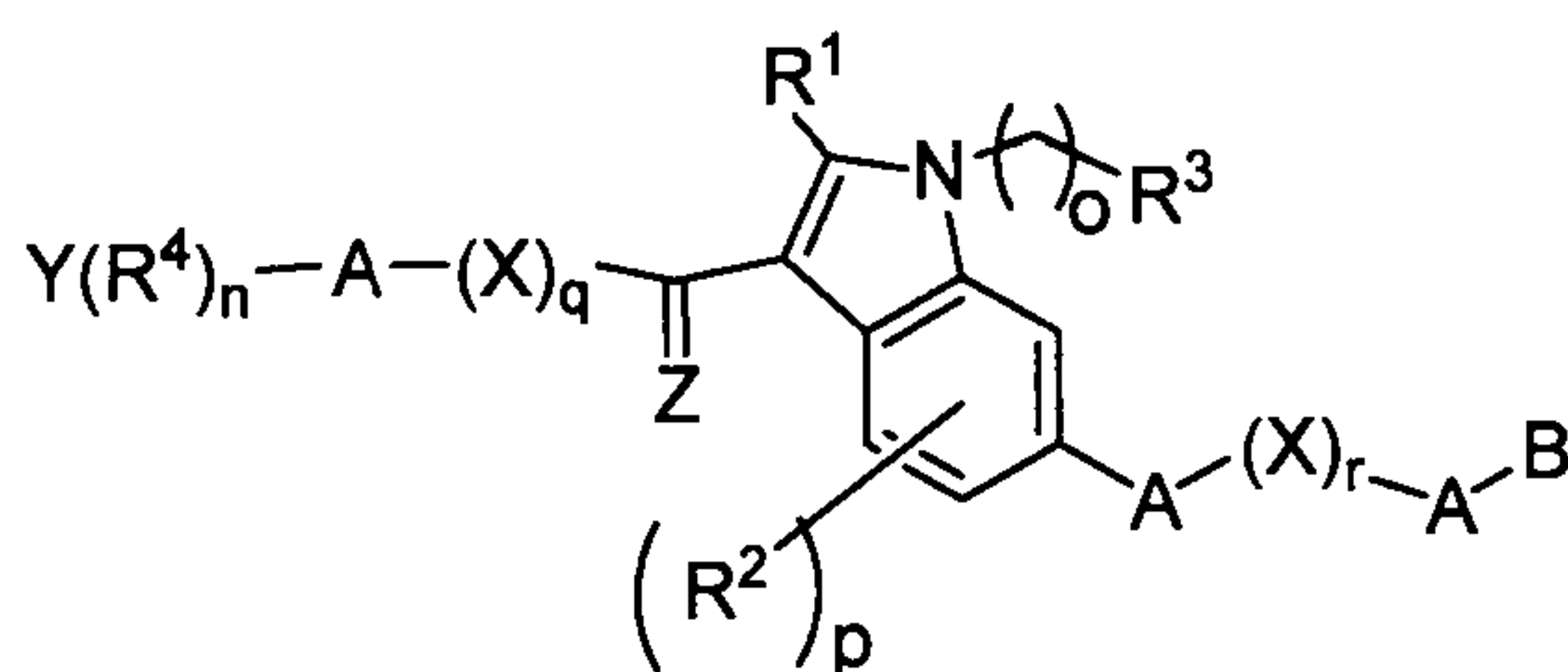
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(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, R⁴, n, o, A, A¹, A², X, Z, R¹, R³, R², 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

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

**Inventors
RICHARD L. BEARD
HAIGING YUAN**

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.

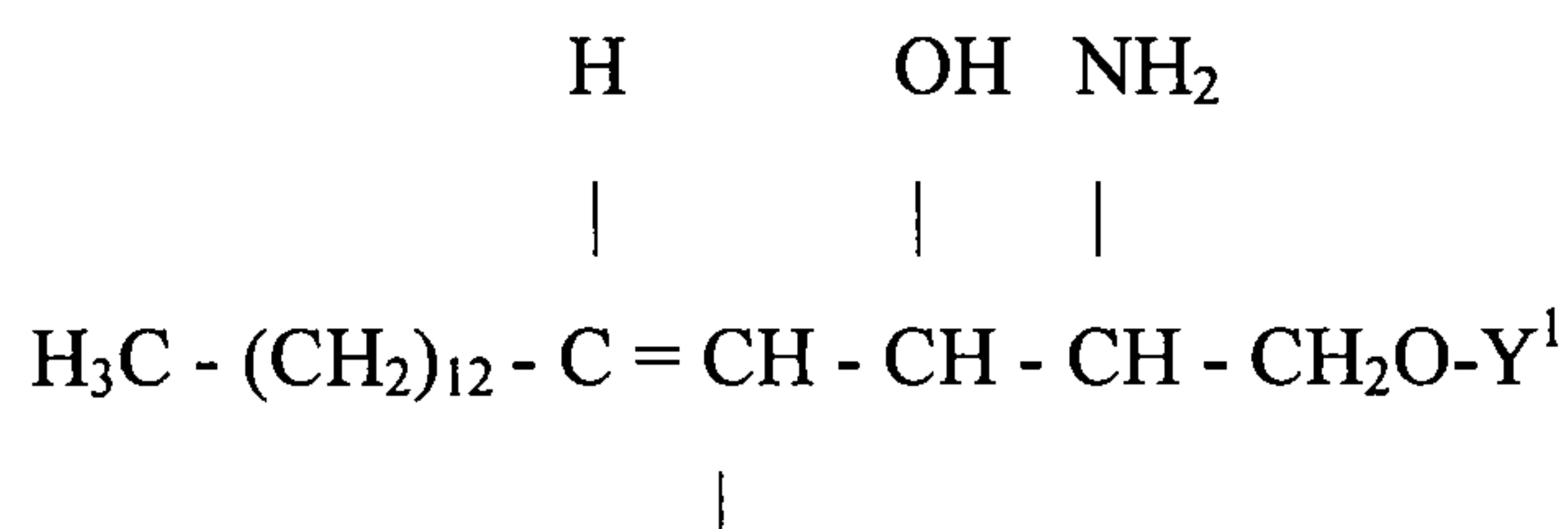
BACKGROUND OF THE INVENTION

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 Y¹ 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.



H

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 sphingosine levels in cells is critical for their viability. In common with the

5 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.

10 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

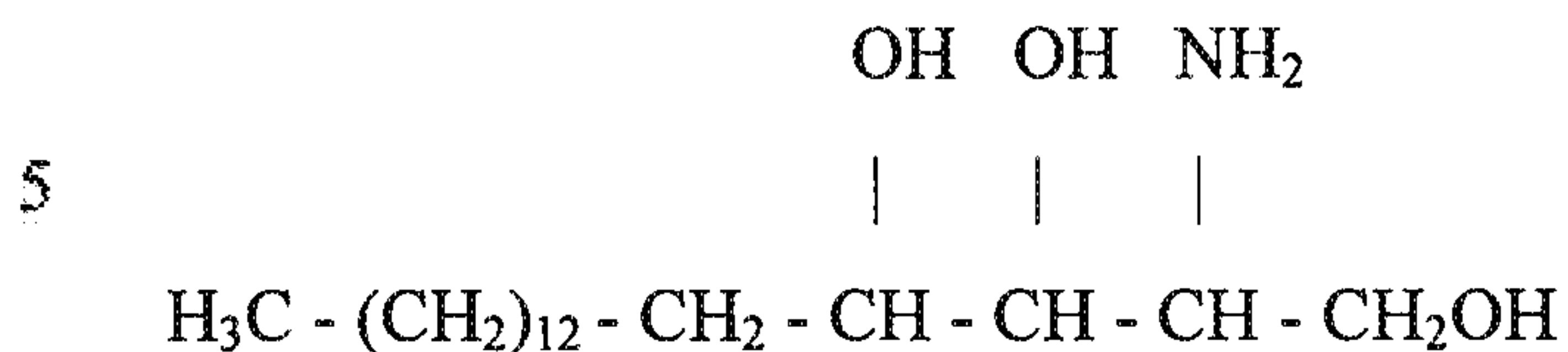
15 critical role in platelet aggregation and thrombosis and could aggravate cardiovascular disease. On the other hand the relatively high concentration of the metabolite in high-density lipoproteins (HDL) may have beneficial implications for atherogenesis. For example, there are recent suggestions that sphingosine-1-phosphate, together with other lysolipids such as

20 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

25 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.

30 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.

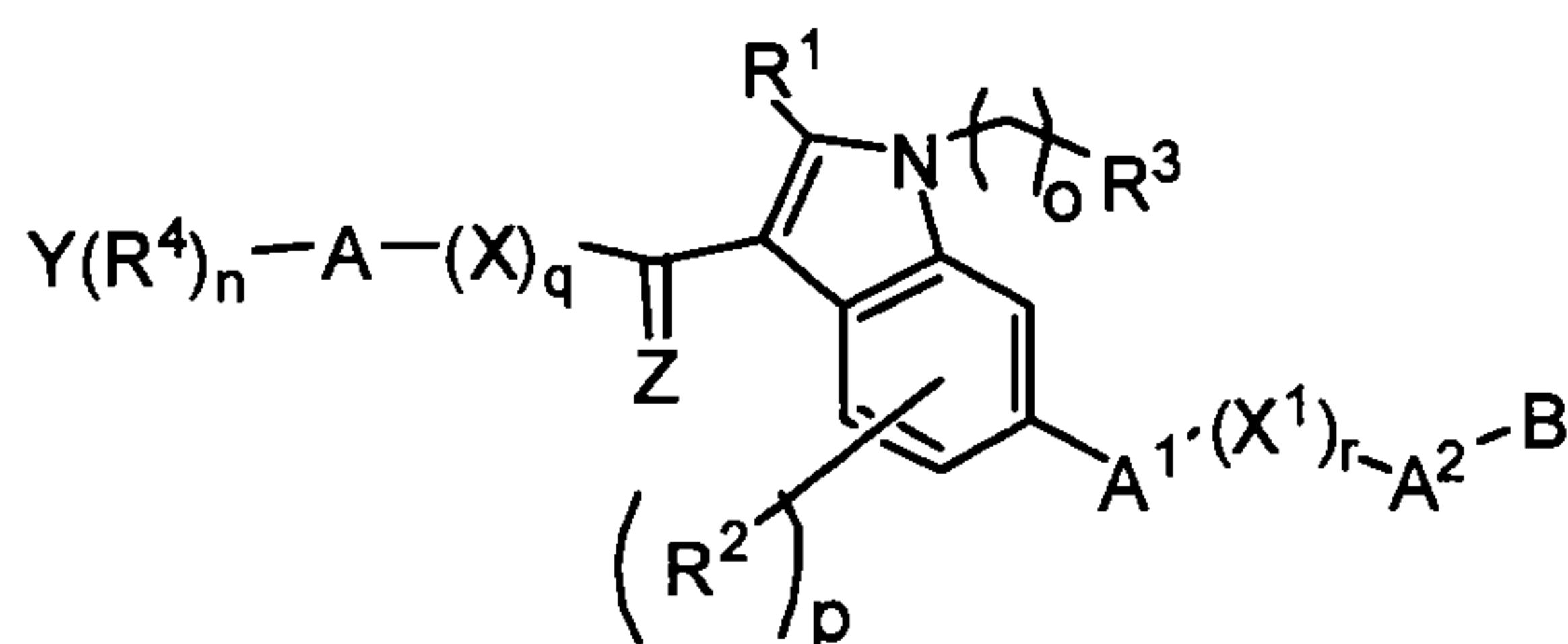
Also, compounds which are similar to certain sphingosine derivatives, but which are not reported as being ligands for the sphingosine receptors are reported in various patents and published patent applications. See for example, U.S. Patents 5,294,722; 5,102,901; 5,403,851 and 5,580,878. U.S. Patent Application 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

wherein:

10 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
15 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;

20

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

25

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;

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, A¹ and A² are independently selected from the group consisting of

10 (CH₂)_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, OR⁶, COOR⁷,

15 NR⁸R⁹, CONR⁸R⁹, COR¹⁰, CH=NOR¹¹, CH=NNR¹²R¹³ wherein R⁶, R⁷,

R¹⁰ and R¹¹ 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

20 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, R⁸, R⁹, R¹² and R¹³ 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

25 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 R⁸
and R⁹ and/or R¹² and R¹³, together, can form a divalent carbon radical
of 2 to 5 carbons to form a heterocyclic ring with nitrogen, wherein any of
R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² or R¹³ may be substituted with one or more
5 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
10 carbocyclic or heterocyclic group B may be bonded to A² at any position,
or a pharmaceutically acceptable salt of said compound.

15

The aryl group is a carbocyclic aryl or heterocyclic aryl group wherein said
20 carbocyclic 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,
25 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 C₁ to C₁₂ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, halo, C₁ to C₁₂ haloalkyl, hydroxyl, C₁ to C₁₂ alkoxy, C₁ to C₁₂ alkylcarbonyl, formyl, oxycarbonyl, carboxyl, C₁ to C₁₂ alkyl carboxylate, C₁ to C₁₂ alkyl amide, aminocarbonyl, amino, cyano, diazo, 5 nitro, thio, sulfoxyl, or sulfonyl groups.

Preferably Z is O.

10 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.

15 Preferably, A is CH₂.

Preferably, X is NH.

Preferably, n is 0 or an integer of 1 or 2 and R⁴ is fluoro.

20 Preferably, R¹ is i-propyl.

Preferably, R³ is selected from the group consisting of phenyl, which may be substituted with one or two fluoro groups, and pyridyl.

25 Preferably, p is 0.

Preferably, A¹ and A² are absent.

Preferably, B is OR⁶ or COOR⁷.

30 Preferably, X is O, r is 1, A¹ is absent, A² is (CH₂)_v, wherein v is 1 or 2, and B is OR⁶ or NR⁸R⁹

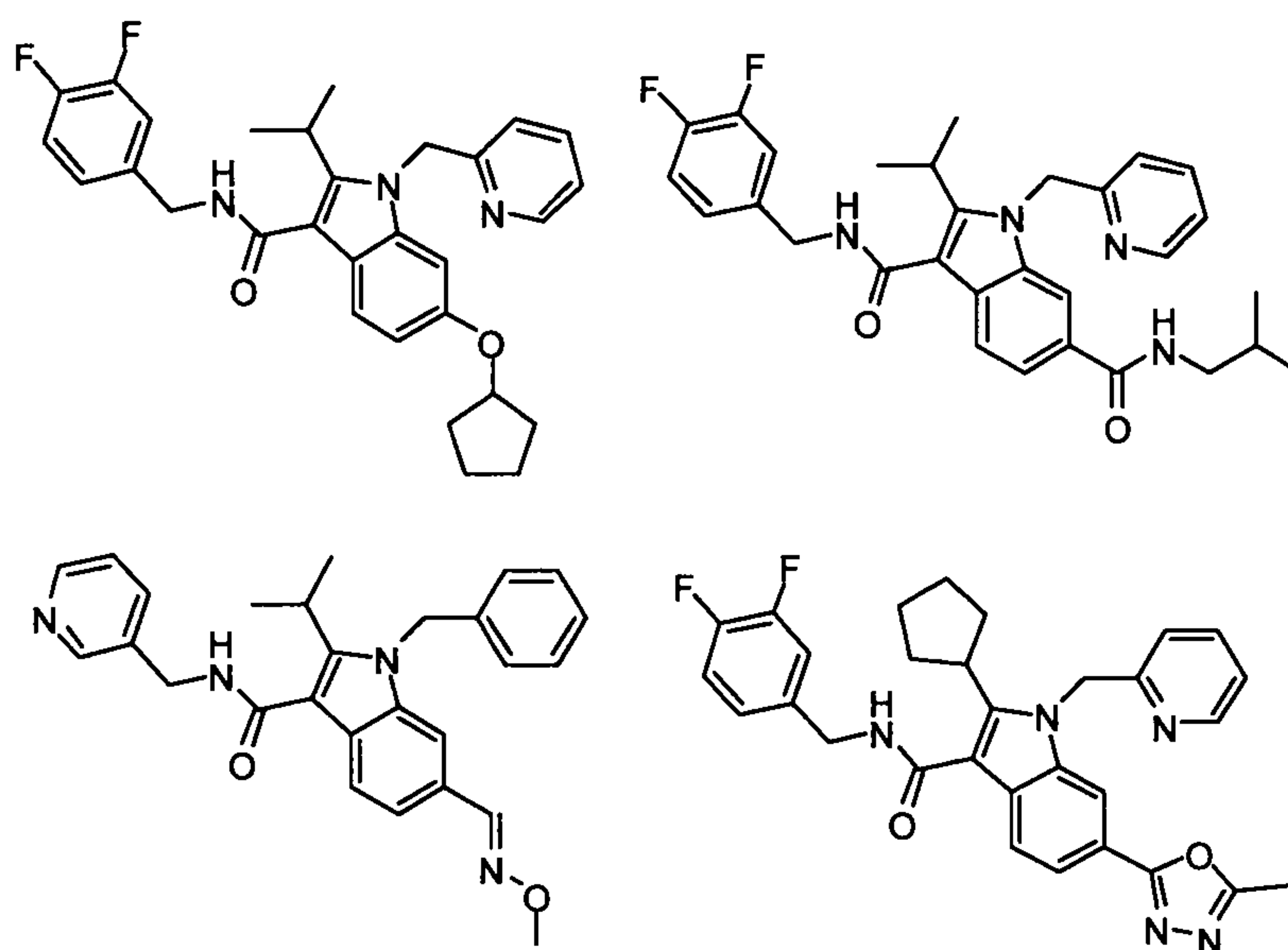
and R⁶, R⁸ and R⁹ are methyl.

Preferably, B is $\text{CR}^{10}=\text{NOR}^{11}\text{R}^{10}$ 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.

- 5 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



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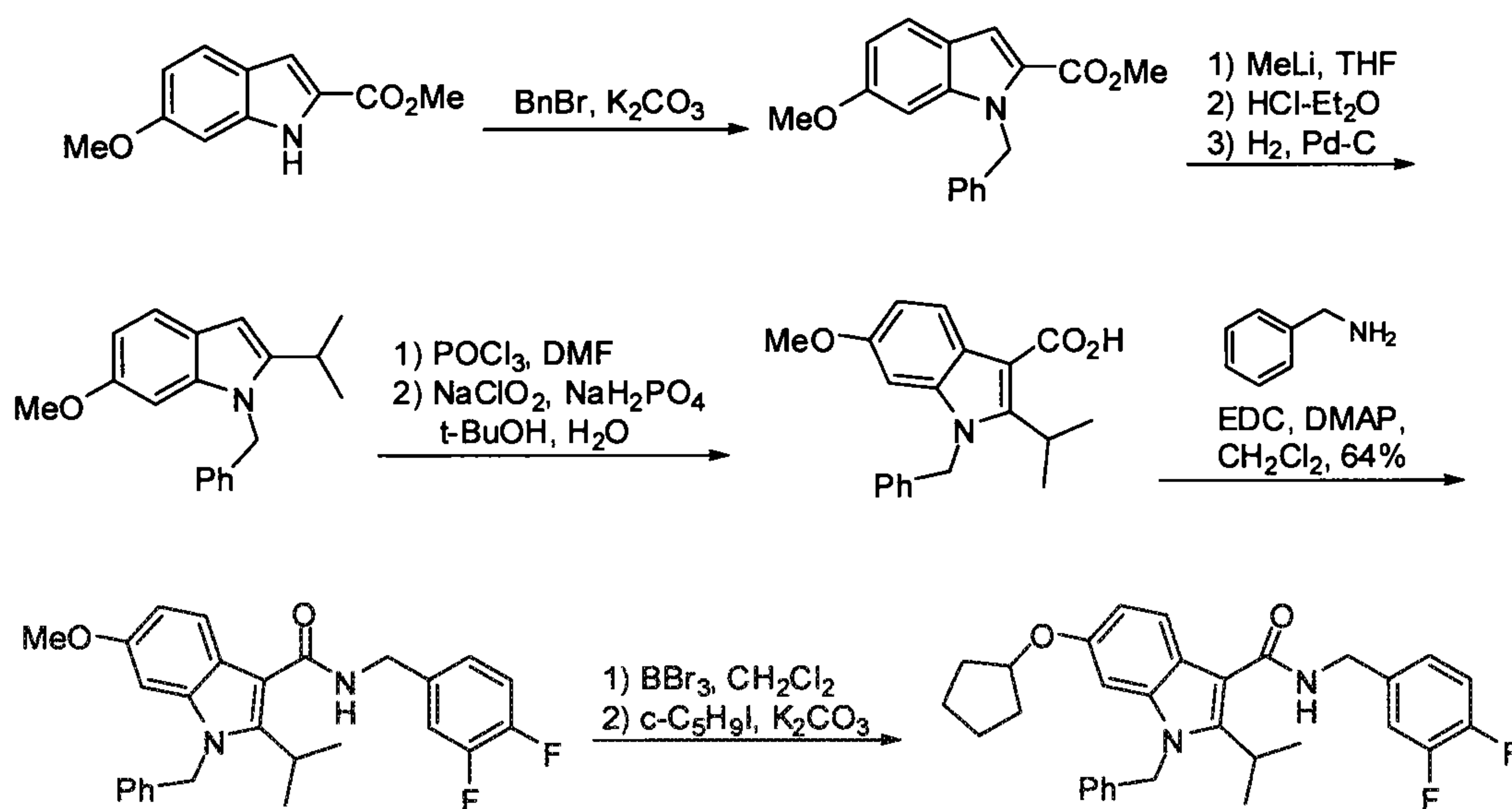
Some compounds within the scope of the invention may be prepared as depicted in Scheme 1. Thus, methyl 6-methoxyindole-2-carboxylate is treated with an electrophilic compound (e.g. benzyl bromide) in the presence of an weak base (e.g. potassium carbonate) to produce an N-alkylated indole (e.g. methyl 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*'-ethylcarbodiimide (EDC) to produce a 6-methoxyindole-3-carboxamide derivative (e.g. 3,4-difluorophenylmethyl 6-

15

20

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
 5 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

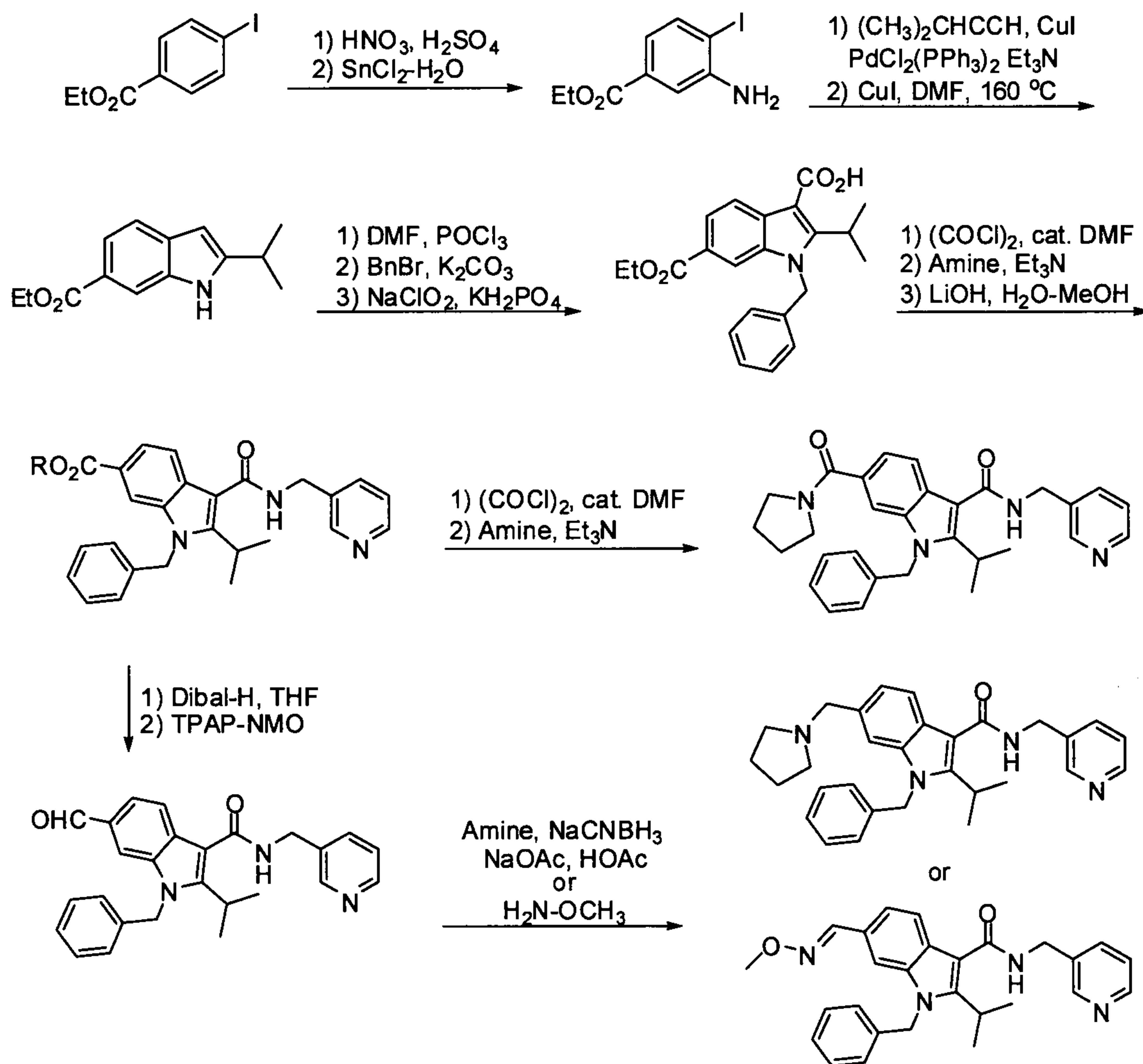


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Many other compounds within the scope of the invention may be prepared as depicted in Scheme 2. Thus, ethyl 4-iodobenzoate may be nitrated in the 3-position with fuming nitric acid and the resulting nitro compound reduced
 15 under mild conditions (e.g. $\text{SnCl}_2\text{-H}_2\text{O}$) 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
 20 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



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produce a 6-methoxyindole-3-carboxamide derivative (e.g. 3-pyridylmethyl 1-benzyl-6-carboethoxy-2-isopropylindole-3-carboxamide). The carboxylic acid

10 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

15 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-pyridylmethyl-1-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

5 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

10 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

15 specification have the following meanings:

"Me" refers to methyl.

"Et" refers to ethyl.

20

"tBu" refers to t-butyl.

"iPr" refers to i-propyl.

25

"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,

30 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
5 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, NO₂, halogen, dimethyl amino and SH.

"Alkenyl" refers to a straight-chain, branched or cyclic unsaturated hydrocarbon
10 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, NO₂, halogen, dimethyl amino and
15 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,
20 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, NO₂, halogen, dimethyl amino and SH.

"Alkoxy" refers to an "O-alkyl" group.
25

"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,
30 hydroxyl, SH, OH, NO₂, 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.

5

"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.

10

"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.

15

"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.

20

"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.

25

"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,

30

hydroxyl, phosphate, thiol, etc.

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

5

"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.

10

"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.

15

"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.

20

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.)

25

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

30

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

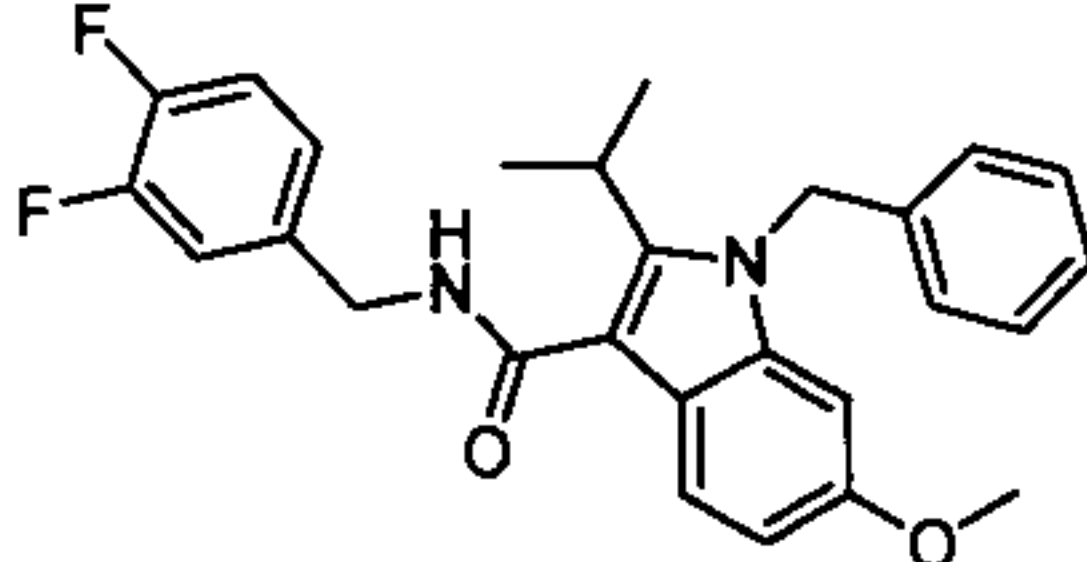
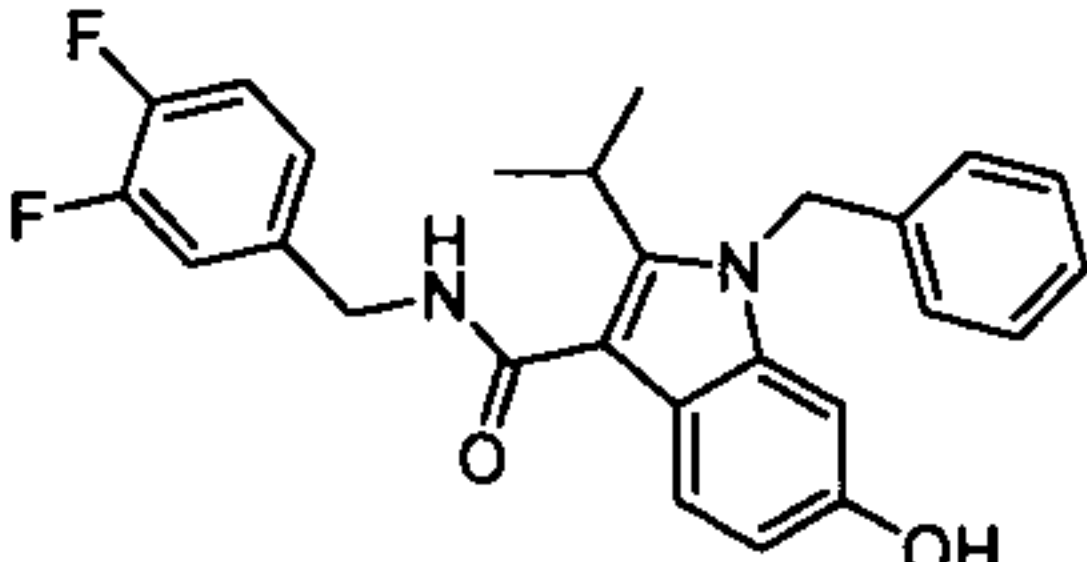
5 experiment, the cells were washed twice with Hank's Balanced Salt Solution supplemented with 20 mM HEPES (HBSS/Hepes buffer). The cells were then dye loaded with 2 µM Fluo-4 diluted in the HBSS/Hepes buffer with 1.25 mM Probenecid and incubated at 37°C for 40 minutes. Extracellular dye was

10 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

15 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. IC₅₀ values were determined through a linear regression

20 analysis using the Levenburg Marquardt algorithm.

Table 1

Compound Number	<u>Structure</u>	S1P3 IC₅₀ (% inh) Kb
7		560 nM (98)
8		3.1 µM (71)

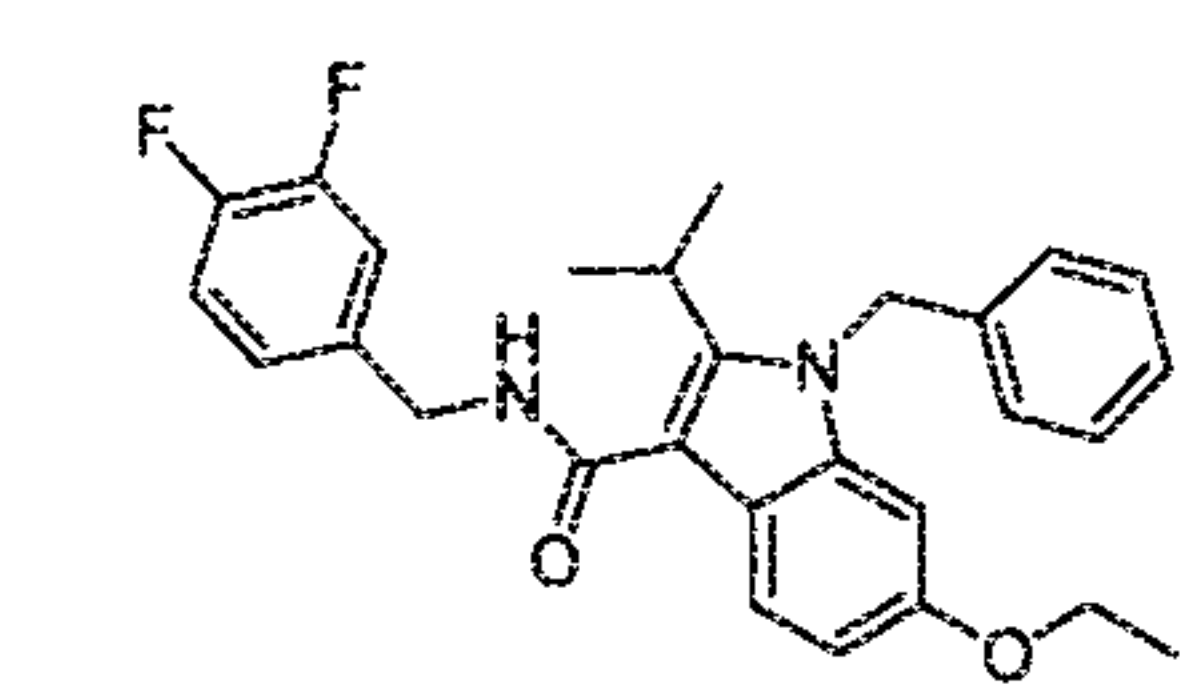
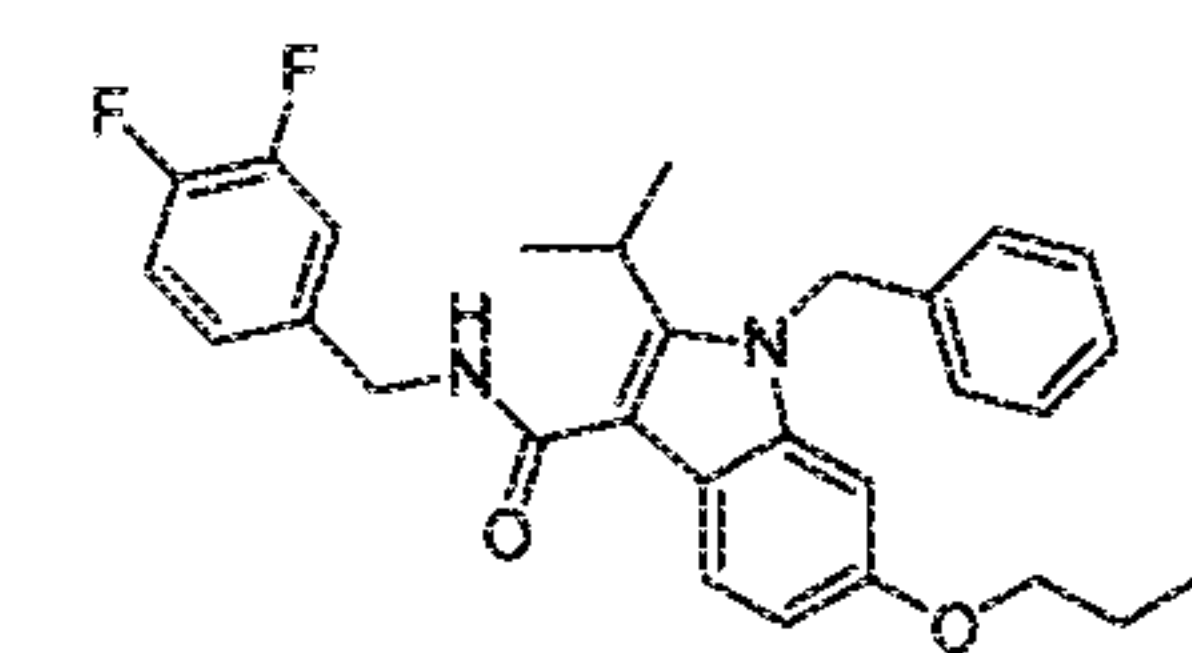
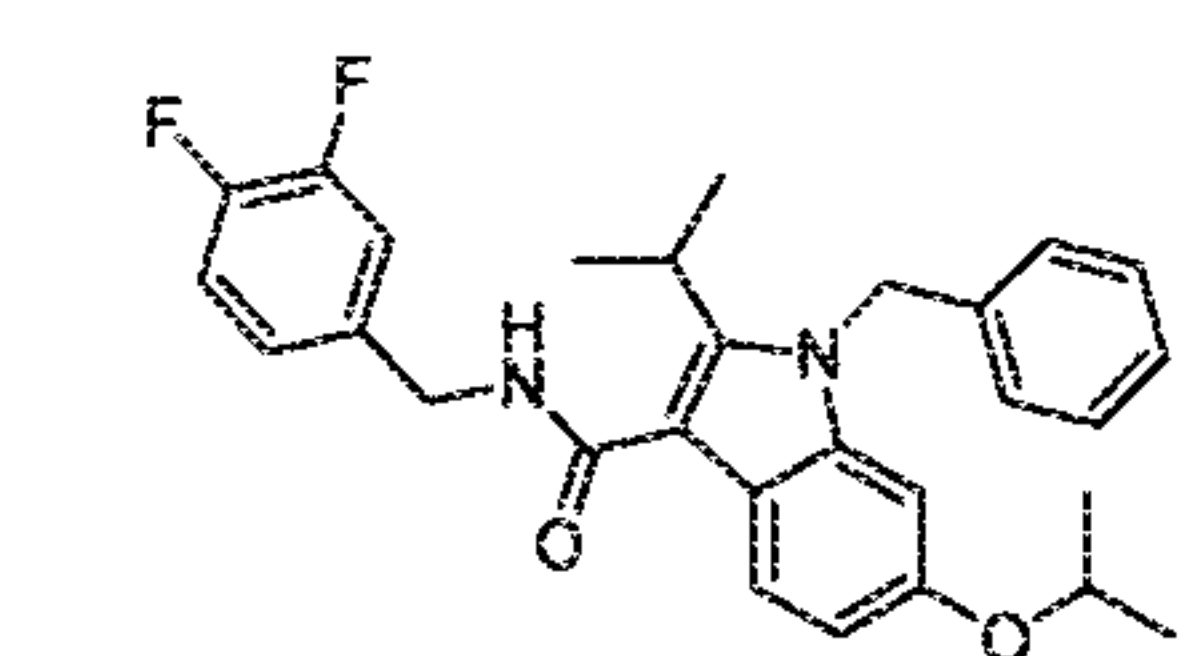
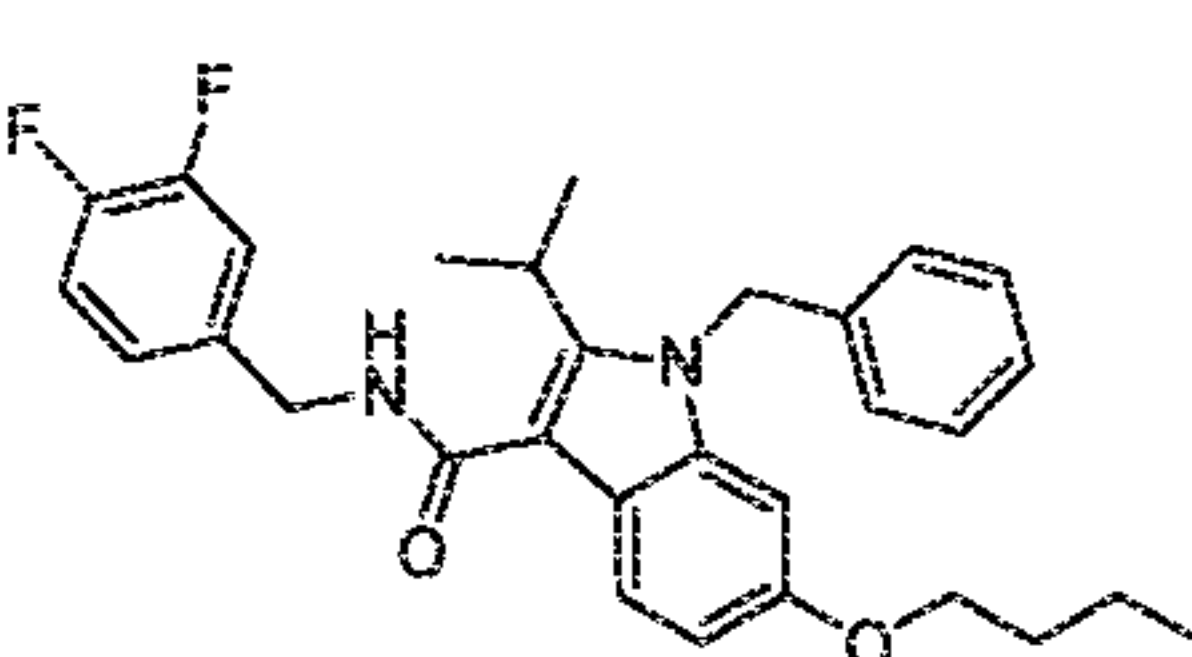
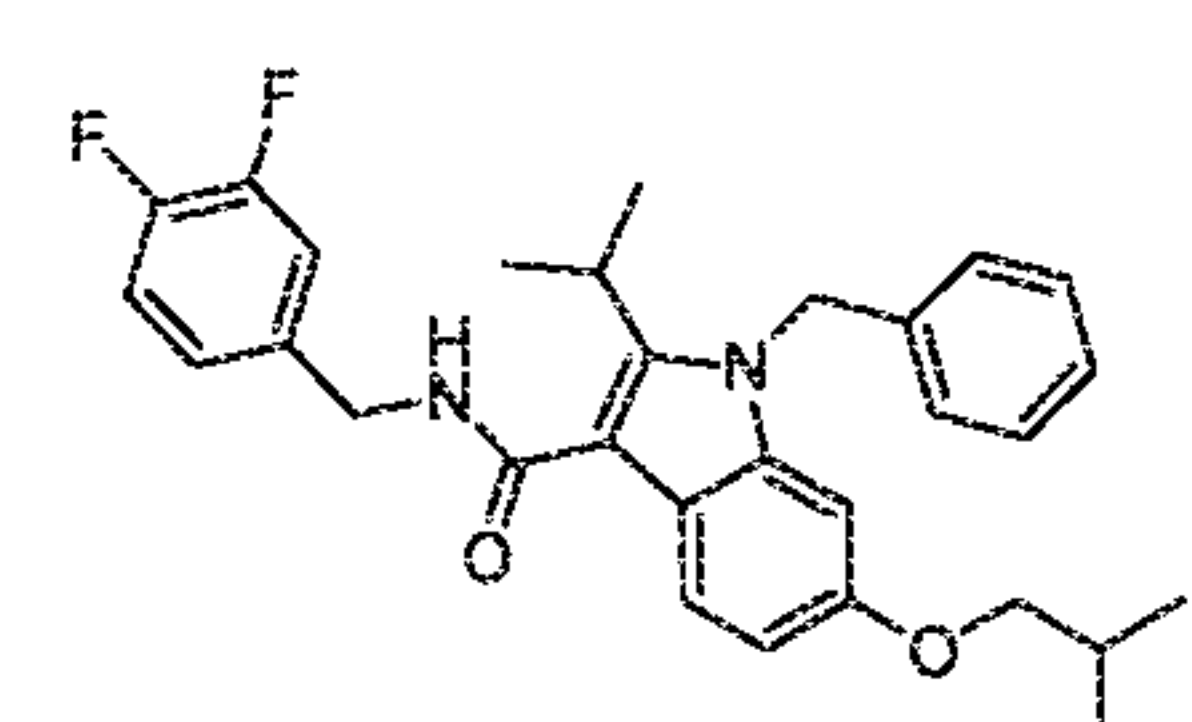
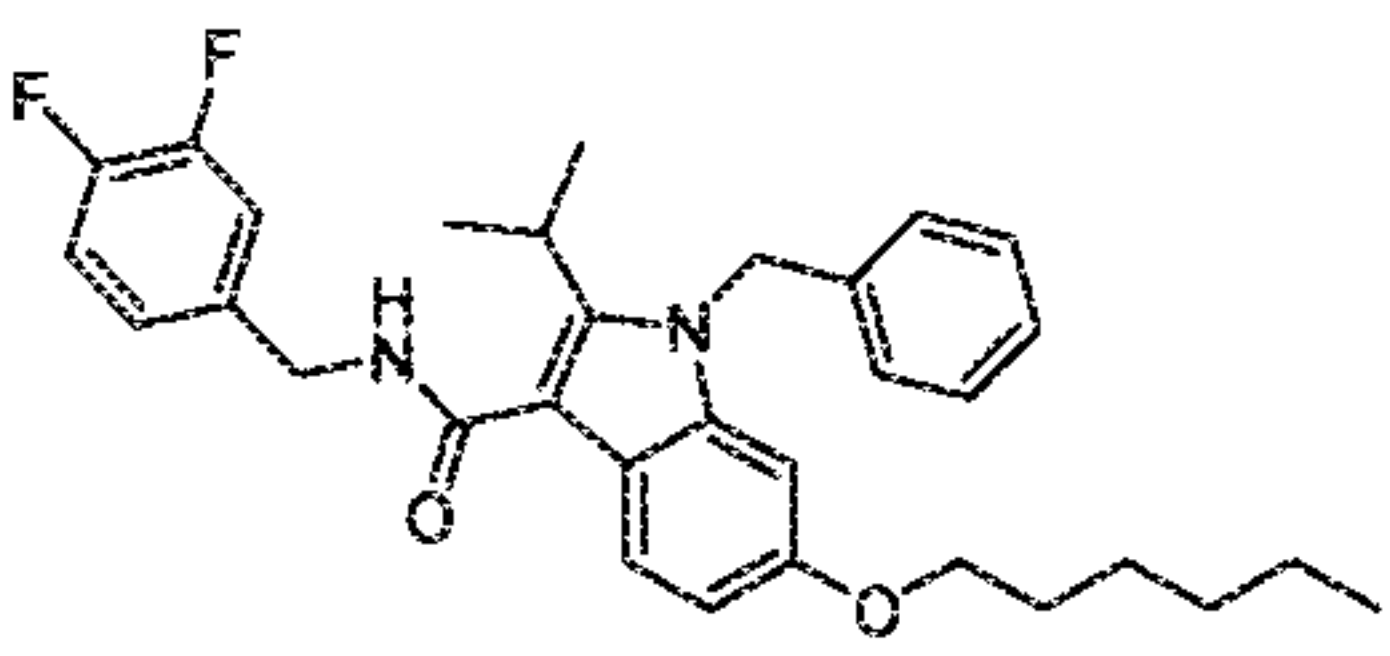
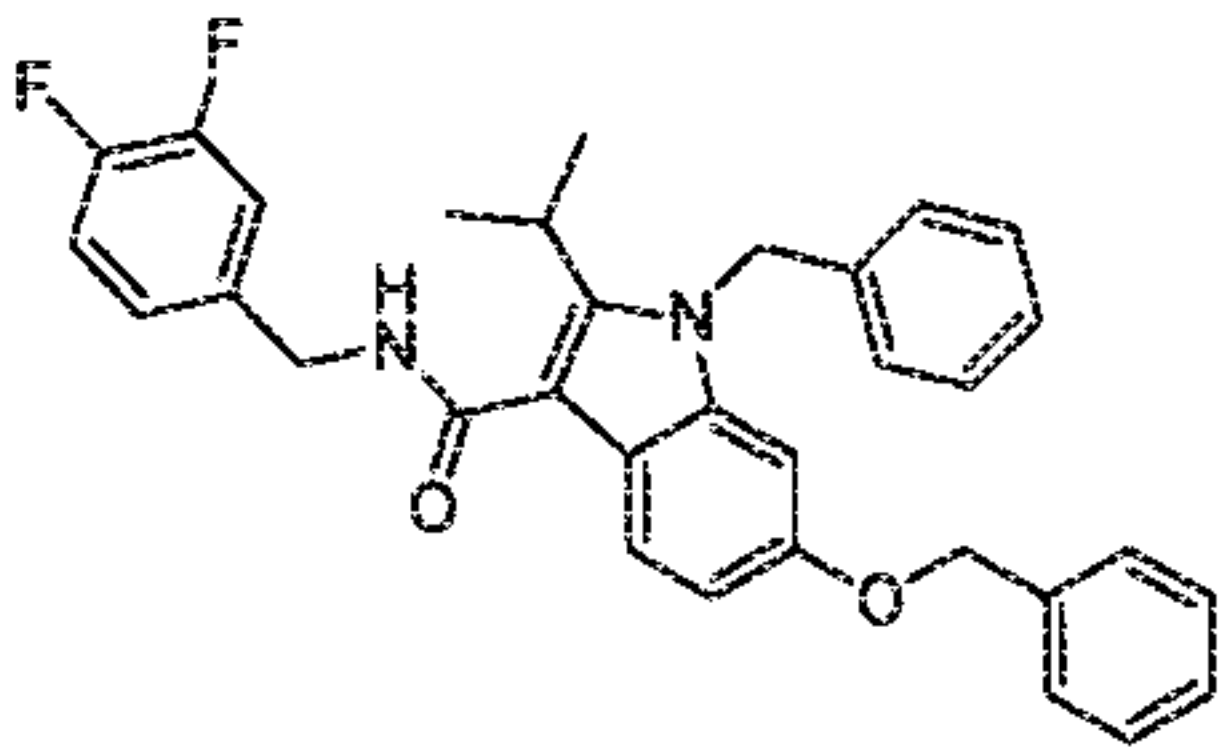
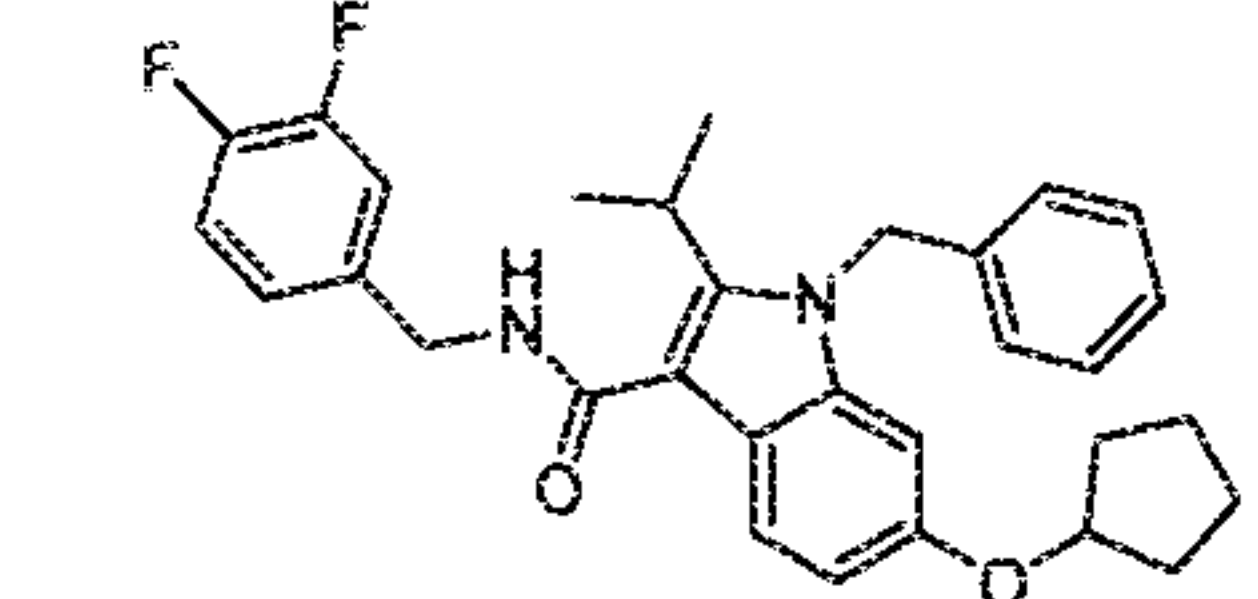
9		19 nM (100)
10		5 nM (100) 2 nM
11		6 nM (100) 2 nM
12		3 nM (100) ND
13		1.2 nM (100) 1.6 nM

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

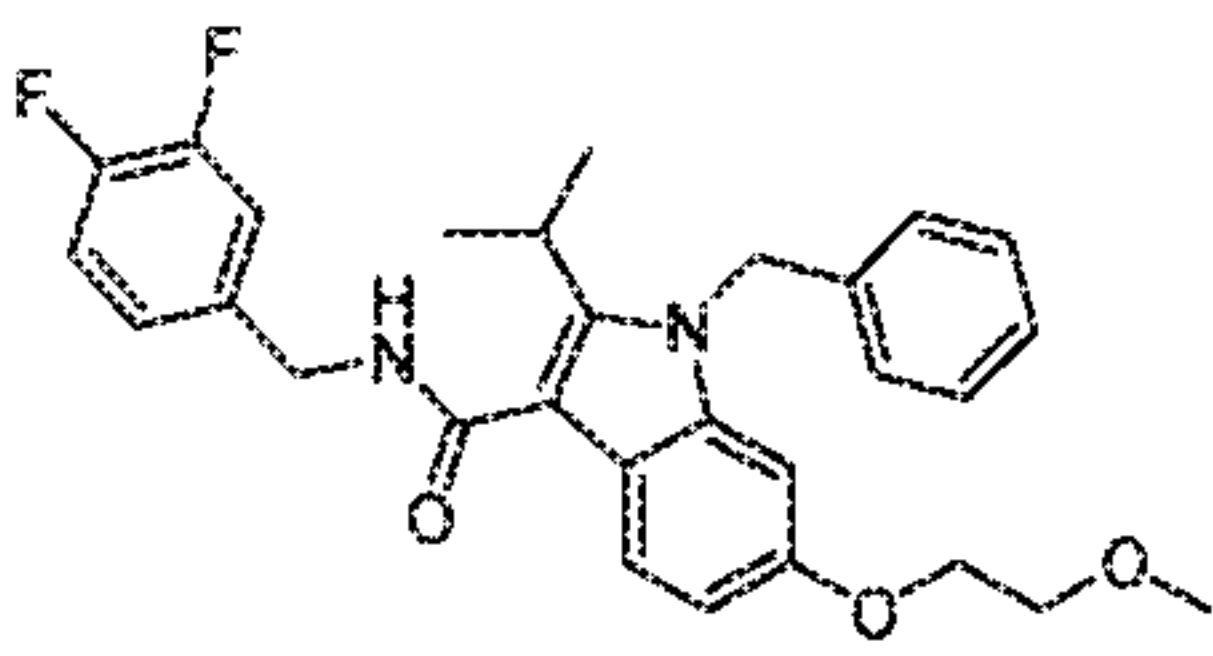
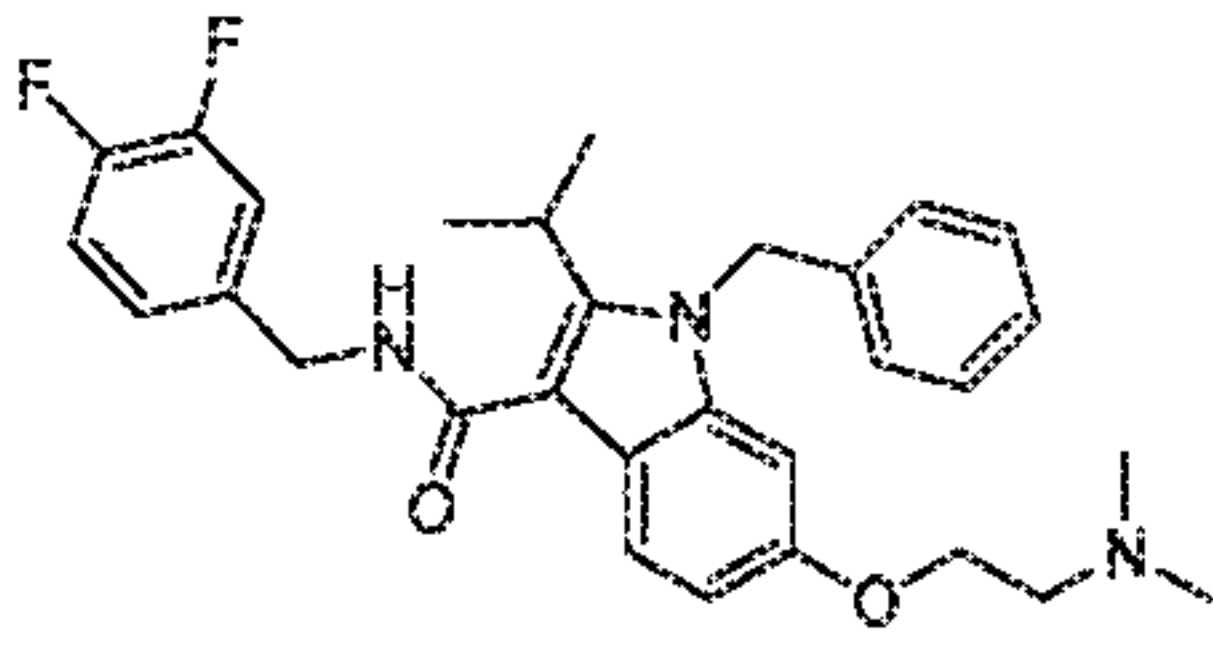
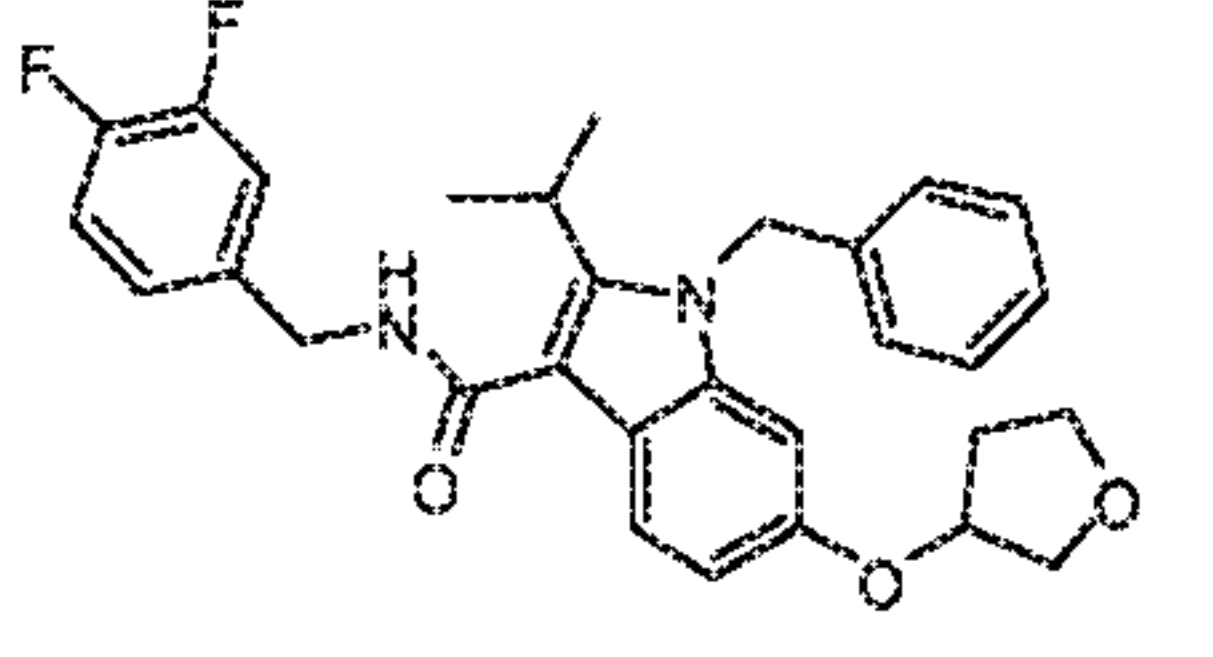
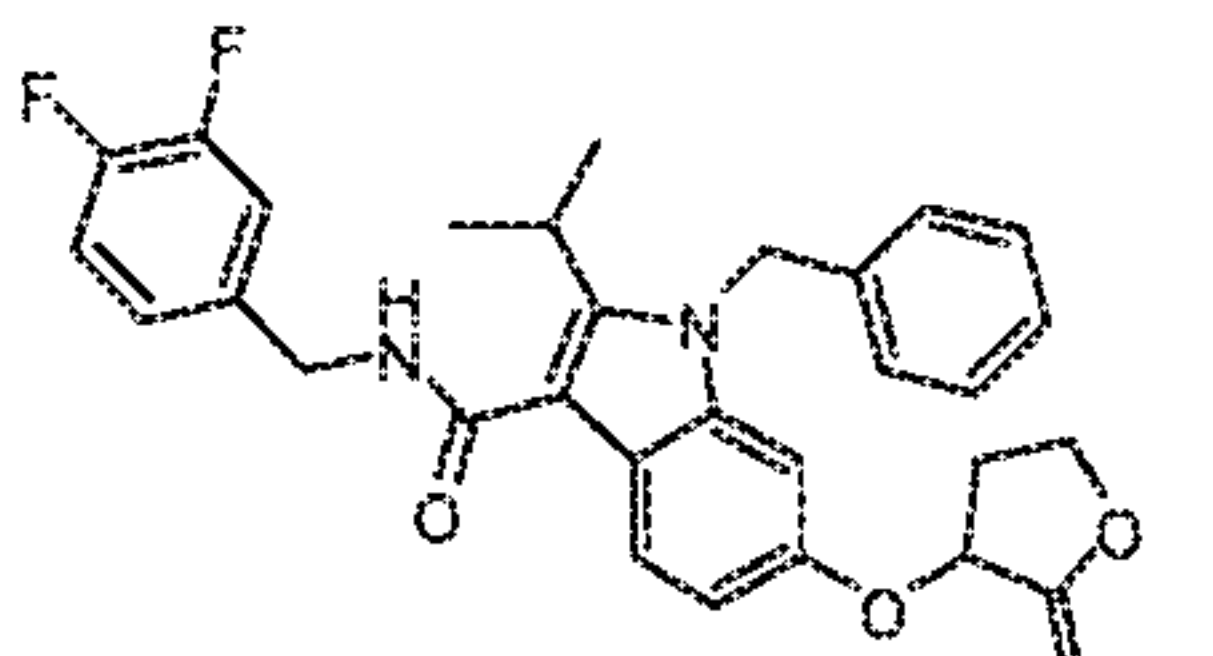
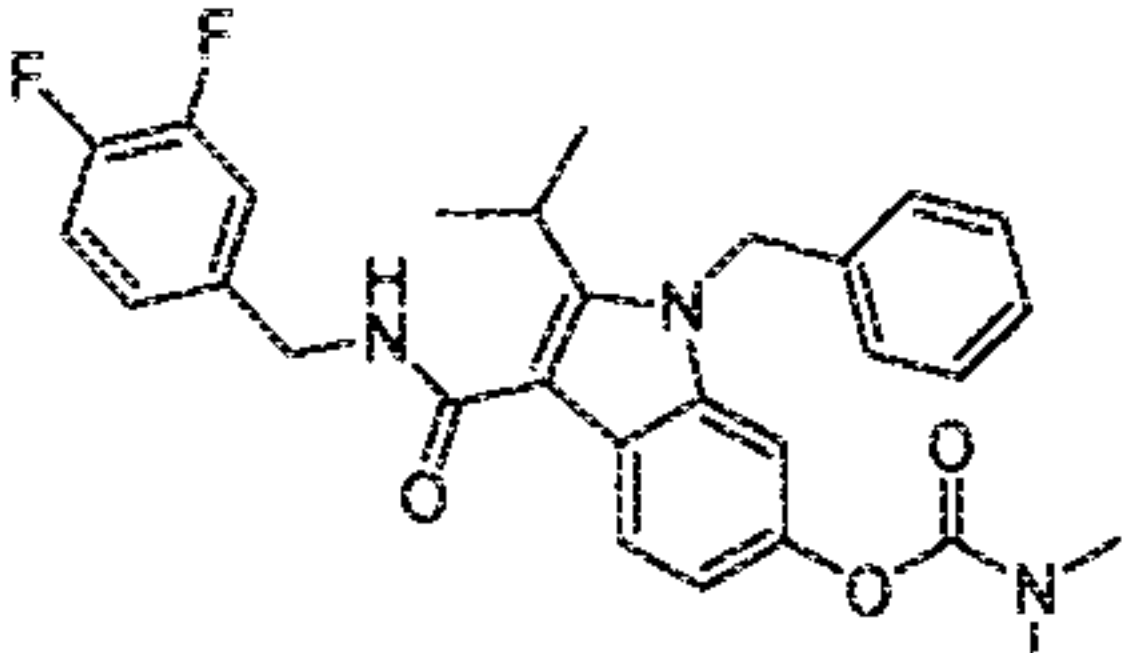
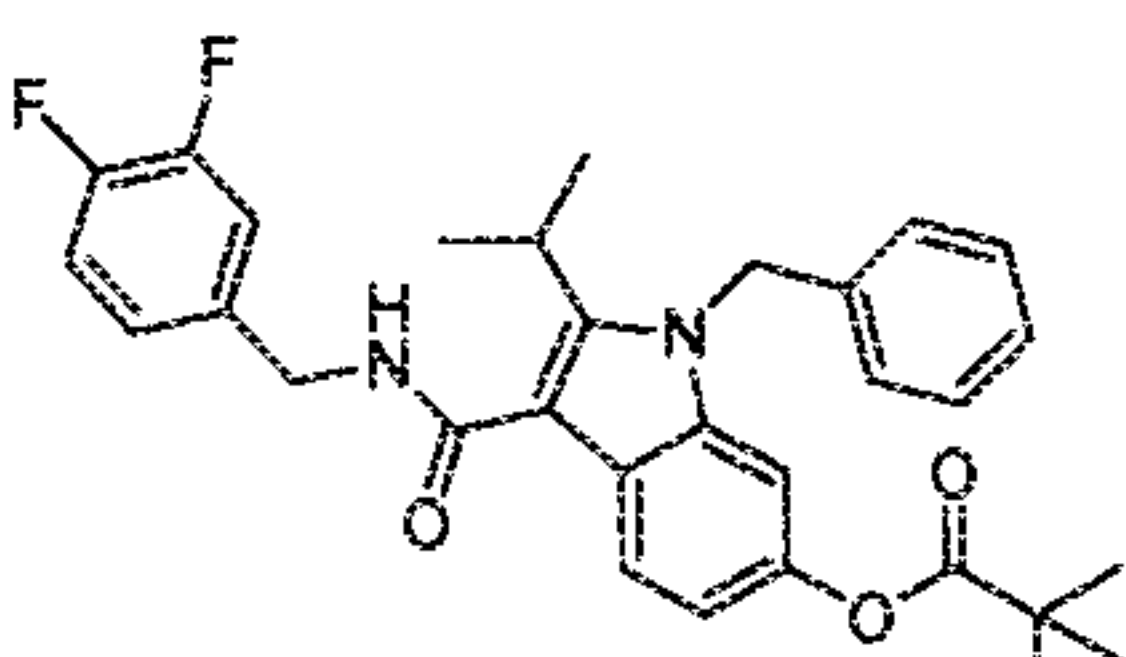
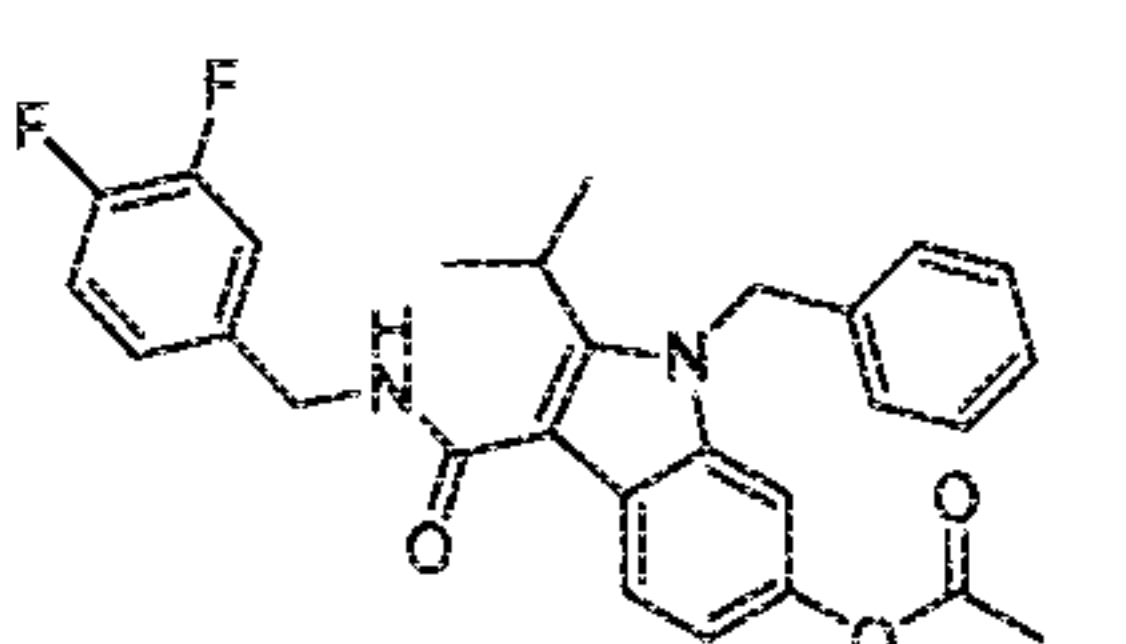
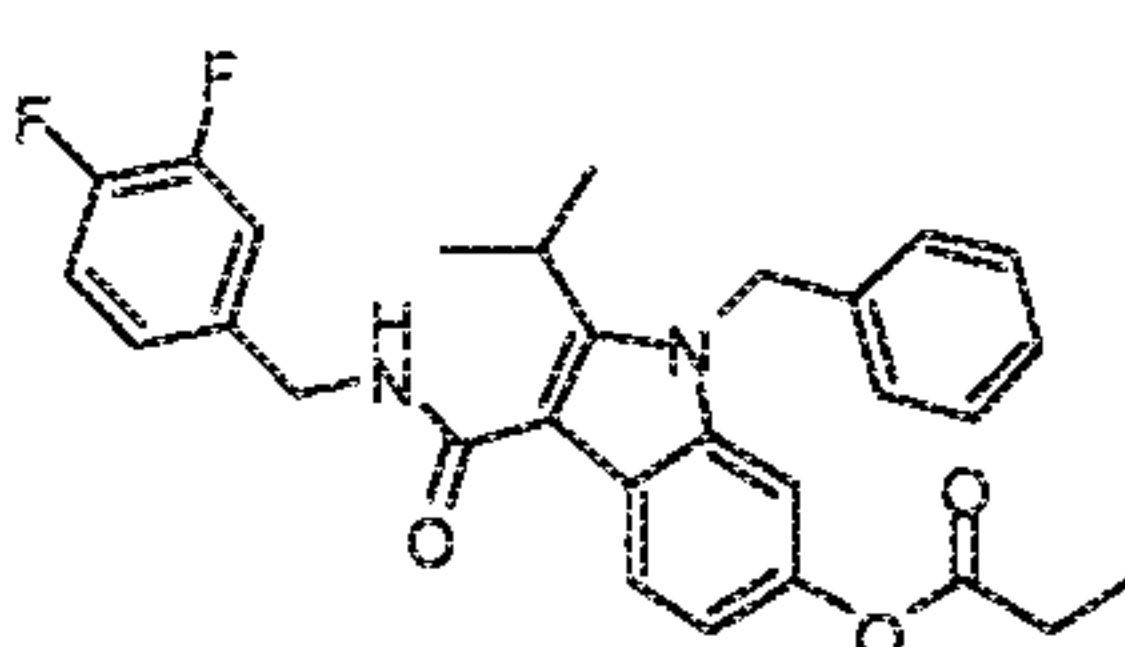
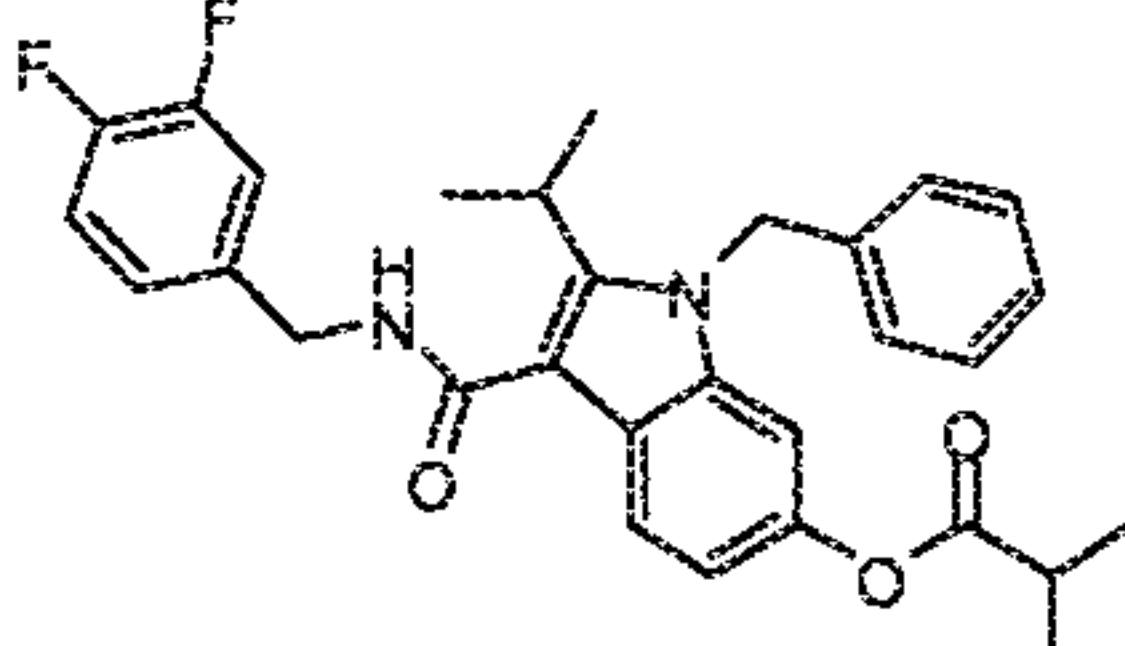
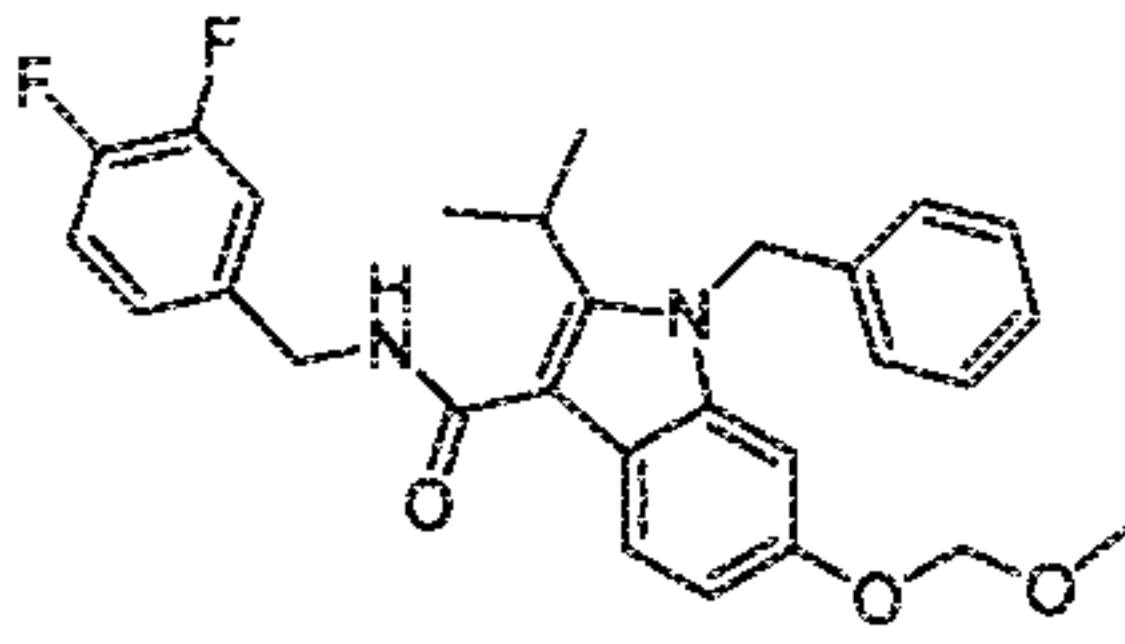
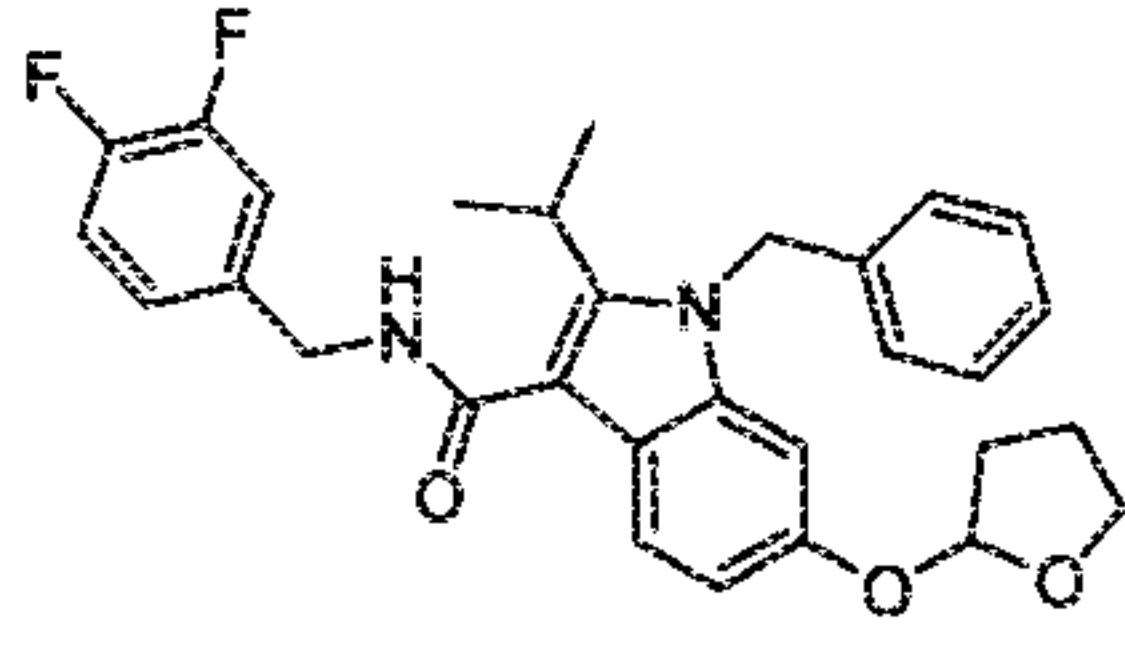
17		6.5 nM (99)
18		242 nM (94)
19		6 nM (100)
20		81 nM (100)

Table 1

5

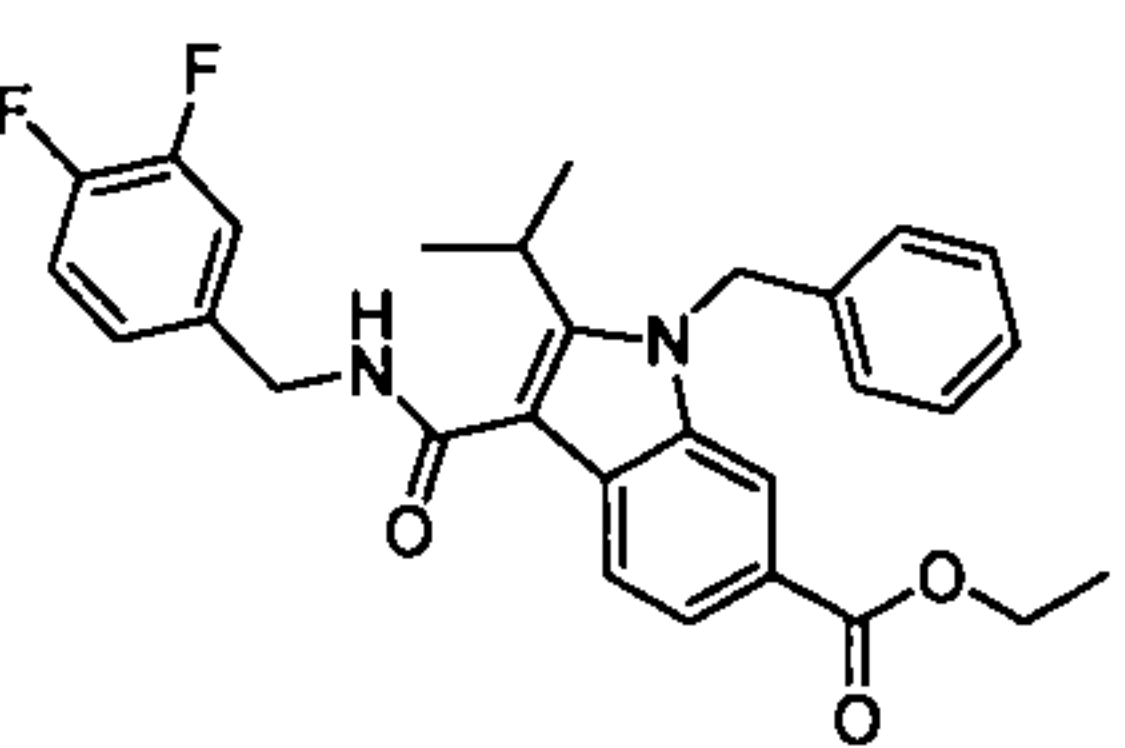
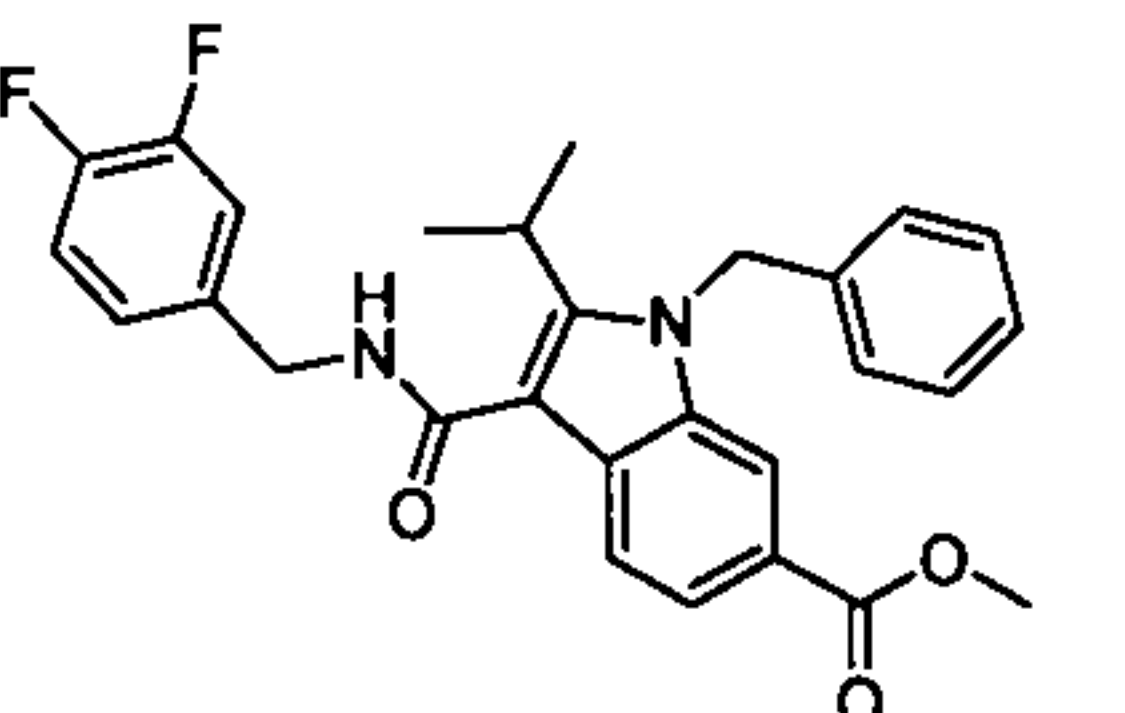
Compound Number	Structure	S1P3 IC ₅₀ (% inh) Kb
21		24 nM (99)
22		4 nM (99)
23		14 nM (100)

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

5 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

10

Compound Number	<u>Structure</u>	S1P3 IC₅₀ (% inh) Kb
		7 nM (100) 8 nM
		12 nM (100)

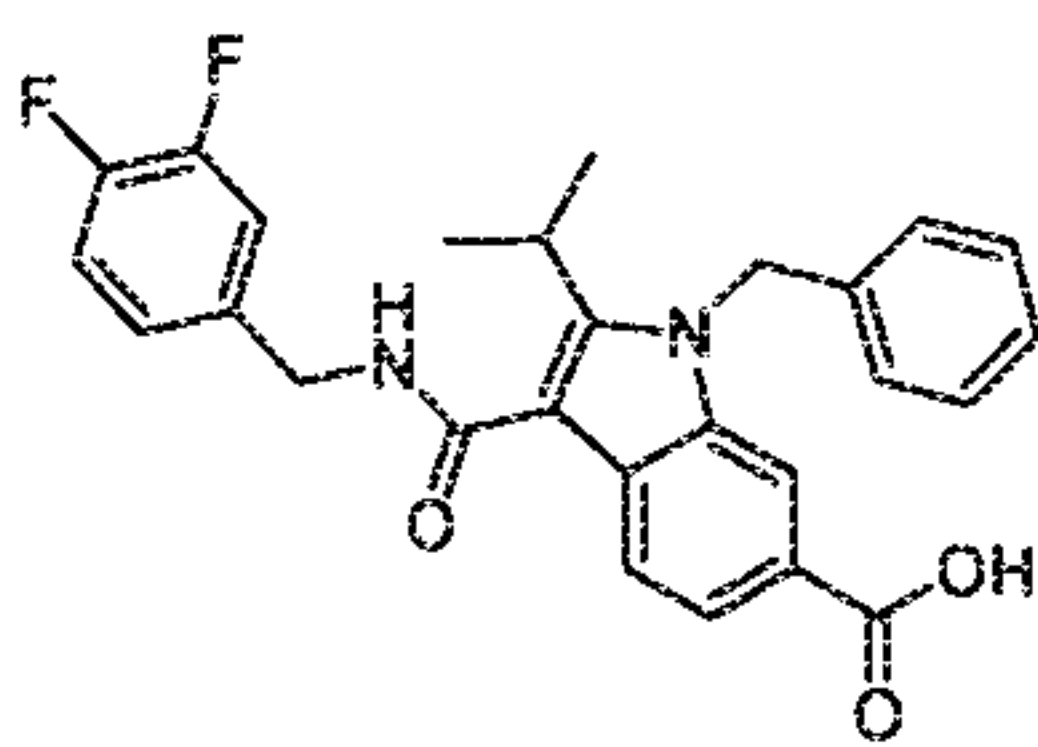
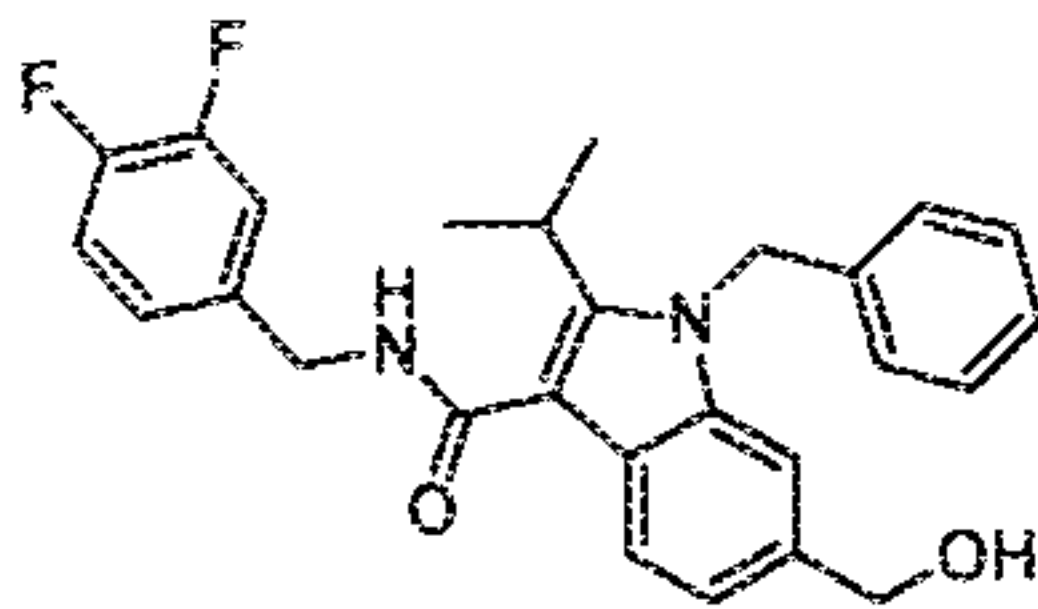
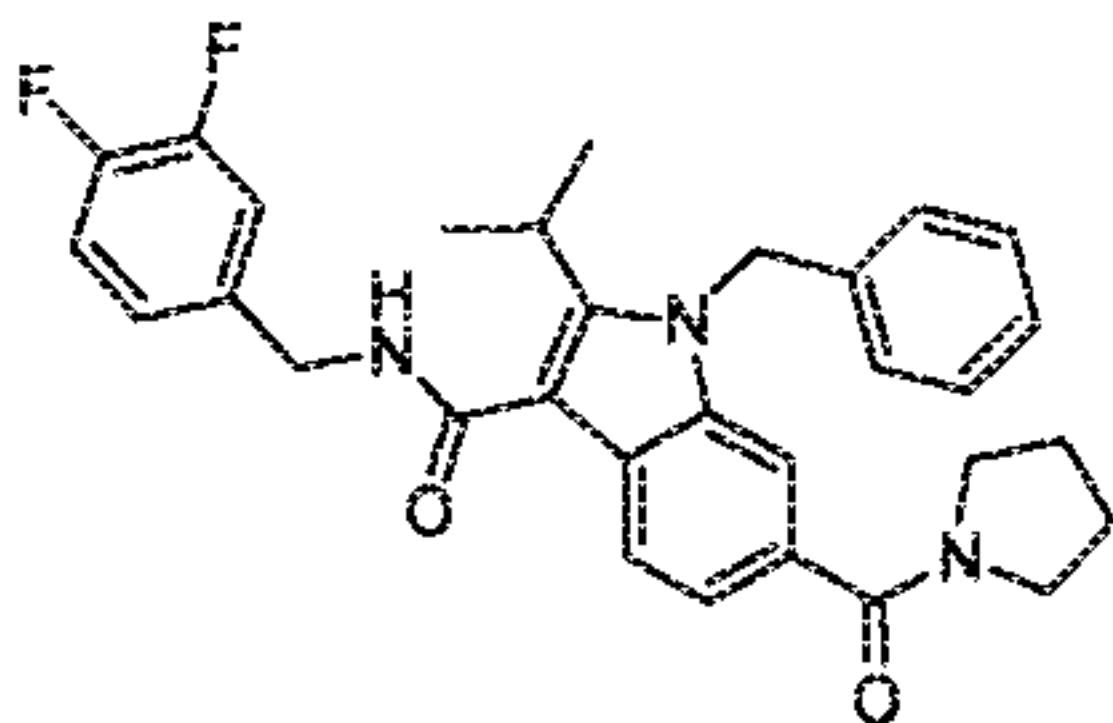
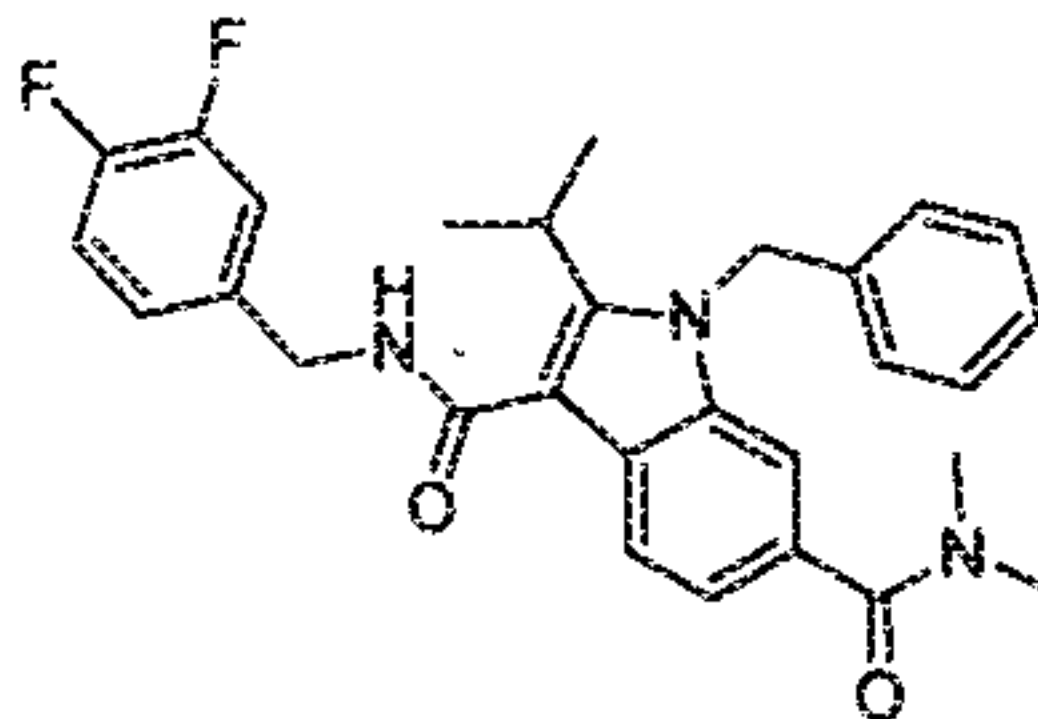
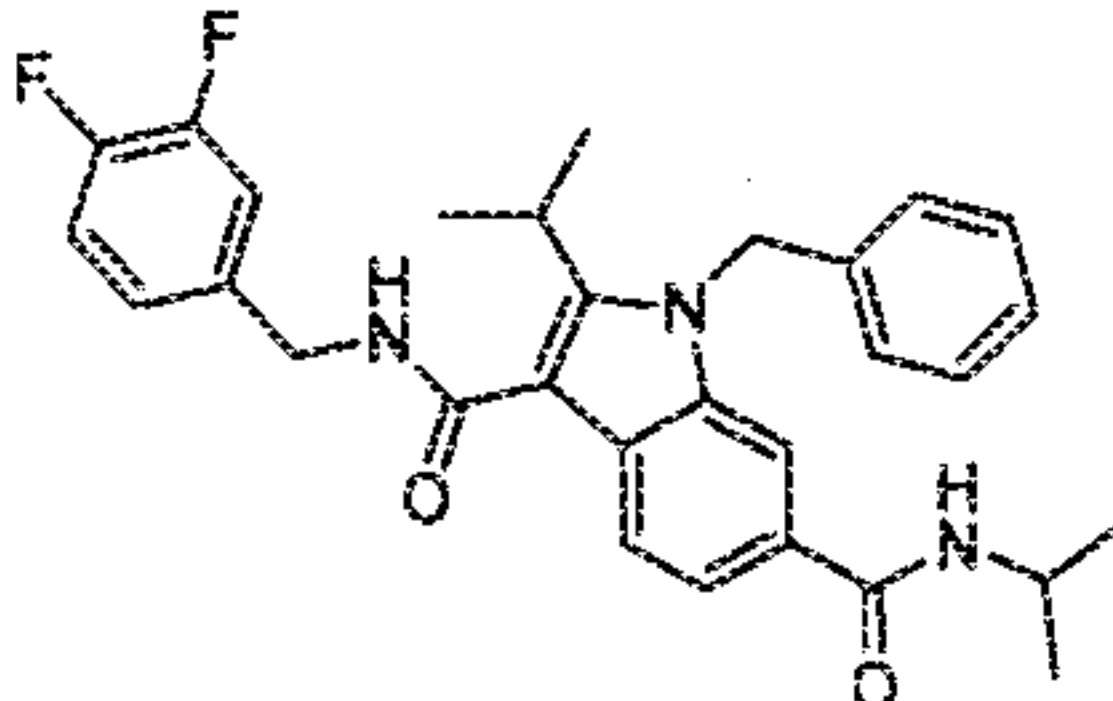
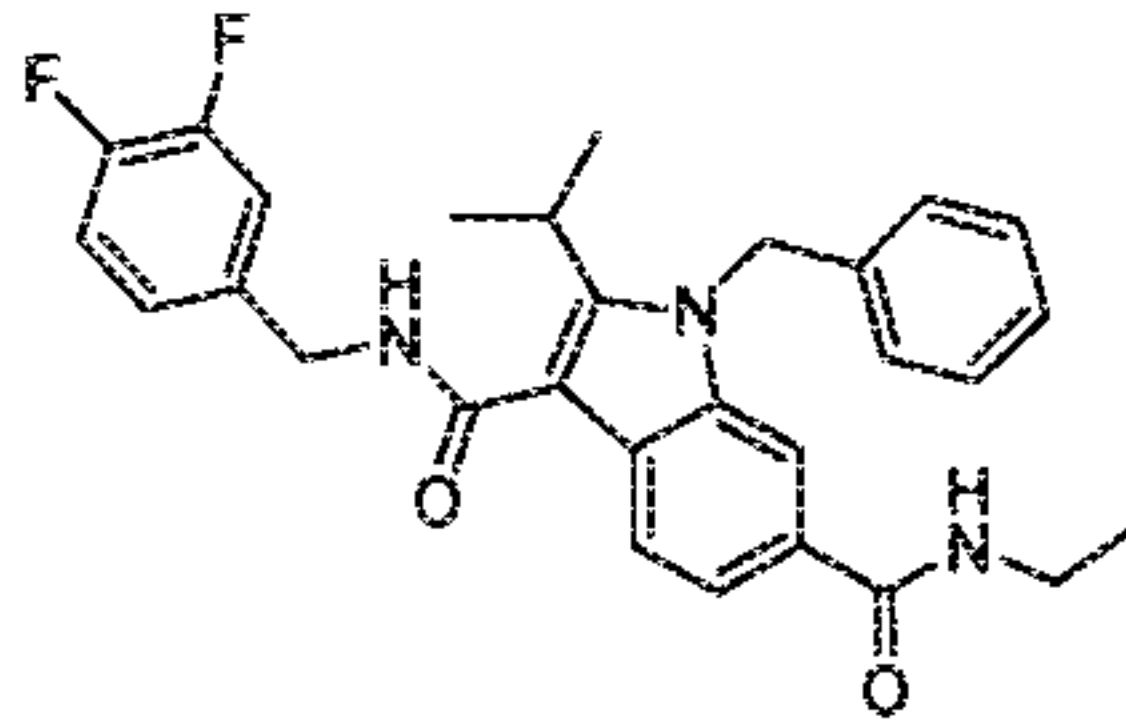
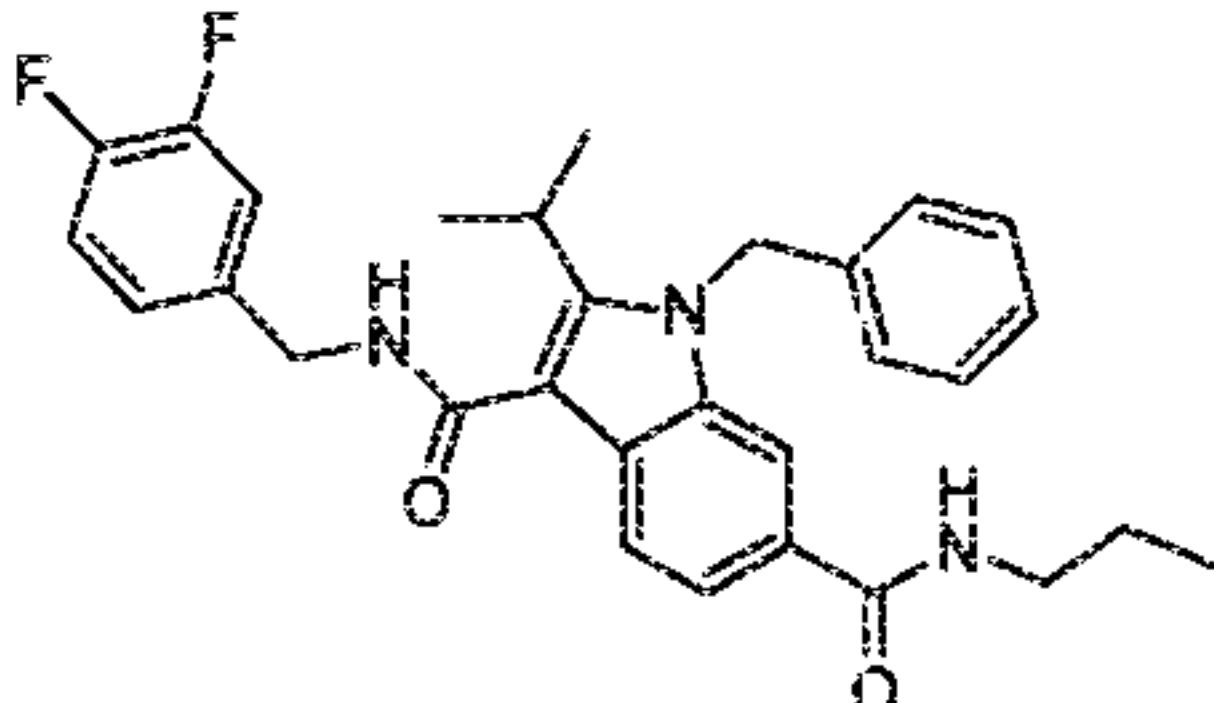
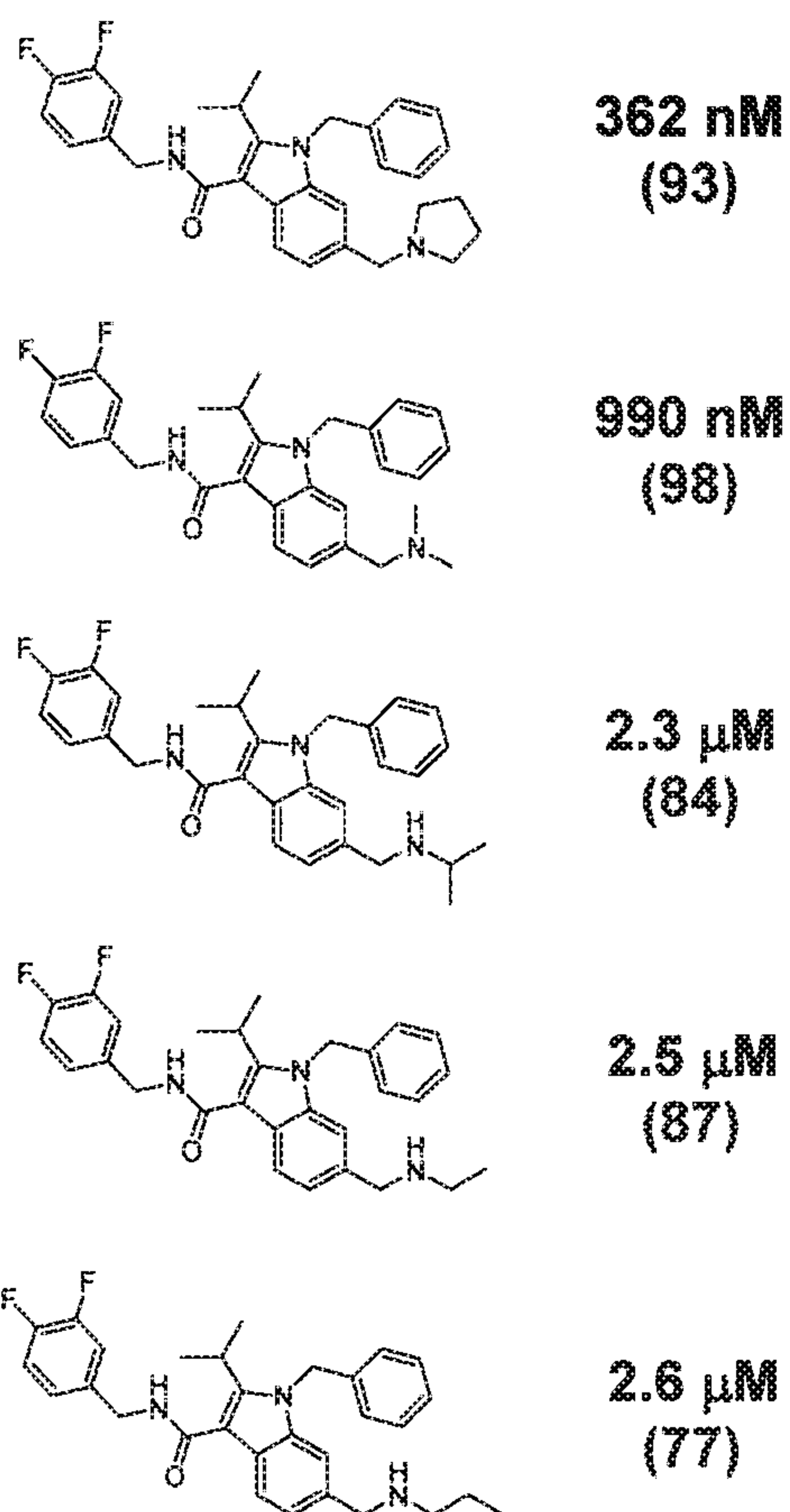
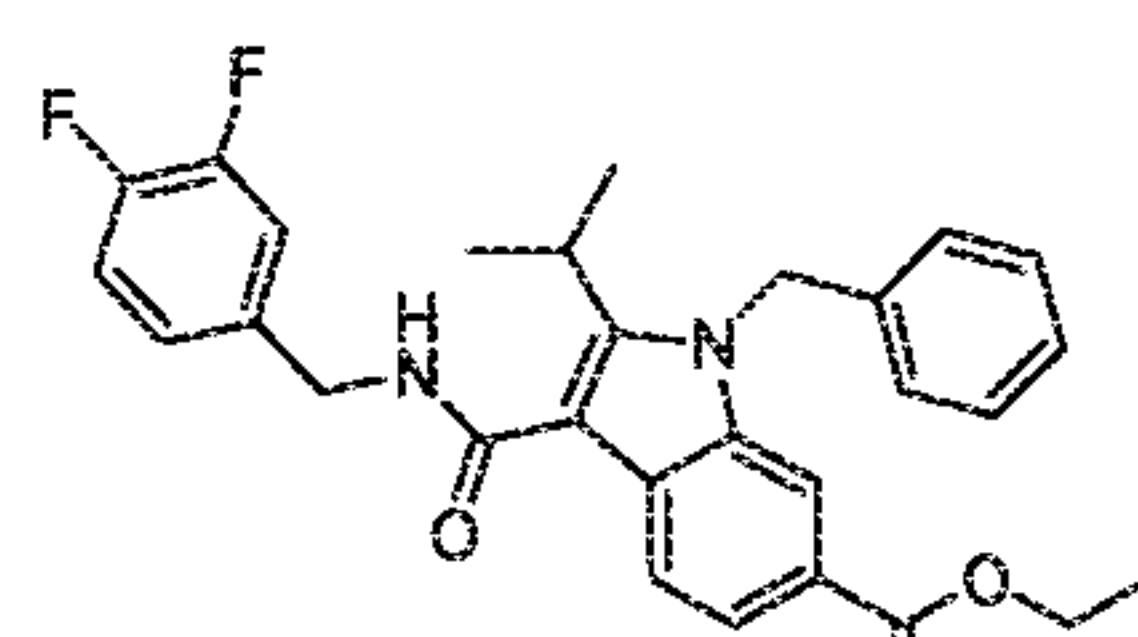
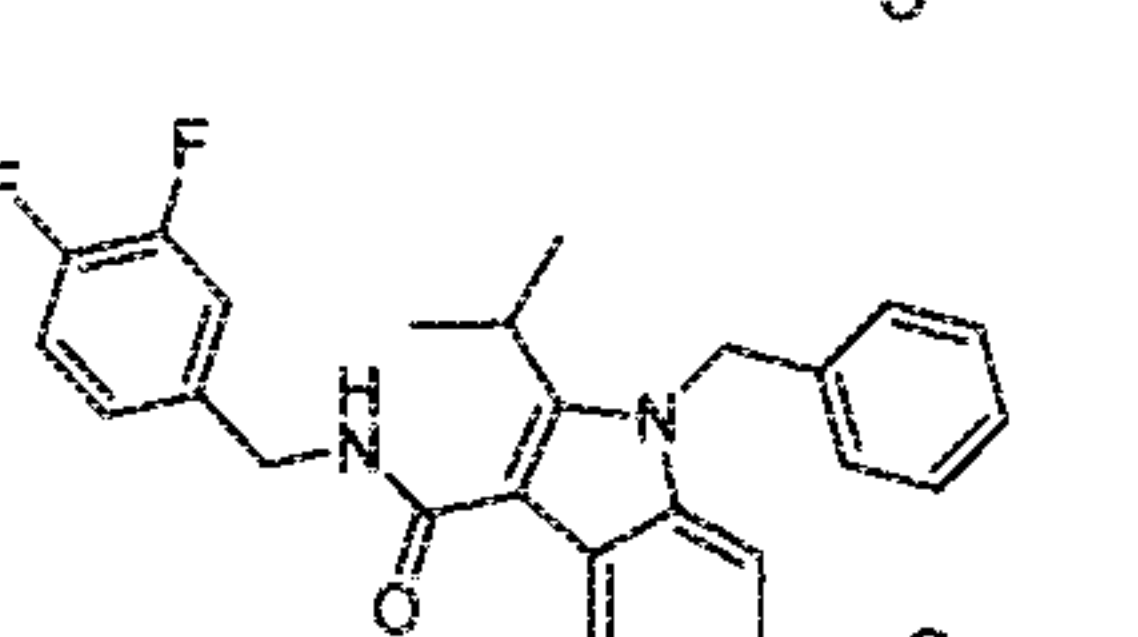
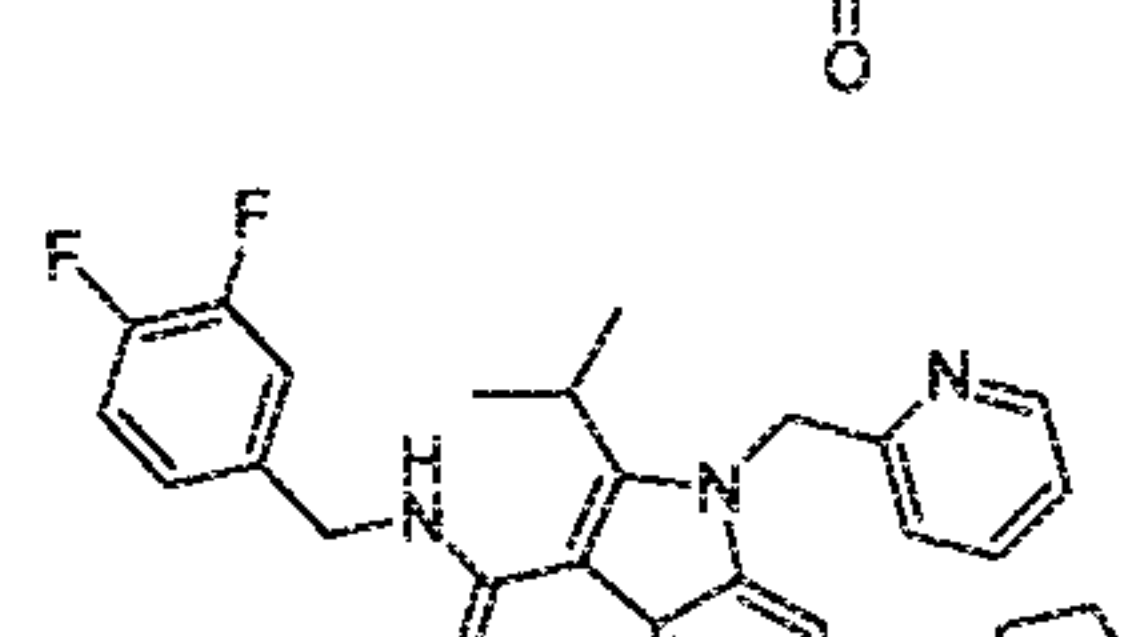
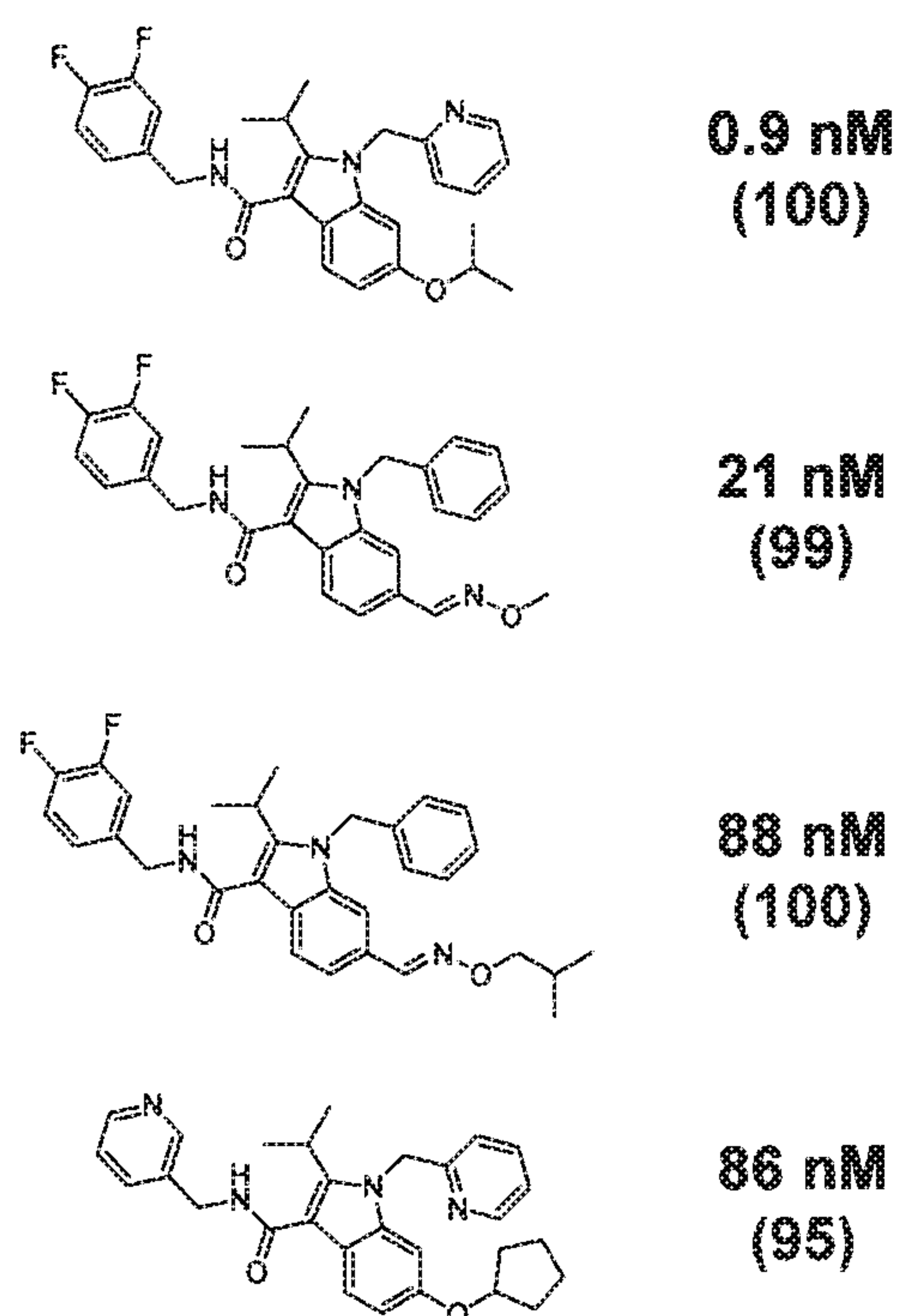
	>10 μM (40)
	2.0 μM (85)
	170 nM (100)
	197 nM (100)
	634 nM (100)

Table 1B

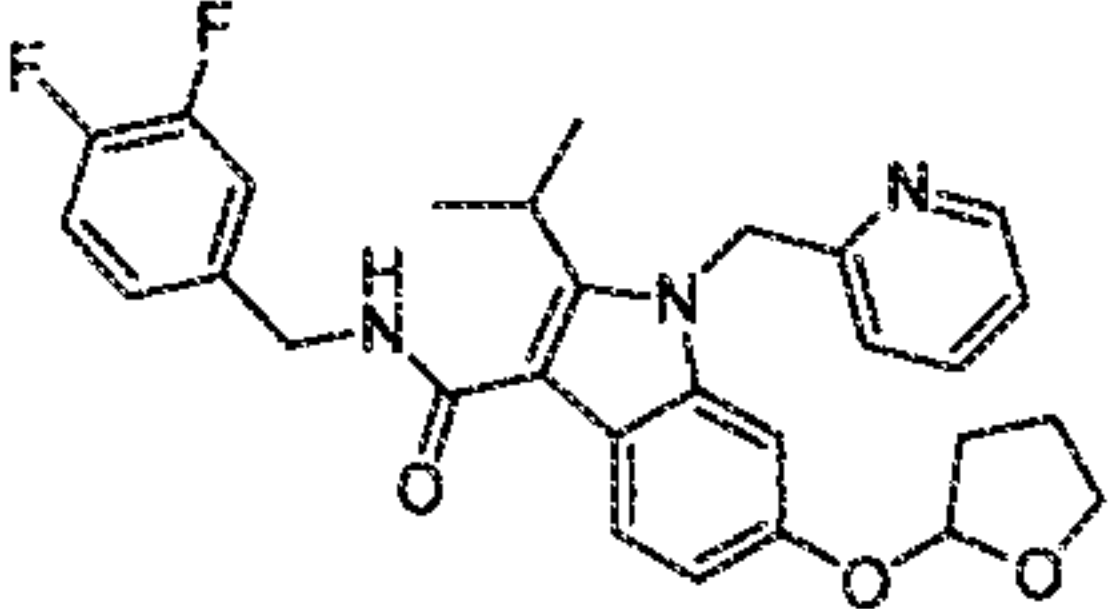
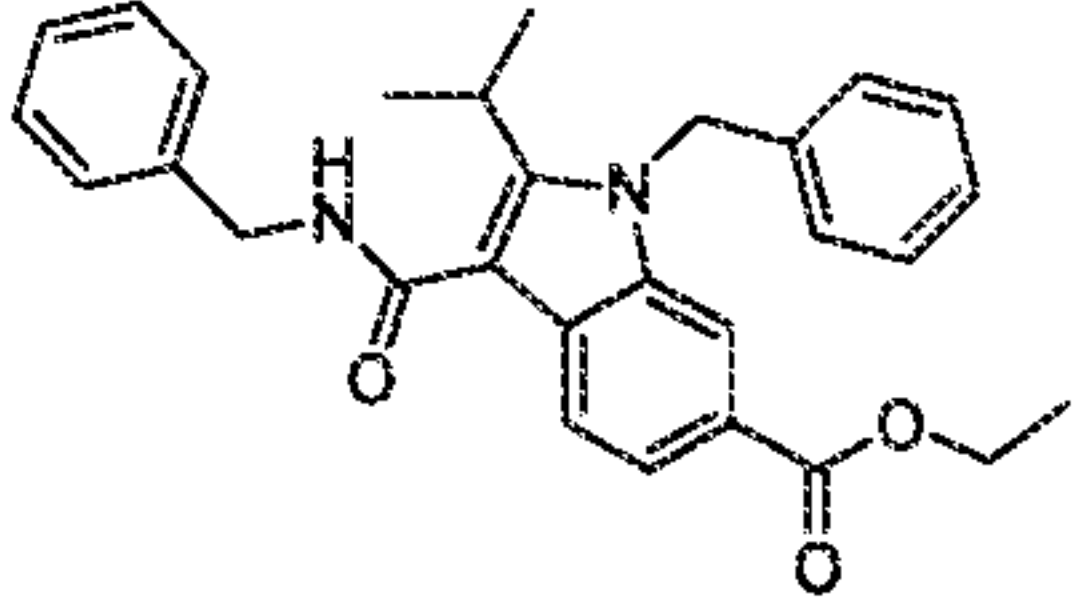
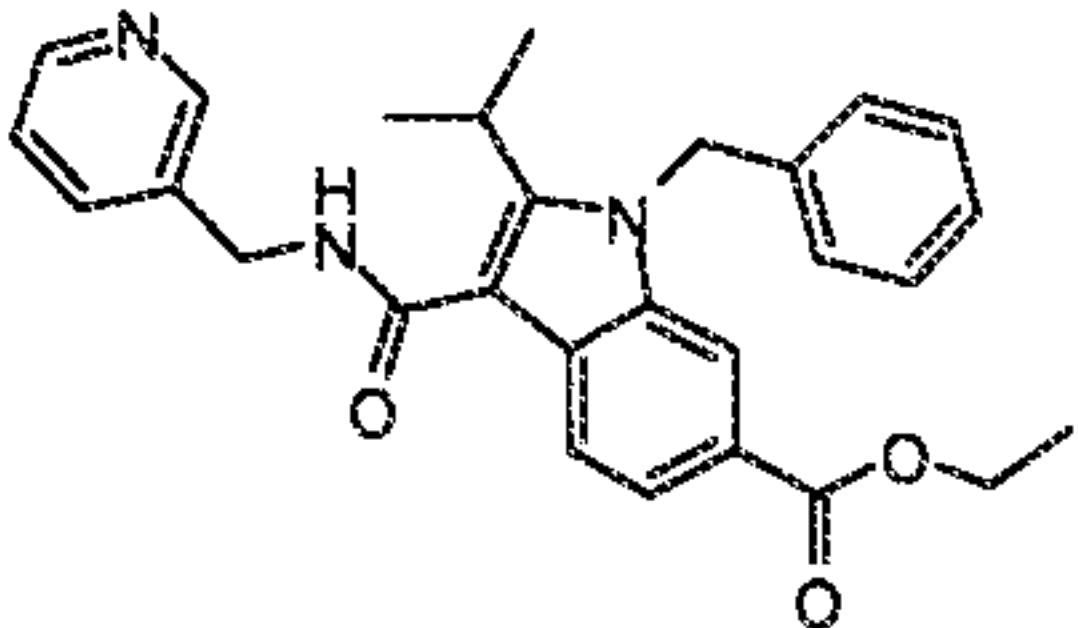
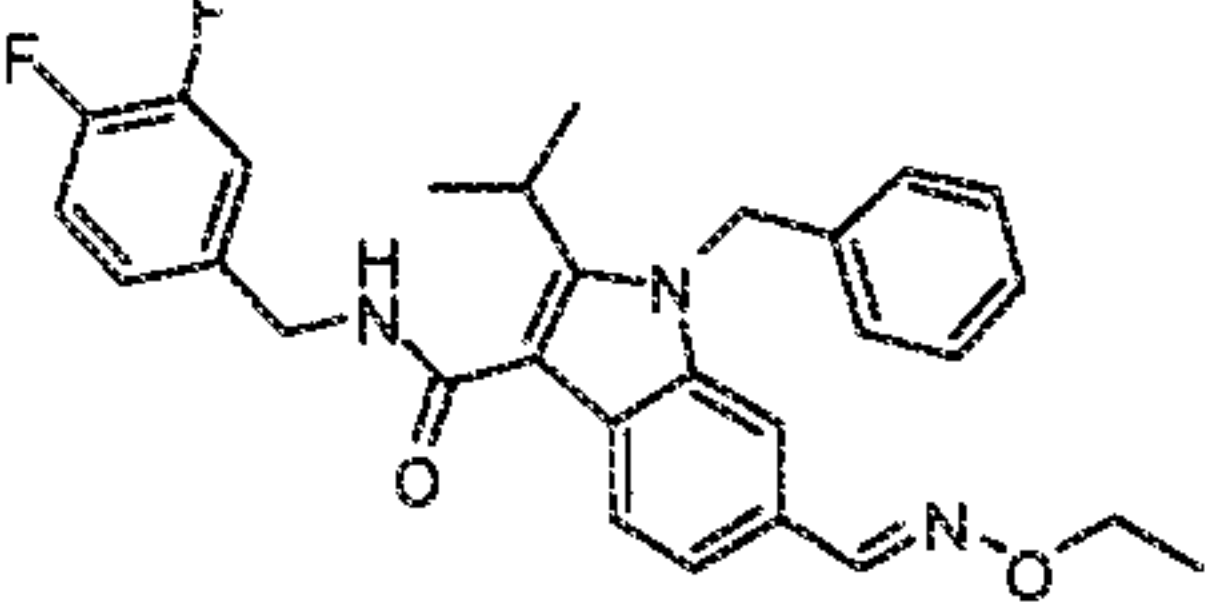
Compound Number	<u>Structure</u>	S1P3 IC₅₀ (% inh) Kb
		346 nM (99)
		146 nM (99)

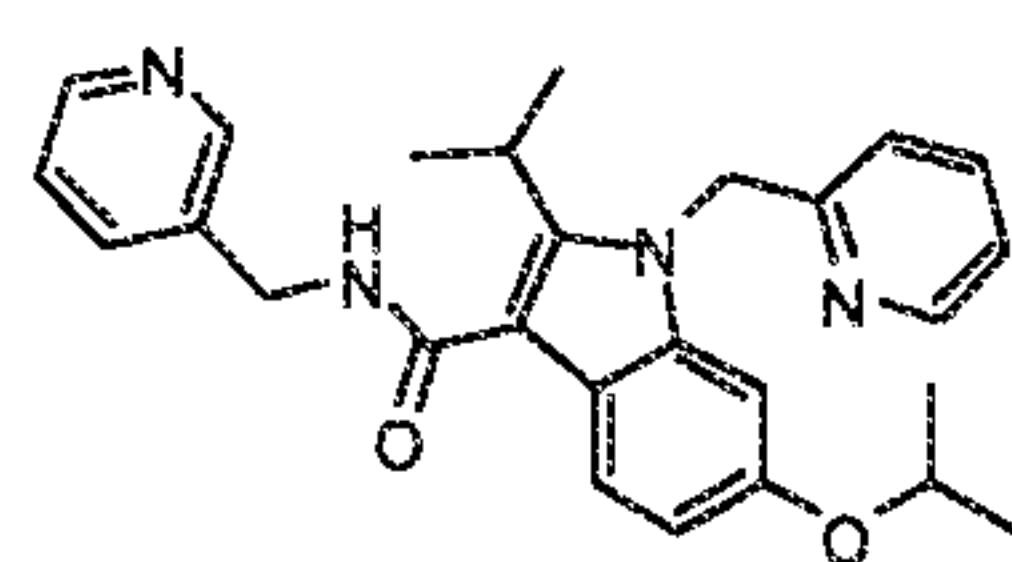
**Table 1B**

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

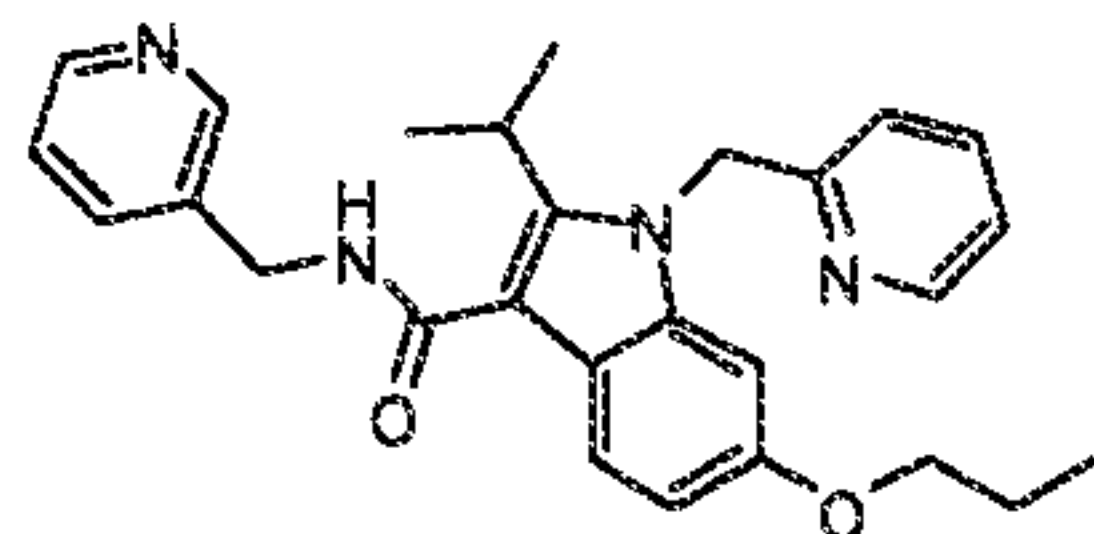
**Table 1B**

5

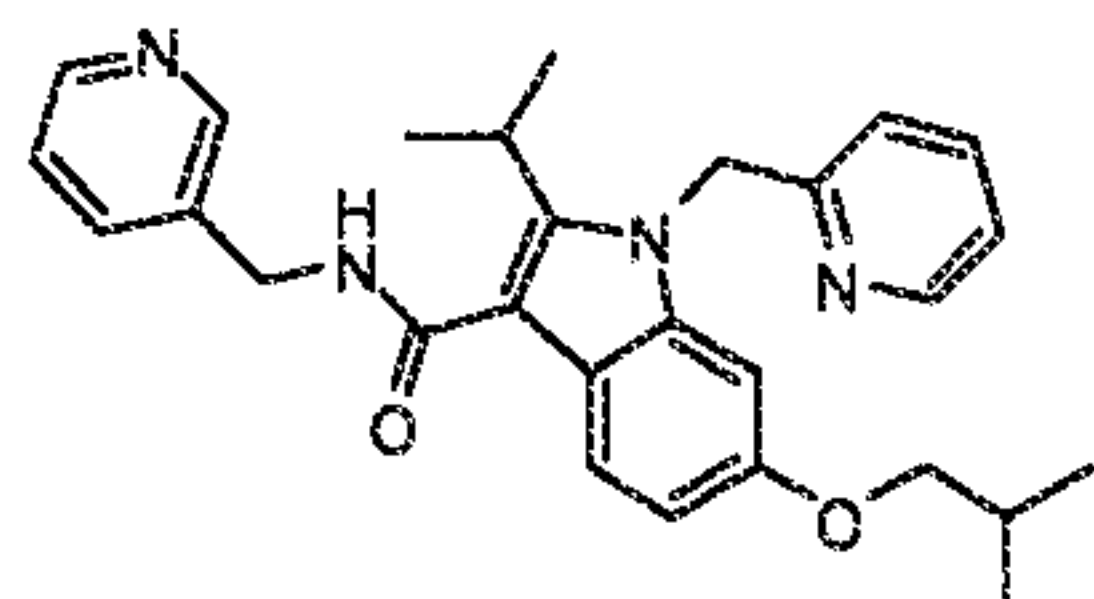
Compound Number	Structure	S1P3 IC ₅₀ (% inh) Kb
		9 nM (100)
		9 nM (96)
		187 nM (95)
		145 nM (99)



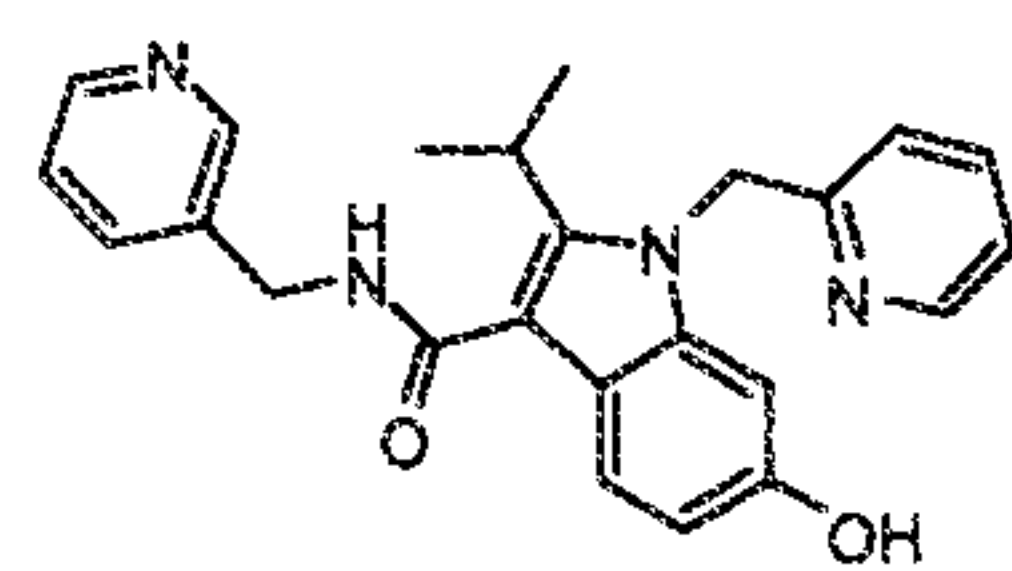
ND
(98)



1.2 μ M
(99)



124 nM
(99)



ND
(54)

Table 1B

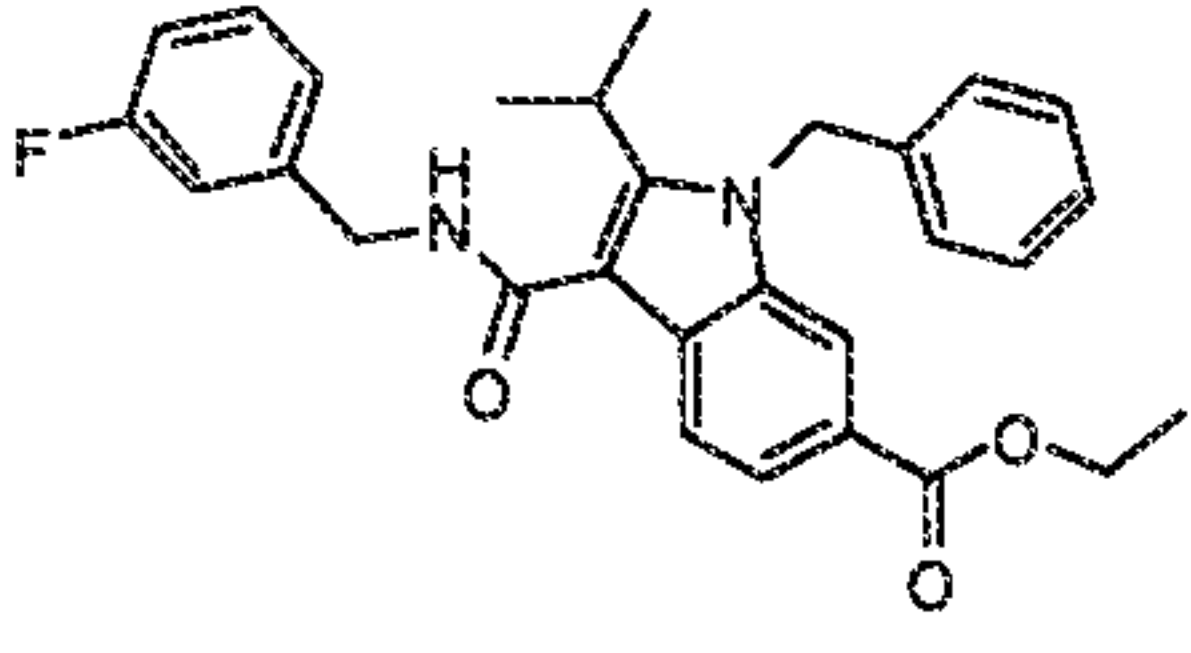
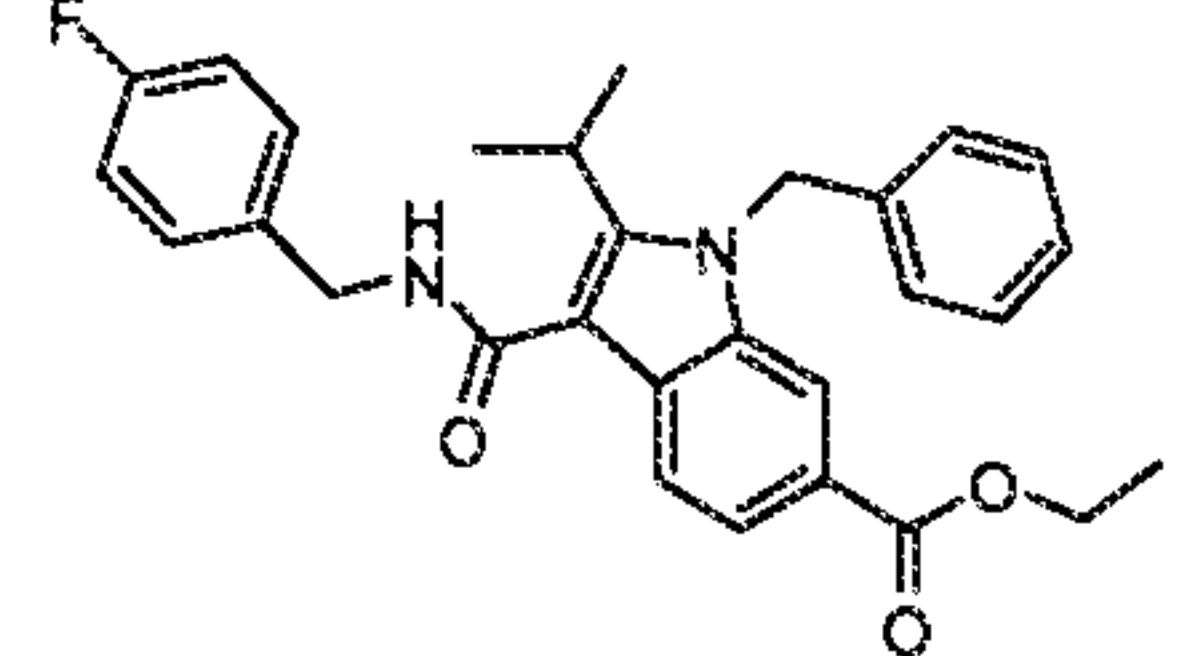
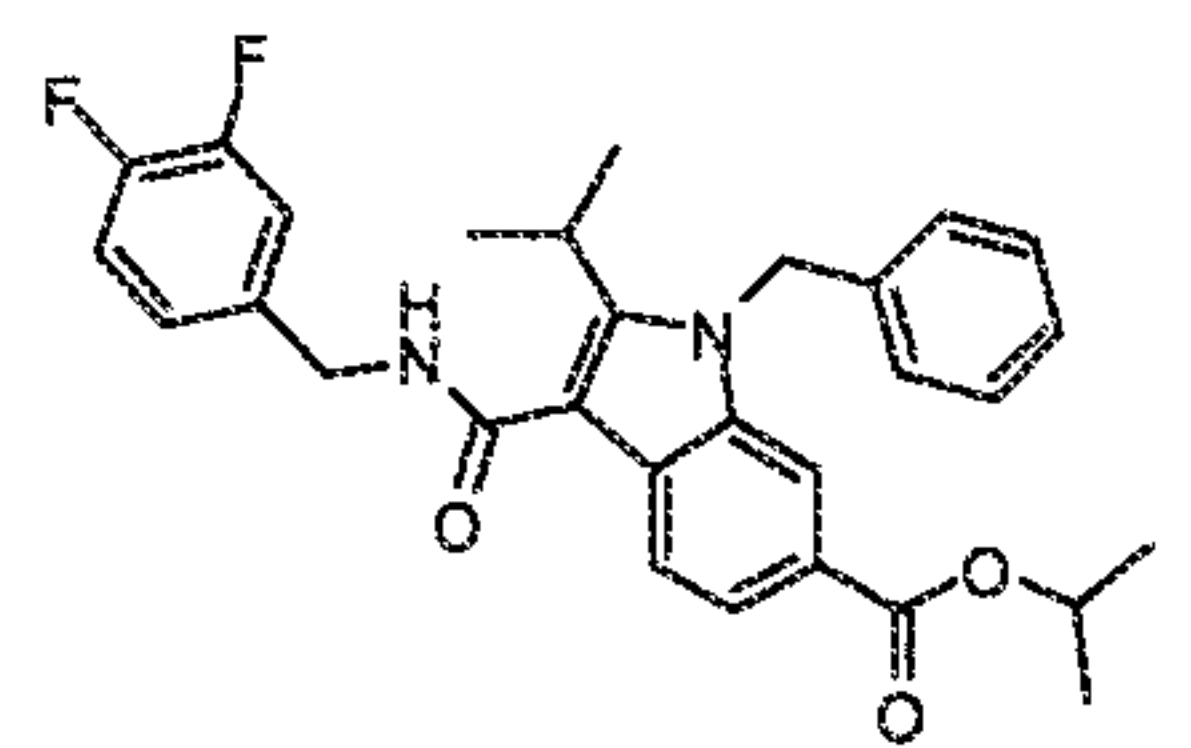
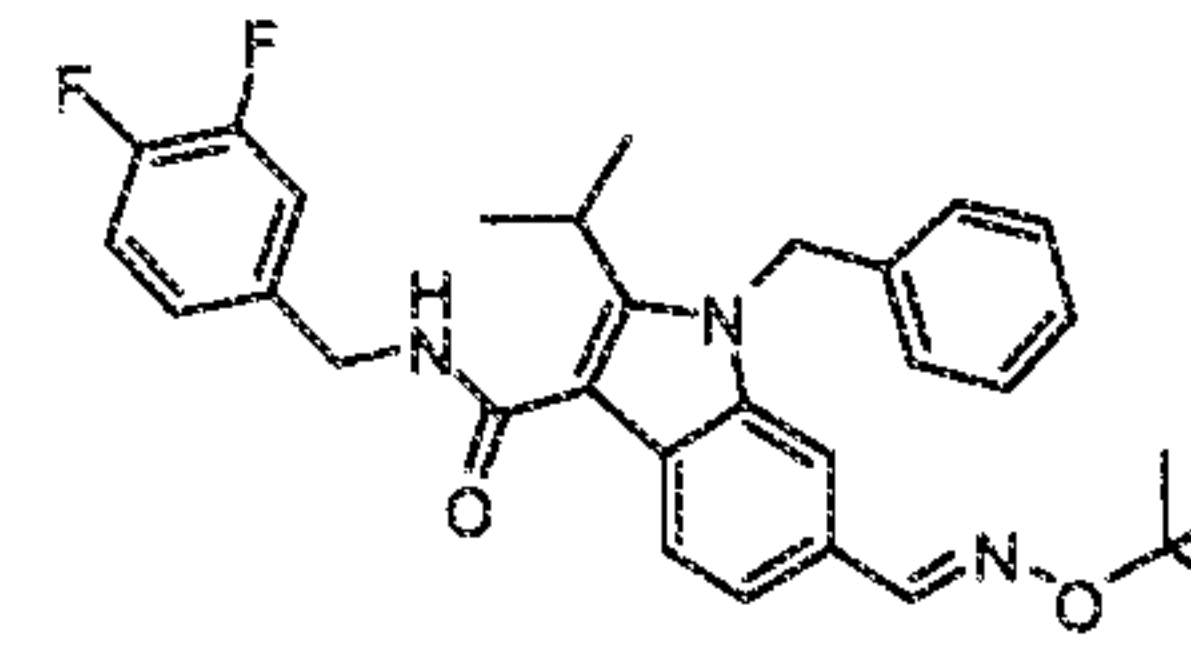
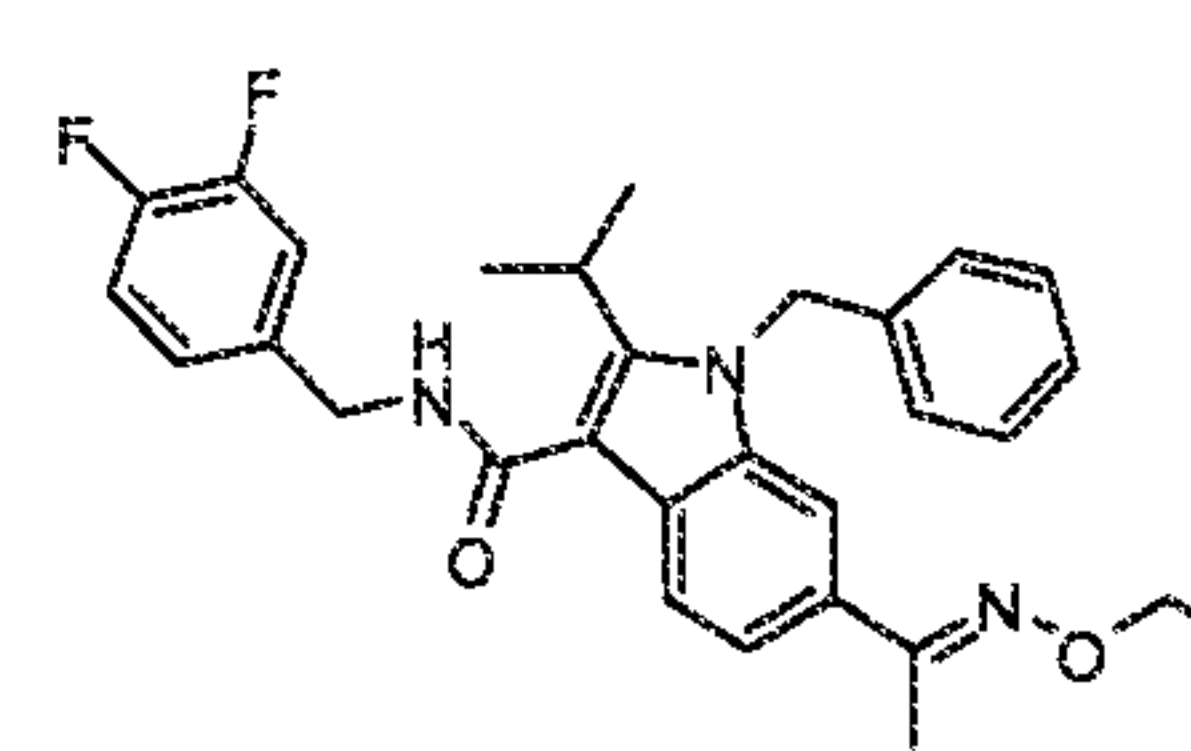
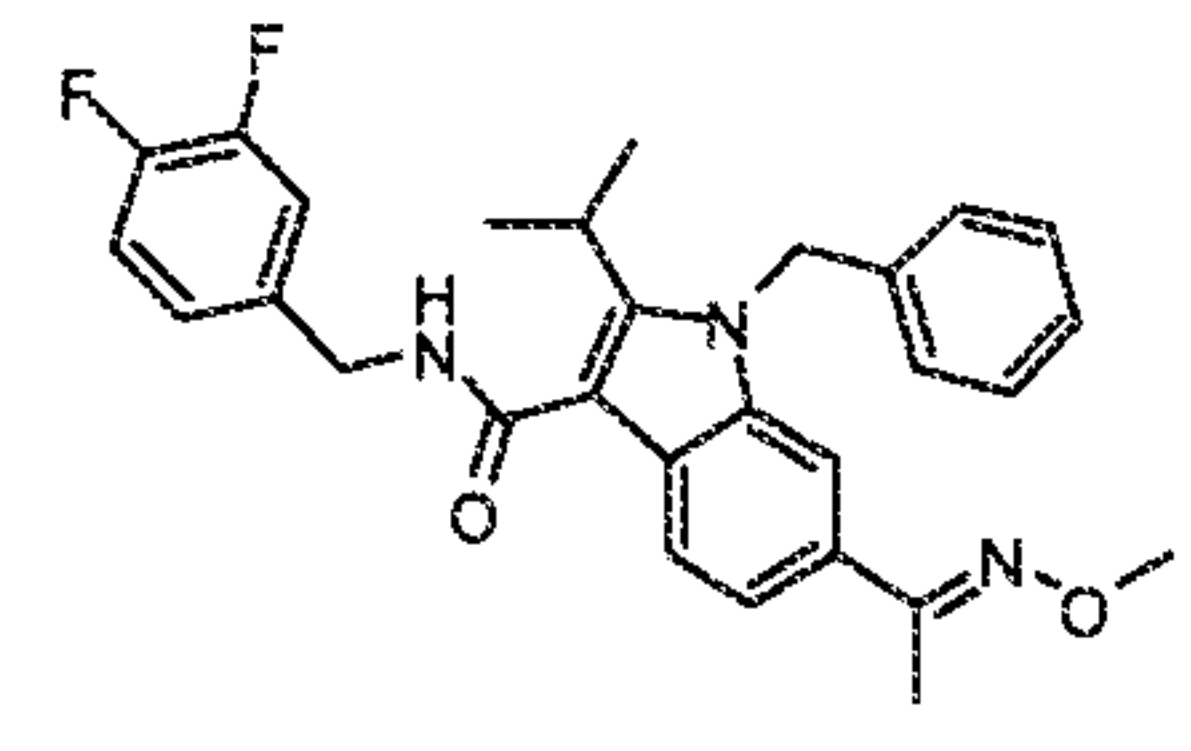
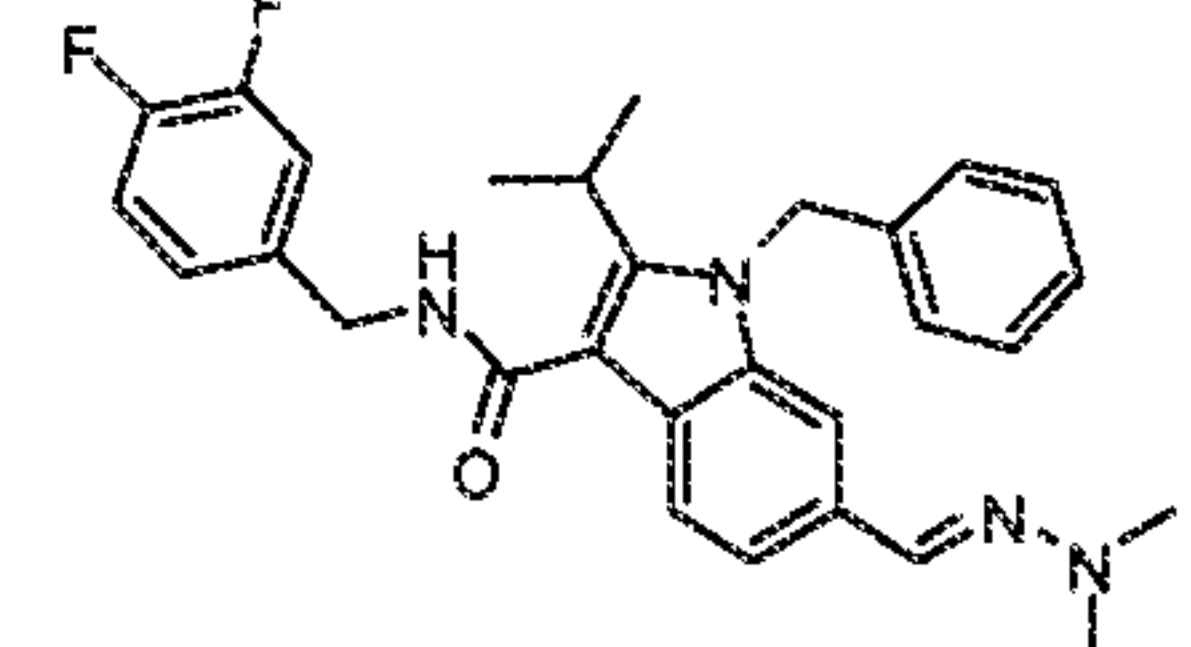
Compound Number	Structure	S1P3 IC₅₀ (% inh) Kb
		42 nM (99)
		43 nM (99)
		45 nM (99)
		145 nM (99)
		262 nM (98)
		147 nM (100)
		33 nM (100) 7 nM

Table 1B

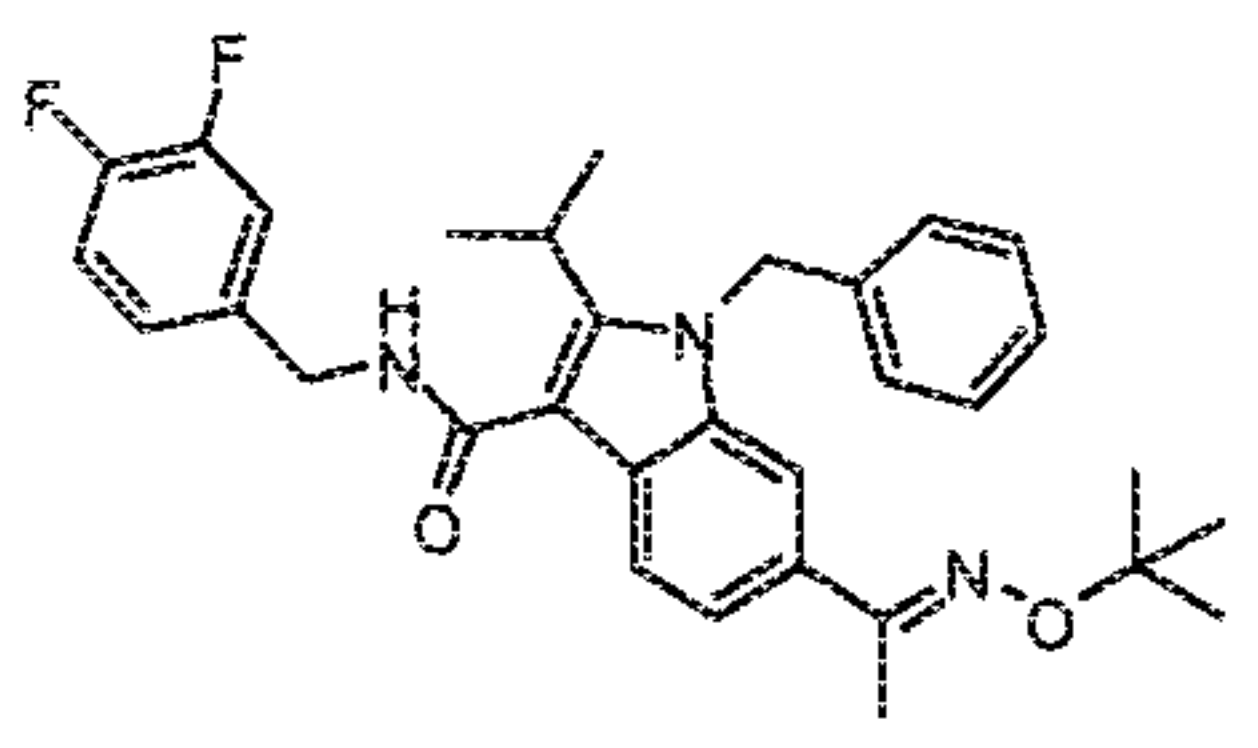
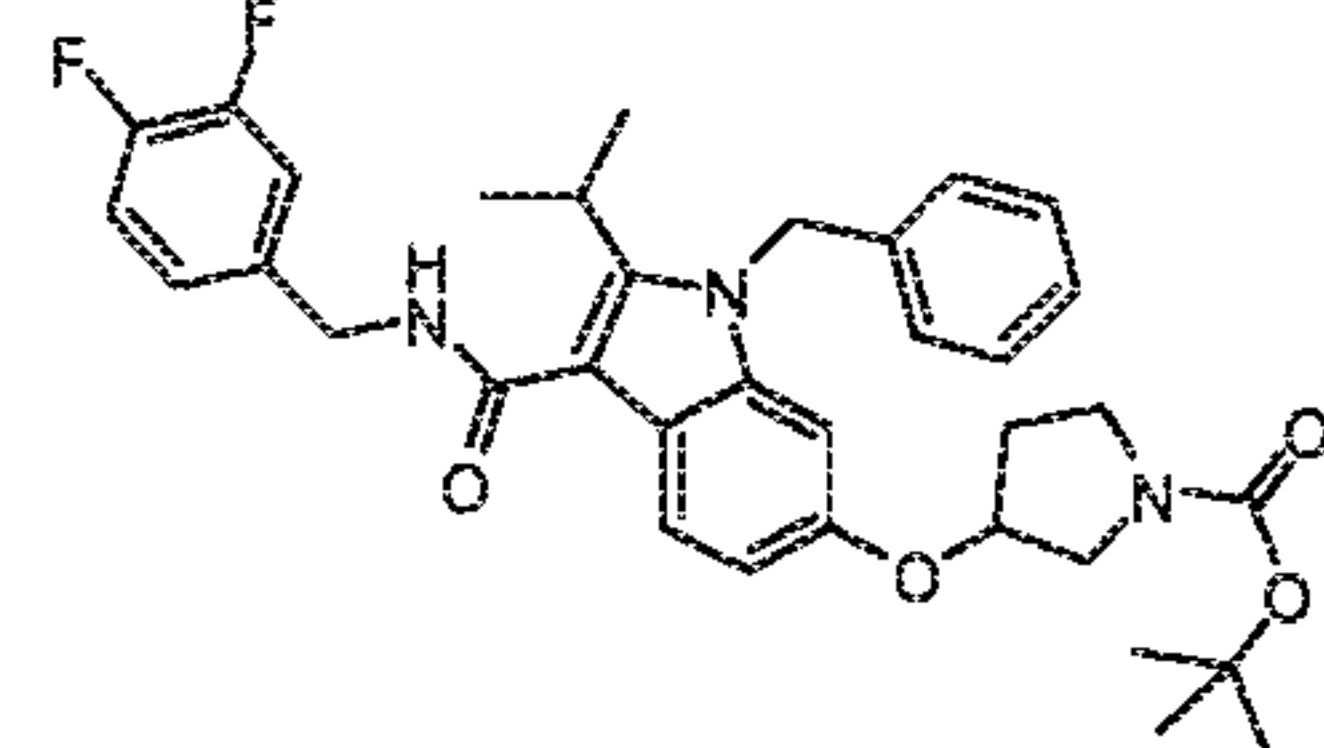
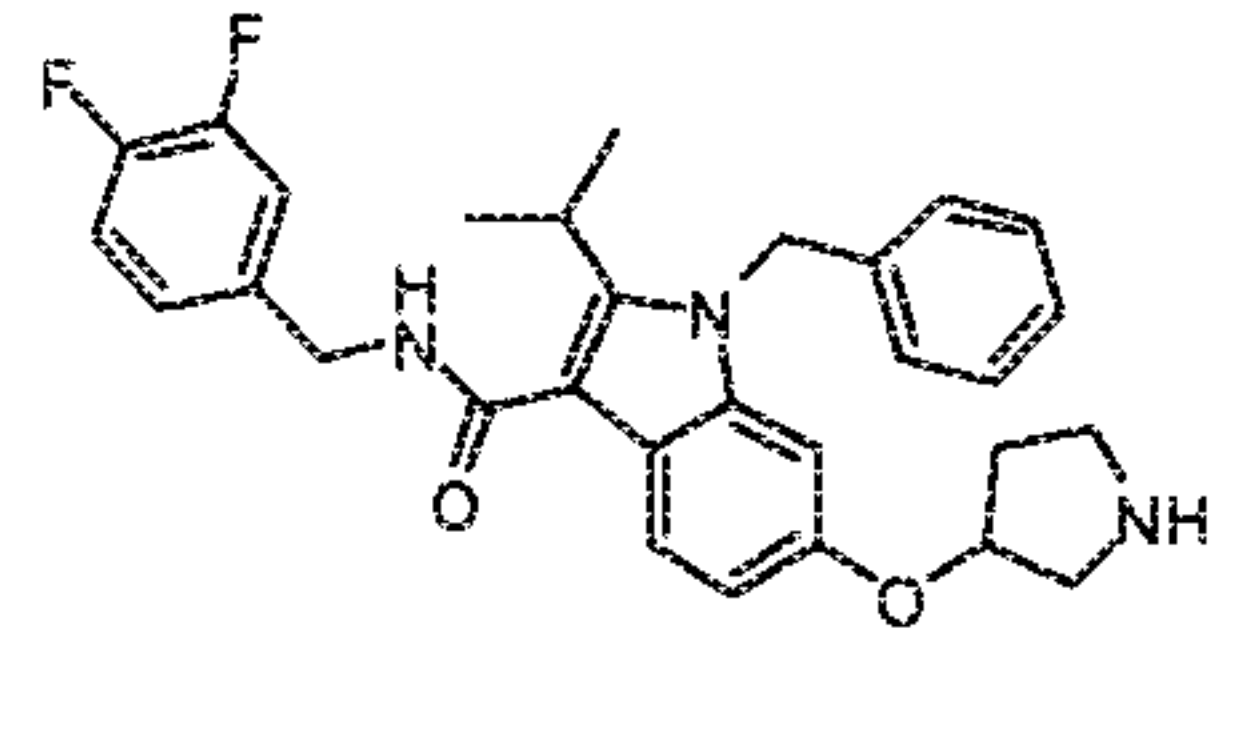
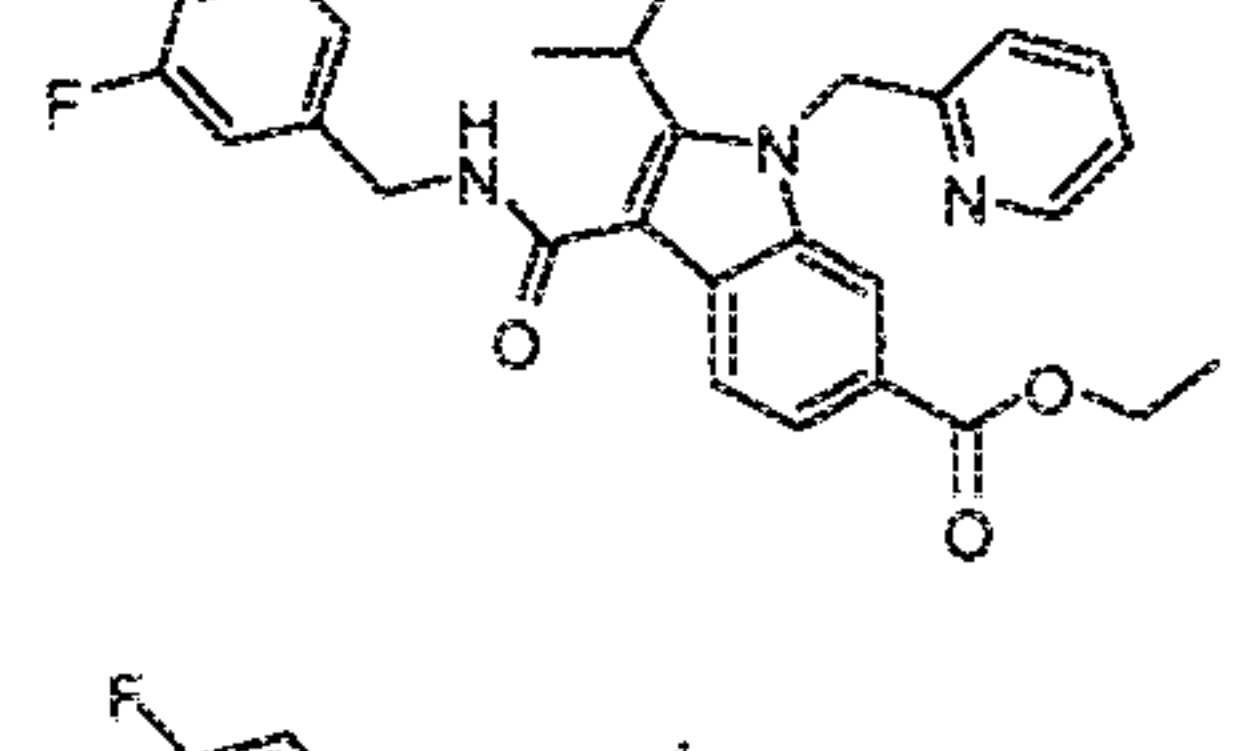
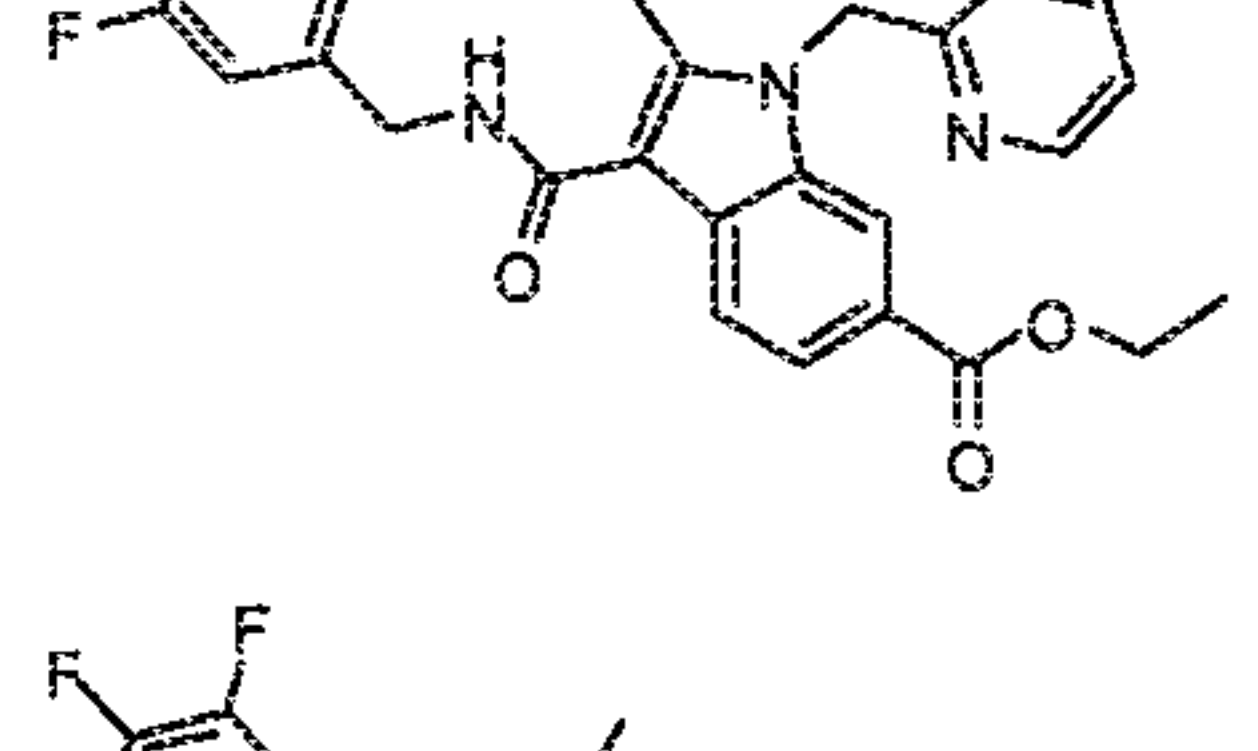
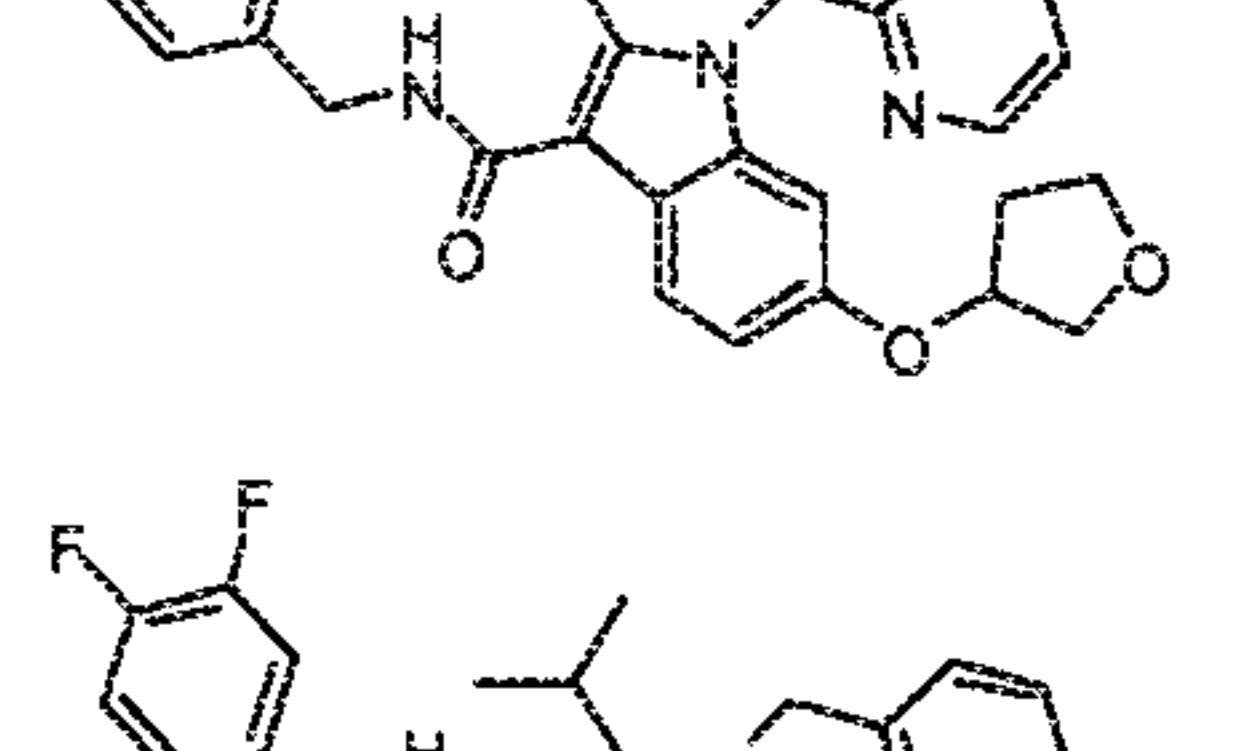
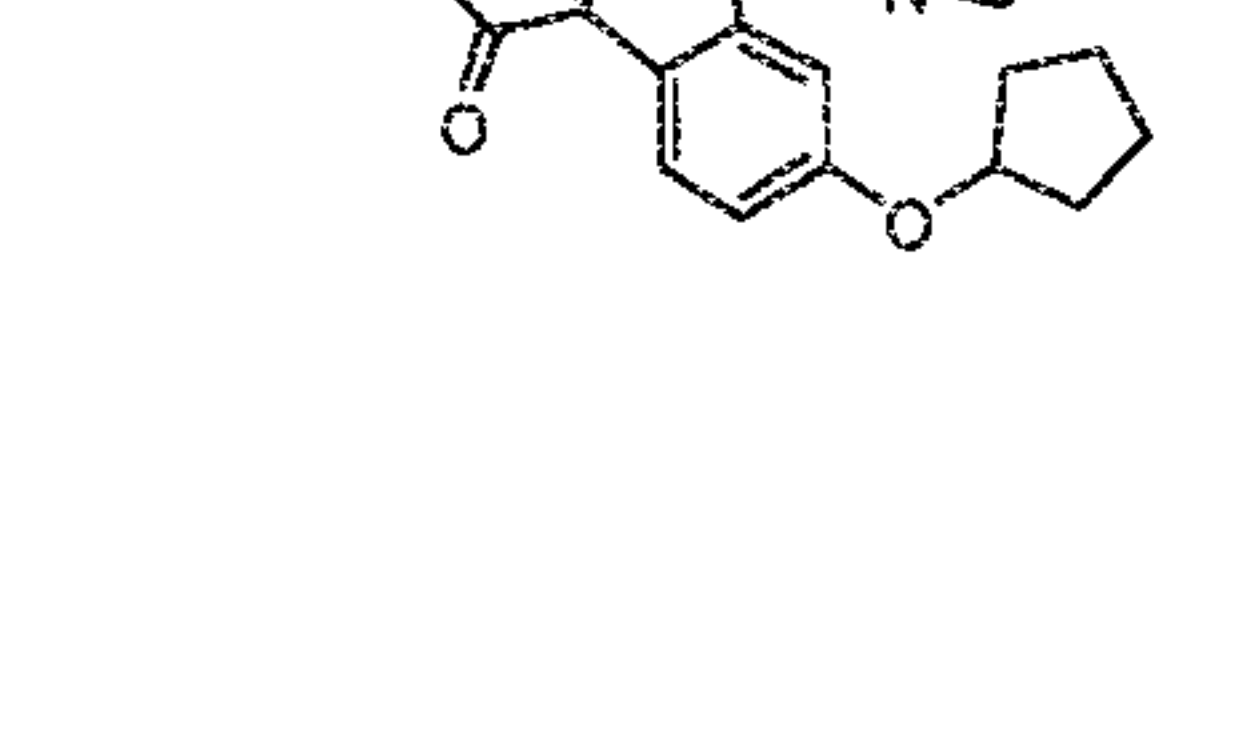
Compound Number	Structure	S1P3 IC ₅₀ (% inh) Kb
		NA
		673 nM (100)
		2.4 μM (80)
		174 nM (100)
		58 nM (100)
		19 nM (100) 21 nM
		3 nM (100) 4 nM

Table 1B

5

Compound Number	Structure	S1P3 IC ₅₀ (% inh)
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Kb

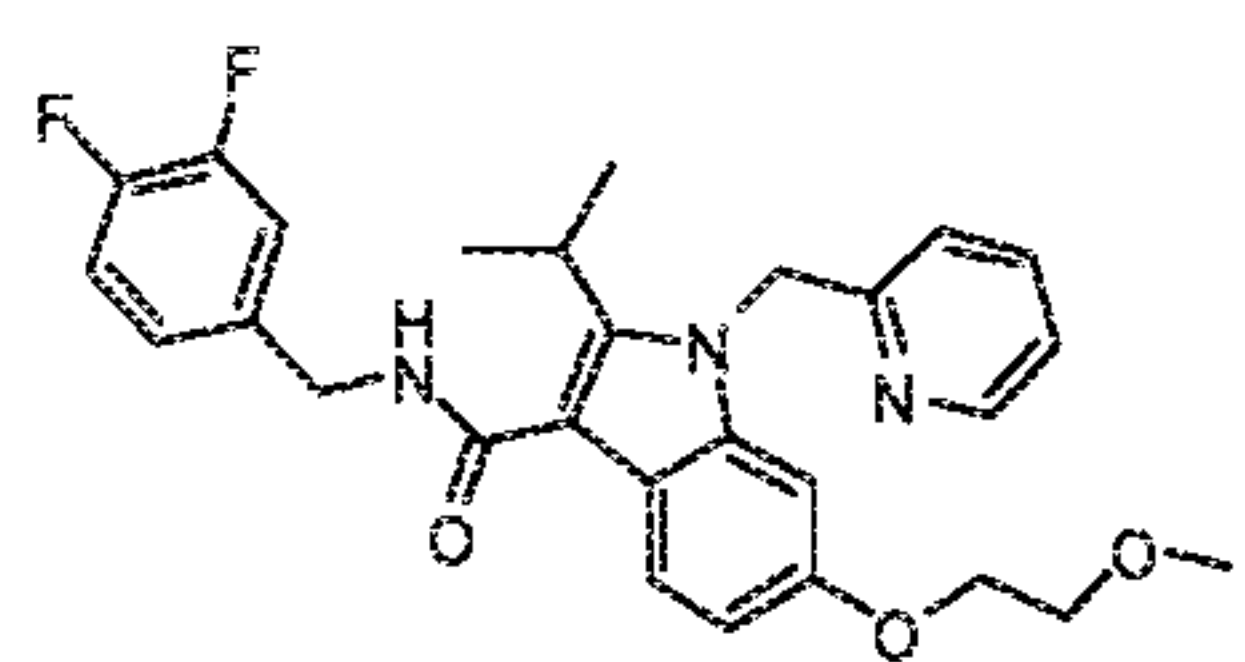
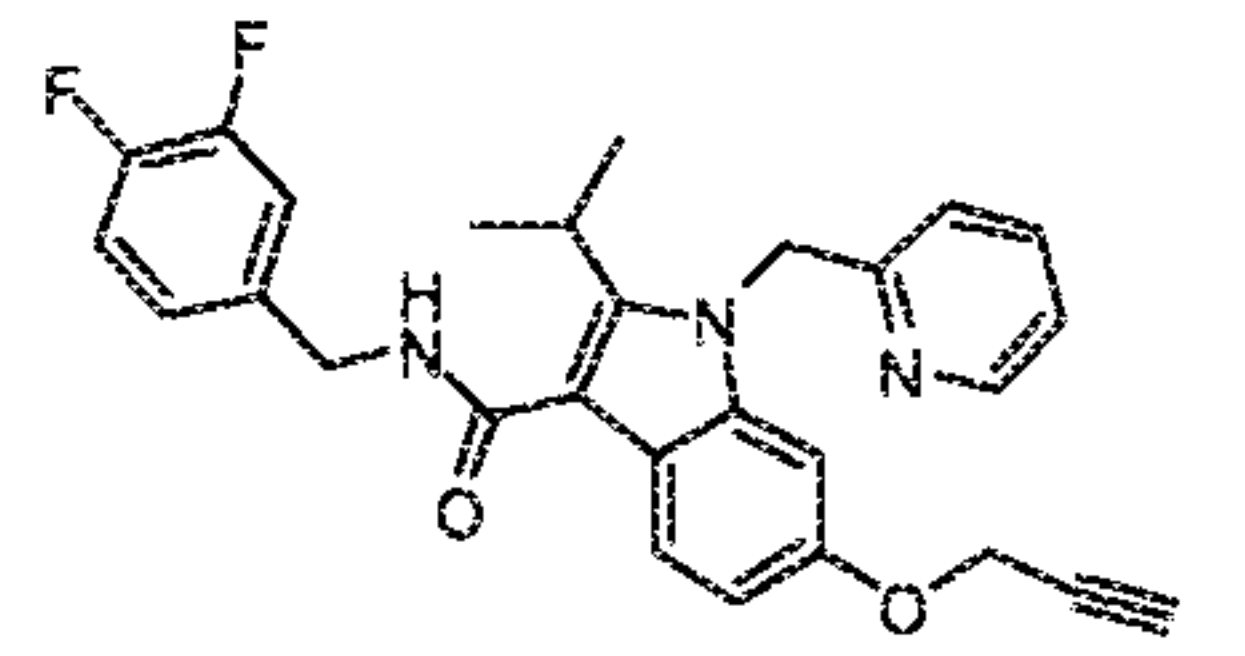
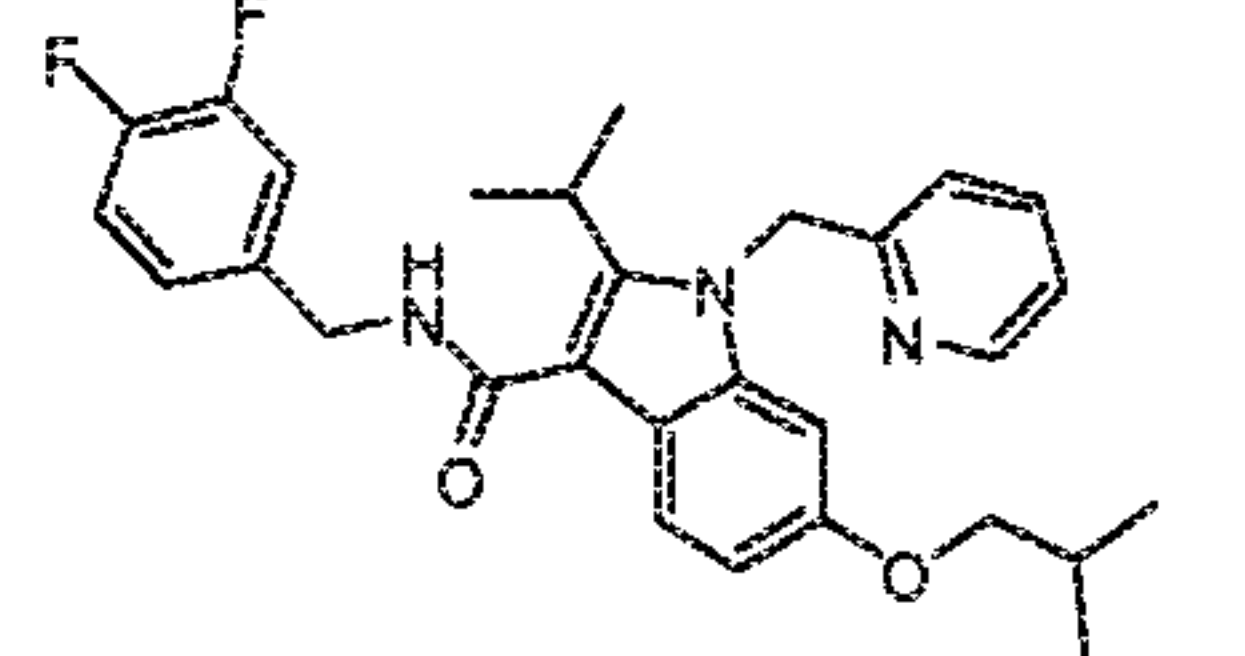
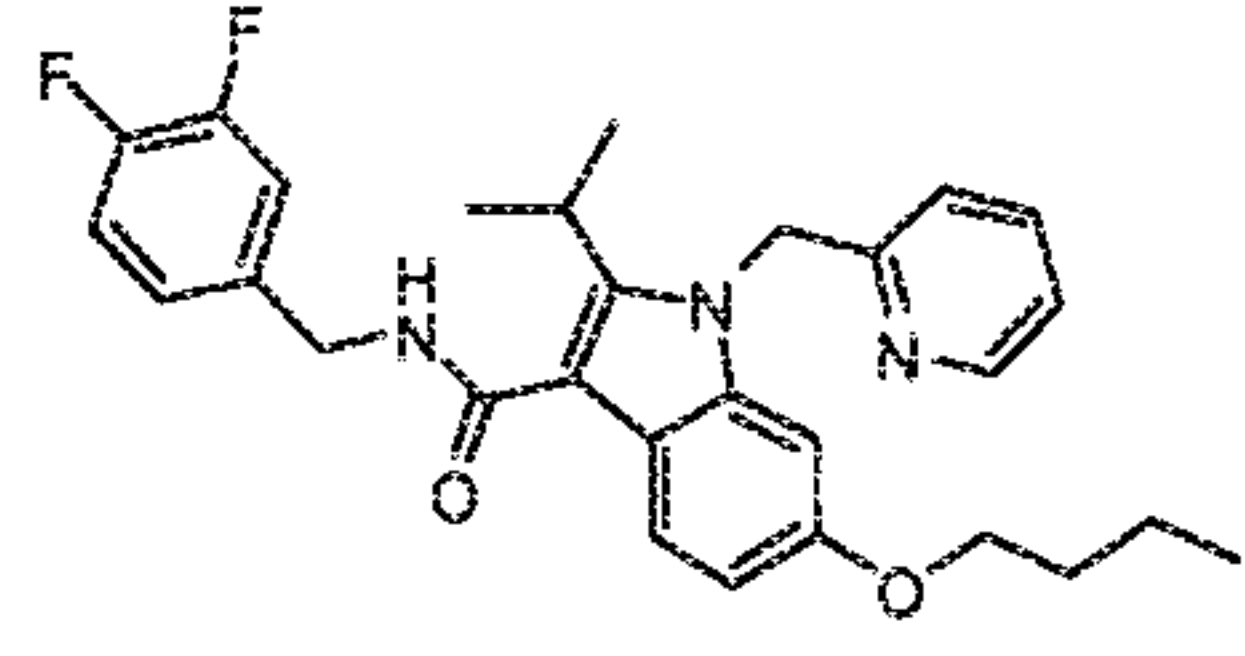
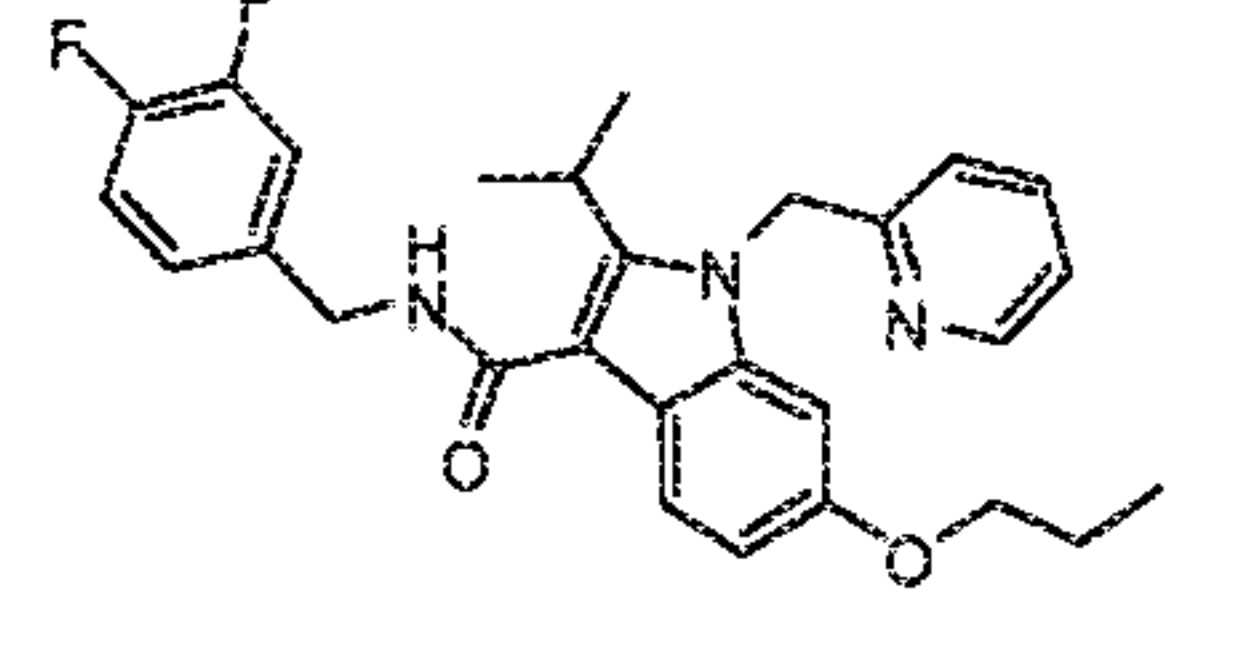
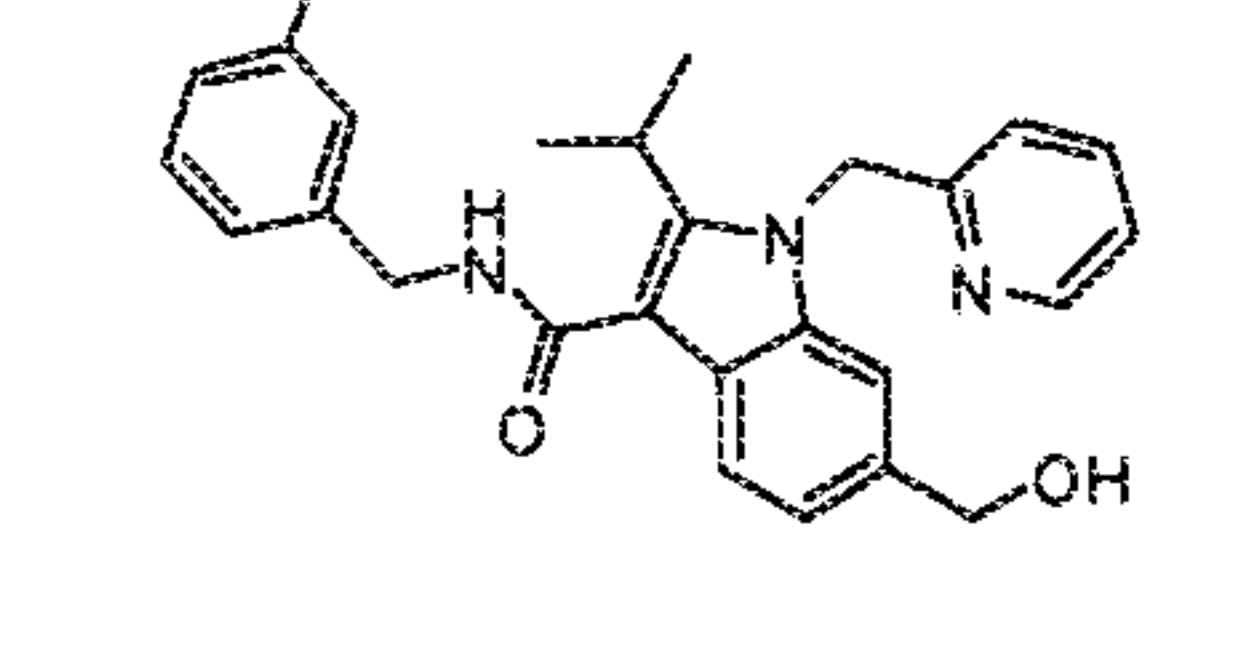
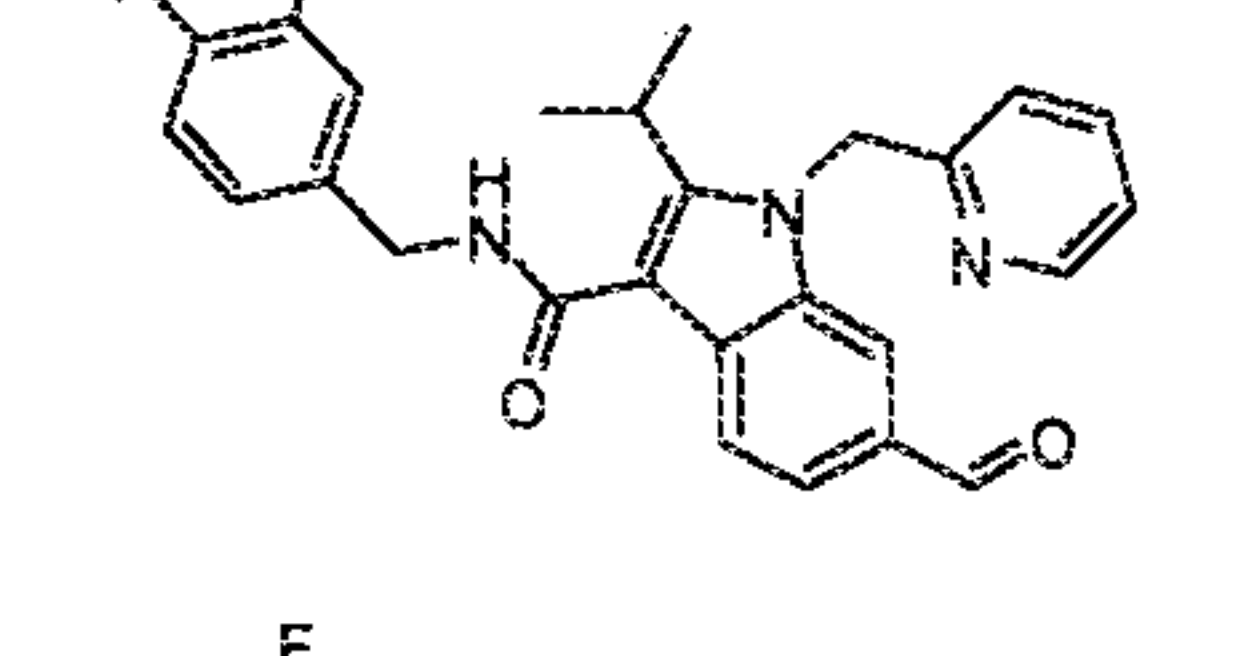
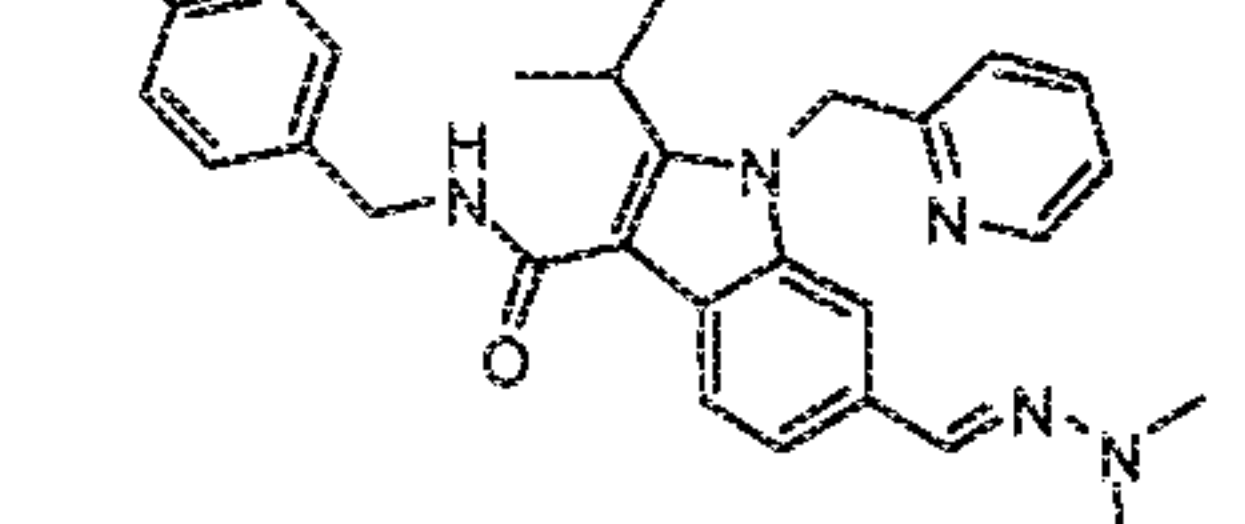
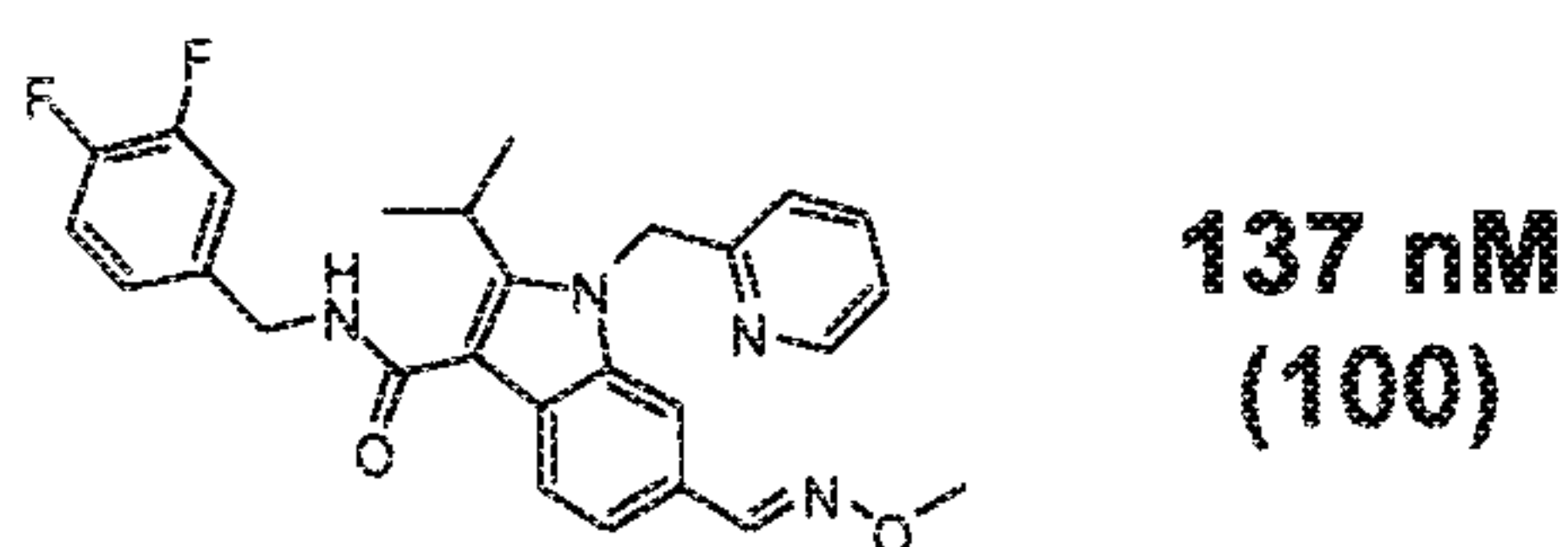
	288 nM (100)
	324 nM (99)
	5 nM (100) 9 nM
	8 nM (100)
	15 nM (100) 13 nM
	NA
	ND (65)
	93 nM (100)

Table 1B

Compound Number	<u>Structure</u>	S1P3
		IC₅₀
		(% inh)
		Kb



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.

5 **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.

10 **Dry Eye/Immunology**

Induces lymphocyte sequestration without affecting T cell proliferation.

Angiogenesis disorders

15 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.

20

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.

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

BBr₃: 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
5 $NaClO_2$: sodium hypochlorite
NaI: sodium iodide
 Na_2SO_4 : sodium sulfate
 $MgSO_4$: magnesium sulfate
 $POCl_3$: phosphorus oxychloride
10 t-BuOH: *tert*-butyl alcohol
MeOH: methanol
EtOH: ethanol
i-PrOH: isopropanol
EtOAc: ethyl acetate
15 Et_2O : diethyl ether
 CH_2Cl_2 : methylene chloride
 CH_3CN : acetonitrile
DHP: dihydropyran
DMAP: 4-(dimethylamino)pyridine
20 DMF: *N,N*-dimethylformamide
DMSO: dimethylsulfoxide
EDC : 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide
LDA: lithium diisopropylamide
 $LiAlH_4$: lithium aluminum hydride
25 MOMCl: methyl chloromethyl ether
MeLi: methyllithium
MeMgBr: Methylmagnesium bromide
 $NaBH_3CN$: sodium cyanoborohydride
NMO: 4-methylmorpholine, N-oxide
30 Pd-C: palladium on activated carbon
PhCHO: benzaldehyde

THF: tetrahydrofuran

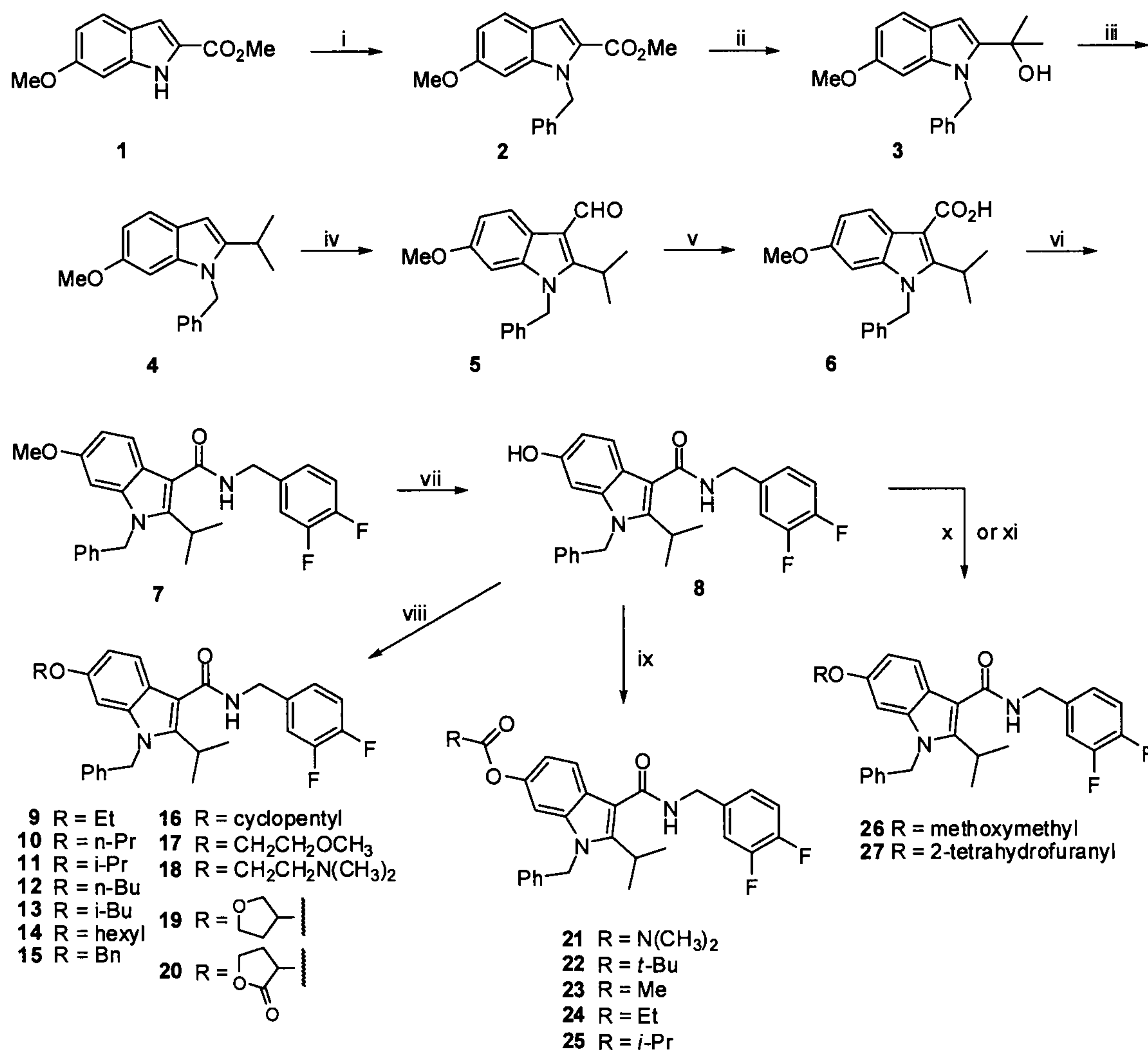
THP: tetrahydropyran

TPAP: tetrapropylammonium perruthenate

PTLC: preparative thin layer chromatography

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

Scheme 3^a



- ^a Reagents and conditions: (i) BnBr, K₂CO₃, DMF; (ii) MeLi, THF; (iii) H₂, Pd-C, EtOAc, EtOH, HCl-Et₂O; (iv) POCl₃, DMF; (v) NaClO₂, KH₂PO₄, isobutene, *t*-BuOH, CH₃CN, H₂O; (vi) 3,4-difluorobenzylamine, EDC, DMAP, CH₂Cl₂; (vii) BBr₃, CH₂Cl₂; (viii) RX, K₂CO₃, DMF; (ix) RCOCl, pyridine; (x) MOMCl, *i*-Pr₂NEt, CH₂Cl₂; (xi) 2,3-dihydrofuran, PPTS, CH₂Cl₂.

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 K₂CO₃ (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 H₂O, brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by crystallization from Et₂O to yield the title compound as an off-white solid.

¹H 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 1 h, cooled to -78 °C, quenched with dry ice, diluted with EtOAc, washed with H₂O, brine, dried over Na₂SO₄, concentrated *in vacuo* to yield the crude title compound as a yellow solid.

¹H 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-Et₂O (1.0 M, 1.25 ml, 1.25 mmol). The mixture was stirred
5 under hydrogen gas (atmospheric pressure) for 1h and was filtered. To the filtrate was added NaHCO₃ (0.5 g) and H₂O (0.5 ml), followed by Na₂SO₄ and MgSO₄. This was then filtered and concentrated *in vacuo* to yield the crude title compound as a yellow solid.

¹H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.31 (d, *J* = 6.7 Hz, 6 H), 2.90
10 - 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

15 **1-Benzyl-2-isopropyl-6-methoxy-1H-indole-3-carbaldehyde (Compound 5).** POCl₃ (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
20 stirred for 1 h at 0 °C and 30 min at room temperature, diluted with EtOAc, washed with aqueous NaHCO₃, brine, dried over Na₂SO₄, 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.

¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.45 (d, *J* = 7.3 Hz, 6 H), 3.40
25 - 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

30 **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), CH₃CN (15 ml), and 2-methyl-2-butene (10 ml) was added a solution of KH₂PO₄ (5.4 g, 39.6 mmol) and NaClO₂ (80%, 4.5 g, 39.6 mmol) in H₂O (50 ml). The mixture was stirred at room temperature and additional 2-methyl-2-butene, KH₂PO₄, and NaClO₂ 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 Na₂SO₄, 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.

¹H 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 CH₂Cl₂ (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 H₂O, brine, dried over Na₂SO₄ 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.

¹H 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).

30

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 CH₂Cl₂ (20 ml) at 0 °C was added BBr₃ (1.0 M in CH₂Cl₂, 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 Na₂SO₄, 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.

¹H 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).

15

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 K₂CO₃ (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 H₂O, brine, dried over Na₂SO₄ 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.

25

¹H 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)

30

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

5 (Compound 8, 8.0 mg, 0.018 mmol) in DMF (1.0 ml) was reacted with K₂CO₃ (8.0 mg, 0.055 mmol) and 1-iodopropane (9.0 µl, 0.092 mmol) to yield the title compound as a white solid.

¹H 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

15 **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 K₂CO₃ (8.0 mg, 0.055 mmol) and 2-iodopropane (9.0 µl, 0.092 mmol) to yield the title compound as a white solid.

¹H 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).

25

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

30 (Compound 8, 10.7 mg, 0.025 mmol) in DMF (1.0 ml) was reacted with K₂CO₃

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

¹H 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).

10 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 K₂CO₃ (10.0 mg, 0.074 mmol) and 2-iodobutane (14.0 μ l, 0.12 mmol) to yield the title compound as a white solid.

¹H 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 K₂CO₃ (10.0 mg, 0.074 mmol) and 1-iodohexane (18.0 μ l, 0.12 mmol) to yield the title compound as a white solid.

¹H 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).

5

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

10 (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 μ l, 0.12 mmol), and catalytic amount of NaI to yield the title compound as an off-white solid.

1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.37 (d, $J = 7.3$ Hz, 6 H), 3.65
15 - 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).

20 **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
25 (38 mg, 0.28 mmol), cyclopentyl iodide (53 μ l, 0.46 mmol) to yield the title compound as a white solid.

1H 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, $J =$
30 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 K₂CO₃ (28 mg, 0.20 mmol), 2-bromoethyl methyl ether (18 μ l, 0.20 mmol) to yield the title compound (9 mg, 49%).

¹H NMR (300 MHz, CDCl₃) 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 K₂CO₃ (28 mg, 0.20 mmol), 2-dimethylamino ethyl chloride hydrochloride (20 mg, 0.20 mmol) to yield the title compound (10 mg, 53%).

¹H NMR (300 MHz, CD₃OD) 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 K₂CO₃ (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%).

¹H NMR (300 MHz, CDCl₃) 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).

10 **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
15 reacted with K₂CO₃ (30 g, 0.22 mmol), 3-bromodihydrofuran-2(3H)-one (20 mg, 0.22mmol) to yield the title compound (16mg, 71%).

¹H NMR (300 MHz, acetone-d₆) 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,
20 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
30 overnight. The reaction was quenched with water, extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over Na₂SO₄,

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%).

¹H NMR (300 MHz, CD₃OD) δ ppm 1.32 (d, *J* = 7.04 Hz, 6 H), 2.96 (s, 3 H),
5 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

10 **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%).

15 ¹H NMR (300 MHz, CD₃OD) 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

20 **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%).

25 ¹H NMR (300 MHz, CDCl₃) 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).

30 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 μ l, 0.16 mmol) to yield the title compound (8 mg, 100%).

^1H 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 μ l, 0.21 mmol) to yield the title compound (8 mg, 80%).

^1H 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*-Pr₂NEt (47 μ l, 0.27 mmol) and MOMCl (35 μ l, 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.

^1H NMR (300 MHz, $\text{CHLOROFORM-}d$) 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

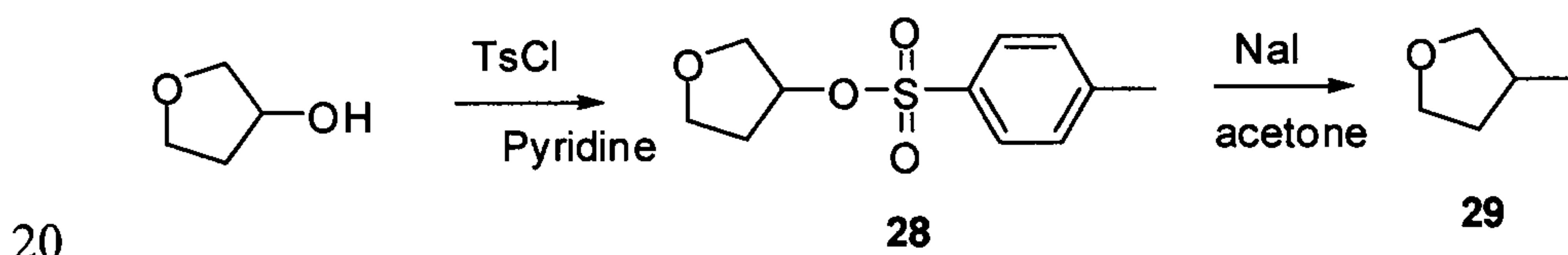
H), 6.29 (t, $J = 5.7$ Hz, 1 H), 6.85 (d, $J = 2.1$ Hz, 1 H), 6.89 - 7.01 (m, 3 H), 7.10 - 7.17 (m, 2 H), 7.20 - 7.34 (m, 4 H), 7.52 (d, $J = 8.5$ Hz, 1 H).

Example 27

5 **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
10 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.

^1H NMR (300 MHz, $\text{CHLOROFORM-}d$) 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, $J = 4.7$
15 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



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
25 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).

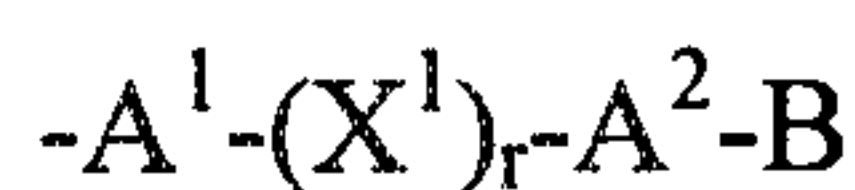
¹H NMR (300 MHz, CDCl₃) δ ppm 1.91 - 2.23 (m, 2 H), 3.61 - 4.05 (m, 4 H), 4.95 - 5.24 (m, 1 H), 7.36 (d, *J* = 7.92 Hz, 2 H), 7.80 (d, *J* = 8.50 Hz, 2 H).

Example 29

5 **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,
10 dried over Na₂SO₄ and concentrated in vacuo to yield crude oil which was used directly without purification.

¹H NMR (300 MHz, CDCl₃) 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
15 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
20 indole-3-carboxylic acid-N- arylmethyl amide having sphingosine-1-phosphate antagonist activity wherein the 6-substituent is represented by the formula



25 wherein X₁ is O;

r is 0 or 1;

A² is absent or is (CH₂)_v, wherein v is 1 or 2;

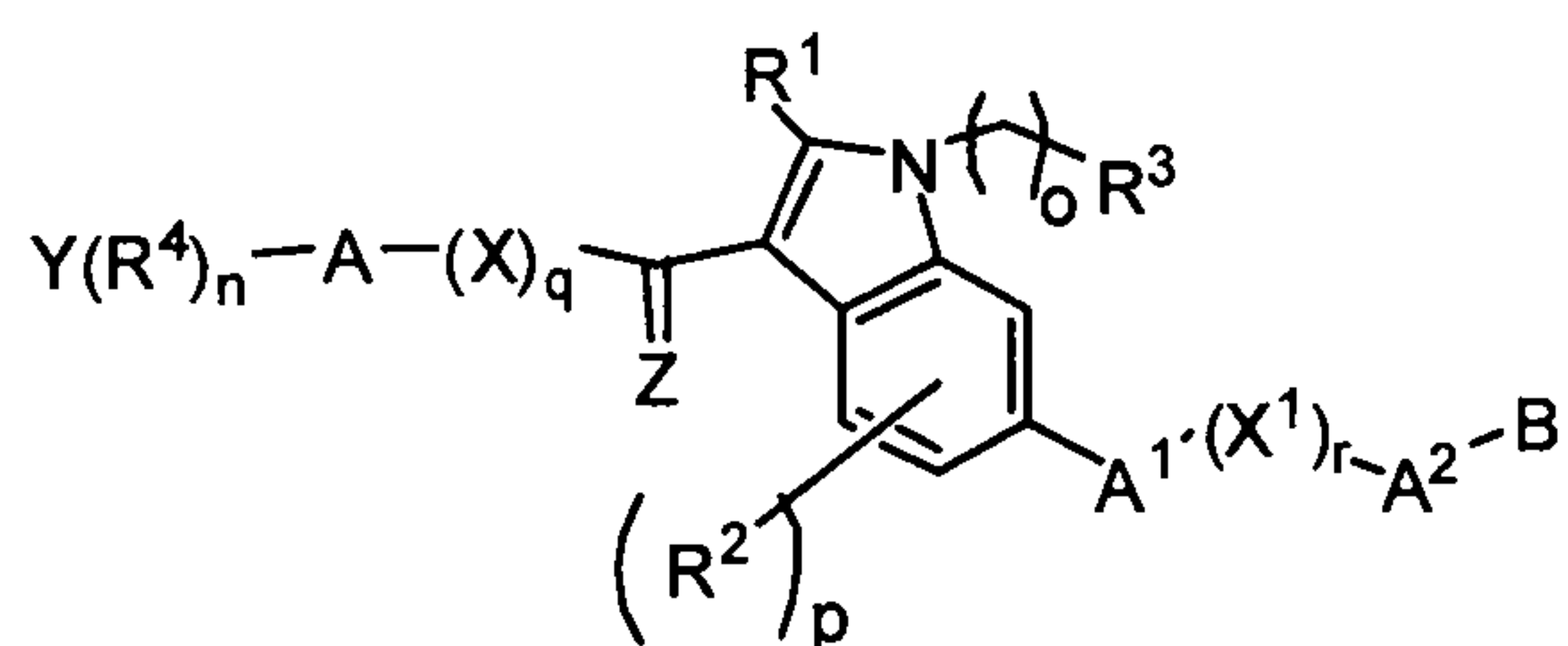
B is OR⁶ or NR⁸R⁹, wherein R⁶, R⁸ and R⁹ are methyl; or

B is CR¹⁰=NO R¹¹R¹⁰ wherein R¹⁰ 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.

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:

10

15

20

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;

25

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;

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, A¹ and A² are independently selected from the group consisting of

10 (CH₂)_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, OR⁶, COOR⁷,

15 NR⁸R⁹, CONR⁸R⁹, COR¹⁰, CH=NOR¹¹, CH=NNR¹²R¹³

wherein R⁶, R⁷, R¹⁰ and R¹¹ 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

20 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, R⁸, R⁹, R¹² and R¹³ 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

25 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.

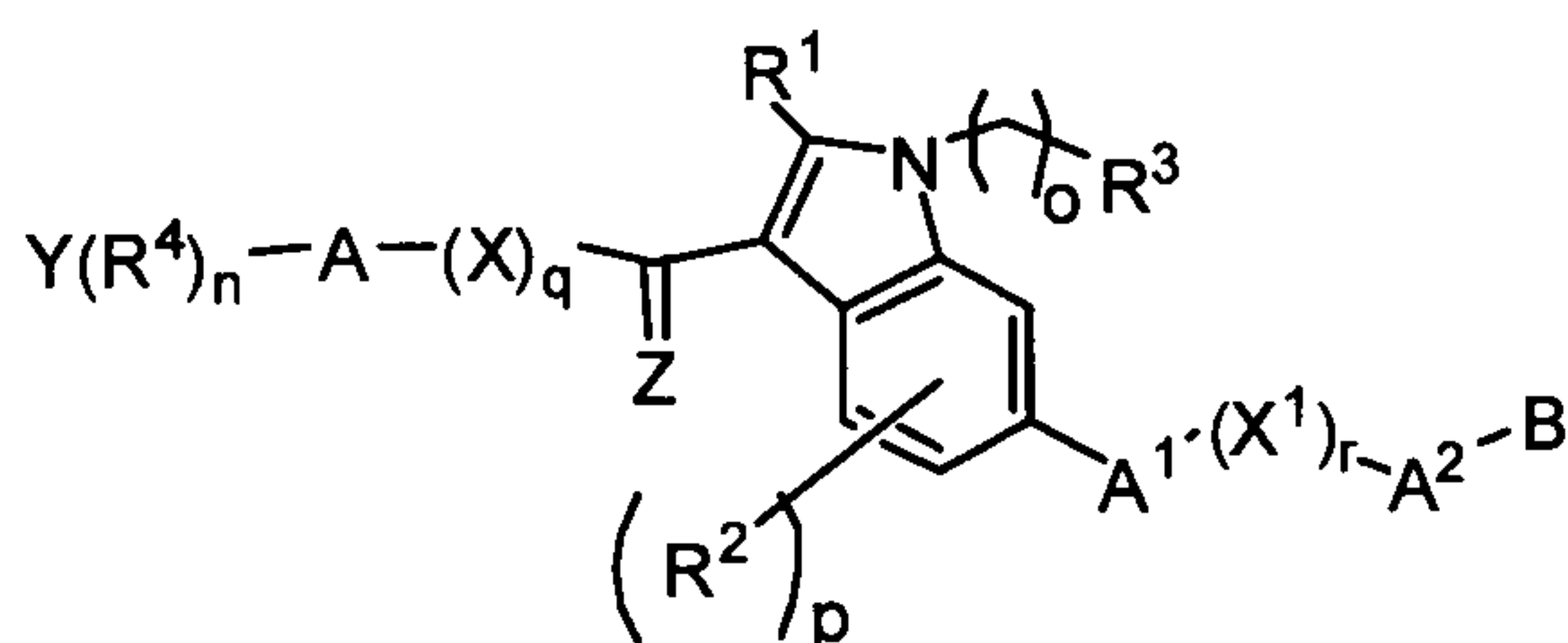
2. The compound of claim 1 wherein Z is O.
3. The compound of claim 2 wherein Y is a phenyl group or a pyridyl group.
4. The compound of claim 3 wherein A is CH_2 .
5. The compound of claim 4 wherein X is NH.
6. The compound of claim 5 wherein n is 0 or an integer of 1 or 2 and R^4 is fluoro.
7. The 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 fluoro 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 .
- 5 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 .
- 10 14. The compound of claim 13 wherein R^6 , R^8 and R^9 are methyl.
- 15 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.
- 20 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.
- 25 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
- $$(X^1)_r-A^2-B$$
- 30 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
 35 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.

5

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

15

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 X¹ are independently selected from the group consisting of NR⁵, O and S;

R⁵ is hydrogen, an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons, phenyl or lower alkylphenyl;

5 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;

10 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;

15 r is 0 or 1;

A, A¹ and A² are independently selected from the group consisting of

(CH₂)_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

20 and 1 to 3 triple bonds;

B is selected from the group consisting of hydrogen, OR⁶, COOR⁷,

NR⁸R⁹, CONR⁸R⁹, COR¹⁰, CH=NOR¹¹, CH=NNR¹²R¹³

wherein R⁶, R⁷, R¹⁰ and R¹¹ are independently selected from the group

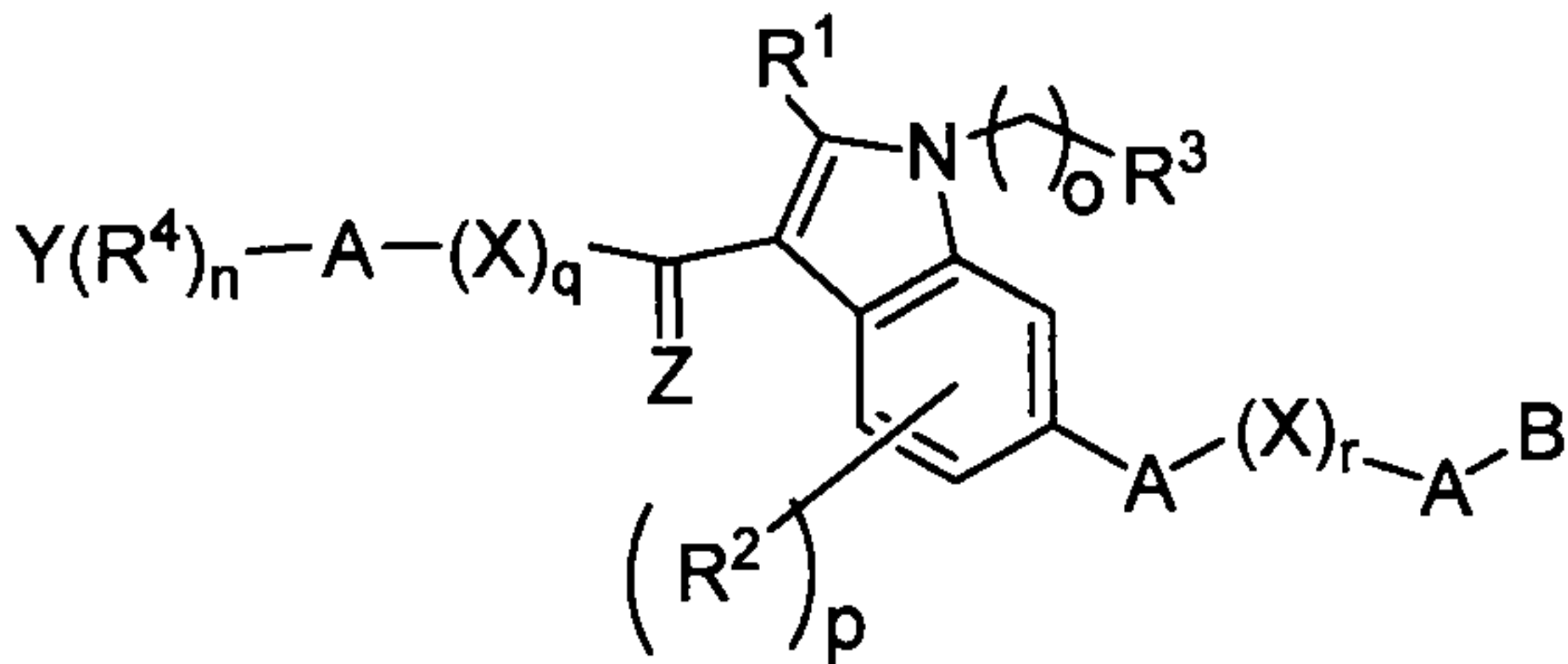
consisting of hydrogen, straight or branched chain alkyl having 1 to 12

25 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
5 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,
10 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
15 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.



Formula I