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(71) Applicant *(for all designated States except US)*: **ALCON UNIVERSAL LTD.** [CH/CH]; P.O. Box 62, Bosch 60, CH-6331 Hunenberg (CH).

(71) Applicant and
(72) Inventor: **CHEN, Hwang-Hsing** [US/US]; 7649 Grassland Drive, Fort Worth, TX 76133 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MAY, Jesse, A.** [US/US]; 4132 Hildring Drive, Fort Worth, TX 76109 (US). **DANTANARAYANA, Anura, P.** [US/US]; 5824 Bayside Drive, Fort Worth, TX 76132 (US).

(74) Agents: **YEAGER, Sally, S.** et al.; R & D Counsel, Mail Code Q-148, 6201 South Freeway, Fort Worth, TX 76134 (US).

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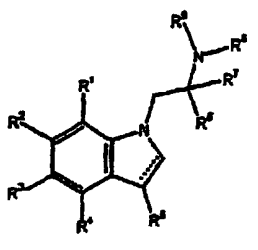
(54) Title: 1-AMINOALKYL-1*H*-INDOLES FOR TREATING GLAUCOMA

(57) Abstract: 1-Aminoalkyl-1*H*-indoles receptor agonists (I) for treating ocular hypertension and glaucoma are disclosed.



(I)

1-AMINOALKYL-1*H*-INDOLES FOR TREATING GLAUCOMA

The present invention is directed to substituted 1-aminoalkyl-1*H*-indoles. These novel compounds are useful for lowering and controlling normal or elevated intraocular pressure (IOP) and treating glaucoma.

Background of the Invention

The disease state referred to as glaucoma is characterized by a permanent loss of visual function due to irreversible damage to the optic nerve. The several morphologically or functionally distinct types of glaucoma are typically characterized by elevated IOP, which is considered to be causally related to the pathological course of the disease. Ocular hypertension is a condition wherein intraocular pressure is elevated but no apparent loss of visual function has occurred; such patients are considered to be a high risk for the eventual development of the visual loss associated with glaucoma. If glaucoma or ocular hypertension is detected early and treated promptly with medications that effectively reduce elevated intraocular pressure, loss of visual function or its progressive deterioration can generally be ameliorated. Drug therapies that have proven to be effective for the reduction of intraocular pressure include both agents that decrease aqueous humor production and agents that increase the outflow facility. Such therapies are in general administered by one of two possible routes, topically (direct application to the eye) or orally.

There are some individuals who do not respond well when treated with certain existing glaucoma therapies. There is, therefore, a need for other topical therapeutic agents that control IOP.

It has been found that serotonergic compounds which possess agonist activity at 5-HT_2 receptors effectively lower and control normal and elevated IOP and are useful for treating glaucoma, see commonly owned co-pending application, PCT/US99/19888. Compounds that act as agonists at 5-HT_2 receptors are well known and have shown a variety of utilities, primarily for disorders or conditions associated with the central nervous system (CNS). U.S. Patent 5,494,928 discloses certain 2-(indol-1-yl)-ethylamine derivatives that are 5-HT_{2C} agonists for the treatment of obsessive compulsive disorder and other CNS derived personality disorders. U.S. Patent 5,571,833 discloses tryptamine derivatives that are 5-HT_2 agonists for the treatment of portal hypertension and migraine. U.S. Patent 5,874,477 discloses a

method for treating malaria using 5-$HT_{2A/2C}$ agonists. U.S. Patent 5,902,815 discloses the use of 5-HT_{2A} agonists to prevent adverse effects of NMDA receptor hypo-function. WO98/31354A2 discloses 5-HT_{2B} agonists for the treatment of depression and other CNS conditions. WO00/12475 discloses indoline derivatives as 5-HT_{2B} and 5-HT_{2C} receptor agonists for the treatment of a variety of disorders of the central nervous system, but especially for the treatment of obesity. WO00/35922 discloses certain pyrazino[1,2-a]quinoxaline derivatives as 5-HT_{2C} agonists for the treatment of obsessive-compulsive disorder, depression, eating disorders, and other disorders involving the CNS. Agonist response at the 5-HT_{2A} receptor is reported to be the primary activity responsible for hallucinogenic activity, with some lesser involvement of the 5-HT_{2C} receptor possible [Psychopharmacology, Vol. 121:357, 1995].

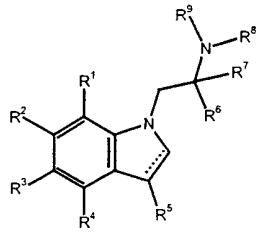
Summary of the Invention

The present invention is directed to new and known 2-(indol-1-yl)-ethylamines which can be used to lower and control IOP associated with normotension glaucoma, ocular hypertension, and glaucoma in warm blooded animals, including man. The compounds are formulated in pharmaceutical compositions suitable for topical delivery to the eye.

Description of the Preferred Embodiments

Compounds which are useful according to the present invention are represented by the following Formula I.

FORMULA I



wherein R^1 to R^4 are independently chosen from hydrogen, halogen, C_{1-6}alkyl, trifluoromethyl, O-W, C_{1-6}alkylthio, C_{1-6}alkylsulfoxyl, C_{1-6}alkylsulfonyl, or cyano;
R^5 can be hydrogen, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy;

R^6 and R^7 are independently chosen from hydrogen or C_{1-4}alkyl, or R^6, R^7 and the carbon atom to which they are attached can form a cyclopropyl ring, or furthermore, R^7 and R^8 together can be $(CH_2)_m$ to form a saturated heterocycle;
R^8 and R^9 are independently chosen from hydrogen or C_{1-4}alkyl;
R^1 to R^4 cannot simultaneously be hydrogen;
W is hydrogen, C_{1-6}alkyl, C(=O)X, or P(=O)(OY)(OZ),
X is C_{1-6}alkyl, NR^8R^9, $N(R^8)CH_2(CH_2)_nC(=O)NR^8R^9$, OC_{1-6}alkyl, C_{1-6}alkyl (which can be substituted with halogen, hydroxyl, CO_2C_{1-4}alkyl, $CON(C_{1-4}alkyl)_2$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, NH_2), C_{2-4}alkenyl (substituted by phenyl, unsubstituted or substituted with one or more of C_{1-4}alkyl, C_{1-4}alkoxy or halogen);
Y and Z are independently chosen from hydrogen, C_{1-10}alkyl or Y and Z can together form a lower alkyl chain of $(CH_2)_m$;
m is 2 – 4;
n is 1 or 2;
the dashed bond (-----) can be either a double or single bond, but when a single bond R^5 is hydrogen;
and pharmaceutically acceptable salts and solvates of the compounds of Formula I.

Compounds that are novel and which are useful according to the present invention can be defined as follows:

R^1 and R^2 are independently chosen from hydrogen, halogen, C_{1-6}alkyl, trifluoromethyl, O-W, C_{1-6}alkylthio, C_{1-6}alkylsulfoxyl, C_{1-6}alkylsulfonyl, or cyano;
R^3 and R^4 are independently chosen from hydrogen, halogen, C_{1-6}alkyl, trifluoromethyl, or cyano;
R^5 can be hydrogen, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy;
R^6 and R^7 are independently chosen from hydrogen or C_{1-4}alkyl, or R^6, R^7 and the carbon atom to which they are attached can form a cyclopropyl ring, or furthermore, R^7 and R^8 together can be $(CH_2)_m$ to form a saturated heterocycle;
R^8 and R^9 are independently chosen from hydrogen or C_{1-4}alkyl;
R^1 to R^4 cannot simultaneously be hydrogen;
R^6 and R^7 cannot both be hydrogen;
W is hydrogen, C_{1-6}alkyl, C(=O)X, or P(=O)(OY)(OZ),
X is C_{1-6}alkyl, NR^8R^9, $N(R^8)CH_2(CH_2)_nC(=O)NR^8R^9$, OC_{1-6}alkyl, C_{1-6}alkyl (which can be substituted with halogen, hydroxyl, CO_2C_{1-4}alkyl, $CON(C_{1-4}alkyl)_2$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, NH_2), C_{2-4}alkenyl (substituted by phenyl, unsubstituted or substituted with one or more of C_{1-4}alkyl, C_{1-4}alkoxy or halogen);

Y and Z are independently chosen from hydrogen, C_{1-10}alkyl or Y and Z can together form a lower alkyl chain of $(CH_2)_m$;
m is 2 – 4;
n is 1 or 2;
the dashed bond (-----) is a double bond;
and pharmaceutically acceptable salts and solvates.

Preferred novel compounds are:

where R^1, R^3, and R^4 are independently chosen from hydrogen, halogen, C_{1-6}alkyl, trifluoromethyl, or cyano;
R^2 is O-W;
R^5 can be hydrogen, C_{1-6}alkyl, or C_{1-4}alkoxy, halogen;
R^6 and R^7 are independently chosen from hydrogen, C_{1-4}alkyl or R^6, R^7 and the carbon atom to which they are attached can form a cyclopropyl ring, or furthermore, R^7 and R^8 together can be $(CH_2)_m$ to form a saturated heterocycle;
R^8 and R^9 are independently chosen from hydrogen or C_{1-4}alkyl;
W is hydrogen, C_{1-4}alkyl, C(=O)X, or P(=O)(OY)(OZ);
X is C_{1-6}alkyl, NR^8R^9, $N(R^8)CH_2(CH_2)_nC(=O)NR^8R^9$, OC_{1-6}alkyl, C_{1-6}alkyl (which can be substituted with halogen, hydroxyl, CO_2C_{1-4}alkyl, $CON(C_{1-4}alkyl)_2$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, NH_2), C_{2-4}alkenyl (substituted by phenyl, unsubstituted or substituted with one or more of C_{1-4}alkyl, C_{1-4}alkoxy or halogen);
Y and Z are independently chosen from hydrogen, C_{1-10} alkyl or Y and Z can together form a lower alkyl chain of $(CH_2)_m$;
m is 2 – 4;
n is 1 or 2;
the dashed bond (-----) is a double bond;

The more preferred novel compounds are:

where R^1, R^3, and R^4 are independently chosen from hydrogen or halogen;
R^2 is O-W;
R^5 can be hydrogen, C_{1-6}alkyl;
R^6 and R^7 are independently chosen from hydrogen, C_{1-4}alkyl or R^6, R^7 and the carbon atom to which they are attached can form a cyclopropyl ring;
R^8 and R^9 are independently chosen from hydrogen or C_{1-4}alkyl;
W is hydrogen, C_{1-4}alkyl;

The most preferred novel compounds are:

where R^1, R^3, and R^4 are independently chosen from hydrogen or halogen;
R^2 is O-W;
R^5 is hydrogen or C_{1-6}alkyl;
R^6 is hydrogen and R^7 is methyl;
R^8 and R^9 are hydrogen;
W is hydrogen, C_{1-4}alkyl;
the dashed bond (-----) is a double bond;

Representative examples of preferred novel compounds of Formula I are:

2-(6-methoxy-indol-1-yl)-1-methyl-ethylamine
(S)-2-(6-methoxy-indol-1-yl)-1-methyl-ethylamine
2-(6-methoxy-3-methyl-indol-1-yl)-1-methyl-ethylamine
2-(6-chloro-indol-1-yl)-1-methyl-ethylamine
2-(5-fluoro-indol-1-yl)-1-methyl-ethylamine
1-(2-amino-propyl)-7-fluoro-1*H*-indol-6-ol
1-(2-amino-propyl)-4-methyl-1*H*-indol-6-ol
1-(2-amino-propyl)-4,5-difluoro-1*H*-indol-6-ol
1-(2-amino-propyl)-1*H*-indol-7-ol
2-(7-methoxy-indol-1-yl)-1-methyl-ethylamine
2-(5-fluoro-6-methoxy-indol-1-yl)-1-methyl-ethylamine

Some especially preferred novel representative compounds of Formula I are:

1-(2-amino-propyl)-1*H*-indol-6-ol
(S)-1-(2-amino-propyl)-1*H*-indol-6-ol
1-(2-amino-propyl)-5-fluoro-1*H*-indol-6-ol
(S)-1-(2-amino-propyl)-5-fluoro-1*H*-indol-6-ol

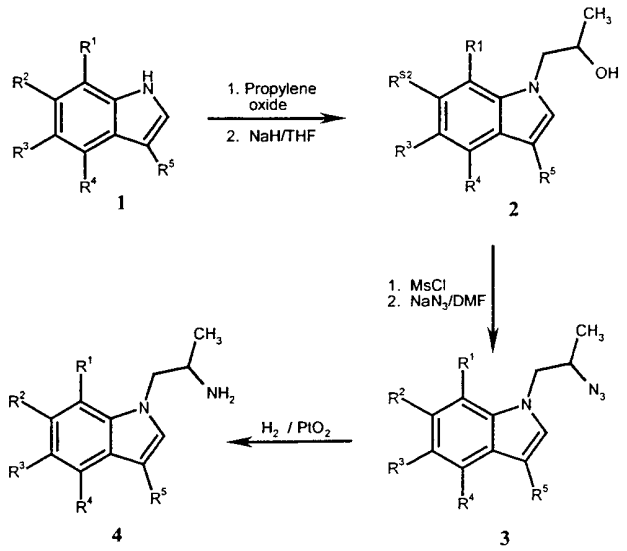
When a phenolic moiety is included in this substitution, e.g. a hydroxyl group at indole ring position six, such compounds can be particularly sensitive to oxidation reactions well known to occur with phenolic compounds in general, including hydroxytryptamines [*J. Phys. Chem.* 103, 8606 (1999), *Chem. Res. Toxicol.* 11, 639 (1998), *J. Org. Chem.* 52, 2817 (1987), *J. Pharm. Sci.* 77, 911 (1988)], which are of particular relevance to the present application. Protection of such hydroxy substituted tryptamines from oxidation can be accomplished by derivatization of the aryl hydroxy group to provide a suitable ester, carbamate, or carbonate. Though the ester, carbamate, or carbonate derivatives do not themselves possess a high affinity for the

above mentioned receptors, they do have utility in the treatment of glaucoma since suitably protected phenols can be cleaved in vivo either by chemical hydrolysis or through the action of tissue esterases, thereby delivering the desired therapeutic agent, that is, the desired hydroxy-isotryptamine compound in the present case. The concept of utilizing such derivatized phenolic compounds as chemical delivery agents is well known in the art [*Drugs Pharm. Sci.* 53, 221 (1992), *Pharm. Res.*, 168 (1984)].

SYNTHESIS

The novel compounds of Formula I can be prepared from the appropriately substituted indole **1** by methods well known in the art and described in Scheme 1 [U.S. Patent 5,494,928; J. Med. Chem., Vol. 40:2762, 1997]. Alternately, and

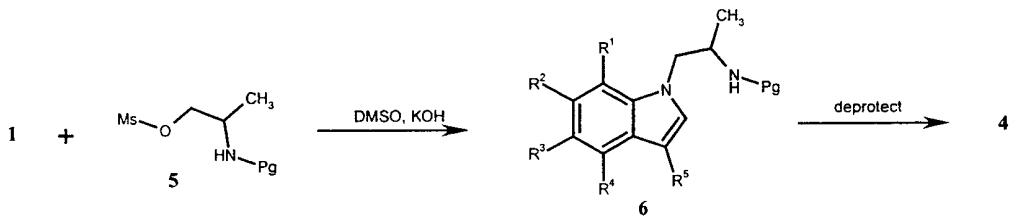
Scheme 1



preferably, the compounds of Formula I can be prepared by the method of Scheme 2. Reaction of indole **1** with the activated alaninol **5**, wherein the hydroxyl group has been suitably activated toward subsequent nucleophilic amination by formation of a sulfonate ester [J. Chem. Soc., Perkins Vol. 1:1479, 1981], e.g. methansulfonyl, toluenesulfonyl, bromophenylsulfonyl, or nitrophenylsulfonyl, provides **6** which following *N*-deprotection gives compounds **4** of Formula I. Replacement of **5** in Scheme 2 with, for example, an activated sulfonate ester of *N*-protected (e.g. with *t*-butyloxycarbonyl, benzyloxycarbonyl) pyrrolidin-3-methanol would, following removal of the amine protective group, provide yet another compound of Formula I.

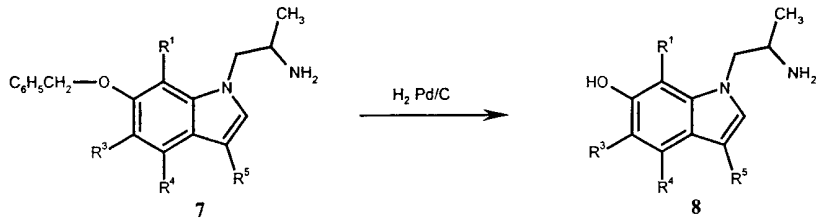
Further, replacement of **5** in Scheme 2 with an activated sulfonate ester of *N*-(2-hydroxy-1,1-dimethyl-ethyl)-phthalimide [J. Amer. Chem. Soc., Vol. 108:3811, 1986], 2-[(*t*-butyloxycarbonyl)amino]-2-methylpropanol [J. Amer. Chem. Soc. Vol. 113:8879, 1991], 1-[(*t*-butyloxycarbonyl)amino]-cyclopropyl-1-methanol [J. Med. Chem., Vol. 31:1694, 1988], or 2-methyl-2-nitro-propan-1-ol [J. Amer. Chem. Soc., Vol. 68:12, 1946] would, following removal of the *N*-protective groups in the first three cases, or reduction of the nitro group in the latter, provide yet other examples of Formula I. It is evident to those skilled in the art that the aforementioned intermediate compounds **5** contain one chiral center. Therefore compounds **5** can exist as racemates or as one of the two individual and distinct enantiomers which together comprise the racemate. The herewith-defined synthetic procedures are applicable to each of these structural manifestations.

Scheme 2



Other compounds of Formula I, particularly when R^1 or R^2 are hydroxyl (e.g., **8**), can be prepared from, for example, **7** under suitable hydrogenolysis conditions well known in the art (Scheme 3).

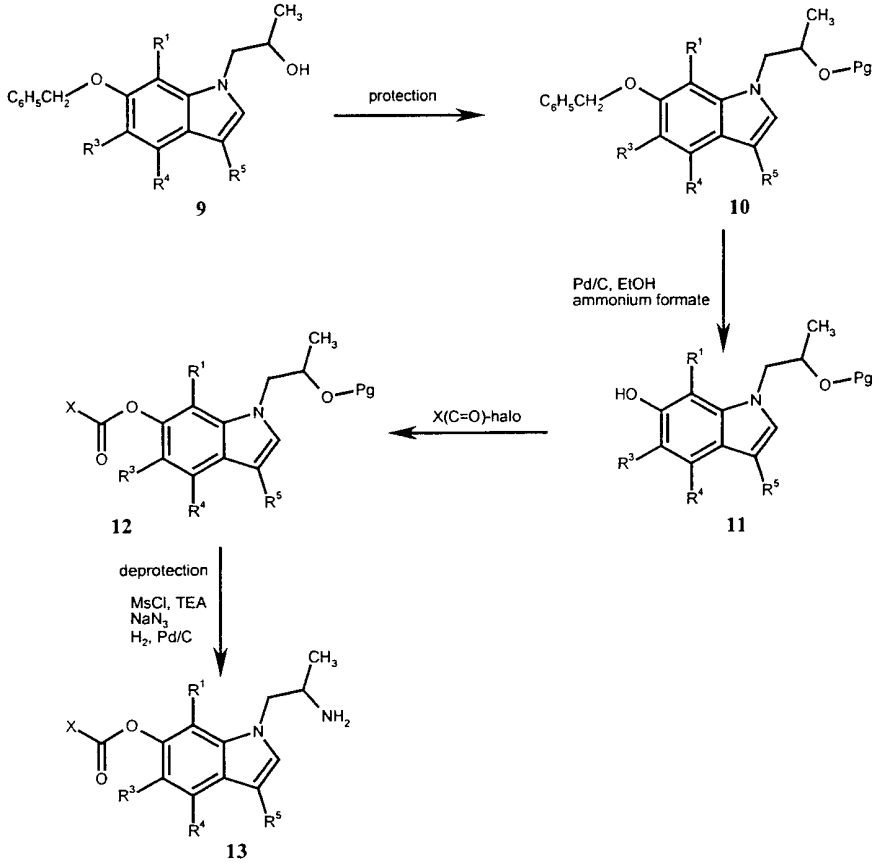
Scheme 3



Compounds of Formula I wherein R^1 or R^2 are OC(=O)X can be prepared as outlined in Scheme 4. The hydroxyl group of compound **9**, prepared as outlined in Scheme 1, can be protected from subsequent reactions by incorporation of a suitable

O-protective group, such as *t*-butyldiphenylsilyl (**10**), and followed by removal of the benzyl group by well known hydrogenolysis procedures to provide the phenol **11**. Reaction of **11** with a suitable acid chloride or acid anhydride by procedures well known in the art will provide intermediate esters **12**. Subsequent removal of the hydroxyl protective group and conversion of the hydroxyl group to a primary amine as described in Scheme 1 provides esters **13**.

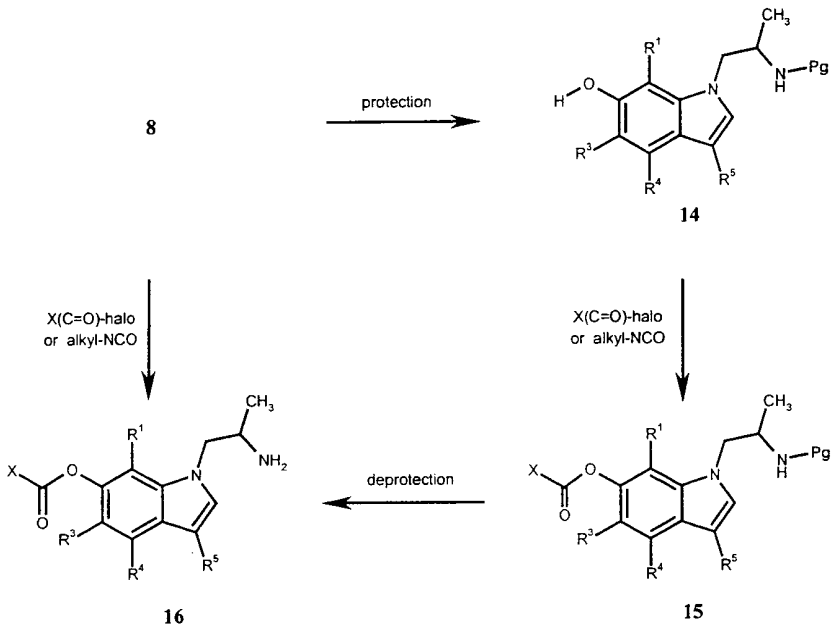
Scheme 4



Yet other compounds of Formula I, where R^1 or R^2 are OC(=O)X, can be prepared by reacting the appropriate indole, e.g. **8**, or a suitable amino-protected intermediate, e.g. **14**, (Scheme 5) with the desired activated acid derivative, such as an acid halide or active ester, or the like, to provide the esters **16** directly or intermediate esters **15**, or with the appropriate alkyl isocyanate, or the like, to provide the intermediate carbamates, **15**. Similarly, reaction of **14** with suitable alkyl chloroformates, or the like, would provide the desired carbonate intermediates **15**.

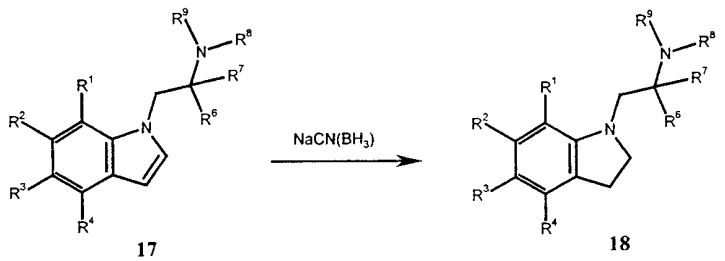
Removal of the *N*-protective group from the intermediate **15** provides the desired compounds **16** of Formula I as described previously (Scheme 5).

Scheme 5



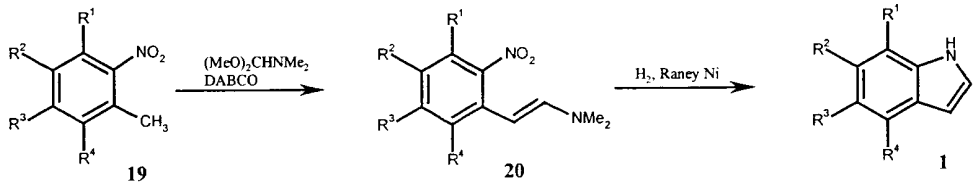
Compounds of Formula I were the dashed bound is a single bond, that is indolines (**18**), can be prepared by reduction of the corresponding substituted indole (Scheme 6) using procedures well known in the art. Suitable reagents for achieving this reduction include, for example, bis(trifluoroacetoxy)borane, borane, sodium cyanoborohydride, and sodium borohydride in conjunction with an appropriate solvent, preferably acetic acid.

Scheme 6



The indole derivatives (**1**) of interest for use as starting materials for the preparation of the compounds of Formula I can be either purchased from commercial suppliers, such as Biosynth, A.G., or prepared by known methods [Comp. Heterocycl. Chem. II, Vol. 2:119, 1996; J. Org. Chem., Vol. 62:2676, 1997]. For example, one such approach begins with the desired 4-alkoxy-2-nitrotoluene **19** and proceeds via a Leimgruber-Batcho indole synthesis [J. Med. Chem., Vol. 22:63, 1979 and U.S. Patent 3,732,245] to give desired indoles **1** (Scheme 7).

Scheme 7



The compounds can also be used in combination with other agents for treating glaucoma, such as, but not limited to, β-blockers (e.g., timolol, betaxolol, levobetaxolol, carteolol, levobunolol, propranolol), carbonic anhydrase inhibitors (e.g., brinzolamide and dorzolamide), α_1 antagonists (e.g. nipradolol), α_2 agonists (e.g., iopidine and brimonidine), miotics (e.g., pilocarpine and epinephrine), prostaglandin analogs (e.g., latanoprost, travaprost, unoprostone, and compounds set forth in U.S. Patent Nos. 5,889,052; 5,296,504; 5,422,368; and 5,151,444, "hypotensive lipids" (e.g., lumigan and compounds set forth in 5,352,708), and neuroprotectants (e.g., compounds from U.S. Patent No. 4,690,931, particularly eliprodil and R-eliprodil, as set forth in a pending application U.S.S.N. 06/203350, and appropriate compounds from WO94/13275, including memantine.

The following examples are given to illustrate the preparation of compounds that are the subject of this invention but should not be construed as implying any limitations to the claims. The preferred compounds of Formula I are described in Examples 3, 5, 6, and 9. Especially preferred compounds are those set forth in Examples 5 and 6. The most preferred is the compound of Example 6. The proton magnetic resonance spectrum of each compound of the Examples was consistent with the assigned structure.

METHOD 1

5-HT_2 Receptor Binding Assay

In order to determine the relative affinities of serotonergic compounds at the 5-HT_2 receptors, their ability to compete for the binding of the agonist radioligand [^{125}I]DOI to brain 5-HT_2 receptors is determined as described below with minor modification of the literature procedure [Neuropharmacology, 26, 1803 (1987)]. Aliquots of post mortem rat cerebral cortex homogenates (400 µl) dispersed in 50 mM TrisHCl buffer (pH 7.4) are incubated with [^{125}I]DOI (80 pM final) in the absence or presence of methiothepin (10 µM final) to define total and non-specific binding, respectively, in a total volume of 0.5 ml. The assay mixture is incubated for 1 hour at 23°C in polypropylene tubes and the assays terminated by rapid vacuum filtration over Whatman GF/B glass fiber filters previously soaked in 0.3% polyethyleneimine using ice-cold buffer. Test compounds (at different concentrations) are substituted for methiothepin. Filter-bound radioactivity is determined by scintillation spectrometry on a beta counter. The data are analyzed using a non-linear, iterative curve-fitting computer program [Trends Pharmacol. Sci., 16, 413 (1995)] to determine the compound affinity parameter. The concentration of the compound needed to inhibit the [^{125}I]DOI binding by 50% of the maximum is termed the IC_{50} value. Compounds of the present disclosure are considered to possess high affinity for the 5-HT_2 receptor if their IC_{50} values are < 75 nM.

METHOD 2

5-HT_2 Functional Assay: Phosphoinositide (PI) turnover assay

The relative agonist activity of serotonergic compounds at the 5-HT_2 receptor can be determined in vitro using the ability of the compounds to stimulate the production of [^{3}H]inositol phosphates in [^{3}H]*myo*-inositol-labeled A7r5 rat vascular smooth muscle cells by their ability to activate the enzyme phospholipase C. These cells are grown in culture plates, maintained in a humidified atmosphere of 5% CO_2 and 95% air and fed semi-weekly with Dulbecco's modified Eagle medium (DMEM) containing 4.5 g/l glucose and supplemented with 2mM glutamine, 10 µg/ml gentamicin, and 10% fetal bovine serum. For the purpose of conducting the phosphoinositide (PI) turnover experiments, the A7r5 cells are cultured in 24-well plates as previously described [J. Pharmacol. Expt. Ther., 286, 411 (1998)]. Confluent cells are exposed for 24-30 hrs to 1.5 µCi [^{3}H]-*myo*-inositol (18.3 Ci/mmol) in 0.5 ml of serum-free medium. Cells are then rinsed once with DMEM/F-12

containing 10 mM LiCl prior to incubation with the test agent (or solvent as the control) in 1.0 ml of the same medium for 1 hr at 37°C, after which the medium is aspirated and 1 ml of cold 0.1 M formic acid added to stop the reaction. The chromatographic separation of [^{3}H]-inositol phosphates ([^{3}H]-IPs) on an AG- 1-X8 column is performed as previously described [J. Pharmacol. Expt. Ther. 286, 411 (1998)] with sequential washes with H_2O and 50 mM ammonium formate, followed by elution of the total [^{3}H]-IPs fraction with 1.2 M ammonium formate containing 0.1 M formic acid. The eluate (4 ml) is collected, mixed with 15 ml scintillation fluid, and the total [^{3}H]-IPs determined by scintillation counting on a beta-counter. Concentration-response data are analyzed by the sigmoidal fit function of the Origin Scientific Graphics software (Microcal Software, Northampton, MA) to determine agonist potency (EC_{50} value) and efficacy (E_{max}). Serotonin (5-HT) is used as a positive control (standard) agonist compound and the efficacy of test compounds is compared to that of 5-HT (set at 100%). The concentration of the compound needed to stimulate the production of [^{3}H]-IPs by 50% of the maximum response is termed the EC_{50} value. Compounds are considered potent agonists if their EC_{50} values in this functional assay are < 2.5 μM and are considered full agonists if their efficacy (E_{max}) is > 80% of that of 5-HT.

The above procedures were used to generate the data shown in Table 1.

Table 1. 5-HT_2 Receptor Binding and Functional Data.

Example	IC_{50}, nM	EC_{50}, μM	Efficacy (E_{max}, %)
(R)-DOI	0.46	0.028	82
1	2.50	0.196	86
1.1	0.98	1.53	93
1.2	2.2	1.74	86
1.3	23	0.99	73
1.4	4.2	2.6	72
1.5	37.1	1.17	104
1.6	0.34	0.16	99
1.7	1.0	0.13	113
1.8	9.44	1.02	46
1.9	8.3	0.44	99
1.10	6.98	0.78	86
1.11	2.11	2.2	90
2	2.18	0.460	110
3	7.05	0.158	102
5	5.95	0.577	86
6	2.81	0.467	80
8	0.891	0.106	84
9	68.1	2.10	103
9.1	1.0	0.86	91

METHOD 3

Acute IOP Response in Lasered (Hypertensive) Eyes of Conscious Cynomolgus Monkeys

Intraocular pressure (IOP) was determined with an Alcon Pneumatonometer after light corneal anesthesia with 0.1% proparacaine. Eyes were washed with saline after each measurement. After a baseline IOP measurement, test compound was instilled in one 30 μL aliquot to the right eyes only of nine cynomolgus monkeys. Vehicle was instilled in the right eyes of six additional animals. Subsequent IOP measurements were taken at 1, 3, and 6 hours. A compound is considered efficacious in this model of ocular hypertension if there is a decrease in the baseline IOP of the lasered eye (O.D.) of at least 20% following topical administration.

The profile of the IOP response following topical administration of representative compounds is provided in Table 2.

Table 2. IOP Response in Conscious Cynomolgus Monkeys

Compound	Dose, µg	Baseline IOP (mmHg)	Percent IOP Reduction ± SEM Hours after Dose		
			1	3	6
(R)-DOI	100	31.9	11.0 ± 4.98	25.3 ± 2.97	34.4 ± 4.98
Example 1	300	36.7	22.0 ± 3.49	33.0 ± 4.07	33.6 ± 6.37
Example 1.5	300	39.0	11.2 ± 3.11	16.0 ± 4.07	20.1 ± 3.67
Example 1.8	300	41.0	15.6 ± 4.66	19.5 ± 6.97	20.7 ± 5.93
Example 3	300	38.6	19.2 ± 5.88	27.2 ± 6.63	23.7 ± 8.33
Example 5	300	33.9	16.5 ± 5.18	30.0 ± 3.75	27.3 ± 8.37

EXAMPLE 1

2-(6-methoxy-indol-1-yl)-1-methyl-ethylamine fumarate

Step A: 1-(6-methoxy-indol-1-yl)-propan-2-ol

To a solution of 6-methoxyindole (2.0 g, 13.6 mmol) in THF (20 mL) at 0°C was added sodium hydride (60% in oil, 0.71 g, 17.7 mmol). After stirring for 1 h, propylene oxide (1.88 mL, 27.0 mmol) was added and the solution stirred for 48 h. The reaction was quenched by the addition of water (50 mL) and the mixture was extracted with ethyl acetate (3 x 65 mL). The combined ethyl acetate extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to a residue which was purified by chromatography (silica, 30% ethyl acetate in hexane) to give a syrup (2.4 g, 86%); MS (ES) *m/z* 206 (M^+), 188.

Step B: 1-(2-azido-propyl)-6-methoxy-1*H*-indole

To a solution of the product from Step A (2.4 g, 12.0 mmol) in dichloromethane (10 mL) at 0°C was added triethylamine (5.1 mL, 36.1 mmol) followed by methanesulfonyl chloride (1.8 mL, 23.4 mmol). After 1 h ether (50 mL) and water (50 mL) were added. The organic layer was removed and the aqueous was extracted with ether (2 x 50 mL). The combined extracts were washed with brine (30 mL), dried and evaporated to a residue which was dissolved in DMF (6 mL) and sodium azide (1.5 g, 23.4 mmol) was added. The reaction mixture was heated at 60°C for 8 h, poured into water, and extracted with ether (3 x 50 mL). The combined

extracts were washed with brine, dried and evaporated to a residue which was purified by chromatography (silica, hexane to 10% ethyl acetate in hexane) to give a syrup (2.1 g, 76%): MS (ES) *m/z* 231(M^+).

Step C: 2-(6-methoxy-indol-1-yl)-1-methyl-ethylamine fumarate

A suspension of platinum oxide (0.27 g) in ethanol (10 mL) was stirred under an atmosphere of hydrogen for 0.5 h. To this mixture was added a solution of the product from Step B (2.1 g, 9.4 mmol) in ethanol (5 mL) and the mixture was stirred for 6 h. Additional platinum oxide (0.05 g) was added and stirring continued for 12 h. The mixture was filtered and the filtrate evaporated to a residue (1.3 g, 67%) which was dissolved in methanol (10 mL) and a solution of fumaric acid (0.75 g) in methanol was added. Evaporation provided a solid that was crystallized from methanol/ether (0.9 g): mp 195-197°C; MS (ES) *m/z* 205 (M^+), 188. Analysis. Calculated for $C_{12}H_{16}N_2O \cdot C_4H_4O_4$: C, 59.99; H, 6.29; N, 8.74. Found: C, 59.99; H, 6.35; N, 8.78.

The following compounds were prepared in a similar manner but using the appropriate substituted indole in Step A instead of 6-methoxyindole:

1.1. 2-(4-methyl-indol-1-yl)-1-methyl-ethylamine fumarate; *m/z* 189 (M+1).
1.2. 2-(7-ethyl-indol-1-yl)-1-methyl-ethylamine fumarate; *m/z* 203 (M+1).
1.3 2-(5-bromo-indol-1-yl)-1-methyl-ethylamine fumarate; *m/z* 253 (M+1).
1.4. 2-(6-chloro-indol-1-yl)-1-methyl-ethylamine fumarate; *m/z* 209 (M+1).
1.5. 2-(5-chloro-indol-1-yl)-1-methyl-ethylamine fumarate; *m/z* 209 (M+1).
1.6. 2-(4-chloro-indol-1-yl)-1-methyl-ethylamine fumarate; *m/z* 209 (M+1).
1.7. 2-(4-bromo-indol-1-yl)-1-methyl-ethylamine fumarate; *m/z* 253 (M+1).
1.8. 2-(5-fluoro-indol-1-yl)-1-methyl-ethylamine fumarate; *m/z* 193 (M+1).
1.9 2-(5,6-dichloro-indol-1-yl)-1-methyl-ethylamine fumarate; *m/z* 243 (M+1).
1.10. 2-(4,5-difluoro-indol-1-yl)-1-methyl-ethylamine fumarate; *m/z* 211 (M+1).
1.11. 2-(5,7-difluoro-indol-1-yl)-1-methyl-ethylamine fumarate; *m/z* 209 (M+1).

EXAMPLE 2

2-(6-methoxy-3-methyl-indol-1-yl)-1-methyl-ethylamine maleate

This compound was prepared by following the procedure described in Example 1 but using 6-methoxy-3-methyl-indole (0.70 g, 4.35 mmol) as the indole starting material in Step A: mp 181-182°C; MS (ES) *m/z* 219 (M^+). Analysis.

Calculated for $C_{13}H_{18}N_2O \cdot C_4H_4O_4$: C, 61.07; H, 6.63; N, 8.38. Found: C, 61.03; H, 6.74; N, 8.39.

EXAMPLE 3

(S)-2-(6-methoxy-indol-1-yl)-1-methyl-ethylamine fumarate

This compound was prepared by following the procedure described in Example 1 but replacing racemic propylene oxide with R-(+)-propylene oxide in Step A: mp 174-176°C; $[\alpha]_D$ +17.9° (c 0.50, MeOH); MS (ES) m/z 205 (M^+). Analysis. Calculated for $C_{12}H_{16}N_2O \cdot C_4H_4O_4$: C, 59.99; H, 6.29; N, 8.74. Found: C, 60.04; H, 6.36; N, 8.70.

EXAMPLE 4

(R)-2-(6-methoxy-indol-1-yl)-1-methyl-ethylamine fumarate

This compound was prepared by following the procedure described in Example 1 but replacing racemic propylene oxide with S-(-)-propylene oxide in Step A: mp 174-176°C; $[\alpha]_D$ –16.8° (c 0.50, MeOH); MS (ES) m/z 205 (M^+). Analysis. Calculated for $C_{12}H_{16}N_2O \cdot C_4H_4O_4$: C, 59.99; H, 6.29; N, 8.74. Found: C, 60.02; H, 6.28; N, 8.71.

EXAMPLE 5

1-(2-amino-propyl)-1*H*-indol-6-ol fumarate

Step A: 1-(6-benzyloxy-indol-1-yl)-propan-2-ol

To a solution of 6-benzyloxyindole (0.75 g, 3.4 mmol) in THF (20 mL) at 0°C was added sodium hydride (60% in oil, 0.17 g, 4.4 mmol). After stirring for 1 h, propylene oxide (0.47 mL, 6.7 mmol) was added and the mixture stirred at room temperature for 48 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 65 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to a residue that was purified by chromatography (silica, 30% ethyl acetate in hexane) to give a syrup (0.75 g, 79%): MS (ES) *m/z* 282 (M^+).

Step B: 1-(2-azido-propyl)-6-benzyloxy-1*H*-indole

To a solution of the product from Step A (0.75 g, 2.70 mmol) in dichloromethane (10 mL) at 0°C was added triethylamine (1.1 mL, 8.0 mmol) and methanesulfonyl chloride (0.42 mL, 5.3 mmol). After stirring for 1 h, ether (50 mL)

and water (50 mL) were added. The organic layer was removed and the aqueous extracted with ether (2 x 50 mL). The combined extracts were washed with brine (30 mL), dried and evaporated. The residue was dissolved in DMF (6 mL) followed by the addition of sodium azide (0.35 g, 5.4 mmol). The reaction mixture was heated at 60°C for 8 h, poured into water, and extracted with ether (3 x 50 mL). The combined extracts were washed with brine, dried and evaporated to a residue that was purified by chromatography (silica, hexane to 10% ethyl acetate in hexane) to give a syrup (0.67 g, 82%): MS (ES) *m/z* 307 (M^+).

Step C: 1-(2-amino-propyl)-1*H*-indol-6-ol fumarate

A suspension of platinum oxide (0.15 g) in ethanol (10 mL) at room temperature was stirred under a hydrogen atmosphere for 30 minutes. A solution of the product from Step B (0.67 g, 2.2 mmol) in ethanol was added and the mixture stirred for 20 h. The reaction mixture was filtered and 5% Pd/C (0.10 g) was added followed by shaking at room temperature and under an atmosphere of hydrogen (50 psi) for 20 h. The catalyst was removed and the filtrate concentrated to a residue which was purified by chromatography (silica, 5% to 20% methanol in dichloromethane) to give a syrup (0.32 g, 76%). This material was dissolved in methanol (10 mL) and treated with a solution of fumaric acid (0.2 g) in methanol to give a solid (0.22 g, from methanol/ether): mp 165-167°C; MS (ES) *m/z* 191 (M^+). Analysis. Calculated for $C_{11}H_{14}N_2O \cdot 1.05\ M\ C_4H_4O_4$: C, 58.49; H, 5.88; N, 8.98. Found: C, 58.84; H, 6.28; N, 8.67.

EXAMPLE 6

1-((S)-2-amino-propyl)-1*H*-indol-6-ol

This compound was prepared by following the procedure described in Example 5 but replacing racemic propylene oxide with R-(+)-propylene oxide in Step A and by not forming the salt in Step B, but isolating the free base: mp 165-167°C; $[\alpha]_D$ +38.5° (c 0.14, MeOH); MS (ES) *m/z* 191 (M^+). Analysis. Calculated for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.23; H, 7.36; N, 14.55.

EXAMPLE 7

1-((R)-2-amino-propyl)-1*H*-indol-6-ol

This compound was prepared by following the procedure described in Example 6 but replacing R-(+)-propylene oxide with S-(-)-propylene oxide: 165-

167°C; $[\alpha]_D$ -26.6° (c 0.17, MeOH); MS (ES) *m/z* 191 (M^+). Analysis. Calculated for $C_{11}H_{14}N_2O \cdot 0.2$ M H_2O: C, 68.16; H, 7.49; N, 14.45. Found: C, 68.49; H, 7.48; N, 14.63.

EXAMPLE 8

2-(5-fluoro-6-methoxy-indol-1-yl)-1-methyl-ethylamine fumarate

Step A. 4-fluoro-2-iodo-5-methoxy-aniline

Iodine (4.0 mg, 15.6 mmol) was added to a suspension of 4-fluoro-5-methoxy-aniline (2.2 g, 15.6 mmol) in a 5% aqueous solution of sodium bicarbonate (2.0 mL) and the mixture was stirred for 18 h at room temperature. The reaction mixture was extracted with ether (4 x 50 mL) and the combined extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated to a residue which was purified by chromatography (silica, 30% ethyl acetate in hexane) to give an oil (2.6 g, 62%).

Step B: 5-fluro-6-methoxy-2-trimethylsilanyl-1*H*-indole

To a solution of the product from Step A (2.6 g, 9.7 mmol) in DMF (20 mL) at room temperature was added palladium acetate (0.25 g, 4.9 mmol), acetyl trimethylsilane (4.2 mL, 29.4 mmol), and DABCO (3.2 g, 29.4 mmol). This mixture was heated at 105°C for 5 h, water (50 mL) was added to quench the reaction followed by extraction of this mixture with ethyl acetate (3 x 65 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to a residue which was purified by chromatography (silica, 20% ethyl acetate in hexane) to give an oil (1.5 g, 94%): MS (ES) m/z 238(M^+).

Step C. 1-(5-fluoro-6-methoxy-indol-1-yl)-propan-2-ol

To a stirred solution of the product from Step B (1.2 g, 7.2 mmol) in DMF (12 mL) at 0°C was added sodium hydride (60% in oil, 0.43 g, 10.8 mmol). After 1 h, propylene oxide (1.30 mL, 14.5 mmol) was added, and the mixture was stirred for 48 h at room temperature. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 65 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to a residue which was purified by chromatography (silica, 50% ethyl acetate in hexane) to give an oil (2.4 g, 86%): MS (ES) *m/z* 223(M^+).

Step D. 1-(2-azidopropyl)-5-fluoro-6-methoxy-1*H*-indole

A solution of the product from Step C (1.9 g, 8.9 mmol) in dichloromethane (10 mL) was treated as described for Step B, Example 1 to provide, after chromatography (50% ethyl acetate in hexane), an oil (1.3 g, 59%).

Step E. 2-(5-fluoro-6-methoxy-indol-1-yl)-1-methyl-ethylamine fumarate

To a solution of the product from Step D (1.3 g, 5.0 mmol) in methanol (10 mL) under a nitrogen atmosphere was added 10% palladium-on-carbon (0.2 g). The nitrogen was replaced with a balloon of hydrogen gas and the suspension stirred for 16 h. The catalyst was removed and the filtrate evaporated to a residue (0.70 g, 63%) which was dissolved in methanol (10 mL) and treated with a solution of fumaric acid (0.75 g) in methanol. The solid that formed was recrystallized from methanol/ether to give a colorless solid (0.73 g): mp 182-183°C; MS (ES) *m/z* 223(M^+). Analysis. Calculated for $C_{12}H_{15}FN_2O \cdot 1.2\ C_4H_4O_4 \cdot 1.0\ H_2O$: C, 55.28; H, 6.00; N, 7.58. Found: C, 55.28; H, 6.34; N, 7.51.

EXAMPLE 9

2-(6-methoxyindolin-1-yl)-1-methyl-ethylamine fumarate

To a solution of the product from Example 1 (0.51 g, 1.45 mmol) in acetic acid (10 mL) was added sodium cyanoborohydride (0.92 g, 14.5 mmol) at room temperature. After 2 h the solution was carefully added to a saturated aqueous solution of potassium carbonate and extracted with dichloromethane (3 x 65 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to a residue (0.36 g, 70%). The residue was dissolved in ethanol (10 mL) and treated with an ethanolic solution of fumaric acid (0.30 g). The solid was crystallized from a mixture of methanol and ether to give a colorless solid (0.20 g): m.p. 174-176°C; MS (ES) *m/z* 207(M^+), 190. Analysis. Calculated for $C_{12}H_{18}N_2O \cdot C_4H_4O_4$: C, 59.62; H, 6.88; N, 8.69. Found: C, 59.37; H, 6.96; N, 8.56.

The following compound was prepared in a similar manner but by reduction of the product from Example 1.8:

9.1 2-(4-chloroindolin-1-yl)-1-methyl-ethylamine fumarate; *m/z* 211 (M+1).

EXAMPLE 10

2,2-dimethyl-propionic acid 1-(2-amino-propyl)-1*H*-indol-6-yl ester fumarate

Step A: 6-benzyloxy-1-[2-(*tert*-butyl-diphenylsilanyloxy)-propyl]-1*H*-indole

To a solution of the product from Example 5, Step A (6.2 g, 22.0 mmol) in dichloromethane (10 mL) at 0°C was added imidazole (1.8 g, 26.6), DMAP (0.2 g) and *tert*-butylchlorodiphenylsilane (6.9 mL, 26.4 mmol). The cooling bath was removed and the reaction mixture warmed to room temperature and stirred for 2 hours. A saturated aqueous solution of ammonium chloride (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated to a residue which was purified by chromatography (silica, 10% to 20% ethyl acetate in hexane) to give a syrup (4.1 g, 38%): MS (ES) *m/z* 520 (M^+).

Step B: 1-[2-(tert-butyl-diphenylsilanyloxy)-propyl]-1*H*-indol-6-ol

To a solution of the product of Step A (4.0 g, 7.7 mmol) in ethanol (10 mL) at room temperature and under a nitrogen atmosphere was added 10% Pd/C (0.5 g) followed by ammonium formate (1.45 g, 23.0 mmol); this suspension was stirred for 16 h. The solids were removed and the filtrate evaporated to a residue which was purified by chromatography (silica, 30% to 50% ethyl acetate in hexane) to give a syrup (1.3 g, 39%): MS (ES) *m/z* 430 (M^+).

Step C: 2,2-dimethyl-propionic acid 1-[2-(*tert*-butyl-diphenylsilanyloxy)-propyl]-1*H*-indol-6-yl ester

To a solution of the product from Step B (1.1 g, 2.6 mmol) in dichloromethane (10.0 mL) at room temperature was added triethylamine (0.55 mL, 3.9 mmol), DMAP (0.10 g) and trimethylacetyl chloride (0.49 mL, 3.9 mmol). After stirring for 2 h, a saturated aqueous solution of ammonium chloride (20 mL) was added and the mixture extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with brine (10mL), dried ($MgSO_4$) and evaporated to give a residue which was purified by chromatography (silica, 20% to 30% ethyl acetate in hexane) to give an oil (1.3 g, 100%): MS (ES) *m/z* 520 (M^+).

Step D: 2,2-dimethyl-propionic acid 1-(2-hydroxy-propyl)-1*H*-indol-6-yl ester

To a solution of the product from Step C (1.3 g, 2.5 mmol) in THF at room temperature was added tetrabutylammonium fluoride (1.0 M, 3.0 mL, 3.0 mmol); this mixture was stirred for 18 h. A saturated aqueous solution of ammonium chloride (20 mL) was added and the mixture extracted with ethyl acetate (3 x 50 mL). The

combined extracts were washed with brine (10mL), dried ($MgSO_4$) and evaporated to give a residue which was purified by chromatography (silica, 20% to 50% ethyl acetate in hexane) to give an oil (0.41 g, 57%): MS (ES) *m/z* 276 (M^+).

Step E: 2,2-dimethyl-propionic acid 1-(2-azido-propyl)-1*H*-indol-6-yl ester

To a stirred solution of the product from Step D (0.41 g, 1.42 mmol) in dichloromethane (10 mL) at 0°C was added triethylamine (0.60 mL, 4.26 mmol) and methanesulfonyl chloride (0.22 mL, 2.85 mmol). After stirring the mixture for 1 h, ether (50 mL) and water (50 mL) were added. The organic layer was removed and the aqueous extracted with ether (2 x 50 mL). The combined extracts were washed with brine (30 mL), dried and evaporated to a residue that was dissolved in DMF (6 mL) and sodium azide (0.19 g, 2.85 mmol) was added. The reaction mixture was heated at 50°C for 18 h, poured into water, and extracted with ether (3 x 50 mL). The combined extracts were washed with brine (10 mL), dried and evaporated to a residue which was purified by chromatography (silica, hexane to 10% ethyl acetate in hexane) to give an oil (0.31 g, 71%): MS (ES) *m/z* 301 (M^+).

Step F: 2,2-dimethyl-propionic acid 1-(2-amino-propyl)-1*H*-indol-6-yl ester fumarate

A solution of the product from Step E (0.31g, 1.03 mmol) in ethanol (50 mL) at room temperature was shaken with 5% Pd/C (0.10 g) under a hydrogen atmosphere (40 psi) for 18 h. The catalyst was removed and the filtrate evaporated to a residue that was purified by chromatography (silica, 5% to 10% methanol in dichloromethane) to give an oil (0.25 g, 88%). The oil was dissolved in methanol (10 mL) and treated with a solution of fumaric acid (0.09 g) in methanol to give a solid (0.12 g from methanol/ether): mp 190-192°C; MS (ES) *m/z* 275 (M^+). Analysis. Calculated for $C_{16}H_{22}N_2O_2 \cdot 0.6\ M\ C_4H_4O_4$: C, 64.24; H, 7.15; N, 8.14. Found: C, 64.22; H, 7.26; N, 8.25.

EXAMPLE 11

2,2-dimethyl-propionic acid 1-((S)-2-amino-propyl)-1*H*-indol-6-yl ester fumarate

Step A: (S)-[2-(6-benzyloxyindol-1-yl)-1-methylethyl]-carbamic acid *tert*-butyl ester

To a solution of 6-benzyloxyindole (2.5 g,11.2 mmol) in DMSO (10 mL) at room temperature was added KOH (1.88 g, 33.6 mmol) and the mixture was stirred for 45 min. A solution of (S)-(-)-3-methanesulfonyloxy-2-(*tert*-

butoxycarbonylamino)-propane (4.2 g, 16.6 mmol) in DMSO (10 mL) and sodium iodide (0.1 g) were added. This mixture was heated at 55°C for 18 h, diluted with a saturated aqueous solution of ammonium chloride (30 mL), and extracted with ethyl acetate (3 x 60 mL). The combined extracts were washed with brine (10mL), dried ($MgSO_4$) and evaporated to give a residue which was purified by chromatography (silica, 10% to 20% ethyl acetate in hexane) to give a syrup (2.2 g, 51%): MS (ES) *m/z* 381 (M^+).

Step B: (S)-[2-(6-hydroxyindol-1-yl)-1-methylethyl]-carbamic acid *tert*-butyl ester

To a solution of the product from Step A (1.07 g, 2.8 mmol) in ethanol (10 mL) at room temperature and under a nitrogen atmosphere was added 10% Pd/C (0.5 g) followed by ammonium formate (0.53 g, 8.4 mmol); this mixture was stirred for 20 h. The reaction mixture was filtered and the filtrate evaporated to a residue which was purified by chromatography (silica, 30% to 50% ethyl acetate in) to give an oil (0.28 g, 35%): MS (ES) *m/z* 291 (M^+).

Step C: 2,2-dimethyl-propionic acid [1-(S)-2-(*tert*-butoxycarbonylamino)-propyl]-1*H*-indol-6-yl ester

To a solution of the product from Step B (0.34 g, 1.17 mmol) in dichloromethane (10.0 mL) at room temperature was added triethylamine (0.19 mL, 1.12 mmol), DMAP (0.05 g), and trimethylacetyl chloride (0.18 mL, 1.41 mmol); this mixture was stirred for 1 h. A saturated aqueous solution of ammonium chloride (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated to a residue which was purified by chromatography (silica, 20% to 30% ethyl acetate in hexane) to give an oil (0.43 g, 100%): MS (ES) *m/z* 375 (M^+).

Step D: 2,2-dimethyl-propionic acid 1-((S)-2-amino-propyl)-1*H*-indol-6-yl ester fumarate

To a solution of the product from Step C (0.43g, 1.15 mmol) in dichloromethane (10 mL) at room temperature was added trifluoroacetic acid (2.0 mL). After stirring for 1 h, the reaction mixture was evaporated to a residue and a saturated aqueous solution of sodium bicarbonate (20 mL) was added. This mixture was extracted with dichloromethane (3 x 60 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated to a residue which was purified by chromatography (silica, 2% to 5% methanol in dichloromethane) to give a

syrup (0.23g, 73%). This material was dissolved in methanol (10 mL) and treated with a solution of fumaric acid (0.10 g) in methanol to provide a solid (0.12 g, from methanol/ether): mp 189-191°C; $[\alpha]_D$ + 16.7° (c 0.28, MeOH); MS (ES) *m/z* 275 (M^+). Analysis. Calculated for $C_{16}H_{22}N_2O_2 \cdot 0.6$ M $C_4H_4O_4$: C, 64.24; H, 7.15; N, 8.14. Found: C, 64.56; H, 7.31; N, 8.25.

EXAMPLE 12

2,2-dimethyl-propionic acid 1-((R)-2-amino-propyl)-1*H*-indol-6-yl ester fumarate

This compound was prepared by following the procedure described in Example 9 but using (R)-(-)-3-methanesulfonyloxy-2-(*tert*-butoxycarbonylamino)-propane in Step A: mp 190-191°C; $[\alpha]_D$ - 17.9 (c 0.33, MeOH); MS (ES) *m/z* 275 (M^+). Analysis. Calculated for $C_{16}H_{22}N_2O_2.0.6$ M $C_4H_4O_4$: C, 64.24; H, 7.15; N, 8.14. Found: C, 64.50; H, 7.31; N, 8.22.

EXAMPLE 13

2-(6-acetoxy-indol-1-yl)-1-methyl-ethylamine maleate

Step A: [2-(6-hydoxyindol-1-yl)-1-methylethyl]-carbamic acid benzyl ester

To a solution of the product from Example 5, Step B (1.70 g, 8.99 mmol) in THF (50 mL) was added a saturated aqueous solution of sodium bicarbonate (10 mL). This mixture was cooled (ice bath) and benzyl chloroformate (1.69 g, 9.89 mmol) was added. The reaction mixture was stirred for 30 min and extracted with ethyl acetate (3 x 50 mL). The extracts were dried ($MgSO_4$) and evaporated to a residue that was purified by column chromatography (10% to 25% ethyl acetate in hexane) to give an oil (1.83 g, 63%): LCMS *m/z* 325 (M+1).

Step B: 2-(6-acetoxy-indol-1-yl)-*N*-(benzyloxycarbonyl)-1-methyl-ethylamine

To a solution of the product from Step A (0.40 g, 1.23 mmol) in THF ((50 mL) containing triethylamine (0.373 g, 3.69 mmol) at 0°C was added acetic anhydride (0.164 g, 1.60 mmol) and a catalytic amount of 4-dimethylaminopyridine. After stirring for 30 min additional acetic anhydride (0.088 g, 0.86 mmol) was added. The mixture was stirred for 30 min and evaporated to a residue that was purified by column chromatography (10% to 20% ethyl acetate in hexane) to give an oil (0.44 g, 98%): MS *m/z* 367 (M+H).

Step C: 2-(6-acetoxy-indol-1-yl)-1-methyl-ethylamine maleate

A solution of the product from Step B (0.44 g, 1.2 mmol) in methanol (10 mL) was stirred under a hydrogen atmosphere in the presence of 10% palladium-on-carbon (0.045 g). After 18 h the reaction mixture was evaporated to a residue that was dissolved in methanol and filtered. The filtrate was evaporated to a residue (0.26 g) that was dissolved in methanol and combined with a solution of maleic acid (0.13 g, 1.12 mmol) in methanol (5 mL). Evaporation of this mixture provided a viscous syrup (0.39 g, 93%): MS *m/z* 233 (M+H).

EXAMPLE 14

cyclopropanecarboxylic acid 1-(2-amino-propyl)-1*H*-indol-6-yl ester maleate

This compound was prepared by following the procedure described in Example 11 but using cyclopropanecarbonyl chloride instead of acetic anhydride in Step B: 70% yield; MS(APCI) *m/z* 259 (M+H). Analysis. Calculated for $C_{15}H_{18}N_2O_4 \cdot C_4H_4O_4 \cdot 0.5\ H_2O$: C, 59.51; H, 6.04; N, 7.41. Found: C, 59.67; H, 6.02; N, 7.31.

EXAMPLE 15

2-(6-methoxycarbonyloxy-indol-1-yl)-1-methyl-ethylamine maleate

This compound was prepared by following the procedure described in Example 11 but using methyl chloroformate instead of acetic anhydride in Step B: 76% yield; MS *m/z* 249 (M+H). Analysis. Calculated for $C_{13}H_{16}N_2O_3 \cdot C_4H_4O_4$: C, 56.04; H, 5.53; N, 7.69. Found: C, 56.13; H, 5.57; N, 7.63.

EXAMPLE 16

Ingredients	Amount (wt %)
1-((S)-2-Aminopropyl)-1*H*-indol-6-ol	0.01 – 2%
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 17

Ingredients	Amount (wt %)
1-((S)-2-Aminopropyl)-1*H*-indol-6-ol	0.01 – 2%
Methyl cellulose	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 18

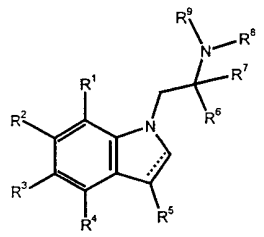
Ingredients	Amount (wt %)
1-((S)-2-Aminopropyl)-1*H*-indol-6-ol	0.01 – 2%
Guar gum	0.4- 6.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 19

Ingredients	Amount (wt %)
2,2-Dimethyl-propionic acid 1-((S)-2-amino-propyl)-1*H*-indol-6-yl ester	0.01 – 2%
White petrolatum and mineral oil and lanolin	Ointment consistency
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4

We Claim:

1. A compound of the formula:



wherein R^1 and R^2 are independently chosen from hydrogen, halogen, C_{1-6}alkyl, trifluoromethyl, O-W, C_{1-6}alkylthio, C_{1-6}alkylsulfoxyl, C_{1-6}alkylsulfonyl, or cyano;
R^3 and R^4 are independently chosen from hydrogen, halogen, C_{1-6}alkyl, trifluoromethyl, or cyano;
R^5 can be hydrogen, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy;
R^6 and R^7 are independently chosen from hydrogen or C_{1-4}alkyl, or R^6, R^7 and the carbon atom to which they are attached can form a cyclopropyl ring, or furthermore, R^7 and R^8 together can be $(CH_2)_m$ to form a saturated heterocycle;
R^8 and R^9 are independently chosen from hydrogen or C_{1-4}alkyl;
R^1 to R^4 cannot simultaneously be hydrogen;
R^6 and R^7 cannot both be hydrogen;
W is hydrogen, C_{1-6}alkyl, C(=O)X, or P(=O)(OY)(OZ),
X is C_{1-6}alkyl, NR^8R^9, $N(R^8)CH_2(CH_2)_nC(=O)NR^8R^9$, OC_{1-6}alkyl, C_{1-6}alkyl (which can be substituted with halogen, hydroxyl, CO_2C_{1-4}alkyl, $CON(C_{1-4}alkyl)_2$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, NH_2), C_{2-4}alkenyl (substituted by phenyl, unsubstituted or substituted with one or more of C_{1-4}alkyl, C_{1-4}alkoxy or halogen);
Y and Z are independently chosen from hydrogen, C_{1-10}alkyl or Y and Z can together form a lower alkyl chain of $(CH_2)_m$;
m is 2 – 4;
n is 1 or 2;
the dashed bond (-----) is a double bond;
and pharmaceutically acceptable salts and solvates.

2. The compounds of Claim 1:
where R^1, R^3, and R^4 are independently chosen from hydrogen, halogen, C_{1-6}alkyl, trifluoromethyl, or cyano;

R^2 is chosen from O-W;
R^5 can be hydrogen, C_{1-6}alkyl, or C_{1-4}alkoxy, halogen;
R^6 and R^7 are independently chosen from hydrogen, C_{1-4}alkyl or R^6, R^7 and the carbon atom to which they are attached can form a cyclopropyl ring, or furthermore, R^7 and R^8 together can be $(CH_2)_m$ to form a saturated heterocycle;
R^8 and R^9 are independently chosen from hydrogen or C_{1-4}alkyl;
W is hydrogen, C_{1-4}alkyl, C(=O)X, or P(=O)(OY)(OZ);
X is C_{1-6}alkyl, NR^8R^9, $N(R^8)CH_2(CH_2)_nC(=O)NR^8R^9$, OC_{1-6}alkyl, C_{1-6}alkyl (which can be substituted with halogen, hydroxyl, CO_2C_{1-4}alkyl, $CON(C_{1-4}alkyl)_2$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, NH_2), C_{2-4}alkenyl (substituted by phenyl, unsubstituted or substituted with one or more of C_{1-4}alkyl, C_{1-4}alkoxy or halogen);
Y and Z are independently chosen from hydrogen, C_{1-10} alkyl or Y and Z can together form a lower alkyl chain of $(CH_2)_m$;
m is 2 – 4;
n is 1 or 2;
the dashed bond (-----) is a double bond.

3. The compounds of Claim 1:
where R^1, R^3, and R^4 are independently chosen from hydrogen or halogen;
R^2 is O-W;
R^5 can be hydrogen, C_{1-6}alkyl;
R^6 and R^7 are independently chosen from hydrogen, C_{1-4}alkyl or R^6, R^7 and the carbon atom to which they are attached can form a cyclopropyl ring;
R^8 and R^9 are independently chosen from hydrogen or C_{1-4}alkyl;
W is hydrogen, C_{1-4}alkyl.

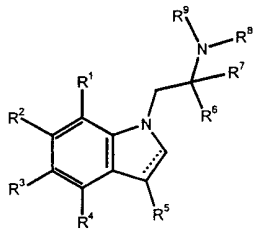
4. The compounds of Claim 1:
where R^1, R^3, and R^4 are independently chosen from hydrogen or halogen;
R^2 is O-W;
R^5 is hydrogen or C_{1-6}alkyl;
R^6 is hydrogen and R^7 is methyl;
R^8 and R^9 are hydrogen;
W is hydrogen, C_{1-4}alkyl;
the dashed bond (-----) is a double bond.

5. The compounds of Claim 1 where the compound is:
2-(6-methoxy-indol-1-yl)-1-methyl-ethylamine

(S)-2-(6-methoxy-indol-1-yl)-1-methyl-ethylamine
2-(6-methoxy-3-methyl-indol-1-yl)-1-methyl-ethylamine
2-(6-chloro-indol-1-yl)-1-methyl-ethylamine
2-(5-fluoro-indol-1-yl)-1-methyl-ethylamine
1-(2-amino-propyl)-7-fluoro-1*H*-indol-6-ol
1-(2-amino-propyl)-4-methyl-1*H*-indol-6-ol
1-(2-amino-propyl)-4,5-difluoro-1*H*-indol-6-ol
1-(2-amino-propyl)-1*H*-indol-7-ol
2-(7-methoxy-indol-1-yl)-1-methyl-ethylamine
2-(5-fluoro-6-methoxy-indol-1-yl)-1-methyl-ethylamine.

6. The compounds of Claim 1 where the compound is:
1-(2-amino-propyl)-1*H*-indol-6-ol
(S)-1-(2-amino-propyl)-1*H*-indol-6-ol
1-(2-amino-propyl)-5-fluoro-1*H*-indol-6-ol
(S)-1-(2-amino-propyl)-5-fluoro-1*H*-indol-6-ol.

7. A method for controlling normal and elevated intraocular pressure and treating glaucoma, which comprises, administering a pharmaceutically effective amount of a compound of the formula:



wherein R^1 to R^4 are independently chosen from hydrogen, halogen, C_{1-6}alkyl, trifluoromethyl, O-W, C_{1-6}alkylthio, C_{1-6}alkylsulfoxyl, C_{1-6}alkylsulfonyl, or cyano;
R^5 can be hydrogen, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy;
R^6 and R^7 are independently chosen from hydrogen or C_{1-4}alkyl, or R^6, R^7 and the carbon atom to which they are attached can form a cyclopropyl ring, or furthermore, R^7 and R^8 together can be $(CH_2)_m$ to form a saturated heterocycle;
R^8 and R^9 are independently chosen from hydrogen or C_{1-4}alkyl;
R^1 to R^4 cannot simultaneously be hydrogen;
W is hydrogen, C_{1-6}alkyl, C(=O)X, or P(=O)(OY)(OZ),

X is C_{1-6}alkyl, NR^8R^9, $N(R^8)CH_2(CH_2)_nC(=O)NR^8R^9$, OC_{1-6}alkyl, C_{1-6}alkyl (which can be substituted with halogen, hydroxyl, CO_2C_{1-4}alkyl, $CON(C_{1-4}alkyl)_2$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, NH_2), C_{2-4}alkenyl (substituted by phenyl, unsubstituted or substituted with one or more of C_{1-4}alkyl, C_{1-4}alkoxy or halogen);

Y and Z are independently chosen from hydrogen, C_{1-10}alkyl or Y and Z can together form a lower alkyl chain of $(CH_2)_m$;

m is 2 – 4;

n is 1 or 2;

the dashed bond (-----) can be either a double or single bond, but when a single bond R^5 is hydrogen;

and pharmaceutically acceptable salts and solvates.

8. The method of Claim 7 wherein the compound of Claim 7 is defined as follows:

R^1, R^3, and R^4 are independently chosen from hydrogen, halogen, C_{1-6}alkyl, trifluoromethyl, or cyano;

R^2 is chosen from O-W;

R^5 can be hydrogen, C_{1-6}alkyl, or C_{1-4}alkoxy, halogen;

R^6 and R^7 are independently chosen from hydrogen, C_{1-4}alkyl or R^6, R^7 and the carbon atom to which they are attached can form a cyclopropyl ring, or furthermore, R^7 and R^8 together can be $(CH_2)_m$ to form a saturated heterocycle;

R^8 and R^9 are independently chosen from hydrogen or C_{1-4}alkyl;

W is hydrogen, C_{1-4}alkyl, C(=O)X, or P(=O)(OY)(OZ);

X is C_{1-6}alkyl, NR^8R^9, $N(R^8)CH_2(CH_2)_nC(=O)NR^8R^9$, OC_{1-6}alkyl, C_{1-6}alkyl (which can be substituted with halogen, hydroxyl, CO_2C_{1-4}alkyl, $CON(C_{1-4}alkyl)_2$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, NH_2), C_{2-4}alkenyl (substituted by phenyl, unsubstituted or substituted with one or more of C_{1-4}alkyl, C_{1-4}alkoxy or halogen);

Y and Z are independently chosen from hydrogen, C_{1-10} alkyl or Y and Z can together form a lower alkyl chain of $(CH_2)_m$;

m is 2 – 4;

n is 1 or 2;

the dashed bond (-----) is a double bond.

9. The method of Claim 7 wherein the compound of Claim 7 is defined as follows:

R^1, R^3, and R^4 are independently chosen from hydrogen or halogen;

R^2 is O-W;

R^5 can be hydrogen, C_{1-6}alkyl;
R^6 and R^7 are independently chosen from hydrogen, C_{1-4}alkyl or R^6, R^7 and the carbon atom to which they are attached can form a cyclopropyl ring;
R^8 and R^9 are independently chosen from hydrogen or C_{1-4}alkyl;
W is hydrogen, C_{1-4}alkyl.

10. The method of Claim 7 wherein the compound of Claim 7 is defined as follows:
R^1, R^3, and R^4 are independently chosen from hydrogen or halogen;
R^2 is O-W;
R^5 is hydrogen or C_{1-6}alkyl;
R^6 is hydrogen and R^7 is methyl;
R^8 and R^9 are hydrogen;
W is hydrogen, C_{1-4}alkyl;
the dashed bond (-----) is a double bond.

11. The method of Claim 7 wherein the compound is:
2-(6-methoxy-indol-1-yl)-1-methyl-ethylamine
(S)-2-(6-methoxy-indol-1-yl)-1-methyl-ethylamine
2-(6-methoxy-3-methyl-indol-1-yl)-1-methyl-ethylamine
2-(6-chloro-indol-1-yl)-1-methyl-ethylamine
2-(5-fluoro-indol-1-yl)-1-methyl-ethylamine
1-(2-amino-propyl)-7-fluoro-1*H*-indol-6-ol
1-(2-amino-propyl)-4-methyl-1*H*-indol-6-ol
1-(2-amino-propyl)-4,5-difluoro-1*H*-indol-6-ol
1-(2-amino-propyl)-1*H*-indol-7-ol
2-(7-methoxy-indol-1-yl)-1-methyl-ethylamine
2-(5-fluoro-6-methoxy-indol-1-yl)-1-methyl-ethylamine.

12. The method of Claim 7 wherein the compound is:
1-(2-amino-propyl)-1*H*-indol-6-ol
(S)-1-(2-amino-propyl)-1*H*-indol-6-ol
1-(2-amino-propyl)-5-fluoro-1*H*-indol-6-ol
(S)-1-(2-amino-propyl)-5-fluoro-1*H*-indol-6-ol.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 00/31248

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/32 A61P27/06 A61K31/40

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)
IPC 7 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2001	05/04/2001

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	Gettins, M

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INTERNATIONAL SEARCH REPORT

national Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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