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(54) Title: NOVEL FUSED INDAZOLES AND INDOLES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

(57) Abstract: Novel fused indazoles and indoles are disclosed. Also disclosed are methods for the lowering and controlling of normal or elevated intraocular pressure as well as a method for the treatment of glaucoma using compositions containing one or more of the compounds of the present invention.

**NOVEL FUSED INDAZOLES AND INDOLES AND THEIR USE FOR THE
TREATMENT OF GLAUCOMA**

5 This application claims the benefit of U.S. Provisional Patent Application No. 60/295,428 filed June 1, 2001, which is incorporated in its entirety by reference herein.

BACKGROUND OF THE INVENTION

10 The present invention relates to various indazoles and indoles. These novel compounds are useful for lowering and controlling normal or elevated intraocular pressure (IOP) and for treating glaucoma.

 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
15 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 at high risk for the eventual development of the visual loss associated with glaucoma. If glaucoma or ocular hypertension
20 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,
25 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.

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Serotonergic 5-HT_{1A} agonists have been reported as being neuroprotective in animal models and many of these agents have been evaluated for the treatment of acute stroke among other indications. This class of compounds has been mentioned for the treatment of glaucoma (lowering and controlling IOP), see e.g., WO 98/18458 (DeSantis, et al.) and EP 0771563A2 (Mano, et al.). Osborne, et al. (Ophthalmologica, Vol. 210:308-314, 1996) teach that 8-hydroxydipropylaminotetralin (8-OH-DPAT) (a 5-HT_{1A} agonist) reduces IOP in rabbits. Wang, et al. (Current Eye Research, Vol. 16(8):769-775, August 1997, and IVOS, Vol. 39(4), S488, March, 1998) indicate that 5-methylurapidil, an α_{1A} antagonist and 5-HT_{1A} agonist lowers IOP in the monkey, but due to its α_{1A} receptor activity. Also, 5-HT_{1A} antagonists are disclosed as being useful for the treatment of glaucoma (elevated IOP) (e.g., WO 92/0338, McLees). Furthermore, DeSai, et al. (WO 97/35579) and Macor, et al. (U.S. 5,578,612) relate to the use of 5-HT₁ and 5-HT_{1-like} agonists for the treatment of glaucoma (elevated IOP). These anti-migraine compounds, e.g., sumatriptan and naratriptan and related compounds, are 5-HT_{1B,D,E,F} agonists.

It has been found that serotonergic compounds which possess agonist activity at 5-HT₂ receptors effectively lower and control normal and elevated IOP and are useful for treating glaucoma, see commonly owned co-pending application, PCT/US99/19888, incorporated in its entirety by reference herein. Compounds that act as agonists at 5-HT₂ 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 No. 5,494,928 relates to 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 No. 5,571,833 relates to tryptamine derivatives that are 5-HT₂ agonists for the treatment of portal hypertension and migraine. U.S. Patent No. 5,874,477 relates to a method for treating malaria using 5-HT_{2A/2C} agonists. U.S. Patent No. 5,902,815 relates to the use of 5-HT_{2A} agonists to

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prevent adverse effects of NMDA receptor hypo-function. WO 98/31354 relates to 5-HT_{2B} agonists for the treatment of depression and other CNS conditions. WO 00/12475 relates to indoline derivatives and WO 00/12510 and WO 00/44753 relate to certain indole 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. WO 00/35922 relates to 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. WO 00/77002 and WO 00/77010 relate to certain substituted tetracyclic pyrido[4,3-*b*]indoles as 5-HT_{2C} agonists with utility for the treatment of central nervous system disorders including obesity, anxiety, depression, sleep disorders, cephalic pain, and social phobias among others. 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].

U.S. Patent Nos. 5,561,150 and 5,646,173 relate to certain tricyclic pyrazole derivative compounds which are identified as being 5-HT_{2C} agonists for the treatment of CNS diseases and are primarily directed to lipophilic analogs that have a high probability of entering the brain. Similarly, WO 98/56768 relates to tricyclic 5-HT_{2C} agonists for the treatment of CNS diseases. All the patents, patent applications, and publications mentioned above and throughout are incorporated in their entirety by reference herein and form a part of the present application.

5-Hydroxytryptamine (serotonin) does not cross the blood-brain barrier and enter the brain. However, in order to increase brain serotonin levels the administration of 5-hydroxytryptophan can be employed. The transport of 5-hydroxytryptophan into the brain readily occurs, and once in the brain 5-hydroxytryptophan is rapidly decarboxylated to provide serotonin.

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The chemical synthesis of 2-(4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-ethylamine has been reported [J. Heterocyclic Chem. 11, 387 (1974), Chem. Heterocycl. Compd. (Engl. Transl.) 9, 196 (1973)] with no mention of utility. The synthesis of selected 2-(4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-ethylamine derivatives, such as 2-(8-fluoro-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-ethylamine, has been reported [Bioorg. Med. Chem. Lett. 10, 919 (2000)]. It was suggested that such compounds could have utility in the treatment of epilepsy and obesity. The preparation of 1- and 2-substituted 2*H*-indeno[1,2,3-*cd*]indazoles is disclosed in Belg. 718,057 (1968); these compounds are noted as having psychotherapeutic activity. Various ring substituted amides and esters of 7,8-dihydro-6*H*-pyrazolo[4,5,1-*ij*]quinoline-2-carboxylic acid have been disclosed as antagonists at 5-HT₃ receptors [U.S. Patent 4,985,424].

Accordingly, there is a need to provide new compounds which avoid the disadvantages described above and which provide increased chemical stability and a desired length of therapeutic activity, for instance, in decreasing intraocular pressure and treating glaucoma.

15 SUMMARY OF THE PRESENT INVENTION

A feature of the present invention is to provide novel compounds which are 5-HT₂ agonists.

Another feature of the present invention is to provide compounds which have increased chemical stability and which are useful in lowering and controlling normal or elevated intraocular pressure and/or treating glaucoma.

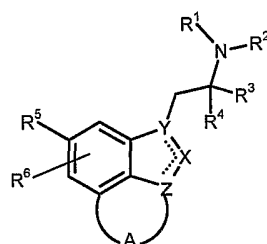
Another feature of the present invention is to provide compounds which provide a desired level of therapeutic activity in lowering and controlling normal or elevated intraocular pressure and/or treating glaucoma.

Additional features and advantages of the present invention will be set forth in part in the description that follows, and in part will be apparent from the description, or may be

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learned by practice of the present invention. The objectives and other advantages of the present invention will be realized and attained by means of the elements and combinations particularly pointed out in the description and appended claims.

To achieve these and other advantages, and in accordance with the purposes of the present invention, as embodied and broadly described herein, the present invention relates to a compound having the Formula I:



wherein R^1 and R^2 are independently chosen from hydrogen or an alkyl group such as C_{1-4} alkyl;

R^3 and R^4 are independently chosen from hydrogen, an alkyl group such as C_{1-4} alkyl, or R^3 , R^4 and the carbon atom to which they are attached can form a cycloalkyl ring, or

furthermore, R^2 and R^3 together can be $(CH_2)_m$ to form a saturated heterocycle;

R^5 is chosen from hydroxyl, an alkoxy group such as C_{1-4} alkoxy, an alkyl group such as C_{1-4} alkyl, halogen, or $OC(=O)W$;

R^6 is chosen from hydrogen, halogen, a unsubstituted or substituted alkyl group such as C_{1-4} alkyl or C_{1-4} alkyl substituted with halogen;

R^7 and R^8 are hydrogen or an alkyl group, such as C_{1-4} alkyl;

W is an alkyl group such as C_{1-6} alkyl, NR^7R^8 , $N(R^7)CH_2(CH_2)_nN(R^7)(R^8)$, O-alkyl such as OC_{1-6} alkyl, a substituted alkyl group such as C_{1-6} alkyl (substituted with halogen, hydroxyl, CO_2C_{1-4} alkyl, $CON(C_{1-4}$ alkyl) $_2$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, or NH_2), an alkenyl group such as C_{2-4} alkenyl (substituted by phenyl that is unsubstituted or substituted with one or more of an alkyl such as C_{1-4} alkyl, an alkoxy such as C_{1-4} alkoxy, or halogen);

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m is 3 or 4;

n is 2 or 3;

A is selected to complete a 5- to 7-membered ring optionally containing one heteroatom chosen from NR⁷, O, or S;

5 X is either N or C;

Y and Z are either N or C, wherein Y and Z cannot be the same; and

the dashed bonds denote a suitably appointed single and double bond;

and pharmaceutically acceptable salts and solvates of the compounds of Formula I.

The present invention further relates to pharmaceutical compositions containing at
10 least one compound of Formula I.

The present invention further relates to methods to lower and/or control normal or elevated intraocular pressure by administering an effective amount of a composition containing a compound having Formula I as described above.

The present invention also relates to a method for treating glaucoma which involves
15 administering an effective amount of a composition containing a compound having Formula I as described above.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are intended to provide a further explanation of the present invention, as claimed.

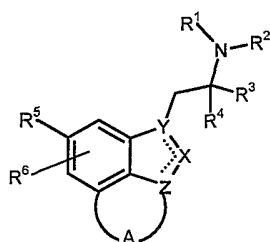
20 **DETAILED DESCRIPTION OF THE PRESENT INVENTION**

The present invention relates to a variety of compounds which are useful according to the present invention. These compounds are generally represented by the following

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Formula I:



10 In Formula I, R^1 and R^2 are independently chosen from hydrogen or an alkyl group such as C_{1-4} alkyl;

R^3 and R^4 are independently chosen from hydrogen, an alkyl group such as C_{1-4} alkyl, or R^3 , R^4 and the carbon atom to which they are attached can form a cycloalkyl ring (such as a cyclopropyl ring), or furthermore, R^2 and R^3 together can be $(CH_2)_m$ to form a saturated

15 heterocycle;

R^5 is chosen from hydroxyl, an alkoxy group such as C_{1-4} alkoxy, an alkyl group such as C_{1-4} alkyl, halogen, or $OC(=O)W$;

R^6 is chosen from hydrogen, halogen, a unsubstituted or substituted alkyl group such as C_{1-4} alkyl or C_{1-4} alkyl substituted with halogen;

20 R^7 and R^8 are hydrogen or an alkyl group such as C_{1-4} alkyl;

W is an alkyl group such as C_{1-6} alkyl, NR^7R^8 , $N(R^7)CH_2(CH_2)_nN(R^7)(R^8)$, O-alkyl such as OC_{1-6} alkyl, a substituted alkyl group such as C_{1-6} alkyl (substituted with halogen, hydroxyl, CO_2C_{1-4} alkyl, $CON(C_{1-4}alkyl)_2$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, or NH_2), an alkenyl group such as C_{2-4} alkenyl (substituted by phenyl, unsubstituted or substituted with one or more of

25 an alkyl such as C_{1-4} alkyl, an alkoxy such as C_{1-4} alkoxy or halogen);

m is 3 or 4;

n is 2 or 3;

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A represents a 5- to 7-membered ring optionally containing one heteroatom chosen from NR⁷, O, or S;

X is either N or C;

Y and Z are either N or C, wherein Y and Z are different from each other; and

5 the dashed bonds denote a suitably appointed single and double bond;

and pharmaceutically acceptable salts and solvates of the compounds of Formula I. Since the treatment of glaucoma is preferably with compounds that do not enter the CNS, relatively polar compounds that are 5-HT₂ agonists and have incorporated into their structure a phenolic hydroxyl group that can be considered comparable to that of serotonin, are of particular
10 interest.

Preferred compounds are:

Wherein R¹, R², and R³ are hydrogen;

R⁴ is C₁₋₄alkyl or R² and R³ together can be (CH₂)_m to form a pyrrolidine;

R⁵ is chosen from hydroxyl, C₁₋₄alkoxy, or OC(=O)W;

15 R⁶ is chosen from hydrogen, halogen, C₁₋₄alkyl, C₁₋₄alkyl substituted with halogen;

R⁷ and R⁸ are hydrogen or C₁₋₄alkyl;

W is C₁₋₆alkyl, NR⁷R⁸, C₁₋₆alkyl (which can be substituted with halogen, hydroxyl, CO₂C₁₋₄alkyl);

m is 3;

20 A is selected to complete a 6-membered ring optionally containing one heteroatom chosen from NR⁷ or O;

X is either N or C;

Y is N and Z is C; and

the dashed bonds denote a suitably appointed single and double bond;

25 or pharmaceutically acceptable salts and solvates of the above preferred compounds.

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Representative examples of preferred novel compounds of Formula I are:

- 2-(2-Aminopropyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol;
- 2-(2-Dimethylaminoethyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol;
- 2-(2-Aminopropyl)-5-methyl-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol;
- 5 2-(2-Aminopropyl)-5-fluoro-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol;
- 2-(6-Fluoro-7-methoxy-4,5-dihydro-3*H*-benzo[*cd*]indazol-1-yl)-1-methylethylamine;
- Cyclopropanecarboxylic acid 2-(2-aminopropyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-yl ester;
- 1-(2-Aminopropyl)-1,3,4,5-tetrahydro-benzo[*cd*]indol-7-ol;
- 10 1-(2-Aminopropyl)-5*H*-pyrano[4,3,2-*cd*]indazol-7-ol; or
- 1-(2-Aminopropyl)-4-methyl-1,3,4,5-tetrahydro-pyrazolo[4,3,2-*de*]isoquinolin-7-ol; or combinations thereof.

It is recognized that compounds of Formula I can contain one or more chiral centers.

This invention contemplates all enantiomers, diastereomers and, mixtures thereof.

- 15 In the above definitions, the total number of carbon atoms in a substituent group is indicated by the C_{*i,j*} prefix where the numbers *i* and *j* define the number of carbon atoms. This definition includes straight chain, branched chain, and cyclic alkyl or (cyclic alkyl)alkyl groups. A substituent may be present either singly or multiply when incorporated into the indicated structural unit. For example, the substituent halogen, which means fluorine,
- 20 chlorine, bromine, or iodine, would indicate that the unit to which it is attached may be substituted with one or more halogen atoms, which may be the same or different.

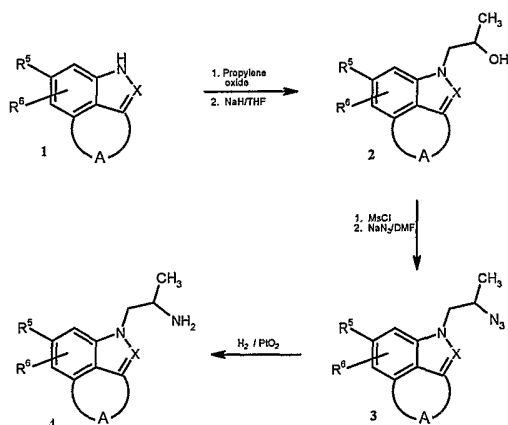
SYNTHESIS

- The compounds of Formula I can be prepared by processes analogous to those known in the art. The preparation of compounds 2 of Formula I wherein X is nitrogen or
- 25 carbon, Y is nitrogen, and Z is carbon can be prepared from the desired fused tricyclic

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indazole or indole intermediates **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].

Scheme 1

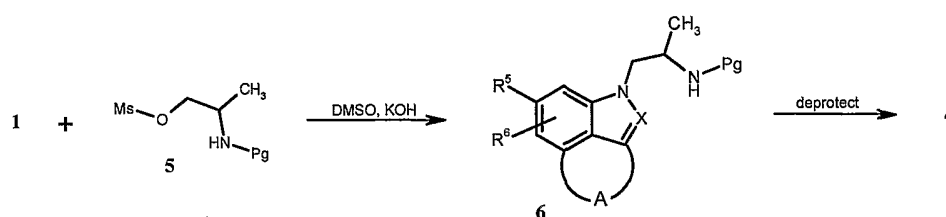


- 5 Alternately, and preferably, the compounds **2** can be prepared by the method of Scheme 2. Reaction of **1** with the activated alaninol **5**, wherein the hydroxyl group has been suitably activated toward subsequent nucleophilic amination by formation of, for example, a halide or a sulfonate ester [J. Chem. Soc., Perkins Vol. 1:1479, 1981], e.g. methanesulfonyl, toluenesulfonyl, bromophenylsulfonyl, or nitrophenylsulfonyl, provides **6** which following
- 10 *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
- 15 [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

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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.

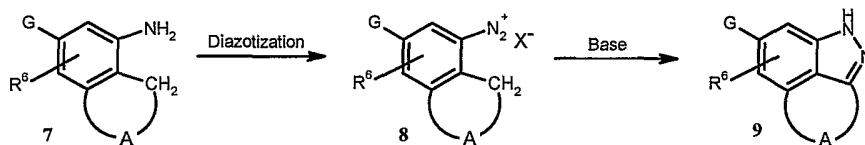
Scheme 2



The fused tricyclic indazoles **9** of structure **1** can be prepared from the desired ortho-alkyl-phenyldiazonium salts **8** using appropriate Jacobson indazole synthesis conditions as outlined in Scheme 3 [*Synthesis*, 1998, 986; *Ann. Chem.* 1980, 908; *Chem. Ber.* **111**, 367 (1978)]. Substituents G in intermediates **7** can be the same as substituents R^5 of compounds **4**. However, it can be desirable, because of chemical reactivity or commercial availability of specific synthetic intermediates, that G be a group that can subsequently be transformed to the desired groups R^5 by functional group transformations well known to the art. For example, it could be advantageous for G to be a nitro group in **7**, which would be converted to a hydroxyl group later in the sequence, for example, at the corresponding compounds **2**. Other such functional group transformations may be desirable and would be implemented as required to obtain a specific compound **4**.

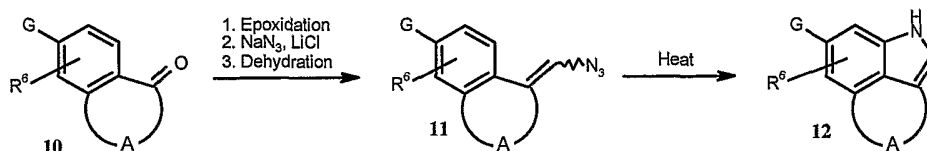
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Scheme 3



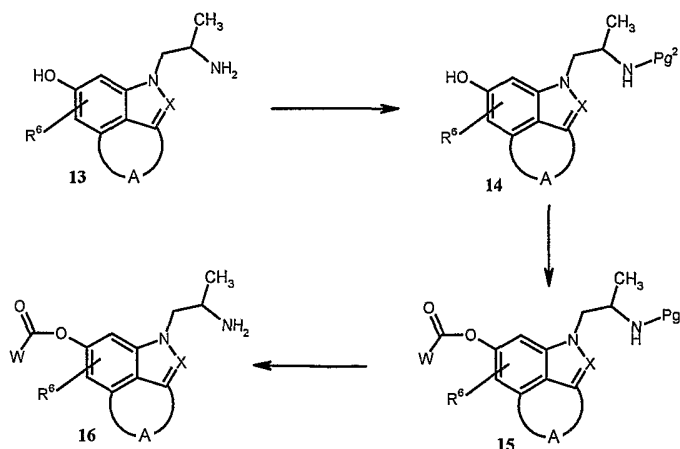
The fused tricyclic indoles **12** of structure **1** can be prepared from the desired ketone **10** via thermolysis of the intermediate vinyl azide **11** (Scheme 4) [*J. Chem. Soc., Perkin*
5 *Trans* 1, 1990, 89)].

Scheme 4



Compounds of Formula I, wherein R^5 is $OC(=O)W$, can be prepared by reacting the appropriate compound **4**, such as **13**, or preferably a suitable amino-protected intermediate,
10 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 **15**. Removal of the *N*-protective group from the intermediate **15** provides the desired compounds **16** of Formula I.

Scheme 5



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The compounds of the present invention can be used to lower and control IOP including IOP associated with normotension glaucoma, ocular hypertension, and glaucoma in warm blooded animals including humans. The compounds are preferably formulated in pharmaceutical compositions which are preferably suitable for topical delivery to the eye of the patient.

The compounds of this invention, Formula I, can be incorporated into various types of pharmaceutical compositions, such as ophthalmic formulations for delivery to the eye (e.g., topically, intracamerally, or via an implant). The compounds are preferably incorporated into topical ophthalmic formulations for delivery to the eye. The compounds may be combined with ophthalmologically acceptable preservatives, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the compound. Furthermore, the ophthalmic solution may contain an agent to increase viscosity, such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-974, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

The compounds are preferably formulated as topical ophthalmic suspensions or

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solutions, with a pH of about 5 to 8. The compounds will normally be contained in these formulations in an amount 0.01% to 5% by weight, but preferably in an amount of 0.25% to 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the discretion of a skilled
5 clinician.

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),
10 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. 06/203,350, and appropriate
15 compounds from WO 94/13275, including memantine.

In the formulas described above, the alkyl group can be straight-chain, branched or cyclic and the like. Halogen includes Cl, Br, F, or I. Alkoxy is understood as an alkyl group bonded through an oxygen atom.

The compounds of the present invention preferably function as 5-HT₂ agonists and
20 preferably do not enter the CNS. In more detail, the particular compounds of the present invention have incorporated into their structure a phenolic hydroxyl group which is considered comparable to that of serotonin and thus the compounds of the present invention preferably do not cross the blood-brain barrier and enter the brain. Compounds having the ability to be a 5-HT₂ agonist are beneficial for controlling IOP as well as the treatment of glaucoma as shown
25 in International Published Patent Application No. WO 00/16761, incorporated in its entirety by

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reference herein.

The compounds of the present invention preferably provide increased chemical stability and preferably achieve the desired level of therapeutic activity which includes a lowering or controlling of IOP.

5 The compounds of the present invention can be used in controlling or lowering IOP in warm blooded animals including humans. Preferably, an effective amount of the compound is administered to the patient such that the IOP is controlled or lowered to acceptable levels. Furthermore, the compounds of the present invention can be used to treat glaucoma in warm blooded animals, including humans, by administering an effective
10 amount of the compound to a patient in need of such treatment to treat the glaucoma.

In another embodiment of the present invention, the present invention relates to a method to block or bind to serotonin receptors and involves administering at least one compound of the present invention to a patient in an amount effective to block or bind serotonin receptors, such as the dosage levels described herein.

15 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 compound of Formula I is described in Example 1. The proton magnetic resonance spectrum of each compound of the Examples was consistent with the assigned structure.

20

METHOD 1

5-HT₂ Receptor Binding Assay

To determine the affinities of serotonergic compounds at the 5-HT₂ receptors, their ability to compete for the binding of the agonist radioligand [¹²⁵I]DOI to brain 5-HT₂
25 receptors is determined as described below with minor modification of the literature procedure [Neuropharmacology, 26, 1803 (1987)]. Aliquots of post mortem rat or human

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cerebral cortex homogenates (400 μ L) 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 μ M 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
5 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
10 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 IC₅₀ or K_i value.

METHOD 2

5-HT₂ Functional Assay: Phosphoinositide (PI) turnover assay

15 The relative agonist activity of serotonergic compounds at the 5-HT₂ 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
20 plates, maintained in a humidified atmosphere of 5% CO₂ 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 μ g/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 [J. Pharmacol. Expt. Ther. 286, 411 (1998)].
Confluent cells are exposed for 24-30 hrs to 1.5 μ Ci [3 H]-myo-inositol (18.3 Ci/mmol) in
25 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

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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 [³H]-inositol phosphates ([³H]-IPs) on an AG- 1-X8 column is performed as previously described [J. Pharmacol. Expt. Ther. 286, 411 (1998)] with sequential washes with H₂O and 50 mM ammonium formate, followed by elution of the total [³H]-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 [³H]-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 (EC₅₀ 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 [³H]-IPs by 50% of the maximum response is termed the EC₅₀ value.

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

15

TABLE 1
5-HT₂ Receptor Binding and Functional Data

Compound	IC₅₀, nM	EC₅₀, nM	Efficacy (E_{max}, %)
Example 1	0.714	374	85
Example 2	9.62	1440	55
5-HT	0.941	469	100

20

METHOD 3
Acute IOP Response in Lasered (Hypertensive) Eyes of Conscious Cynomolgus Monkeys

Intraocular pressure (IOP) was determined with an Alcon Pneumatometer 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

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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 Change in IOP \pm SEM Hours after Dose		
			1	3	6
Example 1	300	34.3	-5.9 \pm 2.69	-20.0 \pm 3.54	-21.6 \pm 4.91
Vehicle Control	-	34.7	-4.6 \pm 3.09	1.20 \pm 1.80	2.10 \pm 7.57

Example 1

2-(2-Aminopropyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol dihydrochloride

Step A: 3-Nitro-5,6,7,8-tetrahydro-naphthalen-1-ylamine and 2-Nitro-5,6,7,8-tetrahydro-naphthalen-1-ylamine

To a solution of 1-amino-5,6,7,8-tetrahydronaphthalene (13.0 g, 88.0 mmol) in concentrated sulfuric acid (80 mL) at 0°C was added a solution of sodium nitrite (8.3 g, 97.0 mmol) in concentrated sulfuric acid (60 mL) also at 0°C over 30 min and the resultant dark solution was stirred at this temperature for 3 h. The reaction mixture was added to ice and basified with a saturated solution of sodium hydroxide. This mixture was extracted with ethyl acetate (4 x 200 mL) and the combined extracts were washed with brine, dried (MgSO₄), and evaporated to a residue that was purified by column chromatography (silica, 20% to 30% ethyl acetate in hexane) to give two products: 3-nitro-5,6,7,8-tetrahydro-naphthalen-1-ylamine (7.5 g, 44%) [MS (ES) *m/z* 192 (M⁺); ¹H NMR (CDCl₃) δ 7.39(1H, d, J = 2.0 Hz), 7.31(1H, d, J =

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2.0 Hz), 3.84 (2H, brs), 2.82 (2H, t, J = 6.0 Hz), 2.48 (2H, t, J = 6.0 Hz), 1.81 (2H, m)] and 2-nitro-5,6,7,8-tetrahydro-naphthalen-1-ylamine (3.7 g, 22%) [MS (ES) m/z 192 (M^+); 1H NMR ($CDCl_3$) δ 7.85 (1H, d, J = 8.0 Hz), 6.52 (1H, d, J = 8.0 Hz), 4.17 (2H, brs), 3.06 (2H, t, J = 6.0 Hz), 2.44 (2H, t, J = 6.0 Hz), 1.84 (2H, m)].

5 Step B: 7-Nitro-1,3,4,5-tetrahydro-benzo[*cd*]indazole

To a solution of 3-nitro-5,6,7,8-tetrahydro-naphthalen-1-ylamine (5.9 g, 31.0 mmol) prepared in Step A in glacial acetic acid (100 mL) was added a solution of sodium nitrite (2.13 g, 31.0 mmol) in water (5.0 mL) at 0°C, and the resultant dark solution was stirred at this temperature for 20 h. The volatiles were evaporated and the residue was basified with a saturated solution of sodium bicarbonate (100 mL). The aqueous was extracted with ethyl acetate (4 x 200 mL) and the combined extracts were washed with brine, dried ($MgSO_4$) and evaporated to a residue that was purified by column chromatography (silica, 20% to 30% gradient of ethyl acetate in hexane) to give an oil (3.8 g, 60%): MS (ES) m/z 204 (M^+); 1H NMR ($CDCl_3$) δ 8.22 (1H, s), 7.77 (1H, s), 3.06 (4H, m), 2.26 (2H, m).

15 Step C: 1-(7-Nitro-4,5-dihydro-3*H*-benzo[*cd*]indazol-1-yl)-propan-2-ol

To a solution of the product from Step B (4.85 g, 23.9 mmol) in ethanol (50 mL) was added sodium ethoxide (14.2 mL, 35.0 mmol, 21% solution in ethanol) at room temperature. After 30 min, propylene oxide (4.14 mL, 47.8 mmol) was added, and the resultant solution was stirred for 18 h at room temperature. A saturated aqueous ammonium chloride solution (20 mL) was added to the reaction mixture and the ethanol was evaporated. This mixture was extracted with ethyl acetate (3 x 65 mL) and the combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography (silica, 50% to 80% gradient of ethyl acetate in hexane) to yield the desired product as a solid (2.0 g, 32%): m.p: 147-148°C; MS (ES) m/z 262 (M^+); 1H NMR ($CDCl_3$) δ 8.17 (1H, s), 7.74 (1H, s), 4.31 (3H, m), 3.05 (4H, 2d, J = 6.0

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Hz), 2.19 (4H, m), 1.30 (3H, t, J = 6.0 Hz). The regioisomer formed during the alkylation was also isolated as a solid (1.4 g, 22%): mp 140-141°C.

Step D: 1-(7-Amino-4,5-dihydro-3*H*-benzo[*cd*]indazol-1-yl)-propan-2-ol

To a solution of the product from Step C (2.0, 7.6 mmol) in ethanol was added Pd/C (10%, 0.10 g) and the resultant suspension was stirred under a hydrogen atmosphere for 20 h at room temperature. The reaction mixture was filtered through a filter-aid and the filtrate was concentrated to yield a solid (1.7 g, 97%): m.p: 125-127°C; MS (ES) *m/z* 232 (M⁺); ¹H NMR (CDCl₃) δ 6.27 (2H, s), 4.31-3.93 (3H, m), 2.93-2.78 (4H, m), 2.14 (2H, m), 1.25 (3H, t, J = 6.0 Hz).

Step E: 2-(2-Hydroxypropyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol

The product from Step D (1.90 g, 8.4 mmol) was dissolved in H₂SO₄/H₂O (1:2, 60 mL) and cooled to 0°C. A solution of NaNO₂ (0.64 g, 9.2 mmol) in H₂O (2.0 mL) was added dropwise and the resultant dark solution was stirred for 2 h. Water (40 mL) was added to this solution and the mixture was heated to 110°C for 2 h. After cooling the mixture to room temperature it was carefully neutralized with a saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 x 65 mL). The combined extracts were washed with brine (10 mL), dried (MgSO₄) and evaporated to a residue which was purified by column chromatography (silica, 50% to 60% gradient of ethyl acetate in hexane) to give a solid (1.2 g, 83%): m.p: 153-155°C; MS (ES) *m/z* 233(M⁺); ¹H NMR (CDCl₃) δ 9.39 (1H, s), 6.50 (1H, s), 6.34 (1H, s), 4.84 (1H, d, J = 4.0 Hz), 4.00 (3H, m), 2.76 (2H, q, J = 6.0 Hz), 2.01 (2H, m), 1.01 (3H, d, J = 6.0 Hz).

Step F: 1-(7-Benzyloxy-4,5-dihydro-3*H*-benzo[*cd*]indazol-1-yl)-propan-2-ol

To a stirred solution of the product from Step E (1.2 g, 5.2 mmol) in ethanol (20 mL) was added K₂CO₃ (0.86 g, 6.3 mmol) followed by benzyl bromide (0.74 mL, 6.3 mmol) at room temperature. The resultant dark solution was heated at reflux for 4 h. Solvent was

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evaporated, the residue was diluted with 2 N HCl (60 mL), and this solution was extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with brine (30 mL), dried, and evaporated to a residue which was purified by column chromatography (silica, 40% ethyl acetate in hexane) to give an oil (0.79 g, 47%): MS (ES) m/z 232 (M^+); 1H NMR (CDCl₃) δ 7.32 (5H, m), 6.60 (1H, s), 6.59 (1H, s), 5.29 (2H, s), 4.31 (2H, m), 4.19 (1H, m), 2.90 (2H, m), 2.11 (2H, m), 1.21 (3H, d, $J = 6.0$ Hz).

Step G: 1-(2-Azidopropyl)-7-benzyloxy-1,3,4,5-tetrahydro-benzo[*cd*]indazole

To a stirred solution of the product from Step F (0.77 g, 2.4 mmol) in dichloromethane (10 mL) was added triethylamine (0.40 mL, 2.9 mmol) followed by methanesulfonyl chloride (0.22 mL, 2.9 mmol) at 0°C. After 30 min, dichloromethane (50 mL) was added followed by water (50 mL). The organic layer was separated and the aqueous was extracted with dichloromethane (2 x 50 mL). The combined extracts were washed with brine (30 mL), dried (MgSO₄), and evaporated to a residue that was taken up in DMF (6 mL) and sodium azide (0.33 g, 5.0 mmol) was added. The reaction mixture was heated at 70°C for 17 h, poured into water, and extracted with ether (3 x 50 mL). The combined extracts were washed with brine, dried (MgSO₄), and evaporated to a residue that was purified by column chromatography (silica, hexane to 10% ethyl acetate in hexane) to give an oil (0.75 g, 90%): MS (ES) m/z 348 (M^+).

Step H: 2-(2-Aminopropyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol

To a solution of the product from Step G (0.74 g, 2.2 mmol) in ethanol under a nitrogen atmosphere at room temperature was added Pd/C (10%, 0.10 g) followed by ammonium formate (0.54 g, 8.5 mmol). This suspension was stirred for 24 h at room temperature followed by filtration through a filter-aid. The filtrate was evaporated to a residue that was purified by column chromatography (silica, 5% to 20% gradient of methanol in dichloromethane) to give a solid that was converted to the dihydrochloride salt,

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which was crystallized from methanol/ether (0.38 g, 58%): m.p 286-288°C; MS (ES) m/z 232 (M^+); 1H NMR (DMSO- d_6) δ 8.28 (3H, brs), 6.59 (1H, s), 6.43 (1H, s), 4.40-4.22 (2H, m), 3.61 (1H, m), 2.79 (4H, m), 2.27 (2H, m), 1.18 (3H, d, $J = 8.0$ Hz).

Analysis. Calculated for $C_{13}H_{17}N_3O \cdot 2 HCl \cdot 0.2 H_2O$: C, 50.73; H, 6.35; N, 13.65.

5 Found: C, 50.44; H, 6.40; N, 13.45.

Example 2

2-(2-Aminopropyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-3-ol dihydrochloride

10 Step A: 8-Nitro-1,3,4,5-tetrahydro-benzo[*cd*]indazole

A solution of 2-nitro-5,6,7,8-tetrahydro-naphthalen-1-ylamine (6.0 g, 31.4 mmol) in glacial acetic acid (50 mL) was treated as described in Step B of Example 1 to give an oil (5.2 g, 82%): MS (ES) m/z 202 ($M-H$).

Step B: 1-(8-Nitro-4,5-dihydro-3*H*-benzo[*cd*]indazol-1-yl)-propan-2-ol

15 A solution of the product from Step A (3.5 g, 17.2 mmol) in ethanol (50 mL) was treated as described in Step C of Example 1 to provide a solid (0.90 g, 20%): m.p 151-152°C; MS (ES) m/z 262(M^+); 1H NMR (CDCl₃) δ 8.21(1H, d, $J = 8.0$ Hz), 7.73 (1H, d, $J = 8.0$ Hz), 4.32 (2H, m), 3.45 (2H, t, $J = 6.0$ Hz), 3.01(2H, t, $J = 6.0$ Hz), 2.19 (2H, m), 1.29 (3H, $J = 6.0$ Hz). The regioisomer formed during the alkylation was also isolated (0.60 g, 13%): mp
20 144-146°C.

Step C: 1-(8-Amino-4,5-dihydro-3*H*-benzo[*cd*]indazol-1-yl)-propan-2-ol

A solution of the product from Step B (0.85, 3.3 mmol) in ethanol was treated as described for Step D of Example 1 to provide a solid (0.71 g, 99%): m.p 129-131°C; MS (ES) m/z 232 (M^+); 1H NMR (DMSO- d_6) δ 7.03 (1H, d, $J = 8.0$ Hz), 6.72 (1H, d, $J = 8.0$
25 Hz), 4.80 (1H, d, $J = 4.0$ Hz), 4.51(2H, brs), 4.01 (3H, m), 2.78 (2H, t, $J = 6.0$ Hz), 2.62 (2H, t, $J = 6.0$ Hz), 2.02 (2H, m), 1.00 (3H, d, $J = 6.0$ Hz).

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Step D: 2-(2-Hydroxypropyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-3-ol

The product from Step C (0.70 g, 3.2 mmol) was dissolved in H₂SO₄/H₂O (1:2, 30 mL) and treated as described in Step E of Example 1 to provide a solid (0.60 g, 86%): m.p 162-
5 163°C; MS (ES) *m/z* 233(M⁺).

Step E: 1-(8-Benzyloxy-4,5-dihydro-3*H*-benzo[*cd*]indazol-1-yl)-propan-2-ol

A solution of the product from Step D (0.59 g, 2.6 mmol) in ethanol (20 mL) was treated as described in Step F of Example 1 to provide a solid (0.46 g, 54%): m.p 95-97°C; MS (ES) *m/z* 323 (M⁺); ¹H NMR (CDCl₃) δ 7.34 (5H, m), 7.14 (1H, s), 5.08 (2H, s), 4.31 (2H, m),
10 4.13 (2H, m), 3.02 (5H, m), 2.19 (3H, m), 1.27(3H, t, J = 6.0 Hz).

Step F: 1-(2-Azidopropyl)-8-benzyloxy-1,3,4,5-tetrahydro-benzo[*cd*]indazole

A solution of the product from Step E (0.46 g, 1.4 mmol) in dichloromethane (10 mL) was treated as described for Step G of Example 1 to provide an oil (0.20 g, 42%): MS (ES) *m/z* 348 (M⁺).

15 Step G: 2-(2-Aminopropyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-3-ol dihydrochloride

A solution of the product from Step F (0.19, 0.54 mmol) in ethanol was treated as described in Step H of Example 1 to provide the dihydrochloride salt (0.10 g, 62%): m.p 284-286°C; MS (ES) *m/z* 232 (M⁺); ¹H NMR (DMSO-*d*₆) δ 8.29 (3H, brs), 7.21 (1H, d, J = 6.0 Hz), 6.94 (1H, d, J = 6.0 Hz), 4.48 (2H, m), 3.61 (1H,m), 2.79 (4H, m), 2.00 (2H, m),
20 1.16 (3H, d, J = 6.0 Hz).

Analysis. Calculated for C₁₃H₁₇N₃O · 2 HCl: C, 51.33; H, 6.30; N, 13.81. Found: C, 51.41; H, 6.34; N, 13.67.

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Example 3

Ingredients	Amount (wt %)
2-(2-Amino-propyl)-2,6,7,8-tetrahydro-benzo[<i>cd</i>]indazol-4-ol dihydrochloride	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
Purified water	q.s. to 100%

5

Example 4

Ingredients	Amount (wt %)
2-(2-Amino-propyl)-2,6,7,8-tetrahydro-benzo[<i>cd</i>]indazol-4-ol dihydrochloride	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
Purified water	q.s. to 100%

10

15

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Example 5

Ingredients	Amount (wt %)
2-(2-Amino-propyl)-2,6,7,8-tetrahydro-benzo[<i>cd</i>]indazol-4-ol dihydrochloride	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
Purified water	q.s. to 100%

Example 6

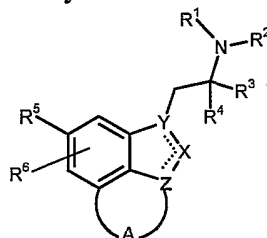
Ingredients	Amount (wt %)
2-(2-Amino-propyl)-2,6,7,8-tetrahydro-benzo[<i>cd</i>]indazol-4-ol dihydrochloride	0.01 – 2%
White petrolatum and mineral oil and lanolin	Ointment consistency
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting Ph

5 Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the present specification and practice of the present invention disclosed herein. It is intended that the present specification and examples be considered as exemplary only with a true scope and spirit of the invention being indicated by the following claims and equivalents thereof.

WHAT IS CLAIMED IS:

1. A compound represented by Formula I:

5



- wherein R^1 and R^2 are independently chosen from hydrogen or an alkyl group;
 R^3 and R^4 are independently chosen from hydrogen, an alkyl group or R^3 , R^4 and the carbon
 10 atom to which they are attached form a cycloalkyl ring, or R^2 and R^3 together represent
 $(CH_2)_m$ to form a saturated heterocycle;
 R^5 is chosen from hydroxyl, alkoxy, alkyl, halogen, or $OC(=O)W$;
 R^6 is chosen from hydrogen, halogen, a substituted or unsubstituted alkyl group;
 R^7 and R^8 are hydrogen or an alkyl group;
 15 W is a substituted or unsubstituted alkyl group, NR^7R^8 , $N(R^7)CH_2(CH_2)_nN(R^7)(R^8)$, O-
 alkyl, or a substituted or unsubstituted alkenyl;
 m is 3 or 4;
 n is 2 or 3;
 A is a 5- to 7-membered ring optionally containing one heteroatom chosen from NR^7 , O, or
 20 S;
 X is either N or C;
 Y and Z are either N or C, wherein Y and Z are different; and
 the dashed bonds denote a suitably appointed single and double bond;
 or pharmaceutically acceptable salts or solvates thereof.

- 25 2. The compound of claim 1, wherein R^1 and R^2 are independently chosen from
 hydrogen or C_{1-4} alkyl;
 R^3 and R^4 are independently chosen from hydrogen, C_{1-4} alkyl or R^3 , R^4 and the carbon atom
 to which they are attached form a cyclopropyl ring, or R^2 and R^3 together represent $(CH_2)_m$
 to form a saturated heterocycle;
 30 R^5 is chosen from hydroxyl, C_{1-4} alkoxy, C_{1-4} alkyl, halogen, or $OC(=O)W$;
 R^6 is chosen from hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkyl substituted with halogen;

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R⁷ and R⁸ are hydrogen or C₁₋₄alkyl;

W is C₁₋₆alkyl, NR⁷R⁸, N(R⁷)CH₂(CH₂)_nN(R⁷)(R⁸), OC₁₋₆alkyl, C₁₋₆alkyl optionally substituted with halogen, hydroxyl, CO₂C₁₋₄alkyl, CON(C₁₋₄alkyl)₂, C(=NH)NH₂,

5 NHC(=NH)NH₂, or NH₂, C₂₋₄alkenyl optionally substituted by phenyl, unsubstituted or substituted with one or more of C₁₋₄alkyl, C₁₋₄alkoxy or halogen;

m is 3 or 4;

n is 2 or 3;

A is a 5- to 7-membered ring optionally containing one heteroatom chosen from NR⁷, O, or S;

10 X is either N or C;

Y and Z are either N or C, wherein Y and Z are different; and

the dashed bonds denote a suitably appointed single and double bond;

or pharmaceutically acceptable salts or solvates thereof.

3. The compound of claim 1, wherein said R² and R³ form a saturated (CH₂)_m heterocycle or said R³ and R⁴ together form a cycloalkyl ring.

4. The compound of claim 1, wherein R¹, R², and R³ are hydrogen; or R² and R³ together represent (CH₂)_m to form a pyrrolidine;

R⁴ is C₁₋₄alkyl;

R⁵ is chosen from hydroxyl, C₁₋₄alkoxy, or OC(=O)W;

20 R⁶ is chosen from hydrogen, halogen, C₁₋₄alkyl, C₁₋₄alkyl substituted with halogen;

R⁷ and R⁸ are hydrogen or C₁₋₄alkyl;

W is C₁₋₆alkyl, NR⁷R⁸, C₁₋₆alkyl optionally substituted with halogen, hydroxyl, or CO₂C₁₋₄alkyl;

m is 3;

25 A is a 6-membered ring optionally containing one heteroatom chosen from NR⁷ or O;

X is either N or C;

Y is N and Z is C; and

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the dashed bonds denote a suitably appointed single and double bond.

5. The compound of claim 1, wherein the compound is:

2-(2-Aminopropyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol;

2-(2-Dimethylaminoethyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol;

5 2-(2-Aminopropyl)-5-methyl-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol;

2-(2-Aminopropyl)-5-fluoro-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol;

2-(6-Fluoro-7-methoxy-4,5-dihydro-3*H*-benzo[*cd*]indazol-1-yl)-1-methylethylamine;

Cyclopropanecarboxylic acid 2-(2-aminopropyl)-2,6,7,8-tetrahydro-

benzo[*cd*]indazol-4-yl ester;

10 1-(2-Aminopropyl)-1,3,4,5-tetrahydro-benzo[*cd*]indol-7-ol;

1-(2-Aminopropyl)-5*H*-pyrano[4,3,2-*cd*]indazol-7-ol; or

1-(2-Aminopropyl)-4-methyl-1,3,4,5-tetrahydro-pyrazolo[4,3,2-*de*]isoquinolin-7-ol

or combinations thereof.

6. The compound of claim 1, wherein said X is N.

15 7. The compound of claim 1, wherein said X is C.

8. A method of controlling normal or elevated intraocular pressure comprising administering a pharmaceutically effective amount of a composition comprising at least one compound of claim 1.

20 9. The method of claim 8, wherein R² and R³ form a saturated (CH₂)_m heterocycle.

10. The method of claim 8, wherein said R³ and R⁴ together form a cycloalkyl ring.

11. The method of claim 8, wherein said compound is 2-(2-Aminopropyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol;

2-(2-Dimethylaminoethyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol;

25 2-(2-Aminopropyl)-5-methyl-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol;

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2-(2-Aminopropyl)-5-fluoro-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-ol;2-(6-Fluoro-7-methoxy-4,5-dihydro-3*H*-benzo[*cd*]indazol-1-yl)-1-methylethylamine;Cyclopropanecarboxylic acid 2-(2-aminopropyl)-2,6,7,8-tetrahydro-benzo[*cd*]indazol-4-yl ester;5 1-(2-Aminopropyl)-1,3,4,5-tetrahydro-benzo[*cd*]indol-7-ol;1-(2-Aminopropyl)-5*H*-pyrano[4,3,2-*cd*]indazol-7-ol; or1-(2-Aminopropyl)-4-methyl-1,3,4,5-tetrahydro-pyrazolo[4,3,2-*de*]isoquinolin-7-ol;

or combinations thereof.

12. The method of claim 8, wherein wherein R¹, R², and R³ are hydrogen;10 or R² and R³ together represent (CH₂)_m to form a pyrrolidine;R⁴ is C₁₋₄alkyl ;R⁵ is chosen from hydroxyl, C₁₋₄alkoxy, or OC(=O)W;R⁶ is chosen from hydrogen, halogen, C₁₋₄alkyl, C₁₋₄alkyl substituted with halogen;R⁷ and R⁸ are hydrogen or C₁₋₄alkyl;15 W is C₁₋₆alkyl, NR⁷R⁸, C₁₋₆alkyl optionally substituted with halogen, hydroxyl, or CO₂C₁₋₄alkyl;

m is 3;

A is a 6-membered ring optionally containing one heteroatom chosen from NR⁷ or

O;

20 X is either N or C;

Y is N and Z is C; and

the dashed bonds denote a suitably appointed single and double bond.

13. The method of claim 9, wherein said X is N.

14. The method of claim 9, wherein said X is C.

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15. A method for the treatment of glaucoma comprising administering a pharmaceutically effective amount of a composition comprising at least one compound of claim 1.

16. The method of claim 15, wherein R^1 , R^2 , and R^3 are hydrogen;

5 or R^2 and R^3 together represent $(CH_2)_m$ to form a pyrrolidine;

R^4 is C_{1-4} alkyl;

R^5 is chosen from hydroxyl, C_{1-4} alkoxy, or $OC(=O)W$;

R^6 is chosen from hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkyl substituted with halogen;

R^7 and R^8 are hydrogen or C_{1-4} alkyl;

10 W is C_{1-6} alkyl, NR^7R^8 , C_{1-6} alkyl optionally substituted with halogen, hydroxyl, or CO_2C_{1-4} alkyl;

m is 3;

A is a 6-membered ring optionally containing one heteroatom chosen from NR^7 or O ;

15 X is either N or C ;

Y is N and Z is C ; and

the dashed bonds denote a suitably appointed single and double bond.

17. The method of claim 15, wherein said compound is:

1-(2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;

20 1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;

(R)-1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;

(S)-1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;

1-((S)-2-Aminopropyl)-3-methyl-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;

1-(S)-1-Pyrrolidin-2-ylmethyl-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;

25 1-((S)-2-Aminopropyl)-5-fluoro-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;

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[1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-yl]-
dimethylamine;

[1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-yl]-methanol;

1-(2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[3,2-g]indazol-8-ol;

5 1-(Pyrrolidin-2-ylmethyl)-3,7,8,9-tetrahydro-pyrano[3,2-e]indazol-8-ol;

1-((S)-2-Aminopropyl)-3,7,8,9-tetrahydro-pyrano[3,2-e]indazol-8-ol; or

1-((S)-2-Aminopropyl)-3-methyl-3,7,8,9-tetrahydro-pyrano[3,2-e]indazol-8-ol; or

mixtures thereof.

18. A pharmaceutical composition comprising the compound of claim 1 and at
10 least one carrier.

19. A method to block or bind to serotonin receptors comprising administering an
effective amount of at least one compound of claim 1 to a patient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/17114

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 231/54; A61K 31/416
US CL : 548/359.1; 514/403
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)
U.S. : 548/359.1; 514/403

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,385,928 A (FLAUGH) 31 January 1995 (31/01/95), see entire document, especially columns 1 and 2.	5, 11 and 17

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 18 JULY 2002	Date of mailing of the international search report 23 AUG 2002
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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer <i>Valerie Bell-Harris</i> R. W. RAMSUER Telephone No. (703) 308-1235
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/17114

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

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

2. Claims Nos.: 1-4, 6-10, 12-16, 18 and 19
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

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

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/17114

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, W, X, Y, the dashed lines, etc.) and their voluminous, complex meanings and their seemingly endless permutations and combinations and the lengthy list of divergent named compounds in claims 5, 11, and 17, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable invention of claims 5, 11, and 17, the first three compounds involved therein.