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(54) Titre : COMPOSES D'AMINOALKYL-BENZOFURAN-5-OL POUR LE TRAITEMENT DU GLAUCOME
(54) Title: AMINOALKYL-BENZOFURAN-5-OL COMPOUNDS FOR THE TREATMENT OF GLAUCOMA

(57) Abrégé/Abstract:
The present invention provides novel compounds, compositions containing the compounds of the invention in a pharmaceutically acceptable excipient and methods for using the compositions for lowering intraocular pressure.

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(54) Title: AMINOALKYL-BENZOFURAN-5-OL COMPOUNDS FOR THE TREATMENT OF GLAUCOMA

(57) Abstract: The present invention provides novel compounds, compositions containing the compounds of the invention in a pharmaceutically acceptable excipient and methods for using the compositions for lowering intraocular pressure.

AMINOALKYL-BENZOFURAN-5-OL COMPOUNDS FOR THE TREATMENT OF GLAUCOMA

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to treatment for lowering intraocular pressure and to compounds for use in such treatments. More particularly, the present invention relates to the use of compounds with serotonergic 5-HT5-HT$_2$ agonist activity to lower intraocular pressure (IOP), treat glaucoma, and to provide neuroprotection.

2. Description of the Related Art

Serotonin (5-hydroxy tryptamine; 5-HT5-HT) is an endogenous biogenic amine with a well defined neurotransmitter function in many tissues of the body including the eye [Zifa and Fillion 1992; Hoyer *et al.* 1994; Tobin *et al.* 1988].

5-HT is known to interact with at least seven major 5-HT receptors (5-HT$_1$ - 5-HT$_7$) and additional subtypes within these families to initiate intracellular biochemical events such as stimulation of second messengers (e.g. cAMP, inositol trisphosphate) eventually leading to the final biological response, for example, tissue contraction or hormone release, etc. [Hoyer *et al.* 1994; Martin *et al.* 1998]. Receptor subtypes within the 5-HT$_1$ family are negatively coupled to adenylyl cyclase (AC) and cause inhibition of cAMP production, while 5-HT$_4$, 5-HT$_6$, and 5-HT$_7$ receptors are positively coupled to AC and thus stimulate cAMP production when activated by 5-HT [Martin *et al.* 1998]. The receptors in the 5-HT$_2$ family are positively coupled to phospholipase C (PLC) and thus

generate inositol phosphates and mobilize intracellular calcium when activated to mediate the effects of 5-HT. The 5-HT_3 receptor is unique in that it couples to an ion channel which gates sodium, potassium, and calcium [Hoyer *et al.* 1994].

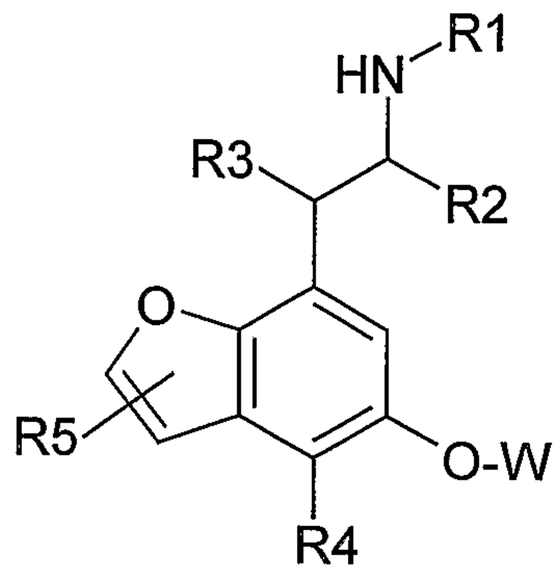
The human and animal 5-HT_7 receptor has only recently been cloned, expressed, and shown to be present in various brain areas and peripheral tissues [Eglen *et al.* 1997]. Recent studies have shown there to be four splice variants of the 5-HT_7 receptor [Heidmann *et al.* 1997]. It has been proposed that the 5-HT_7 receptor may be involved in the pathophysiology of sleep disorders, depression, and other psychiatric disorders [Eglen *et al.* 1997]. In the periphery, stimulation of 5-HT_7 receptors results in relaxation of blood vessels and hence vasodilation [Eglen *et al.* 1997].

Known compounds exhibiting 5-HT_2 agonist activity have typically been designed to treat numerous central nervous system (CNS)-related conditions, particularly the treatment of obesity and depression, by activation of 5-HT_{2C} receptors. Thus, one desired property of known 5-HT_2 agonist compounds is that they easily penetrate the blood brain barrier. Compounds possessing the property of penetration into the CNS generally do not contain polar groups.

To treat ocular diseases, it is desirable to administer compositions orally or topically that will remain in the ocular tissues and not cross the blood brain barrier to enter the CNS. What are needed are 5-HT_2 agonist compounds that are useful in the treatment of ocular diseases characterized by an elevated intraocular pressure, the treatment of glaucoma and neuroprotection. Such compounds would not have a propensity to cross the blood brain barrier.

SUMMARY OF THE INVENTION

The present invention overcomes these and other drawbacks of the prior art by providing compounds having 5-HT_2 agonist activity that do not cross the blood brain barrier. More specifically, the present invention provides compounds having the following general formula:



wherein R^1 is hydrogen or C_{1-4}alkyl; R^2 is hydrogen, C_{1-4}alkyl, or R^1 and R^2 can together be $(CH_2)_{2-4}$ to complete a heterocyclic ring; R^3 is hydrogen, hydroxyl, C_{1-4}alkoxy, or fluorine; R^4 is selected from C_{1-4}alkyl, halogen, nitrile, C_{1-6}alkylthiol, trifluoromethyl, C_{1-4}alkyl substituted by HO or C_{1-3}alkoxy, R^5 is hydrogen, halogen, C_{1-4}alkoxy, nitrile, W is hydrogen or C(=O)C_{1-8}alkyl. In preferred embodiments, R^1, R^3 and R^5 are hydrogen, R^2 is methyl, R^4 is halogen, methyl or trifluoromethyl, and W is hydrogen. Most preferably, the compounds of the invention have an R-configuration at the carbon atom bearing the primary amine.

In another aspect, the present invention provides compositions containing the compounds described above in a pharmaceutically acceptable excipient. The compositions are most preferably in the form of topical ophthalmic formulations for delivery to the eye. The compounds of the invention may be combined with ophthalmologically acceptable

preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution to form the compositions of the invention.

The compositions of the invention are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The compounds of the invention as described above will normally be contained in these formulations in an amount .01% to 5% by weight, but preferably in an amount of .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 routine discretion of a skilled clinician.

The present invention further provides a method of lowering intraocular pressure in a mammal by administering to a patient in need thereof a therapeutically effective amount of a composition comprising a compound having the structure as described above in a pharmaceutically acceptable excipient. In preferred embodiments, the composition can be administered systemically or locally to the eye (e.g., topically, intracamerally, or via an implant).

DETAILED DESCRIPTION PREFERRED EMBODIMENTS

It has been found that serotonergic compounds which possess agonist activity at 5-HT_2 receptors effectively lower and control elevated IOP and glaucoma. Serotonergic nerves innervate the eye [Tobin *et al.* 1988] and 5-HT has been found in the aqueous humor of human eyes [Martin *et al.* 1988]. In addition, receptor binding sites for [^{3}H]5-HT have been demonstrated and pharmacologically characterized in the iris-ciliary body

(ICB) of rabbits [Mallorga and Sugrue 1987; Chidlow *et al.* 1995]. These 5-HT binding sites have been shown to be functionally coupled to second messenger generation in rabbits [Tobin and Osborne 1989; Tobin *et al.* 1988]. In the human ICB these binding sites are characterized as 5-HT_{1A} and 5-HT_2 receptors [Barnet and Osborne 1993]. In addition, the presence of mRNAs for 5-HT_{1A} and 5-HT_7 receptors in the rabbit ICB have been reported [Chidlow *et al.* 1995; Osborne and Chidlow 1996]. The precise functions of these receptors in the eye are unknown, especially the 5-HT_7 subtype(s).

5-HT or 5-carboxamidotryptamine (5-CT) topically applied to the rabbit eye raise intraocular pressure in the anterior chamber of the eye [Meyer-Bothling *et al.* 1993]. By contrast, it has been shown that topically applied 5-HT lowers IOP [Krootila *et al.* 1987 (intracamerally 5-HT raised IOP and caused breakdown of the blood-aqueous barrier)]. In addition, the 5-HT uptake inhibitor, fluoxetine (Prozac®), also raises IOP in human subjects upon oral administration [Costagliola *et al.* 1996] and may cause glaucoma [Ahmad 1992]. However, the 5-HT receptor subtype(s) involved in the IOP-elevating effects of 5-HT, 5-CT and fluoxetine are unknown.

Studies conducted in rabbits with 8-hydroxy DPAT and MKC-242 (5-HT_{1A} agonists) have shown these compounds lower IOP [Osborne and Chidlow 1996; EP 0771563-A2]. In addition, 5-methylurapidil (5-HT_{1A} agonist) lowered IOP in glaucomatous monkeys [Wang *et al.* 1997]. Both MKC-242 and 5-methylurapidil are relatively potent α1 receptor antagonists (α1 antagonists are known to lower IOP in rabbits, monkeys, and man). The mechanism of action for lowering IOP by 5-methylurapidil has been attributed to its α1 antagonist activity and not its 5-HT_{1A} agonist

activity [Wang *et al.* 1998]. U.S. Patent No. 5,693,654, discloses 5-HT_1 receptor agonists for lowering IOP. WO 92/20333 discloses certain 5-HT_{1A} agonists for the treatment of glaucoma.

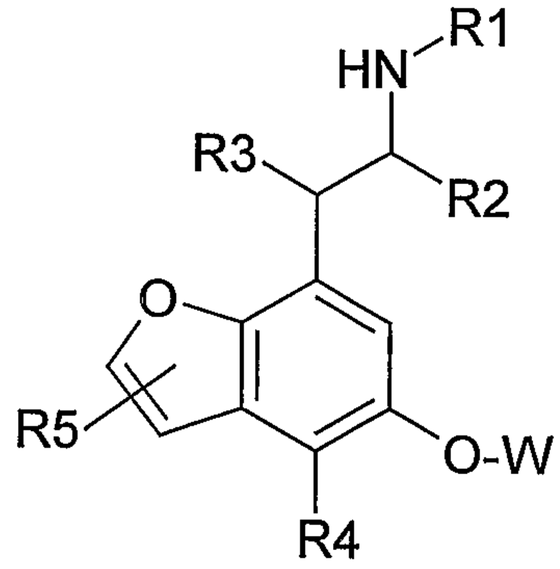
Methysergide (5-HT_2 antagonist) lowered IOP in rabbits [Krootila *et al.* 1987]. Ketanserin (5-$HT_{2A/C}$ antagonist), also with significant α1 antagonist activity, lowers IOP in rabbits and man [Chan *et al.* 1985; Costagliola *et al.* 1991]. Saprogrelate (5-HT_{2A} antagonist) lowers IOP in rabbits and in man when dosed topically or orally [Mano *et al.* 1995; Takenaka *et al.* 1995]. EP 522226 and U.S. Patent No. 5,290,781 disclose the use of ketanserin and its derivatives for treating ocular hypertension. U.S. Patent Nos. 5,290,781 and 5,106,555 discloses the use of certain 5-HT_2 antagonists for lowering IOP. U.S. Patent No. 5,652,272 discloses saprogrelate for reducing IOP. U.S. Patent No. 5,538,974 discloses opthalmic compositions of certain 5-HT_2 antagonists for lowering IOP.

U.S. Patent No. 5,011,846 discloses certain 5-HT_3 receptor antagonists for treating glaucoma.

WO 97/17345 discloses that particular compounds with 5-HT_4 serotonergic receptor agonist or antagonist activity are useful for treating psychiatric, gastrointestinal, lower urinary, and cardiovascular disorders. The publication mentions the compounds may also be useful for glaucoma.

The present inventor has discovered that compounds with the general formula (**I**) have 5-HT_2 agonist activity and may be useful in lowering IOP, treating glaucoma, and/or provide neuroprotection for retinal ganglion cells.

Formula (I)

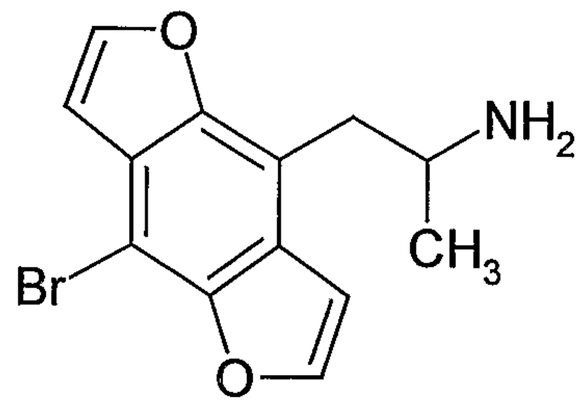


In Formula I, R^1 is hydrogen or C_{1-4} alkyl; R^2 is hydrogen, C_{1-4}alkyl, or R^1 and R^2 together can be $(CH_2)_{2-4}$ to complete a heterocyclic ring; R^3 is hydrogen, hydroxyl, C_{1-4}alkoxy, or fluorine; R^4 is selected from C_{1-4}alkyl, halogen, nitrile, C_{1-6}alkylthiol, trifluoromethyl, C_{1-4}alkyl substituted by HO or C_{1-3}alkoxy, R^5 is hydrogen, halogen, C_{1-4}alkoxy, nitrile and W is hydrogen or $C(=O)C_{1-8}$alkyl.

The compounds of the invention will preferably possess the following properties: 1) agonist acitivty at the 5-HT_2 receptors, and 2) significantly greater chemical stability than serotonin, the endogenous receptor ligand.

D.E. Nichols and colleagues at Purdue University have developed a number of benzofuran- and benzodifuranyl-alkylamines over the past decade and have demonstrated their affinity and efficacy at the 5-HT_{2A} receptor as well as their hallucinogenic activity as

evaluated in animals. Dr. Nichols' focus has been on the development of compounds with CNS activity, that is, that readily cross the blood brain barrier. Thus, these known compounds are outside of the scope of the compounds encompassed by Formula I above.

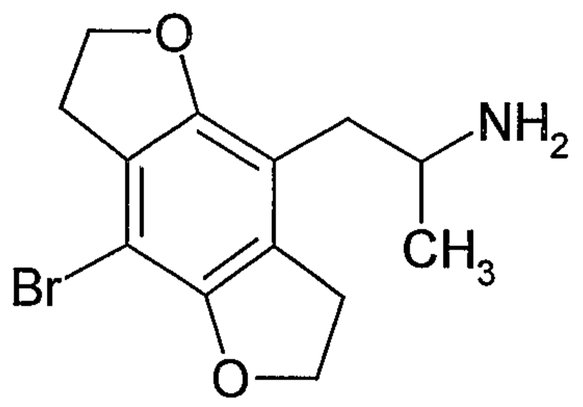


For example, Nichols has developed a compound with the following structure (compound 1) (Parker *et al.* 1998).

Compound 1

The Nichols compound has been shown to have a high affinity for the 5-HT_{2A} receptor and to generalize to LSD in drug discrimination studies. Nichols and colleagues also studied compounds in the class of that shown below (compound 2) for CNS activity.

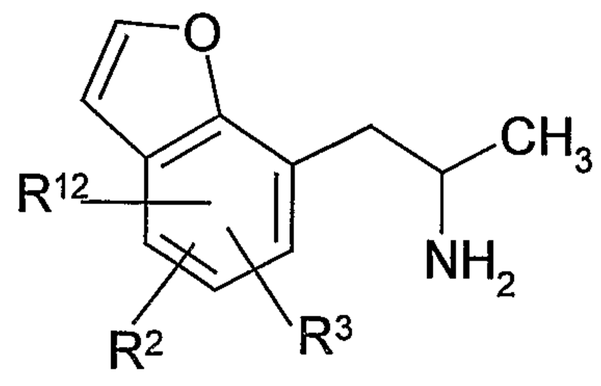
Compound 2



(Monte *et al.* 1996). Neither of the compounds studied by Nichols and colleagues is within the scope of the present invention. Furthermore, Nichols does not discuss use of compounds 1 or 2 for the treatment of any ocular diseases, ocular hypertension or glaucoma. The goal in creating compounds 1 and 2 was to produce compounds useful for CNS disorders and such compounds would necessarily have to have the ability to penetrate

the blood brain barrier. In contrast, the compounds of the present invention are designed not to cross the blood brain barrier but to remain in the ocular tissue.

Eli Lilly developed a series of benzofuran compounds that are similar to the compounds of Formula I herein. (WO 00/44737). Lilly's compounds have the following general formula:



These compounds are described as having utility for numerous CNS-related conditions, particularly the treatment of obesity and depression by activation of 5-HT_{2C} receptors. Thus, it is desirable that these compounds would penetrate into the brain. None of the compounds described in Lilly come within scope of the present invention. The compounds of the invention are designed to avoid penetration into the brain whereas the Lilly compounds are specifically aimed at crossing the blood brain barrier in order to treat CNS diseases.

The compounds of the invention have a low propensity to enter the CNS, or to cross the blood brain barrier, due to the presence of the highly polar hydroxyl group. Thus, the compounds of the invention are less likely to elicit undesirable centrally mediated side effects, such as those associated with the CNS active compounds described by Nichols and Lilly. The preferred 4-substituted 7-(2-aminopropyl)-benzofuran-5-ol

compounds of Formula I have a greater chemical stability than serotonin or other indole analogs.

The compounds of the invention may be prepared by known synthetic procedures, such as those reported in WO 00/44737, and other well known synthetic transformations.

The compounds of the invention can be administered systemically or locally to the eye (e.g., topically, intracamerally, or via an implant). The compounds are preferrably incorporated into topical ophthalmic formulations for delivery to the eye. The compounds may be combined with ophthalmologically acceptable preservatives, surfactants, 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. Additionally, 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-940, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

The compounds of the invention are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The compounds will normally be contained in these formulations in an amount .01% to 5% by weight, but preferably in an amount of .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 routine discretion of a skilled clinician.

The compounds can also be used in combination with other IOP lowering agents, such as, but not limited to, β-blockers, prostaglandins, carbonic anhydrase inhibitors, α-$_2$ agonists and miotics. The compounds can also be used in combination with other agents useful for treating glaucoma, such as, but not limited to, calcium channel blockers and NMDA antagonists. These agents may be administered topically, but usually systemically.

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both

chemically and structurally related may be substituted for the agents described herein to achieve similar results. All such substitutions and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

References

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

United States Patents

5,011,846

5,106,555

5,290,781

5,538,974

5,652,272

5,693,654

Foreign Patents and Published Applications

EP 0771563-A2

EP 522226

WO 92/20333

WO 97/17345

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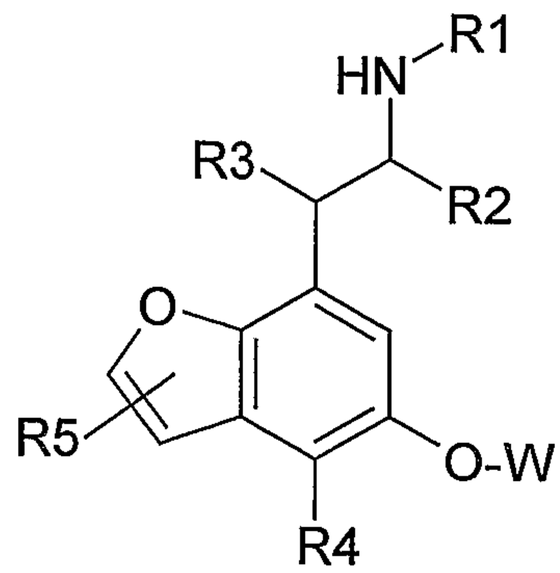
Wang *et al.*, *Invest. Ophthal. Vis. Sci.*, 39(Suppl):2236-488, 1998.

Zifa and Fillion, *Pharmacol. Rev.*, 44:401-458, 1992.

We Claim:

1. A compound having the structure as follows:

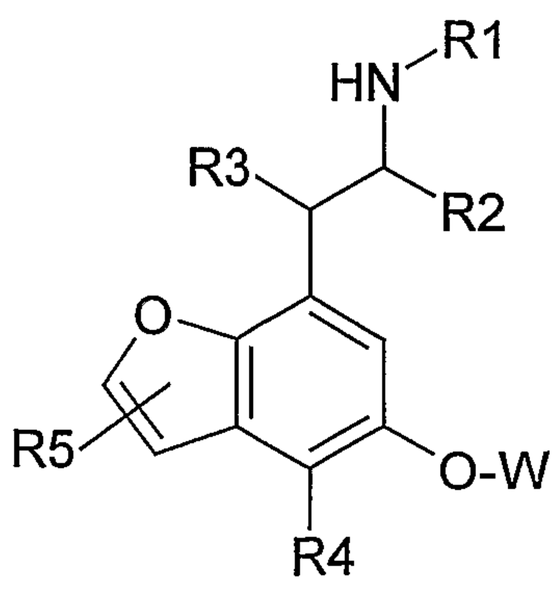


wherein R^1 is hydrogen or C_{1-4}alkyl; R^2 is hydrogen, C_{1-4}alkyl, or R^1 and R^2 can together be $(CH_2)_{2-4}$ to complete a heterocyclic ring; R^3 is hydrogen, hydroxyl, C_{1-4}alkoxy, or fluorine; R^4 is selected from C_{1-4}alkyl, halogen, nitrile, C_{1-6}alkylthiol, trifluoromethyl, C_{1-4}alkyl substituted by HO or C_{1-3}alkoxy, R^5 is hydrogen, halogen, C_{1-4}alkoxy, nitrile, W is hydrogen or $C(=O)C_{1-8}$alkyl.

2. The compound of claim 1, wherein R^1, R^3 and R^5 are hydrogen, R^2 is methyl, R^4 is halogen, methyl or trifluoromethyl, C_{1-4}alkyl substituted by HO or C_{1-3}alkoxy, and W is hydrogen.

3. The compound of claim 2, further defined as the stereoisomer with an R-configuration at the carbon atom bearing the primary amine.

4. A composition comprising at least one compound having the structure as



follows and a pharmaceutically acceptable excipient:

wherein R^1 is hydrogen or C_{1-4}alkyl; R^2 is hydrogen, C_{1-4}alkyl, or R^1 and R^2 can together be $(CH_2)_{2-4}$ to complete a heterocyclic ring; R^3 is hydrogen, hydroxyl, C_{1-4}alkoxy, or fluorine; R^4 is selected from C_{1-4}alkyl, halogen, nitrile, C_{1-6}alkylthiol, trifluoromethyl, C_{1-4}alkyl substituted by HO or C_{1-3}alkoxy, R^5 is hydrogen, halogen, C_{1-4}alkoxy, nitrile, W is hydrogen or $C(=O)C_{1-8}$alkyl.

5. The composition of claim 4, wherein the compound is further defined as follows: R^1, R^3 and R^5 are hydrogen, R^2 is methyl, R^4 is halogen, methyl or trifluoromethyl, C_{1-4}alkyl substituted by HO or C_{1-3}alkoxy, and W is hydrogen.

6. The composition of claim 5, wherein the compound is further defined as the stereoisomer with an R-configuration at the carbon atom bearing the primary amine.

7. The composition of claim 4, further comprising ophthalmologically acceptable preservatives.

8. The composition of claim 4, further comprising ophthalmologically acceptable surfactants.

9. The composition of claim 4, further comprising an agent to increase viscosity.

10. The composition of claim 9, wherein the agent is selected from the group consisting of hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, and polyvinylpyrrolidone.

11. The composition of claim 4, further comprising ophthalmologically acceptable preservatives, ophthalmologically acceptable surfactants and at least one agent to increase viscosity.

12. The composition of claim 4, further defined as a topical ophthalmic suspension or solution having a pH of about 5 to about 8.

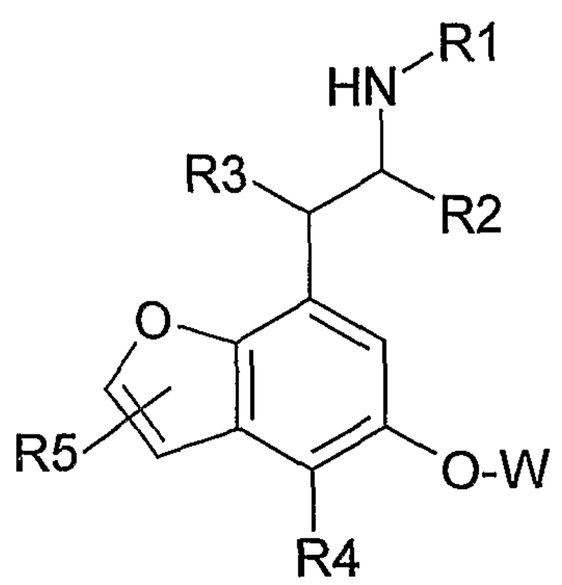
13. The composition of claim 12, wherein the concentration of the compound is from .01% to 5% by weight.

14. The composition of claim 13, wherein the composition of the compound is from .25% to 2% by weight.

15. The composition of claim 4, further comprising at least one agent selected from the group consisting of β-blockers, prostaglandins, carbonic anhydrase inhibitors, α-$_2$ agonists and miotics.

16. The composition of claim 4, further comprising at least one agent selected from the group consisting of calcium channel blockers and NMDA antagonists.

17. A method of lowering intraocular pressure in a mammal, said method comprising administering to a patient in need thereof a therapeutically effective amount of a composition comprising a compound having the structure as follows:



wherein R^1 is hydrogen or C_{1-4}alkyl; R^2 is hydrogen, C_{1-4}alkyl, or R^1 and R^2 can together be $(CH_2)_{2-4}$ to complete a heterocyclic ring; R^3 is hydrogen, hydroxyl, C_{1-4}alkoxy, or fluorine; R^4 is selected from C_{1-4}alkyl, halogen, nitrile, C_{1-6}alkylthiol, trifluoromethyl, C_{1-4}alkyl substituted by HO or C_{1-3}alkoxy, R^5 is hydrogen, halogen, C_{1-4}alkoxy, nitrile, W is hydrogen or $C(=O)C_{1-8}$alkyl.

18. The method of claim 17, wherein R^1, R^3 and R^5 are hydrogen, R^2 is methyl, R^4 is halogen, methyl or trifluoromethyl, C_{1-4}alkyl substituted by HO or C_{1-3}alkoxy, and W is hydrogen.

19. The method of claim 18, wherein the compound is further defined as the diastereomer with an R-configuration at the carbon atom bearing the primary amine.

20. The method of claim 17, wherein the composition is in the form of a topical ophthalmic suspension or solution.

21. The method of claim 17, wherein the composition is administered by topical application to the eye.