

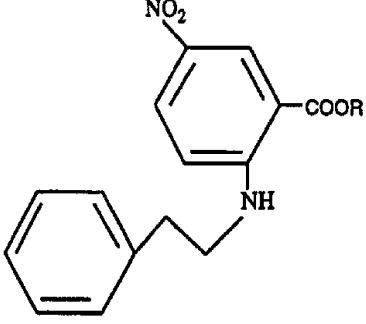




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(54) Title: USE OF CHLORIDE CHANNEL BLOCKERS FOR REDUCING INTRAOCULAR PRESSURE			
(57) Abstract			
<p>Pharmaceutical compositions and a method are disclosed for treating glaucoma and/or ocular hypertension in the mammalian eye by administering to the mammalian eye the pharmaceutical composition of the invention which contains, as the active ingredient, one or more compounds having chloride channel blocking activity. Examples of chloride channel blockers utilized in the pharmaceutical composition and method of treatment are represented by formula (I), wherein R is hydrogen or a pharmaceutically-acceptable cation, e.g. an alkali or alkaline earth metal, or a quaternary amine; or R represents a ester-forming moiety, e.g. a lower alkyl radical, having up to six carbon atoms, that may be derived from a lower alkanol.</p>			
			
		(I)	

see folio 3

## USE OF CHLORIDE CHANNEL BLOCKERS FOR REDUCING INTRAOCULAR PRESSURE

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## BACKGROUND OF INVENTION

Field of the Invention

The present invention is directed to pharmaceutical compositions, and primarily to topically applied ophthalmic compositions comprising as the active ingredient one or more compounds having the ability to block chloride channels in the ciliary epithelium, e.g. to inhibit the transport of chloride ions and fluid secretion in epithelia. The pharmaceutical compositions are useful for reducing intraocular pressure in animals of the mammalian species. In another aspect, the present invention is directed to administering such formulations and compositions to animals of the mammalian species (including humans) for reducing intraocular pressure in the eye.

20 Brief Description of the Art

Glaucoma is an optical neuropathy associated with elevated intraocular pressures which are too high for normal function of the eye, and results in irreversible loss of visual function. It is estimated in medical science that glaucoma afflicts approximately 2 per cent of the population over the age of forty years, and is therefore a serious health problem. Ocular hypertension, i.e. the condition of elevated intraocular pressure, which has not yet caused irreversible damage, is believed to represent the earliest phase of glaucoma. Many therapeutic agents have been devised and discovered in the prior art for the treatment or amelioration of glaucoma and of the condition of increased intraocular pressure which precedes glaucoma.

The drugs currently utilized in the treatment of glaucoma include miotics (e.g., pilocarpine, carbachol, and acetylcholinesterase inhibitors), sympathomimetics (e.g., epinephrine and dipivalylepinephrine), beta-blockers (e.g., betaxolol, levobunolol and timolol), alpha-2 agonists (e.g.,

para-amino clonidine) and carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide and ethoxzolamide). Miotics and sympathomimetics are believed to lower intraocular pressure by increasing the outflow of aqueous humor, while beta-blockers, alpha-2 agonists and carbonic anhydrase inhibitors are believed to lower intraocular pressure by decreasing the formation of aqueous humor. All five types of drugs have potential side effects. Miotics, such as pilocarpine, can cause blurring of vision and other visual side effects which may either decrease patient compliance or require termination of miotic drug therapy. Carbonic anhydrase inhibitors can also cause serious side effects which affect patient compliance and/or necessitate withdrawal of the drug therapy. At least one beta-blocker, timolol, has increasingly become associated with serious pulmonary side effects attributable to its effect on beta-2 receptors in pulmonary tissue.

As a result additional antiglaucoma drugs are being developed, e.g., prostaglandin derivatives, muscarinic antagonists, etc.

In light of the foregoing circumstances, it is clear that a need exists for new, more potent antiglaucoma compositions which avoid or reduce the above-cited side effects and enhance patient compliance, since the foregoing and other anti-glaucoma and ocular hypotensive compounds and agents of the prior art do not provide a treatment or cure for glaucoma and ocular hypertension which is satisfactory in all respects. Therefore, the pharmacological and related arts and sciences continue searching for additional and better anti-glaucoma and ocular hypotensive agents.

Chloride channel blockers such as 5-nitro-2-(3-phenylpropylamino)-benzoate (NPPB) have been shown to inhibit  $\text{Cl}^-$  transport and fluid secretion/absorption in rat intestine. (See for example, *Acta Physiol Scand*: No. 149, 1993: pp. 365-376, Fryklund et al., "The effects of chloride transport inhibitors on intestinal fluid and ion transport in vivo and in vitro".)

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## SUMMARY OF THE INVENTION

Surprisingly it has been discovered in accordance with the present invention that chloride channel blockers are effective as anti-glaucoma agents and as agents for reducing intraocular pressure, when such agents are applied to the mammalian eye in a pharmaceutical composition, preferably in a topical ophthalmic composition.

Thus according to an aspect of the present invention there is provided a method of treating animals of the mammalian species, including humans, for the purpose of reducing intraocular pressure in the eye of the mammal comprising the step of administering to the mammal a pharmaceutical composition which comprises as its active ingredient one or more compounds having chloride channel blocking activity.

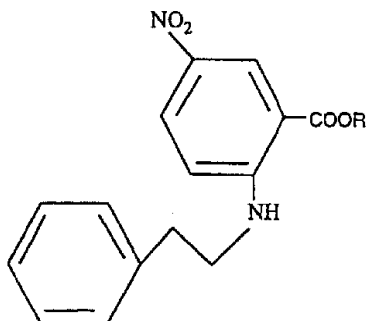
According to another aspect of the present invention there is provided a method of treating animals of the mammalian species, including humans, for the purpose of reducing intraocular pressure in the eye of the mammal comprising the step of administering to the mammal an ophthalmic composition which comprises as its active ingredient one or more compounds having chloride channel blocking activity compounds selected from the group consisting of N-phenylanthranilic acid, DPC (diphenylamine-2-carboxylic acid), IAA-94 (R(+)-methyldiazole, indanyloxyacetic acid 94), 2-aminomethyl phenols, MK-447 (2-aminomethyl-4-(1,1-dimethyl ethyl)-6-iodophenol hydrochloride, disulfonic stilbenes including DIDS (4,4'-diisothiocyanostilbene-2,2'-disulfonic acid) and 5-nitro-2-(3 phenyl propyl amino)-benzoate (NPPB).

According to yet another aspect of the present invention there is provided a method for providing neuroprotective effect to the eye of a mammal which comprises the step of administering to the mammal a pharmaceutical composition which comprises as its active ingredient one or more compounds having chloride channel blocking activity wherein said compound having a chloride channel blocking activity is selected from the group consisting of N-phenylanthranilic acid, DPC (diphenylamine-2-carboxylic acid), IAA-94 (R+)-methyldiazole, indanyloxyacetic acid 94), MK-447 (2-aminoethyl-4-(1,1-dimethyl ethyl)-6-iodophenol hydrochloride, DIDS (4,4'-diisothiocyanostilbene-2,2'-disulfonic acid) and compounds represented by the formula:



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wherein R is hydrogen or a pharmaceutically-acceptable cation, or R represents a ester-forming moiety.

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According to still yet another aspect of the present invention there is provided a method of treating animals of the mammalian species for glaucoma which comprises administering to the eye of a mammal having glaucoma a pharmaceutical composition comprising as its active ingredient one or more compounds having chloride channel blocking activity.

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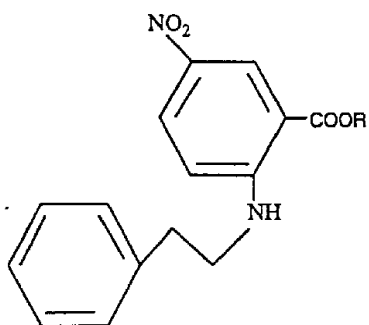
Further aspects of the present invention provide the use of one or more compounds having chloride channel blocking activity for the preparation of a medicament for the purpose of reducing intraocular pressure in the eye of a mammal, for providing a neuroprotective effect to the eye of a mammal and/or for treating glaucoma in a mammalian species.

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A preferred example of chloride channel blockers suitable as the active ingredients of the ophthalmic compositions of the invention are:

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3a





cells".) Thus, aqueous secretion is inhibited and hence intraocular pressure (IOP) is lowered by blocking  $\text{Cl}^-$  channels in the NPE cells.

The ophthalmic compositions of the invention contain the active ingredient in a concentration range of approximately 0.0001 to 0.1 per cent weight by volume. The composition itself includes, in addition to  
5 the active ingredient, such excipients which are per se well known in the art for preparing ophthalmic compositions, particularly ophthalmic solutions. In accordance with the method of the invention the ophthalmic compositions, preferably ophthalmic solutions are applied  
10 topically to the mammalian eye approximately 1 or 2 times daily.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the effect of the presence of the drug NPPB on the regulatory volume decrease (RVD) of a suspension of  
15 cultured human non-pigmented ciliary epithelial (NPE) cells.

Figure 2 is a graph showing the effect of intracameral administration of the drug NPPB on the intraocular pressure (IOP) in the rabbit eye.

#### 20 DETAILED DESCRIPTION OF THE INVENTION

The compounds which are utilized in accordance with the method of the present invention, and in the pharmaceutical compositions of the present invention, are chloride channel blockers. In this regard the term chloride channel blocker is defined as those  
25 compounds or agents which inhibit net  $\text{Cl}^-$  flux (current) through a  $\text{Cl}^-$  specific pathway (channel, integral membrane protein) within biological membranes. Specific and preferred examples of chloride channel blockers which are utilized in accordance with the present invention are provided below.

30 Pharmaceutically acceptable salts of the chloride channel blockers can also be used in accordance with the present invention. A pharmaceutically acceptable salt may be any salt which retains the activity of the parent compound and does not impart any deleterious or untoward effect on the subject to which it is administered and in the  
35 context in which it is administered.



Such a salt may be derived from any organic or inorganic acid or base. The salt may be a mono or polyvalent ion. Of particular interest where the acid function is concerned are the inorganic ions, such as alkali ions, e.g. sodium, potassium, etc. Organic amine salts may be  
5 made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines, e.g. alkyl amines wherein each alkyl group may comprise up to six carbon atoms, or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. It is only  
10 important that the cation of any salt of a chloride channel blocker utilized in the compositions or methods of this invention be able to block chloride channels in the ciliary epithelium.

For reducing intraocular pressure in a mammalian eye, and particularly for treatment of glaucoma in humans suffering from that condition, the active compounds (or mixtures or salts thereof) are  
15 administered in accordance with the present invention to the eye admixed with an ophthalmically acceptable carrier. Any suitable, e.g., conventional, ophthalmically acceptable carrier may be employed. A carrier is ophthalmically acceptable if it has substantially no long term or permanent detrimental effect on the eye to which it is administered.  
20 Examples of ophthalmically acceptable carriers include water (distilled or deionized water), saline and other aqueous media. In accordance with the invention, the active compounds are preferably soluble in the carrier which is employed for their administration, so that the active compounds are administered to the eye in the form of a solution.  
25 Alternatively, a suspension of the active compound or compounds (or salts thereof) in a suitable carrier may also be employed.

In accordance with the invention the active compounds (or mixtures or salts thereof) are administered in an ophthalmically acceptable carrier in sufficient concentration so as to deliver an effective  
30 amount of the active compound or compounds to the eye. Preferably, the ophthalmic, therapeutic solutions contain one or more of the active compounds in a concentration range of approximately 0.0001% to approximately 1% (weight by volume) and more preferably approximately 0.0005% to approximately 0.1% (weight by volume).

Any method of administering drugs directly to a mammalian eye may be employed to administer, in accordance with the present invention, the active compound or compounds to the eye to be treated. By the term "administering directly" is meant to exclude those general systemic drug administration modes, e.g., injection directly into the patient's blood vessels, oral administration and the like, which result in the compound or compounds being systemically available. The primary effect on the mammal resulting from the direct administering of the active compound or compounds to the mammal's eye is preferably a reduction in intraocular pressure. More preferably, the active useful compound or compounds are applied topically to the eye or are injected directly into the eye. Particularly useful results are obtained when the compound or compounds are applied topically to the eye in an ophthalmic solution, i.e. as ocular drops.

Topical ophthalmic preparations, for example ocular drops, gels or creams, are preferred because of ease of application, ease of dose delivery and fewer systemic side effects, such as cardiovascular hypotension. An exemplary topical ophthalmic formulation is shown below in Table I. The abbreviation q.s. means a quantity sufficient to effect the result or to make volume.

TABLE I

	<u>Ingredient</u>	<u>Amount(% W/V)</u>
25	Active Compound in accordance with the invention,	about 0.0001 to about 1
	Preservative	0-0.10
	Vehicle	0-40
30	Tonicity Adjustor	1-10
	Buffer	0.01-10
	pH Adjustor	q.s. pH 4.5-7.5
	antioxidant	as needed
35	Purified Water	as needed to make 100%

Various preservatives may be used in the ophthalmic preparation described in Table I above. Preferred preservatives include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, and phenylmercuric nitrate. Likewise, various preferred vehicles may be used in such ophthalmic preparation. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose and hydroxyethyl cellulose.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride etc., mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include but are not limited to, acetate buffers, citrate buffers, phosphate buffers, and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, ophthalmically acceptable antioxidants include, but are not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole, and butylated hydroxytoluene.

The ophthalmic solution (ocular drops) may be administered to the mammalian eye as often as necessary to maintain an acceptable level of intraocular pressure in the eye. In other words, the ophthalmic solution (or other formulation) which contains the chloride channel blocker as the active ingredient, is administered to the mammalian eye as often as necessary to maintain the beneficial hypotensive effect of the active ingredient in the eye. Those skilled in the art will recognize that the frequency of administration depends on the precise nature of the active ingredient and its concentration in the ophthalmic formulation. Within these guidelines it is contemplated that the ophthalmic formulation of the present invention will be administered to the mammalian eye approximately once or twice daily.

Specific examples of chloride channel blockers which are used as the active effective ingredients in the ophthalmic compositions of the present invention are described and shown below:

N-phenylanthranilic acid, DPC (diphenylamine-2-carboxylic acid), IAA-94 (R(+)-methylandazole, indanyloxyacetic acid 94), 2-aminomethyl phenols such as MK-447 (2-aminomethyl-4-(1,1-dimethyl ethyl)-6-iodophenol hydrochloride, disulfonic stilbenes such as DIDS (4,4'-diisothiocyanostilbene-2-2'-disulfonic acid).

Alternatively, a chloride channel blocker may be defined as a pharmaceutical compound showing activity in the following assay:

Inhibition of current mediated by Cl ions using patch clamp technology in the whole cell, cell attached or cell excised mode. (See for Example, Biochimica et al Biophysica Acta, Vol. 947, 1988, pp. 521-547, Gogelein, H., "Chloride channels in epithelia".)

#### EXAMPLES

15 The present invention is demonstrated by *in vitro* and *in vivo* data. In Figure 1, 5 $\mu$  M NPBB were found to depress the regulatory volume decrease (RVD) that occurs following hyposmotic swelling of cultured human non-pigmented ciliary epithelial (NPE) cells. In this example, NPE cells were suspended in an isosmotic (290 mOsm) solution containing 5 $\mu$ M NPBB for 30 minutes prior to suspension in a hyposmotic (198 mOsm) solution. Control cells were subjected to the same hyposmotic solution but without NPBB in the medium. Changes in cell volume were measured using a Coulter Counter interfaced to a Coulter Channelyzer. It is noted that, following osmotic swelling, control cells regulate towards their original isosmotic volume while NPBB-treated cells remain swollen. The above findings indicate that intracellular NPBB, via blocking of the chloride channel, inhibits solute and osmotically obliged H<sub>2</sub>O efflux. Because the chloride-dependent ion flux pathways, activated following osmotic cell swelling of NPE cells, are involved in aqueous secretion, NPBB will inhibit aqueous humor formation and, thus, lower IOP.

In the *in vivo* studies normotensive rabbits were injected intracamerally with 100 $\mu$  M NPBB. Figure 2 shows that 100 $\mu$  M NPBB lowered IOP by 7 mm of Hg and IOP remained depressed for 24 hours. Taken together, the above *in vitro* and *in vivo* experiments



demonstrate that blocking the chloride ion channel in the ciliary epithelium will reduce IOP.

5 One advantage Cl<sup>-</sup> channel inhibition has over other IOP lowering therapies is that the effector, i.e. the ion channel, is targeted rather than the receptor. Since effector blockage is direct, it should be the most potent and effective way of inhibiting aqueous secretion and hence lowering IOP. On the other hand, targeting a receptor to block an effector is indirect and relies on modulation of a series of cellular events (intracellular messengers/signals) prior to effector inhibition.

10 In view of the above, it is clear that the scope of the present invention should be interpreted solely on the basis of the following claims, as such claims are read in light of the disclosure.

Throughout this specification and the claims which follow, unless the text requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

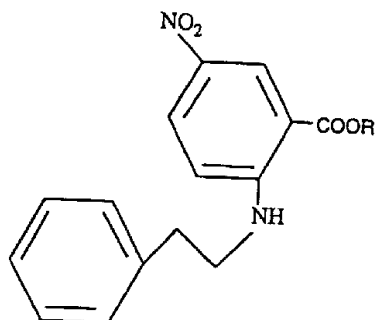
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The claims defining the invention are as follows:

1. A method of treating animals of the mammalian species, including humans, for the purpose of reducing intraocular pressure in the eye of the mammal comprising the step of administering to the mammal a pharmaceutical composition which comprises as its active ingredient one or more compounds having chloride channel blocking activity.
2. A method of treatment of claim 1, where the composition is an ophthalmic solution adapted for administration to the eye of a mammal in the form of eye droplets.
3. A method of treatment of claim 2, wherein in the ophthalmic composition the concentration of the compound having chloride channel blocking activity is in the range of approximately 0.0001 to 1 per cent weight by volume.
4. A method of treating animals of the mammalian species, including humans, for the purpose of reducing intraocular pressure in the eye of the mammal comprising the step of administering to the mammal an ophthalmic composition which comprises as its active ingredient one or more compounds having chloride channel blocking activity compounds selected from the group consisting of N-phenylanthranilic acid, DPC (diphenylamine-2-carboxylic acid), IAA-94 (R(+)-methyldiazone, indanyloxyacetic acid 94), 2-aminomethyl phenols, MK-447 (2-aminomethyl-4-(1,1-dimethyl ethyl)-6-iodophenol hydrochloride, disulfonic stilbenes including DIDS (4,4'-diisothiocyanostilbene-2-2'-disulfonic acid) and 5-nitro-2(3 phenyl propyl amino)-benzoate (NPPB).
5. A method of claim 4, wherein the compound having chloride channel blocking activity is selected from the group consisting of compounds represented by the formula:

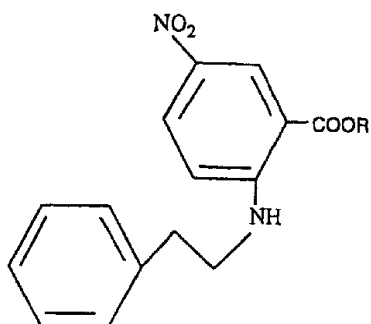




wherein R is hydrogen or a pharmaceutically-acceptable cation of R represents a ester-forming moiety.

6. The method of claim 5, wherein R is hydrogen, or an alkali metal ion, or a quaternary amine selected from the group consisting of mono-, di- and trialkyl amines, wherein each alkyl group may comprise up to six carbon atoms, or ethanol amine, or caffeine, or tromethamine, or a lower alkyl radical having up to six carbon atoms.
7. A method of treatment of claim 5 or 6, where the composition is an ophthalmic solution adapted for administration to the eye of a mammal in the form of eye droplets.
8. The method of treatment of claim 7, wherein in the ophthalmic composition the concentration of the compound having chloride channel blocking activity is in the range of approximately 0.0001 to 1 percent weight by volume.
9. A method for providing neuroprotective effect to the eye of a mammal which comprises the step of administering to the mammal a pharmaceutical composition which comprises as its active ingredient one or more compounds having chloride channel blocking activity wherein said compound having a chloride channel blocking activity is selected from the group consisting of N-phenylanathracilic acid, DPC (diphenylamine-2-carboxylic acid), IAA-94 (R(+)-methylidazone, indanyloxyacetic acid 94), MK-447 (2-aminoethyl-4-(1,1-dimethyl ethyl)-6-iodophenol hydrochloride, DIDS (4,4'-diisothiocyanostilbene-2,2'-disulfonic acid) and compounds represented by the formula:





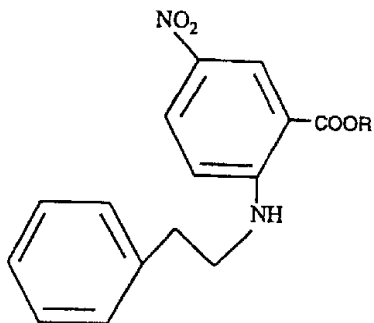
wherein R is hydrogen or a pharmaceutically-acceptable cation, or R represents a ester-forming moiety.

10. A method of claim 9, wherein R is hydrogen, or an alkali metal ion, or a quaternary amine selected from the group consisting of mono-, di- and trialkyl amines, wherein each alkyl group may comprises up to six carbon atoms, or ethanol amine, or caffeine, or tromethamine, or a lower alkyl radical having up to six carbon atoms.
11. A method of claim 9 or 10, wherein the composition contains approximately 0.0001 to 1 percent weight by volume of said compound having chloride channel blocking activity.
12. A method of treating animals of the mammalian species for glaucoma which comprises administering to the eye of a mammal having glaucoma a pharmaceutical composition comprising as its active ingredient one or more compounds having chloride channel blocking activity.
13. A method of claim 12, wherein the compound having chloride channel blocking activity is selected from the group consisting of N-phenylanthranilic acid, DPC (diphenylamine-2-carboxylic acid), IAA-94 (R(+)-methylindazole, indanyloxyacetic acid 94), 2-aminomethyl phenols, MK-447 (2-aminomethyl-4-(1,1-dimethyl ethyl)-6-iodophenol hydrochloride, disulfonic stilbenes including DIDS (4,4'-diisothiocyanostilbene-2,2'-disulfonic acid) and 5-nitro-2(3 phenyl propyl amino)-benzoate (NPPB).





14. A method of claim 13, wherein the compound having chloride channel blocking activity is selected from the group consisting of compounds represented by the formula:



wherein R is hydrogen or a pharmaceutically-acceptable cation.



15. A method of claim 14, wherein R is hydrogen or an alkali metal ion or a quaternary amine selected from the group consisting of mono-, di- and trialkyl amines, wherein each alkyl group may comprise up to six carbon atoms, ethanolamine, or caffeine or tromethamine, or a lower alkyl radical having up to six carbon atoms.



16. A method of any one of claims 12-15, where the composition is an ophthalmic solution adapted for administration to the eye of a mammal in the form of eye droplets.



17. A method of claim 16, wherein the composition contains approximately 0.0001 to 1 per cent weight by volume of said compound having chloride channel blocking activity.

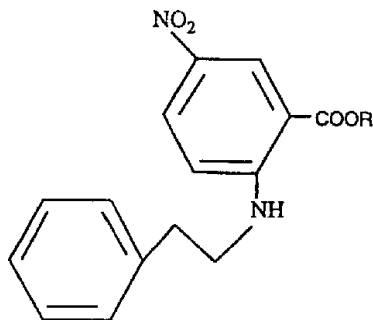
18. Use of one or more compounds having chloride channel blocking activity for the preparation of a medicament for the purpose of reducing intraocular pressure in the eye of a mammal.

19. Use of claim 18, wherein the compounds having channel blocking activity are selected from the group consisting of N-phenylanthranilic acid, DPC (diphenylamine-2-carboxylic acid), IAA-94 (R(+))methylindazone, indanyloxyacetic acid 94), 2-



2-carboxylic acid), IAA-94 (R(+)-methylindazone, indanyloxyacetic acid 94), 2-aminomethyl phenols, MK-447 (2-aminomethyl-4-(1,1-dimethyl ethyl)-6-iodophenol hydrochloride, disulfonic stilbenes including DIDS (4,4'-diisothiocyanostilbene-2,2'-disulfonic acid) and 5-nitro-2(3 phenyl propyl amino)-benzoate (NPPB).

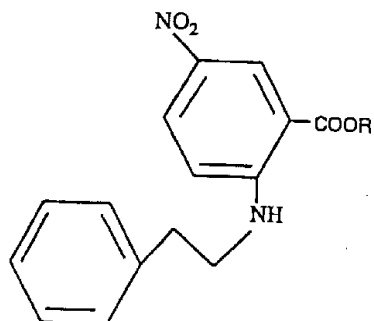
20. Use of claim 18, wherein the compounds having channel blocking activity are selected from the group consisting of compounds represented by the formula:



wherein R is hydrogen or a pharmaceutically-acceptable cation of R represents a ester-forming moiety.

21. Use of claim 20, wherein R is hydrogen, or an alkali metal ion, or a quaternary amine selected from the group consisting of mono-, di- and trialkyl amines, wherein each alkyl group may comprise up to six carbon atoms, or ethanol amine, or caffeine, or tromethamine, or a lower alkyl radical having up to six carbon atoms.
22. Use of one or more compounds having chloride channel blocking activity for the purpose of providing neuroprotective effect to the eye of a mammal, wherein said compound having a chloride channel blocking activity is selected from the group consisting of N-phenylanathracilic acid, DPC (diphenylamine-2-carboxylic acid), IAA-94 (R(+)-methylidazone, indanyloxyacetic acid 94), MK-447 (2-aminoethyl-4-(1,1-dimethyl ethyl)-6-iodophenol hydrochloride, DIDS (4,4'-diisothiocyanostilbene-2,2'-disulfonic acid) and compounds represented by the formula:





wherein R is hydrogen or a pharmaceutically-acceptable cation, or R represents a ester-forming moiety.

23. Use of one or more compounds having chloride channel blocking activity for the preparation of a medicament for treating glaucoma in a mammalian species.

DATED this 1<sup>st</sup> day of July 1999

ALLERGAN SALES, INC.

By its Patent Attorneys  
DAVIES COLLISON CAVE



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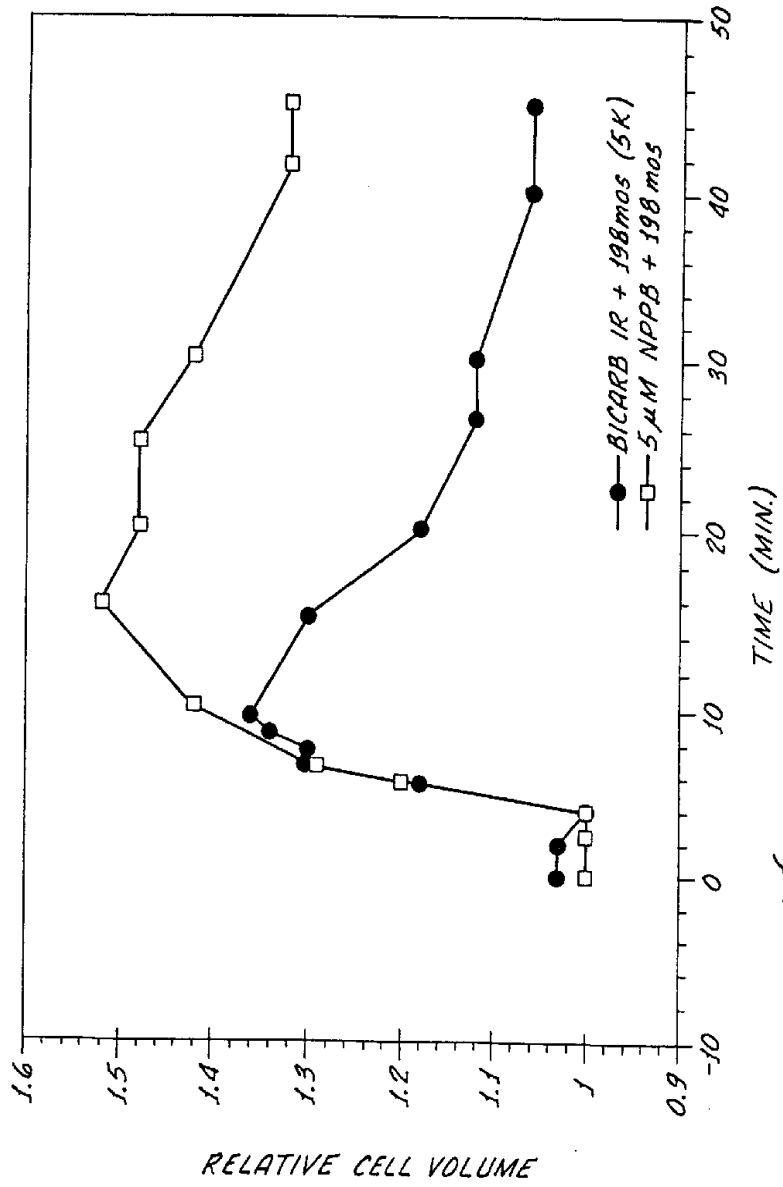


FIG. 1.

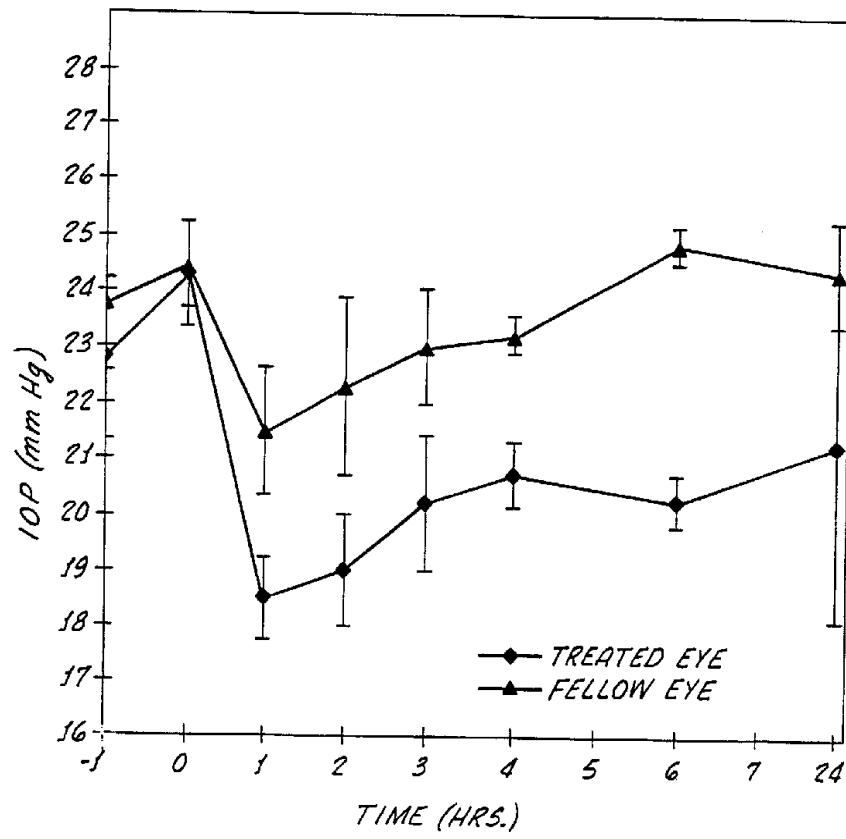


FIG. 2.