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[54] **PROSTAGLANDIN DERIVATIVES FOR THE TREATMENT OF GLAUCOMA OR OCULAR HYPERTENSION**

[75] Inventors: **Johan W. Stjernschantz; Bahram Resul, both of Uppsala, Sweden**

[73] Assignee: **Kabi Pharmacia, Sweden**

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281239	9/1988	European Pat. Off. ...	C07C 177/00
289349	11/1988	European Pat. Off. ...	C07C 177/00
308135	3/1989	European Pat. Off. ...	A61K 31/577
364417	4/1990	European Pat. Off. ...	A61K 31/557
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*Primary Examiner*—Robert Gerstl  
*Attorney, Agent, or Firm*—Kenyon & Kenyon

### [57] ABSTRACT

The invention relates to ophthalmological compositions for topical treatment of glaucoma or ocular hypertension comprising an effective intraocular pressure reducing amount of a prostaglandin derivative of PGA, PGB, PGD, PGE or PGF, in which the omega chain contains a ring structure, in an ophthalmologically compatible carrier. The invention further relates to the preparation of said compositions and their use for treatment of glaucoma or ocular hypertension.

**16 Claims, No Drawings**

### Related U.S. Application Data

[63] Continuation of Ser. No. 469,442, Apr. 10, 1990, abandoned.

### [30] Foreign Application Priority Data

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[51] Int. Cl.<sup>5</sup> ..... **A01K 31/557**

[52] U.S. Cl. .... **514/530**

[58] Field of Search ..... **514/530**

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## PROSTAGLANDIN DERIVATIVES FOR THE TREATMENT OF GLAUCOMA OR OCULAR HYPERTENSION

This application is a continuation of application Ser. No. 07/469,442, filed on Apr. 10, 1990, now abandoned.

The invention is concerned with the use of prostaglandin derivatives of PGA, PGB, PGD, PGE and PGF, in which the omega chain has been modified with the common feature of containing a ring structure, for the treatment of glaucoma or ocular hypertension. The invention relates also to ophthalmic compositions, containing an active amount of these prostaglandin derivatives, and the manufacture of such compositions.

Glaucoma is an eye disorder characterized by increased intraocular pressure, excavation of the optic nerve head and gradual loss of the visual field. An abnormally high intraocular pressure is commonly known to be detrimental to the eye, and there are clear indications that, in glaucoma patients, this probably is the most important factor causing degenerative changes in the retina. The pathophysiological mechanism of open angle glaucoma is, however, still unknown. Unless treated successfully glaucoma will lead to blindness sooner or later, its course towards that stage is typically slow with progressive loss of the vision.

The intraocular pressure, IOP (abbr. of intraocular pressure) can be defined as according to the formula:

$$IOP = P_e + F \times R \quad (1)$$

where  $P_e$  is the episcleral venous pressure, generally regarded as being around 9 mm Hg, F the flow of aqueous humor, and R the resistance to outflow of aqueous humor through the trabecular meshwork and adjacent tissue into Schlemm's canal.

Besides passing through Schlemm's, canal aqueous humor might also pass through the ciliary muscle into the suprachoroidal space and finally leave the eye through sclera. This uveoscleral route has been described for instance by Bill (1975). The pressure gradient in this case is insignificant compared to the gradient over the interior wall of Schlemm's canal and adjacent tissue in the former case. The flow limiting step along the uveoscleral route is assumed to be the flow from the anterior chamber into the suprachoroidal space.

A more complete formula is given by:

$$IOP = P_e + (F_t - F_u) \times R \quad (2)$$

where  $P_e$  and R are defined as above,  $F_t$  is the total outflow of aqueous humor and  $F_u$  is the fraction passing via the uveoscleral route.

IOP in human beings is normally in the range of 12-22 mm Hg. At higher values, for instance over 22 mm Hg, there is a risk that the eye may be affected. In one particular form of glaucoma, low tension glaucoma, damage may occur at intraocular pressure levels otherwise regarded as physiologically normal. The reason for this could be that the eye in these individuals is unusually sensitive to pressure. The opposite situation is also known, that some individuals may exhibit an abnormally high intraocular pressure without any manifest defects in the visual field or optic nerve head. Such conditions are usually referred to as ocular hypertension.

Glaucoma treatments can be given by means of drugs, laser or surgery. In drug treatment, the purpose

is to lower either the flow (F) or the resistance (R) which, according to formula (1) above, will result in a reduced IOP; alternatively to increase the flow via the uveoscleral route which according to formula (2) also gives a reduced pressure. Cholinergic agonists, for instance pilocarpine, reduce the intraocular pressure mainly by increasing the outflow through Schlemm's canal.

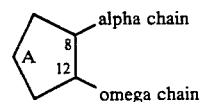
Prostaglandins, which recently have met an increasing interest as IOP-lowering substances may be active in that they will cause an increase in the uveoscleral outflow (Crawford et al, 1987, and Nilsson et al, 1987). They do not appear, however to have any effect on the formation of aqueous humor or on the conventional outflow through Schlemm's canal (Crawford et al, 1987).

The use of prostaglandins and their derivatives is described for instance in U.S. Pat. No. 4,599,353 and EP 87103714.9, and by Bito LZ et al (1983), Camras CB et al (1981, 1987a, 1987b, 1988), Giuffrè G (1985), Kaufman PL (1986), Kersetter JR et al (1988), Lee P-Y et al (1988) and Villumsen J et al (1989).

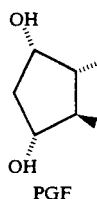
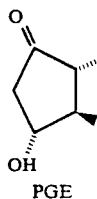
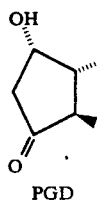
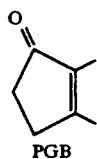
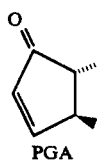
With respect to the practical usefulness of some of the previously described prostaglandins and derivatives, as suitable drugs for treating glaucoma or ocular hypertension, a limiting factor is their property of causing superficial irritation and vasodilation in the conjunctive. It is probable, moreover, that prostaglandins have an irritant effect on the sensory nerves of the cornea. Thus local side effects will arise in the eye already when the amounts of prostaglandin administered are quite small—that is, already when the doses are lower than those that would be desirable for achieving maximum pressure reduction. It has thus been found, for instance, that for this reason it is clinically impossible to use PGF<sub>2α</sub>-1-isopropyl ester in the amount that would give maximum pressure reduction. Prostaglandins, being naturally occurring autacoids, are very potent pharmacologically and affect both sensory nerves and smooth muscle of the blood vessels. Since the effects caused by administrations of PGF<sub>2α</sub> and its esters to the eye, comprise in addition to pressure reduction also irritation and hyperemia (increased blood flow), the doses currently practicable in clinical tests are necessarily very low. The irritation experienced when PGF<sub>2α</sub> or its esters are applied, consists mainly in a feeling of grittiness or of having a foreign body in one's eye, this being usually accompanied by increased lacrimation.

We have now found that a solution to the problems discussed above is the use of certain derivatives of prostaglandins A, B, D, E and F, in which the omega chain has been modified with the common feature of containing a ring structure, for the treatment of glaucoma or ocular hypertension.

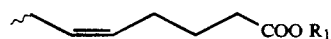
The prostaglandin derivatives have the general structure



wherein A represents the alicyclic ring C<sub>8</sub>-C<sub>12</sub> and the bonds between the ring and the side chains represent the various isomers. In PGA, PGB, PGD, PGE and PGF A has the formula

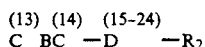


The invention is based on the use of derivatives characterized by their omega chain and various modifications of the alpha chain is therefore possible still using the inventive concept. The alpha chain could typically be the naturally occurring alpha chain, which is esterified to the structure



in which  $R_1$  is an alkyl group, preferably with 1-10 carbon, especially 1-6 atoms, for instance methyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl or benzyl or a derivative giving the final substance equivalent properties as a glaucoma agent. The chain could preferably be a  $C_6$ - $C_{10}$  chain which might be saturated or unsaturated having one or more double bonds, and allenes, or a triple bond and the chain might contain one or more substituents such as alkyl groups, alicyclic rings, or aromatic rings with or without hetero atoms.

The omega chain is defined by the following formula:



wherein

- I C is a carbon atom (the number is indicated within parenthesis);  
 B is a single bond, a double bond or a triple bond;  
 D is a chain with 1-10, preferably 2-8, and especially 2-5, and particularly 3 carbon atoms, optionally interrupted by preferably not more than two hetero atoms (O, S, or N), the substituent on each carbon atom being H, alkyl groups, preferably lower alkyl groups within 1-5 carbon atoms, a carbonyl group, or a hydroxyl group, whereby the substituent on  $C_{15}$  preferably being a carbonyl group, or (R)—OH or (S)—OH; each chain D containing preferably not more than three hydroxyl groups or not more than three carbonyl groups;
- II  
 10  
 15  
 III  $R_2$  is a ring structure such as a phenyl group which is unsubstituted or has at least one substituent selected from  $C_1$ - $C_5$  alkyl groups,  $C_1$ - $C_4$  alkoxy groups, trifluoromethyl groups,  $C_1$ - $C_3$  aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl group; or an aromatic heterocyclic group having 5-6 ring atoms, like thiazole, imidazole, pyrrolidine, thiophene and oxazole; or a cycloalkane or a cycloalkene with 3-7 carbon atoms in the ring, optionally substituted with lower alkyl groups with 1-5 carbon atoms.
- IV  
 20  
 25

Some examples on derivatives which were evaluated are the following (for structure information see Table I):

- 30 (1) 16-phenyl-17,18,19,20-tetranor-PGF $_{2\alpha}$ -isopropylester  
 (2) 17-phenyl-18,19,20-trinor-PGF $_{2\alpha}$ -isopropylester  
 V (3) 15-dehydro-17-phenyl-18,19,20-trinor-PGF $_{2\alpha}$ -isopropylester  
 35 (4) 16-phenoxy-17,18,19,20-tetranor-PGF $_{2\alpha}$ -isopropylester  
 (5) 17-phenyl-18,19,20-trinor-PGE $_2$ -isopropylester  
 (6) 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA $_2$ -isopropylester  
 40 (7) 15-(R)-17-phenyl-18,19,20-trinor-PGF $_{2\alpha}$ -isopropylester  
 (8) 16-[4-(methoxy)-phenyl]-17,18,19,20-tetranor-PGF $_{2\alpha}$ -isopropylester  
 (9) 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF $_{2\alpha}$ -isopropylester  
 45 (10) 18-phenyl-19,20-dinor-PGF $_{2\alpha}$ -isopropylester  
 (20) 19-phenyl-20-nor-PGF $_{2\alpha}$ -isopropylester

The most preferred derivatives at present are those in which the omega chain of the prostaglandin has the 18, 19,20-trinor form, and especially the 17-phenyl analogs, such as the 15-(R)-, 15-dehydro and 13,14-dihydro-17-phenyl-18,19,20-trinor forms. Such derivatives are represented by (3), (6), (7) and (9) in the formulas given in Table I.

55 In the formula given above the most preferred structure at present is accordingly obtained when the prostaglandin is a derivative of PGA, PGB, PGD, PGE or PGF, especially of PGA $_2$ , PGD $_2$ , PGE $_2$  and PGF $_{2\alpha}$

B is a single bond or a double bond;

- 60 D is a carbon chain with 2-5, especially 3 atoms;  $C_{15}$  having a carbonyl or (S)—OH substituent and  $C_{16}$ - $C_{19}$  having lower alkyl substituents, or preferably H;

- 65  $R_2$  is a phenyl ring optionally having substituents selected among alkyl and alkoxy groups.

The invention thus relates to the use of certain derivatives of PGA, PGB, PGD, PGE and PGF for the treatment of glaucoma or ocular hypertension. Among these

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