US005296504A

United States Patent [19]

Stjernschantz et al.

[11] Patent Number: 5,296,504

[45] Date of Patent: Mar. 22, 1994

[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

[21] Appl. No.: **987,520**

[22] Filed: **Dec. 8, 1992**

Related U.S. Application Data

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

[30] **Foreign Application Priority Data**

Sep. 6, 1988 [SE] Sweden 8803110
Oct. 28, 1988 [SE] Sweden 8803855

[51] **Int. Cl.**[5] **A01K 31/557**
[52] **U.S. Cl.** **514/530**
[58] **Field of Search** 514/530

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,956,284	5/1976	Hess et al.	260/240 R
3,962,312	6/1976	Hayashi et al.	260/468 D
4,011,262	3/1977	Hess et al.	260/520 B
4,116,988	9/1978	Nelson	260/413
4,117,119	9/1978	Kurono et al.	424/180
4,131,738	12/1978	Smith	560/121
4,599,353	7/1986	Bito	514/530
4,820,728	4/1989	Collins et al.	514/530
4,824,857	4/1989	Goh et al.	514/398
4,883,819	11/1989	Bito	514/573
5,001,153	3/1991	Ueno et al.	514/530
5,057,621	10/1991	Cooper et al.	560/53
5,151,444	9/1992	Ueno et al.	514/530
5,166,178	11/1992	Ueno	514/573
5,194,429	3/1993	Ueno	514/63

FOREIGN PATENT DOCUMENTS

573018	2/1986	Australia	C07C 177/00
600168	8/1990	Australia	A61K 31/557
170258	2/1986	European Pat. Off.	C07C 177/00
242580	10/1987	European Pat. Off.	A61K 31/557
253094	1/1988	European Pat. Off.	A61K 31/557
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
366279	5/1990	European Pat. Off.	A61K 31/557
455264A2	11/1991	European Pat. Off.	A61K 31/557
2234709	2/1973	Fed. Rep. of Germany	C07C 57/02
1324737	7/1973	United Kingdom	C07C 61/00

OTHER PUBLICATIONS

Bill A (1975) "Blood Circulation and fluid dynamics in the eye". *Physiol. Rew.* 55: 383–417.

Bito L. Z., Draga A., Blanco D. J., Camras C. B. (1983) "Long Term Maintenance of Reduced intraocular Pressure by Daily or Twice Daily Topical Application of Prostaglandins to Cat or Rhesus Monkey Eyes" *Invest. Ophthalmol. Vis. Sci.* 24: 312–319.

Bito, L. Z., Camras C. B., Gum G. G. and Resul B. (1989), "The Ocular Hypotensive Effects and Side Effects of Prostaglandins on the Eyes of Experimental Animals" *Progress in Clinical and Biological Research* 312 Ed. L. Z. Bito and Johan Stjernschantz, A. R. Liss, Inc., New York.

Burke et al., "Prostaglandin $F_{2\alpha}$ Effects on Rabbit IOP Negatively Correlate with Classical $PGF_{2\alpha}$ -Receptor Stimulation", Presented at ARVO annual meeting in Florida May 1–6, 1988.

Bundy, Chem Abst. 90:168141d, 1979.

(List continued on next page.)

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

OTHER PUBLICATIONS

Camras C. B., Bito L. Z. (1981). Reduction of intraocular pressure in normal and glaucomatous primate (Aotus trivirgatus) eyes by topically applied prostaglandin $F_{2\alpha}$. "Curr Eye Res" 1:205–209.

Camras, C. B., Podos S. M., Rosenthal J. S., Lee P. Y., Severin C. H. (1987a). Mulitple dosing of prostaglandin $F_{2\alpha}$ or epinephrine on cynomolgus monkey eyes. I. Aqueous humor dynamics. *Invest Ophthalmol Vis Sci* 28:463–469.

Camras C. B., Bhuyan K. C., Podos S. M., Bhuyan D. K. Master R. W. P. (1987b) "Multiple Dosing of Prostaglandin $F_{2\alpha}$ or epinephrine on cynomologus mokey eyes. II. Slitlamp biomicroscopy, aqueous humor analysis, and flourescein angiography." *Invest. Ophthalmol. Vis. Sci* 28:921–926.

Camras C. B., Siebold E. C., Lustgarten J. S., Serle J. B., Frisch S. C., Podos S. M., Bito L. Z. (1988) "Reduction of IOP by prostaglandin $F_{2\alpha}$ –1–isopropyl ester topically applied in glaucoma patients", *Ophthalmology* 95(Supp.) 129 [This article is referrenced in the specification, and was raised as prior art in an opposition to Australian patent application 625096, which is related to the instant application. However, we have been unable to locate a copy of this article.].

Crawford K., Kaufman P. L. and True Gable, B. A. (1987), "Pilocarpine antagonizes $PGF_{2\alpha}$ –induced ocular hypotension: Evidence for enhancement of uveoscleral outflow of $PGF_{2\alpha}$". *Invest. Ophthalmol. Vis. Sci.* (Supp.) ARVO Abstracts 11.

Crawford, K. and Kaufman, P. L., (1987) "Pilocarpine Antagonizes Prostaglandin $F_{2\alpha}$–Induced Ocular Hypotension in Monkeys" Arch. Ophthamology 105 1112.

Flach A. J., Elisason J. A. (1988), "Topical prostaglandin E_2 effects on normal human intraocular pressure". *J. Ocu. Pharmacol.* 4:13–18.

Gabelt, B. and Kaufman, P. L., (1989) "Prostaglandin $F_{2\alpha}$ Increases Uvelscleral Outflow in the Cynomologus Monkey", Exp. Eye Res. 49 389–402.

Giuffré G. (1985). "The effects of prostaglandin $F_{2\alpha}$ in the human eye." *Graefes Arch Clin. Exp. Ophthalmol.* 222:139–141.

Granstrom, E., (1975) "Metabolism of 17–-Phenyl–18,19,20–Trinor–Prostaglandin $F_{2\alpha}$ in the Cynomolgus Monkey and the Human Female", *Prostaglandins* 9:19–45.

Kaufman P. L. (1986). "Effects of intracamerally infused prostaglandins on outflow facility in cynomolgus monkey eyes with intact or retrodisplaced ciliary muscle." *Exp. Eye Res.* 43:819–827.

Kerstetter J. R., Brubaker R. F., Wilson S. E., Kullerstrand L. J. (1988). "Prostaglandin $F_{2\alpha}$ –1–isopropylester lower intraocular pressure without decreasing aqueous humor flow." *Am. J. Ophthalmol.* 105:30–34.

Kirk–Othmar "Encyclopedia of Chemical Technology", 3d Ed. Supplement vol. 711–752 (1984).

Lee, P.–Y., Shae H., XZu L., Qu C.–K. (1988). "The effect of prostaglandin $F_{2\alpha}$ on intraocular pressure in normotensive human subjects." *Invest. Ophthalmol. Vis. Sci.* 29:1474–1477.

Miller, "Biological Activities of 17–phenyl–18,19,20–-trinorprostaglandins", *Prostaglandins* 9 9–18 (1975).

Nilsson, S. F. E., Stjernschantz J. and Bill A. (1987) "$PGF_{2\alpha}$ increase uveoscleral outflow", *Invest. Ophthalmol Vis. Sci. Suppl.* 284.

Villumsen J. Alm A (1989) "Prostaglandin $F_{2\alpha}$ isopropylester eye drops. Effects in normal human eyes." *Br. J. Ophthalmol.* 73:419–426.

Yankee, Chem Abst. 88:62048x, 1978.

Woodward et al., "Prostaglandin $F_{2\alpha}$ Effects on IOP Negatively Correlate with Classical $PGF_{2\alpha}$ –Receptor Stimulation" Presented in Eightly International Congress of Eye Research in San Francisco Sep. 4–8, 1988.

Woodward et al. (1989) "Prostaglandin $F_{2\alpha}$ Effects on Intraocular Pressure Negatively Correlate with FP–Receptor Stimulation" *Invest. Ophthal.* 30 (8) 1838–1842.

Kirk–Othmar "Encyclopedia of Chemical Technology", 3d Ed. Supplement vol. 711–752 (1984).

Lee, P–Y, Shae H, XZu, L, Qu C–K (1988). "The effect of prostaglandin $F_{2\alpha}$ on intraocular pressure in normotensive human subjects." *Invest. Ophthalmol. Vis. Sci.* 29:1474–1477.

Miller, "Biological Activities of 17–phenyl–18,19,20–-trinorprostaglandins", *Prostaglandins* 9 9–18 (1975).

Nilsson SFE, Stjernschantz J. and Bill A. (1987) "$PGF_{2\alpha}$ increase uveoscleral outflow." *Invest. Ophthalmol Vis. Sci. Suppl.* 284.

Villumsen J. Alm A (1989) "Prostaglandin $F_{2\alpha}$ isopropylester eye drops. Effects in normal human eyes." *Br. J. Ophthalmol.* 73:419–426.

Yankee, Chem. Abst. 88:62048x, 1978.

OTHER PUBLICATIONS

Woodward et al., "Prostaglandin $F_{2\alpha}$ Effects of IOP Negatively Correlate with Classical $PGF_{2\alpha}$-Receptor Stimuluation" Presented in Eightly International Congress of Eye Research in San Francisco Sep. 4–8, 1988.

Woodward et al. (1989) "Prostaglandin $F_{2\alpha}$ Effects on Intraocular Pressure Negatively Correlate with FP-Receptor Stimulation" *Invest. Ophthal.* 30(8) 1838–1842.

Camras C. B., Bito L. Z. and Eakins K. E. (1977): "Reduction of intraocular pressure by prostaglandins applied to the eyes of concious rabbits", Invest Ophthalmol Vis. Sic, 16:1125.

Kerstetter J. R., Brubaker R. F., Wilson S. E. and Kullerstrand L. (1988) "Prostaglandin $F2_{\alpha}$-1-Isopropylester Lowers Intracolor Pressure Without Decreasing Aqueous Humor Flow". Am. J. Ophthalmology 105:30–34.

Bito, Baroody and Miranda (1987): "Eicosanoids as a new class of ocular Hypotensive agents. The apparent therapeutic advantage of derived Prostaglandins of the A and B type as compared with primary prostaglandins of the E, F and D types", Experimental Eye Research, 44:825.

Villumser, J., Alm A., Soderstrom M., (1989) "Prostaglandin $F2_{\alpha}$-isopropylester Eye Drops: Effect on Intraocular Pressure in Open Angle Glaucoma". Brit. J. Ophthalmology 73, 975–79.

Ritch, Shields and Krupin (1989): "The Glaucomas", C. V. Mosby, p. 561.

Supplement to Investigative Ophthalmology and Visual Science 22 39 (1982), L. Z. Bito, A. Draga, J. Blanco, and C. B. Camras, "Maintenance of Reduced Intraocular Pressure (IOP) for several months by topical application of prostaglandin (PG) E_1 ti Eyes of Trained Cats".

Starr, M. S. (1971) "Further studies on the effect of prostaglandin on intraocular pressure in the rabit", Exp. Eye, Res. 11:170.

Kass, M. A., Posos, S. M., Moses, R. A., and Becker B. (1972): "Prostaglandin E1 and aqueous humor dynamics", Invest Ophthalmol. 11:1022.

Villumsen J. and Alm A. (1987): "The effect of prostaglandin F2α eye drops in open angle glaucoma", Invest Opthalmol. Vis. Sci. 28:378.

Wang R-F, Cmamras C. B., Lee P-Y, Podos S. M. and Bito L. Z. (1987) "The ocular hypotensive effects of Prostaglandins F2α isopropyl ester and A2 in glautomatous monkeys" Invest Ophthalmol Vis Sci ARVO Supl. 28:266.

Kass M. A., Mandell Al, Goldbert I, Paine J. M. and Becker B (1979) "Dipivefrin and epinephrine treatment of elevated intraocular pressure: A comparative study", Arch Ophthalmol. 97:1865.

Goldberg, I., Kolker A. E., Kass M. A. and Becker B. (1980) "Dipivefrin: current concepts", Australia J. Ophthalmol., 8:147.

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 suprachoraidal 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.

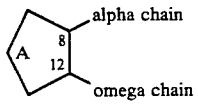
Prostaglandins, which recently have met an increasing interest as IOP-lowering substances may be active in that they will cause an increase in the uveoscleral outflow (Crawford et al, 1987, and Nilsson et al, 1987). They do not appear, however to have any effect on the formation of aqueous humor or on 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, 1987*a*, 1987*b*, 1988), Giuffrè G (1985), Kaufman PL (1986), Kersetter JR et al (1988), Lee P-Y et al (1988) and Villumsen J et al (1989).

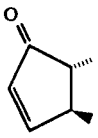
With respect to the practical usefulness of some of the previously described prostaglandins and derivatives, as suitable drugs for treating glaucoma or ocular hypertension, a limiting factor is their property of causing superficial irritation and vasodilation in the conjunctive. It is probable, moreover, 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 $PGF_{2\alpha}$-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 $PGF_{2\alpha}$ 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 $PGF_{2\alpha}$ 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.

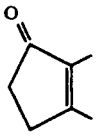
The prostaglandin derivatives have the general structure



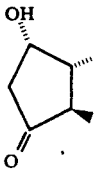
wherein A represents the alicyclic ring C_8–C_{12} and the bonds between the ring and the side chains represent the various isomers. In PGA, PGB, PGD, PGE and PGF A has the formula



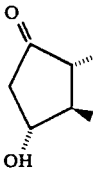
PGA



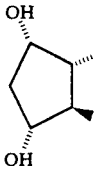
PGB



PGD

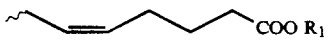


PGE



PGF

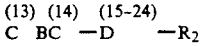
The invention is based on the use of derivatives characterized by their omega chain and various modifications of the alpha chain is therefore possible still using the inventive concept. The alpha chain could typically be the naturally occuring alpha chain, which is esterified to the structure



in which R_1 is an alkyl group, preferably with 1–10 carbon, especially 1–6 atoms, for instance metyl, 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:

I



wherein

II

III

IV

V

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;

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 thiazol, imidazole, pyrrolidine, thiophene and oxazole; or a cycloalkane or a cyclcalkene with 3–7 carbon atoms in the ring, optionally substituted with lower alkyl groups with 1–5 carbon atoms.

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

(1) 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-isopropylester

(2) 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

(3) 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

(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

(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

(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.

In the formula given above the most preferred structure at present is accordingly obtained when the prostaglandin is a derivative of PGA, 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;

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;

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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.