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TITLE

15-FLUORO PROSTAGLANDINS AS OCULAR HYPOTENSIVES

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U.S. DEPARTMENT OF COMMERCE
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (b)(2).

Docket Number	1540 Pr	Type a plus sign (+) inside this box→	+

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1-00 2-00 3-00 1X et al

TITLE OF THE INVENTION (280 characters max)

15-FLUORO PROSTAGLANDINS AS OCULAR HYPOTENSIVES

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒	Specification *Number of Pages*	20	☐	Small Entity Statement	
☐	Drawing(s) *Number of Sheets*		☒	Other *(specify)*	22 claims; 11 pages Abstract - 1 page

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

SIGNATURE Barry L. Copeland Date 11-8-96

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☐ Additional inventors are being named on separately numbered sheets attached hereto

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15-FLUORO PROSTAGLANDINS AS OCULAR HYPOTENSIVES

Background of the Invention

The present invention relates to compounds for the treatment of glaucoma and ocular hypertension. In particular, the present invention relates to the use of certain 15-fluoro analogs of F series prostaglandins to treat glaucoma and ocular hypertension.

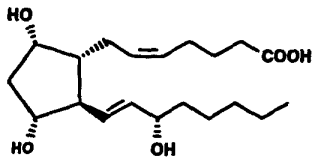
Glaucoma is a progressive disease which leads to optic nerve damage, and, ultimately, total loss of vision. The causes of this disease have been the subject of extensive studies for many years, but are still not fully understood. The principal symptom of and/or risk factor for the disease is elevated intraocular pressure or ocular hypertension due to excess aqueous humor in the anterior chamber of the eye.

The causes of aqueous humor accumulation in the anterior chamber are not fully understood. It is known that elevated intraocular pressure ("IOP") can be at least partially controlled by administering drugs which either reduce the production of aqueous humor within the eye, such as beta-blockers and carbonic anhydrase inhibitors, or increase the flow of aqueous humor out of the eye, such as miotics and sympathomimetics.

Most types of drugs conventionally used to treat glaucoma have potentially serious side effects. Miotics such as pilocarpine can cause blurring of vision and other visual side effects, which may lead either to decreased patient compliance or to termination of therapy. Systemically administered carbonic anhydrase inhibitors can also cause serious side effects, such as nausea, dyspepsia, fatigue, and metabolic acidosis, which side effects can affect patient compliance and/or necessitate the termination of treatment. Some beta-blockers have increasingly become associated with serious pulmonary side effects attributable to

their effects on beta-2 receptors in pulmonary tissue. Sympathomimetics may cause tachycardia, arrhythmia and hypertension. There is therefore a continuing need for therapies which control the elevated intraocular pressure associated with glaucoma.

Prostaglandins, which are metabolite derivatives of arachidonic acid, have recently been pursued for possible efficacy in lowering IOP. Arachidonic acid in the body is converted to prostaglandin G_2, which is subsequently converted to prostaglandin H_2. Other naturally occurring prostaglandins are derivatives of prostaglandin H_2. A number of different types of prostaglandins have been discovered including A, B, D, E, F, G, I and J-Series prostaglandins (EP 0 561 073 A1). Of interest in the present invention are compounds which are believed to exhibit IOP lowering effects similar to those exhibited by $PGF_{2\alpha}$ (an F-series prostaglandin):



The relationship of $PGF_{2\alpha}$ receptor activation and IOP lowering effects is not well understood. It is believed that $PGF_{2\alpha}$ receptor activation leads to increased outflow of aqueous humor. Regardless of mechanism, $PGF_{2\alpha}$ and analogs have been shown to lower IOP (Giuffre, *The Effects of Prostaglandin $F_{2\alpha}$ the Human Eye*, Graefe's Archive Ophthalmology, volume 222, pages 139-141 (1985); and Kerstetter et al., *Prostaglandin $F_{2\alpha}$-1-Isopropylester Lowers Intraocular Pressure Without Decreasing Aqueous Humor Flow*, American Journal of Ophthalmology, volume 105, pages 30-34 (1988)). Thus, it has been of interest in the field to develop synthetic $PGF_{2\alpha}$ analogs with IOP lowering efficacy.

Synthetic $PGF_{2\alpha}$-type analogs have been pursued in the art (Graefe's Archive Ophthalmology, volume 229, pages 411-413 (1991)). Though $PGF_{2\alpha}$-type molecules lower

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