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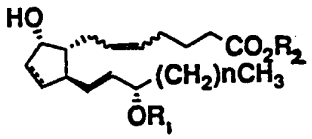

(1)

(57) Abstract

Intraocular pressure is lowered in the eye of a mammal by administration of a pharmaceutical composition containing as active ingredient a compound of formula (1), where the dotted line represents a bond or the absence of a bond, wavy lines connected to the olefinic bond represent cis or trans configuration about the olefinic bond; R_1 represents H, or CO-R_3 where R_3 is lower alkyl of 1 to 6 carbons, carbocyclic aryl or heterocyclic aryl; or carbocyclic aryl or heteroaryl substituted lower alkyl group; R_2 represents H or lower alkyl of 1 to 6 carbons, and n is an integer between 0 and 8.

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METHOD OF LOWERING INTRAOCULAR PRESSURE BY ADMINISTERING A PHARMACEUTICAL COMPOSITION CONTAINING 7-(5-SUBSTITUTED CYCLOPENTYL) AND 7-(5-SUBSTITUTED-CYCLOPENTENYL)-5-HEPTENOIC ACIDS AND DERIVATIVES

1. Field of the Invention

The present invention is in the field of methods of lowering intraocular pressure in the eye of a mammal. More particularly the present invention is in the field of lowering intraocular pressure in the eye of a mammal by administering to the mammal a pharmaceutical composition which contains as its active ingredient one or more 7-(5-substituted cyclopentyl) or 7-(5-substituted-cyclopentenyl)-5-heptenoic acids or lower alkyl ester derivatives of said heptanoic acids.

2. Background of the Invention

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its

anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupillary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing compete posterior synechia in iris bombe and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical B-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Postaglandins were earlier regarded as potent ocular hypertensives; however, evidence accumulated in the last two decades shows that some prostaglandins are highly effective ocular hypotensive agents and are ideally suited for the long-term medical management of

glaucoma. (See, for example, M. S. Starr, Exp. Eye Res. 11,170-177 (1971) Bito, L. Z. Biological Protection with Prostaglandins Cohen, M. M., ed., Boca Raton, Fla. CRC Press Inc., 1985, pp. 231-252; and Bito, L. Z., Applied Pharmacology in the Medical Treatment of Glaucomas Drance, S. M. and Neufeld, A. H. eds., New York, Grune & Stratton, 1984, pp. 477-505). Such prostaglandins include $PGF_{2\alpha}$, $PGF_{1\alpha}$, PGE_2, and certain lipid-soluble esters, such as C_1 to C_5 alkyl esters, e.g. 1-isopropyl ester, of such compounds.

In the United States Patent No. 4,599,353 certain prostaglandins, in particular PGE_2 and $PGF_{2\alpha}$ and the C_1 to C_5 alkyl esters of the latter compound, were reported to possess ocular hypotensive activity and were recommended for use in glaucoma management.

Although the precise mechanism is not yet known, recent experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et al., Invest, Ophthalmol. Vis. Sci. 28 (suppl), 284 (1987)].

The isopropyl ester of $PGF_{2\alpha}$ has been shown to have significantly greater hypotensive potency than the parent compounds, which was attributed to its more effective penetration through the cornea. In 1987 this compound was described as "the most potent ocular hypotensive agent ever reported." [See, for example, Bito, L. Z., Arch. Ophthalmol, 105, 1036 (1987), and Siebold et al., Prodrug 5, 3 (1989)].

Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical

ocular use of such compounds, in particular $PGF_{2\alpha}$ and its prodrugs, e.g. its 1-isopropyl ester, in humans. The clinical potential of postaglandins in the management of conditions associated with increased ocular pressure, e.g. glaucoma, is greatly limited by these side effects.

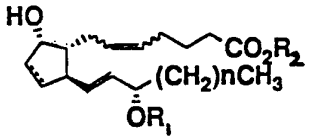
Certain phenyl and phenoxy mono, tri and tetra nor prostaglandins and their 1-esters are disclosed in European Patent Application 0,364,417 as useful in the treatment of glaucoma or ocular hypertension.

In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending USSN 386,835 (filed 27 July 1989), relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl $PGF_{2\alpha}$. Intraocular pressure reducing 15-acyl prostaglandins are disclosed in the co-pending application USSN 357,394 (filed 25 May 1989). Similarly, 11,15- 9,15- and 9,11-diesters of prostaglandins, for example 11,15-dipivaloyl $PGF_{2\alpha}$ are known to have ocular hypotensive activity. See the co-pending patent applications USSN No. 385, 645 filed 27 July 1990, now U.S. Patent No. 4,494,274; 584,370 which is a continuation of USSN No. 386,312, and 585,284, now U.S. Patent No. 5,034,413 which is a continuation of USSN 385,834, where the parent applications were filed on 27 July 1989. The disclosures of these patent applications are hereby expressly incorporated by reference.

SUMMARY OF THE INVENTION

It was found in accordance with the present

invention that intraocular pressure in the eye of a mammal is lowered significantly when a pharmaceutical composition containing certain 7-(5-substituted cyclopentyl) and 7-(5-substituted cyclopentenyl)-5-heptenoic acids or their derivatives, including their pharmaceutically acceptable salts, shown by **Formula 1**, is administered to the mammal.



Formula 1

In **Formula 1** the dotted line represents a bond, or the absence of a bond, and wavy lines attached to the double bond indicate cis or trans configuration about the double bond;

R_1 represents H, or CO-R_3 where R_3 is lower alkyl of 1 to 6 carbons, carbocyclic aryl or heterocyclic aryl; or carbocyclic aryl or heteroaryl substituted lower alkyl group;

R_2 represents H or lower alkyl of 1 to 6 carbons, and

n is an integer between 0 and 8.

Thus, the present invention relates to pharmaceutical compositions adapted for lowering intraocular pressure in the eye of a mammal, said compositions containing as active ingredient one or more compounds of **Formula 1**, and to methods of administering said compositions to a mammal for the purpose of lowering intraocular pressure.

DETAILED DESCRIPTION OF THE INVENTION

GENERAL EMBODIMENTS

The present invention relates to the use of

compounds of **Formula 1** in pharmaceutical compositions and methods for the purpose of lowering intraocular pressure in the eye of a mammal.

Definitions

In **Formula 1** as well as in all other chemical formulas in the present application for United States letters patent, bonds shown with hashed lines indicate a bond below the plane of the paper, thus signifying α configuration; bonds shown as a solid triangle indicate a bond above the plane of the paper, thus signifying β configuration; a dashed or dotted line represents a single bond or absence of a bond, and wavy lines attached to a double bond indicate that the configuration of substituents about the double bond can be cis or trans. Trans (E) configuration of substituents about a double bond is indicated by bonds pointing in opposite directions about a double bond, whereas cis (Z) configuration of substituents about a double bond is indicated by bonds pointing in the same direction about a double bond.

The term alkyl refers to and covers any and all groups which are known as normal alkyl, branch-chain alkyl and cycloalkyl. The term alkenyl refers to and covers normal alkenyl, branch chain alkenyl and cycloalkenyl groups having one or more sites of unsaturation. Lower alkyl means the above-defined broad definition of alkyl groups having 1 to 6 carbons, and as applicable, 3 to 6 carbons for branch chained and cyclo-alkyl groups.

The term "ester" as used here refers to and covers any compound falling within the definition of that term classically used in organic chemistry. Where the ester is derived from a carboxylic acid corresponding to

Formula 1, the term covers the products derived from the treatment of this function with alcohols, preferably with aliphatic alcohols having 1 - 6 carbons. Where the ester is derived from alcohols corresponding to **Formula 1**, the term covers compounds of the formula $-CH-OOCR_3$ where R_3 is lower alkyl, carbocyclic aryl, heteroaryl, or carbocyclic aryl or heteroaryl substituted lower alkyl group.

A pharmaceutically acceptable salt may be prepared for any compound used in the method of treatment of this invention, if the compound has a functionality capable of forming such salt, for example an acid functionality. 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 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, sodium, potassium, calcium, and magnesium. Organic amine salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethanine and similar molecules.

The compounds utilized in accordance with the method of treatment of the present invention, contain at least one double bond and therefore have trans and cis (E and Z) isomers. In addition, the compounds used in the method of treatment of the present invention contain one or more chiral centers and therefore exist

in enantiomeric and diastereomeric forms. Unless the structural formula or the language of this application specifically designate a particular cis or trans isomer or a particular configuration of a chiral center, the scope of the present invention is intended to cover all such isomers per se, as well as mixtures of cis and trans isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers) as well.

For the sake of ease of description, the side chain in **Formula 1** which contains the heptanoic acid residue is sometimes referred to in the application as the "heptanoic acid side chain", and the other side chain attached to the cyclopentane or cyclopentene ring in accordance with **Formula 1** is sometimes called as the "3-α- hydroxy side chain", or as the "3-α-hydroxy-octenyl side chain".

General Description of Preferred Compounds Used in the Method of the Invention

Referring now to the structure shown in **Formula 1**, preferred compounds used in the method of treatment of the invention are those where R_1 is hydrogen or CO-R_3, where R_3 is alkyl of 1 to 3 carbons.

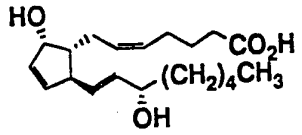
With reference to R_2 in **Formula 1**, the preferred compounds used in accordance with the invention are those where R_2 is hydrogen or a pharmaceutically acceptable cation (the compound is a carboxylic acid a pharmaceutically acceptable salt thereof), or where R_2 is lower alkyl of 1 to 3 carbons.

With respect to the double bond in the heptenoic acid side chain of **Formula 1**, compounds are preferred in accordance with the present invention where that double bond is in the cis (Z) configuration. The double bond in the 3-α-hydroxy side chain is always in

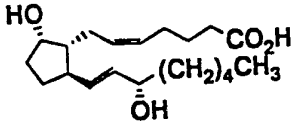
the trans configuration in the compounds used in the method of the present invention.

With regard to **n** in the 3-α-hydroxyl side chain of the compounds of **Formula 1**, **n** is preferably 4.

The most preferred compounds used in the method of the present invention are indicated by their structural formula, as compounds **1-2**, respectively.



Compound 1



Compound 2

Methods of Administration, Formulations

Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable salt thereof, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions

are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 4.5 and 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose cyclodextrin and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, 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 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, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium

thiosulfate, acetylcysteine, butylated hydroxyanisol and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	0-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution. One package may contain one or more unit doses.

Especially preservative-free solutions are often formulated in non-resealable containers containing up to about ten, preferably up to about five units doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop is about 20-35 μl.

Biological Activity

The ability of a pharmaceutical composition which contains a compound of **Formula 1** to lower intraocular pressure in the eye of a mammal, can be demonstrated by an assay performed on the eyes on New Zealand Dutch belted cross-bred rabbits. The assay is performed as follows.

New Zealand, albino/Dutch-belted cross-bred rabbits of either sex and weighing 1.5-2.5 kg were used, which had not previously received topical drugs of any kind. Intraocular pressure was measured with a pneumatonometer (Digilab) calibrated against the eyes of anesthetized rabbits by closed stopcock manometry. The correlation coefficient over a 10-30 mm Hg range was 0.98. The animals were acclimated to pneumatonometry by taking unrecorded measurements before experimental determinations of intraocular pressure. Corneal anesthesia for tonometry was provided by topical application of one drop of proparacaine (Allergan, Irvine, CA).

The data obtained by measuring intraocular pressure in this assay 1,2,4,4 and 6 hours after topical administration of 20 microliters of 0.01% and 0.1% isotonic solutions of **Compound 1** and of **Compound 2** in accordance with the present invention are illustrated below in **Table 1** (**Compound 1**) and **Table 2** (**Compound 2**), respectively

Table 1

EFFECT ON RABBIT INTRAOCULAR PRESSURE (mmHg); CHANGES AT PREDETERMINED TIMES (HR) AFTER DRUG ADMINISTRATION

Compound #	(Dose %)	1hr	2hr	3hr	4hr	6hr
Compound 1	0.1%	-0.60	-2.86	-1.34	-1.94	-1.10

% ANIMALS EXHIBITING OCULAR SURFACE HYPEREMIA AT PREDETERMINED TIMES (HR) AFTER DRUG ADMINISTRATION

Compound #	(Dose %)	1hr	2hr	3hr	4hr	6hr
Compound 1	0.1%	100	50	50	12.5	12.5

Table 2

EFFECT ON RABBIT INTRAOCULAR PRESSURE (mmHg) CHANGES AT PREDETERMINED TIMES (HR) AFTER DRUG ADMINISTRATION

Compound #	(Dose %)	1hr	2hr	3hr	4hr	6hr
Compound 2	0.01%	-2.7	-1.2	-0.7	-0.2	-1.4
Compound 2	0.1%	-3.5	-6.8	-8.4	-7.6	-3.3

% ANIMALS EXHIBITING OCULAR SURFACE HYPEREMIA AT PREDETERMINED TIMES (HR) AFTER DRUG ADMINISTRATION

Compound #	(Dose %)	1hr	2hr	3hr	4hr	6hr
Compound 2	0.01%	16.5	16.5	16.5	0	0
Compound 2	0.1%	100	100	100	66	50

The tables also show the percentage of rabbits which exhibited **hyperemia** (redness in the eye) 1,2,3,4 and 6 hours after topical administration of the active compound. As is well known hyperemia is an undesirable

side effect, and the data illustrate that administration of the compounds in accordance with the method of the invention causes this side effect only to a moderate to minimal degree.

An in vitro assay by which the beneficial IOP lowering activity of the compounds utilized in the method of the present invention can be demonstrated is the intracellular Ca^{2+} concentration assay, which is described as follows:

Measurement of intracellular [Ca^{2+}] is achieved by incorporating the Ca^{2+} sensitive fluorescent probe Fura-2AM into Swiss 3T3 cells in suspension as described by Yamaguchi, D.T. et al., J. Biol. Chem. 263: 10745-10753. Fluorescence is measured in a Perkin-Elmer LS-5 spectrophotometer at excitation and emission wavelengths of 340 and 492 nM, respectively. Each experimental determination employs 10^6 cells suspended in Schmuells buffer. For studies in Ca^{2+}-free Schmuells buffer, each cuvette also contains -.4 mN EGTA. Calibration of the Fura 2 signal is as previously described for Quin 2 (Tsien, R.Y. et al., (1982), J. Cell. Biol. 94: 325-334) and Fura 2 (Yamaguchi, supra). Briefly the cells are lysed with digitonin (10 μl x 100 mg/ml) in DMSO). EGTA (100 mM) and sufficient 10N NaOH to adjust the pH to 8.5 were then successively added to obtain minimum fluorescence.

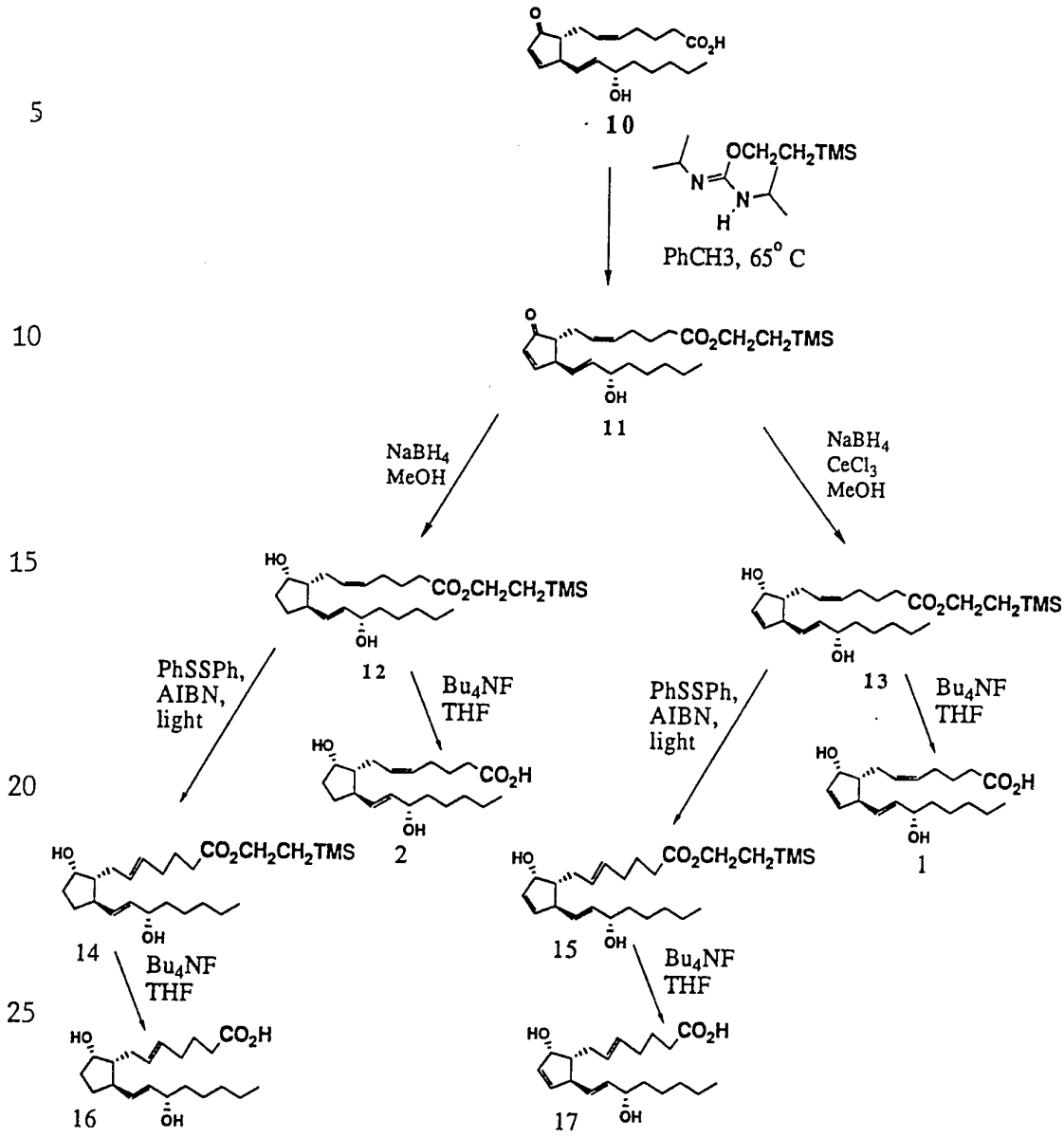
As is known in the art, and is described in an article titled "Ca^{2+} transients evoked by prostanoids in Swiss 3T3 cells...." by D. F. Woodward et al., Advances in Prostaglandin, Thromboxane and Leukotriene Research, Vol. 21, B. Samuelson et al., editors, Raven Press Ltd. New York, activity in this assay indicates action as an agonist of the biological FP receptor,

which in turn is believed to be a prime mediator for facilitating outflow of aqueous humor from the mammalian eye, thereby lowering intraocular pressure.

Synthetic Procedures For Obtaining Compounds Used In The Method of the Invention.

The compounds used in the novel methods of treatment of the invention can be made by a number of different synthetic chemical pathways. To illustrate the invention, the following detailed description is provided, with primary emphasis on the synthesis of preferred Compounds **1** and **2**. The synthetic chemist will readily appreciate that the conditions set out here are specific embodiments which can be generalized to obtain any and all compounds described in the present specification.

Referring now to **Reaction Scheme 1**, the compound 7α-[2-oxo-5β-(3α-hydroxyl-1-trans-octenyl)-3-cyclopentenyl]-5-cis-heptenoic acid (**Compound 10**) serves as a starting material. **Compound 10** is also called prostaglandin A_2, and is available commercially (Cayman Chemical Co., Ann Arbor, Michigan). In order to obtain **Compounds 1** and **2**, through steps of reduction, the carboxylic acid group of **Compound 10** is protected by reaction with O-(2-trimethylsilyl)ethyl-N,N'-diisopropylisourea, to yield the intermediate compound (2-trimethylsilyl)ethyl 7α-[2-oxo-5β-(3α-hydroxyl-1-trans-octenyl)-3-cyclopentenyl]-5-cis-heptenoate (**Compound 11**).



Reaction Scheme 1

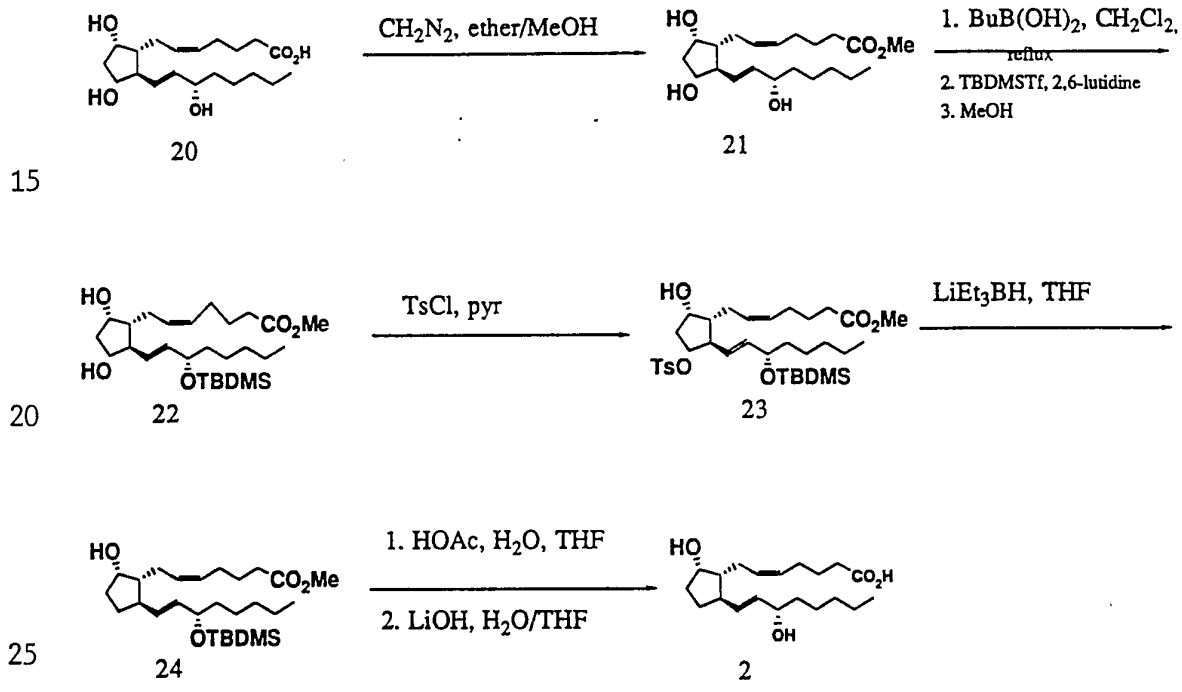
The oxo function and the double bond of the cyclopentene ring of **Compound 11** are reduced with sodium tetrahydridoborate to provide a mixture of α and β-cyclopentanol derivatives, which are separated by chromatography. The cyclopentanol of α configuration (**Compound 12**) is thereafter deprotected on the carboxylic acid function by treatment with tetrabutylammonium fluoride to yield **Compound 2**.

The oxo function of the cyclopentene ring of **Compound 11** is selectively reduced (without affecting the double bond in the ring) by treatment with sodium tetrahydridoborate in the presence of cerium trichloride, to yield a mixture of α and β-cyclopentenols, which are separated by chromatography. The α-cyclopenten-ol (**Compound 13**) is deprotected (on the carboxylic acid group) to yield **Compound 1**).

In order to obtain the isomers of Compounds **1** and **2** where the olefhinic bond of the 5-heptenoic acid moiety is in the trans configuration, intermediate **Compound 12** or intermediate **Compound 13** is isomerized by irradation with U.V. light (for approximately 4 hours) in toluene as a solvent, in the presence of phenyldisulfide and 2,2'-azobisisobutyronitrile (AIBN). The resulting intermediates, **Compounds 14** and **15** are deprotected by removal of the (2-trimethylsilyl)ethyl group from the carboxylic acid moiety, to yield **Compounds 16** and **17**, which are the trans isomers (in the heptenoic acid chain) of **Compounds 2** and **1**, respectively.

An alternative procedure for obtaining **Compound 2** is described with reference to **Reaction Scheme 2** from commercially available (Cayman Chemical) 7-[3α,5α-dihydroxyl-2β- (3α-hydroxyl-1-trans-octenyl)-1α-

cyclopentyl]-5-cis-heptenoic acid (**Compound 20**). The conditions of this sequence of reactions are indicated in the reaction scheme itself, and are further elaborated as follows. **Compound 20** is reacted with diazomethane to yield the methyl ester (**Compound 21**) of the heptenoic acid moiety.



Reaction Scheme 2

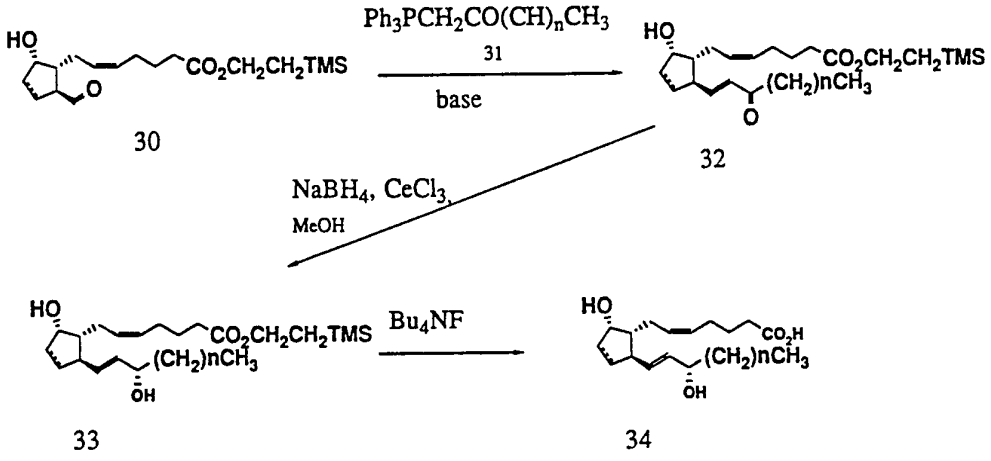
The 1,3-diol function of **Compound 21** is then temporarily blocked by treatment with butylboronic acid ($BuB(OH)_2$), and a t-butyl-dimethylsilyl protecting group is introduced to the 3-α-hydroxy group in the 3-α-hydroxy octenyl side chain. This is followed by deprotection of the 1,3-diol function by methanol, to yield **Compound 22**. **Compound 22** is p-toluenesulphonylated (tosylated) on the 4-α-hydroxyl group of the cyclopentane ring to yield **Compound 23**. **Compound 23** is then reduced with lithium triethylborohydride (also known as Super-Hydride, which is a registered trademark of Aldrich Chemical Co.) to yield **Compound 24** wherein one of the hydroxyl groups of the cyclopentane ring has been replaced with hydrogen. Thereafter, the t-butyldimethylsilyl blocking group of **Compound 24** is removed by treatment with aqueous acetic acid, and the methyl ester of the heptenoic acid side chain is saponified with aqueous base (LiOH), to yield **Compound 2**.

Esters of the heptenoic acid moiety can be made in accordance with synthetic methods well known in the art. In this regard it is noted that carboxylic acids are typically esterified by refluxing the acid in a solution of the appropriate alcohol in the presence of an acid catalyst such as hydrogen chloride or thionyl chloride. Alternatively, the carboxylic acid can be condensed with the appropriate alcohol in the presence of dicyclohexylcarbodiimide in dimethylaminopyridine. The ester is recovered and purified by conventional means.

The 3α-hydroxyl group of the 3α-hydroxyl side chain can be esterified by standard methods of esteri-

fication to give compounds of **Formula 1** where R_1 represents an acyl ($CO-R_3$) group. The standards methods of esterification (such as DMAP catalyzed reaction with a carboxylic acid anhydride $(R_3-CO)_2O$, reaction with an acid chloride R_3-COCl, or reaction with an acid R_3-COOH in dimethylaminopyridine in the presence of dicyclohexylcarbodiimide) preferentially esterify the 3α-hydroxyl group over the hydroxyl group attached to the cyclopentane or cyclopentene ring.

Compounds used in the method of the present invention where, with reference to **Formula 1**, **n** is other than 4, can be obtained in accordance with **Reaction Scheme 3.**



Reaction Scheme 3

In accordance with this scheme, the starting material **Compound 30** is an appropriately protected aldehyde which is reacted in a Wittig reaction with the phosphonium ylide reagent of **Compound 31** to yield the "enone", **Compound 32**. The "enone" (**Compound 32**) is reduced by treatment with sodium borohydride in the presence of cerium trichloride to provide **Compound 33**. The 2-(trimethylsilyl) ethyl protecting group is then removed from the heptenoic acid side chain to provide the compounds which are used in the method of treatment of the present invention.

Specific Examples

(2-Trimethylsilyl)ethyl 7α-[2-oxo-5β-(3α-hydroxy-1-trans-octenyl)-3-cyclopentenyl]-5-cis-heptenoate (**Compound 11**)

A solution of 7α-[2-oxo-5β-(3α-hydroxy-1-transoctenyl)-3-cyclopentenyl)-5-cis heptenoic acid (**Compound 10**, 500 mg, 1.49 mmol) and O-(2-trimethylsilyl)ethyl-N,N'-diisopropylisourea (547 mg, 2.24 mmol) in toluene (4.5 mL) was heated to 65°C for 16 hours. The reaction was allowed to cool to room temperature and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, 2:1 hexane/EtOAc) afforded 508 mg (79%) of the title compound as a clear, colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50 (dd, J = 2.0, 4.8 Hz, 1H), 6.19 (dd, J = 2.0, 4.8 Hz, 1H), 5.62-5.35 (m, 2H), 4.16 (t, J = 7.0 Hz, 2H), 4.12 - 4.08 (m, 1H), 3.26 - 3.23 (m, 1H), 3.04 (d, J = 4.2 Hz, 1H), 2.75 - 2.08 (m, 7H), 1.74 - 1.29 (m, 10H), 0.98 (t, J = 7.0 Hz, 2H), 0.90 (t, J = 5.8 Hz, 3H), 0.05 (s, 9H).

(2-Trimethylsilyl)ethyl 7α-[2α-hydroxy-5β-(3α-hydroxy-1-trans-octenyl)cyclopentyl]-5-cis-

heptenoate(**Compound 12**)

Sodium tetrahydridoborate (9.1 mg, 0.241 mmol) was added to a solution of (2-trimethylsilyl)ethyl 7α-[2-oxo-5β-(3α-hydroxy-1-trans-octenyl)-3-cyclopentenyl]-5-cis-heptenoate (**Compound 11**, 105 mg, 0.241 mmol) in methanol (0.6 mL) at 23°C. The reaction was stirred for 2 hours and quenched with saturated aqueous ammonium chloride (2.0 mL). The resultant mixture was extracted with CH_2Cl_2 (2X) and the combined organics were dried (Na_2SO_4), filtered and the filtrate concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, 3:1 hexane/EtOAc) afforded 20.7 mg (20 %) of the title compound, α-alcohol and 40.4 mg (38%) of the corresponding β-alcohol. ^1H NMR (250 MHz, $CDCl_3$) for α-alcohol 3:δ 5.49-5.35 (m, 2H), 4.25-4.20 (m, 1H), 4.16 (t, J = 7.0 Hz, 2H), 4.10-4.00 (m, 1H), 2.41 - 1.90 (m, 8H), 1.70-1.28 (m, 16H), 0.98 (t, J = 7.0 Hz, 2H), 0.87 (t, J = 5.8 Hz, 3H), 0.04 (s, 9H).

(2-Trimethylsilyl)ethyl 7α-[2α-hydroxy-5β-(3α-hydroxy-1-trans-octenyl)-3-cyclopentenyl]-5-cis-heptenoate (**Compound 13**)

The solution of the (2-trimethylsilyl)ethyl 7α-[2-oxo-5β-(3α-hydroxy-1-trans-octenyl)-3-cyclopentenyl]-5-cis-heptenoate (**Compound 11**, 110 mg, 0.253 mmol) in methanolic cerium trichloride heptahydrate (0.63 mL of a 0.4 M solution in MeOH, 0.253 mmol) was treated with sodium tetrahydridoborate (9.6 mg, 0.253 mmol) at 23°C. The reaction was stirred for 2 hours and quenched with saturated aqueous ammonium chloride (2.0 mL). The resultant mixture was extracted with CH_2Cl_2 (2X) and the combined organics were dried (Na_2SO_4), filtered and the filtrate concentrated in vacuo. Purification of

the residue by flash column chromatography (silica gel, 4:1 hexane/EtOAc) afforded 17.9 mg (16%) of the title compound, α-alcohol and 28.4 mg (26%) of the corresponding β-alcohol. ^{1}H NMR (250 MHz, $CDCl_3$) for α-alcohol 4:δ 5.96-5.88 (m, 2H), 5.53 - 5.35 (m, 4H), 4.67-4.65 (m, 1H), 4.15 (t, J = 7.0 Hz, 2H), 4.08- 4.02 (m, 1H), 3.05 - 3.02 (m, 1H), 2.32 - 2.09 (m, 7H), 1.76-1.23 (m, 12H), 0.98 (t, J = 7.0 Hz, 2H), 0.88 (t, J = 5.8 Hz, 3H), 0.04 (s, 9H).

7α-[2α-hydroxy-5β-(3α-hydroxy-1-trans-octenyl)-cyclopentyl]-5-cis-heptenoic acid (**Compound 2**).

A solution of (2-trimethylsilyl)ethyl 7α-[2α-hydroxy-5β-(3α-hydroxy-1-trans-octenyl)cyclopentyl]-5-cis-heptenoate (**Compound 12**) and tetrabutylammonium fluoride (62μL of a 1.0 M solution in THF, 0.062 mmol) in THF (0.5 mL) was stirred for 16 hours at 23°C. The reaction was diluted with EtOAc and washed with H_2O. The organic portion was dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, 9:1 CH_2Cl_2/MeOH) afforded 8.2 mg (60%) of the title compound. ^{1}H NMR (250 MHz, $CDCl_3$): δ 12.0 (brs, 1H), 5.57 - 5.33 (m, 4H), 4.25 - 4.21 (m, 1H), 4.16 (4.09 (m, 1H), 3.20 (br s, 2H), 2.35 - 2.19 (m, 3H), 2.17 - 1.90 (m, 6H), 1.72 - 1.20 (m, 13H), 0.86 (t, J = 5.8 Hz, 3H).

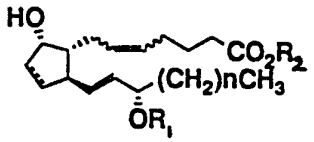
7α-[2α-hydroxy-5β-(3α-hydroxy-1-trans-octenyl)-3-cyclopentenyl]-5-cis-heptenoic acid (**Compound 1**)

Similarly to the deprotection of **Compound 12**, (2-trimethylsilyl)ethyl 7α-[2α-hydroxy-5β-(3α-hydroxy-1-trans-octenyl)-3-cyclopentenyl]-5-cis-heptenoate (**Compound 13**) was treated with tetrabutylammonium fluoride to yield 12.7 mg (82%) of the title compound.

^{1}H NMR δ 11.5 (br s, 1H), 5.98 - 5.85 (m, 2H), 5.65 - 5.33 (m, 4H), 4.68 - 4.66 (m, 1H), 4.20 - 4.16 (m, 1H), 3.70 (br s, 2H), 3.10 - 3.03 (m, 1H), 2.37 - 2.06 (m, 7H), 1.76 - 1.25 (m, 10H), 0.88 (t, J = 5.0 Hz, 3H).

WHAT IS CLAIMED IS:

1 A method for lowering intraocular pressure in the eye of a mammal, which comprises administering to the mammal a pharmaceutical composition containing a pharmaceutically acceptable excipient and an effective amount of a compound having the formula



wherein the dotted line represents a bond or the absence of a bond, wavy lines attached to a double bond indicate cis or trans configuration about the double bond,

R_1 represents H, or CO-R_3 where R_3 is lower alkyl of 1 to 6 carbons, carbocyclic aryl, or heterocyclic aryl;

R_2 represents H or lower alkyl of 1 to 6 carbons, and

n is an integer between 0 and 8.

2. The method of Claim 1 wherein the bonds indicated by wavy lines define cis configuration about the olefinic bond.

3. The method of Claim 1 wherein the bonds indicated by wavy lines define trans configuration about the olefinic bond.

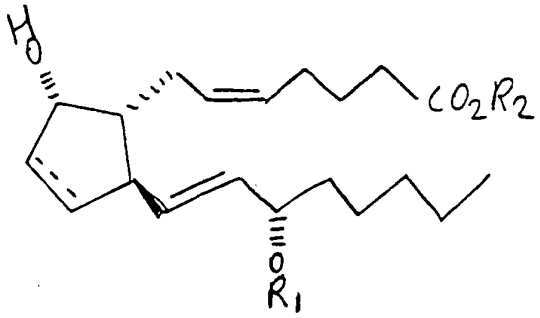
4. The method of Claim 1 wherein R_1 is hydrogen.

5. The method of Claim 1 wherein R_2 is H.

6. The method of Claim 1 wherein n is 4.

7. A method for lowering intraocular pressure in the eye of a mammal, which comprises administering to

the mammal a pharmaceutical composition containing a pharmaceutically acceptable excipient and an effective amount of a compound having the formula:



wherein the dotted line within the 5-membered alicyclic ring represents a bond or the absence of a bond;

R_1 is H or CO-R_3 where R_3 is lower alkyl of 1 to 6 carbons or phenyl, or phenyl substituted with lower alkyl, lower alkoxy or halogen groups, and

R_2 is H or lower alkyl of 1 to 6 carbons.

8. The method of Claim 7 wherein the dotted line represents a bond.

9. The method of Claim 8 wherein R_1 is H.

10. The method of Claim 8 wherein R_2 is H.

11. The method of Claim 8 wherein R_1 and R_2 are hydrogen.

12. The method of Claim 7 wherein the dotted line represents absence of a bond.

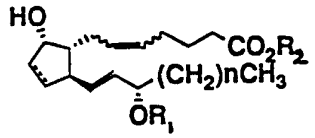
13. The method of Claim 12 wherein R_1 is H.

14. The method of Claim 12 wherein R_2 is H.

15. The method of Claim 12 wherein R_1 and R_2 are hydrogen.

16. A method for lowering intraocular pressure, in the eye of a mammal, which comprises topically administering to the mammal a pharmaceutical composition adapted for topical administration, the

composition containing a pharmaceutically acceptable excipient and an effective amount of a compound which has the formula



wherein the dotted line within the ring represents a bond or the absence of a bond, the wavy lines connected to the olefinic bond represent bonds which can be in cis or trans configuration about the olefinic bond;

R_1 represents H or CO-R_3 where R_3 is lower alkyl of 1 to 6 carbons,. carbocyclic aryl or heteroyclic aryl;

R_2 represents H or lower alkyl of 1 to 6 carbons, and

n is an integer between 0 and 8.

17. The method of Claim 16 wherein the pharmaceutical composition is an ophtalmic solution.

18. The method of Claim 17 wherein **n** is 4.

19. The method of Claim 18 wherein the wavy lines connected to the olefinic bond represent cis configuration about the bond.

20. The method of Claim 19 wherein the dashed line in the ring represents absence of a bond.

21. The method of Claim 20 wherein R_1 and R_2 are H.

22. The method of Claim 19 wherein the dashed line in the ring represents a bond.

23. The method of Claim 22 wherein R_1 and R_2 are H.

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 93/08422

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 093 380 (THE TRUSTEES OF COLUMBIA UNIVERSITY) 9 November 1983 cited in the application & US,A,4 599 353 (BITO LASZLO Z.) see abstract; examples	1-23
Y	EP,A,0 242 580 (THE TRUSTEES OF COLUMBIA UNIVERSITY) 28 October 1987 see abstract see page 11, line 1 - line 30 see page 19, line 30 - page 24, line 20	1-23
Y	US,A,4 822 820 (DESANTIS ET AL.) 18 April 1989 see the whole document	1-23
Y	WO,A,91 14428 (ALLERGAN) 3 October 1991 see the whole document	1-23

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 1993	12. 93

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Hoff, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 399 839 (ALLERGAN) 28 November 1990 cited in the application see abstract; claims	1-23
Y	US,A,4 033 992 (GRUDZINSKAS ET AL.) 5 July 1977 see abstract; claims; examples 9,12	1-23
Y	GB,A,1 434 620 (THE UPJOHN COMPANY) 5 May 1976 see page 7, line 30 - line 46; claims; example 4	1-23
Y	US,A,3 903 143 (MUELLER) 2 September 1975 see the whole document, in particular example 8	1-23

INTERNATIONAL SEARCH REPORT

Inter...ional application No.
PCT/US 93/ 08422

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 1-23 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. onal Application No
PCT/US 93/08422

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		JP-A-	59001418	06-01-84
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/US 93/08422

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