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(54) Title: METHOD FOR TREATMENT OF OCULAR HYPERTENSION AND GLAUCOMA

(57) Abstract: A method for treating ocular hypertension and glaucoma, which comprises administration of a 15-keto-prostaglandin compound having a ring structure at the end of the Ω chain to mammal eyes in a dose of more than 5 μ g and less than 50 μ g per eye.

METHOD FOR TREATMENT OF OCULAR HYPERTENSION AND GLAUCOMA

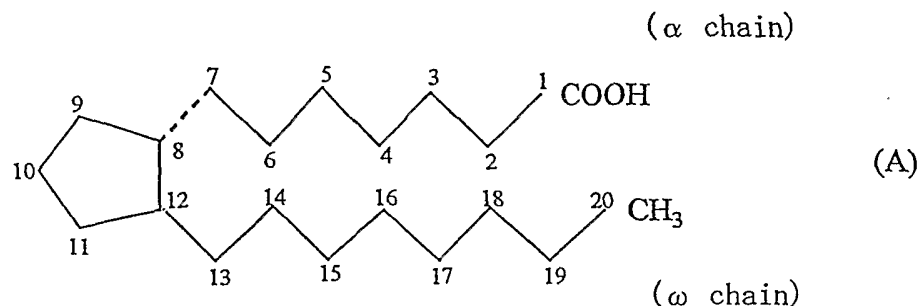
This application claims the benefit of U.S. Provisional Application No. 60/308,589, filed July 31, 2001. The disclosure is incorporated by reference herein in its entirety.

TECHNICAL FIELD

The present invention relates to a method for treating ocular hypertension and glaucoma that is associated with substantially reduced ocular irritation such as conjunctival hyperemia, which comprises administration of a 15-keto-prostaglandin compound having a ring structure at the end of the ω chain to mammal eyes in a high dose.

BACKGROUND ART

Prostaglandins (hereinafter referred to as PG(s)) are the members of class of organic carboxylic acids that are contained in the tissues or organs of humans or other mammals and exhibit a wide range of physiological activity. PGs found in nature (primary PGs) generally have a prostanoic acid skeleton as shown in the formula (A):



On the other hand, some of synthetic analogues of primary PGs have modified skeletons. The primary PGs are

classified to PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs according to the structure of the five-membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond at the carbon chain moiety:

Subscript 1: 13,14-unsaturated-15-OH

Subscript 2: 5,6- and 13,14-diunsaturated-15-OH

Subscript 3: 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

Further, the PGFs are classified, according to the configuration of the hydroxyl group at the 9-position, into α type (the hydroxyl group is of an α -configuration) and β type (the hydroxyl group is of a β -configuration).

PGE₁, PGE₂ and PGE₃ are known to have vasodilation, hypotension, gastric secretion decreasing, intestinal tract movement enhancement, uterine contraction, diuretic, bronchodilation and anti ulcer activities. PGF_{1 α} , PGF_{2 α} and PGF_{3 α} have been known to have hypertension, vasoconstriction, intestinal tract movement enhancement, uterine contraction, lutein body atrophy and bronchoconstriction activities.

Some 15-keto (i.e., having oxo at the 15-position instead of hydroxy)-PGs and 13,14-dihydro-15-keto-PGs are known as the substances naturally produced by the action of enzymes during the metabolism of primary PGs. It is also known that some 15-keto-PG compounds have intraocular pressure reducing effects and are effective for the treatment of ocular

hypertension and glaucoma (U.S. Patent Nos. 5,001,153, 5,151,444, 5,166,178 and 5,212,200, all of which are incorporated herein by reference).

Meanwhile, "Xalatan[®]" that has been launched as an eye drops for ocular hypertension and glaucoma contains, as an active ingredient thereof, latanoprost, i.e., 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF₂ α isopropyl ester, which is a prostaglandin derivative having a ring structure at the end of the ω chain and having hydroxy at the 15-position. The clinical concentration of latanoprost in the "Xalatan[®]" eye drops is 0.005% and, estimating from about 30-35μl of one drop volume, the clinical dose of latanoprost is about 1.5μg-1.75μg per eye. Problematic side effects of this eye drops in clinically applied dose, including iris pigmentation, ocular irritation such as conjunctival hyperemia and chemosis of conjunctiva have been reported.

It is known that a 15-keto-prostaglandin compound having a ring structure at the end of the ω chain has intraocular pressure reducing effects. U.S. Patent No. 5,321,128 describes that administration of 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-PGF₂ α isopropyl ester to healthy human eyes and monkey eyes in a dose of 5μg and 3μg, respectively, showed intraocular pressure reducing effects, and showed no side effect such as conjunctival hyperemia, ocular irritation and foreign body sensation in the human.

There is another document reporting that administration of 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-PGF₂ α isopropyl ester to monkey eyes (50 μ g per eye) showed intraocular pressure reducing effects (Clinical Report Vol. 28, No. 11, pages 3505-3509, 1994).

However, in the treatment of ocular hypertension and glaucoma, nobody has known the extent of ocular irritation such as conjunctival hyperemia shown in the administration of a 15-keto-prostaglandin compound having a ring structure at the end of the ω chain to mammal eyes in a high dose.

DISCLOSURE OF THE INVENTION

The present inventor has conducted intensive studies on the biological activity of a 15-keto-prostaglandin compound having a ring structure at the end of the ω chain and found that administration of said compound to mammal eyes even in a high dose substantially reduces an ocular irritation such as conjunctival hyperemia, which has resulted in the completion of the present invention.

Namely, the present invention relates to a method for treating ocular hypertension and glaucoma, which comprises administration of a 15-keto-prostaglandin compound having a ring structure at the end of the ω chain to mammal eyes in a dose of more than 5 μ g and less than 50 μ g per eye. The present invention particularly provides a method for treating ocular hypertension and glaucoma associated with substantially

reduced ocular irritation such as conjunctival hyperemia.

The present invention further relates to a composition for treating ocular hypertension and glaucoma of mammals, which comprises, as an active ingredient thereof, a 15-keto-prostaglandin compound having a ring structure at the end of the ω chain in a dose of more than 5 μ g and less than 50 μ g per eye.

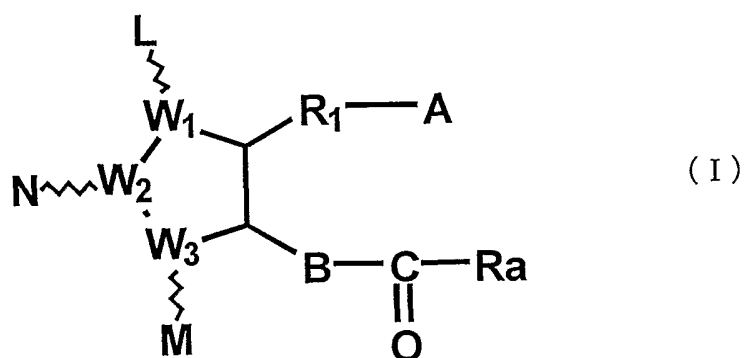
The present invention further relates to a use of a 15-keto-prostaglandin compound having a ring structure at the end of the ω chain for manufacturing a composition for treating ocular hypertension and glaucoma of mammals in a dose of more than 5 μ g and less than 50 μ g per eye.

In the present invention, the "15-keto-prostaglandin compound" (hereinafter, referred to as "15-keto-PG compound") may include any of derivatives or analogs, including substituted derivatives of a compound having an oxo group at 15-position of the prostanoid acid skeleton instead of the hydroxy group, irrespective of the configuration of the five-membered ring, the number of double bonds, presence or absence of a substituent, or any other modification in the α or ω chain.

The nomenclature of the 15-keto-PG compounds used herein is based on the numbering system of the prostanoid acid represented in the above formula (A).

A preferred compound used in the present invention is

represented by the formula (I):



[wherein W_1 , W_2 and W_3 are carbon atom or oxygen atom, L , M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl or oxo (wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond);

A is $-\text{CH}_2\text{OH}$, $-\text{COCH}_2\text{OH}$, $-\text{COOH}$ or a functional derivative thereof;

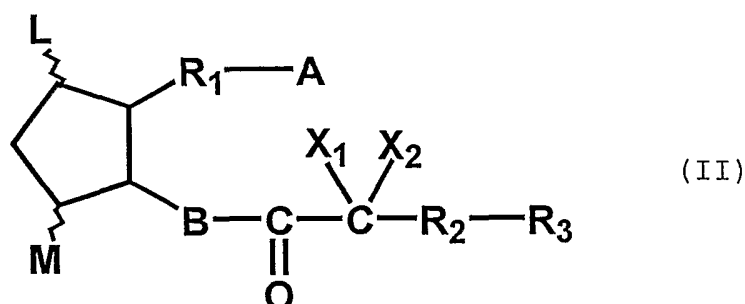
B is $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group; and

R_a is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is substituted at the end by cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group.]

A group of particularly preferable compounds among the above-described compounds are represented by the formula

(II):



[wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl or oxo (wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond);

A is $-\text{CH}_2\text{OH}$, $-\text{COCH}_2\text{OH}$, $-\text{COOH}$ or a functional derivative thereof;

B is $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$;

X_1 and X_2 are hydrogen, lower alkyl, or halogen;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group

R_2 is a single bond or lower alkylene; and

R_3 is cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group.]

In the above formula, the term "unsaturated" in the definitions for R_1 and R_a is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main

and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower or medium aliphatic hydrocarbon" refers to a straight or branched chain hydrocarbon group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms are preferable) and preferably 1 to 10, especially 6 to 10 carbon atoms for R_1 and 1 to 10, especially 1 to 8 carbon atoms for R_a .

The term "halogen atom" covers fluorine, chlorine, bromine and iodine.

The term "lower" throughout the specification is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to a group of lower alkyl-O-, wherein lower alkyl is as defined above.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl

and 1-methyl-1-hydroxyethyl.

The term "lower alkanoyloxy" refers to a group represented by the formula RCO-O-, wherein RCO- is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O-, wherein cyclo(lower)alkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic hydrocarbon rings (preferably monocyclic groups), for example, phenyl, tolyl, xylyl. Examples of the substituent include halogen atom and halo substituted (lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula ArO-, wherein Ar is aryl as defined above.

The term "heterocyclic group" may include mono- to tri-cyclic, preferably monocyclic heterocyclic group which is 5 to 14, preferably 5 to 10 membered ring having optionally substituted carbon atom(s) and 1 to 4, preferably 1 to 3 of 1 or 2 type of hetero atoms selected from nitrogen atom, oxygen

atom and sulfur atom. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazoliny, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, purinyl, quinazolinyl, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazoliny, benzothiazolyl, phenothiazinyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group are as described above.

The term "heterocyclic-oxy group" means a group represented by the formula $HcO-$, wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts (preferably pharmaceutically acceptable salts), ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include conventionally used non-toxic salts, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt (such

as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)ethane salt, monomethylmonoethanolamine salt, lysine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-di-methoxyphenyl ether and benzamidophenyl ether; and aryl (lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower)alkyl ester such as hydroxyethyl ester; lower alkoxy (lower) alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A means a group represented by the formula $-CONR'R''$, wherein each of R' and R'' is hydrogen atom, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and include for example lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or aryl-sulfonylamides such as methylsulfonylamide, ethylsulfonyl-amide and tolylsulfonylamide.

Preferred examples of L and M include hydroxy which provides a 5-membered ring structure of, so called, PGF type.

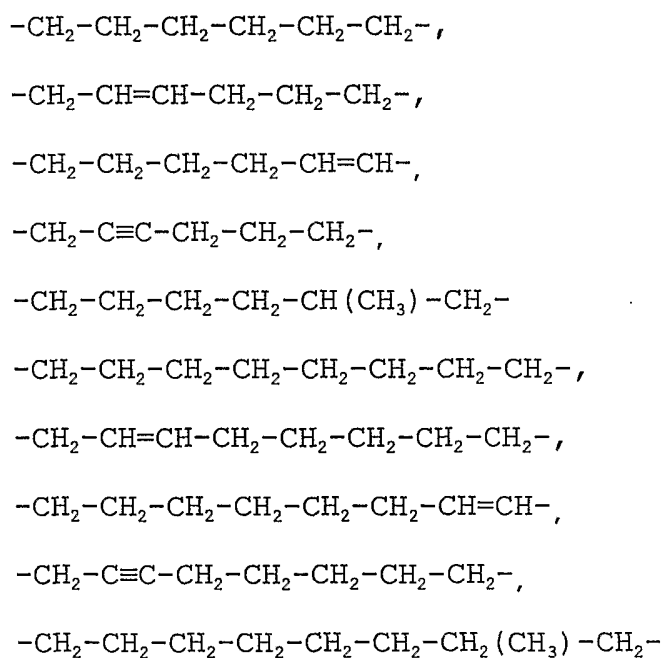
Preferred A is $-COOH$, its pharmaceutically acceptable salt, ester or amide thereof.

Preferred B is $-\text{CH}_2-\text{CH}_2-$, which provide the structure of so-called, 13,14-dihydro type.

Preferred example of X_1 and X_2 is that at least one of them is halogen, more preferably, both of them are halogen, especially, fluorine that provides a structure of, so called 16,16-difluoro type.

Preferred R_1 is a hydrocarbon containing 1-10 carbon atoms, preferably, 6-10 carbon atoms.

Examples of R_1 include, for example, the following groups:



Preferred R_a is a hydrocarbon containing 1-10 carbon atoms, more preferably, 1-8 carbon atoms which is substituted by aryl or aryloxy at the end.

The configuration of the ring and the α - and/or ω chains in the above formula (I) and (II) may be the same as or different

from that of the primary PGs. However, the present invention also includes a mixture of a compound having a primary type configuration and a compound of a non-primary type configuration.

The typical example of the present compound is a 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-prostaglandin F compound and its derivative or analogue.

The 15-keto-PG compound of the present invention may be in the keto-hemiacetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and oxo at position 15.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the 15-keto-PG compounds used in the invention include both isomers. Further, while the compounds used in the invention may be represented by a structure formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exclude the hemiacetal type compound.

In the present invention, any of isomers such as the individual tautomeric isomers, the mixture thereof, or optical isomers, the mixture thereof, a racemic mixture, and other

steric isomers may be used in the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in USP Nos. 5,073,569, 5,166,174, 5,221,763, 5,212,324 and 5,739,161 and U.S. patent application Ser. No. 09011218 (these cited references are herein incorporated by reference).

The term "treatment" used herein includes any means of control such as prevention, care, relief of the condition, attenuation of the condition, arrest of progression of the condition.

The present compound is applied by means of eye local administration (eye drop and eye ointment, etc.).

In the case of administering the compound as a dosage formulation, the formulation may be manufactured in a conventional manner. The dosage form may be any formulations for local eye administration used in the ophthalmic field such as eye drop and eye ointment. The eye drops may be prepared by dissolving the active ingredients in a sterile aqueous solution such as saline and buffering solution, or by providing the active ingredients as combined powder composition to be dissolved in the aqueous solution before use.

Eye drops such as the ones as described in EP-A-0406791 are preferred. If desired, additives ordinarily used in conventional eye drops may be added. Such additives may include isotonizing agents (e.g., sodium chloride), buffering

agent (e.g., boric acid, sodium monohydrogen phosphate, sodium dihydrogen phosphate), preservatives (e.g., benzalkonium chloride, benzethonium chloride, chlorobutanol), thickeners (e.g., saccharide such as lactose, mannitol, maltose; hyaluronic acid or its salt such as sodium hyaluronate, potassium hyaluronate; mucopolysaccharide such as chondroitin sulfate; sodium polyacrylate, carboxyvinyl polymer, crosslinked polyacrylate.) The disclosure of the above publication is incorporated herein by reference.

Eye ointment can be prepared by mixing the active ingredient into a base component ordinarily used for a conventional eye ointment and formulating it according to an ordinary method under a sterile condition. Examples of the base for the eye ointment include petrolatum, selen 50, Plastibase and macrogol, but not limited thereto. Further, in order to increase the hydrophilicity, a surface-active agent can be added to the composition. Regarding the eye ointment, the above-mentioned additives such as the preservatives and the like can be combined, if necessary.

The present eye drops may be formulated as a sterile unit dose type eye drops containing no preservatives.

The dose and frequency of administration of the active ingredients of eye drops used in the present invention may vary according to the compound to be used, the type of subject such as animals or human, age, weight, symptom to be treated,

desirable therapeutic effect, administration route, administration amount and period for treatment. Although suitable concentration and frequency may be chosen as desired, formulations adjusted for administration of the active ingredients to an adult human within the range of more than 5 μ g and less than 50 μ g per eye may be administered at least once a day. In using ointment, formulations adjusted for administration of the active ingredients within the range of more than 5 μ g and less than 50 μ g per eye may be applied several times a day, preferably one to six times, more preferably one to four times.

The present formulations may contain a single active ingredient or a combination of two or more active ingredients. In a combination of plural active ingredients, their respective contents may be suitably increased or decreased in consideration of their therapeutic effects and safety.

Further, the present formulations may suitably contain any other pharmaceutically active ingredients as far as they are not contrary to the objects of the present invention.

The present invention particularly provides a method for treating ocular hypertension and glaucoma, associated with substantially reduced ocular irritation such as conjunctival hyperemia, comprising administering a 15-keto-prostaglandin compound having a ring structure at the end of the ω chain to mammal eyes in a dose of more than 5 μ g and less than 50 μ g per

eye. The method allows to conduct a safe and comfortable treatment of ocular hypertension and glaucoma for a long period of time. Besides, the present preparations may be administered safely to subjects with ocular hypertension and glaucoma having some disorders on their cornea or conjunctiva such as allergic disease and dry eye.

The present invention will be described in more detail with reference to the following example, which is not intended to limit the present invention.

EXAMPLE

The incidence rate of conjunctival hyperemia was compared between the present compound 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-PGF_{2α} isopropyl ester and 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF_{2α} isopropyl ester.

1) Method

Either 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-PGF_{2α} isopropyl ester or 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF_{2α} isopropyl ester was ocularly administered once to one eye of white rabbits (three cases each, total of 12 cases) in a dose of 1.75μg or 50μg.

2) Evaluation Method

The presence of conjunctival hyperemia was examined at two hours after the administration and the ratio of cases showing conjunctival hyperemia was evaluated by percent in each group.

3) Results

Table 1 shows the results.

Table 1

Groups	Incidence Rate of Conjunctival Hyperemia	
	1.75 μ g eye drop	50 μ g eye drop
13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-PGF _{2α} isopropyl ester	0%	33%
13,14-dihydro-17-phenyl-18,19,20-trinor-PGF _{2α} isopropyl ester	67%	100%

In the administration of 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF_{2 α} isopropyl ester, 67% of the subjects receiving a clinical dose of 1.75 μ g and 100% of the subjects receiving 50 μ g showed conjunctival hyperemia.

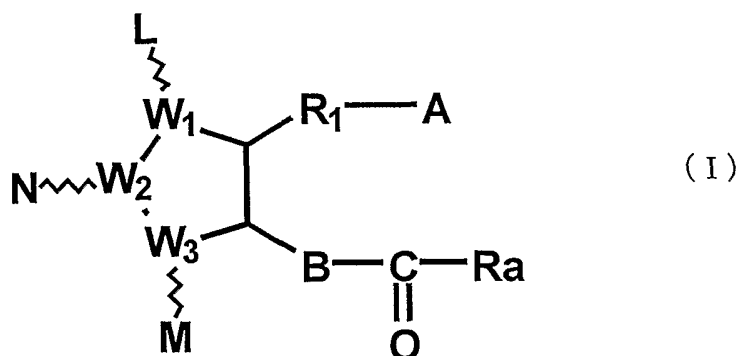
On the other hand, in the administration of the present compound 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-PGF_{2 α} isopropyl ester, none of the subjects receiving the dose of 1.75 μ g showed conjunctival hyperemia. Even in the administration of a high dose of 50 μ g, the percent of the subjects showing conjunctival hyperemia was only about half the percent of the subjects receiving 1.75 μ g of 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF_{2 α} isopropyl ester.

These results demonstrate that the present compound substantially reduces ocular irritation such as conjunctival hyperemia even in a high dose.

CLAIMS

1. A method for treating ocular hypertension and glaucoma, which comprises administration of a 15-keto-prostaglandin compound having a ring structure at the end of the ω chain to mammal eyes in a dose of more than 5 μ g and less than 50 μ g per eye.

2. The method as described in Claim 1, wherein said 15-keto-prostaglandin compound is a compound represented by the following general formula (I):



wherein W_1 , W_2 and W_3 are carbon atom or oxygen atom, L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl or oxo provided that at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-\text{CH}_2\text{OH}$, $-\text{COCH}_2\text{OH}$, $-\text{COOH}$ or a functional derivative thereof;

B is $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or

substituted by halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is substituted at the end by cyclo (lower) alkyl, cyclo (lower) alkyloxy, aryl, aryloxy, heterocyclic group or hetrocyclic-oxy group.

3. The method as described in Claim 1, wherein said 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-prostaglandin compound.

4. The method as described in Claim 1, wherein said 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-prostaglandin compound.

5. A composition for treating ocular hypertension and glaucoma of mammals, which comprises, as an active ingredient thereof, a 15-keto-prostaglandin compound having a ring structure at the end of the ω chain in a dose of more than 5 μ g and less than 50 μ g per eye.

6. Use of a 15-keto-prostaglandin compound having a ring structure at the end of the ω chain for manufacturing a composition for treating ocular hypertension and glaucoma of mammals in a dose of more than 5 μ g and less than 50 μ g per eye.