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(54) Title: METHOD FOR TREATING ASTHENOPIA

(57) Abstract: The present invention relates to a method for treating asthenopia, accommodative dysfunction or ocular pain comprising an administration of a specific prostaglandin compound to a mammalian subject. The present invention also relates to a composition for treating asthenopia, accommodative dysfunction or eye pain comprising a specific prostaglandin compound.

## DESCRIPTION

## METHOD FOR TREATING ASTHENOPIA

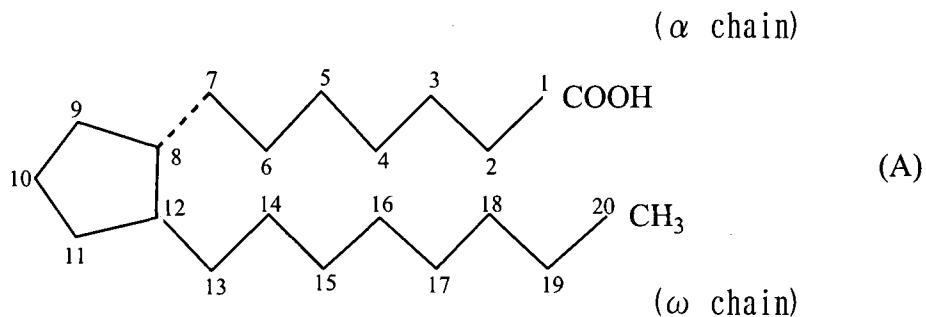
## 5 TECHNICAL FIELD

The present invention relates to a method for prophylactic and therapeutic treatment of asthenopia.

## BACKGROUND

Asthenopia is characterized by weakness or fatigue of the eyes, often accompanied by eye pain, red eyes, headache, dimming or blurring of vision and intermittent double vision. These symptoms tend to occur after tedious visual tasks such as reading or computer work. Asthenopia may be due to refractive errors, accommodation errors or abnormalities in monocular or binocular vision including myopia (nearsightedness or shortsightedness), presbyopia, farsightedness and astigmatism. Conventional treatments include the use of the eye drops containing Vitamin B1, B6 or B12, but it is not satisfied treatment.

20 Fatty acid derivatives are members of class of organic carboxylic acids, which are contained in tissues or organs of human or other mammals, and exhibit a wide range of physiological activity. Some fatty acid derivatives found in nature generally have a prostanoic acid skeleton 25 as shown in the formula (A):



On the other hand, some of synthetic prostaglandin (PG) analogues have modified skeletons. The primary PGs are classified into 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:

5

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

10 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  
15 α type (the hydroxyl group is of an α-configuration) and β type (the hydroxyl group is of a β-configuration).

PGs are known to have various pharmacological and physiological activities, for example, vasodilatation, inducing of inflammation, platelet aggregation, stimulating 20 uterine muscle, stimulating intestinal muscle, anti-ulcer effect and the like.

PGs have been known as drugs used in the ophthalmic field, for example, for lowering intraocular pressure or treating glaucoma. For example, (+)-Isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate (general name: latanoprost), Isopropyl (5Z)-7-((1R,2R,3R,5S)-3,5-dihydroxy-2-{(1E,3R)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]but-1-enyl}cyclopentyl)hept-5-enoate (general name: travoprost), (5Z)-7-{(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenylpent-1-en-1-yl]cyclopentyl}-N-ethylhept-5-enamide (general name: bimatoprost) and 1-Methylethyl (5Z)-7-{(1R,2R,3R,5S)-2-[(1E)-3,3-difluoro-4-phenoxy-1-butenyl]-3,5-dihydroxy cyclopentyl}-5-heptenoate (general name: tafluprost) have been marketed as ophthalmic solution for the treatment of glaucoma and/or ocular hypertension under the name of Xalatan®, Travatan®, Lumigan® and tapros®, respectively.

Prostones, having an oxo group at position 15 of prostanoic acid skeleton (15-keto type) and having a single bond between positions 13 and 14 and an oxo group at position 15 (13,14-dihydro-15-keto type), are fatty acid derivatives known as substances naturally produced by enzymatic actions during metabolism of the primary PGs and have some therapeutic effect. Prostones have been disclosed in USP Nos. 5,073,569, 5,534,547, 5,225,439,

5,166,174, 5,428,062 5,380,709 5,886,034 6,265,440,  
5,106,869, 5,221,763, 5,591,887, 5,770,759 and 5,739,161,  
the contents of these references are herein incorporated by  
reference.

5 Prostanes have also been known to be useful in the  
ophthalmic field, for example, for lowering intraocular  
pressure and treating glaucoma (USPs 5,001,153, 5,151,444,  
5,166,178, 5,194,429 and 5,236,907), for treating cataract  
(USPs 5,212,324 and 5,686,487), for increasing the  
10 choroidal blood flow (USP 5,221,690), for treating optic  
nerve disorder (USP 5,773,471), the contents of these  
references are herein incorporated by reference.

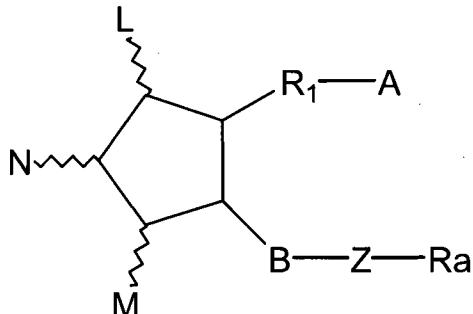
Ophthalmic solution comprising (+)-isopropyl (Z)-7-  
[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)  
15 cyclopentyl]hept-5- enoate (general name: isopropyl  
unoprostone) has been marketed under the name of Rescula®  
as a pharmaceutical product for the treatment of glaucoma  
and ocular hypertension.

However it is not known how fatty acid derivatives  
20 act on asthenopia.

#### DISCLOSURE OF THE INVENTION

In one aspect, the present invention provides a  
method for the treatment of asthenopia in a mammalian  
subject, which comprises administering to the subject in  
25 need thereof an effective amount of a fatty acid derivative

represented by the formula (I):



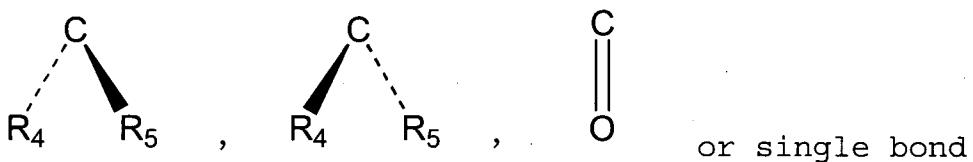
wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo,

5 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  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

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

Z is



wherein  $\text{R}_4$  and  $\text{R}_5$  are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein 15  $\text{R}_4$  and  $\text{R}_5$  are not hydroxy and lower alkoxy at the same time;

$\text{R}_1$  is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is

unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

5           Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or 10 hetrocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

15           In another aspect, the present invention provides a method for the treatment of accommodative dysfunction in a mammalian subject, which comprises administering to the subject in need thereof an effective amount of a fatty acid derivative represented by the formula (I) wherein L, M, N, 20 A, B, Z, R<sub>1</sub> and Ra are as described above.

          In another aspect, the present invention provides a method for the treatment of ocular pain in a mammalian subject, which comprises administering to the subject in need thereof an effective amount of a fatty acid derivative represented by the formula (I) wherein L, M, N, A, B, Z, R<sub>1</sub> 25

and Ra are as described above.

In further aspect, the present invention provides a pharmaceutical composition for the treatment described above, which comprises an effective amount of a fatty acid derivative represented by the formula (I) wherein L, M, N, 5 A, B, Z, R<sub>1</sub> and Ra are as described above.

In still further aspect, the present invention provides use of an effective amount of a fatty acid derivative represented by the formula (I) wherein L, M, N, 10 A, B, Z, R<sub>1</sub> and Ra are as described above for the preparation of a pharmaceutical composition for the treatment described above or in the treatment described above.

#### DETAILED DESCRIPTION OF THE INVENTION

15 The nomenclature of the fatty acid derivative used herein is based on the numbering system of the prostanoic acid represented in the above formula (A).

The formula (A) shows a basic skeleton of the C-20 fatty acid derivative, but the present invention is not 20 limited to those having the same number of carbon atoms. In the formula (A), the numbering of the carbon atoms which constitute the basic skeleton of the fatty acid derivatives starts at the carboxylic acid (numbered 1), and carbon atoms in the  $\alpha$ -chain are numbered 2 to 7 towards the five- 25 membered ring, those in the ring are 8 to 12, and those in

the  $\omega$ -chain are 13 to 20. When the number of carbon atoms is decreased in the  $\alpha$ -chain, the number is deleted in the order starting from position 2; and when the number of carbon atoms is increased in the  $\alpha$ -chain, compounds are 5 named as substitution compounds having respective substituents at position 2 in place of carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the  $\omega$ -chain, the number is deleted in the order starting from position 20; and when the number of carbon atoms is 10 increased in the  $\omega$ -chain, the carbon atoms at the position 21 or later are named as a substituent at position 20. Stereochemistry of the compounds is the same as that of the above formula (A) unless otherwise specified.

In general, each of PGD, PGE and PGF represents a 15 fatty acid derivative having hydroxy groups at positions 9 and/or 11, but in the present specification they also include those having substituents other than the hydroxy groups at positions 9 and/or 11. Such compounds are referred to as 9-deoxy-9-substituted-fatty acid derivatives 20 or 11-deoxy-11-substituted-fatty acid derivatives. A fatty acid derivative having hydrogen in place of the hydroxy group is simply named as 9- or 11-deoxy-fatty acid derivative.

As stated above, the nomenclature of a fatty acid 25 derivative is based on the prostanoic acid skeleton. In

the case the compound has similar partial structure as the primary PG, the abbreviation of "PG" may be used. Thus, a fatty acid derivative whose  $\alpha$ -chain is extended by two carbon atoms, that is, having 9 carbon atoms in the  $\alpha$ -chain 5 is named as 2-decarboxy-2-(2-carboxyethyl)-PG compound. Similarly, a fatty acid derivative having 11 carbon atoms in the  $\alpha$ -chain is named as 2-decarboxy-2-(4-carboxybutyl)-PG compound. Further, a fatty acid derivative whose  $\omega$ -chain is extended by two carbon atoms, that is, having 10 10 carbon atoms in the  $\omega$ -chain is named as 20-ethyl-PG compound. These compounds, however, may also be named according to the IUPAC nomenclatures.

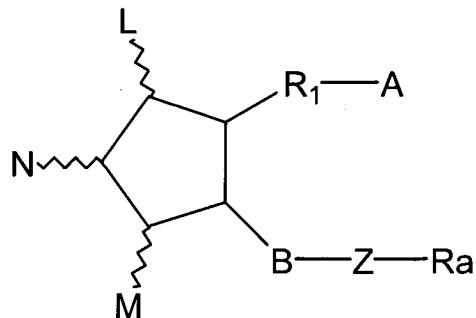
Examples of the analogues including substitution compounds or derivatives of the above described fatty acid derivative include a fatty acid derivative whose carboxy group at the end of the alpha chain is esterified; a fatty acid derivative whose  $\alpha$  chain is extended, a physiologically acceptable salt thereof, a fatty acid derivative having a double bond between positions 2 and 3 20 or a triple bond between positions 5 and 6; a fatty acid derivative having substituent(s) on carbon atom(s) at position(s) 3, 5, 6, 16, 17, 18, 19 and/or 20; and a fatty acid derivative having a lower alkyl or a hydroxy (lower) alkyl group at position 9 and/or 11 in place of the hydroxy 25 group.

According to the present invention, preferred substituents on the carbon atom at position(s) 3, 17, 18 and/or 19 include alkyl having 1-4 carbon atoms, especially methyl and ethyl. Preferred substituents on the carbon atom at position 16 include lower alkyls such as methyl and ethyl, hydroxy, halogen atom such as chlorine and fluorine, and aryloxy such as trifluoromethylphenoxy. Preferred substituents on the carbon atom at position 17 include lower alkyl such as methyl and ethyl, hydroxy, halogen atom such as chlorine and fluorine, and aryloxy such as trifluoromethylphenoxy. Preferred substituents on the carbon atom at position 20 include saturated or unsaturated lower alkyl such as C<sub>1-4</sub> alkyl, lower alkoxy such as C<sub>1-4</sub> alkoxy, and lower alkoxy alkyl such as C<sub>1-4</sub> alkoxy-C<sub>1-4</sub> alkyl.

Preferred substituents on the carbon atom at position 5 include halogen atoms such as chlorine and fluorine. Preferred substituents on the carbon atom at position 6 include an oxo group forming a carbonyl group. Stereochemistry of PGs having hydroxy, lower alkyl or hydroxy(lower)alkyl substituent on the carbon atom at positions 9 and 11 may be  $\alpha$ ,  $\beta$  or a mixture thereof.

Further, the above described analogues or derivatives may have a  $\omega$  chain shorter than that of the primary PGs and a substituent such as alkoxy, cycloalkyl, cycloalkyloxy, phenoxy and phenyl at the end of the truncated  $\omega$ -chain.

A fatty acid derivative used in the present invention is represented by the formula (I):

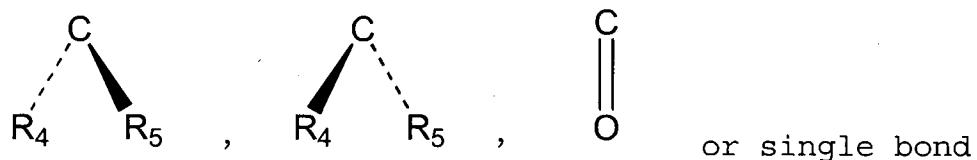


wherein L, M and N are hydrogen, hydroxy, halogen, 5 lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional 10 derivative thereof;

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

Z is



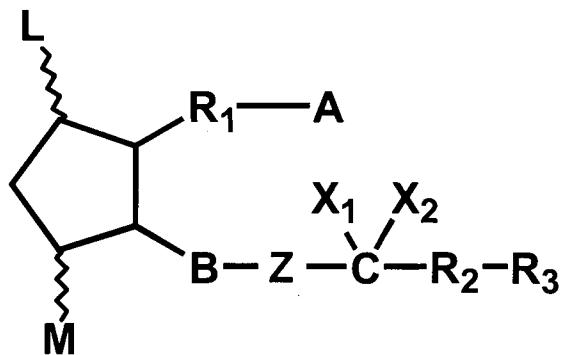
15 wherein  $\text{R}_4$  and  $\text{R}_5$  are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein  $\text{R}_4$  and  $\text{R}_5$  are not hydroxy and lower alkoxy at the same time;

$\text{R}_1$  is a saturated or unsaturated bivalent lower or

medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

5 Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, 10 cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group, and at least one of carbon atom in the aliphatic hydrocarbon is 15 optionally substituted by oxygen, nitrogen or sulfur.

A preferred compound used in the present invention is represented by the formula (II):



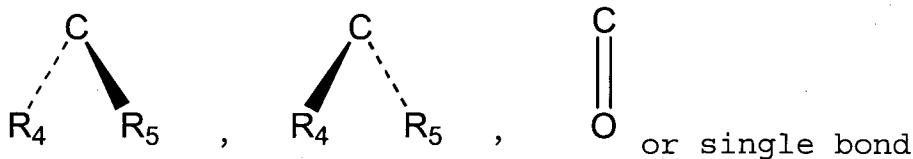
20 wherein L and M are hydrogen atom, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo,

wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

5 A is  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

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

Z is



10 wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

X<sub>1</sub> and X<sub>2</sub> are hydrogen, lower alkyl, or halogen;

15 R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R<sub>2</sub> is a single bond or lower alkylene; and

R<sub>3</sub> is lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy,

heterocyclic group or heterocyclic-oxy group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

In the above formula, the term "unsaturated" in the 5 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 10 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" 15 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 1 to 8 carbon atoms.

The term "halogen atom" covers fluorine, chlorine, 20 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 25 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 alkylene" refers to a straight or branched chain bivalent saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, t-butylene, pentylene and hexylene.

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, toyl, xylyl.

5 Examples of the substituents are halogen atom and halo(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.

10 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 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-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, purinyl, quinazolinyl, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazolinyl, benzothiazolyl, phenothiazinyl. Examples 15 of the substituent in this case include halogen, and 20 25

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  $\text{HcO-}$ , wherein  $\text{Hc}$  is a heterocyclic group as described above.

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

Suitable "pharmaceutically acceptable salts" include 10 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 15 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, monomethyl- monoethanolamine salt, procaine salt and 20 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.

25 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, 5 trityl ester and benzhydryl ester.

The amide of A mean a group represented by the formula -CONR'R", wherein each of R' and R" is hydrogen, 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 methylsulfonylamine, ethylsulfonyl-amide and tolylsulfonylamine.

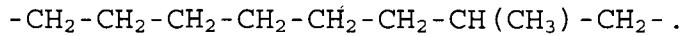
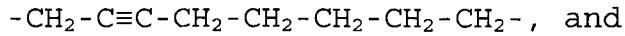
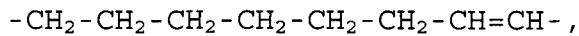
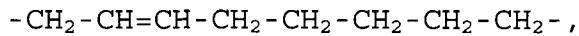
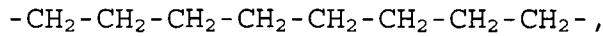
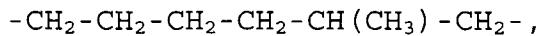
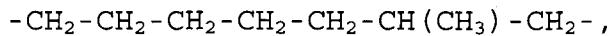
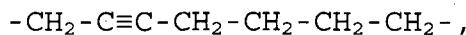
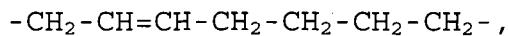
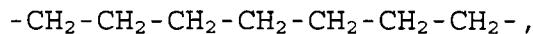
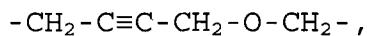
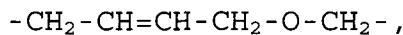
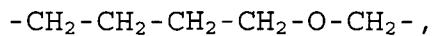
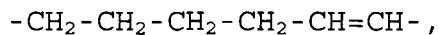
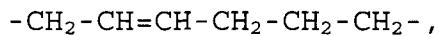
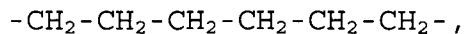
Preferred examples of L and M include hydrogen, 15 hydroxy and oxo, and especially, L and M are both hydroxy, or L is oxo and M is hydrogen or hydroxy.

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

Preferred example of X<sub>1</sub> and X<sub>2</sub> are both being halogen atoms, and more preferably, fluorine atoms, so called 20 16,16-difluoro type.

Preferred R<sub>1</sub> is a hydrocarbon residue containing 1-10 carbon atoms, preferably 6-10 carbon atoms. Further, at least one carbon atom in the aliphatic hydrocarbon is 25 optionally substituted by oxygen, nitrogen or sulfur.

Examples of R<sub>1</sub> include, for example, the following groups:



20 Preferred Ra is a hydrocarbon containing 1-10 carbon atoms, more preferably, 1-8 carbon atoms. Ra may have one or two side chains having one carbon atom. Further, at least one carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

25 A typical example of fatty acid derivative in this

invention is (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoic acid and its derivatives or analogues. The most favorable example of fatty acid derivative in this invention is (+)-isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoate (hereinafter, isopropyl unoprostone).

The configuration of the ring and the  $\alpha$ - and/or  $\omega$  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.

In the present invention, the fatty acid derivative which is dihydro between 13 and 14, and keto(=O) at 15 position may be in the keto-hemiacetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and keto at position 15.

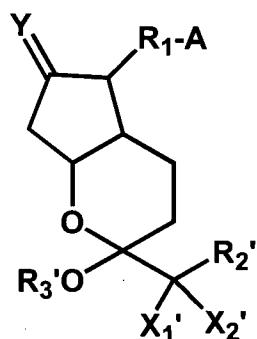
For example, it has been revealed that when both of  $X_1$  and  $X_2$  are halogen atoms, especially, fluorine atoms, the compound contains a tautomeric isomer, bicyclic compound.

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 present invention includes both isomers.

5 Further, the fatty acid derivatives used in the invention include the bicyclic compound and analogs or derivatives thereof.

The bicyclic compound is represented by the formula (III)

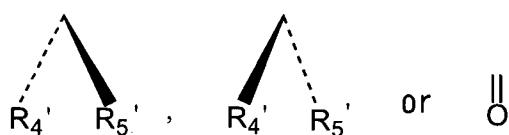


10

wherein, A is -CH<sub>3</sub>, or -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or a functional derivative thereof;

X<sub>1</sub>' and X<sub>2</sub>' are hydrogen, lower alkyl, or halogen;

Y is



15

wherein R<sub>4</sub>' and R<sub>5</sub>' are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub>' and R<sub>5</sub>' are not hydroxy and lower alkoxy at the same time.

R<sub>1</sub> is a saturated or unsaturated divalent lower or medium aliphatic hydrocarbon residue, which is

unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

5           R<sub>2</sub>' is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or 10 hetrocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

15           R<sub>3</sub>' is hydrogen, lower alkyl, cyclo(lower)alkyl, aryl or heterocyclic group.

Furthermore, while the compounds used in the invention may be represented by a formula or name based on keto-type regardless of the presence or absence of the 20 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, 25 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, 5,739,161 and 6,242,485 (these cited references are herein 5 incorporated by reference).

According to the present invention, a mammalian subject may be treated by the instant invention by administering the compound used in the present invention. The subject may be any mammalian subject including a human. 10 The compound can be applied systemically or topically. Usually, the compound may be administered by oral administration, intravenous injection (including infusion), ocular topical administration (e.g. periocular (e.g., subTenon's), subconjunctival, intraocular, intravitreal, 15 intracameral, subretinal, suprachoroidal, and retrobulbar administrations) and the like.

The dose may vary depending on the strain of the animal, age, body weight, symptom to be treated, desired therapeutic effect, administration route, term of treatment 20 and the like. A satisfactory effect can be obtained by systemic administration 1-4 times per day or continuous administration at the amount of 0.00001-500mg/kg per day, more preferably 0.0001-100mg/kg per day.

The compound may preferably be formulated in a 25 pharmaceutical composition suitable for administration in a

conventional manner. The composition may be those suitable for oral administration, ocular topical administration, injection or perfusion as well as it may be an external agent.

5           The composition of the present invention may further contain physiologically acceptable additives. Said additives may include the ingredients used with the present compounds such as excipient, diluent, filler, resolvent, lubricant, adjuvant, binder, disintegrator, coating agent, 10        cupsulating agent, ointment base, suppository base, aerozolizing agent, emulsifier, dispersing agent, suspending agent, thickener, tonicity agent, buffering agent, soothing agent, preservative, antioxidant, corrigent, flavor, colorant, a functional material such as cyclodextrin, and 15        biodegradable polymer, stabilizer. The additives are well known to the art and may be selected from those described in general reference books of pharmaceutics.

20           The amount of the above-defined compound in the composition of the invention may vary depending on the formulation of the composition, and may generally be 0.000001-10.0%, more preferably 0.00001-5.0%, most preferably 0.0001-1%.

25           Examples of solid compositions for oral administration include tablets, troches, sublingual tablets, capsules, pills, powders, granules and the like. The solid

composition may be prepared by mixing one or more active ingredients with at least one inactive diluent. The composition may further contain additives other than the inactive diluents, for example, a lubricant, a 5 disintegrator and a stabilizer. Tablets and pills may be coated with an enteric or gastroenteric film, if necessary.

They may be covered with two or more layers. They may also be adsorbed to a sustained release material, or microcapsulated. Additionally, the compositions may be 10 capsulated by means of an easily degradable material such gelatin. They may be further dissolved in an appropriate solvent such as fatty acid or its mono, di or triglyceride to be a soft capsule. Sublingual tablet may be used in need of fast-acting property.

15 Examples of liquid compositions for oral administration include emulsions, solutions, suspensions, syrups and elixirs and the like. Said composition may further contain a conventionally used inactive diluents e.g. Purified water or ethyl alcohol. The composition may 20 contain additives other than the inactive diluents such as adjuvant e.g. wetting agents and suspending agents, sweeteners, flavors, fragrance and preservatives.

The composition of the present invention may be in 25 the form of spraying composition, which contains one or more active ingredients and may be prepared according to a

known method.

Examples of injectable compositions of the present invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions.

5 Diluents for the aqueous solution or suspension may include, for example, distilled water for injection, physiological saline and Ringer's solution.

Non-aqueous diluents for solution and suspension may include, for example, propylene glycol, polyethylene glycol, 10 vegetable oils such as olive oil, alcohols such as ethanol and polysorbate. The composition may further comprise additives such as preservatives, wetting agents, emulsifying agents, dispersing agents and the like. They may be sterilized by filtration through, e.g. a bacteria-15 retaining filter, compounding with a sterilizer, or by means of gas or radioisotope irradiation sterilization.

The injectable composition may also be provided as a sterilized powder composition to be dissolved in a sterilized solvent for injection before use.

20 The present compound may also be formulated as ophthalmic composition such as eye drops and eye ointments. The form may include all ophthalmic formulations for ocular topical administration used in the ophthalmic field.

25 The eye drops are prepared by dissolving active ingredients in a sterile aqueous solution such as saline

and buffering solution. The eye drops may be provided as a powder composition to be dissolved before use, or by combining powder compositions to be dissolved before use. The eye ointments are prepared by mixing the active 5 ingredient into an ointment base. The formulations are prepared according to the conventional methods.

Osmolarity modifiers include sodium chloride, potassium chloride, calcium chloride, sodium bicarbonate, sodium carbonate, magnesium sulfate, sodium hydrogen 10 phosphate, sodium dihydrogen phosphate, dipotassium hydrogen phosphate, boric acid, borax, sodium hydroxide, hydrochloric acid, mannitol, isosorbitol, propylene glycol, glucose and glycerine, but not limited thereto, as far as they are ordinarily used in the ophthalmic field.

15 Further, additives ordinarily used in the ophthalmic field may be added to the present composition as desired. Such additives include, for example, buffer agent (e.g., boric acid, sodium monohydrogen phosphate, sodium dihydrogen phosphate, etc.), preservatives (e.g., 20 benzalkonium chloride, benzethonium chloride, chlorobutanol, etc.), thickeners (e.g., saccharide such as lactose, mannitol, maltose, etc.; e.g., hyaluronic acid or its salt such as sodium hyaluronate, potassium hyaluronate, etc.; e.g., mucopolysaccharide such as chondroitin sulfate, etc.; 25 e.g., sodium polyacrylate, carboxyvinyl polymer,

crosslinked polyacrylate, etc.), all of which are included herein by reference.

In preparing the present composition as an eye ointment, other than the above additives, the composition 5 may contain ordinarily used eye ointment base. Such eye ointment base includes, but not limited to, oil base such as vaseline, liquid paraffin, polyethylene, selen 50, plastibase, macrogol or a combination thereof; emulsion base having oil phase and water phase emulsified with 10 surfactant, etc.; and water soluble base such as hydroxypropylmethylcellulose, carboxypropylmethylcellulose, polyethylene glycol, etc.

According to the present invention, the preferable embodiment includes that ophthalmic composition contains 15 substantially no benzalkonium chloride. The phrase of "the ophthalmic composition contains substantially no benzalkonium chloride" used herein means that the composition contains no benzalkonium chloride, or the composition contains benzalkonium chloride as low as 20 possible. In the present invention, the ophthalmic composition may contain Benzalkonium chloride at a concentration of less than 0.01%, preferably 0.005% or less, more preferably 0.003% or less.

The present eye drops may be formulated as a sterile 25 unit dose type formulation (one day type or single unit

dose type) containing no preservatives such as benzalkonium chloride.

The ophthalmic composition further includes sustained release forms such as gel formulation, liposome formulation, lipid microemulsion formulation, microsphere formulation, nanosphere formulation and implant formulation in order to provide the active compound sustainedly to the back of the eye.

The concentration and administration number of the active ingredient of the eye drops used in the present invention vary according to the compound to be used, the kind of subjects (such as animals or humans), age, weight, symptoms to be treated, effects of treatment to be desired, administration methods, administration volume, period of treatment, etc. Accordingly, suitable concentration and administration number may be chosen as desired. Taking an example of isopropyl unoprostone, which is one form of the present invention, the formulation containing 0.0001 - 1.0%, preferably 0.001 - 0.5%, for example, 0.001-0.15% or 0.001-0.06% of isopropyl unoprostone may be ordinarily administered to an adult 1-10 times a day.

Some of the ophthalmic composition used in the present invention may be prepared by the method disclosed in US publication No. 2011/0275715 (these cited references is herein incorporated by reference).

According to the present invention, the fatty acid derivatives of the present invention are useful for treating asthenopia.

As used herein, asthenopia refers to an ophthalmological condition where symptoms such as fatigue of the eyes, pain of the eyes, blurred vision, red eye (hyperemia), intermittent double vision, headache, shoulder stiffness and nausea appear. The symptoms may appear after reading, computer work, or other close activities that involve tedious visual tasks.

Since asthenopia is characterized by weakness or fatigue of the eyes, often accompanied by eye pain, red eyes, headache, dimming or blurring of vision and intermittent double vision, the present invention further includes the treatment of one or more symptoms or conditions associated with or accompanied by asthenopia. Examples of the symptoms or conditions associated with or accompanied by asthenopia include, but are not limited to, eye pain, red eyes, headache, dimming or blurring of vision, intermittent double vision, eye discharge, accommodative dysfunction, impairment in adaptation to brightness and darkness, ocular motility disorder or impaired motor function of muscle around eye such as blepharospasm and any combination of them.

In addition, according to the present invention, the

fatty acid derivatives of the present invention are useful for improving accommodation ability and treating accommodative dysfunction.

As used herein, "accommodation" refers to the process by which the vertebrate eye changes optical power to maintain a clear image (focus) on an object as its distance varies. Examples of accommodation dysfunction include, but are not limited to myopia (nearsightedness or shortsightedness), presbyopia, hyperopia (i.e. farsightedness), astigmatism, cycloplegia and accommodative spasm.

In one embodiment, the fatty acid derivatives of the present invention are useful for improving ability of ciliary muscle to focus on an object as the distance varies.

In another embodiment, the fatty acid derivatives of the present invention are useful for treating accommodative asthenopia. "Accommodative asthenopia" which is one type of asthenopia, can be caused by refractive error (e.g. myopia (nearsightedness or shortsightedness), hyperopia (i.e. farsightedness), astigmatism, use of contact lenses or eye glasses which are not adjusted for one's eyesight) or accommodation error (e.g. presbyopia, cycloplegia, accommodative spasm).

It is known that the patients with Parkinson's disease have asthenopia and accommodative dysfunctions

including or derived from blepharospasm, paucity of blinking, apraxia of lid opening, reduced vergence, reduced upgaze, blurred vision, upgaze deficiency, convergence insufficiency.

5           In further aspect of the present invention, the fatty acid derivatives of the present invention are useful for treating asthenopia and accommodative dysfunctions in a subject suffering from Parkinson's disease. The asthenopia and accommodative dysfunctions seen in a subject suffering 10 from Parkinson's disease, which can be treated by the fatty acid derivatives of the present invention, may be caused by etiology of Parkinson's disease, or anti-Parkinson's disease drugs administered to a subject (e.g. dopamine receptor agonist (e.g. Cabergoline), anticholinergic drug 15 (e.g. trihexyphenidyl hydrochloride)); or both of them. Examples of the symptoms or conditions associated with or accompanied by asthenopia and Examples of accommodative dysfunctions seen in a subject suffering from Parkinson's disease are the same with those as described above.

20           In further aspect of the present invention, the fatty acid derivatives of the present invention are useful for treating eye pain.

Based on the method which is provided by the present invention, the skilled person can understand that a 25 pharmaceutical composition which is useful for the method

is prepared; that the compound described above is used for the preparation of a pharmaceutical composition which is useful for the method; and that the compound described above is used in the treatment of the disease described 5 above. Thus, according to the present invention, a pharmaceutical composition comprising the compound described above for the treatment of the disease described above; use of the compound described above for preparation of a pharmaceutical composition for the treatment of the 10 disease described above; and, use of the compound described above in the treatment of the disease described above etc are also provided.

The term "treating" or "treatment" used herein includes prophylactic and therapeutic treatment, and any 15 means of control such as prevention, care, relief of the condition, attenuation of the condition, arrest of progression, etc.

The pharmaceutical composition of the present invention may contain a single active ingredient or a 20 combination of two or more active ingredients, as far as they are not contrary to the objects of the present invention. In a combination of plural active ingredients, their respective contents may be suitably increased or decreased in consideration of their therapeutic effects and 25 safety.

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

Example 1

5           A subject who had blurring of vision received eye drop comprising 0.12 % isopropyl unoprostone. After single administration of it, eye discharge and blurry vision were improved. On the other hand, after single administration of placebo, eye discharge and blurry vision were not 10 improved.

Example 2

A subject who had eye pain received eye drop comprising 0.12% isopropyl unoprostone. After single 15 administration of it, eye pain was improved. On the other hand, after single administration of placebo, eye pain was not improved.

Example 3

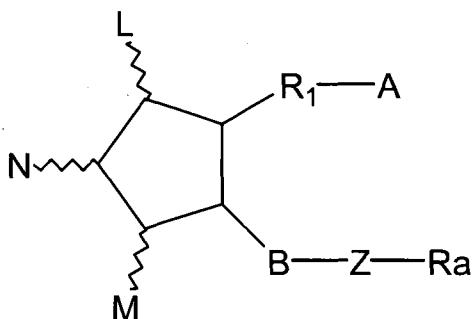
20           A subject who was difficult to focus on the objects even using the farsighted glasses received eye drop comprising 0.12% isopropyl unoprostone twice a day. He was presbyopia and astigmatism. After seven days administration of it, he was able to focus on the objects 25 easier and quicker than before the administration, and the

improvement was continued for three weeks..

The result indicates that the present compound is useful for improving the accommodative function.

## CLAIMS

1. A pharmaceutical composition for treating asthenopia in a mammalian subject, which comprises administering to the subject in need thereof an effective amount of a fatty acid derivative represented by the formula (I):

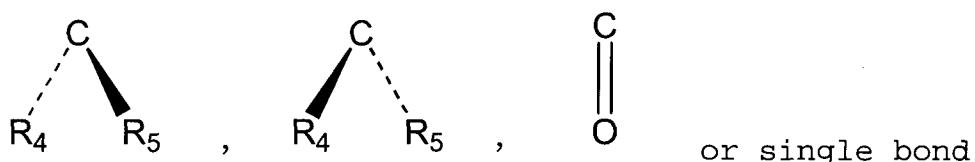


wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

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

Z is



wherein  $\text{R}_4$  and  $\text{R}_5$  are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein

$R_4$  and  $R_5$  are not hydroxy and lower alkoxy at the same time;

$R_1$  is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

$R_a$  is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

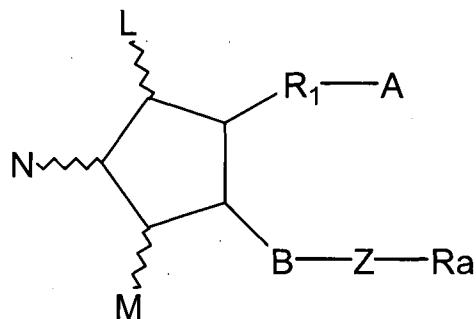
2. The pharmaceutical composition as described in Claim 1, wherein eye pain, eye discharge or blurry vision associated with or accompanied by said asthenopia is treated.

3. The pharmaceutical composition as described in claim 1, wherein the asthenopia is accommodative asthenopia.

25 4. The pharmaceutical composition as described in claim

1, wherein presbyopia, farsightedness or astigmatism associated with or accompanied by said asthenopia is treated.

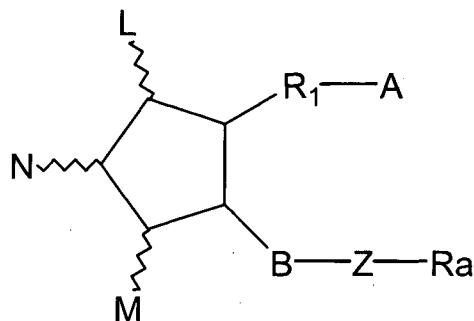
5. A pharmaceutical composition for treating accommodative dysfunction in a mammalian subject, which comprises administering to the subject in need thereof an effective amount of a fatty acid derivative represented by the formula (I):



10 wherein L, M, N, A, B, Z, R<sub>1</sub> and R<sub>a</sub> are as described in Claim 1.

6. The pharmaceutical composition as described in Claim 5, wherein said accommodative dysfunction is presbyopia, farsightedness or astigmatism.

15 7. A pharmaceutical composition for treating ocular pain in a mammalian subject, which comprises administering to the subject in need thereof an effective amount of a fatty acid derivative represented by the formula (I):



wherein L, M, N, A, B, Z, R<sub>1</sub> and R<sub>a</sub> are as described in Claim 1.

8. The pharmaceutical composition as described in any

5 one of Claims 1-7, wherein Z is C=O.

9. The pharmaceutical composition as described in any one of Claims 1-8, wherein B is -CH<sub>2</sub>-CH<sub>2</sub>-.

10. The pharmaceutical composition as described in any one of Claims 1-9, wherein L is hydroxy or oxo, M is hydrogen or hydroxy, N is hydrogen, B is -CH<sub>2</sub>-CH<sub>2</sub>- and Z is C=O.

11. The pharmaceutical composition as described in any one of Claims 1-10, wherein said fatty acid derivative is isopropyl unoprostone.

15 12. The pharmaceutical composition as described in any one of Claims 1-11 which is formulated as a composition for topical administration.

13. The pharmaceutical composition as described in Claim 12, wherein said composition is an ophthalmic composition 20 for ocular topical administration.

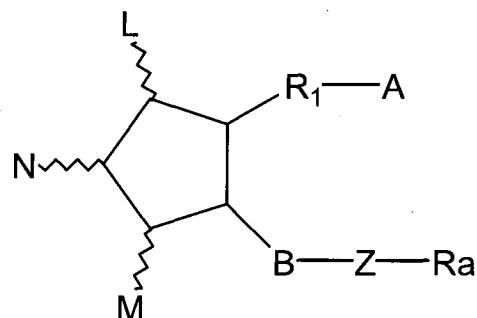
14. The pharmaceutical composition as described in Claim

13, wherein said ophthalmic composition is formulated as eye drop.

15. The pharmaceutical composition as described in Claim 14, wherein said eye drop is formulated as a sterile unit dose type containing no preservatives.

16. The pharmaceutical composition as described in Claim 15, wherein said ophthalmic composition comprises substantially no benzalkonium chloride.

17. Use of a fatty acid derivative represented by the formula (I):

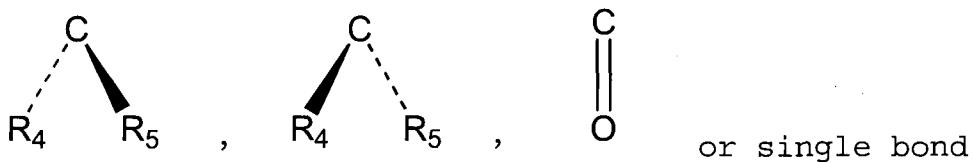


wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

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

Z is



wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

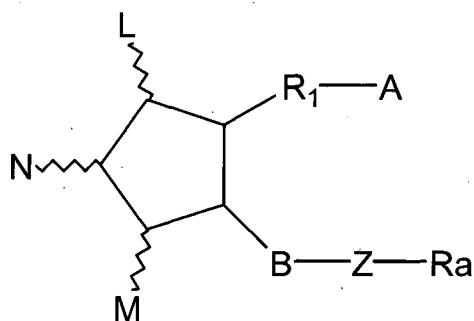
R<sub>a</sub> is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur, for the preparation of a pharmaceutical composition for treating asthenopia in a mammalian subject.

18. Use as described in Claim 17, wherein eye pain, eye discharge or blurry vision associated with or accompanied by said asthenopia is treated.

19. Use as described in Claim 17, wherein the asthenopia is accommodative asthenopia.

20. Use as described in claim 17, wherein presbyopia, farsightedness or astigmatism associated with or accompanied by said asthenopia is treated.

21. Use of a fatty acid derivative represented by the formula (I):

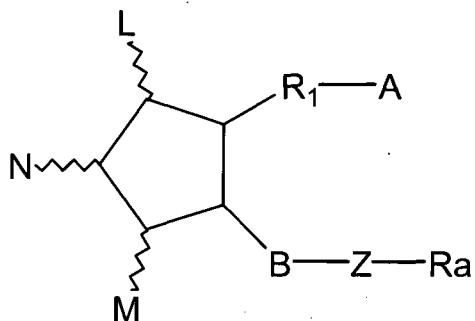


wherein L, M, N, A, B, Z, R<sub>1</sub> and Ra are as described in Claim 17

for the preparation of a pharmaceutical composition for 15 treating accommodative dysfunction in a mammalian subject.

22. Use as described in Claim 21, wherein said accommodative dysfunction is presbyopia, farsightedness or astigmatism.

23. Use of a fatty acid derivative represented by the formula (I):



wherein L, M, N, A, B, Z, R<sub>1</sub> and Ra are as described

in Claim 17

for the preparation of a pharmaceutical composition for

5 treating ocular pain in a mammalian subject.

24. Use as described in any one of Claims 17-23, wherein  
Z is C=O.

25. Use as described in any one of Claims 17-24, wherein  
B is -CH<sub>2</sub>-CH<sub>2</sub>-.

10 26. Use as described in any one of Claims 17-25, wherein  
L is hydroxy or oxo, M is hydrogen or hydroxy, N is  
hydrogen, B is -CH<sub>2</sub>-CH<sub>2</sub>- and Z is C=O.

27. Use as described in any one of Claims 17-26, wherein  
said fatty acid derivative is isopropyl unoprostone.

15 28. Use as described in any one of Claims 17-26 wherein  
the pharmaceutical composition is formulated as a  
composition for topical administration.

29. Use as described in Claim 28, wherein said  
composition is an ophthalmic composition for ocular topical  
20 administration.

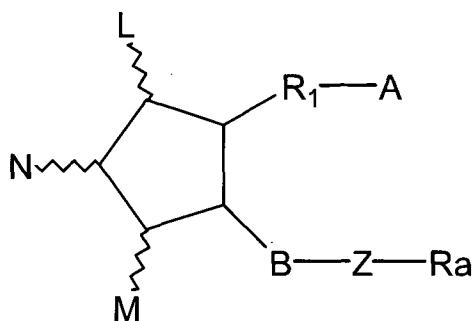
30. Use as described in Claim 29, wherein said

ophthalmic composition is formulated as eye drop.

31. Use as described in Claim 30, wherein said eye drop is formulated as a sterile unit dose type containing no preservatives.

5 32. Use as described in Claim 31, wherein said ophthalmic composition comprises substantially no benzalkonium chloride.

33. Use of an effective amount of a fatty acid derivative represented by the formula (I):



10

wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy 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;

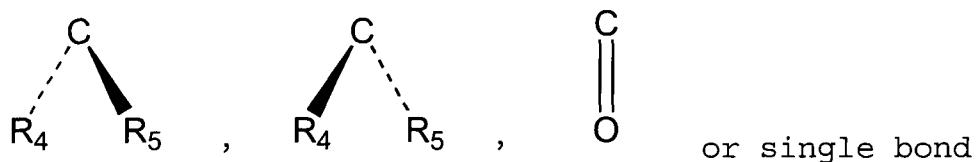
15

A is -CH<sub>3</sub>, or -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or a functional derivative thereof;

B is single bond, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH-, -C≡C-CH<sub>2</sub>- or -CH<sub>2</sub>-C≡C-;

20

Z is



wherein  $R_4$  and  $R_5$  are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein  $R_4$  and  $R_5$  are not hydroxy and lower alkoxy at the same time;

5

$R_1$  is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

10

$R_a$  is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur, in the treatment of asthenopia in a mammalian subject.

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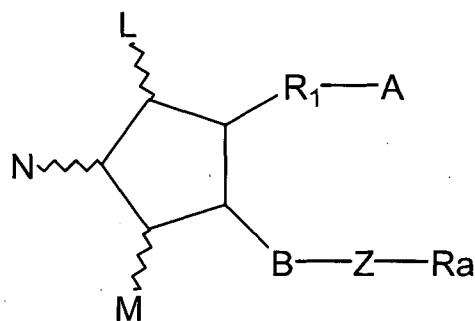
34. Use as described in Claim 33, wherein eye pain, eye

discharge or blurry vision associated with or accompanied by said asthenopia is treated.

35. Use as described in Claim 34, wherein the asthenopia is accommodative asthenopia.

5 36. Use as described in Claim 33, wherein wherein presbyopia, farsightedness or astigmatism associated with or accompanied by said asthenopia is treated.

37. Use of an effective amount of a fatty acid derivative represented by the formula (I):



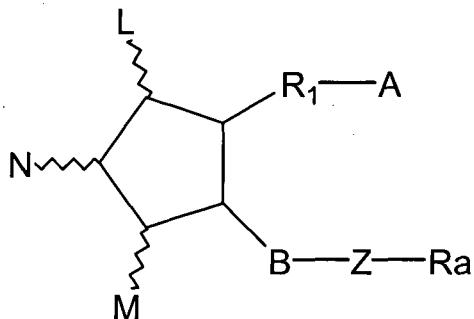
10

wherein L, M, N, A, B, Z, R<sub>1</sub> and Ra are as described in Claim 33,

in the treatment of accommodative dysfunction in a mammalian subject.

15 38. Use as described in Claim 37, wherein said accommodative dysfunction is presbyopia, farsightedness or astigmatism.

39. Use of an effective amount of a fatty acid derivative represented by the formula (I):



wherein L, M, N, A, B, Z, R<sub>1</sub> and Ra are as described in Claim 33,

in the treatment of ocular pain in a mammalian subject.

5 40. Use as described in any one of Claims 33-39, wherein Z is C=O.

41. Use as described in any one of Claims 33-40, wherein B is -CH<sub>2</sub>-CH<sub>2</sub>-.

42. Use as described in any one of Claims 33-41, wherein 10 L is hydroxy or oxo, M is hydrogen or hydroxy, N is hydrogen, B is -CH<sub>2</sub>-CH<sub>2</sub>- and Z is C=O.

43. Use as described in any one of Claims 33-42, wherein said fatty acid derivative is isopropyl unoprostone.

44. Use as described in any one of Claims 33-43 wherein 15 said fatty acid derivative is formulated as a composition for topical administration.

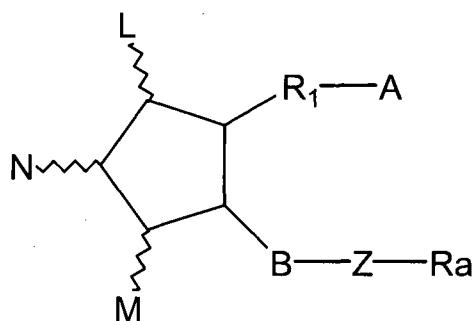
45. Use as described in Claim 44, wherein said composition is an ophthalmic composition for ocular topical administration.

20 46. Use as described in Claim 45, wherein said ophthalmic composition is formulated as eye drop.

47. Use as described in Claim 46, wherein said eye drop is formulated as a sterile unit dose type containing no preservatives.

48. Use as described in Claim 47, wherein said ophthalmic 5 composition comprises substantially no benzalkonium chloride.

49. A method for treating asthenopia in a mammalian subject, which comprises administering to the subject in need thereof an effective amount of a fatty acid derivative 10 represented by the formula (I):

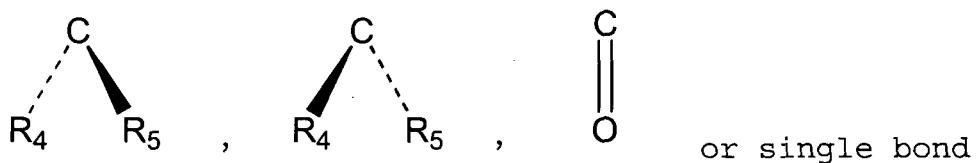


wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

B is single bond,  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{CH}_2-$  20  $\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}=\text{CH}-$ ,  $-\text{C}\equiv\text{C}-\text{CH}_2-$  or  $-\text{CH}_2-\text{C}\equiv\text{C}-$ ;

Z is



wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

5

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one 10 of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

R<sub>a</sub> is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower 15 alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group, and at least 20 one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

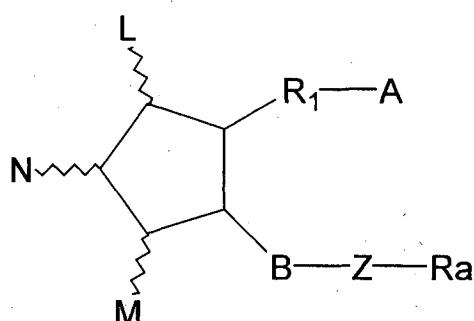
50. The method as described in Claim 49, wherein eye pain, eye discharge or blurry vision associated with or

accompanied by said asthenopia is treated.

51. The method as described in Claim 49, wherein the asthenopia is accommodative asthenopia.

52. The method as described in Claim 49, wherein presbyopia, farsightedness or astigmatism associated with or accompanied by said asthenopia is treated.

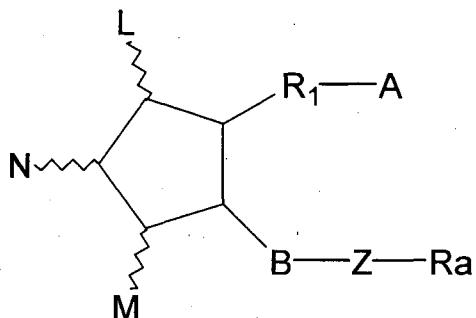
53. A method for treating accommodative dysfunction in a mammalian subject, which comprises administering to the subject in need thereof an effective amount of a fatty acid derivative represented by the formula (I):



wherein L, M, N, A, B, Z, R<sub>1</sub> and Ra are as described in Claim 49.

54. The method as described in Claim 53, wherein said accommodative dysfunction is presbyopia, farsightedness or astigmatism.

55. A method for treating ocular pain in a mammalian subject, which comprises administering to the subject in need thereof an effective amount of a fatty acid derivative represented by the formula (I):



wherein  $L$ ,  $M$ ,  $N$ ,  $A$ ,  $B$ ,  $Z$ ,  $R_1$  and  $Ra$  are as described in Claim 49.

56. The method as described in any one of Claims 49-55, wherein  $Z$  is  $C=O$ .

57. The method as described in any one of Claims 49-56, wherein  $B$  is  $-CH_2-CH_2-$ .

58. The method as described in any one of Claims 49-57, wherein  $L$  is hydroxy or oxo,  $M$  is hydrogen or hydroxy,  $N$  is hydrogen,  $B$  is  $-CH_2-CH_2-$  and  $Z$  is  $C=O$ .

59. The method as described in any one of Claims 49-58, wherein said fatty acid derivative is isopropyl unoprostone.

60. The method as described in any one of Claims 49-59 wherein said fatty acid derivative is formulated as a composition for topical administration.

61. The method as described in Claim 60, wherein said composition is an ophthalmic composition for ocular topical administration.

62. The method as described in Claim 61, wherein said ophthalmic composition is formulated as eye drop.

63. The method as described in Claim 62, wherein said

eye drop is formulated as a sterile unit dose type containing no preservatives.

64. The method as described in Claim 63, wherein said ophthalmic composition comprises substantially no benzalkonium chloride.

**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/JP2012/060094

**A. CLASSIFICATION OF SUBJECT MATTER**

Int.Cl. A61K31/5575 (2006.01)i, A61P27/00 (2006.01)i, A61P27/10 (2006.01)i

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)

Int.Cl. A61K31/5575, A61P27/00, A61P27/10

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

Published examined utility model applications of Japan 1922-1996  
Published unexamined utility model applications of Japan 1971-2012  
Registered utility model specifications of Japan 1996-2012  
Published registered utility model applications of Japan 1994-2012

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

CA/REGISTRY/MEDLINE/EMBASE/BIOSIS (STN), JSTPlus/JMEDPlus/JST/580 (JDreamII)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/023784 A1 (SHOWA UNIVERSITY) 2008.02.28, [0012], [0022], Claims	7, 9, 23, 25
A	(No Family)	1-6, 8, 10-22, 24, 26-32
Y	JP 2004-521960 A (SUCAMPO AG) 2004.07.22, Claims	7-16, 23-32
A	& US 2003/0060511 A1 & EP 1420793 A & WO 2003/018025 A1 & NO 20031779 A & BR 205932 A & CA 2458230 A & MX PA04001604 A & CN 1575178 A & ZA 200302911 A & AR 36276 A	1-6, 17-22

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents:

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

“E” earlier application or patent but published on or after the international filing date

“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

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

22.05.2012

Date of mailing of the international search report

29.05.2012

Name and mailing address of the ISA/JP

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## INTERNATIONAL SEARCH REPORT

International application No. PCT/JP2012/060094
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## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 2011-507831 A (MAZENCE INC) 2011.03.10, [0007] & US 2011/0020448 A1 & EP 2231146 A & WO 2009/082124 A2 & KR 10-2009-0068476 A & CN 101917986 A	7-16, 23-32
A	JP 09-87179 A (R-TECH UENO LTD) 1997.03.31, & US 5773471 A & EP 730866 A2 & DE 69626232 D & DE 69626232 T & NO 960974 A & AU 701620 B & AU 4800396 A & CA 2171226 A & NZ 286141 A & TW 420611 B & AT 232729 T & ES 2192599 T & CN 1140057 A & NO 960974 A0	1-32
A	KATSUMURA, K. et al., Effects of latanoprost instillation on the accommodation and pupil size in normal young adults, RINSHO GANKA, 2001, Vol.55, No.2, pp.221-225	1-32
A	TEZUKA, H. et al., A mechanism for reducing intraocular pressure in normal volunteers using UF-021, a prostaglandin-related compound, Nihon Ganka Gakkai Zasshi, 1992, Vol.96, No.4, pp.496-500	1-32

**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/JP2012/060094

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.  Claims Nos.: 33–64  
because they relate to subject matter not required to be searched by this Authority, namely:  
The subject matter of claims 33–64 relates to a method for treatment of the human body by therapy, which does not require an international search by the International Searching Authority in accordance with PCT Article 17(2)(a)(i) and Rule 39.1(iv).
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 No. III Observations where unity of invention is lacking (Continuation of item 3 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 searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
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 and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.