(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 471 856 A1**

(12) **EUROPEAN PATENT APPLICATION published in accordance with Art. 158(3) EPC**

(21) Application number: **91905484.1**

(51) Int. Cl.[5]: **C07C 405/00**, A61K 31/557

(22) Date of filing: **07.03.91**

(86) International application number:
PCT/JP91/00305

(87) International publication number:
WO 91/13869 (19.09.91 91/22)

(30) Priority: **08.03.90 JP 57476/90**

(43) Date of publication of application:
26.02.92 Bulletin 92/09

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(71) Applicant: **SHIONOGI & CO., LTD.**
1-8, Doshomachi 3-chome Chuo-ku
Osaka 541(JP)

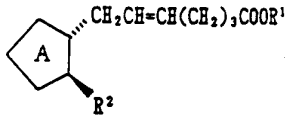
(72) Inventor: **KISHI, Morio, 31-26,**
Katagihara-takodencho
Nishiky0-ku
Kyoto-shi, Kyoto 615(JP)
Inventor: **TAKAHASHI, Kimio, 1-115,**
Furukawa-cho 3-chome
Nishinomiya-shi
Hyogo 663(JP)
Inventor: **KAWADA, Kenji, C22-107, 3-1,**
Shinsenrinishi-machi
Toyonaka-shi
Osaka 565(JP)
Inventor: **GOH, Yasumasa, 5-8, Yayoigaoka**
4-chome
Sanda-shi
Hyogo 669-13(JP)

(74) Representative: **Hardisty, David Robert et al**
BOULT, WADE & TENNANT 27 Furnival Street
London EC4A IPQ(GB)

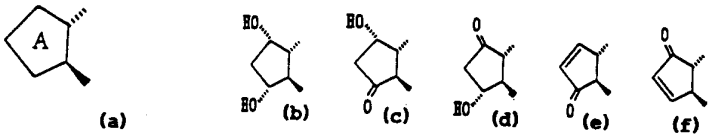
(54) **15-DEOXYPROSTAGLANDIN DERIVATIVE.**

(57) A 15-deoxyprostaglandin derivative of general formula (I) and an intraocular pressure depressant containing said derivative or a pharmaceutically acceptable salt thereof as the active ingredient. In formula (I), (a) is a five-membered ring selected from among (b), (c), (d), (e), (f); R^1 represents hydrogen or lower alkyl; and R^2 represents C_6 to C_{12} alkyl, C_6 to C_{12} alkenyl or C_6 to C_{12} alkadienyl, provided that a compound of formula (II) (wherein R' represents H or CH_3) is excluded.

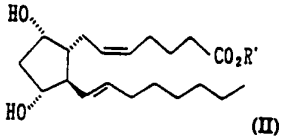
EP 0 471 856 A1



(I)



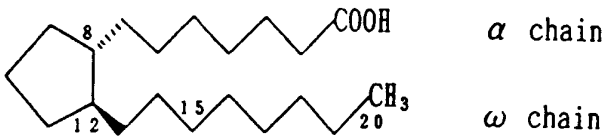
(a) (b) (c) (d) (e) (f)



(II)

The present invention relates to 15-deoxyprostaglandin derivatives and to pharmaceutical composition containing the same.

Prostaglandins are a class of physiologically active substances which are derived from eicosapolyenoic acid such as arachidonic acid through biosynthetic pathway in animal tissues and have, as a fundamental chemical structure, prostanoic acid of the formula:



Prostaglandins are produced through biosynthesis in various tissues, and classified into several families. Thus, prostaglandins are categorized into A - J groups depending on the position of oxgen atom attached to the 5 membered ring moiety and the position of a double bond in the ring moiety. Alternatively, prostaglandins can be categorized into 3 groups depending on the number of bouble bonds in the side chains. As a result, prostaglandins are designated as PGA_2, PGE_1, $PGF_{2\alpha}$, according to both categorizations.

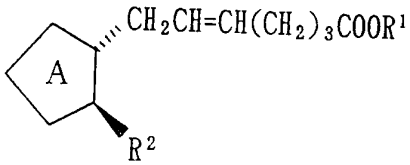
Prostaglandins possess as a whole diverse bioactivities, which include, for example, vasodilator activity, platlet aggregation-inhibiting activity, uterotonic activity, gastrointestinal motility-promoting activity, etc.

Futher, some prostaglandins have intraocular pressure-reducing activity. For example, Japanese Patent Publication (kokai) No. 1418/1984 describes that $PGF_{2\alpha}$ has high intraocular pressure-reducing activity and that 15-keto-$PGF_{2\alpha}$ has the same activity although it is less potent. However, these natural prostaglandins are chemically and biologically labile, and are easily subject to metabolic degradation because they contain in the chemical structure a labile ally alcohol moiety comprising a double bond between 13 and 14 positions and a hydroxy group at 15 position in ω chain.

13,14-Dihydro-15-ketoprostaglandin which is a metabolic product of prostaglandins has been known as a compound which does not contain the labile moiety and has been known to be a useful compound having the intraocular pressure-reducing activity.

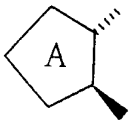
The inventors of the invention have found new useful compounds by screening a large amount of prostaglandin derivatives which are stable and capable of being chemically synthesized.

Thus, the present invention provides 15-deoxyprostaglandin derivatives of the formula (I):

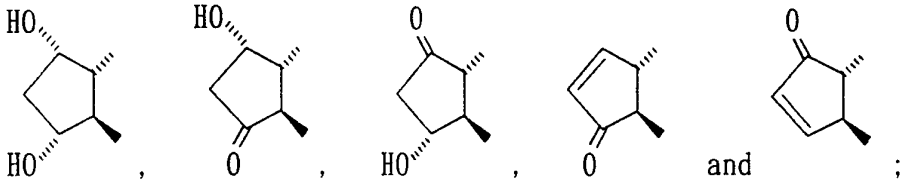


(I)

in which



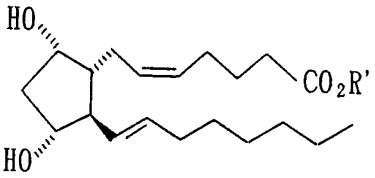
is a 5 membered ring which is selected from a group consisting of



R^1 is hydrogen or lower alkyl;

R^2 is C_6-C_{12} alkyl, C_6-C_{12} alkenyl or C_6-C_{12} alkadienyl;

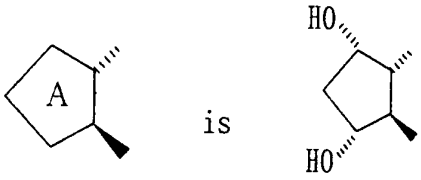
provided that the compound of the following formula is excluded:



wherein R' is hydrogen or methyl;

or pharmaceutically acceptable salts thereof. The term "C_6-C_{12} alkyl" in the definition of R^2 refers to hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl. R^2 may be an unsaturated haydrocarbon chain containing one or more double bonds, with C_8-C_{10} alkenyl or C_8-C_{10} alkadienyl being preferred. Specific examples of the unsaturated hydrocarbon chain are 1-hexenyl, 2-hexenyl, 1,3-hexadienyl, 1-heptenyl, 2-heptenyl, 1,3-heptadienyl, 1-octenyl, 2-octenyl, 1,3-octadienyl, 1-nonenyl, 2-nonenyl, 1,3-nonadienyl, 1-decenyl, 2-decenyl, 1,3-decadienyl, 1-undecenyl, 2-undecenyl, 1,3-undecadienyl, 1-dodecenyl, 2-dodecenyl, and 1,3-dodecadienyl.

Further, 15-deoxyprostaglandin derivatives of the above foumula in which



are also preferred.

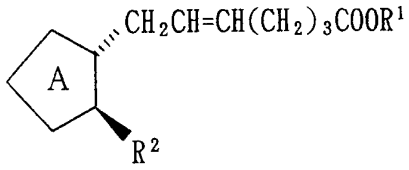
15-Deoxyprostaglandin derivatives of the formula (I) include all of the stereoisomers and mixture thereof.

As another embodiment, the invention provides a new formulation which is useful as an intraocular pressure-reducing agent. The inventors of the invention found that derivatives of conventional prostaglandins which are derived from said conventional prostaglandins by deleting the hydroxy group at 15-position are more stable, particularly in liquid phase, than the conventional prostaglandins, and that they show the intraocular pressure-reducing activity. Thus, the invention provides a new use of these derivatives. In particular, the compounds of the invention as described above have a significant intraocular pressure-reducing activity, while they do not produce any side effects such as hyperemia of conjunctiva, and initial increase in intraocular pressure which are often observed in known prostaglandins. Accordingly, the 15-deoxyprostaglandins of the invention may be a therapeutical agent useful for treating an ocular disease, in particular glaucoma, which is assumed to be caused by increased intaocular pressure.

The term "15-deoxyprostaglandin derivatives" used in the specification and the claims refer to any derivatives from natural prostaglandins (preferably, PGA_1, PGA_2, PGB_1, PGB_2, PGE_1, PGE_2, PGE_3, $PGF_{1\alpha}$, $PGF_{2\alpha}$, $PGF_{3\alpha}$, PGJ_1, or PGJ_2), which lack the hydroxy group at 15 position in the ω chain. Said ω chain may be saturated or unsaturated, and may have one or more double and/or triple bonds. Further, the double bonds may be E form, Z form or a mixture thereof. Preferably, however, the α chain has Z form and the ω chain has E form. Further, the derivatives of the invention include those in which the terminal carbon in the ω chain (20 position) is bound to a lower alkyl or a lower alkenyl. The derivatives may have 2 - 4

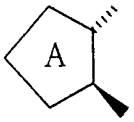
asymmetric carbon atoms. The invention includes all of the optical isomers and the mixture thereof.

Among the 15-deoxyprostaglandin derivatives of the invention which are useful as an intraocular pressure-reducing agent, preferred derivatives are those having the formula (I):

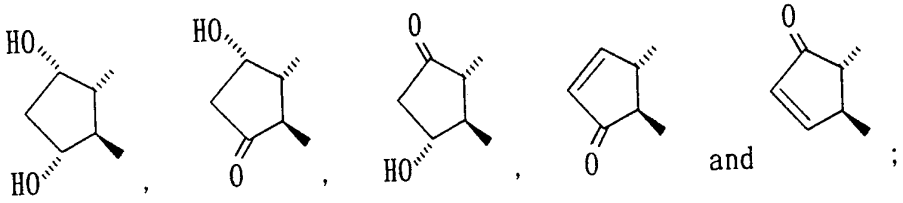


(I)

in which

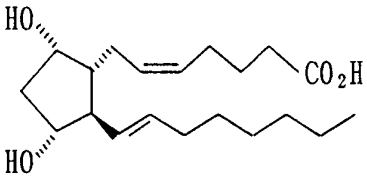


is a 5-membered ring selected from



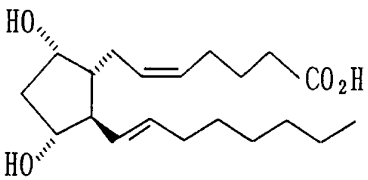
R^1 is hydrogen or lower alkyl;
R^2 is C_6-C_{12} alkyl, C_6-C_{12} alkenyl or C_6-C_{12} alkadienyl;
or pharmaceutically acceptable salts thereof.

Most preferred derivatives are (5Z,13E,9S,11R)-9,11-dihydroxy-5,13-prostadienoic acid of the formula:



or pharmaceutically acceptable salts or esters thereof. Among the above preferred derivatives, a sodium salt of (5Z,13E,9S,11R)-9,11-dihydroxy-5,13-prostadienoic acid is especially preferred in the light of solubility in water.

It should be noted that (5Z,13E,9S,11R)-9,11-dihydroxy-5,13-prostadienoic acid of the formula:



and methyl ester thereof have been described in Gorman, Proc., Natl., Acad., Sci., U.S.A. 74 vol.,9,4007-

DOCKET ALARM

Explore Litigation Insights

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

Real-Time Litigation Alerts

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

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

Advanced Docket Research

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

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

Analytics At Your Fingertips

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

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

API

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

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

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

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

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