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(54) Title: AGENT FOR TOPICAL OPHTHALMIC TREATMENT OF OCULAR INFLAMMATORY DISEASES

(57) Abstract: The present invention provides an agent for topical ophthalmic treatment of a human for ocular inflammatory diseases, containing a tricyclo compound as shown by the general formula (I) or its pharmaceutically acceptable salt as the active ingredient in the concentration of 0.01% - 0.1%. The present agent for topical ophthalmic treatment continuously shows superior ocular anti-inflammatory effects by topically administering it in a low dose to the eye of the human having the ocular inflammatory diseases. The present agent is effective for symptoms caused by the ocular inflammatory diseases such as itching, flare, edema, ulcer, etc. The present agent is also effective for a subject in whom conventional anti-inflammatory agents show no improving effect (e.g., steroid and cyclosporins). The present agent is also effective for a subject for whom other anti-inflammatory agents cannot be used (e.g., steroid contraindication). The present agent is very useful especially for the reason that it shows sufficient effects by topically administering it to the eye for one to four times.

AGENT FOR TOPICAL OPHTHALMIC TREATMENT OF OCULAR INFLAMMATORY DISEASES

TECHNICAL FIELD

The present invention relates to an agent for topical ophthalmic treatment of ocular inflammatory diseases comprising a tricyclo compound as its active ingredient.

BACKGROUND ART

The ocular inflammatory diseases have many forms of ocular disorders accompanying various pains, depending on the position of inflammation. The ocular inflammatory diseases include uveitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, corneal ulcer, conjunctival ulcer, etc. Further, the ocular inflammatory diseases may be caused by various ocular disorders, an ophthalmic operation or a physical injury to the eye.

The symptoms of the ocular inflammatory diseases include itching, flare, edema, ulcer, etc.

The patients with ocular inflammatory diseases account for more than half of all the patients with ocular diseases. Accordingly, agents having ocular anti-inflammatory effects play an important role in the medical scene. Today, steroid drugs and nonsteroidal drugs are mainly used for the ocular inflammatory diseases.

The steroid drugs, which have excellent effects on the ocular inflammatory diseases, are clinically indispensable drugs. However, whether they are administered systemically or topically, they have the risk of bringing serious side effects. Such side effects include, for example, steroid glaucoma, infectious eye diseases, steroidal cataract, etc. Especially, patients with chronic ocular inflammatory diseases have a high risk of such side effects. For the specific patients having an already increased intraocular pressure (e.g., glaucoma

patients), such side effects can never be acceptable. Under these circumstances, it has been strongly desired to develop a nonsteroidal ocular anti-inflammatory agent.

Presently, several tens of nonsteroidal anti-inflammatory agents for internal use have been launched. However, in the case of an agent for treating ocular inflammatory diseases, especially in the case of eye drops, which are the formulations for topical administration to the eye, in addition to the anti-inflammatory effects, the contained agent needs to have characteristics that satisfy necessary requirements unique to the eye drops, such as improvement of water solubility, release of topical irritations on the eye, good transition to the eye tissues, etc. Therefore, it has not been easy to develop the nonsteroidal agent which satisfies these requirements and is effective for the ocular inflammatory diseases.

Besides, in the case of the eye drops, compared to the agent for internal use, the amount administrable at one time is small. Thus, in many cases, even the agent effective as the internal agent does not show sufficient effect in the ocular instillation, or it is necessary to administer the agent frequently (at least four times a day). Therefore, it has been desired to develop the non-steroidal anti-inflammatory eye drops having greater effects in a small amount. An object of the present invention is to provide a non-steroidal ocular anti-inflammatory agent having the superior ocular anti-inflammatory effects in a small amount with high safety.

It is known that FK506 and cyclosporins are effective for the treatment of allergic diseases such as allergic conjunctivitis, vernal conjunctivitis, atopic dermatitis, etc. (e.g., WO92/19278).

However, it is not yet known that some kind of tricyclo compound such as FK506 shows the superior ocular anti-

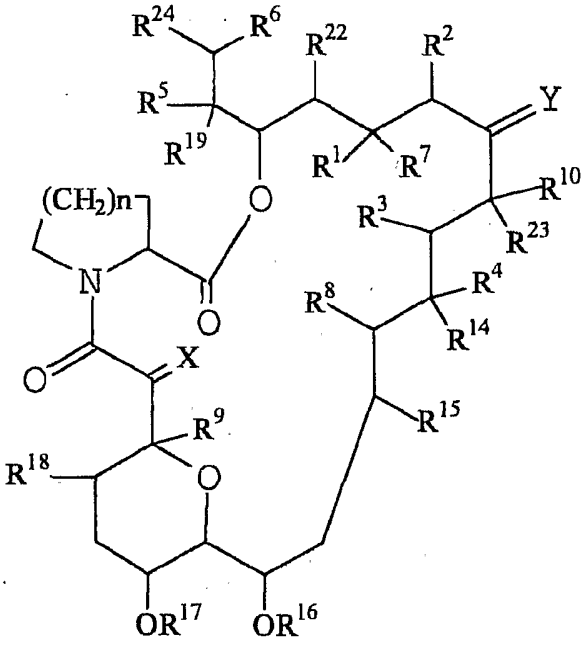
inflammatory effects by topically administering it in a low dose to the eye of a human suffering from ocular inflammatory diseases, that it is effective even for a subject in whom conventional anti-inflammatory agents show no improving effect, and that it is effective even for a subject for whom other anti-inflammatory agents cannot be used (e.g., steroid contraindication).

DISCLOSURE OF THE INVENTION

The present inventor has conducted intensive studies and has found that some kind of tricyclo compound continuously shows the superior ocular anti-inflammatory effects by topically administering it in a low dose to the eye of a human suffering from ocular inflammatory diseases. Further, the present inventor has found that the present agent for topical ophthalmic treatment is effective for the symptoms caused by ocular inflammatory diseases such as itching, flare, edema, ulcer, etc. Furthermore, the present inventor has found that the present agent for topical ophthalmic treatment is effective even for a subject in whom conventional anti-inflammatory agents (e.g., steroid and cyclosporins) show no improving effect, and that it is effective even for a subject for whom other anti-inflammatory agents cannot be used (e.g., steroid contraindication). In this way, the present invention has been completed.

Accordingly the present invention provides the following.

(1) A method for treating ocular inflammatory diseases, comprising topical administration of an agent for topical ophthalmic treatment comprising a tricyclo compound as shown by the following general formula (I) or its pharmaceutically acceptable salt to the eye of a human in need of a treatment of ocular inflammatory diseases in the concentration of 0.01% - 0.1%:



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond optionally between carbon atoms binding with the members of said pairs;

R^7 is hydrogen atom, hydroxy, protected hydroxy or alkyloxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkyl substituted by one or more hydroxy, alkenyl, alkenyl substituted by one or more hydroxy or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2,

in addition to the meaning noted above, Y, R^{10} and R^{23} may show, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, the heterocyclic group being optionally substituted by one or more group(s) selected from alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy, or its pharmaceutically acceptable salt.

(2) The method as described in (1) wherein the tricyclo compound is FK506.

(3) The method as described in (1) wherein the topical administration to the eye is one to four times a day.

(4) The method as described in (1) wherein the agent for topical ophthalmic treatment is an eye drop or eye ointment.

(5) The method as described in (1) wherein the ocular inflammatory diseases are selected from a group consisting of uveitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, corneal ulcer, conjunctival ulcer and symptoms caused by them; ocular inflammatory disease caused by ocular disorders; ocular inflammatory diseases after an ophthalmic operation; and ocular inflammatory diseases caused by a physical injury.

(6) The method as described in (1) wherein the treatment of the ocular inflammatory diseases is aimed at treating itching on the eye.

(7) The method as described in (1) wherein the treatment of the ocular inflammatory diseases is aimed at treating flare on the eye.

(8) The method as described in (1) wherein the treatment of the ocular inflammatory diseases is aimed at treating edema on the eye.

(9) The method as described in (1) wherein the treatment of

the ocular inflammatory diseases is aimed at treating ulcer on the eye.

(10) The method as described in (1) comprising the administration to the human in whom other ocular anti-inflammatory agents show no improving effect.

(11) The method as described in (10) wherein the other ocular anti-inflammatory agents are cyclosporins and/or steroid drugs.

(12) The method as described in (1) comprising the administration to the human for whom other ocular anti-inflammatory agents cannot be used.

(13) The method as described in (12) wherein the other ocular anti-inflammatory agents are steroid drugs.

(14) An agent for topical ophthalmic treatment of a human for ocular inflammatory diseases, comprising a tricyclo compound as shown by the general formula (I) or its pharmaceutically acceptable salt as an active ingredient in the concentration of 0.01% - 0.1%.

(15) The agent as described in (14) wherein the tricyclo compound is FK506.

(16) The agent as described in (14) wherein the topical ophthalmic treatment comprises administering the agent one to four times a day to the eye.

(17) The agent as described in (14), which is an eye drop or eye ointment.

(18) The agent as described in (14) wherein the ocular inflammatory diseases are selected from a group consisting of uveitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, corneal ulcer, conjunctival ulcer and symptoms caused by them; ocular inflammatory disease caused by ocular disorders; ocular inflammatory diseases after an ophthalmic operation; and ocular inflammatory diseases caused by a physical injury.

(19) The agent as described in (14) wherein the topical

ophthalmic treatment is aimed at treating itching on the eye.

(20) The agent as described in (14) wherein the topical ophthalmic treatment is aimed at treating flare on the eye.

(21) The agent as described in (14) wherein the topical ophthalmic treatment is aimed at treating edema on the eye.

(22) The agent as described in (14) wherein the topical ophthalmic treatment is aimed at treating ulcer on the eye.

(23) The agent as described in (14), which is used for administration to the human in whom other ocular anti-inflammatory agents show no improving effect.

(24) The agent as described in (23) wherein the ocular anti-inflammatory agents are cyclosporins and/or steroid drugs.

(25) The agent as described in (14), which is used for administration to the human for whom other ocular anti-inflammatory agents cannot be used.

(26) The agent as described in (25) wherein the ocular anti-inflammatory agents are cyclosporins and/or steroid drugs.

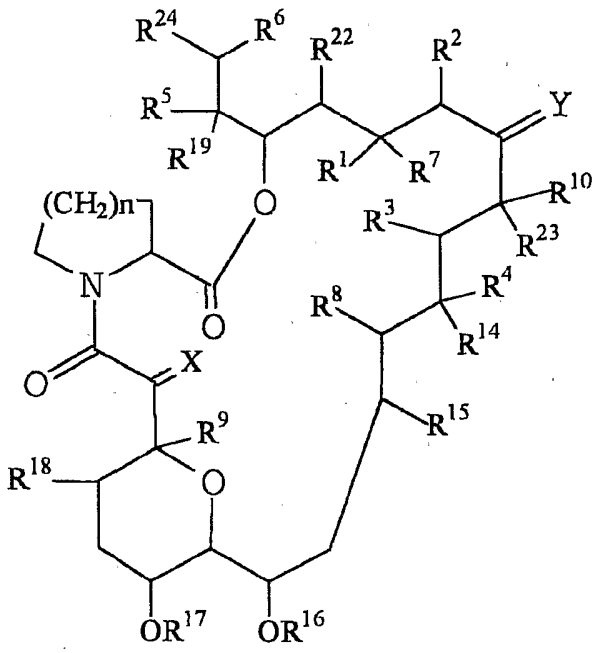
(27) A use of a tricyclo compound as shown by the general formula (I) or its pharmaceutically acceptable salt for manufacturing an agent for topical ophthalmic treatment of a human for treating ocular inflammatory diseases characterized in that said agent for treatment comprises said tricyclo compound in the concentration of 0.01% - 0.1%.

BRIEF DESCRIPTION OF DRAWINGS

Fig.1 is a graph showing the itching decreases by instillation of FK506 eye drop.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an agent for topical ophthalmic treatment of a human for ocular inflammatory diseases, comprising a tricyclo compound as shown by the following general formula (I) or its pharmaceutically acceptable salt as the active ingredient in the concentration of 0.01% - 0.1%:



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond optionally between carbon atoms binding with the members of said pairs;

R^7 is hydrogen atom, hydroxy, protected hydroxy or alkyloxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkyl substituted by one or more hydroxy, alkenyl, alkenyl substituted by one or more hydroxy or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2,

in addition to the meaning noted above, Y, R^{10} and R^{23} may show, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, the heterocyclic group being optionally substituted by one or more group(s) selected from alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy, or its pharmaceutically acceptable salt.

Further, the present invention relates to a method for treating ocular inflammatory diseases, comprising a topical administration of an agent for topical ophthalmic treatment comprising a tricyclo compound as shown by the above general formula (I) or its pharmaceutically acceptable salt to the eye of a human in need of the treatment of ocular inflammatory diseases in the concentration of 0.01% - 0.1%.

Further, the present invention relates to a use of a tricyclo compound as shown by the above general formula (I) or its pharmaceutically acceptable salt for manufacturing an agent for topical ophthalmic treatment of a human for treating ocular inflammatory diseases, wherein said agent comprises a tricyclo compound in the concentration of 0.01% - 0.1%.

In the general formula (I), preferable R^{24} is, for example, cyclo(C_5-C_7)alkyl optionally having suitable substituent, such as the following.

(a) 3,4-dioxocyclohexyl,

(b) 3-R^{20}-4-R^{21}-cyclohexyl,

wherein R^{20} is hydroxy, alkyloxy or $-OCH_2OCH_2CH_2OCH_3$, and R^{21} is hydroxy, -OCN, alkyloxy, heteroaryloxy having suitable substituent, $-OCH_2OCH_2CH_2OCH_3$, protected hydroxy, chloro, bromo, iodo, aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO-$ (wherein R^{25} is hydroxy optionally protected where desired or protected amino, and R^{26} is hydrogen atom or methyl,

or R^{20} and R^{21} in combination form an oxygen atom of epoxide ring); or

(c) cyclopentyl wherein cyclopentyl is substituted by methoxymethyl, optionally protected hydroxymethyl where desired, acyloxymethyl (wherein acyl moiety is optionally quaternized dimethylamino or optionally esterified carboxy), one or more optionally protected amino and/or hydroxy, or aminooxalyloxymethyl. Preferable examples include 2-formyl-cyclopentyl.

The definition of each symbol used in the formula (I), specific examples thereof and preferable embodiments thereof will be explained in detail in the following.

"Lower" means a group having 1 to 6 carbon atoms unless otherwise indicated.

Preferable examples of the alkyl moiety of "alkyl" and "alkyloxy" include linear or branched aliphatic hydrocarbon residue, such as lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl and the like).

Preferable examples of "alkenyl" include linear or branched aliphatic hydrocarbon residue having one double bond, such as lower alkenyl (e.g., vinyl, propenyl (e.g., allyl and the like), butenyl, methylpropenyl, pentenyl, hexenyl and the like).

Preferable examples of "aryl" include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl and the like.

Preferable examples of the protective group for "protected hydroxy" and "protected amino" include 1-(loweralkylthio)(lower)alkyl such as lower alkylthiomethyl (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl and the like), with more preference given to C_1 - C_4 alkylthiomethyl and most preference given to methylthiomethyl;

tri-substituted silyl such as tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyl dimethylsilyl, tri-tert-butylsilyl and the like), and lower alkyldiarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl and the like), with more preference given to tri(C_1 - C_4)alkylsilyl and C_1 - C_4 alkyldiphenylsilyl, and most prefererence given to tert-butyl-dimethylsilyl and tert-butyldiphenylsilyl;

acyl such as aliphatic acyl, aromatic acyl and aliphatic acyl substituted by aromatic group, which are derived from carboxylic acid, sulfonic acid and carbamic acid; and the like.

The aliphatic acyl is exemplified by lower alkanoyl optionally having one or more suitable substituent(s) (e.g., carboxy) such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl and the like;

cyclo(lower)alkyloxy(lower)alkanoyl optionally having one or more suitable substituent(s) (e.g., lower alkyl) such as cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, mentyloxyacetyl, mentyloxypropionyl, mentyloxybutyryl, mentyloxypentanoyl, mentyloxyhexanoyl and the like;

camphorsulfonyl;

lower alkylcarbamoyl having one or more suitable substituent(s) such as carboxy or protected carboxy and the like, such as carboxy(lower)alkylcarbamoyl (e.g., carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl) and tri(lower)alkylsilyl(lower)alkyloxycarbonyl(lower)alkyl-carbamoyl (e.g., trimethylsilylmethoxycarbonylethylcarbamoyl,

trimethylsilylethoxycarbonylpropylcarbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyl dimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl).

Aromatic acyl is exemplified by aroyl optionally having one or more suitable substituent(s) (e.g., nitro), such as benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl and the like; and arenesulfonyl optionally having one or more suitable substituent(s) (e.g., halogen), such as benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl and the like.

The aliphatic acyl substituted by aromatic group may be, for example, ar(lower)alkanoyl optionally having one or more suitable substituent(s) (e.g., lower alkyloxy or trihalo(lower)alkyl and the like), wherein specific examples are phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl and the like.

Of the above-mentioned acyl, more preferable acyl includes C_1 - C_4 alkanoyl optionally having carboxy, cyclo(C_5 - C_6)alkyloxy(C_1 - C_4)alkanoyl having two (C_1 - C_4)alkyl in the cycloalkyl moiety, camphorsulfonyl, carboxy (C_1 - C_4)alkylcarbamoyl, tri(C_1 - C_4)alkylsilyl(C_1 - C_4)alkyloxycarbonyl(C_1 - C_4)alkylcarbamoyl, benzoyl optionally having one or two nitro groups, and benzenesulfonyl having halogen, phenyl(C_1 - C_4)alkanoyl having C_1 - C_4 alkyloxy and trihalo(C_1 - C_4)alkyl. Of these, most preferred are acetyl, carboxypropionyl, mentyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl and the like.

Preferable examples of the "heterocyclic group

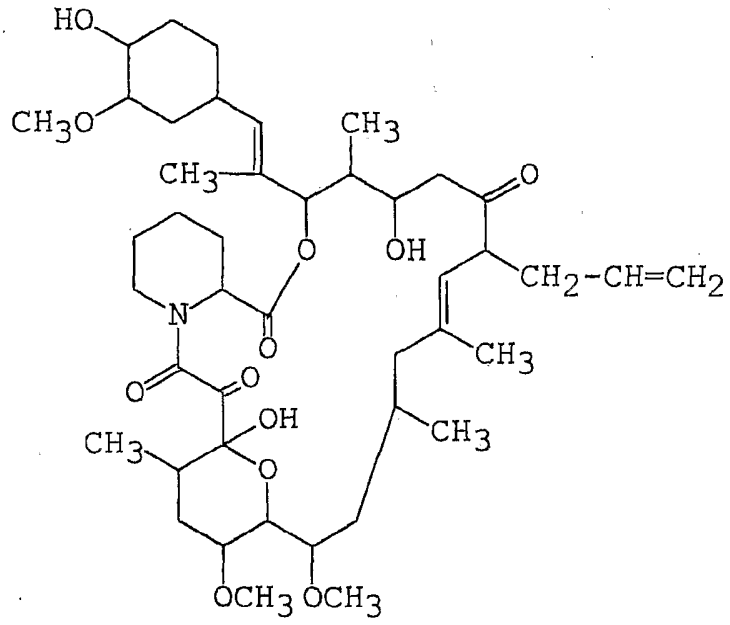
consisting of saturated or unsaturated 5 or 6-membered ring having nitrogen atom, sulfur atom and/or oxygen atom" are pyrrolyl, tetrahydrofuryl and the like.

The "heteroaryl optionally having a suitable substituent moiety" of the "heteroaryloxy optionally having a suitable substituent" is that exemplified for R^1 of the compound of the formula I of EP-A-532088, with preference given to 1-hydroxyethylindol-5-yl. The disclosure is incorporated hereinto by reference.

The tricyclo compound (I) used in the present invention is described in the publications EP-A-184162, EP-A-323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059 and the like. The disclosures of these publications are incorporated hereinto by reference.

In particular, the compounds called FR900506 (=FK506), FR900520 (Ascomycin), FR900523 and FR900525 are produced by the genus *Streptomyces*, such as *Streptomyces tsukubaensis*, No. 9993 (depository: National Institute of Advanced Industrial Science and Technology, International Patent Organism Depositary, Central 6, 1-1, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly: Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit : October 5, 1984, deposit number: FERM BP-927) or *Streptomyces hygroscopicus subsp. Yakushimaensis*, No. 7238 (depository: National Institute of Advanced Industrial Science and Technology, International Patent Organism Depositary, Central 6, 1-1, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly: Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit: January 12, 1985, deposit number: FERM BP-928 (EP-A-0184162)), and

the compound of the following formula, FK506 (general name : Tacrolimus) is a representative compound.



Chemical name: 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

Of the tricyclo compounds (I), more preferred is a compound wherein adjacent pairs of R^3 and R^4, and R^5 and R^6 each independently form another bond optionally between carbon atoms binding with the members of said pairs;

R^8 and R^{23} each independently show hydrogen atom;

R^9 is hydroxy;

R^{10} is methyl, ethyl, propyl or allyl;

X is (hydrogen atom, hydrogen atom) or oxo;

Y is oxo;

R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{22} each independently show methyl;

R^{24} is 3-R^{20}-4-R^{21}-cyclohexyl,

wherein R^{20} is hydroxy, alkyloxy or $-OCH_2OCH_2CH_2OCH_3$, and

R^{21} is hydroxy, -OCN, alkyloxy, heteroaryloxy having suitable substituent, $-OCH_2OCH_2CH_2OCH_3$, protected hydroxy, chloro, bromo, iodo, aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy or $R^{25}R^{26}CHCOO-$ (wherein R^{25} is optionally protected hydroxy as desired, or protected amino, and R^{26} is hydrogen atom or methyl), or R^{20} and R^{21} in combination form an oxygen atom of epoxide ring; and

n is 1 or 2.

Particularly preferable tricyclo compounds (I) include, besides FK506, Ascomycin derivatives such as halogenated derivative of 33-epi-chloro-33-desoxy Ascomycin described in Example 66a of EP-A-427680 and the like.

The tricyclo compound (I) and its pharmaceutically acceptable salt are nontoxic and pharmaceutically acceptable conventional salts, which are exemplified by salts with inorganic or organic base such as alkali metal salt (e.g., sodium salt, potassium salt and the like), alkaline earth metal salt (e.g., calcium salt, magnesium salt and the like), ammonium salt, and amine salt (e.g., triethylamine salt, N-benzyl-N-methylamine salt and the like).

In the tricyclo compound of the present invention, conformers or one or more pairs of stereoisomers such as optical isomers and geometric isomers due to asymmetric carbon atom and double bond may be present. Such conformers or isomers are also encompassed in the present invention. In addition, the tricyclo compound can form solvates, which case is also encompassed in the present invention. Examples of preferable solvates include hydrates and ethanolates.

In the present invention, the ocular inflammatory diseases include the ocular inflammatory diseases as expressed in connection with, or as a result of, uveitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, corneal ulcer,

conjunctival ulcer, etc.; the ocular inflammatory diseases caused by the ocular disorders such as dry eye, ocular infection, optic nerve disorder, etc.; the ocular inflammatory diseases caused by an ophthalmic operation; and the ocular inflammatory diseases caused by a physical injury to the eye. Also included in the inflammatory diseases in the present invention are the ocular inflammatory diseases of unknown cause, such as chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, etc.

The present invention also includes the treatment of symptoms caused by the ocular inflammatory diseases including itching, flare, edema, ulcer, etc.

The present agent for topical ophthalmic treatment shows the excellent ocular anti-inflammatory effects by topically administering it in a low dose to the eye of a human suffering from the ocular inflammatory diseases. Particularly, the present agent for topical ophthalmic treatment contains a tricyclo compound, as shown by the general formula (I), as the active ingredient in the concentration of 0.01% - 0.1%.

Further, the present agent is effective even for a subject in whom conventional anti-inflammatory agents (e.g., steroid, cyclosporins, etc.) show no improving effect.

Furthermore, unlike steroid treatment, the present agent shows the ocular anti-inflammatory effects without bringing the intraocular pressure increase, thus reducing the side effects caused by anti-inflammatory agents. Accordingly, the agent is effective even for a subject for whom other anti-inflammatory agents cannot be used (e.g., steroid contraindication).

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, etc.

The compound of general formula (I) used as the active ingredient of the present invention is administered topically

to the eye in the forms of eye drops, eye ointment, etc.

In the case of administering a formulation, the formulation manufactured according to ordinary means can be administered. The form includes all the formulations for topical administration to the eye used in the ophthalmic field such as eye drops, eye ointment, etc. The eye drops are prepared by dissolving the active ingredient in a sterile aqueous solution such as saline, buffering solution, etc., or by combining powder compositions to be dissolved before use. The eye ointment is prepared by mixing the active ingredient into a base. Such formulations can be prepared according to ordinary means.

Eye drops such as the ones as described in EP-A-0406791 are preferred. If desired, additives ordinarily used in the eye drops can be added. Such additives include isotonizing agents (e.g., sodium chloride, etc.), buffer agent (e.g., boric acid, sodium monohydrogen phosphate, sodium dihydrogen phosphate, etc.), preservatives (e.g., 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.; e.g., sodium polyacrylate, carboxyvinyl polymer, crosslinked polyacrylate, etc.). The disclosure of the above publication is incorporated herein by reference.

Mixing the active ingredient into the base ordinarily used for the eye ointment and formulating it according to ordinary methods can sterilely prepare the eye ointment. Examples of the base for the eye ointment include petrolatum, selen 50, Plastibase, macrogol, etc., but not limited thereto. Further, in order to increase the hydrophilicity, a surface-active agent can be added. Regarding the eye ointment, the above-mentioned additives such as the preservatives, etc. can

be combined, if necessary.

The present agent for topical ophthalmic treatment can be formulated as a sterile unit dose type containing no preservatives.

The amount of administration and the number of administration of the active ingredient used in the present invention vary according to the sex, age and weight of a human, symptoms to be treated, effects of treatment to be desired, administration methods, period of treatment, etc. Ordinarily, in the case of using the formulation of eye drops for an adult, the formulation containing 0.01% - 0.1% of the active ingredient can be instilled several times a day per eye, preferably one to six times, more preferably one to four times, several drops per time, preferably one to four drops. In the case of using the formulation of an eye ointment, the formulation containing 0.01% - 0.1% of the active ingredient can be applied several times a day, preferably one to six times, more preferably one to four times. The present agent for topical ophthalmic treatment is very useful especially for the reason that it shows sufficient effects by one to four times of ocular instillation or application.

In the present invention, the formulation can include one active ingredient only or a combination of two or more active ingredients. In a combination of plural active ingredients, their respective contents can be suitably increased or decreased in consideration of their effects, safety, etc.

Further, the present formulation can suitably include other pharmacologically active ingredients as far as they do not contradict the object of the present invention.

The further details of the present invention will follow with reference to the examples, which, however, are not intended to limit the present invention.

Example 1

Method 1

In a total of four groups each having 30 persons, FK506 eye drops (0.01%, 0.06% and 0.1%) were instilled in the respective experimental groups for once, and placebo was instilled in the control group for once. Three hours after the ocular instillation, various foreign bodies (cat hair, cat dander, and pollens of a tree, ragweed or grass) were ocularly instilled in both the experimental groups and the control group, thus causing inflammations. Five minutes later, itching on the eye was graded according to five-rank scores (0 - 4). The decreases from the score (baseline) in instilling only foreign bodies were calculated. These results are shown in Fig. 1.

As shown in Fig. 1, the decreases of itching were greater in the experimental groups instilled with 0.01%, 0.06% and 0.1% of FK506 eye drops than in the control groups instilled with placebo. These results confirmed that the instillation of FK506 eye drops in a low dose of 0.01% - 0.1% shows the ocular anti-inflammatory effects.

Example 2

FK506 was ocularly instilled in the subjects once a day for one week, and the same amount of placebo was ocularly instilled in the control group. At 16 hours after the final ocular instillation, various foreign bodies (cat hair, cat dander, and pollens of a tree, ragweed or grass) were ocularly instilled in both the experimental groups and the control group, thus causing the inflammations. Ten minutes later, conjunctival hyperemia and chemosis were graded according to five-rank scores (0 - 4). The changes from the score (baseline) in instilling only foreign bodies were calculated. These results are shown in Tables 1 and 2.

Table 1 conjunctival hyperemia

Groups	Number of subjects	Changes of conjunctival hyperemia scores from the baseline, mean±S.E.
Control (placebo)	50	-0.17±0.07
0.1% FK506 eye drops	53	-0.51±0.07**

** p<0.01

Table 2 chemosis

Groups	Number of subjects	Changes of chemosis scores from the baseline, mean±S.E.
Control (placebo)	50	0.12±0.07
0.1% FK506 eye drops	53	-0.30±0.07**

** p<0.01

As shown in Tables 1 and 2, compared to the control group instilled with placebo, the instillation of 0.1% FK506 eye drops clearly decreased the scores of both conjunctival hyperemia and chemosis. These results confirmed that the instillation of FK506 eye drops in a low dose shows the ocular anti-inflammatory effects (antiedemic effect and anti-flare effect) for at least 16 hours.

The following are the examples of the instillation of FK506 eye drops in a low dose in patients having various ocular inflammatory diseases.

Example 3

A patient suffering from progressive corneal ulcer caused by pemphigoid was instilled with 0.06% FK506 eye drops three times a day. As a result, significant improving effects were observed and such effects were maintained at 43 weeks later.

Example 4

A patient suffering from progressive Mooren's ulcer was instilled with 0.06% FK506 eye drops three times a day. As a result, significant improving effects were observed and such effects were maintained at 41 weeks later.

Example 5

A patient suffering from chronic nummular keratitis was instilled with 0.06% FK506 eye drops three times a day. As a result, significant improving effects were observed within two weeks and such effects were maintained at 43 weeks later.

Example 6

A patient suffering from Thygeson keratitis, for whom no conventional therapy is available (the topical administration of corticosteroid shows no improving effect, or corticosteroid cannot be used for the topical or systemic administration) and the ocular instillation of cyclosporin A shows no improving effect, was instilled with 0.06% FK506 eye drops three times a day. As a result, significant improving effects were observed within three weeks and such effects were maintained at 41 weeks later.

Example 7

A patient performed a penetrating keratoplasty and having a history of steroid glaucoma and also having a history of chronic rejection despite the ocular instillation of cyclosporin A was instilled with 0.06% FK506 eye drops three times a day. As a result, the progression of inflammations caused by injury was arrested and such effects were maintained at 34 weeks later. Besides, no intraocular pressure increase was observed.

Example 8

A patient suffering from blepharokeratoconjunctivitis, for whom no conventional therapy is available (the topical administration of corticosteroid shows no improving effect, or corticosteroid cannot be used for the topical or systemic

administration) and the ocular instillation of cyclosporin A shows no improving effect, was instilled with 0.06% FK506 eye drops three times a day. As a result, significant improving effects were observed within two weeks and such effects were maintained at 18 weeks later.

Example 9

A patient performed a penetrating keratoplasty due to keratoconus and having a history of refractoriness to the topical cyclosporins A, for whom no conventional therapy is available (the topical administration of corticosteroid shows no improving effect, or corticosteroid cannot be used for the topical or systemic administration), was instilled with 0.06% FK506 eye drops three times a day. As a result, significant improving effects were observed and such effects were maintained at 25 weeks later.

Industrial applicability

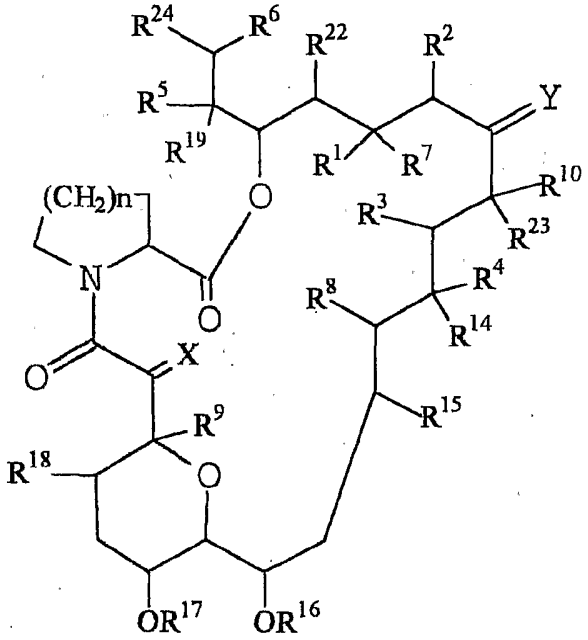
As shown in the foregoing examples 3 - 9, it was confirmed that the topical instillation of FK506 eye drops in a low dose in the eye of a human having various ocular inflammatory diseases shows the anti-inflammatory effects.

It was further confirmed that the present agent for topical ophthalmic treatment is effective even for a subject in whom conventional anti-inflammatory agents show no improving effect (e.g., steroid, cyclosporins, etc.), and that the present agent shows the anti-inflammatory effects in a subject for whom other anti-inflammatory agents cannot be used (e.g., steroid contraindication).

This application is based on application No. 60/283,169 filed in United States of America, the content of which is incorporated hereinto by reference.

CLAIMS

1. A method for treating ocular inflammatory diseases, comprising topical administration of an agent for topical ophthalmic treatment comprising a tricyclo compound as shown by the following general formula (I) or its pharmaceutically acceptable salt to the eye of a human in need of a treatment of ocular inflammatory diseases in the concentration of 0.01% - 0.1%:



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond optionally between carbon atoms binding with the members of said pairs;

R^7 is hydrogen atom, hydroxy, protected hydroxy or alkyloxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkyl substituted by one or more hydroxy, alkenyl, alkenyl substituted by one or more hydroxy or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom,

hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2,

in addition to the meaning noted above, Y, R^{10} and R^{23} may show, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, the heterocyclic group being optionally substituted by one or more group(s) selected from alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy, or its pharmaceutically acceptable salt.

2. The method as described in Claim 1 wherein the tricyclo compound is FK506.

3. The method as described in Claim 1 wherein the topical administration to the eye is one to four times a day.

4. The method as described in Claim 1 wherein the agent for topical ophthalmic treatment is an eye drop or eye ointment.

5. The method as described in Claim 1 wherein the ocular inflammatory diseases are selected from a group consisting of uveitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, corneal ulcer, conjunctival ulcer and symptoms

caused by them; ocular inflammatory diseases caused by ocular disorders; ocular inflammatory diseases after an ophthalmic operation; and ocular inflammatory diseases caused by a physical injury.

6. The method as described in Claim 1 wherein the treatment of the ocular inflammatory diseases is aimed at treating itching on the eye.

7. The method as described in Claim 1 wherein the treatment of the ocular inflammatory diseases is aimed at treating flare on the eye.

8. The method as described in Claim 1 wherein the treatment of the ocular inflammatory diseases is aimed at treating edema on the eye.

9. The method as described in Claim 1 wherein the treatment of the ocular inflammatory diseases is aimed at treating ulcer on the eye.

10. The method as described in Claim 1 comprising the administration to the human in whom other ocular anti-inflammatory agents show no improving effect.

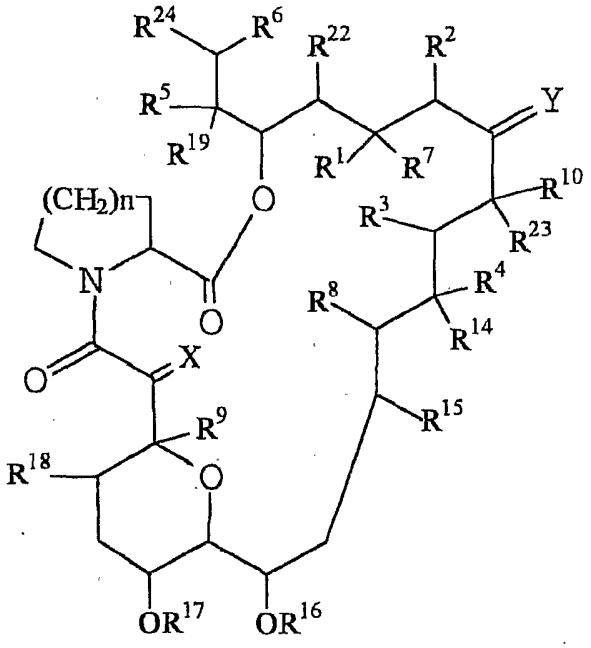
11. The method as described in Claim 10 wherein the other ocular anti-inflammatory agents are cyclosporins and/or steroid drugs.

12. The method as described in Claim 1 comprising the administration to the human for whom other ocular anti-inflammatory agents cannot be used.

13. The method as described in Claim 12 wherein the other

ocular anti-inflammatory agents are steroid drugs.

14. An agent for topical ophthalmic treatment of a human for ocular inflammatory diseases, comprising a tricyclo compound as shown by the following general formula (I) or its pharmaceutically acceptable salt as an active ingredient in the concentration of 0.01% - 0.1%:



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond optionally between carbon atoms binding with the members of said pairs;

R^7 is hydrogen atom, hydroxy, protected hydroxy or alkyloxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkyl substituted by one or more hydroxy, alkenyl, alkenyl substituted by one or more hydroxy or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula N-$NR^{11}R^{12}$ or N-OR^{13};

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2,

in addition to the meaning noted above, Y, R^{10} and R^{23} may show, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, the heterocyclic group being optionally substituted by one or more group(s) selected from alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy, or its pharmaceutically acceptable salt.

15. The agent as described in Claim 14 wherein the tricyclo compound is FK506.

16. The agent as described in Claim 14 wherein the topical ophthalmic treatment comprises administering the agent one to four times a day to the eye.

17. The agent as described in Claim 14, which is an eye drop or eye ointment.

18. The agent as described in Claim 14 wherein the ocular inflammatory diseases are selected from a group consisting of uveitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, corneal ulcer, conjunctival ulcer and symptoms caused by them; ocular inflammatory diseases caused by ocular

disorders; ocular inflammatory diseases after an ophthalmic operation; and ocular inflammatory diseases caused by a physical injury.

19. The agent as described in Claim 14 wherein the topical ophthalmic treatment is aimed at treating itching on the eye.

20. The agent as described in Claim 14 wherein the topical ophthalmic treatment is aimed at treating flare on the eye.

21. The agent as described in Claim 14 wherein the topical ophthalmic treatment is aimed at treating edema on the eye.

22. The agent as described in Claim 14 wherein the topical ophthalmic treatment is aimed at treating ulcer on the eye.

23. The agent as described in Claim 14, which is used for administration to the human in whom other ocular anti-inflammatory agents show no improving effect.

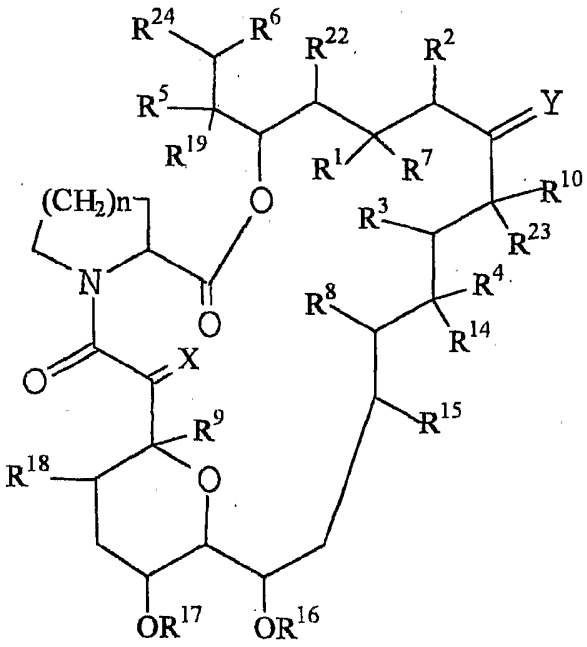
24. The agent as described in Claim 23 wherein the ocular anti-inflammatory agents are cyclosporins and/or steroid drugs.

25. The agent as described in Claim 14, which is used for administration to the human for whom other ocular anti-inflammatory agents cannot be used.

26. The agent as described in Claim 25 wherein the ocular anti-inflammatory agents are cyclosporins and/or steroid drugs.

27. A use of a tricyclo compound as shown by the following general formula (I) or its pharmaceutically acceptable salt for manufacturing an agent for topical ophthalmic treatment of a human for treating ocular inflammatory diseases

characterized in that said agent for treatment comprises said tricyclo compound in the concentration of 0.01% - 0.1%:



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond optionally between carbon atoms binding with the members of said pairs;

R^7 is hydrogen atom, hydroxy, protected hydroxy or alkyloxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkyl substituted by one or more hydroxy, alkenyl, alkenyl substituted by one or more hydroxy or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each

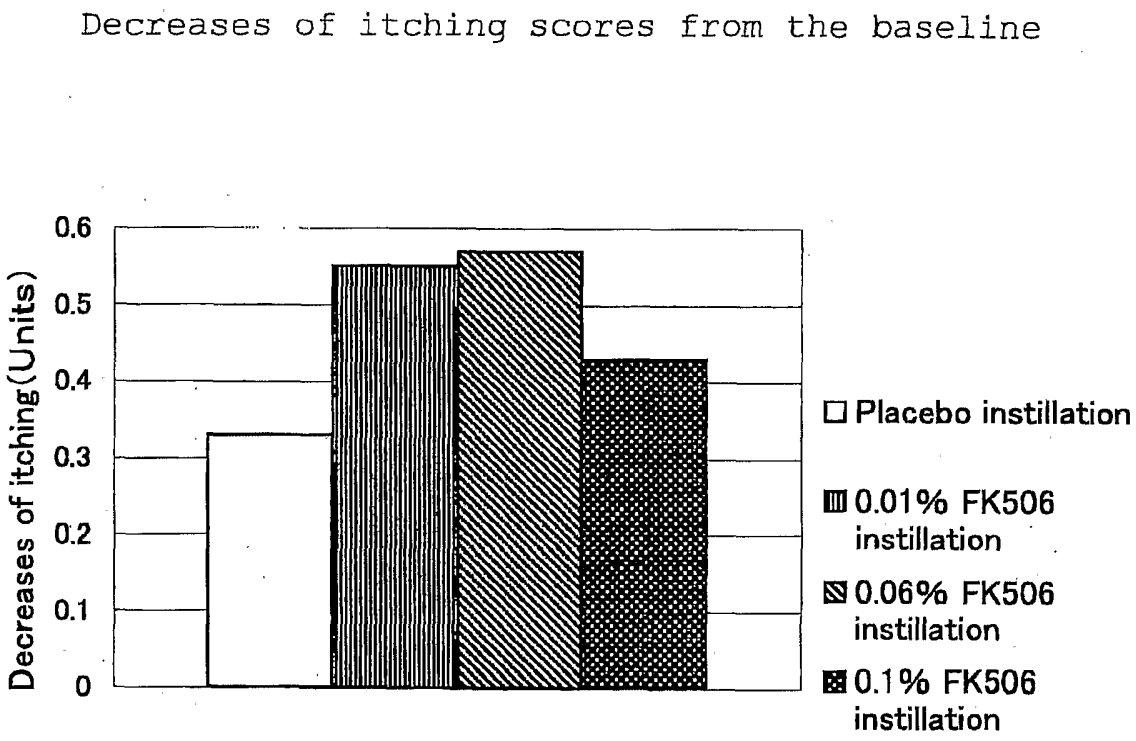
independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2,

in addition to the meaning noted above, Y, R^{10} and R^{23} may show, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, the heterocyclic group being optionally substituted by one or more group(s) selected from alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy, or its pharmaceutically acceptable salt.

Fig. 1


Decreases of itching scores from the baseline
Decreases of itching(Units)
0.6
0.5
0.4
0.3
0.2
0.1
0
Placebo instillation
0.01% FK506 instillation
0.06% FK506 instillation
0.1% FK506 instillation

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/03664

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61P27/02 A61P29/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 406 791 A (FUJISAWA PHARMACEUTICAL CO) 9 January 1991 (1991-01-09) page 4, line 3 - line 51 page 6, line 14 - line 16 page 7, line 45 - line 59 ---	1-27
X	EP 0 484 936 A (FUJISAWA PHARMACEUTICAL CO) 13 May 1992 (1992-05-13) page 6, line 28 - line 56 page 11, line 16 - line 35 examples --- -/--	1-27

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

"E" earlier document 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	Date of mailing of the international search report
8 August 2002	02/09/2002

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

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

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 19278 A (KURUME UNIVERSITY) 12 November 1992 (1992-11-12) cited in the application page 2 page 8 page 10, line 6 - line 8 example 2	1-27
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X	US 5 925 649 A (NAEF RETO ET AL) 20 July 1999 (1999-07-20) column 9, line 38 - line 44 column 11, line 57 - line 67	1,3-14, 16-27
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/03664

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MOCHIZUKI M ET AL: "USE OF IMMUNOSUPPRESSIVE AGENTS IN OCULAR DISEASES" PROGRESS IN RETINAL AND EYE RESEARCH, OXFORD, GB, vol. 13, no. 2, 1994, pages 479-506, XP000952456 ISSN: 1350-9462 page 500 -page 501 ---	1-27
A	US 4 894 366 A (GOTO TOSHIO ET AL) 16 January 1990 (1990-01-16) cited in the application the whole document -----	1-27

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/03664

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

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1 to 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 02/03664

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