Description

This invention relates to the use of angiostatic steroids in the manufacture of a medicament for treating ocular hypertension, associated with primary open angle glaucoma.

Steroids functioning to inhibit angiogenesis in the presence of heparin or specific heparin fragments are disclosed in Crum, et al., A New Class of Steroids Inhibits Angiogenesis in the Presence of Heparin or a Heparin Fragment, Science, Vol.230, pp.1375-1378 (December 20, 1985). The authors refer to such steroids as "angiostatic" steroids. Included within the new class of steroids found to be angiostatic are the dihydro and tetrahydro metabolites of cortisol and cortexolone. In a follow-up study directed to testing a hypothesis as to the mechanism by which the steroids inhibit angiogenesis, it was shown that heparin/angiostatic steroid compositions cause dissolution of the basement membrane scaffolding to which anchorage dependent endothelia are attached resulting in capillary involution; see, Ingber, et al., A Possible Mechanism for Inhibition of Angiogenesis by Angiostatic Steroids: Induction of Capillary Basement Membrane Dissolution, Endocrinology 119, pp.1768-1775 (1986).

A group of tetrahydro steroids useful in inhibiting angiogenesis is disclosed in International Patent Application No. PCT/US86/02189, Aristoff, et al., (The UpJohn Company). The compounds are disclosed for use in treating head trauma, spinal trauma, septic or traumatic shock, stroke and hemorrhage shock. In addition, the patent application discusses the utility of these compounds in embryo implantation and in the treatment of cancer, arthritis and arteriosclerosis. The compounds are not disclosed for ophthalmic use.

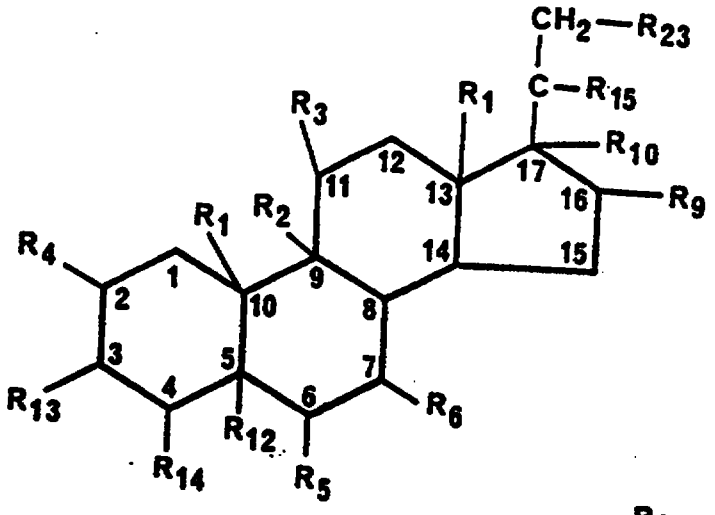
Tetrahydrocortisol (THF) has been disclosed for its use in lowering the intraocular pressure (IOP) of rabbits made hypertensive with dexamethasone alone, or with dexamethasone/5-beta-dihydrocortisol; see Southren, et al., Intraocular Hypotensive Effect of a Topically Applied Cortisol Metabolite: 3-alpha, 5-beta-tetrahydrocortisol, Investigative Ophthalmology and Visual Science, Vol.28 (May, 1987). The authors suggest THF may be useful as an antiglaucoma agent. In European Patent Application, Publication Number 250,088, Southren, et al., pharmaceutical compositions containing THF and a method for using these compositions to control intraocular pressure are disclosed. THF has been disclosed as an angiostatic steroid in Folkman, et al., Angiostatic Steroids, Ann. Surg., Vol.206, No.3 (1987) wherein it is suggested angiostatic steroids may have potential use for diseases dominated by abnormal neovascularization, including diabetic retinopathy, neovascular glaucoma and retrolental fibroplasia. U.S. Patent No. 4,771,042 discloses the use of non-glucocorticoid steroids and heparin or heparin fragments to inhibit angiogenisis.

This invention is directed to use of an angiostatic steroid for the manufacture of a medicament for controling ocular hypertension. The compositions are particulary useful in the treatment of primary open angle glaucoma.

The development of blood vessels for the purpose of sustaining viable tissue is known as angiogenesis. Agents which inhibit angiogenesis are known by a variety of terms such as angiostatic, angiolytic or angiotropic agents. For purposes of this specification, the term "angiostatic agent" means compounds which can be used to inhibit angiogenesis.

The angiostatic agents of the present invention are steroids or steroid metabolites. For purposes herein, the term "angiostatic steroids" means steroids and steroid metabolites which inhibit angiogenesis. The present invention is based on the finding that angiostatic steroids can be used for the control of ocular hypertension. In particular, the agents can be used for the treatment of primary open angle glaucoma.

Agents which can be used according to the present invention comprise angiostatic steroids. Angiostatic steroids which can be used will typically comprise the angiostatic steroids disclosed in PCT/US86/02189 which have the following formula:



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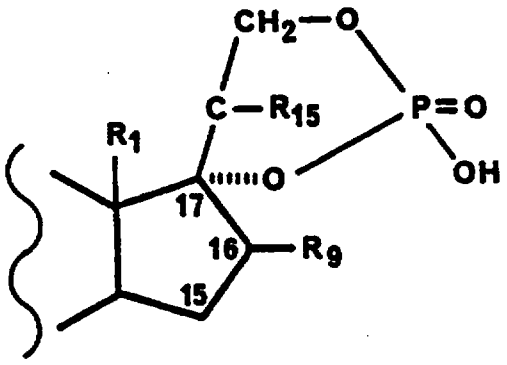


[II]

wherein R_1 is β-CH_3 or β-CH_2H_5;
R_2 is H or -Cl;
R_3 is H, =O, -OH, -O-alkyl(C_1-C_{12}), -OC (=O)alkyl(C_1-C_{12}), -OC(=O)ARYL, -OC(=O)N(R)$_2$ or α-OC(=O)-OR_7, wherein ARYL is furyl, thienyl, pyrrolyl, or pyridyl and each of said moieties is optionally substituted with one or two (C_1-C_4)alkyl groups, or ARYL is -$(CH_2)_f$-phenyl wherein f is 0 to 2 and the phenyl ring is optionally substituted with 1 to 3 groups selected from chlorine, fluorine, bromine, alkyl(C_1-C_3), alkoxy(C_1-C_3), thioalkoxy-(C_1-C_3), Cl_3C-, F_3C-, -NH_2 and -$NHCOCH_3$ and R is hydrogen, alkyl (C_1-C_4),or phenyl and each R can be the same or different, and R_7 is ARYL as herein defined, or alkyl(C_1-C_{12});
or
wherein R_2 and R_3 taken together are oxygen (-0-) bridging positions C-9 and C-11; or
wherein R_2 and R_3 taken together form a double bond between positions C-9 and C-11;
or R_2 is α-F and R_3 is β-OH;
or R_2 is α-Cl and R_3 is β-Cl;
and R_4 is H, CH_3, Cl or F;
R_5 is H, OH, F, Cl, Br, CH_3, phenyl, vinyl or allyl;
R_6 is H or CH_3;
R_9 is H, OH, CH_3, F or $=CH_2$;
R_{10} is H, OH, CH_3 or R_{10} forms a second bond between positions C-16 and C-17;
R_{12} is -H or forms a double bond with R_{14};
R_{13} is H, -OH, =0, -0-P(0)$(OH)_2$, or -0-C(=0)-$(CH_2)_t$COOH where t is an integer from 2 to 6;
R_{14} is H or forms a double bond with R_{12};
R_{15} is =0 or -OH;
and R_{23} with R_{10} forms a cyclic phosphate as depicted by Formula II;
wherein R_9 and R_{15} have the meaning defined above;
or wherein R_{23} is -OH, O-C(=0)-R_{11}, -OP(0)-$(OH)_2$, or -O-C(=0)-$(CH_2)_t$COOH wherein t is an integer from 2 to 6; and R_{11} is -Y-$(CH_2)_n$-X-$(CH_2)_m$-SO_3H, -Y'-$(CH_2)_p$-X'-$(CH_2)_q$-$NR_{16}R_{17}$ or -$Z(CH_2)_r$Q, wherein Y is a bond or -0-; Y' is a bond, -0-, or -S-; each of X and X' is a bond,-CON(R_{18})-, -N(R_{18})CO-, -0-, -S-, -S(0)-, or -S-(0_2)-; R_{18} is hydrogen or alkyl (C_1-C_4); each of R_{16} and R_{17} is a lower alkyl group of from 1 to 4 carbon atoms optionally substituted with one hydroxyl or R_{16} and R_{17} taken together with the nitrogen atom to which each is attached forms a monocyclic heterocyclic selected from pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or N(lower)alkyl-piperazino wherein alkyl has from 1 to 4 carbon atoms; n is an integer of from 4 to 9; m is an integer of from 1 to 5; p is an integer of from 2 to 9; q is an integer of from 1 to 5;

Z is a bond or -0-; r is an integer of from 2 to 9; and Q is one of the following:

(1) -R_{19}-CH_2COOH wherein R_{19} is -S-, -S(O)-, -$S(O)_2$-, -$SO_2N(R_{20})$-, or $N(R_{20})SO_2$-; and R_{20} is hydrogen or lower alkyl-(C_1-C_4); with the proviso that the total number of carbon atoms in R_{20} and $(CH_2)_r$ is not greater than 10; or

(2) -CO-COOH; or

(3) $CON(R_{21})CH(R_{22})COOH$ wherein R_{21} is H and R_{22} is H, CH_3, -CH_2COOH, -CH_2CH_2COOH, -CH_2OH, -CH_2SH, -$CH_2CH_2SCH_3$, or -CH_2Ph-OH wherein Ph-OH is p-hydroxyphenyl;

or R_{21} is CH_3 and R_{22} is H;

or R_{21} and R_{22} taken together are -$CH_2CH_2CH_2$-;

or -$N(R_{21})CH(R_{22})COOH$ taken together is -$NHCH_2CONHCH_2COOH$; and pharmaceutically acceptable salts thereof;

with the proviso that except for the compound wherein R_1 is -CH_3, R_2 and R_3 taken together form a double bond between positions 9 and 11, R_4 and R_6 are hydrogen, R_{12} and R_{14} taken together form a double bond between positions 4 and 5, R_5 is α -F, R_9 is β -CH_3, R_{10} is α -OH, R_{13} and R_{15} are =0 and R_{23} is -OP(O)-$(OH)_2$, R_{13} is =0 only when R_{23} with R_{10} forms the above described cyclic phosphate.

Excepted from the compounds of Formula I is the compound 3,11β, 17α, 21-tetrahydroxy-5 -pregnane-20-one (the 3-alpha, 5-beta; 3-alpha, 5-alpha; 3-beta, 5-alpha; and 3-beta, 5-beta isomers of tetrahydrocortisol) wherein:

R_{15} is =0; R_{10} is α OH;

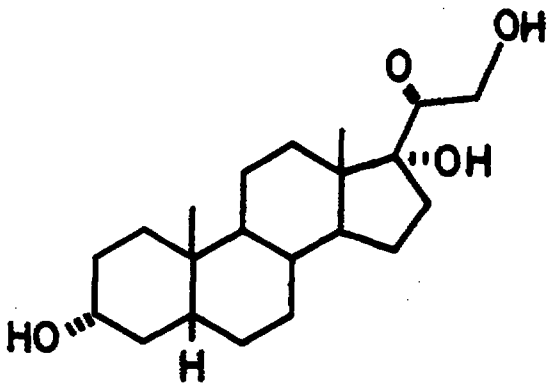
R_1 is CH_3; R_3 is β OH; R_2 is H;

R_4 is H; R_{13} is α or β OH; R_{14} is H;

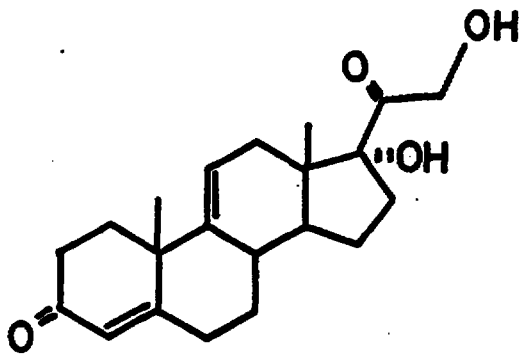
R_{12} is α or β H; R_5 is H; R_6 is H; R_9 is H and R_{23} is OH.

Unless specified otherwise, all substituent groups attached to the cyclopenta phenanthrene moiety of Formula I may be in either the alpha or beta position. Additionally, the above structures include all pharmaceutically acceptable salts of the angiostatic steroids.

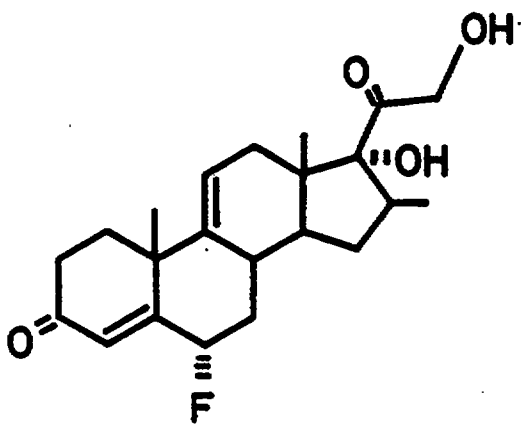
Preferred angiostatic steroids are:



Tetrahydrocortexolone (THS) and its pharmaceutically acceptable salts;



4,9(11)-pregnadien 17α ,21-diol-3,20-dione and its pharmaceutically acceptable salts;



6α -fluoro-17α ,21-dihydroxy-16β -methyl-pregna-4,9(11)-diene-3,20-dione and its pharmaceutically acceptable salts.

Without intending to be bound by any theory, it is believed that the angiostatic steroids of the type described above act to control intraocular pressure by inhibiting the accumulation or stimulating the dissolution of amorphous extracellular material in the trabecular meshwork of the eye. The presence of this amorphous extracellular material alters the integrity of the healthy trabecular meshwork and is a symptom associated with primary open angle glaucoma (POAG). It is not well understood why this amorphous extracellular material builds up in the trabecular meshwork of persons suffering from POAG. However, it has been found that the amorphous extracellular material is generally composed of glycosaminoglycans (GAGs) and basement membrane material; see, Ophthalmology, Vol.90, No.7 (July 1983); (Mayo Clin. Proc, Vol.61, pp.59-67 (Jan.1986); and Pediat. Neurosci. Vol.12, pp.240-251 (1985-86). When these materials build up in the trabecular meshwork, the aqueous humor, normally present in the anterior chamber of the eye, cannot leave this chamber through its normal route (the trabecular meshwork) at its normal rate. Therefore, a normal volume of aqueous humor is produced by the ciliary processes of the eye and introduced into the anterior chamber, but its exit through the trabecular meshwork is abnormally slow. This results in a buildup of pressure in the eye, ocular hypertension, which can translate into pressure on the optic nerve. The ocular hypertension so generated can lead to blindness due to damage to the optic nerve.

Many methods for treating primary open angle glaucoma and ocular hypertension concentrate on blocking production of aqueous humor by the eye. However, aqueous humor is the fundamental source of nourishment for the tissues of the eye, particularly the cornea and lens which are not sustained by blood supply. Therefore, it is not desirable to deprive these tissues of the necessary irrigation and nutrition provided by the aqueous humor. It is desirable to strive for normal exit of the aqueous humor by maintaining the normal integrity of the trabecular meshwork. This is accomplished according to the present invention by the administration of angiostatic steroids.

It is believed that the angiostatic steroids disclosed herein function in the trabecular meshwork in a similar manner as shown by Ingber, et al., wherein it was shown that angiostatic steroids caused dissolution of the basement membrane scaffolding using a chick embryo neovascularization model; Endocrinology, 119, pp.1768-1775 (1986). It is believed that the angiostatic steroids of the present invention prevent the accumulation, or promote the dissolution of, amorphous extracellular materials in the trabecular meshwork by inhibiting the formation of basement membrane materials and glycosaminoglycans. Thus, by preventing the development of these materials or promoting their dissolution, the normal integrity of the trabecular meshwork is retained and aqueous humor may flow through the trabecular meshwork at normal rates. As a result, the intraocular pressure of the eye is controlled.

The angiostatic steroids of the present invention may be incorporated in various formulations for delivery to the eye. For example, topical formulations can be used and can include ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, buffers, sodium chloride and water to form aqueous sterile ophthalmic solutions and suspensions. In order to prepare sterile ophthalmic ointment formulations, an angiostatic steroid is combined with a preservative in an appropriate vehicle, such as mineral oil, liquid lanolin or white petrolatum. Sterile ophthalmic gel formulations comprising the angiostatic steroids of the present invention can be prepared by suspending an angiostatic steroid in a hydrophilic base

prepared from a combination of, for example, Carbopol-940 (a carboxyvinyl polymer available from the B.F. Goodrich Company) according to published formulations for analogous ophthalmic preparations. Preservatives and tonicity agents may also be incorporated in such gel formulations.

The specific type of formulations selected will depend on various factors, such as the angiostatic steroid or its salt being used, and the dosage frequency. Topical ophthalmic aqueous solutions, suspensions, ointments and gels are the preferred dosage forms. The angiostatic steroid will normally be contained in these formulations in an amount of from about 0.005 to about 2.0 weight percent (wt.%). Preferable concentrations range from about 0.05 to about 1.0 wt.%. Thus, for topical administration, these formulations are delivered to the surface of the eye one to four times per day, depending upon the routine discretion of the skilled clinician.

Example 1

The formulation set out below illustrates a topical ophthalmic composition which can be used according to the present invention.

Component	Wt.%
THS	0.005 to 2.0
Tyloxapol	0.01 to 0.05
Benzalkonium Chloride	0.01
Sodium Chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 ml

Example 2

It has been shown that young rabbits can be made ocular hypertensive by topical administration of a potent glucocorticoid; see, Experimental Eye Research, 27:567 (1978); Investigative Ophthalmology and Visual Science, 26:1093 (1985); or by a combination of glucocorticoid with the cortisol metabolite dihydrocortisol; see, Investigative Ophthalmology and Visual Science, Vol.26 (March, 1985). Ocular injections of glucocorticoids have also been shown to induce ocular hypertension in rabbits; see, J. Ocular Pharmacology, 3:185-189 (1987). This ocular injection rabbit model was used to test the effect of the angiostatic steroid, tetrahydrocortexolone (THS), on ocular hypertension. New Zealand red rabbits weighing approximately 1 kg. were given weekly Subtenon's injections of dexamethasone-acetate and 5β-dihydrocortisol in two quadrants of each eye (approximately 1 mg dexamethasone-acetate and 5β-dihydrocortisol/kg body wt./week). Intraocular pressures were taken weekly with an Alcon application pneumotonometer. Each group contained 4-5 animals. After two weeks of steroid treatment, IOP was elevated by 5mm Hg. Half the animals then received Subtenon's injections of THS (approximately 3 mg/kg body wt./week) in addition to the 1 mg/kg body wt./week of dexamethasone/5β-dihydrocortisol. The other half continued to receive dexamethasone/5β-dihydrocortisol injections of approximately 1 mg/kg body wt./week.

Figure I illustrates the IOP lowering effect of the angiostatic steroid, THS, in the rabbits with glucocorticoid induced ocular hypertension described above. The plots show average IOP data of the animals through a four week period. After four weeks, the group which was given THS in addition to dexamethasone/5β-dihydrocortisol (-□-□-) exhibited an approximately 4mm Hg drop in IOP compared to the control group (-0-0-) which received dexamethasone acetate/5β-dihydrocortisol. These results indicate that the angiostatic steroid, THS, is effective in lowering intraocular pressure in rabbits with steroid induced ocular hypertension.

Claims

1. Use of an angiostatic steroid for the manufacture of a medicament for controlling ocular hypertension associated with primary open angle glaucoma wherein:
   the angiostatic steroid has the formula:

prepared from a combination of, for example, Carbopol-940 (a carboxyvinyl polymer available from the B.F. Goodrich Company) according to published formulations for analogous ophthalmic preparations. Preservatives and tonicity agents may also be incorporated in such gel formulations.

The specific type of formulations selected will depend on various factors, such as the angiostatic steroid or its salt being used, and the dosage frequency. Topical ophthalmic aqueous solutions, suspensions, ointments and gels are the preferred dosage forms. The angiostatic steroid will normally be contained in these formulations in an amount of from about 0.005 to about 2.0 weight percent (wt.%). Preferable concentrations range from about 0.05 to about 1.0 wt.%. Thus, for topical administration, these formulations are delivered to the surface of the eye one to four times per day, depending upon the routine discretion of the skilled clinician.

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Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 ml

Example 2

It has been shown that young rabbits can be made ocular hypertensive by topical administration of a potent glucocorticoid; see, Experimental Eye Research, 27:567 (1978); Investigative Ophthalmology and Visual Science, 26:1093 (1985); or by a combination of glucocorticoid with the cortisol metabolite dihydrocortisol; see, Investigative Ophthalmology and Visual Science, Vol.26 (March, 1985). Ocular injections of glucocorticoids have also been shown to induce ocular hypertension in rabbits; see, J. Ocular Pharmacology, 3:185-189 (1987). This ocular injection rabbit model was used to test the effect of the angiostatic steroid, tetrahydrocortexolone (THS), on ocular hypertension. New Zealand red rabbits weighing approximately 1 kg. were given weekly Subtenon's injections of dexamethasone-acetate and 5β-dihydrocortisol in two quadrants of each eye (approximately 1 mg dexamethasone-acetate and 5β-dihydrocortisol/kg body wt./week). Intraocular pressures were taken weekly with an Alcon application pneumotonometer. Each group contained 4-5 animals. After two weeks of steroid treatment, IOP was elevated by 5mm Hg. Half the animals then received Subtenon's injections of THS (approximately 3 mg/kg body wt./week) in addition to the 1 mg/kg body wt./week of dexamethasone/5β-dihydrocortisol. The other half continued to receive dexamethasone/5β-dihydrocortisol injections of approximately 1 mg/kg body wt./week.

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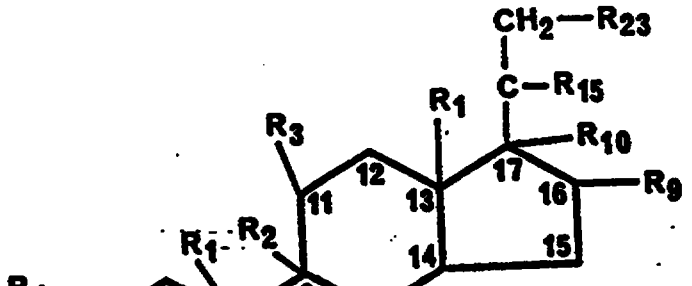
Claims

1. Use of an angiostatic steroid for the manufacture of a medicament for controlling ocular hypertension associated with primary open angle glaucoma wherein:
   the angiostatic steroid has the formula:

* C L M S *



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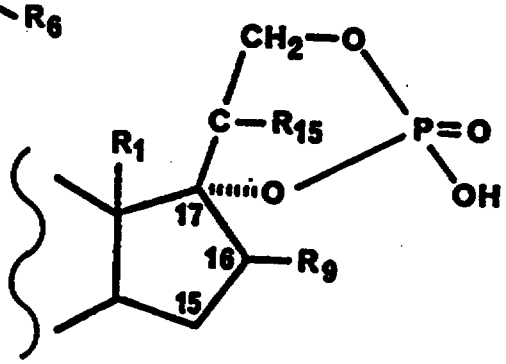

[II]

wherein R_1 is β-CH_3 or β-CH_2H_5;
R_2 is H or -Cl;
R_3 is =0, -OH, -0-alkyl(C_1-C_{12}), -OC (=0)alkyl(C_1-C_{12}), -OC(=0)ARYL, -OC(=0)N(R)$_2$ or α-OC(=0)-OR_7, wherein ARYL is furyl, thienyl, pyrrolyl, or pyridyl and each of said moieties is optionally substituted with one or two (C_1-C_4)alkyl groups, or ARYL is -$(CH_2)_f$-phenyl wherein f is 0 to 2 and the phenyl ring is optionally substituted with 1 to 3 groups selected from chlorine, fluorine, bromine, alkyl-(C_1-C_3), alkoxy(C_1-C_3), thioalkoxy-(C_1-C_3), Cl_3C-, F_3C-, -NH_2 and -$NHCOCH_3$ and R is hydrogen, alkyl (C_1-C_4),or phenyl and each R can be the same or different, and R_7 is ARYL as herein defined, or alkyl-(C_1-C_{12});
or
wherein R_2 and R_3 taken together are oxygen (-0-) bridging positions C-9 and C-11; or
wherein R_2 and R_3 taken together form a double bond between positions C-9 and C-11;
or R_2 is α-F and R_3 is β-OH;
or R_2 is α-Cl and R_3 is β-Cl;
and R_4 is H, CH_3, Cl or F;
R_5 is H, OH, F, Cl, Br, CH_3, phenyl, vinyl or allyl;
R_6 is H or CH_3;
R_9 is H, OH, CH_3, F or $=CH_2$;
R_{10} is H, OH, CH_3 or R_{10} forms a second bond between positions C-16 and C-17;
R_{12} is -H or forms a double bond with R_{14};
R_{13} is H, -OH, =0, -0-P(0)$(OH)_2$, or -0-C(=0)-$(CH_2)_t$COOH where t is an integer from 2 to 6;
R_{14} is H or forms a double bond with R_{12};
R_{15} is =0 or -OH;
and R_{23} with R_{10} forms a cyclic phosphate as depicted by Formula II;
wherein R_9 and R_{15} have the meaning defined above;
or wherein R_{23} is -OH, O-C(=0)-R_{11}, -OP(0)-$(OH)_2$, or -O-C(=0)-$(CH_2)_t$COOH wherein t is an integer from 2 to 6; and R_{11} is -Y-$(CH_2)_n$-X-$(CH_2)_m$-SO_3H, -Y'-$(CH_2)_p$-X'-$(CH_2)_q$-$NR_{16}R_{17}$ or -$Z(CH_2)_r$Q, wherein Y is a bond or -0-; Y' is a bond, -0-, or -S-; each of X and X' is a bond,-CON(R_{18})-, -N(R_{18})CO-, -0-, -S-, -S(O)-, or -$S(0_2)$-; R_{18} is hydrogen or alkyl (C_1-C_4); each of R_{16} and R_{17} is a lower alkyl group of from 1 to 4 carbon atoms optionally substituted with one hydroxyl or R_{16} and R_{17} taken together with the nitrogen atom to which each is attached forms a monocyclic heterocyclic selected from pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or N(lower)alkyl-piperazino wherein alkyl has from 1

* C L M S *

to 4 carbon atoms; n is an integer of from 4 to 9; m is an integer of from 1 to 5; p is an integer of from 2 to 9; q is an integer of from 1 to 5;
Z is a bond or -O-; r is an integer of from 2 to 9; and Q is one of the following:
(1) $-R_{19}-CH_2COOH$ wherein R_{19} is -S-, -S(O)-, $-S(O)_2-$, $-SO_2N(R_{20})-$, or $N(R_{20})SO_2-$; and R_{20} is hydrogen or lower alkyl-(C_1-C_4);with the proviso that the total number of carbon atoms in R_{20} and $(CH_2)_r$ is not greater than 10; or
(2) -CO-COOH; or
(3) $CON(R_{21})CH(R_{22})COOH$ wherein R_{21} is H and R_{22} is H, CH_3, $-CH_2COOH$, $-CH_2CH_2COOH$, $-CH_2OH$, $-CH_2SH$, $-CH_2CH_2SCH_3$, or $-CH_2Ph$-OH (wherein Ph-OH is p-hydroxyphenyl);
or R_{21} is CH_3 and R_{22} is H;
or R_{21} and R_{22} taken together are $-CH_2CH_2CH_2-$;
or $-N(R_{21})CH(R_{22})COOH$ taken together is $-NHCH_2CONHCH_2COOH$; and pharmaceutically acceptable salts thereof;
with the proviso that except for the compound wherein R_1 is $-CH_3$, R_2 and R_3 taken together form a double bond between positions 9 and 11, R_4 and R_5 are hydrogen, R_{12} and R_{14} taken together form a double bond between positions 4 and 5, R_5 is α-F, R_9 is β-CH_3, R_{10} is α -OH, R_{13} and R_{15} are =O and R_{23} is $-OP(O)-(CH)_2$, R_{13} is =O only when R_{23} with R_{10} forms the above described cyclic phosphate and except the compounds wherein:
R_{15} is =O; R_{10} is α OH;
R_1 is CH_3; R_3 is β OH; R_2 is H;
R_4 is H; R_{13} is α or β OH; R_{14} is H;
R_{12} is α or β H; R_5 is H; R_6 is H; R_9 is H and R_{23} is OH.

2. Use of an angiostatic steroid for the manufacture of a medicament according to claim 1 wherein the angiostatic steroid is present at a concentration of between about 0.005 and 2.0 wt.%.

3. Use of an angiostatic steroid for the manufacture of a medicament according to claim 1 or 2, wherein the angiostatic steroid comprises tetrahydrocortexolone or its pharmaceutically acceptable salts.

4. Use of an angiostatic steroid for the manufacture of a medicament according to claim 1 wherein the angiostatic steroid comprises 6α-fluoro-17α,21-dihdroxy-16β-methyl-pregna-4,9(11)-diene-3,20-dione or its pharmaceutically acceptable salts.

5. Use of an angiostatic steroid for the manufacture of a medicament according to claim 1, wherein the angiostatic steroid comprises 4,9(11)-pregnadien 17α,21-diol-3, 20- dione or its pharmaceutically acceptable salts.

Patentansprüche

1. Verwendung eines angiostatischen Steroids und der pharmazeutisch unbedenklichen Salze desselben für die Herstellung eines Medikaments zur Bekämpfung der mit einem primären Weitwinkel-Glaucom zusammenhängenden Augendruck-Erhöhung, worin das angiostatische Steroid die Formel

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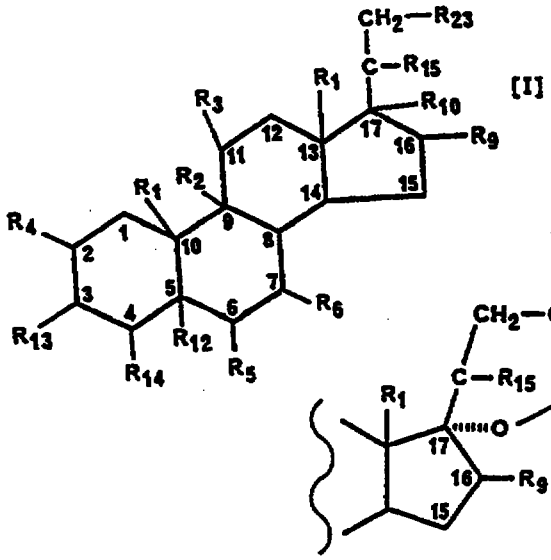

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hat, worin

R_1 β-CH_3 oder β-C_2H_5 ist;

R_2 H oder -Cl ist;

R_3 =O, -OH, -O-alkyl(C_1-C_{12}), -OC(=O)alkyl(C_1-C_{12}), -OC(=O)ARYL, -OC(=O)N(R)$_2$ oder α-OC(=O)OR_7 ist, worin ARYL Furyl, Thienyl, Pyrrolyl oder Pyridyl ist und jede dieser Struktureinheiten gegebenenfalls mit einer oder zwei (C_1-C_4)alkyl-Gruppen substituiert ist oder ARYL -$(CH_2)_f$-Phenyl ist, worin f 0 bis 2 ist und der Phenyl-Ring gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus Chlor, Fluor, Brom, Alkyl(C_1-C_3), Alkoxy(C_1-C_3), Thioalkoxy(C_1-C_3), Cl_3C-, F_3C-, -NH_2 und -$NHCOCH_3$ ausgewählt sind, und

R Wasserstoff, Alkyl(C_1-C_3) oder Phenyl ist und die R jeweils gleich oder verschieden sein können und

R_7 ARYL, wie es hierin definiert ist, oder Alkyl(C_1-C_{12}) ist;

oder worin

R_2 und R_3 zusammen genommen Sauerstoff (-O-) sind, der die Positionen C-9 und C-11 verbrückt; oder worin

R_2 und R_3 zusammen genommen eine Doppelbindung zwischen den Positionen C-9 und C-11 bilden; oder

R_2 α-F ist und R_3 β-OH ist; oder

R_2 α-Cl ist und R_3 β-Cl ist; und

R_4 H, CH_3, Cl oder F ist;

R_5 H, OH, F, Cl, Br, CH_3, Phenyl, Vinyl oder Allyl ist;

R_6 H oder CH_3 ist;

R_9 H, OH, CH_3, F oder $=CH_2$ ist;

R_{10} H, OH, CH_3 ist oder R_{10} eine zweite Bindung zwischen den Positionen C-16 und C-17 bildet;

R_{12} H ist oder eine Doppelbindung mit R_{14} bildet;

R_{13} H, OH, =O, -O-P(O)(OH)$_2$ oder -O-C(=O)-$(CH_2)_t$COOH ist, worin t eine ganze Zahl von 2 bis 6 ist;

R_{14} H ist oder eine Doppelbindung mit R_{12} bildet;

R_{15} =O oder -OH ist; und

R_{23} mit R_{10} ein cyclisches Phosphat bildet, wie es durch die Formel (II) dargestellt wird, worin R_9 und R_{15} die oben angegebenen Bedeutungen haben; oder worin

R_{23} -OH, -O-C(=O)-R_{11}, -OP(O)-(OH)$_2$ oder -O-C(=O)-$(CH_2)_t$COOH ist, worin t eine ganze Zahl von 2 bis 6 ist, und R_{11} -Y-$(CH_2)_n$-X-$(CH_2)_m$-SO_3H, -Y'-$(CH_2)_p$-X'-$(CH_2)_q$-$NR_{16}R_{17}$ oder -Z$(CH_2)_r$Q ist, worin

Y eine Bindung oder -O- ist;

Y' eine Bindung, -O- oder -S- ist;

X und X' jeweils eine Bindung, -CON(R_{18})-, -N(R_{18})CO-, -O-, -S-, -S(O)- oder -S(O_2)- sind;

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R_{18} Wasserstoff oder Alkyl(C_1-C_4) ist;

R_{16} und R_{17} jeweils eine Niederalkyl-Gruppe mit 1 bis 4 Kohlenstoff-Atomen sind, die gegebenenfalls mit einem Hydroxyl substituiert ist; oder

R_{16} und R_{17} zusammen genommen mit dem Stickstoff-Atom, an das beide gebunden sind, einen monocyclischen Heterocyclus bilden, der aus Pyrrolidino, Piperidino, Morpholino, Thiomorpholino, Piperazino oder N-(Nieder)alkylpiperazino ausgewählt ist, worin Alkyl 1 bis 4 Kohlenstoff-Atome hat;

n eine ganze Zahl von 4 bis 9 ist;

m eine ganze Zahl von 1 bis 5 ist;

p eine ganze Zahl von 2 bis 9 ist;

q eine ganze Zahl von 1 bis 5 ist;

Z eine Bindung oder -O- ist;

r eine ganze Zahl von 2 bis 9 ist; und

Q eines der folgenden ist:

(1) $-R_{19}-CH_2COOH$, worin R_{19} -S-, -S(O)-, $-S(O)_2-$, $-SO_2N(R_{20})-$ oder $-N(R_{20})-SO_2-$ ist und R_{20} Wasserstoff oder Niederalkyl(C_1-C_4) ist, mit der Maßgabe, daß die Gesamt-Zahl der Kohlenstoff-Atome in R_{20} und $(CH_2)_r$ nicht größer als 10 ist; oder

(2) -CO-COOH; oder

(3) $-CON(R_{21})CH(R_{22})COOH$, worin R_{21} H ist und R_{22} H, CH_3, $-CH_2COOH$, $-CH_2CH_2COOH$, $-CH_2OH$, $-CH_2SH$, $-CH_2CH_2SCH_3$ oder CH_2Ph-OH (worin Ph-OH p-Hydroxyphenyl ist) ist; oder

R_{21} CH_3 ist und R_{22} H ist;

R_{21} und R_{22} zusammen genommen $-CH_2CH_2CH_2-$sind, oder $N(R_{21})CH(R_{22})-$COOH zusammen genommen $-NHCH_2CONHCH_2COOH$ ist;

mit der Maßgabe, daß,

mit Ausnahme der Verbindung, in der R_1 $-CH_3$ ist, R_2 und R_3 zusammen genommen eine Doppelbindung zwischen den Positionen 9 und 11 bilden, R_4 und R_6 Wasserstoff sind, R_{12} und R_{14} zusammen genommen eine Doppelbindung zwischen den Positionen 4 und 5 bilden, R_5 α-F ist, R_9 β-CH_3 ist, R_{10} α-OH ist, R_{13} und R_{15} =O sind und R_{23} $-OP(O)-(OH)_2$ ist, R_{13} nur dann =O ist, wenn R_{23} mit R_{10} das oben beschriebene cyclische Phosphat bildet, und

mit Ausnahme der Verbindungen, in denen

R_{15} =O ist; R_{10} α-OH ist; R_1 $-CH_3$ ist; R_3 β-OH ist; R_2 H ist; R_4 H ist; R_{13} α- oder β-OH ist; R_{14} H ist; R_{12} α- oder β-H ist; R_5 H ist; R_6 H ist; R_9 H ist; und R_{23} OH ist.

2. Verwendung eines angiostatischen Steroids für die Herstellung eines Medikaments nach Anspruch 1, worin das angiostatische Steroid in einer Konzentration zwischen etwa 0,005 und 2,0 Gew.-% vorliegt.

3. Verwendung eines angiostatischen Steroids für die Herstellung eines Medikaments nach Anspruch 1 oder 2, worin das angiostatische Steroid Tetrahydrocortexolon oder dessen pharmazeutisch unbedenkliche Salze umfaßt.

4. Verwendung eines angiostatischen Steroids für die Herstellung eines Medikaments nach Anspruch 1, worin das angiostatische Steroid 6α-Fluor-17α,21-dihydroxy-16β-methylpregna-4,9(11)-dien-3,20-dion oder dessen pharmazeutisch unbedenkliche Salze umfaßt.

5. Verwendung eines angiostatischen Steroids für die Herstellung eines Medikaments nach Anspruch 1, worin das angiostatische Steroid 4,9(11)-Pregnadien-17α,21-diol-3,20-dion oder dessen pharmazeutisch unbedenkliche Salze umfaßt.

Revendications

1. Utilisation d'un stéroïde angiostatique pour fabriquer un médicament destiné à contrôler l'hypertension oculaire associée au glaucome primaire à angle ouvert, dans laquelle :

le stéroïde angiostatique a pour formule :

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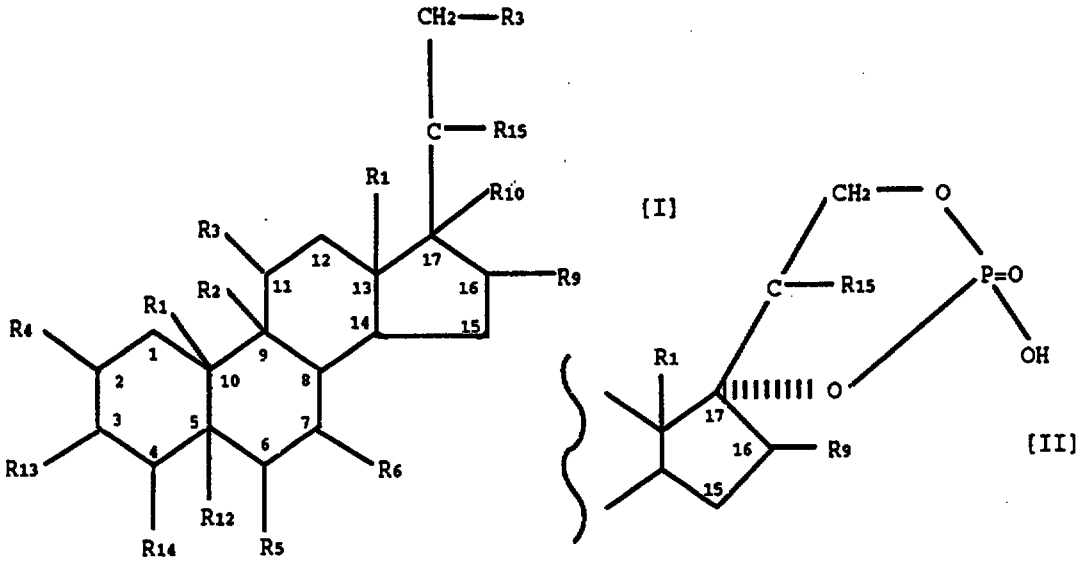

dans laquelle R_1 est β-CH_3 ou β-C_2H_5 ;
R_2 est H ou -Cl ;
R_3 est =O, -OH, -O-alkyle en C_1-C_{12}, -OC(=O)alkyle en C_1-C_{12}, -OC(=O)ARYLE, -OC(=O)N(R)$_2$ ou α-OC(=O)OR_7, où ARYLE est un groupe furyle, thiényle, pyrrolyle ou pyridyle et chacun desdits groupements est éventuellement substitué par un ou deux groupes alkyle en C_1-C_4, ou ARYLE est un groupe -$(CH_2)_f$-phényle, dans lequel f a une valeur de 0 à 2 et le noyau phényle est éventuellement substitué par 1 à 3 groupes choisis parmi un chlore, un fluor, un brome, un groupe alkyle en C_1-C_3, alcoxy en C_1-C_3, thioalcoxy en C_1-C_3, Cl_3C-, F_3C-, -NH_2 et -$NHCOCH_3$, et R est un atome d'hydrogène, un groupe alkyle en C_1-C_4 ou phényle, et chacun des radicaux R peuvent être identiques ou différents, et R_7 est un ARYLE tel que défini ici, ou un groupe alkyle en C_1-C_{12} ;
ou
dans laquelle R_2 et R_3, pris conjointement, sont un atome d'oxygène (-O-) pontant les positions C-9 et C-11 ; ou
dans laquelle R_2 et R_3, pris conjointement, forment une double liaison entre les positions C-9 et C-11 ;
ou R_2 est α-F et R_3 est β-OH ;
ou R_2 est α-Cl et R_3 est β-Cl ;
et R_4 est H, CH_3, Cl ou F ;
R_5 est H, OH, F, Cl, -Br, CH_3, un groupe phényle, vinyle ou allyle ;
R_6 est H ou CH_3 ;
R_9 est H, OH, CH_3, F ou $=CH_2$;
R_{10} est H, OH, CH_3, ou R_{10} forme une deuxième liaison entre les positions C-16 et C-17 ;
R_{12} est -H ou forme une double liaison avec R_{14} ;
R_{13} est H, -OH, =OH, -O-P(O)$(OH)_2$ ou -O-C(=O)-$(CH_2)_t$COOH, où t est un nombre entier de 2 à 6 ;
R_{14} est H ou forme une double liaison avec R_{12} ;
R_{15} est =O ou -OH ;
et R_{23} forme, avec R_{10}, un phosphate cyclique tel que décrit par la formule II ;
dans laquelle R_9 et R_{15} ont les significations définies ci-dessus ;
ou dans laquelle R_{23} est -OH, O-C(=O)-R_{11}, -OP(O)-$(OH)_2$ ou -O-C(=O)-$(CH_2)_t$COOH, où t est un nombre entier de 2 à 6 ; et R_{11} est -Y-$(CH_2)_n$-X-$(CH_2)_m$-SO_3H,
-Y'-$(CH_2)_p$-X'-$(CH_2)_q$-$NR_{16}R_{17}$ ou -Z$(CH_2)_r$Q, où Y est une liaison ou -O- ; Y' est une liaison, -O- ou -S- ; chacun des radicaux X et X' est une liaison, -CON(R_{18})-, -N(R_{18})CO-, -O-, -S-, -S(O)- ou -S(O_2)- ; R_{18} est un atome d'hydrogène ou un groupe alkyle en C_1-C_4 ; chacun des radicaux R_{16} et R_{17} est un groupe alkyle inférieur de 1 à 4 atomes de carbone, éventuellement substitué par un groupe hydroxyle, ou bien R_{16} et R_{17}, pris conjointement avec l'atome d'azote auquel chacun est fixé, forment un hétérocycle monocyclique choisi parmi les cycles pyrrolidino, pipéridino, morpholino, thiomorpholino, pipérazino ou N(alkyl inférieur)pipérazino, dans lequel le groupe alkyle possède de 1 à 4 atomes de carbone ; n est un nombre entier de 4 à 9 ; m est un nombre entier de 1 à 5 ; p est un nombre entier

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de 2 à 9 ; q est un nombre entier de 1 à 5 ;
Z est une liaison ou -O- ; r est un nombre entier de 2 à 9 ; et Q est l'un des groupes suivants :
(1) $-R_{19}-CH_2COOH$, où R_{19} est -S-, -S(O)-, $-S(O)_2-$, $-SO_2N(R_{20})-$ ou $N(R_{20})SO_2-$; et R_{20} est un atome d'hydrogène ou un groupe alkyle inférieur en C_1-C_4 ; à condition que le nombre total d'atomes de carbone dans R_{20} et $(CH_2)_r$ ne soit pas supérieur à 10 ; ou
(2) -CO-COOH ; ou
(3) $CON(R_{21})CH(R_{22})COOH$, dans lequel R_{21} est H et R_{22} est H, CH_3, $-CH_2COOH$, $-CH_2CH_2COOH$, $-CH_2OH$, $-CH_2SH$, $-CH_2CH_2SCH_3$ ou $-CH_2Ph-OH$ (dans lequel Ph-OH est un groupe p-hydroxyphényle) ;
ou R_{21} est CH_3 et R_{22} est H ;
ou R_{21} et R_{22}, pris conjointement, sont $-CH_2CH_2CH_2-$;
ou $-N(R_{21})CH(R_{22})COOH$, pris conjointement, est $-NHCH_2CONHCH_2COOH$; et leurs sels pharmaceutiquement acceptables ;
à la condition que, à l'exception du composé dans lequel R_1 est CH_3, R_2 et R_3, pris conjointement, forment une double liaison entre les positions 9 et 11, R_4 et R_5 soient des atomes d'hydrogène, R_{12} et R_{14}, pris conjointement, forment une double liaison entre les positions 4 et 5, R_5 soit α-F, R_9 soit β-CH_3, R_{10} soit α-OH, R_{13} et R_{15} soient =O et R_{23} soit $-OP(O)-(OH)_2$,
R_{13} soit =O seulement lorsque R_{23} forme avec R_{10} le phosphate cyclique décrit ci-dessus, et à l'exception des composés dans lesquels :
R_{15} est =O ; R_{10} est α-OH ;
R_1 est CH_3 ; R_3 est β-OH ; R_2 est H ;
R_4 est H ; R_{13} est α- ou β-OH ; R_{14} est H ;
R_{12} est α- ou β-H ; R_5 est H ; R_6 est H ; R_9 est H et R_{23} est OH.

2. Utilisation d'un stéroïde angiostatique pour fabriquer un médicament selon la revendication 1, dans laquelle le stéroïde angiostatique est présent en une concentration comprise entre environ 0,005 et 2,0% en poids.

3. Utilisation d'un stéroïde angiostatique pour fabriquer un médicament selon la revendication 1 ou 2, dans laquelle le stéroïde angiostatique comprend la tétrahydrocortexolone ou ses sels pharmaceutiquement acceptables.

4. Utilisation d'un stéroïde angiostatique pour fabriquer un médicament selon la revendication 1, dans laquelle le stéroïde angiostatique comprend la 6α-fluoro-17α,21-dihydroxy-16β-méthylprégna-4,9(11)-diène-3,20-dione ou ses sels pharmaceutiquement acceptables.

5. Utilisation d'un stéroïde angiostatique pour fabriquer un médicament selon la revendication 1, dans laquelle le stéroïde angiostatique comprend la 4,9(11)-pregnadiène-17α,21-diol-3,20-dione ou ses sels pharmaceutiquement acceptables.

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