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Dato de la Creación

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(54) **TREATMENT OF OPHTHALMIC
CONDITIONS**

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(57) **ABSTRACT**

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(30) **Foreign Application Priority Data**

Apr. 8, 2004 (AU) 2004901916
Sep. 3, 2004 (AU) 2004905034
Sep. 3, 2004 (AU) 2004905035

The present invention provides a method of treatment of an individual with an ophthalmic condition that may comprise the step of: administering to the individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye in the individual to be treated. Preferably, said compound may be an anti-oedematous steroid, more preferably a mineralocorticoid.

Figure 1

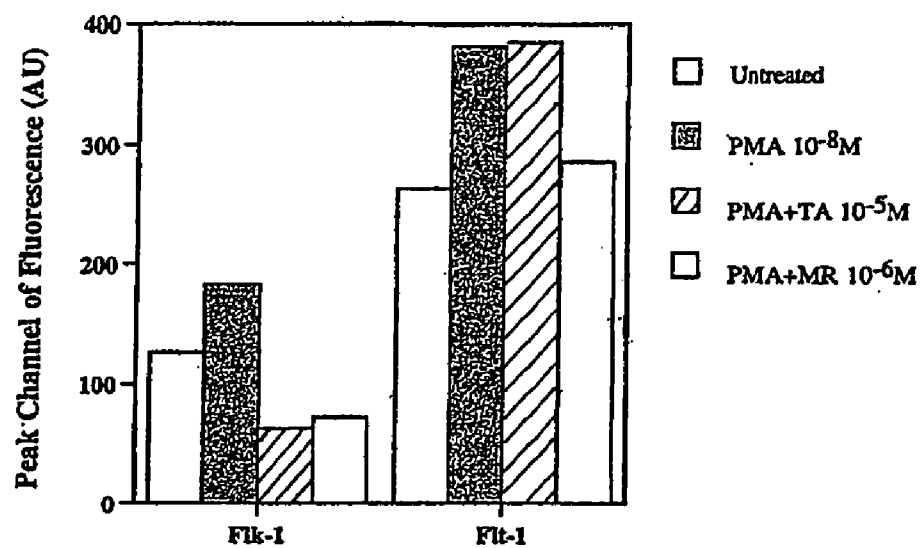


Figure 2

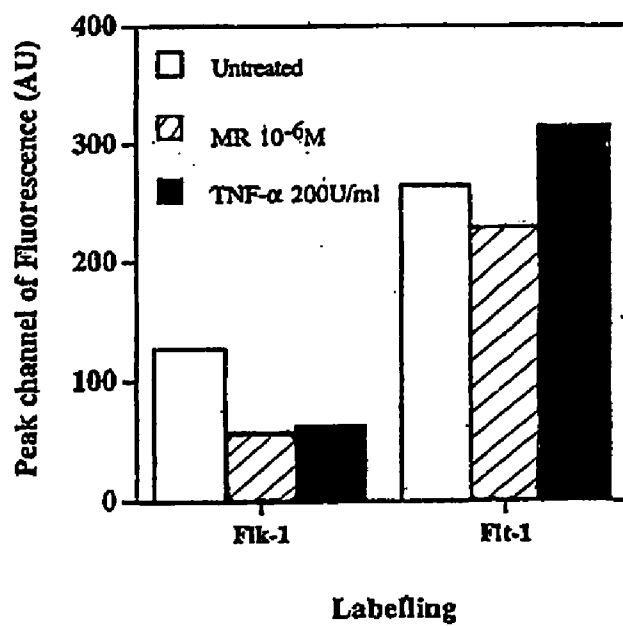


Figure 3

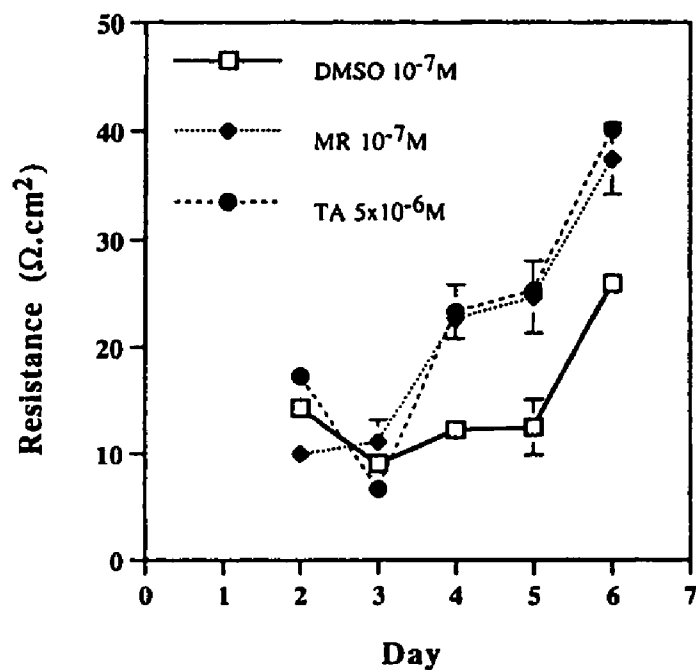


Figure 4

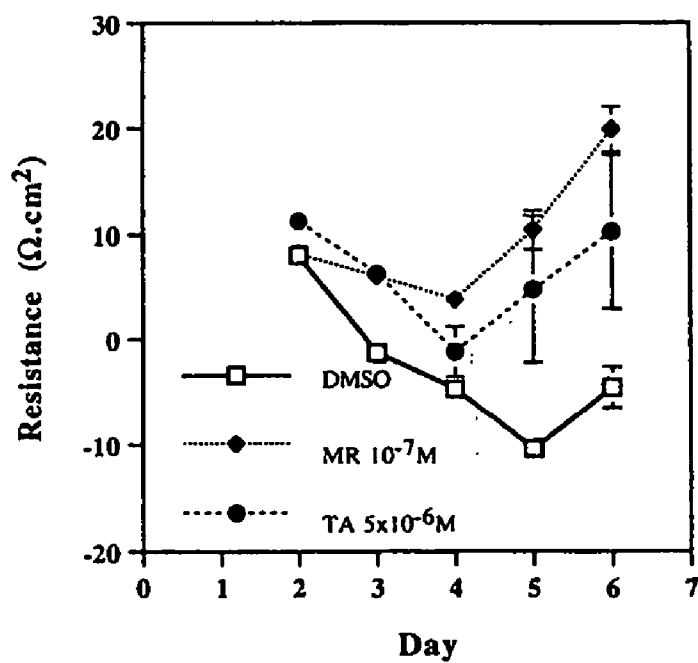
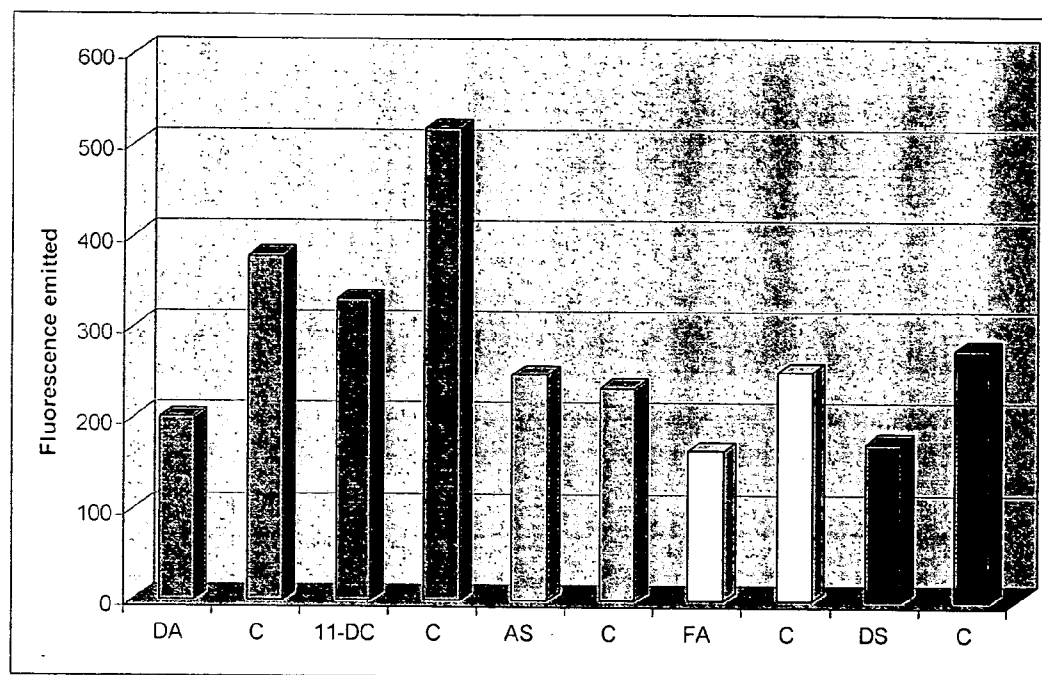


Figure 5



TREATMENT OF OPHTHALMIC CONDITIONS

INCORPORATION BY REFERENCE

[0001] This application claims benefit of Australian Provisional Patent Application No. 2004901916 filed 8 Apr. 2004, Australian Provisional Patent Application No. 2004905034 filed 3 Sep. 2004, and Australian Provisional Patent Application No. 2004905035 filed 3 Sep. 2004.

[0002] The foregoing applications, and all documents cited therein, together with any manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated herein by reference, and may be employed in the practice of the invention.

FIELD OF THE INVENTION

[0003] The present invention is directed to the administration of therapeutic compounds for the treatment of ophthalmic conditions. The invention is also directed to the administration of therapeutic compounds that modulate the activity of mineralocorticoid receptors to treat, ameliorate or prevent ophthalmic conditions. More particularly, the invention is directed to the treatment of ophthalmic conditions in the posterior region of the retina with an anti-oedematous steroid. The invention also relates to a method of manufacturing a medicament for treatment of ophthalmic conditions.

BACKGROUND

[0004] Ophthalmic conditions may comprise front-of-eye diseases such as, for example, corneal oedema, anterior uveitis, pterygium, corneal diseases or opacifications with an exudative or inflammatory component, conjunctivitis, allergy and laser induced exudation or back-of-eye diseases such as, for example, exudative macular degeneration, macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration or retinopathy of prematurity. Back-of-eye diseases comprise the largest number of causes for vision loss in the developed world.

[0005] Conjunctivitis is inflammation of the thin mucus membrane that lines the inside of the eyelids and extends over the front of the sclera, often due to. This inflammation is often due to bacterial or viral infection or allergy. Most conjunctivitis manifests as a pale watery swelling or oedema of the conjunctiva and sometimes the whole eyelid, often with a non-puss containing mucoid discharge. Tenderness and oedema around the eye has also been reported. Corneal oedema is the accumulation of fluid or swelling in the cornea, which can produce clouding of the cornea and significant vision occlusion. Corneal oedema may occur following surgery on the eye, LASIK, LASEK or laser therapy (particularly cataract surgery) or may occur spontaneously, with inflammation of the cornea. When the cornea swells, it thickens and becomes cloudy, reducing the passage of light reaching into the eye.

[0006] Anterior uveitis is the inflammation of uveal tissues (the iris and ciliary body). The exact cause of anterior uveitis is unknown, but it may be associated with certain systemic diseases. The general clinical signs of uveitis include: flare (proteins and/or cells apparent in the anterior chamber, resulting from breakdown in the blood-aqueous barrier), redness or hyperemia of the episcleral/scleral blood vessels, extreme sensitivity to light and keratic precipitates.

[0007] The pathogenesis of exudative retinopathies involves blood-retinal barrier (BRB) compromise and inflammation. The retina is principally formed of neuronal matter, and the barrier between the retina and the complex and vigorous vascular system of the choroid behind the retina is very similar to the blood-brain barrier. The BRB is formed at two principal sites: an inner barrier consisting of retinal vascular endothelial cells that line the blood vessels of the choroid; and an outer barrier consisting of the retinal pigment epithelial (RPE) cells that divide the choroid from the retina. Functionally the BRB is dependant on the integrity of the RPE, the retinal vasculature and associated glial limitations, a sheath of cellular processes that inhibit the direct access of blood vessels to the neuronal environment. The BRB functions to preserve the physiological environment of the neuronal retina.

[0008] When the BRB is compromised, leakage of fluids from the blood system across the BRB into the retina can cause problems such as exudative retinopathies and vision impairment. Ailments associated with breakdown of the BRB in the posterior region of the retina include, for example, oedematous retinal conditions such as, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes arising from various aetiologies, exudative macular degeneration and macular oedema arising from laser treatment of the retina.

[0009] Myopic retinopathy is a condition that results from severe malformation of the retina in part due to overgrowth of the sclera. The deformation leads to restriction of the blood vessels of the choroid, and subsequently abnormal growth of vessels in an attempt to compensate. The new abnormal vessels are fragile and prone to leakage and exudation, leading to exudative retinopathy.

[0010] Macular oedema such as clinical macular oedema or angiographic cystoid macular oedema is a condition involving swelling of the macula and typically occurs as a result of aetiologies such as disease (eg diabetes), injury or more rarely, eye surgery. Fluid collects within the layers of the macula, causing blurred, distorted central vision.

[0011] In exudative macular degeneration (also known as "wet" or neovascular age-related macular degeneration (wet-AMD)) abnormal overgrowth of blood vessels from the choroid into the retina occurs, compromising the BRB. The abnormal blood vessels are fragile and prone to leakage. Treatment of such diseases currently focuses on removing or inhibiting vascular growth by laser treatment, drug therapy or a combination of both.

[0012] Among the angiogenic retinal diseases, diabetic retinopathy is the leading cause of blindness in adults between the ages of 18 to 72. Histological studies consistently implicate endothelial cell dysfunction in the pathology. Diabetic retinopathy is recognised as one of the diabetic microangiopathies, which are severe complications of diabetes. In the initial stage, capillary microaneurysm and dot haemorrhage are observed. Thereafter, cotton wool patches resulting from microvascular obstruction, and retinal oedema, hard exudates or the like resulting from vascular hyperpermeability are observed and neovascularization appears. In the last stage, retinal detachment is caused by the traction of connective tissues grown in the vitreous body. Further, iris rubeosis and neovascular glaucoma are caused, leading to blindness.

[0013] Retinal ischemia or degeneration is another disease state that is quite common. It may be produced by injury,

tumours or the like, or be associated with various disorders such as where occlusion of a blood vessel or elevated intraocular pressure reduces availability of blood, oxygen or other nutrients to the retina or optic nerve which can result in neuronal cell death (degeneration) and loss of vision. Such disorders include e.g. diabetes, atherosclerosis, venous capillary insufficiency, obstructive arterial and venous retinopathies, glaucoma, and senile macular degeneration. Optic nerve injury and damage also can result in vision loss and can arise from a variety of conditions or incidents.

[0014] Although the underlying cause of these angiogenic retinal diseases might be different, the factors initiating the angiogenic process are similar. One of the most important factors in the initiation of an angiogenic response is the up-regulation of the expression of vascular endothelial growth factor (VEGF), a potent angiogenic and permeability factor, the up-regulation of which has been shown in patients suffering from neovascular eye diseases.

[0015] The most widely used treatment for these disorders is retinal laser photocoagulation, an ablative treatment that destroys the peripheral retina to preserve the central macula, which is responsible for 80% of human vision. A wide range of theories have been proposed to explain the beneficial effects of retinal laser photocoagulation in delaying retinal angiogenesis, however, the underlying molecular mechanism remains to be elucidated.

[0016] Laser therapy is directed to removal or blockage of blood vessels via photodynamic therapy or laser photocoagulation. For example, focal laser treatment may be applied to microaneurysms identified in diabetic retinopathy. The therapeutic effects of laser photocoagulation are thought to be due to the destruction of photoreceptors, the highest oxygen consumers in the retina. Subsequently, these photoreceptors are replaced by glial cells allowing increased oxygen diffusion from the choroid to the inner retina thereby relieving inner retinal hypoxia. This improved oxygenation triggers a two-pronged cascade of events where: (1) constriction of the retinal arteries results in decreased hydrostatic pressure in capillaries and the constriction of capillaries and venules; and (2) the cellular production of VEGF is inhibited. Together, these effects are believed to ultimately result in the inhibition of neovascularization and a decrease in oedema. Cell proliferation and regulation of cellular proteins are induced by the laser photocoagulation, and their therapeutic effect might be an essential part of the physiological response.

[0017] However, a complication of laser treatment is inflammation, leading to further oedema. In addition, laser treatment is not always a permanent cure as the blood vessels may begin to grow again, and microaneurysms may reform. Furthermore, laser treatment of abnormal blood vessels cannot be performed on vessels located in certain regions of the retina, such as the central region of the macula.

[0018] Pharmaceutical interventions with drug compounds having anti-angiogenic or angiostatic properties, such as anecortave acetate or anti-vascular endothelial growth factor (VEGF) compounds (Lucentis®, Macugen®), have also been proposed as methods for treatment. However, to date there is insufficient evidence to indicate how successful these compounds will be.

[0019] The present invention seeks to provide an improved method for the treatment of ophthalmic conditions that at least slows the rate of development of the ophthalmic

condition. More particularly the invention seeks to provide a method of treatment and a method of manufacture of a medicament for the treatment of ophthalmic conditions such as exudative eye diseases, which method addresses the principal problem underlying the diseases (eg exudation of fluids from vessels).

[0020] Citation or identification of any document in this application is not an admission that such a document is available as prior art to the present invention.

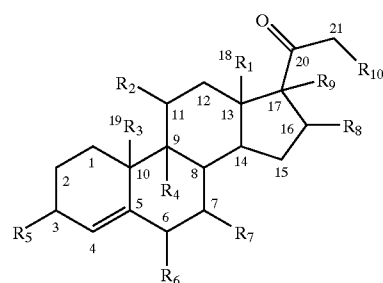
SUMMARY OF THE INVENTION

[0021] The present invention provides a method of treatment of an individual with an ophthalmic condition that may comprise the step of: administering to the individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye in the individual to be treated. Preferably, said compound is an anti-oedematous steroid, more preferably a mineralocorticoid.

[0022] Also provided is a method for the prophylactic or therapeutic treatment of exudative retinopathies in a patient that may comprise the step of: administering a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors to or adjacent to cells or tissue from or in said patient that are afflicted with an exudative retinopathy; and wherein said cells or tissue may include, but are not limited to, retinal cells, retinal pigment epithelial cells, the epithelial cells of the BRB, choroidal endothelial cells.

[0023] The invention further provides a method of prophylactically treating an individual with an ophthalmic condition in a first eye but not a second eye that may comprise the steps of: administering to the second eye of said individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in or adjacent to the eye.

[0024] In a first preferred aspect, the invention provides a method of treatment of an individual with an ophthalmic condition that may comprise the step of: administering to the individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye wherein said compound is a mineralocorticoid of the general structure:



Structure [A]

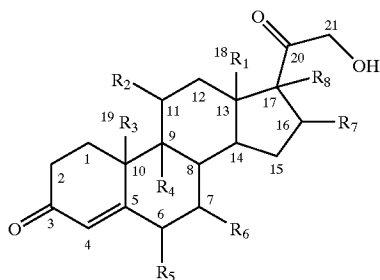
[0025] wherein

[0026] R_1 is CH_3 , $\text{CH}=\text{O}$, CH_2OH , $\text{CR}=\text{O}$, CH_2NH_2 , COCHCH_2 , NO_2X or CH_2X wherein

- [0027] X is F, Cl, Br;
 [0028] R₂ is H, OH, =O, NH₂ or CN;
 [0029] R₃ is H, CH₃ or CH₂OH;
 [0030] R₄ is H, F or Cl;
 [0031] R₅ is H, OH, =O, SH, NH₂, CN, NO₂, CH₃, CH₂OH, CH=O, X, CH₂X, OR, OCOR,
 [0032] OPO(OR)₂, 50 CH₂ or CHR wherein X is F, Cl, Br;
 [0033] R₆ is H, CH₃ or X wherein X is F, Cl, Br;
 [0034] R₇ is H, OH, CH₃, Alkyl, Ph, X, OCH₃, OR, SCOCH₃, SCOR, OCOR, CH₂OH,
 [0035] CH₂X, CH=O, CR=O or NHCOR wherein X is F, Cl, Br;
 [0036] R₈ is H, OH, CH₃, CH₂CH₃, SH, NH₂ or X wherein X is F, Cl, Br;
 [0037] R₉ is H, OH, SH, NH₂, CH₃, CH₂CH₃ or X wherein X is F, Cl, Br;
 [0038] R₁₀ is H, OH, CH₃, CH₂CH₃, SH, NH₂, CH₂OH, CH₂CH₂OH, OR, OCOR, OPO(OR)₂, NHCOR CH=O, X or CH₂X wherein X is F, Cl, Br; and

[0039] wherein said compound is not a compound disclosed in U.S. Pat. No. 6,011,023 where the compound is to be used to treat or prevent ocular diseases that may include, for example, but are not limited to, retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0040] In a second preferred aspect, the invention provides a method of treatment of an individual with an ophthalmic condition that may comprise the step of: administering to the individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye; wherein said compound is a mineralocorticoid of the general structure:



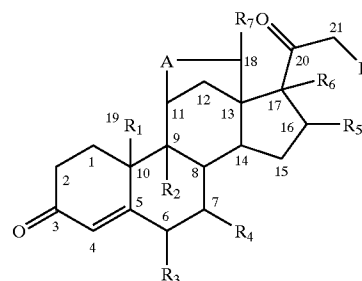
Structure [B]

[0041] wherein

- [0042] R₁ is CH₃, CH=O or COCHCH₂;
 [0043] R₂ is H, OH or =O;
 [0044] R₃ is H, CH₃ or CH₂OH;
 [0045] R₄ is H, or F;
 [0046] R₅ R₆ and R₇ are H;
 [0047] R₈ is H or OH; and

[0048] wherein said compound is not a compound disclosed in U.S. Pat. No. 6,011,023 where the compound is to be used to treat or prevent ocular diseases that may include, for example, but are not limited to, retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0049] In a third preferred aspect, the invention provides a method of treatment of an individual with an ophthalmic condition that may comprise the step of: administering to the individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye wherein said compound is a mineralocorticoid of the general structure:



Structure [C]

[0050] wherein

- [0051] A is O, S, NH, CH₂, CHOH, C=O, CHX, CHCH₃, CH₂CH₂, OCH₂, SCH₂, NHCH₂, NRCH₂, NCOR wherein X is F, Cl, Br;
 [0052] B is H, OH, SH, NH₂, CH₃, CH₂OH, CH₂CH₂OH, CH=O, X, CH₂X, OR, OCOR, OPO(OR)₂, NHCOR wherein X is F, Cl, Br;
 [0053] R₁ is H, CH₃, CH=O, CH₂OH;
 [0054] R₂ is H, F or Cl;
 [0055] R₃ is H, CH₃ or X wherein X is F, Cl, Br;
 [0056] R₄ is H, OH, CH₃, Alkyl, Ph, X, OCH₃, SH, NH₂, OR, SCOCH₃, SCOR, OCOR, CH₂OH, CH₂X, CH=O, CR=O, SR or NHCOR wherein X is F, Cl, Br;

[0057] R_5 is H, CH_3 , CH_2CH_3 , OH, SH, NH_2 or X wherein X is F, Cl, Br;

[0058] R_6 is H, OH, SH, NH_2 , CH_2CH_3 , CH_3 or X wherein X is F, Cl, Br;

[0059] R_7 is H, OH, SH, NH_2 , NO_2 , $CH=O$, CH_3 , CO_2H , CN, CH_2CH_3 , CH_2X or X wherein X is F, Cl, Br; and

[0060] wherein said compound is not a compound disclosed in U.S. Pat. No. 6,011,023 where the compound is to be used to treat or prevent ocular diseases that may include, for example, but are not limited to, retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0061] Also provided by the invention is a method for the treatment of an ophthalmic condition in an individual that may comprise the step of: administering to the ophthalmic condition in the individual a therapeutically effective pharmaceutically acceptable formulation of a combination of:

[0062] (a) a mineralocorticoid wherein said mineralocorticoid is: (i) capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition; (ii) in a pharmaceutically acceptable form suitable for delivery to the eye; and

[0063] (b) at least a second compound in a concentration and dose sufficient to reduce ocular neovascularization wherein the second compound may include, for example, a tetracycline derivative, a steroid, heparin, an antimicrobial, an anti-prostaglandin, and/or a metalloproteinase inhibitor.

[0064] A method is also provided for the treatment of an ophthalmic condition in an individual that may comprise the step of: administering to the ophthalmic condition in the individual a therapeutically effective pharmaceutically acceptable formulation of a combination of:

[0065] (a) a mineralocorticoid wherein said mineralocorticoid is: (i) capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition; and (ii) in a pharmaceutically acceptable form suitable for delivery to the eye; and

[0066] (b) a plurality of compounds in a concentration and dose sufficient to reduce ocular neovascularization wherein the plurality of compounds may include, for example, a tetracycline derivative, a steroid, heparin, an antimicrobial, an anti-prostaglandin, and/or a metalloproteinase inhibitor.

[0067] In another aspect, the invention provides a pharmaceutical composition for the treatment or prophylaxis of ophthalmic conditions that may comprise a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissues located in the eye. Preferably, said compound may be an anti-oedematous steroid, more preferably a mineralocorticoid.

[0068] In a further aspect, the invention provides for the use of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in the manufacture of a medicament for the treatment of an ophthalmic condition. Preferably, said compound may be an anti-oedematous steroid, more preferably a mineralocorticoid.

[0069] The invention also provides for the use of a compound capable of modulating the activity of mineralocorticoid receptors in the manufacture of a medicament for the treatment of an exudative retinopathy in an individual.

[0070] Other objects, features, and advantages of the instant invention, in its details as seen from the above, and from the following description of the preferred embodiment when considered in light of the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0071] Comprehension of the invention is facilitated by reading the following detailed description, in conjunction with the annexed drawings.

[0072] FIG. 1 shows the data from a fluorescence activated cell sorting (FACS) of choroidal endothelial cells comparing untreated cells against cells treated with phorbolmyristate acetate (PMA), cells treated with the glucocorticoid triamcinolone acetonide and cells treated with the mineralocorticoid fludrocortisone.

[0073] FIG. 2 shows the data from FACS on choroidal endothelial cells comparing untreated cells against cells treated with the mineralocorticoid fludrocortisone and cells treated with Tumour Necrosis Factor- α .

[0074] FIG. 3 shows the transendothelial electrical resistance (TER) of choroidal endothelial cells treated with dimethyl sulfoxide (DMSO), cells treated with the mineralocorticoid fludrocortisone, and cells treated with the glucocorticoid triamcinolone acetonide.

[0075] FIG. 4 shows the TER of retinal endothelial cells treated with DMSO, cells treated with the mineralocorticoid fludrocortisone, and cells treated with the glucocorticoid triamcinolone acetonide.

[0076] FIG. 5 shows a graph of the effect of the mineralocorticoids 11-desoxycortisone, deoxycorticosterone acetate, aldosterone, fludrocortisone acetate and deoxycorticosterone on bacterial endotoxin induced exudative response in rabbits [C=control; 11-DC=11-desoxycortisone; DA=deoxycorticosterone acetate; AS=aldosterone; FA=fludrocortisone acetate; DS=deoxycorticosterone]. (mean n=5; Wilcoxon signed rank test)

DESCRIPTION OF THE INVENTION

[0077] Those skilled in the art will appreciate that the invention described herein is susceptible to variations and

modifications other than those specifically described. The invention includes all such variation and modifications. The invention also includes all of the steps, features, formulations and compounds referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

[0078] Each document, reference, patent application or patent cited in this text is expressly incorporated herein in their entirety by reference, which means that it should be read and considered by the reader as part of this text. That the document, reference, patent application or patent cited in this text is not repeated in this text is merely for reasons of conciseness.

[0079] The present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally equivalent products, formulations and methods are clearly within the scope of the invention as described herein.

[0080] The invention described herein may include one or more range of values (eg size, concentration etc). A range of values will be understood to include all values within the range, including the values defining the range, and values adjacent to the range which lead to the same or substantially the same outcome as the values immediately adjacent to that value which defines the boundary to the range.

[0081] The file of this patent contains at least one drawing executed in colour. Copies of this patent with colour drawing(s) will be provided by the United States Patent and Trademark Office upon request and payment of the necessary fee.

[0082] Throughout this specification, unless the context requires otherwise, the word "comprise" or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. It is also noted that in this disclosure and particularly in the claims and/or paragraphs, terms such as "comprises", "comprising", "comprising" and the like can have the meaning attributed to it in U.S. Patent law; e.g., they can mean "includes", "included", "including", and the like; and that terms such as "consisting essentially of" and "consists essentially of" have the meaning ascribed to them in U.S. Patent law, e.g., they allow for elements not explicitly recited, but exclude elements that are found in the prior art or that affect a basic or novel characteristic of the invention.

[0083] Other definitions for selected terms used herein may be found within the description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

[0084] This invention is based on the unexpected discovery that by contacting mineralocorticoid receptors within or adjacent to ocular tissue with agents that are capable of activating the mineralocorticoid receptor it is possible to ameliorate ophthalmic conditions in a patient's eye.

[0085] In one aspect of the present invention, there is provided a method of treatment of an individual with an ophthalmic condition comprising the step of: administering to the individual a therapeutically effective amount of a

compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye in the individual to be treated. Preferably, the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye is an anti-oedematous steroid. More preferably, the anti-oedematous steroid is a mineralocorticoid. Even more preferably the compound is a compound that is not disclosed in U.S. Pat. No. 6,011,023. If, however, the compound is a compound disclosed in U.S. Pat. No. 6,011,023, the compound is not used to treat an ocular disease selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0086] As used herein the phrase "a compound capable of modulating the activity of mineralocorticoid receptors" refers to compounds capable of entering a cell to reach the cytosol or the nuclear membrane where the mineralocorticoid receptors are located, which are able to modulate the activity of the receptor. The activity of the receptor will be modulated when the activity of the receptor changes as a consequence of the compound interacting with the receptor (eg by activating the receptor). Preferably such compounds will have a lipophilic profile, which will facilitate their entry into the cell.

[0087] The role of mineralocorticoids lies in regulating the concentration of minerals, particularly sodium and potassium, in extracellular fluids. They bind to the mineralocorticoid receptor, triggering a series of events that lead to an increase in epithelial sodium channel activity and increased salt (particularly sodium) absorption. This in turn leads to raised blood pressure and increased fluid volume. The present invention has now shown that administration of such compounds to the eye, and in particular vascular areas of the eye such as the retinal region, the conjunctiva, ciliary body and iris, produces anti-oedematous effects. Such effects are of particular value in the treatment of exudative diseases such as exudative retinopathies, or anterior uveitis. It has recently been shown that ocular tissues including retinal cells, retinal pigment epithelial cells, the epithelium of ciliary bodies, the iris, cornea and lens all express mineralocorticoid receptors.

[0088] Preferably the compounds used in the method of the present invention are mineralocorticoids. Mineralocorticoids are able to bind to and activate the mineralocorticoid receptor. A range of steroids have mineralocorticoid activities, that is they can bind the mineralocorticoid receptor and activate it, leading to changes in the concentration of sodium and potassium in extracellular fluids via an increase in epithelial sodium channel activity, modulation of sodium/potassium ATPase activity and increased salt (particularly

sodium) absorption. Some corticosteroids have both mineralocorticoid and glucocorticoid activity and the method of the present invention uses the mineralocorticoid activity of such steroids.

[0089] The term “ophthalmic condition” includes both ‘back-of-eye’ diseases involving the retina, macular, fovea etc in the posterior region of the eye, and ‘front-of-eye’ diseases which predominantly involve the tissues at the front-of-eye, such as the cornea, iris, ciliary body, conjunctiva etc. In a preferred form of the invention ‘ophthalmic condition’ will be understood to refer to a front-of-eye disease or back-of-eye disease caused by either direct or indirect modulation of the mineralocorticoid receptors in cells or tissue in or adjacent to the eye.

[0090] Examples of back-of-eye disease include macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, age-related macular degeneration, retinopathy of prematurity (also known as retrolental fibroplasia), retinal ischemia and choroidal neovascularization, retinal diseases (diabetic retinopathy, diabetic retinal oedema, retinal detachment, senile macular degeneration due to sub-retinal neovascularization, myopic retinopathy); inflammatory diseases; uveitis associated with neoplasms such as retinoblastoma or pseudoglioma; neovascularization following vitrectomy; vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, retinopathies resulting from carotid artery ischemia); neovascularization of the optic nerve.

[0091] Examples of front-of-eye diseases include pterygium, corneal neovascularization (due to inflammation, transplantation, developmental hypoplasia of the iris, lensectomy), corneal diseases or opacifications with an exudative or inflammatory component, diffuse lamellar keratitis, neovascularization due to penetration of the eye or contusive ocular injury; rubeosis iritis; Fuchs’ heterochromic iridocyclitis; chronic uveitis; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch’s dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet’s disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; cytomegalovirus infection.

[0092] Preferably, the ophthalmic condition treated by the method of the present invention is chosen from the list

comprising: diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch’s dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet’s disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; or Cytomegalovirus infection.

[0093] In one embodiment, the invention provides a method of treatment of an ophthalmic condition in an individual comprising the step of: administering to the individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye in the individual to be treated, wherein the ophthalmic condition is selected from the group comprising: myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch’s dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet’s disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory

pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; or Cytomegalovirus infection.

[0094] In a further aspect of the invention there is provided a method of treatment of an ophthalmic condition in an individual comprising the steps of: administering to an individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye in the individual to be treated, wherein the ophthalmic condition is an exudative retinopathy. The present invention also provides a method for the prophylactic or therapeutic treatment of exudative retinopathies comprising administering a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition, to at least a ocular tissue selected from the group consisting of: retinal cells, retinal pigment epithelial cells, the epithelium of ciliary bodies, the iris, cornea and lens.

[0095] In another embodiment the invention provides a method for the treatment of an ailment resulting from the breakdown of the BRB in the posterior region of the retina, said method comprising the step of: administering to an individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to said ailment. Generally, ailments located in the posterior region of the retina arising from breakdown of the BRB will include myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, macular oedema arising from laser treatment of the retina and exudative macular degeneration.

[0096] According to another embodiment the invention provides a method for the treatment or prophylaxis of exudative retinopathies in a patient requiring said treatment or prophylaxis, comprising administering by intravitreal injection to said patient an effective amount of a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye that is preferably sparingly soluble in the vitreous.

[0097] When the ophthalmic condition to be treated is present in one eye, often the other eye will also present with the condition in the future. For example, 50% of cases where a wet-AMD type lesion occurs in one eye, a lesion occurs in the other eye within one year. Prophylactic administration of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition such as an anti-oedematous steroid, or more preferably a mineralocorticoid, may be useful. Prophylactic administration may also be useful in preparation for laser treatment of the retina.

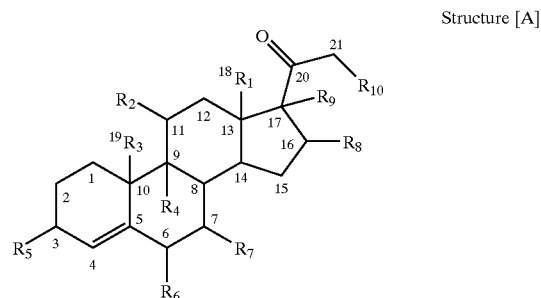
[0098] An 'individual' is a vertebrate, preferably mammal, more preferably a human. Mammals include, but are not limited to, humans, sport animals and pets, such as dogs and horses.

[0099] The terms 'treat', 'treatment' or 'treating' are used synonymously herein to describe the prevention, slowing, reversal or stopping of the exudative retinopathies to which the present invention is directed.

[0100] The phrase "therapeutically effective amount" is used herein to refer to an amount of therapeutic agent either as an individual compound or in combination with other compounds that is sufficient to induce a therapeutic effect on the ailment which the compound is applied to. This phrase should not be understood to mean that the dose must completely eradicate the ailment. What constitutes a therapeutically effective amount will vary depending on, inter alia, the biopharmacological properties of the compound used in the methodology, the condition being treated, the frequency of administration, the mode of delivery, characteristics of the individual to be treated the severity of the disease and the response of the patient. These are the types of factors that a skilled pharmaceutical chemist will be aware of and will be able to account for when formulating compositions for a treatment as here in described.

[0101] An effective quantity of the compound of interest is preferably employed in the method of the invention. For ocular and extraocular formulations, the concentration of the therapeutic compound may be in the range of about 0.01% w/w to about 10% w/w. Typically, the concentration for this mode of delivery is in the range of about 0.025% w/w to about 2.5% w/w.

[0102] In one aspect of the method of the invention, the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in accordance with the method of the invention is a mineralocorticoid of the general structure:



[0103] wherein

[0104] R_1 is CH_3 , $\text{CH}=\text{O}$, CH_2OH , $\text{CR}=\text{O}$, CH_2NH_2 , COCHCH_2 , NO_2X or CH_2X wherein X is F, Cl, Br;

[0105] R_2 is H, OH, $=\text{O}$, NH_2 or CN;

[0106] R_3 is H, CH_3 or CH_2OH ;

[0107] R_4 is H, F or Cl;

[0108] R_5 is H, OH, $=\text{O}$, SH, NH_2 , CN, NO_2 , CH_3 , CH_2OH , $\text{CH}=\text{O}$, X, CH_2X , OR, OCOR, $\text{OPO}(\text{OR})_2$, $=\text{CH}_2$ or CHR wherein X is F, Cl, Br;

[0109] R_6 is H, CH_3 or X wherein X is F, Cl, Br;

[0110] R_7 is H, OH, CH_3 , Alkyl, Ph, X, OCH_3 , OR, SCOCH_3 , SCOR, OCOR, CH_2OH , CH_2X , $\text{CH}=\text{O}$, $\text{CR}=\text{O}$ or NHCOR wherein X is F, Cl, Br;

[0111] R_8 is H, OH, CH_3 , CH_2CH_3 , SH, NH_2 or X wherein X is F, Cl, Br;

[0112] R_9 is H, OH, SH, NH_2 , CH_3 , CH_2CH_3 or X wherein X is F, Cl, Br;

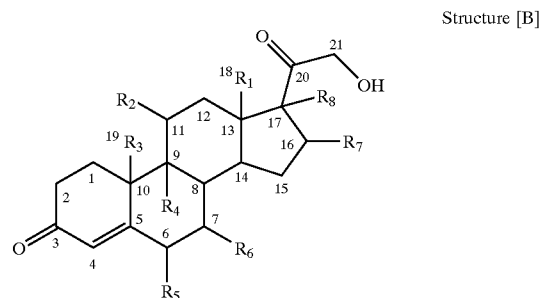
[0113] R_{10} is H, OH, CH_3 , CH_2CH_3 , SH, NH_2 , CH_2OH , CH_2CH_2OH , OR, $OCOR$, $OPO(OR)_2$, $NHCOR$, $CH=O$, X or CH_2X wherein X is F, Cl, Br; and

[0114] wherein said compound is not a compound disclosed in U.S. Pat. No. 6,011,023 where the compound is to be used to treat or prevent ocular diseases selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0115] Preferably, the compound of Structure [A] is used in the method of the present invention to treat or prevent an ophthalmic condition selected from the list comprising: diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; or cytomegalovirus infection.

[0116] In another aspect of the invention, the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in

accordance with the method of the invention is a mineralocorticoid of the general structure:



[0117] wherein

[0118] R_1 is CH_3 , $CH=O$ or $COCHCH_2$;

[0119] R_2 is H, OH or $=O$;

[0120] R_3 is H, CH_3 or CH_2OH ;

[0121] R_4 is H, or F;

[0122] R_5 , R_6 and R_7 are H; and

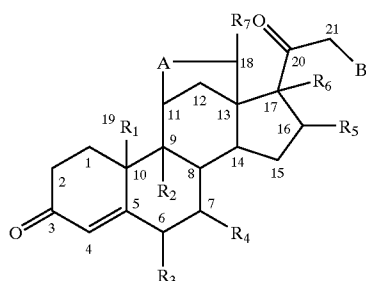
[0123] R_8 is H or OH; and

[0124] wherein said compound is not a compound disclosed in U.S. Pat. No. 6,011,023 where the compound is to be used to treat or prevent ocular diseases selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0125] Preferably, the compound of Structure [B] is used in the method of the present invention to treat or prevent an ophthalmic condition selected from the list comprising: diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic,

conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; Cytomegalovirus infection.

[0126] In a further aspect of the invention, the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in accordance with the method of the invention is a mineralocorticoid of the general structure:



Structure [C]

[0127] wherein

[0128] A is O, S, NH, CH₂, CHOH, C=O, CHX, CHCH₃, CH₂CH₂, OCH₂, SCH₂, NHCH₂, NRCH₂, NCOR wherein X is F, Cl, Br;

[0129] B is H, OH, SH, NH₂, CH₃, CH₂OH, CH₂CH₂OH, CH=O, X, CH₂X, OR, OCOR, OPO(OR)₂, NHCOR wherein X is F, Cl, Br;

[0130] R₁ is H, CH₃, CH=O, CH₂OH;

[0131] R₂ is H, F OR Cl;

[0132] R₃ is H, CH₃ or X wherein X is F, Cl, Br;

[0133] R₄ is H, OH, CH₃, Alkyl, Ph, X, OCH₃, SH, NH₂, OR, SCOCH₃, SCOR, OCOR, CH₂OH, CH₂X, CH=O, CR=O, SR or NHCOR wherein X is F, Cl, Br;

[0134] R₅ is H, CH₃, CH₂CH₃, OH, SH, NH₂ or X wherein X is F, Cl, Br;

[0135] R₆ is H, OH, SH, NH₂, CH₂CH₃, CH₃ or X wherein X is F, Cl, Br;

[0136] R₇ is H, OH, SH, NH₂, NO₂, CH=O, CH₃, CO₂H, CN, CH₂CH₃, CH₂X or X wherein X is F, Cl, Br;

[0137] wherein said compound is not a compound disclosed in U.S. Pat. No. 6,011,023 where the compound is to

be used to treat or prevent ocular diseases selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0138] Preferably, the compound of Structure [C] is used in the method of the present invention to treat or prevent an ophthalmic condition selected from the list comprising: diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; or cytomegalovirus infection.

[0139] The compound used in the method of the present invention to treat or prevent an ocular condition by modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye may further be selected from the group comprising hydrocortisone hemisuccinate, hydrocortisone sodium phosphate, methylprednisolone hemisuccinate, prednisolone hemisuccinate, or prednisolone sodium succinate.

[0140] Alternatively, the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in accordance with the method of the invention may be selected from the group of compounds comprising: dexamethasone sodium phosphate,

hydrocortisone sodium succinate, methylprednisolone sodium succinate, wherein the ophthalmic condition to be treated or prevented is other than an ophthalmic condition selected from the list comprising: allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, chorioretinitis, optic neuritis, anterior ischaemic optic neuropathy, iridocyclitis, iritis, diffuse posterior uveitis, choroiditis, sympathetic ophthalmia, anterior segment inflammation and herpes zoster ophthalmicus.

[0141] In a further alternative, the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in accordance with the method of the invention may be selected from the group of compounds comprising: deoxycorticosterone acetate, deoxycorticosterone pivalate, dexamethasone acetate, hydrocortisone butyrate, hydrocortisone valerate, prednisolone pivalate, prednisolone tebutate, wherein the ophthalmic condition to be treated or prevented is other than an ophthalmic condition selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0142] The compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in accordance with the method of the invention may preferably be selected from the group of compounds comprising: cortisone, cortisone acetate, dexamethasone sodium phosphate, dexamethasone, hydrocortisone, hydrocortisone acetate, methylprednisolone, methylprednisolone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisone, prednisone sodium phosphate, wherein the ophthalmic condition to be treated or prevented is other than an ophthalmic condition selected from the list comprising allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, chorioretinitis, optic neuritis, anterior ischaemic optic neuropathy, iridocyclitis, iritis, diffuse posterior uveitis, choroiditis, sympathetic ophthalmia, anterior segment inflammation and herpes zoster ophthalmicus, nonpurulent conjunctivitis, blepharitis, scleritis, episcleritis, uveitis, retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of

the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0143] In another form of the invention, the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in accordance with the method of the invention may be selected from the group of compounds comprising: amcinonide, clocortolone butyrate, flunisolide, flucuronide, flurandrenolide, fluticasone, fluticasone propionate, halcinonide, mometasone furoate.

[0144] Alternatively, the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in accordance with the method of the invention may be selected from the group of compounds comprising: clobetasol propionate, clobetasol butyrate, clocortolone butyrate, clobetasone pivalate, desoxymetasone, diflorasone, diflorasone diacetate, diflucortolone, diflucortolone valerate, flumethasone, flumethasone pivalate, fluocinolone, fluocortolone, fluocortolone hexanoate, fluocortolone pivalate, fluorometholone, isoflupredone, isoflupredone acetate, mometasone, wherein the ophthalmic condition to be treated or prevented is other than an ophthalmic condition selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0145] Rimexolone and fluocinolone acetonide may also be used in the method of the present invention as the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition, wherein the ophthalmic condition to be treated or prevented is other than an ophthalmic condition selected from the list comprising: anterior chamber inflammation and anterior uveitis, retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0146] In a preferred form of the invention, the compound capable of modulating the activity of mineralocorticoid

receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in accordance with the method of the invention is the mineralocorticoid aldosterone (11β -11,21-dihydroxy-3,20-dioxopregnen-4-en-18-al; CAS 52-39-1) or an analogue, pharmaceutically acceptable salt, conjugate or derivative thereof that is preferably sparingly soluble in the vitreous.

[0147] Aldosterone may be isolated from living tissues by a number of methods such as those disclosed in Simpson et al (1953) *Experimentia* 9:333; Simpson et al (1954) *Helv Chim Acta* 37:1163; Mattox et al (1953) *J Am Chem Soc* 75:4869; or Harman et al (1954) *J Am Chem Soc* 76:5035.

[0148] Alternatively, aldosterone may be synthesised using methods derived from any one of the following references: Schmidlin et al (1957) *Helv Chim Acta* 40:1483; Johnson et al (1958) *J Am Chem Soc* 80:2585; Johnson et al (1963) *J Am Chem Soc* 85:1409; Barton & Beaton (1960) *J Am Chem Soc* 82:2640; Barton & Beaton (1961) *J Am Chem Soc* 83:4083; Barton et al (1975) *J Chem Soc Perkin Trans I* 2243; or Miyano (1981) *J Org Chem* 46:1846.

[0149] In a highly preferred form of the invention, the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in accordance with the method of the invention is a compound selected from the list comprising the mineralocorticoids: fludrocortisone (11β -9 α -fluoro- 11β , 17α ,21-trihydroxy-4-pregene-3,20-dione; CAS 127-31-1) or fludrocortisone acetate; deoxycorticosterone (cortexone or 21-hydroxypregn-4-ene-3,20-dione; CAS 64-85-7); 11-desoxycortisone (17α ,21-dihydroxypregn-4-ene-3,20-dione; CAS 152-58-9); or deoxycorticosterone acetate (21-hydroxypregn-4-ene-3,20-dione 21 acetate; CAS 56-47-3) or an analogue, pharmaceutically acceptable salt, conjugate or derivative thereof that is preferably sparingly soluble in the vitreous, wherein the ophthalmic condition to be treated or prevent is other than an ophthalmic condition selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0150] Preferably, the fludrocortisone, fludrocortisone acetate, deoxycorticosterone, 11-desoxycortisone, or deoxycorticosterone acetate is used in the method of the present invention to treat or prevent an ophthalmic condition selected from the list comprising: diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, dia-

betic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; or cytomegalovirus infection.

[0151] Synthesis of fludrocortisone may be carried out using the method of Fried & Sabo (1954) *J Am Chem Soc* 76:1455, or alternatively fludrocortisone acetate may be synthesised using the method of U.S. Pat. No. 2,957,013.

[0152] Synthesis of deoxycorticosterone may be achieved using the method disclosed in Schindler et al (1941) *Helv Chim Acta* 24:371; DE Patent 875,353; DE Patent 871,153; U.S. Pat. No. 2,778,776; NL Patent 89,575; or DE Patent 1,028,572, and similar methods may be used to manufacture the related compound deoxycorticosterone acetate.

[0153] 11-desoxycortisone synthesis may be carried out using the methods of any of the following articles: Reichstein & von Euw (1938) *Helv Chim Acta* 21:1197; Reichstein (1938) *Helv Chim Acta* 21:1490; Reichstein & von Euw (1940) *Helv Chim Acta* 23:1258; Sarett (1946) *J Biol Chem* 162:627; Gallagher et al (1949) *J Am Chem Soc* 71:3262; Julian et al (1949) *J Am Chem Soc* 71:3574; or Julian et al (1950) *J Am Chem Soc* 72:5145.

[0154] The preferred mineralocorticoids used in the method of the present invention may be administered alone, or in various combinations of two, three, four or more mineralocorticoids. For example, the mineralocorticoids may be administered in combinations of two mineralocorticoids such as: aldosterone and fludrocortisone; aldosterone and deoxycorticosterone; deoxycorticosterone and fludrocortisone acetate; deoxycorticosterone and 11-desoxycortisone; 11-desoxycortisone and fludrocortisone acetate aldosterone and 11-desoxycortisone; fludrocortisone and deoxycorticosterone; 11-desoxycortisone and fludrocortisone, aldosterone and deoxycorticosterone acetate, or any other combination.

[0155] Alternatively, the mineralocorticoids may be administered in triple combinations such as: aldosterone and fludrocortisone and 11-desoxycortisone; aldosterone and deoxycorticosterone and 11-desoxycortisone; fludrocortisone and deoxycorticosterone and 11-desoxycortisone; aldosterone and deoxycorticosterone and fludrocortisone acetate; or deoxycorticosterone acetate and 11-desoxycortisone and fludrocortisone or any other combination.

[0156] The mineralocorticoids may also be administered as a quadruple therapy if required eg. aldosterone, fludrocortisone, deoxycorticosterone and 11-desoxycortisone; or aldosterone, deoxycorticosterone acetate, 11-desoxycortisone and fludrocortisone acetate.

[0157] Combinations of five preferred compounds are also contemplated.

[0158] In another embodiment the invention resides in a method for the treatment of an ophthalmic condition in an individual comprising administering to the individual a therapeutically effective pharmaceutically acceptable formulation (that is, containing buffers and excipients as known to one skilled in the art) of a combination of: (a) a mineralocorticoid wherein said mineralocorticoid is (i) capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition; and (ii) in a pharmaceutically acceptable form suitable for delivery to the eye; and (b) at least a second compound in a concentration and dose sufficient to reduce ocular neovascularization wherein the second compound is selected from the group consisting of: a tetracycline derivative, a steroid, heparin, an antimicrobial, an anti-prostaglandin, and/or a metalloproteinase inhibitor.

[0159] In one form, formulations used in the method of the invention comprise a mineralocorticoid at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and a steroid at a concentration from about 0.1 mg/ml to about 40 mg/ml . Steroids are usually administered for ocular pathologies such as uveitis, diabetic retinopathy, idiopathic juxtafoveal telangiectasias, macular oedema secondary to diabetes mellitus, central retinal vein occlusion, pseudophakia, during photodynamic therapy for age related macular degeneration, etc., and for intraoperative visualization of the posterior hyaloid, which also desirably inhibits ocular neovascularization.

[0160] An undesirable and serious side effect of ocular steroid therapy is increased intraocular pressure, termed glaucoma or ocular hypertension. For patients with glaucoma or predisposed to glaucoma, steroid therapy presents a risk of unacceptably high intraocular pressure, such that surgery may be required to lower the intraocular pressure. Such risks and benefits must be balanced in determining whether to treat the patient with triamcinolone or other steroids.

[0161] The formulations and methods to predict patients at risk for glaucoma from steroid therapy, disclosed in co-pending U.S. patent application Ser. No. 10/787,580, and PCT/AU2005/000263 which are expressly incorporated by reference herein in their entirety. The co-pending applications provide a method to evaluate a patient's risk for the increased intraocular pressure that is known to occur in some patients receiving intraocular steroid therapy. In particular, a method is provided to evaluate a patient's risk for increased intraocular pressure after receiving intraocular steroid therapy comprising the steps of: (a) administering to an eye a steroid at a challenge dose ranging from about 50 μg to about 800 μg ; and (b) determining what the intraocular pressure is in the eye after delivery of the challenge dose.

[0162] According to the method a steroid such as triamcinolone is administered at a challenge dose ranging from

about 50 μg to about 800 μg , and the intraocular pressure is thereafter determined. In one embodiment, about 400 μg triamcinolone is administered. An intraocular pressure of at least 5 mm Hg higher after the challenge dose than an intraocular pressure before the challenge dose indicates that the patient would likely have increased intraocular pressure if a therapeutic dose of a steroid, such as about 4 mg to about 8 mg triamcinolone, were administered. The physician will then be better able to evaluate the benefits and risks of this therapy versus alternate therapy. The challenge dose may be injected into the vitreous of the eye, or it may be injected into another area or site in the eye, or it may be implanted in the eye, etc.

[0163] Steroids for ocular administration include, but are not limited to: triamcinolone (Aristocort®; Kenalog®), betamethasone (Celestone®), budesonide, fluorometholone (fluorometholone acetate (Flarex® (Alcon); Eflone®), fluorometholone alcohol (FML® and FML-Mild®, (Allergan); FluorOP®)), medrysone alcohol (HMSO (Allergan)); loteprednol etabonate (Lotemax® and Alrex® (Bausch & Lomb)), and anecortave acetate (Alcon). It will be appreciated that the above list is representative only and is not exclusive.

[0164] In a highly preferred form of the invention the steroid used in the formulation is a 11-substituted-16 α , 17 α -substituted methylenedioxy steroid selected from the compounds disclosed in U.S. Pat. No. 5,770,589 to Billson and Penfold ("US '589"), which was filed as U.S. application Ser. No. 08/586,750, and is incorporated herein in its entirety by reference. Alternatively, the compound is a steroid disclosed in Fried et al. (1958) J. Am. Chem. Soc. 80, 2338 (1958); U.S. Pat. Nos. 2,990,401; 3,048,581 or 3,035,050 each of which is expressly herein incorporated by reference. Collectively these publications also provide methods for the manufacture of such compounds and are also incorporated for the purposes of disclosing such methods. Desirably the steroid used in the method is triamcinolone acetonide.

[0165] The steroid concentration in the formulation used in the method of the present invention ranges from about 0.1 mg/ml to about 40 mg/ml . More preferably the steroid concentrations range from about 1 mg/ml to about 20 mg/ml . Alternatively, steroid concentrations range from about 20 mg/ml to about 30 mg/ml or they can range from about 20 mg/ml to about 40 mg/ml .

[0166] The steroid concentration used with a particular formulation will depend upon the particular steroid that is used. For example, triamcinolone acetonide (9 α -fluoro-11, 13, 16 α , 17, 21 tetra hydroxy-pregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone ($\text{C}_{24}\text{H}_{31}\text{FO}_6$)) Kenacort®, Kenalog® (Bristol-Myers Squibb, Princeton N.J.) may be administered at a therapeutic dose in the range of about 4 mg to about 8 mg , for example, by intravitreal injection. In comparison, anecortave acetate, a steroid with less potential to cause an increase in intraocular pressure than triamcinolone but not used inside the eye, may be administered at a dose of about 0.5 mg/ml to about 30 mg/ml .

[0167] In a highly preferred form the following formulations may be used in the method of the present invention: a 1:1 combination of about 5 $\mu\text{g/ml}$ fludrocortisone and about 4 mg/ml triamcinolone acetonide; a 1:1 combination of about 5 $\mu\text{g/ml}$ deoxycorticosterone acetate and about 4

mg/ml triamcinolone acetonide. In a second form, formulations used in the method of the invention comprise a mineralocorticoid in a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and heparin in a concentration from about 0.01 $\mu\text{g/ml}$ to about 30 mg/ml.

[0168] Heparin is a heterogeneous group of straight-chain anionic mucopolysaccharides, termed glycosaminoglycans, having anticoagulant activity. The primary sugars are α -L-iduronic acid 2-sulfate, 2-deoxy-2-sulfamino- α -D-glucose 6-sulfate, (3-D-glucuronic acid, 2-acetamido-2-deoxy- α -D-glucose, and α -L-iduronic acid. These sugars are present in different amounts and are joined by glycosidic linkages, forming polymers of varying sizes. Heparin is strongly acidic because of its content of covalently linked sulfate and carboxylic acid groups. In heparin sodium, the acidic protons of the sulfates are partially replaced by sodium ions. In one embodiment of the invention, low molecular weight heparin is used. Low molecular weight heparin is derived from unfractionated heparin through either chemical or enzymatic depolymerization, and is commercially available. Unfractionated heparin has a molecular weight of about 5,000 daltons to about 30,000 daltons, while low molecular weight heparin has a molecular weight of about 1,000 daltons to about 10,000 daltons. Compared to unfractionated heparin, low molecular weight heparin binds less strongly to protein, has enhanced bioavailability, interacts less with platelets and yields a predictable dose response and dose-dependent plasma levels, and produces less bleeding for a given antithrombotic effect. Low molecular weight heparin may be heparin sulfate, a lower-sulfated, higher-acetylated form of heparin. All of these are commercially available (e.g., Sigma Aldrich, St. Louis Mo.).

[0169] A possible mechanism for the beneficial effect of heparin or low molecular weight heparin in reducing vessel growth and proliferation is its polyanionic structure, which readily binds to polycationic angiogenic factors. Angiogenic factors with heparin bound to them have reduced biological activity, and therefore do not promote new vessel growth. In vivo, heparin sulfates are bound to the extracellular matrix (ECM) and endothelial cell surfaces. Heparin sulfate in the ECM may have a role in storing active growth factors that can be released when needed to exert immediate effects. Soluble heparins compete with heparin sulfates on the ECM for growth factors and proteins, and may consequently cause their release. Unfractionated heparin may cause an increase in the plasma level of growth factors. Unlike unfractionated heparin, which may promote angiogenesis, low molecular weight heparin may hinder the binding of growth factors to their high affinity receptors as a result of its smaller size. Low molecular weight heparin may affect the injured neovascular cornea by binding angiogenic factors that have been released from the ECM, as well as competitively (antagonistically) binding to angiogenic receptors.

[0170] In one embodiment, the concentration of heparin or low molecular weight heparin used in the method of the invention to treat or prevent an ophthalmic conditions ranges from about 0.01 $\mu\text{g/ml}$ to about 30 mg/ml. Alternatively, heparin or low molecular weight heparin may be administered in a concentration ranging from about 1 mg/ml to about 10 mg/ml. In a more preferred form of the invention, the concentration of heparin or low molecular weight heparin ranges from about 0.5 mg/ml to about 15 mg/ml to 20 mg/ml (for example, administration of 0.1 ml of a 100 mg/ml

formulation of low molecular weight heparin). In various embodiments, the concentration may be about 0.5 mg/ml to about 2.5 mg/ml, about 1 mg/ml to about 5 mg/ml, about 5 mg/ml to about 10 mg/ml, or about 5 mg/ml to about 30 mg/ml. Any concentration within these ranges may be used.

[0171] In a highly preferred form the following formulations may be used in the method of the present invention: a 1:1 combination of about 5 $\mu\text{g/ml}$ fludrocortisone and about 10 mg/ml low molecular weight heparin; a 1:1 combination of about 5 $\mu\text{g/ml}$ deoxycorticosterone acetate and about 10 mg/ml low molecular weight heparin. In a third form, formulations used in the method of the present invention to treat or prevent an ophthalmic conditions comprise a mineralocorticoid in a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and an anti-prostaglandin in a concentration from about 1 $\mu\text{g/ml}$ to about 10 mg/ml (such as a 1 $\mu\text{g/ml}$ to about 10 mg/ml dose of flurbiprofen).

[0172] Anti-prostaglandins, also termed prostaglandin antagonists, may be administered in a concentration sufficient to result in a prostaglandin-inhibitory effect. As one example, antiprostaglandins such as flurbiprofen may be administered at a concentration in the range of about 0.001%^{w/v} to about 0.5%^{w/v}. As an example, OCUFEN® (flurbiprofen sodium 0.03% (Allergan), sodium ($\pm$)-2-(2-fluoro-4-biphenyl)-propionate dihydrate) 0.03% may be administered at a concentration ranging from about 0.003%^{w/v} to about 0.3%^{w/v}. Anti-prostaglandins other than flurbiprofen may be included. The anti-prostaglandins may be administered at the doses and by the methods previously described, and include indomethacin, ketorolac, tromethamine 0.5% (($\pm$)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) (ACULAR® Allergan, Irvine Calif.), meclofenamate, flurbiprofen, and compounds in the pyrrolo-pyrrole group of non-steroidal anti-inflammatory drugs (NSAIDs). For example, ACUALRD may be administered at a concentration ranging from about 0.003%^{w/v} to about 0.3%^{w/v}. In one embodiment, the concentration of ACULAR® is about 0.03%^{w/v}.

[0173] In specific embodiments, the following formulations may be used in the method of the present invention: a 1:1 combination of about 0.03%^{w/v} flurbiprofen and about 5 $\mu\text{g/ml}$ fludrocortisone; a 1:1 combination of about 0.03%^{w/v} flurbiprofen and about 5 $\mu\text{g/ml}$ deoxycorticosterone acetate. For example, the formulation might comprise an actual concentration of 0.015% flurbiprofen with 5 $\mu\text{g/ml}$ fludrocortisone or 0.015% flurbiprofen with 5 $\mu\text{g/ml}$ deoxycorticosterone acetate.

[0174] In a fourth form, formulations used in the method of the invention comprise a mineralocorticoid in a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and an antimicrobial, like for example a macrolide antibiotic, in a concentration from about 20 $\mu\text{g/ml}$ to about 200 $\mu\text{g/ml}$ (about 0.002%^{w/v} to about 0.02%^{w/v}).

[0175] A possible mechanism for the beneficial effect of macrolide antibiotics are their anti-inflammatory effect.

[0176] Macrolide antibiotics that can be added to the formulation used in the method of treatment of ophthalmic conditions include, inter alia: tacrolimus, cyclosporine, sirolimus, everolimus, ascomycin, erythromycin, azithromycin, clarithromycin, clindamycin, lincomycin, dirithro-

mycin, josamycin, spiramycin, diacetyl-midecamycin, tylosin, roxithromycin, ABT-773, telithromycin, leucomycins, and lincosamide. Other antibiotics include, but are not limited to, aminoglycosides (e.g., streptomycin, amikacin, gentamicin, tobramycin), cephalosporins (e.g., beta lactams including penicillin), tetracyclines, acyclovir, amantadine, polymyxin B, amphotericin B, amoxicillin, ampicillin, atovaquone, azithromycin, azithromycin, bacitracin, cefazolin, cefepime, cefotaxime, cefotetan, cefpodoxime, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cephalexin, chloramphenicol, clotrimazole, ciprofloxacin, clarithromycin, clindamycin, dapsone, dicloxacillin, fluconazole, foscarnet, ganciclovir, gatifloxacin, griseofulvin, isoniazid, itraconazole, ketoconazole, metronidazole, nafcillin, neomycin, nitrofurantoin, nystatin, pentamidine, rifampin, rifamycin, valacyclovir, vancomycin, etc. The indications, effective doses, formulations, contraindications, vendors, etc. of these antibiotics are known to one skilled in the art.

[0177] Macrolide antibiotics can be administered in a concentration ranging from about 20 $\mu\text{g/ml}$ to about 200 $\mu\text{g/ml}$ (about 0.002%^{w/v} to about 0.02%^{w/v}). Formulations and doses of macrolide antibiotics are described in co-pending U.S. patent application Ser. Nos. 10/667,161 and 10/752,124, each of which is expressly incorporated by reference herein in its entirety.

[0178] In addition to a macrolide antibiotic the formulation used in the method can also include mycophenolic acid. Such a formulation when prepared as a pharmaceutically acceptable topically administered solution may include about 0.5%^{w/v} to about 10%^{w/v} mycophenolic acid. Preferably, a concentration of macrolide antibiotic and/or mycophenolic acid in a pharmaceutically acceptable topically administered solution may range from about 3%^{w/v} to about 5%^{w/v}. In another embodiment, a concentration of macrolide antibiotic and/or mycophenolic acid in a pharmaceutically acceptable topically administered solution may range from about 1 %^{w/v} to about 3 %^{w/v}. In another embodiment, a concentration of macrolide antibiotic and/or mycophenolic acid in a pharmaceutically acceptable topically administered solution may range from about 3%^{w/v} to about 10%^{w/v}. In another embodiment, a concentration of macrolide antibiotic and/or mycophenolic acid may range from about 0.1% to about 10% in a topical ocular formulation for treating diabetic retinopathy, age related macular degeneration, or retinitis pigmentosa. In another embodiment, concentrations of macrolide antibiotic and/or mycophenolic acid up to about 2%, up to about 5%, up to about 10%, or exceeding 10% are formulated for topical administration when the compound(s) is bound to a matrix or polymer which slowly releases the compound(s) over time while not exceeding an intraocular concentration of 40 $\mu\text{g/ml}$.

[0179] In a form of this embodiment, the invention is a method of treating or preventing an ophthalmic condition using a formulation comprising a mineralocorticoid in a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml in a pharmaceutically acceptable form suitable for delivery to the eye and a tetracycline derivative (such as doxycycline, demeclocycline, minocycline, oxytetracycline, lymecycline, or a chemically modified tetracycline (CMT)) at a concentration from about 0.01 pg/ml to about 30 mg/ml .

[0180] As used herein a tetracycline or a derivative thereof, including CMTs which inhibit MMP activity, will

include, inter alia: doxycycline, demeclocycline, minocycline, oxytetracycline, lymecycline, or a chemically modified tetracycline. Chemically modified tetracyclines (CMT) include demeclocycline, minocycline, oxytetracycline and like compounds that inhibit the synthesis of MMP-8 and MMP-9. These include CMT such as CMT-315, CMT-3, CMT-8, and CMT-308; 6-demethyl-6-deoxy-4-dedimethylaminotetracycline (COL-3), and others, for example, as described by Liu et al., A Chemically Modified Tetracycline (CMT-3) Is a New Antifungal Agent in Antimicrobial Agents Chemother. 2002 May; 46:1447; Seftor et al., Targeting the Tumor Microenvironment with Chemically Modified Tetracyclines: Inhibition of Laminin 5 γ 2 Chain Promigratory Fragments and Vasculogenic Mimicry 2002 November; 1:1173, which are expressly incorporated by reference herein.

[0181] Tetracyclines exert their biological effects independent of their antimicrobial activity. That is, they inhibit MMPs and can prevent pathogenic tissue destruction. Furthermore, recent studies have suggested that tetracyclines and inhibitors of metalloproteinases suppress tumour progression, bone resorption, and angiogenesis and may have anti-inflammatory properties. Thus, a possible mechanism for the beneficial effect of tetracyclines and like compounds in reducing vessel growth and proliferation in the ocular region is via inhibition of metalloproteinases, which are zinc-dependent proteinase enzymes associated with the tumorigenic process. Selective inhibition of such metalloproteinase by the inventive formulations and methods described herein is believed to inhibit reactions leading to ocular neovascularization. Such metalloproteinase inhibitors are also included in the invention.

[0182] In a highly preferred form of the invention, the tetracycline derivative employed in the formulation is doxycycline. Doxycycline (4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide monohydrate, $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_8\cdot\text{H}_2\text{O}$) is a commercially available broad spectrum antibiotic in the class of tetracycline antibiotics. The doxycycline in this form of the invention is preferably present as a 2% solution of doxycycline at a substantially neutral pH in combination with the mineralocorticoid.

[0183] The concentration of doxycycline employed in this form of the invention will range from 0.01 $\mu\text{g/ml}$ to about 30 mg/ml . More specifically, doxycycline concentrations will range from about 0.05 mg/ml to about 1 mg/ml . Alternatively doxycycline concentrations will range from about 0.05 mg/ml to about 10 mg/ml . Yet again doxycycline concentrations can range from about 1 mg/ml to about 20 mg/ml . These doses are substantially non-toxic to the patient. Besides its anti-angiogenic effect, doxycycline could reduce the incidence of endophthalmitis, which occurs in about 0.5% of eyes in which a steroid is administered.

[0184] In a highly preferred form the formulation used in the method of the invention may comprise: a 1:1 combination of about 20 mg/ml doxycycline and about 5 $\mu\text{g/ml}$ fludrocortisone; a 1:1 combination of about 20 mg/ml doxycycline and about 5 $\mu\text{g/ml}$ deoxycorticosterone acetate.

[0185] In a fifth form, the formulation used in the method of the present invention comprises a mineralocorticoid in a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and an inhibitor of a metalloproteinase in a concentration and dose to reduce ocular neovascularization.

[0186] Inhibitors of metalloproteinases include naturally occurring proteins such as TIMP-1 that specifically inhibit matrix metalloproteinases, and synthetic metalloproteinase inhibitors such as Batimastat (BB-94) and marimastat (BB-2516) which potently and specifically inhibit metalloproteinase production. These inhibitors degrade the extracellular matrix, promoting tumor invasion and metastasis, but also regulate host defense mechanisms and normal cell function. Selective inhibition is expected to inhibit reactions leading to neovascularization in the inventive formulations and methods. Such metalloproteinase inhibitors are also included in the invention. Among the twenty-four MMPs described, eight have been identified in the cornea, i.e., collagenase I and III (MMP-1 and MMP-13), gelatinase A and B (MMP-2 and -9), stromelysin (MMP-3), matrilysin (MMP-7) and membrane type MMP (MMP-14).

[0187] In an alternate embodiment of the invention the formulation used to treat or prevent an ophthalmic condition comprises: (a) a mineralocorticoid wherein said mineralocorticoid is: (i) capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition; and (ii) in a pharmaceutically acceptable form suitable for delivery to the eye; and (b) a plurality of compounds in a concentration and dose to reduce ocular neovascularization, wherein the plurality of compounds are selected from the group consisting of: a tetracycline derivative, a steroid, heparin, an antimicrobial, an anti-prostaglandin, and/or a metalloproteinase inhibitor.

[0188] Where there are a plurality of tetracycline derivative, steroid, heparin, antimicrobial, anti-prostaglandin, and/or metalloproteinase inhibitor compounds employed in the method, the preferred compounds and their doses will be those which are described above.

[0189] In a further aspect of the present invention, there is provided a method of treatment of an individual with an ophthalmic condition by administering to the individual a therapeutically effective amount of an anti-oedematous steroid or a pharmaceutically acceptable salt thereof; wherein said anti-oedematous steroid does not include compounds disclosed in U.S. Pat. No. 6,011,023 when used to treat or prevent ocular diseases selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0190] In one embodiment, the invention provides a method of treatment of an ophthalmic condition in an individual comprising: administering a dose of an anti-oedematous steroid or a pharmaceutically acceptable salt thereof, wherein the ophthalmic condition is selected from the group comprising: diffuse lamellar keratitis, corneal

diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; cytomegalovirus infection.

[0191] In a further aspect of the invention, there is provided a method of treatment of an ophthalmic condition in an individual comprising: administering a dose of an anti-oedematous steroid or a pharmaceutically acceptable salt thereof, wherein the ophthalmic condition is an exudative retinopathy. The present invention also provides a method for the prophylactic or therapeutic treatment of exudative retinopathies comprising administering a therapeutically effective amount of an anti-oedematous steroid, to at least an ocular tissue selected from the group consisting of: retinal cells, retinal pigment epithelial cells, the epithelial cells of the BRB, choroidal endothelial cells.

[0192] In another embodiment the invention provides a method for the treatment of an ailment resulting from the breakdown of the BRB in the posterior region of the retina, said method comprising the step of: administering a therapeutically effective amount of an anti-oedematous steroid to said ailment. Generally, ailments located in the posterior region of the retina arising from breakdown of the BRB will include myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, macular oedema arising from laser treatment of the retina and exudative macular degeneration.

[0193] According to another embodiment the invention provides a method for the treatment or prophylaxis of exudative retinopathies in a patient requiring said treatment or prophylaxis, comprising administering by intravitreal injection to said patient an effective amount of anti-oedematous steroid or a pharmaceutically acceptable salt thereof that is preferably sparingly soluble in the vitreous. Preferably, the anti-oedematous steroid used in the method of the invention is a mineralocorticoid steroid.

[0194] In a further aspect of the present invention, there is provided a method of treatment of an individual with an ophthalmic condition by administering to the individual a therapeutically effective amount of a mineralocorticoid or a pharmaceutically acceptable salt thereof as described herein; wherein said mineralocorticoid does not include compounds disclosed in U.S. Pat. No. 6,011,023 when used to treat or prevent ocular diseases selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0195] In one embodiment, the invention provides a method of treatment of an ophthalmic condition in an individual comprising: administering a dose of a mineralocorticoid or a pharmaceutically acceptable salt thereof as described herein, wherein the ophthalmic condition is selected from the group comprising diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctuate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; cytomegalovirus infection.

[0196] In a further aspect of the invention, there is provided a method of treatment of an ophthalmic condition in an individual comprising: administering a dose of a mineralocorticoid or a pharmaceutically acceptable salt thereof as described herein, wherein the ophthalmic condition is an exudative retinopathy. The present invention also provides a

method for the prophylactic or therapeutic treatment of exudative retinopathies comprising administering a therapeutically effective amount of a mineralocorticoid, to at least an ocular tissue selected from the group consisting of: retinal cells, retinal pigment epithelial cells, the epithelial cells of the BRB, choroidal endothelial cells.

[0197] In another embodiment the invention provides a method for the treatment of an ailment resulting from the breakdown of the BRB in the posterior region of the retina, said method comprising the step of: administering a therapeutically effective amount of a mineralocorticoid as described herein to said ailment. Generally, ailments located in the posterior region of the retina arising from breakdown of the BRB will include myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, macular oedema arising from laser treatment of the retina and exudative macular degeneration.

[0198] According to another embodiment the invention provides a method for the treatment or prophylaxis of exudative retinopathies in a patient requiring said treatment or prophylaxis, comprising administering by intravitreal injection to said patient an effective amount of mineralocorticoid or a pharmaceutically acceptable salt thereof that is preferably sparingly soluble in the vitreous.

[0199] The invention also provides a pharmaceutical composition for the treatment or prophylaxis of ophthalmic conditions comprising a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissues located in the eye. Preferably such a compound is an anti-oedematous steroid.

[0200] The invention further provides a pharmaceutical composition for the treatment or prophylaxis of ophthalmic conditions comprising a therapeutically effective amount of a mineralocorticoid as described herein. Preferably, the mineralocorticoid is aldosterone or a pharmaceutically acceptable analogue, salt, conjugate or derivative thereof together with a pharmaceutically acceptable additive. More preferably, the mineralocorticoid is selected from the group comprising fludrocortisone, fludrocortisone acetate; deoxycorticosterone, 11-desoxycortisone, or deoxycorticosterone acetate or a pharmaceutically acceptable analogue, salt, conjugate or derivatives thereof together with a pharmaceutically acceptable additive.

[0201] The invention also provides a pharmaceutical composition for the treatment or prophylaxis of exudative retinopathies comprising a therapeutically effective amount of a mineralocorticoid selected from the group comprising fludrocortisone, fludrocortisone acetate; deoxycorticosterone, 11-desoxycortisone, or deoxycorticosterone acetate or a pharmaceutically acceptable analogue, salt, conjugate or derivatives thereof together with a pharmaceutically acceptable additive.

[0202] The invention also provides a pharmaceutical composition for the treatment or prophylaxis of exudative retinopathies comprising a therapeutically effective amount of a mineralocorticoid or pharmaceutically acceptable salt thereof as described herein in a biocompatible, biodegradable matrix, for example in a topical form or in a form for intravitreal injection.

[0203] The invention also provides a pharmaceutical composition or formulation for use in the methods of the invention comprising a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye (wherein said compound is preferably an anti-oedematous steroid or a pharmaceutically acceptable salt thereof and more preferably a mineralocorticoid) and at least a pharmaceutically acceptable additive (such as a carrier, adjunct, excipient or non-toxic, non-therapeutic, non-immunogenic stabilizers and the like). Preferably, the pharmaceutically acceptable additive should be compatible with the vitreous and should not leave any vision impairing residue in the eye. Desirably, any pharmaceutically acceptable additive used in the composition should be suited to the delivery of said pharmaceutical composition as an intravitreal depot injection.

[0204] The precise pharmaceutical formulation used in the method of the present invention will vary according to a wide range of commercial and scientific criteria. That is the skilled reader will appreciate that the above formulation of the invention described above may contain other agents.

[0205] For example, the formulations used in the methods of the invention are preferably prepared using a physiological saline solution as a vehicle. The pH of the formulation may be maintained at a substantially neutral pH (for example, about 7.4, in the range of about 6.5 to about 7.4, etc.) with an appropriate buffer system as known to one skilled in the art (for example, acetate buffers, citrate buffers, phosphate buffers, borate buffers).

[0206] Any diluent used in the preparation of the pharmaceutically acceptable formulation may preferably be selected so as not to unduly affect the biological activity of the formulation. Examples of such diluents which are especially useful for injectable formulations are water, the various saline, organic or inorganic salt solutions, Ringer's solution, dextrose solution, and Hank's solution.

[0207] In addition, the pharmaceutical formulation used in the method of the invention may include additives such as other buffers, diluents, carriers, adjuvants or excipients. Any pharmacologically acceptable buffer suitable for application to the eye may be used, e.g., tris or phosphate buffers. Other agents may be employed in the formulation for a variety of purposes. For example, buffering agents, preservatives, cosolvents, surfactants, oils, humectants, emollients, chelating agents, stabilizers or antioxidants may be employed. Water soluble preservatives which may be employed include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, sodium bisulfate, phenylmercuric acetate, phenylmercuric nitrate, ethyl alcohol, methylparaben, polyvinyl alcohol, benzyl alcohol and phenylethyl alcohol. A surfactant may be Tween 80.

[0208] Other vehicles that may be used include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose, purified water, etc. Tonicity adjusters may be included, for example, sodium chloride, potassium chloride, mannitol, glycerin, etc. Antioxidants include, but are not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole, butylated hydroxytoluene, etc. The indications, effective doses, for-

mulations, contraindications, vendors etc, of the compounds in the formulations are available or are known to one skilled in the art.

[0209] These agents may be present in individual amounts of from about 0.001% to about 5% by weight and preferably about 0.01% to about 2%. Suitable water soluble buffering agents that may be employed are sodium carbonate, sodium borate, sodium phosphate, sodium acetate, sodium bicarbonate, etc., as approved by the US FDA for the desired route of administration. These agents may be present in amounts sufficient to maintain a pH of the system of between about 2 to about 9 and preferably about 4 to about 8. As such, the buffering agent may be as much as about 5% (w/w) of the total formulation. Electrolytes such as, but not limited to, sodium chloride and potassium chloride may also be included in the formulation.

[0210] Compositions comprising the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye (which is preferably an anti-oedematous steroid or mineralocorticoid) used in the method of invention are preferably composed of Ringer's lactate and optionally ethyl alcohol, preferably in an amount of 10-20 mg/ml of the total composition, more preferably 15 mg/ml of the total composition. Other solvents may be used, including water. Ethyl alcohol may have an adjuvant effect upon the compound used.

[0211] Solid dispersions of the therapeutic compound as well as solubilized preparations can be used to perform the treatment method of the invention. For intraocular formulations (chemical delivery or delivery by invasive device), the therapeutic compound is delivered at a concentration high enough to achieve a final concentration in the range of about 0.1 $\mu\text{mol/L}$ to about 10 $\mu\text{mol/L}$ within the target ocular compartment (e.g. the posterior chamber for the treatment of retinal diseases). Typically, for this mode of delivery, the final concentration of the therapeutic compound is in the range of about 0.25 $\mu\text{mol/L}$ to about 5 $\mu\text{mol/L}$.

[0212] In a highly preferred form of the invention, when administering the mineralocorticoid by intravitreal injection for the prophylaxis or treatment of an ophthalmic condition, the mineralocorticoid should be as concentrated as feasible to minimise the volume for injection. The dosage of mineralocorticoid may be between about 1 μg and about 10 mg, or between about 1 mg and about 8 mg. Typically, about 4 mg of mineralocorticoid is deposited intravitreally. This dosage range is subject to the disease condition being treated.

[0213] The compositions of the present invention for the treatment or prevention of ophthalmic conditions may be provided in the form of a single unit dose in a pre-prepared syringe, ready for administration.

[0214] For topical administration, the concentration of mineralocorticoid administered may depend upon the particular patient, the underlying disease and its severity, the dosing frequency, etc., as known to one skilled in the art. Sample concentrations include, but are not limited to, about 0.5 $\mu\text{g/ml}$ to about 100 mg/ml, about 1 $\mu\text{g/ml}$ to about 500 $\mu\text{g/ml}$, about 0.5 mg/ml to about 2.5 mg/ml, about 1 mg/ml to about 5 mg/ml, about 5 mg/ml to about 10 mg/ml, about 10 mg/ml to about 15 mg/ml, about 15 mg/ml up to 30 mg/ml, about 20 mg/ml to about 50 mg/ml, 30 mg/ml up to 100 mg/ml etc.

[0215] In performing the method of the invention, pharmaceutically acceptable compounds may be administered to a patient by any method that leads to delivery of the therapeutic agent to the site of the ophthalmic condition (eg the location of an exudative retinopathy, anterior uveitis, pterygium, or macular oedema). Any of the formulations may be administered by an ocular route, such as topical, subconjunctival, sub-Tenon, intraocular, ocular implants etc.

[0216] Administration of the composition to perform the method of the invention is preferably by intraocular injection, although other modes of administration may be effective. Typically, pharmaceutically acceptable compounds will be delivered intraocularly (by chemical delivery system or invasive device) to an individual. However, the invention is not limited to intraocular delivery in that it also includes topically (extraocular application) or systemically (e.g. oral or other parenteral route) provided that a sufficient amount of the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent an eye achieves contact with the site of the ophthalmic condition. Parenteral administration is used in appropriate circumstances apparent to the practitioner. Preferably, the compositions are administered in unit dosage forms suitable for single administration of precise dosage amounts.

[0217] As mentioned above, delivery to areas within the eye, in situ can be accomplished by injection, cannula or other invasive device designed to introduce precisely metered amounts of a desired formulation to a particular compartment or tissue within the eye (e.g. posterior chamber or retina). An intraocular injection may be into the vitreous (intravitreal), or under the conjunctiva (subconjunctival), or behind the eye (retrobulbar), into the sclera, or under the Capsule of Tenon (sub-Tenon), and may be in a depot form. Other intraocular routes of administration and injection sites and forms are also contemplated and are within the scope of the invention.

[0218] Preferably, the intraocular injection is an intravitreal injection, preferably through self sealing 25-30 gauge needles or other suitably calibrated delivery device. Injection into the eye may be through the pars plana via the self-sealing needle. Most preferably, the compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent an eye (preferably an anti-oedematous steroid or mineralocorticoid) is administered as an intravitreal depot injection.

[0219] In one embodiment, the formulation is intraocularly injected (eg, into the vitreous) to treat or prevent an ophthalmic condition. When administering the formulation by intravitreal injection, the active agents should be concentrated to minimise the volume for injection. Preferably, the volume for injection is less than about 5 ml. Volumes such as this may require compensatory drainage of the vitreous fluid to prevent increases in intraocular pressure and leakage of the injected fluid through the opening formed by the delivery needle. More preferably, the volume injected is between about 1.0 ml and 0.05 ml. Most preferably, the volume for injection is approximately 0.1 ml.

[0220] For injection, a concentration less than about 20 mg/ml may be injected, and any amount may be effective depending upon the factors previously described. Preferably a dose of less than 7 mg/ml is administered, with doses of

less than 6 mg/ml, 5 mg/ml, 4 mg/ml 3 mg/ml, 2 mg/ml and 1 mg/ml being more preferred. Sample concentrations include, but are not limited to, about 5 μ g/ml to about 50 μ g/ml; about 25 μ g/ml to about 100 μ g/ml; about 100 μ g/ml to about 200 μ g/ml; about 200 μ g/ml to about 500 μ g/ml; about 500 μ g/ml to about 750 μ g/ml; about 500 μ g/ml up to 1 mg/ml etc.

[0221] Intravitreal injection may be achieved by a variety of methods well known in the art. For example, the eye may be washed with a sterilising agent such as Betadine® and the mineralocorticoid is injected in an appropriate carrier with a fine gauge needle (eg 27 gauge) at a position in the eye such that the steroid crystals will settle to the posterior pole towards the ventral surface. It may be necessary to prepare the eye for injection by application of positive pressure prior to injection. In some cases, paracentesis may be necessary. Local anaesthetic or general anaesthetic may be necessary.

[0222] In one example, to prepare for injection topical alcaine was applied to the ocular surface, followed by 5% povidone iodine. A cotton-tipped applicator soaked in 4% lidocaine was then applied to the injection site, which is 4.0 mm posterior to the limbus in phakic eyes and 3.5 mm posterior to the limbus in pseudophakic eyes. A 27-gauge needle was used for injection at the superior pars plana. Indirect ophthalmoscopy can be used to confirm proper intravitreal placement of the suspension.

[0223] The syringe used in practicing the method of this invention is suitably one which can accommodate a 21 to 30 gauge needle (eg a 23, 24, 25, 26 or 27 gauge needle) and is preferably of a small volume, for example 1.5 mL, or more preferably 0.5 mL. Although it is possible that the needle and syringe may be of the type where the needle is removable from the syringe, it is preferred that the arrangement is of a unitary syringe/needle construction. This would clearly limit the possibility of disengagement of the needle from the syringe. It is also preferred that the arrangement be tamper evident. The formulations of the present invention may therefore be provided in the form of a single unit dose in a pre-prepared syringe, ready for administration.

[0224] A suitable style of syringe is, for example, sold under the name of Uniject™ manufactured by Becton Dickinson and Company. In this style of syringe, the material is expelled through the needle into the eye by pressure applied to the sides of a pliable reservoir supplying the needle, rather than by a plunger. As the name implies, the construction of the reservoir and needle forms a single unit.

[0225] Topical application of formulations of the invention for the treatment or prevention of ophthalmic conditions may be as ointment, gel or eye drops. Preferably a penetrating composition comprising the mineralocorticoid is used. The topical formulation may further be an in situ gellable aqueous formulation. Such a formulation comprises a gelling agent in a concentration effective to promote gelling upon contact with the eye or with lacrimal fluid in the exterior of the eye. Suitable gelling agents include, but are not limited to, thermosetting polymers such as tetra-substituted ethylene diamine block copolymers of ethylene oxide and propylene oxide (e.g., poloxamine); polycarboxylic acid and polysaccharides such as gellan, carrageenan (e.g., kappa-carrageenan and iota-carrageenan), chitosan and alginate gums.

[0226] The phrase "in situ gellable" as used herein embraces not only liquids of low viscosity that form gels upon contact with the eye or with lacrimal fluid in the exterior of the eye, but also more viscous liquids such as semi-fluid and thixotropic gels that exhibit substantially increased viscosity or gel stiffness upon administration to the eye. Indeed, it can be advantageous to formulate a formulation of the invention as a gel, to minimize loss of the formulation immediately upon administration, as a result, for example, of lacrimation caused by reflex blinking. Although it is preferred that such a formulation exhibit further increase in viscosity or gel stiffness upon administration, this is not absolutely required if the initial gel is sufficiently resistant to dissipation by lacrimal drainage to provide the effective residence time specified herein.

[0227] To prepare a topical formulation for the treatment of ophthalmic conditions, a therapeutically effective amount of the formulation of the invention is placed in an ophthalmological vehicle as is known in the art. For example, topical ophthalmic formulations containing steroids are disclosed in U.S. Pat. No. 5,041,434, whilst sustained release ophthalmic formulations of an ophthalmic drug and a high molecular weight polymer to form a highly viscous gel have been described in U.S. Pat. Nos. 4,271,143 and 4,407,792. Further, U.K. Patent Application GB 2007091 A, describes an ophthalmic composition in the form of a gel comprising an aqueous solution of a carboxyvinyl polymer, a water-soluble basic substance and an ophthalmic drug. Alternatively, U.S. Pat. No. 4,615,697, discloses a controlled release composition and method of use based on a bioadhesive and a treating agent, such as an anti-inflammatory agent.

[0228] The amount of the therapeutic compound to be administered and the concentration of the compound in the topical formulations used in the method depend upon the diluent, delivery system or device selected, the clinical condition of the patient, the side effects and the stability of the compound in the formulation. Thus, the physician employs the appropriate preparation containing the appropriate concentration of the therapeutic compound and selects the amount of formulation administered, depending upon clinical experience with the patient in question or with similar patients.

[0229] Where the formulation contains two or more active agents (eg two or more mineralocorticoids, or a mineralocorticoid and another agent such as a tetracycline derivative etc), the active agents may be administered as a mixture, as an admixture, in the same formulation, in separate formulations, in extended release formulations, liposomes, microcapsules, or any of the previously described embodiments. The formulation may be administered topically, or may be injected into the eye, or one active agent may be administered topically and the other agent(s) may be injected.

[0230] The formulation may be also administered as a slow release formulation, with a carrier formulation such as microspheres, microcapsules, liposomes, etc., as a topical ointment or solution, an intravenous solution or suspension, or in an intraocular injection, as known to one skilled in the art to treat or prevent an ophthalmic condition.

[0231] A time-release drug delivery system may be administered intraocularly to result in sustained release of the agent over a period of time. The formulation may be in the form of a vehicle, such as a micro- or macro-capsule or

matrix of biocompatible polymers such as polycaprolactone, polyglycolic acid, polylactic acid, polyanhydrides, polylactide-co-glycolides, polyamino acids, polyethylene oxide, acrylic terminated polyethylene oxide, polyamides, polyethylenes, polyacrylonitriles, polyphosphazenes, poly(ortho esters), sucrose acetate isobutyrate (SAIB), and other polymers such as those disclosed in U.S. Pat. Nos. 6,667,371; 6,613,355; 6,596,296; 6,413,536; 5,968,543; 4,079,038; 4,093,709; 4,131,648; 4,138,344; 4,180,646; 4,304,767; 4,946,931, each of which is expressly incorporated by reference herein in its entirety, or lipids that may be formulated as microspheres or liposomes. A microscopic or macroscopic formulation may be administered through a needle, or may be implanted by suturing within the eye, for example, within the lens capsule. Delayed or extended release properties may be provided through various formulations of the vehicle (coated or uncoated microsphere, coated or uncoated capsule, lipid or polymer components, unilamellar or multilamellar structure, and combinations of the above, etc.). The formulation and loading of microspheres, microcapsules, liposomes, etc. and their ocular implantation are standard techniques known by one skilled in the art, for example, the use of a ganciclovir sustained-release implant to treat cytomegalovirus retinitis, disclosed in *Vitreoretinal Surgical Techniques*, Peyman et al., Eds. (Martin Dunitz, London 2001, chapter 45); *Handbook of Pharmaceutical Controlled Release Technology*, Wise, Ed. (Marcel Dekker, New York 2000), the relevant sections of which are incorporated by reference herein in their entirety. For example, a sustained release intraocular implant may be inserted through the pars plana for implantation in the vitreous cavity.

[0232] The invention also provides a method for the treatment or prophylaxis of ophthalmic condition such as exudative retinopathies comprising: administering a pharmaceutical composition comprising a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye (which is preferably an anti-oedematous steroid or a pharmaceutically acceptable salt thereof, or more preferably a mineralocorticoid) in a biocompatible, biodegradable matrix, for example in the form of a gel or polymer which is preferably suited for insertion into the retina or into a cavity of the eye, anterior or posterior, as an implant. In the case that the composition is delivered as an implant, it may be incorporated in any known biocompatible biodegradable matrix as a liquid, or in the form, for example, of a micelle using known chemistry or as microparticles.

[0233] Slow or extended-release delivery systems include any of a number of biopolymers (biological-based systems), systems employing liposomes, colloids, resins, and other polymeric delivery systems or compartmentalized reservoirs, can be utilized with the compositions described herein to provide a continuous or long term source of therapeutic compound.

[0234] In any slow release device prepared, the mineralocorticoid receptor activity modulating compound is preferably present in an amount of about 10% to 90% by weight of the implant. More preferably, the compound is from about 50% to about 80% by weight of the implant. In a preferred embodiment, the mineralocorticoid receptor activity modulating compound comprises about 50% by weight of the

implant. In a particularly preferred embodiment, the compound mineralocorticoid receptor activity modulating compound comprises about 70% by weight of the implant. In a preferred aspect, the mineralocorticoid receptor activity modulating compound is an anti-oedematous steroid or pharmaceutically acceptable salt thereof, more preferably a mineralocorticoid.

[0235] In one form, implants used in the method of the present invention are formulated with particles of the mineralocorticoid entrapped within the bio-erodible polymer matrix. Release of the agent is achieved by erosion of the polymer followed by exposure of previously entrapped agent particles to the vitreous, and subsequent dissolution and release of agent. The release kinetics achieved by this form of drug release are different than that achieved through formulations which release drug through polymer swelling, such as with hydrogels such as methylcellulose. In that case, the drug is not released through polymer erosion, but through polymer swelling, which releases drug as liquid diffuses through the pathways exposed. The parameters which determine the release kinetics include the size of the drug particles, the water solubility of the drug, the ratio of drug to polymer, the method of manufacture, the surface area exposed, and the erosion rate of the polymer.

[0236] Exemplary biocompatible, non-biodegradable polymers of particular interest include polycarbonates or polyureas, particularly polyurethanes, polymers which may be cross-linked to produce non-biodegradable polymers such as cross-linked poly(vinyl acetate) and the like. Also of particular interest are ethylene-vinyl ester copolymers having an ester content of 4% to 80% such as ethylene-vinyl acetate (EVA) copolymer, ethylene-vinyl hexanoate copolymer, ethylene-vinyl propionate copolymer, ethylene-vinyl butyrate copolymer, ethylene-vinyl pentanoate copolymer, ethylene-vinyl trimethyl acetate copolymer, ethylene-vinyl diethyl acetate copolymer, ethylene-vinyl 3-methyl butanoate copolymer, ethylene-vinyl 3,3-dimethyl butanoate copolymer, and ethylene-vinyl benzoate copolymer.

[0237] Additional exemplary naturally occurring or synthetic non-biodegradable polymeric materials include poly(methylmethacrylate), poly(butylmethacrylate), plasticized poly(vinylchloride), plasticized poly(amides), plasticized nylon, plasticized soft nylon, plasticized poly(ethylene terephthalate), natural rubber, silicone, poly(isoprene), poly(isobutylene), poly(butadiene), poly(ethylene), poly(tetrafluoroethylene), poly(vinylidene chloride), poly(acrylonitrile), cross-linked poly(vinylpyrrolidone), poly(trifluorochloroethylene), chlorinated poly(ethylene), poly(4,4'-isopropylidene diphenylene carbonate), vinylidene chloride-acrylonitrile copolymer, vinyl chloridediethyl fumarate copolymer, silicone, silicone rubbers (especially the medical grade), poly(dimethylsiloxanes), ethylene-propylene rubber, silicone-carbonate copolymers, vinylidene chloride-vinyl chloride copolymer, vinyl chloride-acrylonitrile copolymer, vinylidene chloride-acrylonitrile copolymer, poly(olefins), poly(vinyl-olefins), poly(styrene), poly(halo-olefins), poly(vinyls), poly(acrylate), poly(methacrylate), poly(oxides), poly(esters), poly(amides), and poly(carbonates).

[0238] Diffusion of the drug from the implant may also be controlled by the structure of the implant. For example,

diffusion of the drug from the implant may be controlled by means of a membrane affixed to the polymer layer comprising the drug. The membrane layer will be positioned intermediate to the polymer layer comprising the drug and the desired site of therapy. The membrane may be composed of any of the biocompatible materials indicated above and may vary with the drug employed, the presence of agents in addition to the drug present in the polymer, the composition of the polymer comprising the drug, the desired rate of diffusion and the like. For example, the polymer layer will usually comprise a very large amount of drug and will typically be saturated. Such drug-saturated polymers may generally release the drug at a very high rate. In this situation, the release of the drug may be slowed by selecting a membrane which is of a lower drug permeability than the polymer. Due to the lower drug permeability of the membrane, the drug will remain concentrated in the polymer and the overall rate of diffusion will be determined by the drug permeability of the membrane. Therefore, the rate of release of the drug from the implant is reduced, providing for a more controlled and extended delivery of the drug to the site of therapy.

[0239] The skilled reader will appreciate that the duration over which any of the formulations used in the method of the invention will dwell in the ocular environment will depend, inter alia, on such factors as the physicochemical and/or pharmacological properties of the compounds employed in the formulation, the concentration of the compound employed, the bioavailability of the compound, the disease to be treated, the mode of administration and the preferred longevity of the treatment. Where that balance is struck will often depend on the longevity of the effect required in the eye and the ailment being treated.

[0240] The frequency of treatment according to the method of the invention is determined according to the disease being treated, the deliverable concentration of the mineralocorticoid and the method of delivery. If delivering the mineralocorticoid by intravitreal injection, the dosage frequency may be monthly. Preferably, the dosage frequency is every three months. The frequency of dosage may also be determined by observation, with the dosage being delivered when the previously delivered mineralocorticoid material is visibly degraded, however one should be careful with such a measurement as the mineralocorticoid material may be visibly degraded, but may exist in dissolved therapeutic levels in the eye. Once a therapeutic result is achieved, the drug can be tapered or discontinued. Occasionally, side effects warrant discontinuation of therapy. In general, an effective amount of the compound is that which provides either subjective relief of symptoms or an objectively identifiable improvement as noted by the clinician or other qualified observer.

[0241] Formulations prepared for use in the method of the present invention to prevent or treat ophthalmic conditions will preferably have dwell times from hours to many months and possibly years, although the latter time period requires special delivery systems to attain such a duration. Illustrative forms of such delivery systems are disclosed elsewhere in this specification (eg below). Most preferably the formulations for use in the method of the invention will have a dwell time (ie duration in the eye) of hours (i.e. 1 to 24 hours), days (i.e. 1, 2, 3, 4, 5, 6 or 7 days) or weeks (i.e. 1, 2, 3, 4 weeks). Alternatively, the formulation will have a

dwelling time of at least a few months such as, 1 month, 2 months, 3 months, with dwelling times of greater than 4, 5, 6, 7 to 12 months being achievable.

[0242] Compounds capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition (such as an anti-oedematous steroid, or more preferably a mineralocorticoid) suitable for use in the method of the present invention must be capable of at least reducing, ameliorating or preventing the exudation of fluids from the blood vessels of the eye (eg from the choroidal and retinal vasculature into the retinal space or from the vessels of the conjunctiva, iris or ciliary body into the front-of-eye region). Where a prolonged treatment is required, the mineralocorticoid receptor activity modulating compounds (eg anti-oedematous steroids or mineralocorticoids) are preferably formed of crystals that are sparingly soluble in the vitreous. Such compounds prepared in a crystalline manner may be administered in depot form.

[0243] Where the buffering agent or enhancer is hydrophilic, it may also act as a release accelerator. Hydrophilic additives act to increase the release rates through faster dissolution of the material surrounding the drug particles, which increases the surface area of the drug exposed, thereby increasing the rate of drug bioerosion. Similarly, a hydrophobic buffering agent or enhancer dissolves more slowly, slowing the exposure of drug particles, and thereby slowing the rate of drug bioerosion.

[0244] In order to provide slow release compositions with improved therapeutically effective dwelling time in the vitreous for the method of treating or preventing ophthalmic conditions, the proportion of different crystal sizes of the mineralocorticoid receptor activity modulating compounds (eg anti-oedematous steroids, or more preferably mineralocorticoids) may be manipulated to provide a suitable release profile. A key to increasing the therapeutically effective intravitreal dwelling time of an anti-oedematous steroid, such as, for example, fludrocortisone, without increasing the total concentration of the drug in a therapeutic formulation is to increase the proportion of larger-sized crystals of the anti-oedematous steroid while decreasing the proportion of crystal composites of the anti-oedematous steroid. Accordingly, the dissolution rate of an anti-oedematous steroid drug, such as, for example, fludrocortisone, may be decreased (i.e. longer dissolution time) by increasing the relative proportion of large-sized drug crystals in a therapeutic composition or formulation. The larger-sized drug crystals have a decreased surface area to volume relationship relative to crystal composites, and as such, have a lower rate of dissolution.

[0245] For example, the compounds may be present in the composition with a greater proportion of crystals of about 50 μm to about 600 μm than the proportion of crystals of about 0.5 μm to about 40 μm . As detailed in PCT/AU2005/000146 and U.S. patent application Ser. No. 11/051,028 such compositions provide slow release compositions whose time release profile may be adjusted by altering the proportions of larger crystals to smaller crystals. To this end the compositions used in the method of the present invention may comprise a pharmaceutically acceptable composition comprising an anti-oedematous steroid or pharmaceutically acceptable salt thereof which is present in the form of crystals and crystal composites of varying sizes and wherein

said crystals are concentrated in the size ranges of about 0.5 μm to about 40 μm and about 50 μm to about 600 μm . Preferably the crystals are more concentrated than the crystal composites in the size ranges of about 0.5 μm to about 40 μm and about 50 μm to about 600 μm . Even more preferably the proportion of crystals in the size ranges of about 50 μm to about 600 μm is greater than that provided in the about 0.5 μm to about 40 μm size range.

[0246] In another embodiment, the invention resides in a method for modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition comprising the step of: administering to a patient a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye in a pharmaceutically acceptable formulation suitable for delivery to the eye in an amount and for a duration sufficient to modulate the activity of mineralocorticoid receptors to treat or prevent an ophthalmic condition. It is preferred that the compound capable of modulating the activity of the mineralocorticoid receptors is an anti-oedematous steroid, most preferably a mineralocorticoid as defined herein.

[0247] Desirably, the method for modulating the activity of mineralocorticoid receptors consists of administering to a patient a formulation that contains at least aldosterone in a pharmaceutically acceptable formulation suitable for delivery to the eye in an amount and for a duration sufficient to treat or prevent an ophthalmic condition.

[0248] More desirably the method for modulating the activity of mineralocorticoid receptors consists of administering to a patient a formulation that contains at least one of fludrocortisone, fludrocortisone acetate; deoxycorticosterone, 11-desoxycortisone, or deoxycorticosterone acetate in a pharmaceutically acceptable formulation suitable for delivery to the eye in an amount and for a duration sufficient to treat or prevent an ophthalmic condition wherein the ophthalmic condition to be treated or prevented is other than an ocular disease selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0249] In a more preferred form of the invention the formulation used in the above method is a formulation described above to treat or prevent an ophthalmic condition in the anterior and/or posterior regions of the eye, or in the cornea, retina, choroid, etc.

[0250] The methods of treatment or prophylaxis of ophthalmic conditions of the present invention may be performed alone, or in combination with one or more other

therapies such as photodynamic therapy, laser surgery, laser photocoagulation or one or more biological or pharmaceutical treatments.

[0251] Laser treatment takes a number of forms, depending on the nature of the ophthalmic disorder. Disorders such as myopia may be treated with laser surgery to reshape the cornea (eg. LASIK® surgery), whilst a widely used treatment for disorders such as AMD is laser therapy which is directed to removal or blockage of blood vessels via photodynamic therapy or laser photocoagulation. Laser therapy may further be used to treat or remove neoplasm such as retinoblastomas or pseudogliomas.

[0252] Photocoagulation involves the use of a laser to seal leaking blood vessels, slow the growth of abnormal blood vessels and/or destroy new blood vessels within the eye. In addition, the laser can be used to seal the retina to the eye, helping to prevent retinal detachment. For example, focal laser treatment may be applied to microaneurysms identified in diabetic retinopathy.

[0253] Photodynamic therapy involves the use of a photoactive drug (eg Visudyne®) and a laser to destroy abnormal blood vessels. Visudyne® is injected into the blood and activated with a laser, effectively destroying the blood vessels. This treatment may require several sessions to be effective. A wide range of theories have been proposed to explain the beneficial effects of retinal laser photocoagulation in delaying retinal angiogenesis, however, the underlying molecular mechanism remains to be elucidated.

[0254] The therapeutic effects of laser photocoagulation are thought to be due to the destruction of photoreceptors, the highest oxygen consumers in the retina. Subsequently, these photoreceptors are replaced by glial cells allowing increased oxygen diffusion from the choroid to the inner retina thereby relieving inner retinal hypoxia. This improved oxygenation triggers a two-pronged cascade of events where: (1) constriction of the retinal arteries results in decreased hydrostatic pressure in capillaries and the constriction of capillaries and venules; and (2) the cellular production of VEGF is inhibited. Together, these effects are believed to ultimately result in the inhibition of neovascularization and a decrease in oedema. Cell proliferation and regulation of cellular proteins are induced by the laser photocoagulation, and their therapeutic effect might be an essential part of the physiological response.

[0255] However, a complication of laser treatment (either photodynamic laser therapy or laser photocoagulation) is inflammation, leading to further oedema. This may also occur after laser therapy to remove or treat ocular neoplasm. In addition, laser treatment is not always a permanent cure as the blood vessels may begin to grow again, and microaneurysms may reform. Furthermore, laser treatment of abnormal blood vessels cannot be performed on vessels located in certain regions of the retina, such as the central region of the macula.

[0256] Therefore, in an embodiment of the invention, where laser treatment of the retina is indicated, administration of an anti-oedematous steroid such as a mineralocorticoid may be carried out by injection before or after the laser treatment. Administration of the anti-oedematous steroid may reduce, eliminate or prevent oedema before or after laser therapy and may therefore reduce or eliminate one of the side effects of laser therapy.

[0257] In another embodiment the invention resides in a method for reducing ocular irritation comprising the step of: administering to a patient a formulation as described above to a patient following corneal surgery (e.g., LASIK® surgery, photorefractive keratectomy (PRK), or other corneal procedures). Preferably the formulation administered to the patient is a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located within the eye. Preferably, such mineralocorticoid receptor activity modulating compounds are anti-oedematous steroids or more preferably mineralocorticoids. Such mineralocorticoids reduce or inhibit the exudation of fluids in the eye which may cloud the cornea or the vitreous.

[0258] In addition to the other compounds previously described, formulations of the invention may be injected with anti-angiogenic agents designed to block the actions of VEGF on endothelial cells in combined therapies. Examples of agents that can be employed in the method of the invention are: (a) Lucentis® developed by Genentech; and (b) Macugen® developed by Eyetech Pharmaceuticals. Lucentis® and Macugen® are compounds that are injected into the vitreous and are potent anti-angiogenic compounds. In a highly preferred form, the method of the invention is performed by administering a pharmaceutical formulation of a compound capable of modulating the mineralocorticoid receptors within the cells or tissue of the eye as described above and an anti-angiogenic agent such as Lucentis® or Macugen®. Preferably the compound capable of modulating the activity of mineralocorticoid receptors is an anti-oedematous steroid and more preferably a mineralocorticoid as herein described.

[0259] Lucentis® (ranibizumab), formerly known as rhu-Fab V2 or AMD-Fab is a humanized, therapeutic anti-VEGF (vascular endothelial growth factor) antibody fragment developed by Genentech to bind and inhibit VEGF, a protein that plays a critical role in angiogenesis (the formation of new blood vessels) by binding to VEGF and preventing it from interacting with the VEGF receptor on the surface of endothelial cells. Lucentis is designed to block new blood vessel growth and reduce leakage, which are thought to lead to wet AMD disease progression. Lucentis® is injected into the vitreous, and then passes beneath the retina into the area where the abnormal blood vessels are growing. When administered in conjunction with pharmaceutical formulations prepared according to the present invention Lucentis should be administered in either about 300 µg or about 500 µg doses for four doses.

[0260] Macugen® (pegaptanib sodium, anti-VEGF aptamer or EYE001) developed by Eyetech Pharmaceuticals, consists of a synthetic fragment of genetic material that specifically binds to the VEGF molecule and blocks it from stimulating the receptor on the surface of endothelial cells. When administered in conjunction with pharmaceutical formulations prepared according to the present invention Macugen® should be administered in a dose ranging from either about 0.3 mg to about 3.0 mg every four or six weeks.

[0261] In another aspect of the invention, the method of the invention may be performed by administering a pharmaceutical formulation comprising a compound capable of modulating the mineralocorticoid receptors within the cells or tissue of the eye (preferably an anti-oedematous steroid and more preferably a mineralocorticoid as herein

described) in combination with a glucocorticoid (e.g. prednisolone, prednisone), an oestrogen (e.g. oestradiol), an androgen (e.g. testosterone) retinoic acid derivatives (e.g. 9-cis-retinoic acid, 13-trans-retinoic acid, all-trans retinoic acid), a vitamin D derivative (e.g. calcipotriol, calcipotriene), a non-steroidal anti-inflammatory agent, a vitamin D derivative, an anti-infective agent, a protein kinase C inhibitor, a MAP kinase inhibitor, an anti-apoptotic agent, a growth factor, a nutrient vitamin, an unsaturated fatty acid, and/or ocular anti-infective agents, for the treatment of the ophthalmic conditions set forth herein. In still other embodiments of the invention, a mixture of these agents may be used.

[0262] Ocular anti-infective agents that may be used include, but are not limited to, penicillins (ampicillin, azicillin, carbenicillin, dicloxacillin, methicillin, nafcillin, oxacillin, penicillin G, piperacillin, and ticarcillin), cephalosporins (cefamandole, cefazolin, cefotaxime, cefsulodin, ceftazidime, ceftriaxone, cephalothin, and moxalactam), aminoglycosides (amikacin, gentamicin, netilmicin, tobramycin, and neomycin), miscellaneous agents such as aztreonam, bacitracin, ciprofloxacin, clindamycin, chloramphenicol, cotrimoxazole, fusidic acid, imipenem, metronidazole, teicoplanin, and vancomycin), antifungals (amphotericin B, clotrimazole, econazole, fluconazole, flucytosine, itraconazole, ketoconazole, miconazole, natamycin, oxiconazole, and terconazole), antivirals (acyclovir, ethyldeoxyuridine, foscarnet, ganciclovir, idoxuridine, trifluridine, vidarabine, and (S)-1-(3-dihydroxy-2-phosphorylthioethoxypropyl) cytosine (HPMPC)), antineoplastic agents (cell cycle (phase) nonspecific agents such as alkylating agents (chlorambucil, cyclophosphamide, mechlorethamine, melphalan, and busulfan), anthracycline antibiotics (doxorubicin, daunomycin, and dactinomycin), cisplatin, and nitrosoureas), antimetabolites such as antiprimidines (cytarabine, fluorouracil and azacytidine), antifolates (methotrexate), antipurines (mercaptopurine and thioguanine), bleomycin, vinca alkaloids (vincristine and vinblastine), podophylotoxins (etoposide (VP-16)), and nitrosoureas (carmustine, (BCNU)), immunosuppressant agents such as cyclosporin A and SK506, and anti-inflammatory or suppressive agents (inhibitors), and inhibitors of proteolytic enzymes such as plasminogen activator inhibitors. Doses for topical and sub-conjunctival administration of the above agents, as well as intravitreal dose and vitreous half-life may be found in *Intravitreal Surgery Principles and Practice*, Peyman G A and Shulman, J Eds., 2nd edition, 1994, Appleton-Lange, the relevant sections of which are expressly incorporated by reference herein.

[0263] The present invention provides for the use of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in the manufacture of a medicament for the treatment of an ophthalmic condition. The invention also provides for the use of an anti-oedematous steroid such as a mineralocorticoid or pharmaceutically acceptable salt thereof as herein described in the manufacture of a medicament for the treatment of an ophthalmic condition.

[0264] The use of (a) a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition; and (b) a second compound chosen from the list comprising: a steroid, heparin, a tetracycline derivative, an anti-prostaglandin, a macrocyclic antibiotic, a metalloproteinase inhibitor or an anti-angio-

genic agent designed to block the actions of VEGF on endothelial cells; for the manufacture of a medicament for the treatment of an ophthalmic condition is also provided.

[0265] According to a further form, the invention provides for the use of compounds capable of modulating the activity of mineralocorticoid receptors in the manufacture of a medicament for the treatment of an exudative retinopathy in an individual.

[0266] Further, it provides for use of an effective amount of anti-oedematous steroid or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of an exudative retinopathy in an individual. The invention also provides for the use of a mineralocorticoid as herein described in the preparation of a medicament for the treatment of exudative retinopathies.

EXAMPLES

[0267] Further features of the present invention are more fully described in the following non-limiting Examples. It is to be understood, however, that this detailed description is included solely for the purposes of exemplifying the present invention. It should not be understood in any way as a restriction on the broad description of the invention as set out above.

Example 1

[0268] To show the capacity of a mineralocorticoid, specifically fludrocortisone, to down-regulate receptors involved in biochemical pathways associated with oedema and exudative retinopathies, an assay was conducted looking at the activity of VEGF receptors Flk-1 and Flt-1 in choroidal endothelial cells. Flk-1 is known to be involved in cell proliferation whilst Flt-1 is involved in cell permeability.

[0269] The expression of Flk-1 and Flt-1 was measured, using fluorescence activated cell sorting (FACS) analysis, in untreated cells, cells treated with phorbolmyristate acetate (PMA), cells treated with PMA and then with the glucocorticoid triamcinolone acetonide (TA) and cells treated with PMA and then with the mineralocorticoid fludrocortisone. PMA is a model for pro-inflammatory cytokines and TA is known to block the glucocorticoid receptor

[0270] From FIG. 1 it can be seen that expression of Flk-1 is increased compared to control cells by administration of PMA. However, this increase is reversed by treatment with fludrocortisone, leading to reduced expression of Flk-1 in fludrocortisone treated cells compared to control (untreated) cells. The TA/Flk-1 pathway is via a combination of direct action on receptor expression and anti-inflammatory effects via the glucocorticoid receptor; noting that VEGF and its receptors mediate pro-inflammatory effects.

[0271] Expression of Flt-1 is also increased by administration of PMA, and reduced by treatment with fludrocortisone, with cells treated with fludrocortisone expressing similar levels of Flt-1 as untreated cells.

Example 2

[0272] The expression of Flk-1 and Flt-1 was also investigated in untreated choroidal endothelial cells, choroidal endothelial cells treated with Tumour Necrosis Factor- α (TNF- α) and choroidal endothelial cells treated with the mineralocorticoid fludrocortisone. TNF- α is a pro-inflammatory cytokine.

[0273] Expression of FLK-1 is down-regulated from the levels in untreated cells by administration of fludrocortisone. Cells treated with TNF- α express higher levels of Flt-1 than untreated control cells. However, administration of fludrocortisone slightly reduced the expression of Flt-1 compared to control cells

Example 3

[0274] Transendothelial electrical resistance (TER) is a method of measuring cell permeability and thus exudative capacity. High electrical resistance reflects tight cell barriers and low cell permeability. In contrast, no resistance or negative resistance indicates the presence of looser junctions in the cell barrier.

[0275] Choroidal endothelial cells treated with dimethyl sulfoxide (DMSO), a surfactant which disrupts the cell membrane, have low electrical resistance, as indicated in FIG. 3, compared to cells treated with fludrocortisone or TA. The increased resistance in the presence of fludrocortisone or TA indicates that the steroids aid in the maintenance or repair of the cell membrane barrier, resulting in a reduction in exudation and oedema.

Example 4

[0276] Retinal endothelial cells treated with DMSO exhibit low electrical resistance in contrast to cells treated with fludrocortisone. Fludrocortisone treated cells exhibit higher resistance than those treated with TA. This indicates that in retinal endothelial cells, fludrocortisone is aiding in the maintenance or repair of the cell membrane barrier and thus reducing exudation and oedema.

Example 5

[0277] Thirty New Zealand albino rabbits weighing between 2.5 and 3.0 kg were used for this study. The rabbits

4 mg/ml 11 -deoxycorticosterone (Spectrum Chemical Corp). Group 3 (n=5) received topical 4 mg/ml 11-desoxycortisone (Spectrum Chemical Corp). Group 4 (n=5) received topical 4 mg/ml aldosterone (Farmabios, Italy). Group 5 (n=5) received topical 4 mg/ml deoxycorticosterone (Spectrum Chemical Corp). Group 6 (n=5) received topical fludrocortisone acetate (Farmabios, Italy).

[0279] The rabbits were anaesthetised with 1 ml of a mixture of ketamine hydrochloride (35 mg/kg, intramuscular) and xylazine hydrochloride (5 mg/kg, intramuscular). In all groups, drugs were applied topically to the right eye and saline was applied to the left eye four times (at time 0, 1, 2 and 3 hours). Drugs and saline were administered to the eye as a single 50 μ L drop.

[0280] 20 mg/ml dextran-isothiocyanate-fluorescein (FITC-dextran, Sigma) was prepared and a 20 mg/kg dose was injected into the marginal ear vein at time 1.5 hours.

[0281] Endotoxin (2.5 μ g/kg) isolated from *Salmonella typhimurium* (Sigma) was injected into the same vein at the same time with the third drop occurring at time 2 hours.

[0282] The FITC-dextran concentration in the anterior chamber was determined using a prototype fluorophotometer (OcuMetrics, Mountain View, Calif.) 90 minutes after an endotoxin administration. This instrument has excitation wavelengths of approximately 410 to 490 nm, with emission wavelengths of approximately 520 to 630 nm. The fluorescence emitted by the FITC-dextran was determined in both left and right eyes.

[0283] Statistical analysis was performed, comparing the anterior chamber fluorescence measurements of the test and control eye of each animal. A paired Wilcoxon Signed Rank Test (StatXact) was used, with a one sided p-value. The results of this experiment are presented in FIG. 5 and Table 1 below.

TABLE 1

Anterior Chamber Fluorophotometer Results										
Rabbit	DA	C	11-DC	C	AS	C	FA	C	DS	C
1	220	370	696	791	243	281	27	111	340	533
2	116	312	578	696	75	42	86	162	245	279
3	455	580	141	457	125	224	261	316	59	283
4	100	380	147	457	540	324	445	639	86	112
5	113	253	92	194	256	300	10	30	140	176
Mean	201	379	331	519	248	234	166	252	174	277

C = control;
DA = deoxycorticosterone acetate;
11-DC = 11-desoxycortisone;
AS = aldosterone;
FA = fludrocortisone acetate;
DS = deoxycorticosterone

were treated in accordance with the guidelines of the Association for Research in Vision and Ophthalmology (ARVO). One eye of each animal was used for experimental purposes, the other serving as a control eye. Slit lamp and indirect funduscopy examination was performed on all eyes before and after euthanasia.

[0278] The rabbits were divided into six groups. Group 1 (n=5) received topical 4 mg/ml deoxycortisone acetate (Spectrum Chemical Corp). Group 2 (n=5) received topical

[0284] Administration of 4 mg/ml 11-desoxycortisone gave a 37% reduction in the exudative response ($p<0.03$), 4 mg/ml deoxycorticosterone acetate gave a 47% reduction in the exudative response ($p<0.03$), 4 mg/ml fludrocortisone acetate gave a 34% reduction in the exudative response ($p<0.03$), 4 mg/ml deoxycorticosterone gave a 37% reduction in the exudative response ($p<0.03$). The results for aldosterone were very variable and those for 11 -deoxycorticosterone did not show a reduction in the exudative response.

Example 6

[0285] To determine if mineralocorticoids are active in the regulation of genes controlling exudation in retinal cells, specifically retinal pigment epithelial (RPE) cells and choroidal endothelial (CE) cells, real time competitive PCR was performed on both mouse and non-human primate cells at early passage. Real-Time comparative PCR was performed using a 96-well microtiter plate format on an ABI PRISM 7700 Sequence Detection System (PE Applied Biosystems) equipped with a Sequence Detection System (SDS) software version 1.6.3.

[0286] PCR was performed using 250 ng of cDNA of each sample, specific for the selected gene probes and Taqman PCR master mix and the method follows the manufacturer's protocol with slight modifications. The primers and probes for both mouse and human genes associated with angiogenesis and oedema were obtained from Taqman, Assays On Demand, PE Applied Biosystems, USA. Quantum RNA classic 11 18S Internal Standard (Ambion) were used as an endogenous control. An 18S primer-competimer ratio of 1:4 was used in all experiments.

[0287] To standardise and evaluate RPE and CE gene expression, aliquots of cDNA (250 ng) prepared from the retinal pigment epithelial cells and choroidal endothelial cells were used as templates in all PCR reactions. All experiments were carried out in triplicate. The RT-PCR cycles were 55° C. for 2 minutes, 95° C. for 10 minutes and 40 cycles of 95° C. for 30 sec, 60° C. for 30 sec and 72° C. for 2 minutes.

[0288] The comparative quantification values were obtained from the threshold cycle (C_T) number at which an increase in signal (associated with an exponential growth of PCR products) is detected using SDS software. Three PCRs were carried out (n=3) for each sample/primer set, and the mean experimental value was used as the relative quantification value. For all probes, amplification specificity was confirmed by the manufacturer and the reaction products were separated on 3% agarose gel and stained with ethidium bromide for visual confirmation of PCR products.

[0289] Data Analysis by Comparative C_T ($\Delta\Delta C_T$) Method

[0290] The C_T value represents the PCR cycle at which an increase in reporter fluorescence (ΔRn) above the line of the optimal value (optimal ΔRn) is first detected. The calculation for comparative C_T ($\Delta\Delta C_T$) method (Brink N et al. Comparative quantification of IL-1 β , IL-10, IL-10r, TNF α and IL-7 mRNA levels in UV-irradiated human skin in vivo. Inflamm Res. 2000; 49:290-296). Average C_T value of all genes and 18S rRNA is calculated from each of the triplicate repeats and this is applied for all different experiments. Finally the mean C_T value is calculated from three average C_T values for each cell sample experiment. The ΔC_T value is determined by subtracting the corresponding mean 18S C_T value from the mean MR1 C_T value. The standard deviation of the difference is calculated from the standard deviations of the gene of interest and the corresponding 18S values. The $\Delta\Delta C_T$ value is obtained by subtracting the ΔC_T reference value from the ΔC_T sample value, this is known as the $2^{-\Delta\Delta C_T}$ method. This is the subtraction of an arbitrary constant, so the standard deviation of the $66\Delta C_T$ is similar to the standard deviation of the ΔC_T value. The value given for the gene of interest relative to their corresponding normal,

untreated, value will be determined by evaluating the expression by $2^{-\Delta\Delta C_T}$, as described above.

Example 7

[0291] PDT-induced oedema is induced in Dutch belted rabbits (n=6) using verteporfin as stated in Burke et al, (2004) ARVO abstract.

[0292] The PDT procedure consists of an intravenous infusion of Visudyne (10 mls or 0.2 mg/kg) at a rate of 1 ml/min for 10 min. Then, 20 -25 minutes post-verteporfin injection, two ~1.5 mm spots are induced at the posterior pole using PDT laser treatment, 689 nm for 83 seconds at 600 mW/cm² 50 J/cm² (Burke et al., 2004).

[0293] One to two hours after PDT treatment, intravitreal injection of the mineralocorticoid (100-200 μ g in 0.1 ml) is carried out. One eye of each animal serves as the "test" eye and the other eye serves as the "control" eye. The test eye receives 0.1 ml of the mineralocorticoid intravitreally, while the control eye receives a 0.1 ml intravitreal injection of BSS. Oedema is assessed at 12 and 24 hours and days 3 and 6-9 post-treatment.

[0294] Assessment is performed using fluorescein angiography, fundus examination and OCT measurement of retinal depth.

[0295] The invention is further described by the following numbered paragraphs:

[0296] 1. A method of treatment of an individual with an ophthalmic condition comprising the step of: administering to the individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye in the individual to be treated.

[0297] 2. A method according to paragraph 1 wherein the compound capable of modulating the activity of mineralocorticoid receptors is an anti-oedematous steroid.

[0298] 3. A method according to paragraph 1 wherein the compound capable of modulating the activity of mineralocorticoid receptors is a mineralocorticoid.

[0299] 4. The method of any one of paragraphs 1 to 3 wherein the compound is not a compound disclosed in U.S. Pat. No. 6,011,023.

[0300] 5. The method of any one of paragraphs 1 to 3 wherein the compound is a compound disclosed in U.S. Pat. No. 6,011,023 but the compound is not used to treat an ocular disease selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery

ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0301] 6. The method of any one of paragraphs 1 to 5 wherein the ophthalmic condition is chosen from the list comprising: diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctuate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis and cytomegalovirus infection.

[0302] 7. The method of any one of paragraphs 1 to 6 wherein the ophthalmic condition is an exudative retinopathy.

[0303] 8. A method for the prophylactic or therapeutic treatment of exudative retinopathies in a patient comprising the step of: administering a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors to or adjacent to cells or tissue from or in said patient that are afflicted with and exudative retinopathy; and wherein said cells or tissue are selected from the group consisting of: retinal cells, retinal pigment epithelial cells the epithelial cells of the BRB, choroidal endothelial cells.

[0304] 9. A method for the treatment of an ailment resulting from the breakdown of the BRB in the posterior region of the retina, said method comprising the step of: administering to an individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to said ailment.

[0305] 10. The method of paragraph 9 wherein the ailment is chosen from the list comprising: myopic

retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, macular oedema arising from laser treatment of the retina and exudative macular degeneration.

[0306] 11. A method according to paragraph 8 or 9 wherein the compound is administered by intravitreal injection to said patient.

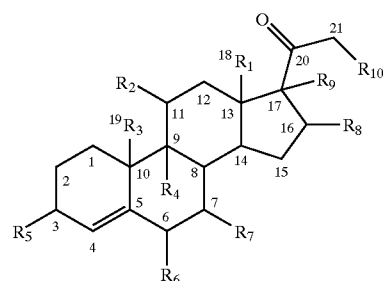
[0307] 12. A method of prophylactically treating an individual with an ophthalmic condition in a first eye but not a second eye comprising the steps of: administering to the second eye of said individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in or adjacent to the eye.

[0308] 13. The method of paragraph 12 wherein the compound administered prophylactically is an anti-oedematous steroid.

[0309] 14. The method of paragraph 12 wherein the compound administered prophylactically is a mineralocorticoid.

[0310] 15. The method of any one of paragraphs 1 to 14 wherein the method comprises the further step of: administering laser treatment to the retina.

[0311] 16. A method of treatment of an individual with an ophthalmic condition comprising the step of: administering to the individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye wherein said compound is a mineralocorticoid of the general structure:



Structure [A]

[0312] wherein

[0313] R_1 is CH_3 , $\text{CH}=\text{O}$, CH_2OH , $\text{CR}=\text{O}$, CH_2NH_2 , COCHCH_2 , NO_2X or CH_2X wherein

[0314] X is F , Cl , Br ;

[0315] R_2 is H , OH , $=\text{O}$, NH_2 or CN ;

[0316] R_3 is H , CH_3 or CH_2OH ;

[0317] R_4 is H , F or Cl ;

[0318] R_5 is H , OH , $=\text{O}$, SH , NH_2 , CN , NO_2 , CH_3 , CH_2OH , $\text{CH}=\text{O}$, X , CH_2X , OR , OCOR , $\text{OPO}(\text{OR})_2$, $=\text{CH}_2$ or CHR wherein X is F , Cl , Br ;

[0319] R_6 is H, CH_3 or X wherein X is F, Cl, Br;

[0320] R_7 is H, OH, CH_3 , Alkyl, Ph, X, OCH_3 , OR, $SCOCH_3$, SCOR, OCOR, CH_2OH , CH_2X , $CH=O$, $CR=O$ or $NHCOR$ wherein X is F, Cl, Br;

[0321] R_8 is H, OH, CH_3 , CH_2CH_3 , SH, NH_2 or X wherein X is F, Cl, Br;

[0322] R_9 is H, OH, SH, NH_2 , CH_3 , CH_2CH_3 or X wherein X is F, Cl, Br;

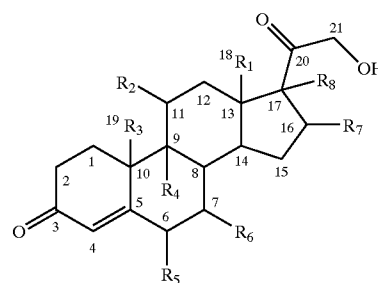
[0323] R_{10} is H, OH, CH_3 , CH_2CH_3 , SH, NH_2 , CH_2OH , CH_2CH_2OH , OR, OCOR, $OPO(OR)_2$, $NHCOR$, $CH=O$, X or CH_2X wherein X is F, Cl, Br; and

[0324] wherein said compound is not a compound disclosed in U.S. Pat. No. 6,011,023 where the compound is to be used to treat or prevent ocular diseases selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0325] 17. The method of paragraph 16 wherein the ophthalmic condition is selected from the list comprising: diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctuate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital

cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; or Cytomegalovirus infection.

[0326] 18. A method of treatment of an individual with an ophthalmic condition comprising the step of: administering to the individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye; wherein said compound is a mineralocorticoid of the general structure:



Structure [B]

[0327] wherein

[0328] R_1 is CH_3 , $CH=O$ or $COCHCH_2$;

[0329] R_2 is H, OH or $=O$;

[0330] R_3 is H, CH_3 or CH_2OH ;

[0331] R_4 is H, or F;

[0332] R_5 , R_6 and R_7 are H;

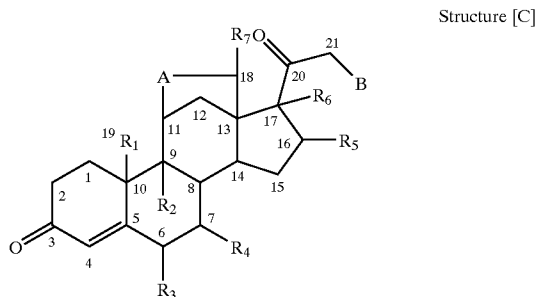
[0333] R_8 is H or OH; and

[0334] wherein said compound is not a compound disclosed in U.S. Pat. No. 6,011,023 where the compound is to be used to treat or prevent ocular diseases selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0335] 19. The method of paragraph 18 wherein the ophthalmic condition is selected from the list comprising: diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration,

retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; cytomegalovirus infection.

[0336] 20. A method of treatment of an individual with an ophthalmic condition comprising the step of: administering to the individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye wherein said compound is a mineralocorticoid of the general structure:



[0337] wherein

[0338] A is O, S, NH, CH₂, CHOH, C=O, CHX, CHCH₃, CH₂CH₂, OCH₂, SCH₂, NHCH₂, NRCH₂, NCOR wherein X is F, Cl, Br;

[0339] B is H, OH, SH, NH₂, CH₃, CH₂OH, CH₂CH₂OH, CH=O, X, CH₂X, OR, OCOR, OPO(OR)₂, NHCOR wherein X is F, Cl, Br;

[0340] R₁ is H, CH₃, CH=O, CH₂OH;

[0341] R₂ is H, F OR Cl;

[0342] R₃ is H, CH₃ or X wherein X is F, Cl, Br;

[0343] R₄ is H, OH, CH₃, Alkyl, Ph, X, OCH₃, SH, NH₂, OR, SCOCH₃, SCOR, OCOR, CH₂OH, CH₂X, CH=O, CR=O, SR or NHCOR wherein X is F, Cl, Br;

[0344] R₅ is H, CH₃, CH₂CH₃, OH, SH, NH₂ or X wherein X is F, Cl, Br;

[0345] R₆ is H, OH, SH, NH₂, CH₂CH₃, CH₃ or X wherein X is F, Cl, Br;

[0346] R₇ is H, OH, SH, NH₂, NO₂, CH=O, CH₃, CO₂H, CN, CH₂CH₃, CH₂X or X

[0347] wherein X is F, Cl, Br; and

[0348] wherein said compound is not a compound disclosed in U.S. Pat. No. 6,011,023 where the compound is to be used to treat or prevent ocular diseases selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0349] 21. The method of paragraph 20 wherein the ophthalmic condition is selected from the list comprising: diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; or Cytomegalovirus infection.

[0350] 22. A method according to any one of paragraphs 1 to 3 wherein said compound is selected from the

group comprising: hydrocortisone hemisuccinate, hydrocortisone sodium phosphate, methylprednisolone hemisuccinate, prednisolone hemisuccinate, or prednisolone sodium succinate.

[0351] 23. A method according to any one of paragraphs 1 to 3 wherein said compound is selected from the group comprising: dexamethasone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone sodium succinate; and wherein the ophthalmic condition to be treated or prevent is other than an ophthalmic condition selected from the list comprising: allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, chorioretinitis, optic neuritis, anterior ischaemic optic neuropathy, iridocyclitis, iritis, diffuse posterior uveitis, choroiditis, sympathetic ophthalmia, anterior segment inflammation and herpes zoster ophthalmicus.

[0352] 24. A method according to any one of paragraphs 1 to 3 wherein said compound is selected from the group comprising: deoxycorticosterone acetate, deoxycorticosterone pivalate, dexamethasone acetate, hydrocortisone butyrate, hydrocortisone valerate, prednisolone pivalate, prednisolone tebutate, and wherein the ophthalmic condition to be treated or prevent is other than an ophthalmic condition selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0353] 25. A method according to any one of paragraphs 1 to 3 wherein said compound is selected from the group comprising: cortisone, cortisone acetate, dexamethasone sodium phosphate, dexamethasone, hydrocortisone, hydrocortisone acetate, methylprednisolone, methylprednisolone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisone, prednisone sodium phosphate, and wherein the ophthalmic condition to be treated or prevented is other than an ophthalmic condition selected from the list comprising allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, chorioretinitis, optic neuritis, anterior ischaemic optic neuropathy, iridocyclitis, iritis, diffuse posterior uveitis, choroiditis, sympathetic ophthalmia, anterior segment inflammation and herpes zoster ophthalmicus, nonpurulent conjunctivitis, blepharitis, scleritis, episcleritis, uveitis, retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal

neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0354] 26. A method according to any one of paragraphs 1 to 3 wherein said compound is selected from the group comprising: amcinonide, clocortolone butyrate, flunisolide, flucinonide, flurandrenolide, fluticasone, fluticasone propionate, halincionide, mometasone furoate.

[0355] 27. A method according to any one of paragraphs 1 to 3 wherein said compound is selected from the group comprising: clobetasol propionate, clobetasol butyrate, clocortolone butyrate, clobetasone pivalate, desoxymetasone, diflorasone, diflorasone diacetate, diflucortolone, diflucortolone valerate, flumethasone, flumethasone pivalate, fluocinolone, fluocortolone, fluocortolone hexanoate, fluocortolone pivalate, fluorometholone, isoflupredone, isoflupredone acetate, mometasone, and wherein the ophthalmic condition to be treated or prevented is other than an ophthalmic condition selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0356] 28. A method according to any one of paragraphs 1 to 3 wherein said compound is selected from the group comprising: rimexolone and fluocinolone acetonide, and wherein the ophthalmic condition to be treated or prevented is other than an ophthalmic condition selected from the list comprising: anterior chamber inflammation and anterior uveitis, retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve,

neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0357] 29. A method according to any one of paragraphs 1 to 3, 16, 18 or 20 wherein said compound is the mineralocorticoid aldosterone or an analogue, pharmaceutically acceptable salt, conjugate or derivative thereof.

[0358] 30. The method of paragraph 29 wherein the compound is sparingly soluble in the vitreous.

[0359] 31. A method according to any one of paragraphs 1 to 3, 16, 18 or 20 wherein said compound is selected from the group comprising the mineralocorticoids: fludrocortisone, fludrocortisone acetate; deoxycorticosterone; 11-desoxycorticosterone; or deoxycorticosterone acetate or an analogue, pharmaceutically acceptable salt, conjugate or derivative thereof, and wherein the ophthalmic condition to be treated or prevent is other than an ophthalmic condition selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

[0360] 32. The method of paragraph 31 wherein the compound is sparingly soluble in the vitreous.

[0361] 33. The method of paragraph 29 or 31 wherein the ophthalmic condition is selected from the list comprising: diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous kerat-

opathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; cytomegalovirus infection.

[0362] 34. The method of any one of paragraphs 1 to 34 wherein more than one mineralocorticoid is administered to said patient.

[0363] 35. A method for the treatment of an ophthalmic condition in an individual comprising the step of: administering to the ophthalmic condition in the individual a therapeutically effective pharmaceutically acceptable formulation of a combination of:

[0364] (a) a mineralocorticoid wherein said mineralocorticoid is (i) capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition; (ii) in a pharmaceutically acceptable form suitable for delivery to the eye; and

[0365] (b) at least a second compound in a concentration and dose sufficient to reduce ocular neovascularization wherein the second compound is selected from the group consisting of: a tetracycline derivative, a steroid, heparin, an antimicrobial, an anti-prostaglandin, and/or a metalloproteinase inhibitor.

[0366] 36. The method of paragraph 35 wherein the second compound is a steroid.

[0367] 37. The method of paragraph 36 where the mineralocorticoid is at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and the steroid is at a concentration from about 0.1 mg/ml to about 40 mg/ml .

[0368] 38. The method of any one of paragraphs 36 or 37 wherein the steroid used in the method is a 11-substituted-16 α ,17 α -substituted methylenedioxy steroid.

[0369] 39. The method of paragraph 38 wherein the steroid used in the method is triamcinolone acetonide.

[0370] 40. The method of paragraph 35 wherein the second compound is heparin.

[0371] 41. The method of paragraph 39 where the mineralocorticoid is at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and the heparin is at a concentration from about 0.01 $\mu\text{g/ml}$ to about 30 mg/ml .

[0372] 42. The method of paragraph 35 wherein the second compound is an antiprostaglandin.

[0373] 43. The method of paragraph 42 wherein the antiprostaglandin is flurbiprofen.

[0374] 44. The method of paragraph 42 or 43 wherein the mineralocorticoid is at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and the anti-prostaglandin is at a concentration from about 1 $\mu\text{g/ml}$ to about 10 mg/ml .

- [0375] 45. The method of paragraph 35 wherein the second compound is an antimicrobial.
- [0376] 46. The method of paragraph 45 wherein the antimicrobial is a macrolide antibiotic.
- [0377] 47. The method of paragraph 45 wherein the antimicrobial is a mycophenolic acid.
- [0378] 48. The method of any one of paragraphs 45 to 47 wherein the mineralocorticoid is at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and the antimicrobial is at a concentration from about 20 $\mu\text{g/ml}$ to about 200 $\mu\text{g/ml}$.
- [0379] 49. The method of paragraph 35 wherein the second compound is a tetracycline derivative.
- [0380] 50. The method of paragraph 49 wherein the tetracycline derivative is doxycycline.
- [0381] 51. The method of paragraph 49 or 50 wherein the mineralocorticoid is at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and the tetracycline derivative is at a concentration from about 0.01 pg/ml to about 30 mg/ml .
- [0382] 52. The method of paragraph 35 wherein the compound is a metalloproteinase inhibitor.
- [0383] 53. The method of paragraph 52 wherein the mineralocorticoid is at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and the metalloproteinase inhibitor is at a concentration and dose to reduce ocular neovascularization.
- [0384] 54. A method for the treatment of an ophthalmic condition in an individual comprising the step of: administering to the ophthalmic condition in the individual a therapeutically effective pharmaceutically acceptable formulation of a combination of:
- [0385] (a) a mineralocorticoid wherein said mineralocorticoid is: (i) capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition; and (ii) in a pharmaceutically acceptable form suitable for delivery to the eye; and
- [0386] (b) a plurality of compounds in a concentration and dose sufficient to reduce ocular neovascularization wherein the plurality of compounds are selected from the group consisting of: a tetracycline derivative, a steroid, heparin, an antimicrobial, an anti-prostaglandin, and/or a metalloproteinase inhibitor.
- [0387] 55. The method of any one of paragraphs 1 to 3, 16, 18 or 20 wherein mineralocorticoid is deposited intravitreally and the dosage is between about 1 mg and about 8 mg .
- [0388] 56. The method of paragraph 55 wherein the dosage is about 4 mg of mineralocorticoid.
- [0389] 57. A pharmaceutical composition for the treatment or prophylaxis of ophthalmic conditions comprising a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissues located in the eye.
- [0390] 58. The composition of paragraph 57 wherein the compound is an anti-oedematous steroid.
- [0391] 59. The composition of paragraph 57 wherein the compound is a mineralocorticoid.
- [0392] 60. The composition of any one of paragraphs 57 to 59 wherein the compound capable of modulating the activity of mineralocorticoid receptors is aldosterone or a pharmaceutically acceptable analogue, salt, conjugate or derivative thereof together with a pharmaceutically acceptable additive.
- [0393] 61. The composition of any one of paragraphs 57 to 59 wherein the compound capable of modulating the activity of mineralocorticoid receptors is selected from the group comprising fludrocortisone, fludrocortisone acetate; deoxycorticosterone, 11-desoxycortisone, or deoxycorticosterone acetate or a pharmaceutically acceptable analogue, salt, conjugate or derivatives thereof together with a pharmaceutically acceptable additive.
- [0394] 62. A pharmaceutical composition for the treatment or prophylaxis of exudative retinopathies comprising a therapeutically effective amount of a mineralocorticoid selected from the group comprising fludrocortisone, fludrocortisone acetate; deoxycorticosterone, 11-desoxycortisone, or deoxycorticosterone acetate or a pharmaceutically acceptable analogue, salt, conjugate or derivatives thereof together with a pharmaceutically acceptable additive.
- [0395] 63. A pharmaceutical composition or formulation for use in the method of any one of paragraphs 1 to 3, 16, 18 or 20 comprising a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye and at least a pharmaceutically acceptable additive.
- [0396] 64. A composition according to paragraph 63 wherein the compound is an anti-edematous steroid.
- [0397] 65. A composition according to paragraph 63 wherein the compound is a mineralocorticoid.
- [0398] 66. A composition according to any one of paragraphs 63 to 65 wherein the pharmaceutically acceptable additive is selected from the group comprising: a carrier; an adjunct; an excipient; or a non-toxic, non-therapeutic, non-immunogenic stabilizer.
- [0399] 67. A composition according to any one of paragraphs 63 to 65 wherein the pharmaceutically acceptable additive is compatible with the vitreous and should not leave any vision impairing residue in the eye.
- [0400] 68. A composition according to any one of paragraphs 63 to 65 wherein the pharmaceutically acceptable additive used in the composition is suited to the delivery of said pharmaceutical composition as an intravitreal depot injection.
- [0401] 69. A composition according to any one of paragraphs 63 to 65 wherein the pharmaceutically acceptable additive used in the composition is suited to the delivery of said pharmaceutical composition as an ointment, a gel, a mist or eye drops.

- [0402] 70. A method according to any one of paragraphs 1 to 3, 16, 18 or 20 comprising the further step of: performing one or more other therapies selected from the list comprising: photodynamic therapy, laser surgery (eg LASIK, LASEK, refractive laser treatment), laser photocoagulation or one or more biological or pharmaceutical treatments.
- [0403] 71. The method according to paragraph 70 wherein the laser treatment is treatment of the retina and administration of the compound capable of modulating the activity of mineralocorticoid receptors is carried out by injection after the laser treatment.
- [0404] 72. The method according to paragraph 70 wherein the laser treatment is treatment of the retina and administration of the compound capable of modulating the activity of mineralocorticoid receptors is carried out by injection before the laser treatment.
- [0405] 73. The method of any one of paragraphs 1 to 3, 16, 18 or 20 wherein the compound capable of modulating the activity of mineralocorticoid receptors is injected in combination with anti-angiogenic agents designed to block the actions of VEGF on endothelial cells.
- [0406] 74. The method of paragraph 73 wherein the anti-angiogenic agent is Lucentis® and/or Macugen®.
- [0407] 75. The method of paragraph 73 or 74 wherein the compound is an anti-oedematous steroid.
- [0408] 76. The method of paragraph 73 or 74 wherein the compound is a mineralocorticoid.
- [0409] 77. The method of any one of paragraphs 1 to 3, 16, 18 or 20 wherein the compound capable of modulating the activity of mineralocorticoid receptors is injected in combination with a glucocorticoid (e.g. prednisolone, prednisone), an oestrogen (e.g. oestradiol), an androgen (e.g. testosterone) retinoic acid derivatives (e.g. 9-cis-retinoic acid, 13-trans-retinoic acid, all-trans retinoic acid), a vitamin D derivative (e.g. calcipotriol, calcipotriene), a non-steroidal anti-inflammatory agent, a vitamin D derivative, an anti-infective agent, a protein kinase C inhibitor, a MAP kinase inhibitor, an anti-apoptotic agent, a growth factor, a nutrient vitamin, an unsaturated fatty acid, and/or ocular anti-infective agents, for the treatment of the ophthalmic conditions.
- [0410] 78. The method of paragraph 77 wherein the compound is an anti-oedematous steroid.
- [0411] 79. The method of paragraph 77 wherein the compound is a mineralocorticoid.
- [0412] 80. A kit comprising the composition of any one of paragraphs 57 to 68 in the form of a single unit dose in a pre-prepared syringe, ready for administration by intravitreal injection.
- [0413] 81. Use of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in the manufacture of a medicament for the treatment of an ophthalmic condition.
- [0414] 82. Use of an anti-oedematous steroid such as a mineralocorticoid or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of an ophthalmic condition.
- [0415] 83. Use of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition in the manufacture of a medicament for the treatment of an ophthalmic condition.
- [0416] 84. Use of:
- [0417] (a) a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition; and
- [0418] (b) a second compound chosen from the list comprising: a steroid, heparin, a tetracycline derivative, an anti-prostaglandin, a macrocyclic antibiotic, a metalloproteinase inhibitor or an anti-angiogenic agent designed to block the actions of VEGF on endothelial cells;
- [0419] for the manufacture of a medicament for the treatment of an ophthalmic condition.
- [0420] 85. Use of a compound capable of modulating the activity of mineralocorticoid receptors in the manufacture of a medicament for the treatment of an exudative retinopathy in an individual.
- [0421] 86. A use according to paragraph 85 wherein the compound capable of modulating the activity of mineralocorticoid receptors is an anti-oedematous steroid or a pharmaceutically acceptable salt thereof.
- [0422] 87. A use according to paragraph 85 wherein the compound capable of modulating the activity of mineralocorticoid receptors is mineralocorticoid or a pharmaceutically acceptable salt thereof.
- [0423] Although the invention has been described with reference to certain preferred embodiments, it will be appreciated that many variations and modifications may be made within the scope of the broad principles of the invention. Hence, it is intended that the preferred embodiments and all of such variations and modifications be included within the scope and spirit of the invention, as defined by the following claims.
- We claim:
1. A method of treatment of an individual with an ophthalmic condition comprising the step of: administering to the individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye in the individual to be treated wherein
 - (a) the compound capable of modulating the activity of mineralocorticoid receptors is an anti-oedematous steroid or
 - (b) the compound capable of modulating the activity of mineralocorticoid receptors is a mineralocorticoid or
 - (c) the compound is not a compound disclosed in U.S. Pat. 6,011,023 or

(d) the compound is a compound disclosed in U.S. Pat. 6,011,023 but the compound is not used to treat an ocular disease selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia or

(e) said compound is selected from the group consisting of: hydrocortisone hemisuccinate, hydrocortisone sodium phosphate, methylprednisolone hemisuccinate, prednisolone hemisuccinate, and prednisolone sodium succinate

(f) said compound is selected from the group consisting of: dexamethasone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone sodium succinate; and wherein the ophthalmic condition to be treated or prevent is other than an ophthalmic condition selected from the list comprising: allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, chorioretinitis, optic neuritis, anterior ischaemic optic neuropathy, iridocyclitis, iritis, diffuse posterior uveitis, choroiditis, sympathetic ophthalmia, anterior segment inflammation and herpes zoster ophthalmicus or

(g) said compound is the mineralocorticoid aldosterone or an analogue, pharmaceutically acceptable salt, conjugate or derivative thereof.

2. The method of claim 1 wherein the ophthalmic condition is selected from the group consisting of: diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctuate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome;

Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis and cytomegalovirus infection.

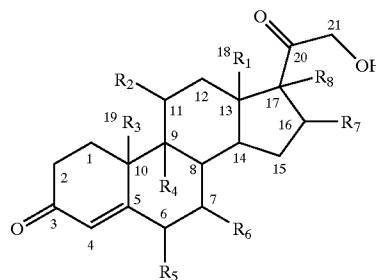
3. The method of claim 1 wherein the ophthalmic condition is an exudative retinopathy and optional which may include the further step of administering laser treatment to the retina.

4. A method for the prophylactic or therapeutic treatment of exudative retinopathies in a patient comprising the step of: administering a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors to or adjacent to cells or tissue from or in said patient that are afflicted with and exudative retinopathy; and wherein said cells or tissue are selected from the group consisting of: retinal cells, retinal pigment epithelial cells the epithelial cells of the BRB, choroidal endothelial cells.

5. The method of any one of claim 4 wherein the method comprises the further step of: administering laser treatment to the retina.

6. A method of treatment of an individual with an ophthalmic condition comprising the step of: administering to the individual a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye; wherein said compound is a mineralocorticoid of the general structure:

Structure [B]



wherein

R₁ is CH₃, CH=O or COCHCH₂;

R₂ is H, OH or =O;

R₃ is H, CH₃ or CH₂OH;

R₄ is H, or F;

R₅, R₆ and R₇ are H;

R₈ is H or OH; and

wherein said compound is not a compound disclosed in U.S. Pat. 6,011,023 where the compound is to be used to treat or prevent ocular diseases selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis,

neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

7. The method of claim 6 wherein the ophthalmic condition is selected from the group consisting of: diffuse lamellar keratitis, corneal diseases or opacifications with an exudative or inflammatory component, myopic retinopathies, macular oedema such as clinical macular oedema or angiographic cystoid macular oedema arising from various aetiologies such as diabetes, exudative macular degeneration and macular oedema arising from laser treatment of the retina, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, retinal ischemia and choroidal neovascularization and like diseases of the retina; anterior uveitis; inflammatory conditions resulting from surgeries such as LASIK, LASEK, refractive surgery, IOL implantation; irreversible corneal oedema as a complication of cataract surgery; oedema as a result of insult or trauma (physical, chemical, pharmacological, etc); inflammation; conjunctivitis (eg. persistent allergic, giant papillary, seasonal intermittent allergic, perennial allergic, toxic, conjunctivitis caused by infection by bacteria, viruses or Chlamydia); keratoconjunctivitis (vernal, atopic, Sicca); iridocyclitis; iritis; scleritis; episcleritis; infectious keratitis; superficial punctate keratitis; keratoconus; posterior polymorphous dystrophy; Fuch's dystrophies (corneal and endothelial); aphakic and pseudophakic bullous keratopathy; corneal oedema; scleral disease; ocular cicatricial pemphigoid; pars planitis; Posner Schlossman syndrome; Behçet's disease; Vogt-Koyanagi-Harada syndrome; hypersensitivity reactions; ocular surface disorders; conjunctival oedema; Toxoplasmosis chorioretinitis; inflammatory pseudotumor of the orbit; chemosis; conjunctival venous congestion; periorbital cellulitis; acute dacryocystitis; non-specific vasculitis; sarcoidosis; cytomegalovirus infection and the mineralocorticoid aldosterone or an analogue, pharmaceutically acceptable salt, conjugate or derivative thereof.

8. A method according to claim 1 wherein said compound is selected from the group comprising: deoxycorticosterone acetate, deoxycorticosterone pivalate, dexamethasone acetate, hydrocortisone butyrate, hydrocortisone valerate, prednisolone pivalate, prednisolone tebutate, and wherein the ophthalmic condition to be treated or prevented is other than an ophthalmic condition selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve,

neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

9. A method according to claim 1 wherein said compound is selected from the group comprising: cortisone, cortisone acetate, dexamethasone sodium phosphate, dexamethasone, hydrocortisone, hydrocortisone acetate, methylprednisolone, methylprednisolone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisone, prednisone sodium phosphate, and wherein the ophthalmic condition to be treated or prevented is other than an ophthalmic condition selected from the list comprising allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, chorioretinitis, optic neuritis, anterior ischaemic optic neuropathy, iridocyclitis, iritis, diffuse posterior uveitis, chorioiditis, sympathetic ophthalmia, anterior segment inflammation and herpes zoster ophthalmicus, nonpurulent conjunctivitis, blepharitis, scleritis, episcleritis, uveitis, retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, retrolental fibroplasia amcinonide, clocortolone butyrate, flunisolide, flucuronide, flurandrenolide, fluticasone, fluticasone propionate, halincionide, mometasone furoate clobetasol propionate, clobetasol butyrate, clocortolone butyrate, clobetasone pivalate, desoxymetasone, diflorasone diacetate, diflucortolone, diflucortolone valerate, flumethasone, flumethasone pivalate, fluocinolone, fluocortolone, fluocortolone hexanoate, fluocortolone pivalate, fluorometholone, isoflupredone, isoflupredone acetate, mometasone, and wherein the ophthalmic condition to be treated or prevented is other than an ophthalmic condition selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

10. A method according to claim 1 wherein said compound is selected from the group consisting of: rimexolone and fluocinolone acetonide, and wherein the ophthalmic condition to be treated or prevented is other than an ophthalmic condition selected from the list comprising: anterior chamber inflammation and anterior uveitis, retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to

subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

11. The method of claim 1 wherein the compound is sparingly soluble in the vitreous.

12. The method of claim 6 wherein the compound is sparingly soluble in the vitreous.

13. A method according to claim 1 wherein said compound is selected from the group comprising the mineralocorticoids: fludrocortisone, fludrocortisone acetate; deoxycorticosterone; 11-desoxycortisone; or deoxycorticosterone acetate or an analogue, pharmaceutically acceptable salt, conjugate or derivative thereof, and wherein the ophthalmic condition to be treated or prevent is other than an ophthalmic condition selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

14. A method according to claim 6 wherein said compound is selected from the group comprising the mineralocorticoids: fludrocortisone, fludrocortisone acetate; deoxycorticosterone; 11-desoxycortisone; or deoxycorticosterone acetate or an analogue, pharmaceutically acceptable salt, conjugate or derivative thereof, and wherein the ophthalmic condition to be treated or prevent is other than an ophthalmic condition selected from the list comprising retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization), rubeosis iritis, inflammatory diseases, chronic uveitis, neoplasms (retinoblastoma, pseudoglioma), Fuchs' heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris, corneal graft neovascularization), neovascularization following a combined vitrectomy and lensectomy, vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia), pterygium, neovascularization of the optic nerve, neovascularization due to penetration of the eye or contusive ocular injury, and retrolental fibroplasia.

15. The method of claim 1 wherein more than one mineralocorticoid is administered to said patient.

16. The method of claim 6 wherein more than one mineralocorticoid is administered to said patient.

17. A method for the treatment of an ophthalmic condition in an individual comprising the step of: administering to the ophthalmic condition in the individual a therapeutically effective pharmaceutically acceptable formulation of a combination of:

(a) a mineralocorticoid wherein said mineralocorticoid is (i) capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye to treat or prevent an ophthalmic condition; (ii) in a pharmaceutically acceptable form suitable for delivery to the eye; and

(b) at least a second compound or a plurality of compounds in a concentration and dose sufficient to reduce ocular neovascularization wherein the second compound is selected from the group consisting of: a tetracycline derivative, a steroid, heparin, an antimicrobial, an anti-prostaglandin, and/or a metalloproteinase inhibitor where

the second compound is a steroid or the mineralocorticoid is at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and the steroid is at a concentration from about 0.1 mg/ml to about 40 mg/ml or

the steroid used in the method is a 11-substituted-16 α , 17 α -substituted methylenedioxy steroid or

the steroid used in the method is triamcinolone acetonide or

the second compound is heparin or

the mineralocorticoid is at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and the heparin is at a concentration from about 0.01 $\mu\text{g/ml}$ to about 30 mg/ml or

the second compound is an antiprostaglandin or

the antiprostaglandin is flurbiprofen or

the mineralocorticoid is at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and the anti-prostaglandin is at a concentration from about 1 $\mu\text{g/ml}$ to about 10 mg/ml or

the second compound is an antimicrobial or

the antimicrobial is a macrolide antibiotic or

the antimicrobial is a mycophenolic acid or

the mineralocorticoid is at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and the antimicrobial is at a concentration from about 20 $\mu\text{g/ml}$ to about 200 $\mu\text{g/ml}$ or

the second compound is a tetracycline derivative or

the tetracycline derivative is doxycycline or

the mineralocorticoid is at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and the tetracycline derivative is at a concentration from about 0.01 pg/ml to about 30 mg/ml or

the compound is a metalloproteinase inhibitor or

the mineralocorticoid is at a concentration from about 0.1 $\mu\text{g/ml}$ to about 40 mg/ml and the metalloproteinase inhibitor is at a concentration and dose to reduce ocular neovascularization or

18. The method of claim 1 wherein mineralocorticoid is deposited intravitreally and the dosage is between about 1 mg and about 8 mg.

19. A pharmaceutical composition for the treatment or prophylaxis of ophthalmic conditions comprising a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissues located in the eye and wherein

- (a) the composition of claim **57** wherein the compound is an anti-oedematous steroid or
- (b) the compound is a mineralocorticoid or
- (c) the compound capable of modulating the activity of mineralocorticoid receptors is aldosterone or a pharmaceutically acceptable analogue, salt, conjugate or derivative thereof together with a pharmaceutically acceptable additive or
- (d) the compound capable of modulating the activity of mineralocorticoid receptors is selected from the group comprising fludrocortisone, fludrocortisone acetate; deoxycorticosterone, 11-desoxycortisone, or deoxycorticosterone acetate or a pharmaceutically acceptable analogue, salt, conjugate or derivatives thereof together with a pharmaceutically acceptable additive or

20. A pharmaceutical composition or formulation for use in the method of claim 1 comprising a therapeutically effective amount of a compound capable of modulating the activity of mineralocorticoid receptors within cells or tissue located in an eye or adjacent to an eye and at least a pharmaceutically acceptable additive and wherein

- (a) the compound is an anti-edematous steroid or
- (b) the compound is a mineralocorticoid or
- (c) the pharmaceutically acceptable additive is selected from the group consisting of a carrier, an adjunct, an excipient, or a non-toxic, non-therapeutic, and a non-immunogenic stabilizer or
- (d) the pharmaceutically acceptable additive is compatible with the vitreous and should not leave any vision impairing residue in the eye or
- (e) the pharmaceutically acceptable additive used in the composition is suited to the delivery of said pharmaceutical composition as an intravitreal depot injection.

21. A method according to claim 1 comprising the further step of: performing one or more other therapies selected from the list comprising: photodynamic therapy, laser surgery (eg LASIK, LASEK, refractive laser treatment), laser photocoagulation or one or more biological or pharmaceutical treatments and wherein

- (a) the laser treatment is treatment of the retina and administration of the compound capable of modulating the activity of mineralocorticoid receptors is carried out by injection after the laser treatment or
- (b) the laser treatment is treatment of the retina and administration of the compound capable of modulating the activity of mineralocorticoid receptors is carried out by injection before the laser treatment.

22. The method of claim 1 wherein the compound capable of modulating the activity of mineralocorticoid receptors is injected in combination with anti-angiogenic agents designed to block the actions of VEGF on endothelial cells and wherein

- (a) the anti-angiogenic agent is Lucentis® and/or Macugen® or
- (b) the compound is an anti-oedematous steroid or
- (c) the compound is a mineralocorticoid.

23. The method of claim 1 wherein the compound capable of modulating the activity of mineralocorticoid receptors is injected in combination with a glucocorticoid (e.g. prednisolone, prednisone), an oestrogen (e.g. oestradiol), an androgen (e.g. testosterone) retinoic acid derivatives (e.g. 9-cis-retinoic acid, 13-trans-retinoic acid, all-trans retinoic acid), a vitamin D derivative (e.g. calcipotriol, calcipotriene), a non-steroidal anti-inflammatory agent, a vitamin D derivative, an anti-infective agent, a protein kinase C inhibitor, a MAP kinase inhibitor, an anti-apoptotic agent, a growth factor, a nutrient vitamin, an unsaturated fatty acid, and/or ocular anti-infective agents, for the treatment of the ophthalmic conditions and wherein

- (a) the compound is an anti-oedematous steroid or
- (b) the compound is a mineralocorticoid.

* * * * *

COMPARISON OF IN VITRO POTENCY OF CORTICOSTEROIDS WITH ABILITY TO RAISE INTRAOCULAR PRESSURE

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The ability of certain topically applied corticosteroids to raise intraocular pressure (IOP) in susceptible individuals, particularly in open-angle glaucoma patients, limits the usefulness of these potent anti-inflammatory agents.^{1,2} Progesterone, a corticosteroid lacking substantial anti-inflammatory activity, reduces IOP.³ Medrysone (HMS), fluorometholone (FML), and tetrahydrotriamcinolone (THT), compounds with structural features in common with both the pressure elevating corticosteroids and progesterone, are effective ocular anti-inflammatory agents⁴⁻⁸ that rarely raise IOP.⁹⁻¹¹

However, whether or not medrysone, fluorometholone, and tetrahydrotriamcinolone demonstrate a true dissociation of anti-inflammatory and ocular hypertensive effects is unknown. It is difficult to measure accurately the ocular anti-inflammatory potency of the various corticosteroids. Models such as experimental uveitis⁸ and corneal graft rejection^{6,12} have the disadvantages of employing subjective grading of response and of using animal rather than human eyes. Furthermore, the inflammatory response is complex, and corticosteroids appear to affect several components of the response, including vascular permeability, phagocytosis, lymphocyte activation, antibody synthesis, and chemotaxis.^{13,14} These individual components of the inflammatory response are affected by varying corticosteroid doses,

bearing little relationship to doses required to treat various ocular inflammatory diseases in man.

If true dissociation of anti-inflammatory and ocular hypertensive effects exists, it may not be unique for medrysone, fluorometholone, and tetrahydrotriamcinolone. Dexamethasone may possess much greater potency than these compounds for both anti-inflammatory and pressure elevating effects. Yet, dexamethasone at lower concentrations may maintain effective anti-inflammatory action and no longer produce significant ocular hypertension.

We have selected lymphocyte transformation by phytohemagglutinin (PHA) as a model of the inflammatory response, and its inhibition by corticosteroids¹⁵ as a measure of their relative potency. This technique is an accurate but, at best, an indirect measure of ocular anti-inflammatory potency.

Lymphocyte transformation by PHA is a good model of cellular immune responsiveness, correlating well with other measures of delayed hypersensitivity in man.^{16,17} Significant inhibition occurs at physiologic to low pharmacologic concentrations of hydrocortisone.¹³ A close correlation exists between the topical ocular response to dexamethasone of an individual and the in vitro lymphocyte sensitivity to corticosteroids of that person.¹⁸ Those who show a high ocular pressure response to dexamethasone have lymphocytes that are more sensitive in vitro to dexamethasone, hydrocortisone, prednisolone, or tetrahydrotriamcinolone.

The present study compares corticosteroid inhibition of lymphocyte transformation with ability to raise IOP in a group of corticosteroid-sensitive patients. We present data

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showing that the rank order of *in vitro* potency of various corticosteroids is not the same as the rank order for ability to raise IOP, particularly in the case of the low IOP response to fluorometholone and medrysone.

MATERIALS AND METHODS

We selected six men and four women with a mean age of 65 years who developed IOP greater than 31 mm Hg after topical application of dexamethasone-21-phosphate 0.1%, four times daily, for two to six weeks. The same eye was sequentially tested for the same period of time with dexamethasone-21-phosphate 0.005%, medrysone 1%, tetrahydrotriamcinolone 0.25%, hydrocortisone 0.5%, and prednisolone-21-acetate 1%. We used commercial preparations when available. Enough time was allowed between testing periods for IOP to return to baseline levels. None of the patients had evidence of visual field loss or were using ocular hypotensive agents. The mean duration of testing was 4.6 weeks.

In vitro corticosteroid potency was determined by the inhibition of PHA-stimulated lymphocyte transformation as previously described.¹⁸ We used dexamethasone-21-phosphate, prednisolone-21-phosphate, fluorometholone, medrysone, tetrahydrotriamcinolone, and hydrocortisone-21-phosphate. Water insoluble preparations were dissolved with minimum amounts of absolute ethyl alcohol and then diluted with distilled water. The final dilution of ethyl alcohol was less than 1:1000 and had no effect on lymphocyte transformation. All corticosteroids were tested simultaneously *in vitro* on the same patient's lymphocytes.

RESULTS

A composite dose-response curve for corticosteroid inhibition of lymphocyte transformation was drawn for one of our patients (Figure). Inhibition was linear from 15 to 85% of PHA-stimulation. The slope

of the dose-response curve was similar for all corticosteroid preparations, a shift in the curve to the left indicating increased potency. The concentration of corticosteroid required to inhibit PHA stimulation by 50% (I-50) was a quantitative measure of this potency. For this particular patient, the I-50 ranged from 7.4 nm for dexamethasone to 141 nm for hydrocortisone.

The results of *in vitro* corticosteroid sensitivity testing in the ten patients using the lymphocyte transformation assay and the mean I-50 value for each of the six corticosteroid preparations were prepared (Table 1). Dexamethasone and fluorometholone were more than 20 times as potent as hydrocortisone, the reference standard. Prednisolone, medrysone, and tetrahydrotriamcinolone were relatively weak corticosteroids with only 2.3, 1.7, and 1.4 times the potency of hydrocortisone, respectively.

The IOP data in the ten patients were compiled for the six topical corticosteroids used (Table 2). The mean baseline pressure was 23.1 mm Hg, and both final IOP and net rise in IOP were shown. Medrysone, tetrahydrotriamcinolone, and hydrocortisone had a modest ocular hypertensive effect. Dexamethasone, prednisolone, and fluorometholone, however, consistently raised IOP in the same group of patients. Dexamethasone used topically in the same concentration as fluorometholone had 3.5 times the ocular hypertensive effect of fluorometholone, despite similar *in vitro* potency. Dexamethasone 0.005% (1/20 dilution) had about the same ocular hypertensive effect as fluorometholone 0.1%. Prednisolone used topically in the same concentration as medrysone had ten times the ocular hypertensive effect, yet *in vitro* was only 1.3 times as potent.

DISCUSSION

Our data suggest that fluorometholone has an *in vitro* potency similar to dexamethasone yet has a much smaller effect on IOP. A comparison of medrysone and prednisolone

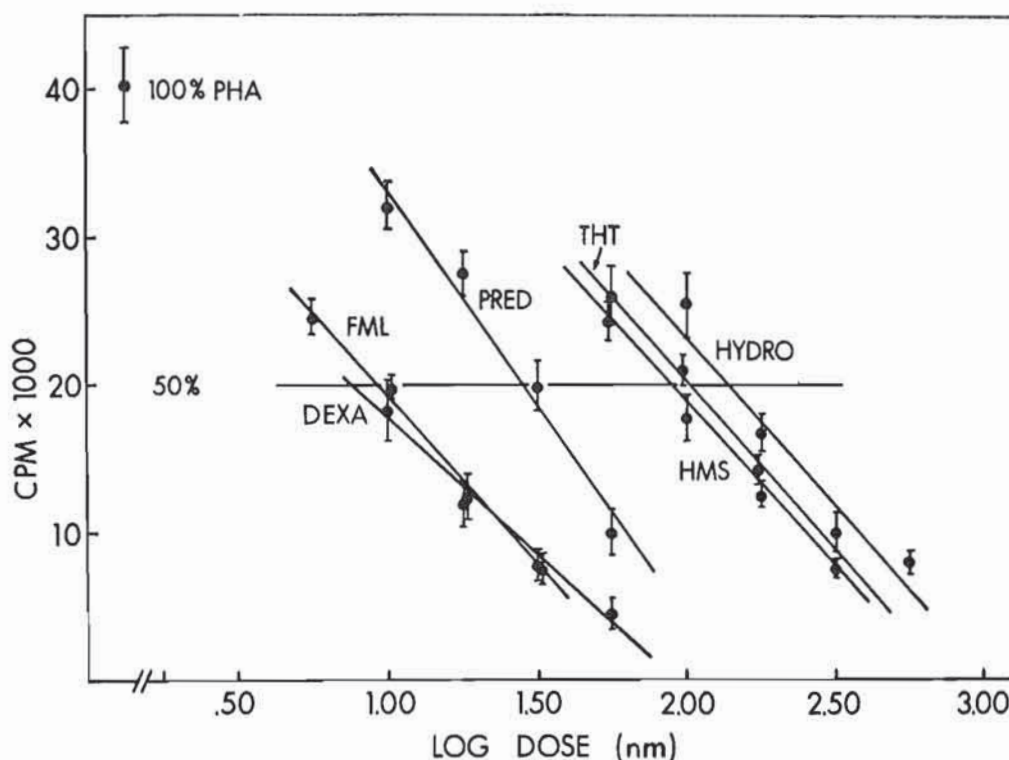


Figure (Cantrill and associates). Corticosteroid inhibition by PHA-stimulated lymphocyte transformation. PHA indicates phytohemagglutinin; FML, fluorometholone; PRED, prednisolone; THT, tetrahydrotriamcinolone; DEXA, dexamethasone; HYDRO, hydrocortisone; and HMS, medrysone.

demonstrates a similar dissociation of effects. This lack of correlation may be explained by differences in the relative action or ocular penetration of the drugs. It could relate to differences in derivative, formulation, vehicle, or concentration tested.

Early studies generally showed greater penetration of the alcohol compared to the acetate derivative.^{10,20} However, those tech-

niques were crude and inconsistent findings were obtained when different corticosteroids were compared. Using sensitive radioisotope techniques, some investigators were unable to measure aqueous concentrations of dexamethasone phosphate,²¹ while others readily measured levels after single applications to the intact cornea.²² Recently Hull and associates²³ reported a quantitative in vitro tech-

TABLE 1

CONCENTRATION OF CORTICOSTEROID REQUIRED TO INHIBIT LYMPHOCYTE TRANSFORMATION BY 50% (I-50)

Corticosteroid	I-50	Potency
	(Mean nm $\pm$ SE)	(Relative to Hydrocortisone)
Dexamethasone	8.4 $\pm$ 2.0	23.8
Fluorometholone	9.7 $\pm$ 2.0	20.8
Prednisolone	87 $\pm$ 18	2.3
Medrysone	117 $\pm$ 15	1.7
Tetrahydrotriamcinolone	142 $\pm$ 37	1.4
Hydrocortisone	201 $\pm$ 57	1.0

TABLE 2

INTRAOCULAR PRESSURE RESPONSE TO TOPICALLY APPLIED CORTICOSTEROIDS IN THE SAME PATIENTS

Corticosteroid	Final IOP	Rise IOP
	(Mean mm Hg $\pm$ SE)	
Dexamethasone 0.1%	45.1 $\pm$ 2.7	22.0 $\pm$ 2.9
Prednisolone 1.0%	32.3 $\pm$ 2.1	10.0 $\pm$ 1.7
Dexamethasone 0.005%	31.3 $\pm$ 2.4	8.2 $\pm$ 1.7
Fluorometholone 0.1%	29.2 $\pm$ 2.2	6.1 $\pm$ 1.4
Hydrocortisone 0.5%	26.3 $\pm$ 1.5	3.2 $\pm$ 1.0
Tetrahydrotriamcinolone 0.25%	24.9 $\pm$ 1.8	1.8 $\pm$ 1.3
Medrysone 1.0%	24.1 $\pm$ 1.8	1.0 $\pm$ 1.3

nique for comparing corneal permeability constants that avoids many of the shortcomings of previous techniques. They found similar permeability constants for prednisolone acetate, prednisolone phosphate, and fluorometholone, but a value 40% lower for dexamethasone phosphate. Presumably, corneal permeability depends upon both lipid and aqueous solubility properties, as well as the corticosteroid being studied. These data suggest that relatively less dexamethasone than fluorometholone penetrates the cornea, yet dexamethasone possesses much greater pressure-raising potency.

Investigators²⁴ found a more than twofold increase in ocular penetration of dexamethasone in a hydroxyethylcellulose vehicle, compared to aqueous preparations. In our study, fluorometholone, medrysone, and prednisolone are in a high viscosity vehicle, while dexamethasone, hydrocortisone, and tetrahydrotriamcinolone are formulated in buffered aqueous solution. If fluorometholone is in contact with the cornea longer than dexamethasone, it should produce a greater IOP effect. Vehicle differences cannot account for the results.

Comparing topical anti-inflammatory potency with ability to raise IOP involves many important considerations. First, the relative anti-inflammatory effects of the corticosteroids must be established by some assay technique. Second, the effect of topical corticosteroids depends on ocular penetration

and local metabolism of the drug. Since all corticosteroid preparations penetrate ocular media relatively poorly, small differences in penetration may have a critical effect on activity.²⁵ Finally, the corticosteroid IOP dose-response curve must be considered. This will clearly depend on concentration, vehicle, formulation, duration, and frequency of administration, and on such poorly controlled factors as blink rate and instillation technique.

The dose-response characteristics of the topical IOP response to corticosteroids are not fully characterized. The points on a log dose-response curve for topical dexamethasone are linear from 20 to 45 mm Hg using concentrations from 0.001% to 0.1% in corticosteroid-responsive patients.^{9,26} The dose-response curves of other corticosteroids are unknown, making it difficult to compare the IOP response obtained with different concentrations of drug. However, we can compare the IOP and lymphocyte responses of dexamethasone with fluorometholone and those of prednisolone with medrysone, since these were studied at the same concentrations.

The lymphocyte transformation assay is a quantitative method of comparing potency of corticosteroids. Other investigators found widely differing relative potencies of corticosteroid drugs.²⁷ This is not surprising, given the variety of *in vitro* and *in vivo* assay techniques used and the marked species variation in sensitivity to corticosteroids.²⁸

Our assay has the advantage, however, of being an in vitro determination of the potency of corticosteroids on human lymphoid cells.

The anti-inflammatory potency of various topical corticosteroids may not correlate with the IOP elevation. This is not surprising since the anti-inflammatory effects of topical corticosteroids are relatively short-term, while the ocular hypertensive response usually requires four to six weeks of instillation. Moreover, the known mechanisms of these two actions appear to be wholly different. The anti-inflammatory effects involve decreases of vascular permeability and cellular reaction while the ocular hypertensive effect involves some means of decreasing outflow facility.

SUMMARY

Corticosteroid inhibition of lymphocyte transformation was compared with ability to raise intraocular pressure in ten corticosteroid-sensitive patients. Dexamethasone used topically in the same concentration as fluorometholone had more than three times the ocular hypertensive effect but was similar in in vitro potency. A dissociation was also found for prednisolone and medrysone.

ACKNOWLEDGMENT

We thank Mamie Penny for her technical assistance.

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OPHTHALMIC MINIATURE

As concerns bats, it is a fact that the more they excel in hearing, the less endowed they seem to be in the field of sight; and not a few of the most experienced authors have denied that their flight could be directed by sight at all and have ascribed to them some special unknown sense; but as you will find in them precisely the same structure of the eyes, tiny though they be, as in the larger nocturnal animals, the similarity of their function can in no way be subject to doubt.

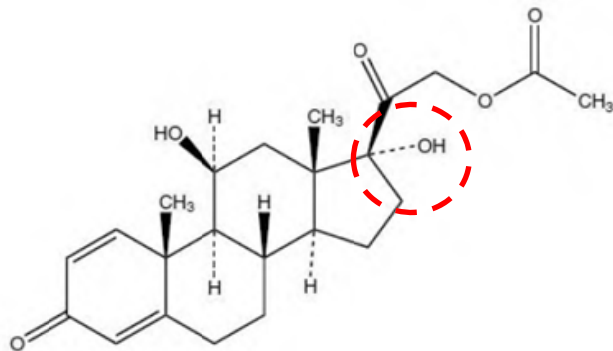
The axis of the eyeball is longer than its horizontal diameter; the cornea is obviously convex and forms in the front an almost complete hemisphere, so that its size almost equals that of the sclerotica and surpasses it in thickness. In the foremost edge of the black choroidea, a corona of very fine processus ciliares is distinguishable. The iris is dark, convex and lies against the lens. It has a nearly oval and narrow pupil.

The very thin optic nerve is inserted into the eyeball towards the outer angle, and expands into the retina, which is thick in proportion to its small extent.

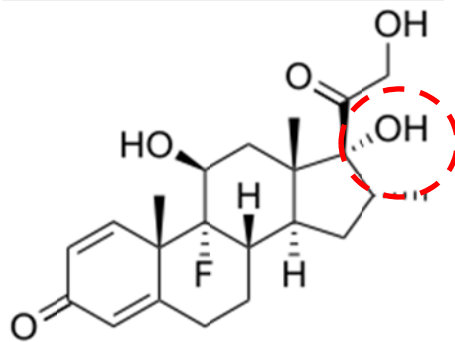
Both the mass of the lens—the two surfaces of which are equally convex—and the quantity of aqueous humour as well, being great, the vitreous humour must necessarily be so much the smaller, an observation to be made also in the eyes of other nocturnal animals.

Sömmering,
De Oculis Animalium

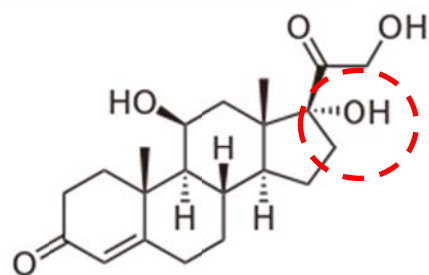
prednisolone acetate



dexamethasone



hydrocortisone



REIVINDICACIONES

(modificadas para fondo)

1. Una composición farmacéutica oftálmica tópica que comprende un portador y un compuesto seleccionado de:

Fenilacetato de (8S,9S,10R,11S,13S,14S,17R)-17-glicololil-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo;

Propionato de (8S,9S,10R,11S,13S,14S,17R)-17-glicololil-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo;

Octanoato de (8S,9S,10R,11S,13S,14S,17R)-17-glicololil-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo;

Hexanoato de (8S,9S,10R,11S,13S,14S,17R)-17-glicololil-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo;

Benzoato de (8R,9R,10S,11R,13R,14R,17S)-17-glicololil-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo;

Heptanoato de (8S,9S,10R,11S,13S,14S,17R)-17-glicololil-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo;

2-Metilpropanoato de (8S,9S,10R,11S,13S,14S,17R)-17-glicololil-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo y

rel-ciclopentanocarboxilato de (8R,9R,10S,11R,13R,14R,17S)-17-glicololil-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo,

en donde el portador se encuentra en una cantidad de 0,999 - 95 % p/v y el compuesto en una proporción de 0,001 - 5 % p/v.

2. Composición farmacéutica de acuerdo con la reivindicación 1 donde el compuesto es:

Benzoato de (8R,9R,10S,11R,13R,14R,17S)-17-glicolol-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo.

3. Composición farmacéutica de acuerdo con la reivindicación 1 donde el compuesto es:

Hexanoato de (8S,9S,10R,11S,13S,14S,17R)-17-glicolol-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo.

4. Composición farmacéutica de acuerdo con la reivindicación 1 donde el compuesto es:

Octanoato de (8S,9S,10R,11S,13S,14S,17R)-17-glicolol-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo.

5. Composición farmacéutica de acuerdo con la reivindicación 1 donde el compuesto es:

Fenilacetato de (8S,9S,10R,11S,13S,14S,17R)-17-glicolol-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo.

6. Composición farmacéutica de acuerdo con la reivindicación 1 donde el compuesto es:

Propionato de (8S,9S,10R,11S,13S,14S,17R)-17-glicolol-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo.

7. Composición farmacéutica de acuerdo con la reivindicación 1 donde el compuesto es:

Heptanoato de (8S,9S,10R,11S,13S,14S,17R)-17-glicolol-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo.

8. Composición farmacéutica de acuerdo con la reivindicación 1 donde el compuesto es:

2-Metilpropanoato de (8S,9S,10R,11S,13S,14S,17R)-17-glicolol-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo.

9. Composición farmacéutica de acuerdo con la reivindicación 1 donde el compuesto es:
rel-ciclopentanocarboxilato de (8R,9R,10S,11R,13R,14R,17S)-17-glicolil-11-hidroxi-10,13-dimetil-3-oxo-
2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo.

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Doctor

José Luis Salazar

Director de División de Nuevas Creaciones (C)

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. _____ S. _____ D. _____

Referencia: Expediente No. 14.124.183

Solicitud de Patente de Invención titulada: “Composiciones farmacéuticas de derivados de 4-pregnen-11 β -17-21-triol-3,20-diona”

Solicitante: Allergan, Inc.

RESPUESTA AL AUTO NOTIFICADO POR FIJACIÓN EN LISTA NO. 29

DEL 21 DE JULIO DE 2015, OFICIO NO. 8192 (EXAMEN DE FONDO)

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, doy respuesta al auto emanado por ese Despacho dentro del término de prórroga solicitado en mi memorial 14-124183-00004-0000 de fecha 14 de octubre de 2015:

1. Objeciones del Examinador

1.1 Título

Su Despacho ha considerado que el título incluye el término “uso” el cual indican el uso que puede darse al producto reivindicado, el cual no es una característica técnica que defina a la invención. Además, el artículo 14 de la D.486 establece que los usos no son patentables, por lo anterior se sugiere eliminar dicho término del título.

1.2 Reivindicaciones

Su Despacho ha considerado en relación con las reivindicaciones que:

1.2.1. La reivindicación 1 no es clara porque la expresión “al menos” precediendo una característica no es limitativa, porque hace opcional a la característica y no precisa el alcance de la reivindicación. Se sugiere incluir una expresión concreta de acuerdo con los ejemplos sustentados.

1.2.2. La reivindicación no es clara porque la expresión “cantidad terapéuticamente efectiva” hace referencia a un método de tratamiento y de acuerdo la D. 486 de 2000 en su artículo 20 establece que los métodos de tratamiento constituyen una excepción a la patentabilidad, además se recuerda, que las composiciones se deben definir en términos de sus ingredientes y proporciones específicas de acuerdo al sustento dado en el capítulo descriptivo.

1.3 Novedad

El Examinador plantea que, después de realizada la búsqueda de anterioridades, encontró documentos que afectan la novedad de las reivindicaciones 1 y 6 de la presente solicitud.

Particularmente, el Examinador considera que el documento WO2005099715 (D1) afectan la novedad de la presente solicitud por cuanto:

“(…) las características esenciales de la composición de la reivindicación 1 habían sido divulgadas previamente en el documento D1, por lo tanto, la materia reivindicada no es nueva.

En consecuencia, la reivindicación 1 carece de novedad, según lo divulgado en el documento D1. La reivindicación dependiente 6 no menciona alguna característica que haga nueva a la composición de la reivindicación 1, por lo cual se considera que no es nueva.”

1.4 Nivel Inventivo

Sobre el requisito del nivel inventivo, el Examinador establece que una persona del nivel técnico medio, versada en la materia, ensayaría las soluciones que se proponen en los documentos WO2005099715 (D1) y US4383992 (D2) y llegaría de manera obvia a la solución que se propone en la presente solicitud. Particularmente, el Examinador considera que las reivindicaciones 2-5 y 7-10 carecen de nivel inventivo debido a las enseñanzas contenidas en dichos documentos D1 y D2.

El Examinador establece:

“Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 2 porque en el caso del documento D1 divulga composiciones oftálmicas que comprenden compuestos mineralocorticoides derivados del núcleo ciclopenta[a]fenantrenilo, útiles en el tratamiento de enfermedades de los ojos (Resumen y Págs. 77-79, Rvs. 6-10). Por su parte, el documento D2 divulga composiciones oftálmicas que comprenden compuestos esteroideos derivados del núcleo ciclopenta[a]fenantrenilo, en cuya posición 17 presentan como sustituyente una cadena $-C(=O)-(CH_2)_x C_6H_5$ donde $X=1$; dichas composiciones son útiles en el tratamiento de inflamaciones oculares (Resumen y Cols. 6-8, Rvs. 2 y 6).

La diferencia entre la composición, definida en la reivindicación 2 y la composición divulgada en el documento D1 consiste en que la composición reclamada incluye un compuesto en cuya estructura la posición 17 del núcleo ciclopenta[a]fenaltrenilo presenta un oxígeno enlazado con grupo $-C(=O)-C_6H_5$, mientras que la composición revelada en el documento D1 incluye un compuesto en cuya estructura el núcleo ciclopenta[a]fenaltrenilo presenta en la posición 17 un oxígeno enlazado con un grupo $-C(=O)-CH_2-CH_2-CH_3$.

El efecto que logra enlazar al oxígeno presente en la posición 17 del núcleo ciclopenta[a]fenaltrenilo con un grupo $-C(=O)-C_6H_5$ consiste en que la actividad mineralocorticoide (EC50) varía entre 2,85nM->100nM (Págs 29-31, Tabla 4).

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: “Cómo proporcionar composiciones oftálmicas útiles en el tratamiento de enfermedades de los ojos”.

Sin embargo, la inclusión de una cadena lateral carboxílica que incluye un anillo C₆H₅ en la posición 17 del núcleo ciclopenta[a]fenaltrenilo en estructuras de compuestos útiles para tratar enfermedades de los ojos, está revelada en el documento D2 que enseña composiciones útiles para tratar enfermedades de los ojos que comprenden compuestos derivados del núcleo ciclopenta[a]fenaltrenilo en donde la posición 17 de éste núcleo presenta una cadena lateral carboxílica que incluye el anillo C₆H₅ (Resumen y Cols. 6-8, Rvs. 2 y 6).

En consecuencia, la persona del oficio normalmente versada en la materia, enlazaría al oxígeno presente en la posición 17 del núcleo ciclopenta[a]fenaltrenilo revelado en el documento D1 con una cadena lateral carboxílica que incluye el anillo C₆H₅ de acuerdo con lo divulgado en el documento D2, para llegar así al objeto de la reivindicación 2 de la solicitud. Por lo cual se considera obvia.

La reivindicación 3 consiste en una "Composición farmacéutica de acuerdo con la reivindicación 1 donde el compuesto es (...)". Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 3 porque en el caso del documento D1 divulga composiciones oftálmicas que comprenden compuestos mineralocorticoides derivados del núcleo ciclopenta[a]fenantrenilo, útiles en el tratamiento de enfermedades de los ojos (Resumen y Págs. 77-79, Rvs. 6-10). Por su parte, el documento D2 divulga composiciones oftálmicas que comprenden compuestos esteroideos derivados del núcleo ciclopenta[a]fenantrenilo, en cuya posición 17 presentan como sustituyente una cadena -O-C(=O)(CH₂)_xCy(CH₂)_z; dichas composiciones son útiles en el tratamiento de inflamaciones oculares (Resumen y Cols. 6-8, Rvs. 2 y 6).

La diferencia entre la composición, definida en la reivindicación 3 y la composición divulgada en el documento D1 consiste en que la composición reclamada incluye un compuesto en cuya estructura la posición 17 del núcleo ciclopenta[a]fenaltrenilo presenta un oxígeno enlazado con un grupo -C(=O)-(CH₂)₄-CH₃, mientras que la composición revelada en el documento D1 incluye un compuesto en cuya estructura el núcleo ciclopenta[a]fenaltrenilo presenta en la posición 17 un oxígeno enlazado con un grupo -C(=O)-CH₂-CH₂-CH₃.

El efecto que logra enlazar al oxígeno presente en la posición 17 del núcleo ciclopenta[a]fenaltrenilo con un grupo $-C(=O)-(CH_2)_4-CH_3$ consiste en que la actividad mineralocorticoide (EC50) varía entre 2,85nM->100nM (Págs 29-31, Tabla 4).

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: "Cómo proporcionar composiciones oftálmicas útiles en el tratamiento de enfermedades de los ojos".

Sin embargo, la inclusión en la posición 17 del núcleo ciclopenta[a]fenaltrenilo de un grupo $-C(=O)-(CH_2)_4-CH_3$ en estructuras de compuestos útiles para tratar enfermedades de los ojos, está divulgada en el documento D2 que enseña composiciones oftálmicas que comprenden compuestos derivados del núcleo ciclopenta[a]fenaltrenilo en donde la posición 17 de éstos está sustituida por un grupo $-C(=O)(CH_2)(x=1-10)Cy(CH_2)z$; dichos compuestos son útiles para tratar enfermedades de los ojos (Resumen y Cols. 6-8, Rvs. 2 y 6).

En consecuencia, la persona del oficio normalmente versada en la materia, enlazaría el oxígeno presente en la posición 17 del núcleo ciclopenta[a]fenaltrenilo revelado en el documento D1 con el grupo $-C(=O)(CH_2)(x=1-10)Cy(CH_2)z$ de acuerdo con lo divulgado en el documento D2, para llegar así al objeto de la reivindicación 3 de la solicitud. Por lo cual se considera obvia.

Puesto que las reivindicaciones 4, 7 y 8-10 no mencionan características inventivas adicionales, tampoco se pueden considerar inventivas.

La reivindicación 5 consiste en una Composición farmacéutica de acuerdo con la reivindicación 1 donde el compuesto es (...)"

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 5 porque en el caso del documento D1 divulga composiciones oftálmicas que comprenden compuestos mineralocorticoides derivados del núcleo ciclopenta[a]fenantrenilo, útiles en el tratamiento de enfermedades de los ojos (Resumen y Págs. 77-79, Rvs. 6-10). Por su parte, el documento D2 divulga composiciones oftálmicas que comprenden compuestos esteroideos derivados del núcleo ciclopenta[a]fenantrenilo,

en cuya posición 17 presentan como sustituyente una cadena $-C(=O)-(CH_2)_x C_6H_5$ donde $X=1-10$; dichas composiciones son útiles en el tratamiento de inflamaciones oculares (Resumen y Cols. 6-8, Rvs. 2 y 6).

La diferencia entre la composición, definida en la reivindicación 5 y la composición divulgada en el documento D1 consiste en que la composición reclamada incluye un compuesto en cuya estructura la posición 17 del núcleo ciclopenta[a]fenaltrenilo presenta un oxígeno enlazado con un grupo $-C(=O)-CH_2-C_6H_5$, mientras que la composición revelada en el documento D1 incluye un compuesto en cuya estructura el núcleo ciclopenta[a]fenaltrenilo presenta en la posición 17 un oxígeno enlazado con un grupo $-C(=O)-CH_2-CH_2-CH_3$.

El efecto que logra enlazar el oxígeno presente en la posición 17 del núcleo ciclopenta[a]fenaltrenilo con un grupo $-C(=O)-CH_2-C_6H_5$ consiste en que la actividad mineralocorticoide (EC50) varía entre $2,85nM > 100nM$ (Págs 29-31, Tabla 4).

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: "Cómo proporcionar composiciones oftálmicas útiles en el tratamiento de enfermedades de los ojos".

Sin embargo, la inclusión en la posición 17 del núcleo ciclopenta[a]fenaltrenilo de un grupo $-C(=O)-CH_2-C_6H_5$ en estructuras de compuestos útiles para tratar enfermedades de los ojos, está divulgada en el documento D2 que enseña composiciones oftálmicas que comprenden compuestos derivados del núcleo ciclopenta[a]fenaltrenilo en donde la posición 17 de éstos está sustituida por un grupo $-C(=O)-CH_2(1-10)C_6H_5$; dichos compuestos son útiles para tratar enfermedades de los ojos (Resumen y Cols. 6-8, Rvs. 2 y 6).

En consecuencia, la persona del oficio normalmente versada en la materia, enlazaría el oxígeno presente en la posición 17 del anillo ciclopenta[a]fenaltrenilo revelado en el documento D1 con el grupo $-C(=O)-CH_2-C_6H_5$ de acuerdo con lo divulgado en el documento D2, para llegar así al objeto de la reivindicación 5 de la solicitud. Por lo cual se considera obvia. ..."

2. Argumentos a favor de la patentabilidad de la solicitud

2.1 Título

De acuerdo con la solicitud de su Despacho el título de la solicitud se ha modificado por: “Composiciones farmacéuticas de derivados de 4-pregnen-11 β -17-21-triol-3,20-diona”

2.2 Reivindicaciones

En relación con las reivindicaciones por favor note que las expresiones "al menos" y "cantidad terapéuticamente efectiva" se han eliminado del nuevo pliego de reivindicaciones.

De otro lado, y de acuerdo con la solicitud de su Despacho, la reivindicación 1 se ha limitado con las proporciones específicas de acuerdo con el sustento encontrado en la tabla 2 de la especificación.

2.3 Novedad

La novedad de una solicitud está legalmente definida en el Artículo 16 de la Decisión 486 así: *“una invención se considerará nueva, cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso de la prioridad reconocida...”*

En virtud de la anterior definición, consideramos que el documento D1 no constituye documento del arte previo que afecte la novedad de la presente solicitud.

Teniendo en cuenta que el compuesto hidrocortisona butirato se ha eliminado del presente capítulo reivindicatorio, es claro que la presente solicitud posee novedad.

2.4 Nivel inventivo

El nivel inventivo de una solicitud se encuentra definido en el Artículo 18 de la Decisión 486 y se establece cuando *“si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”*.

Contrario a lo que plantea el Examinador, el documento del arte previo citado no afecta el nivel inventivo de la presente solicitud por cuanto no es posible derivar la presente invención a partir de las enseñanzas presentadas en los documentos D1 y D2.

Por favor note que su Despacho está haciendo extrapolaciones de citas extraordinariamente amplias en la referencia que no están objetivamente soportadas.

En principio, se hace notar que D1 (WO2005099715) es el mismo documento citado para el asunto CO 14.116.546. Para el presente asunto tal como para el asunto mencionado, su Despacho parece tomar las citas demasiado amplias de D1 para alegar que una persona medianamente versada habría encontrado los compuestos (o composiciones con nuestros compuestos) no inventivos y, en particular, que una persona medianamente versada habría estado motivada a hacer cambios en la posición C17 (y específicamente en el OH de la posición C17) para llegar a los compuestos. Sin embargo, le hacemos notar que las citas en esa referencia son muy amplias (por ejemplo, los compuesto propuestos comprenden potencialmente decenas y hasta cientos de miles de millones de compuestos cuando la referencia es considerada en su totalidad y también el hecho de que ninguno de los compuestos específicos ensayado (que fueron solo 7 de las potencialmente decenas o cientos de miles de millones de compuestos) aporta una clara información de los cambios de actividad al hacer cambios en la posición C17 (y específicamente en el OH de la posición C17).

Una persona normalmente versada en la materia técnica correspondiente no estaría consciente de nuestra invención y de los conocimientos contenidos en el documento D1. Respetuosamente mi representada considera que no hay prácticamente manera para que una persona normalmente versada, ante solamente el documento D1 sin ningún conocimiento de nuestros compuestos pudiera ser capaz de llegar a estos compuestos. Tal resultado

involucrará aleatoriamente variar todos los posibles parámetros (tales como los sustituyentes en las estructuras [A], [B], y [C] con una guía no razonable que se dirija a nuestros compuestos.

En particular, mi representada hace notar que si una persona tiene en cuenta todos los sustituyentes posibles dados por la estructura [B] en el documento D1 (por ejemplo que R1 tiene 12 posibles sustituyentes, R2 tiene 5, R3 tiene 3, etc.), la persona encontraría que hay 1,745,226,000, o por encima de 1.7 mil millones, de posibilidades ($12 \times 5 \times 3 \times \dots$), y que aún no se está considerando el hecho de que algunos de los sustituyentes (por ejemplo R5) tengan sustituyentes tal como "OR", lo cual multiplicaría aún más los 1.7 mil millones antes mencionado.

Mi representada hace notar que los anteriores cálculos solo tienen en cuenta la estructura [B], y las estructuras [A] y [C] tiene una complejidad similar. Por lo tanto, cuando el documento D1 se considera como un todo, la persona medianamente versada en la materia probablemente tendría decenas o cientos de miles de millones de moléculas de partida a modificar con el fin de posiblemente llegar a los compuestos de nuestra invención.

La persona medianamente versada en la materia, aún con los conocimientos generales arriba citados, no estaría en posición de estar confrontada con las decenas o cientos de miles de millones de compuestos que sirvieran como puntos de partida y no tendría ningún conocimiento a modificar, ni sabría exactamente como modificar, para llegar a nuestros compuestos.

La selección arbitraria del examinador de unos compuestos muy específicos a modificar de entre los miles de millones potenciales de posibilidades para la estructura [B] (y decenas o cientos de miles de millones de posibilidades cuando se consideran las otras dos estructuras) parece ser, con todo el debido respeto, una descarada "manipulación" no reflexiva, de la realidad del documento D2 cuando se considera como un todo.

Respetuosamente, mi representada considera que el argumento de que la persona del oficio normalmente versada, cuando se confronta con tal documento tan amplio y no preciso, de alguna manera habría llegado a los compuestos de nuestra invención basados en "conocimiento general", es similar a argumentar que se llegaría a cualquier compuesto

terapéutico en vista de la tabla periódica (la cual revela todos los elementos necesarios para hacer las moléculas) y con el conocimiento general de la química médica y sintética. Tal argumento no es congruente con la realidad de la situación, y constituye un argumento hecho con un análisis en retrospectiva o "hindsight" y condicionado en el conocimiento encontrado en nuestra solicitud ya que claramente tal conocimiento no se encuentra en el documento D2 ni en el raciocinio del examinador.

Adicionalmente, además de la selección arbitraria del examinador de la molécula específica a modificar de entre las decenas o cientos de miles de millones de posibilidades, mi representa hace notar que dicho compuesto específico no fue ni siquiera ensayado en el documento D1 y por lo tanto, el documento D1 no proporciona datos biológicos para dicho compuesto. Por el contrario, los únicos compuestos ensayados en los ejemplos del documento D1 fueron aquellos mostrados en la tabla adjunta.

Por lo tanto, la persona del oficio medianamente versada no solamente no tendría ningún dato biológico para guiarlo a la molécula específica seleccionada por la modificación del examinador fuera de las decenas o cientos de miles de millones de posibilidades, sino que las estructuras que realmente no tienen datos biológicos son diferentes de aquellas de la solicitud en estudio. Nuevamente, mi representada nota que el raciocinio del examinador es hecho con un análisis en retrospectiva o "hindsight" cuando el documento D1 se mira en detalle y considerado como un todo.

Por ultimo, mi representada hace notar que el examinador no solamente ha seleccionado una molécula de entre las decenas o cientos de miles de millones de posibilidades, sino que el examinador ha señalado un sitio específico para modificación (C17 y específicamente un OH en C17) de entre el aparente sin fin de otros posibles sitios en la molécula. Aquí mi representada nota que los datos biológicos reales en el documento D1 no muestran ninguna modificación de este sitio. Por lo tanto, no parece haber ninguna guía en particular que indicara que el OH en C17 (aún si esta presente) sirviera como un sitio de modificación o que tal modificación resultara en un efecto ventajoso.

Por otro lado, nuestra solicitud muestra (ver nuestros ejemplos) que tal modificación resulta en compuestos activos, lo cual es algo que no se aprecia en D1 ni tampoco se indica, tal como se demostró anteriormente.

Por lo tanto, en vista de lo anterior, mi representada considera respetuosamente que el examinador está tratando de forzar una lectura del documento D1 para argumentar que de alguna manera una persona del oficio normalmente versada en la materia habría llegado a los compuestos de la solicitud en estudio. Sin embargo, como se demostró anteriormente, cuando el documento D1 se mira en detalle y se considera como un todo, este no indica los compuestos de la solicitud en estudio, y parece que el examinador se extiende mucho más de la lectura del documento D1 de lo que realmente se menciona.

De conformidad con lo anterior, es claro que la presente invención es inventiva con relación al documento D1.

En relación, ahora, al nivel inventivo con relación al documento D2 (US 4,383,992), hacemos notar que de nuevo, su Despacho esta tomando citas de carácter muy amplio y esta intentado extrapolar cómo una persona medianamente versada hubiera estado motivada a hacer cambios en la posición C17 (y específicamente en el OH de la posición 17) para llegar a los compuestos de la presente invención (o composiciones que contienen esos compuestos).

En particular, se hace notar, primeramente, que tal como en D1, su Despacho se basa en unas estructuras demasiado amplias citadas en la reivindicación 2, para alegar acerca de alterar los sustituyentes en C17 (y específicamente el sustituyente sobre el OH del C17) cuando una indicación semejante nunca se ha especificado de manera clara.

En segundo lugar, hacemos notar que D2 se relaciona con estudios que muestran que "las beta-ciclodextrinas forman unos complejos solubles en agua o compuestos de inclusión con compuestos esteroides" (ver D2, resumen; subrayado fuera de texto). En otras palabras, D2 trata con mejoras en la solubilidad de esteroides cuando las moléculas de las ciclodextrinas se agregan a composiciones que las contienen. No parece haber ningún estudio de cómo tiene algún efecto el patrón de sustitución de los esteroides (y en particular el patrón de sustitución en C17) bien sea sobre las propiedades medicinales de las moléculas o aún el objetivo del estudio: solubilidad de los esteroides. Por lo tanto, el argumento de su Despacho de que "En consecuencia, la persona del oficio normalmente versada en la materia, enlazaría el oxígeno presente en la posición 17 del núcleo ciclopenta[a]fenaltrenilo ... una cadena lateral carboxílica que incluye el anillo C6H5 de acuerdo con lo divulgado en

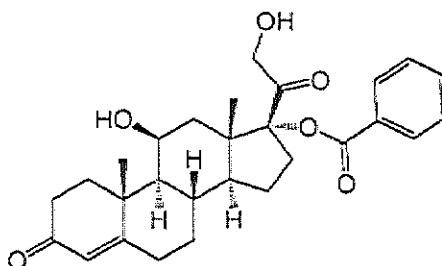
el documento D2, para llegar así al objeto de la reivindicación 2 de la solicitud." es incorrecto ya que no se acomete ningún estudio real sobre el efecto de alterar el sustituyente sobre el OH del C17 en D2.

Como apoyo a lo anterior, hacemos notar que solo tres compuestos específicos se mencionaron en los dos ejemplos dados en D2 que fueron acetato de prednisolona, dexametasona e hidrocortisona, cuyas estructuras incluimos en un documento que se anexa al presente escrito.

Aquí, hacemos notar, primero, que los ejemplos parecen haber sido hechos para estudiar la solubilidad de los esteroides ensayados cuando se combinan con ciclodextrina (ver la declaración de que "los anteriores resultados demuestran que solo la betaciclodextrina formará complejos solubles en agua o complejos de inclusión con los compuestos esteroides" columna 5, renglones 51-54).

Adicionalmente, y casi que mas importante, a todos los compuestos específicos ensayados en D2 les falta algún sustituyente en el OH de C17 (ver los círculos rojos en los documentos anexos). Por lo tanto, no existe comparación con lo que ocurre cuando se hace una sustitución en el OH de C17 en D2, y por lo tanto D2 no apoya las aseveraciones del examinador de que de alguna manera la persona medianamente versada habría modificado los compuestos en D2 (o aún en D1) de manera específica al alterar las sustituciones en C17 (tal como específicamente se menciona el OH de C17) para llegar a los compuestos de la presente invención (o composiciones con estos compuestos).

Finalmente, tal como lo hicimos notar anteriormente, se han visto resultados inesperados, específicamente con el compuesto benzoato de (8R,9R,10S,11R,13R,14R,17S)-17-glicololil-11-hidroxi-10,13-dimetil-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahidro-1H-ciclopenta[a]fenantren-17-ilo (compuesto 6 en la tabla 1 de la descripción):



(este compuesto se nombra específicamente en la reivindicación 2 de las reivindicaciones en estudio).

Para este fin se anexa declaración utilizada en el correspondiente caso en los Estados Unidos y hacemos notar que a esta solicitud le fue otorgada solicitud de patente.

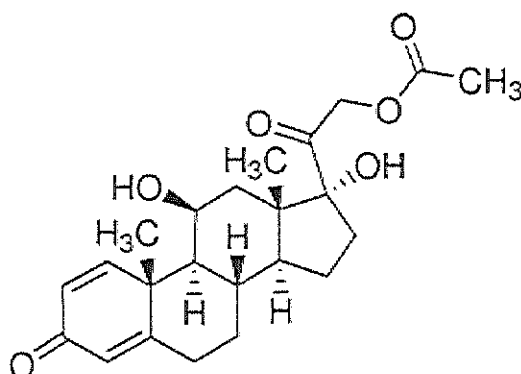
Parte de la declaración (principalmente el "Experimento 1") trata con dos referencias citadas en el caso de los Estados Unidos (aunque no en Colombia). Sin embargo, a pesar del hecho de que no existe una comparación directa con D1, se considera que de todas formas éste explica los resultados inesperados obtenidos con el compuesto 6, que de ninguna manera se podría haber predicho por D1. Con el fin de tener las referencias completas se anexan las dos referencias (Penfold y Sota) que se citaron y a las que se hace referencia en la declaración y respuesta. También se anexan las referencias de Cantrill y James que se utilizaron como evidencia de soporte.

Como se puede ver en la sección de introducción (ver, especialmente punto 4) de la declaración y en la sección anteriormente mencionada de la respuesta, la administración de corticosteroides para tratamientos oftálmicos puede, a menudo, dar como resultado presión intraocular creciente (IOP) y tal incremento es un riesgo asociado con estos tipos de compuestos. Como se puede ver en el "Experimento 2" y el "Experimento 3" y la sección de conclusión de la declaración:

"El compuesto 6 mostró adicionalmente permeabilidad inesperadamente baja en el humor acuoso, y la cantidad que se difundió hacia el humor acuoso mostró una descomposición inferior en metabolito hidrocortisona, que tiene un efecto mucho menor sobre el IOP que la prednisolona (el metabolito de Pred Forte®). Se esperaría que por lo tanto el compuesto 6 demostrara menores efectos adversos, incluyendo los efectos sobre IOP y formación de catarata."

(Subrayado fuera de texto)

Aunque es cierto que la comparación fue con el acetato de prednisolona (que parece ser el nombre del acetato de prednisolona" mencionado en D2, con base en la estructura):



y no con el compuesto específico de D1, los resultados demuestran la patentabilidad de los compuestos de la invención (específicamente del compuesto 6) por al menos un par de razones.

Primero, como se mencionó anteriormente, D1 no indica de manera clara los compuestos de la presente invención (tal como ocurrió en la otra solicitud colombiana). Segundo, las referencias de Cantrill y James citadas en la declaración demuestran que hay problemas (incluyendo los riesgos de IOP y catarata) con varios corticosteroides que tienen diferentes estructuras, aunque los compuestos de la invención (especialmente el compuesto 6) no se espera que tenga estos problemas con base en la evidencia de la declaración). Finalmente, los datos muestran una comparación con los compuestos reales comercializados, Pred Forte® (acetato de prednisolona 21, suspensión oftálmica al 1%), en oposición a los compuestos especulativos en las fórmulas [A], [B], y [C] de D1, o aquellos de la reivindicación 2 de D2. Además, con respecto a D2, tal como se anotó anteriormente, esta evidencia no parece mostrar propiedades inesperadas con referencia al acetato de prednisolona, que es uno de los compuestos en los que se basa su Despacho (ver las observaciones de su Despacho con relación a la reivindicación 6 en D2).

Por lo tanto, en vista de la falta de una guía realista para que una persona medianamente versada pueda llegar al los compuestos de la invención (incluyendo el compuesto 6) tal como se detalló, se considera que los compuestos de la presente invención son inventivos sobre D1 y D2.

De acuerdo con lo anterior le solicitamos, muy comedidamente, que sea otorgada la patente para la presente invención.

3. Solicitudes concedidas en otros países para esta misma invención.

A manera informativa, pongo en conocimiento del Examinador que la patente en Estados Unidos equivalentes a la presente solicitud colombiana ha sido otorgadas. Aún cuando entiendo que estas decisiones de ninguna manera obligan al Despacho para decidir de igual forma, considero que por tratarse de una pregunta fáctica la determinación de la existencia de novedad y nivel inventivo, las decisiones de otras oficinas de patentes constituyen un antecedente persuasivo en la materia.

En virtud de lo anterior, solicito que se acepten las razones expuestas en el presente documento y en consecuencia, se otorgue el privilegio de patente de invención para el invento que se tramita en este expediente.

Atentamente,



ÁLVARO CORREA ORDÓÑEZ
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T.P.20.281

Anexos: Capítulo reivindicatorio modificado conformado por
 Fórmulas de los ejemplos del documento D2
 Referencias de Penfold y Sota
 Referencias de Cantrill y James