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(71) Applicant: **CRESSET BIOMOLECULAR DISCOVERY LTD** [GB/GB]; BioPark Hertfordshire, Broadwater Road, Welwyn Garden City Hertfordshire AL7 3AX (GB).

(72) Inventors: **ROTHAUL, Alan Leslie**; 4 Hill Rise, Woodstock Oxfordshire OX20 1AA (GB). **VINTER, Jeremy Gilbert**; Baylay's Glen, Fore Street, Weston, Hitchin Hertfordshire SG4 7AS (GB). **SCOFFIN, Robert Arthur**; 10 St Paul's Road, Cambridge Cambridgeshire CB1 2EZ (GB).

(74) Agents: **AVIDITY IP** et al.; Kestrel House, Falconry Court, Baker's Lane, Epping, Essex CM16 5DQ (GB).

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(54) Title: THE LOCAL TREATMENT OF INFLAMMATORY OPHTHALMIC DISEASES

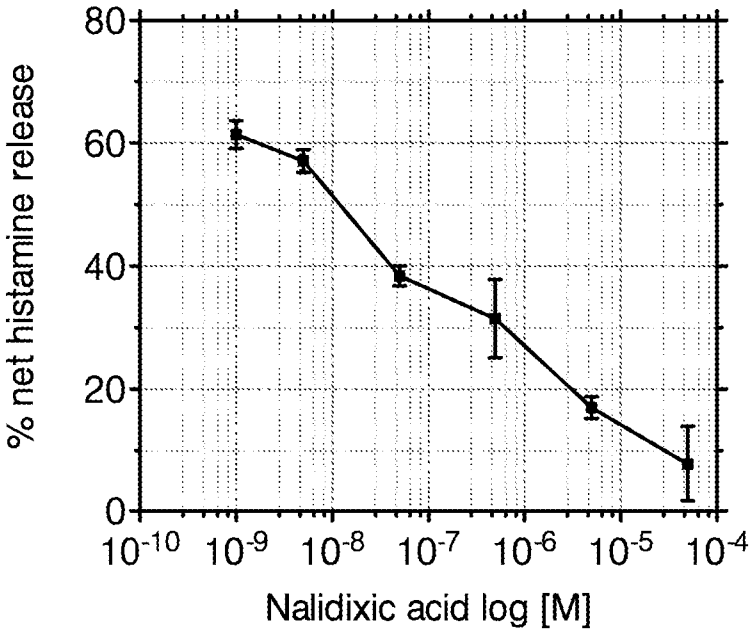

Figure 1

(57) Abstract: The present invention provides Nalidixic acidand analogues of Nalidixic acid for use in the treatment of inflammatory ophthalmic disordersby local administration.

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THE LOCAL TREATMENT OF INFLAMMATORY OPHTHALMIC DISEASES

Field of the invention

This invention relates to the local use of Nalidixic acid and Nalidixic acid analogues for the treatment of inflammatory ophthalmic diseases characterized by ocular inflammation, dry eye disorders, pathologic ocular angiogenesis and/or retinal or sub-retinal edema.

Background of the invention

Dry eye, or keratoconjunctivitis, is a common ophthalmological disease affecting millions of people each year, it is reported to have an overall prevalence of between 5% and 6% of the population, with frequency of occurrence increasing with age. The condition is particularly prevalent in post-menopausal women due to hormonal changes caused by the cessation of fertility. Dry eye is primarily caused by the break-down of the pre-ocular tear film which results in dehydration of the exposed outer surface. There is a strong rationale that ocular inflammation as a result of pro-inflammatory cytokines and growth factors plays a major role in the underlying causes of dry eye. As such, locally administered anti-cytokine or general anti-inflammatory agents are often used in the treatment of dry eye. Other forms of conjunctivitis are also poorly treated; allergic conjunctivitis only responds poorly to standard topical anti-allergy treatment while viral and bacterial conjunctivitis often require long term treatment with anti-infectives or antibiotics.

Another disease of the interior of the eye is uveitis, or inflammation of the uveal tract. The uveal tract (uvea) is composed of the iris, ciliary body and choroid. Uveitis may be caused by trauma, infection or surgery and can affect any age group. The disease is classified anatomically as anterior, intermediate, posterior or diffuse. Anterior uveitis affects the anterior portion of the eye including the iris. Intermediate uveitis, also called peripheral uveitis, is centred in the area immediately behind the iris and lens in the region of the ciliary body. Posterior uveitis may also constitute a form of retinitis, or it may affect the choroids and the optic nerve. Diffuse uveitis involves all parts of the eye. The most common treatment of uveitis is with locally administered glucocorticosteroids often in combination with other anti-inflammatory drugs. Although these drugs are effective in the treatment of many forms of ocular inflammation they have several side-effects including endophthalmitis, cataracts and elevated intra-ocular pressure (IOP). There is a need for potent anti-inflammatory agents with an improved side effect profile, the so called non-steroid steroid, for the treatment of ophthalmic inflammation and edema.

Diseases and degenerative conditions of the optic nerve and retina are the leading causes of blindness in the world. A significant degenerative condition of the retina is age-related macular degeneration (ARMD). ARMD is the most common cause of blindness in people over 50 in the USA and its prevalence increases with age. ARMD is classified as either wet (neovascular) or dry (non-neovascular) where the dry form of the disease is the most common. Macular degeneration occurs when the central retina has become distorted and thinned usually associated with age but also characterised by intra-ocular inflammation and angiogenesis (wet ARMD only) and / or intra-ocular infection.

Retinopathy associated with diabetes is a leading cause of blindness in type I diabetes and is also common in type II diabetes. The degree of retinopathy depends on the duration of diabetes and generally begins to occur ten or more years after onset of diabetes. Diabetic retinopathy may be classified as non-proliferative, where the retinopathy is characterised by increased capillary permeability, edema and exudates, or proliferative, where the retinopathy is characterised by neovascularisation extending from the retina to the vitreous humor, scarring, deposit of fibrous tissue and the potential for retinal detachment. Diabetic retinopathy is believed to be caused by the development of glycosylated proteins due to high blood glucose. The subsequent generation of free-radicals, resulting in oxidative tissue damage, local inflammation and production of growth factors (such as VEGF and FGF) and inflammatory mediators, leads to inappropriate neovascularisation in common with the wet form of ARMD. Several other less common retinopathies include choroidal neovascular membrane (CNVM), cystoid macular edema (CME), epiretinal membrane (ERM) and macular hole. Today, no drugs are approved for the treatment of diabetic retinopathy or macular edema. The current standard treatment is laser photocoagulation which by destroying local tissue, decreases the production of cytokines and growth factors, but is unfortunately cytodestructive and causes permanent impairment of vision. These neovascular diseases have the potential to be treated with angiostatic agents alone or in combination with anti-inflammatory drugs.

Refractive eye surgery is any eye surgery used to improve the refractive state of the eye and thus decrease or eliminate dependency on glasses and contact lenses. This can be taken to include surgical remodelling of the cornea or cataract surgery. Successful refractive eye surgery can reduce or eliminate common vision disorders such as myopia, hyperopia and astigmatism. Common procedures for refractive eye surgery include: Flap techniques in laser ablation, performed under a partial thickness corneal flap (e.g. Laser Assisted In-Situ Keratomileusis-LASIK); Surface

procedures, in which a laser is used to ablate the most anterior portion of the corneal stroma, which do not require a partial thickness cut of the corneal stroma, e.g. Photoreactive Keratectomy (PRK) and Laser Assisted Sub-Epithelium Keratomileusis (LASEK); Corneal incision procedures e.g. radial keratotomy, arcuate keratotomy and limbal relaxing incisions. Following refractive eye surgery localised inflammation at the site of surgery is common and topical and or systemic anti-inflammatory drugs, for example systemic ibuprofen and or topical glucocorticosteroids are commonly administered. In addition, dry-eye or keratoconjunctivitis may occur after refractive eye surgery. This may be temporary or permanent in nature.

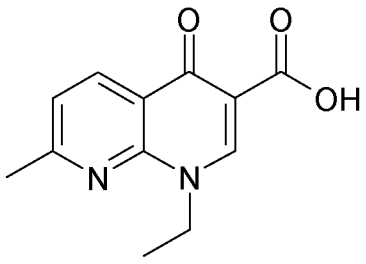
Annexin–A1 (Lipocortin-1) is a 36kDa protein which was first described in the late 1970's. It is found in many cell types and is known to play a key role in modulating the anti-inflammatory activity of exogenous and endogenous glucocorticosteroids. Annexin-A1 enhances the anti-inflammatory activity of steroids and in Annexin-A1 knock-out mice steroids are ineffective in animal inflammation models while Annexin-A1 itself is effective in animal models of inflammation (Perretti M. and Dalli J. British Journal of Pharmacology (2009) 158, p936-946).

Inactive Annexin-A1 is released intracellularly by the nuclear action of glucocorticoid receptor stimulation. It is translocated to the cell membrane where it is phosphorylated by protein kinase C and released as an anti-inflammatory protein. The phosphatase PP2A is responsible for deactivating the anti-inflammatory activity of Annexin-A1 by direct de-phosphorylation and deactivation of protein kinase C (Yazid S. et al. Pharmacological Reports (2010) 62, p511-517). It is hypothesised that an inhibitor of PP2A would provide a potent anti-inflammatory agent.

Summary of the invention

The present invention relates to the use of Nalidixic acid and analogues of Nalidixic acid, by local administration, in the treatment of inflammatory ophthalmic conditions.

Surprisingly it has been found that Nalidixic acid (I) and some analogues of Nalidixic acid are effective at treating inflammatory conditions of the eye.



Nalidixic acid (**I**)

It has been found that Nalidixic acid and some analogues are potent inhibitors of the phosphatase PP2A thereby enhancing the anti-inflammatory activity of endogenous Annexin-A1. Nalidixic acid is an antibiotic most often used to treat urinary tract infections because it is rapidly excreted by the renal route and therefore has poor systemic pharmacokinetics. Typically this agent requires four times daily treatment by the oral route of administration to achieve anti-bacterial activity. It has now been found that the use of Nalidixic acid or a Nalidixic acid analogue or a pharmaceutically acceptable salt thereof is effective in the treatment of inflammatory ophthalmic diseases such as, but not limited to those described above.

Thus, according to the present invention, an inflammatory ophthalmic disease as described above is treated by local administration of a compound of formula (**I**), an analogue of formula (II) or a pharmaceutically acceptable salt thereof.

Description of the Figures

Figure 1 represents the % net histamine release from human mast cells by Nalidixic acid.

Figure 2 represents the inhibition of Prostaglandin D2 release from human mast cells by Nalidixic acid.

Figure 3 represents the release of Annexin-A1 from human mast cells in response to increasing concentrations of Nalidixic acid.

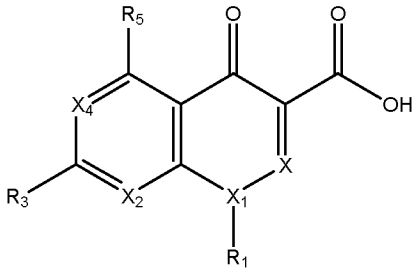
Figure 4 represents the reduction in clinical scores by Nalidixic Acid in a murine model of allergic conjunctivitis.

Figure 5 represents the reduction in neutrophil invasion into retinal tissue by Nalidixic Acid in a murine model of uveitis.

Detailed description of the invention

Local administration of Nalidixic acid (**1**), or a pharmaceutically acceptable salt of Nalidixic acid to the eye is useful for the treatment of a range of ophthalmic conditions such as ocular inflammation, dry eye disorders, pathological ocular angiogenesis and retinal or sub-retinal edema.

According to another aspect of the present invention local administration of a compound of general formula (II)



(II)

wherein,

X and X_1 independently represent CH or N;

X_2 represents $C(R_2)$ or N;

X_4 represents $C(R_4)$ or N;

R_1 is H, CF_3, $CONH_2$, CN, halogen, NH_2, NH-alkyl, alkyl, cycloalkyl or phenyl and is optionally substituted with one or more R_6; wherein R_1 may form part of a cycle with R_2;

R_2 is H, CF_3, $CONH_2$, CN, halogen, NH_2, alkyl, O-alkyl or S-alkyl; wherein R_2 may form part of a cycle with R_1, wherein the cycle is a 5-membered or 6-membered saturated or unsaturated cycle containing one or more atoms selected from C, N, S and O;

R_3 is H, CF_3, $CONH_2$, CN, halogen, NH_2, alkyl, O-alkyl, pyridyl, cycloalkyl or heterocycloalkyl and is optionally substituted with one or more R_6; wherein R_3 may form part of a cycle with R_4;

R_4 is H, F or O-alkyl; wherein R_4 may form part of a cycle with R_3, wherein the cycle is a 5-membered or 6-membered saturated or unsaturated cycle containing one or more atoms selected from C, N, S and O;

R_5 is H, F, Cl, alkyl, O-alkyl or NH_2;

R_6 is F, alkyl, NH_2, NH-alkyl, CH_2NH_2 or OH;

or a pharmaceutically acceptable salt thereof, is useful for the treatment or prevention of an inflammatory ophthalmic condition.

Optionally, R_1, R_2 and R_3 are independently CF_3, $CONH_2$, CN, halogen or NH_2.

Alkyl refers to a linear or branched alkyl group having from 1 to 10 carbon atoms, preferably from 1 to 6 carbon atoms, more preferably, from 1 to 3 carbon atoms. Preferred examples of alkyl are methyl, ethyl, n-propyl and isopropyl.

Cycloalkyl refers to a saturated or partially saturated cyclic group of from 3 to 14 carbon atoms and no ring heteroatoms and having a single ring or multiple rings

including fused, bridged, and spiro ring systems, wherein the cycloalkyl is optionally substituted by one or more substituents selected from CF_3, $CONH_2$, CN, halogen, NH_2, NH-alkyl, alkyl, cycloalkyl or phenyl. A preferred example of cycloalkyl is cyclopropyl.

Heterocycloalkyl refers to a saturated or partially saturated cyclic group having from 1 to 14 carbon atoms and from 1 to 6 heteroatoms selected from nitrogen, sulfur, or oxygen and includes single ring and multiple ring systems including fused, bridged, and spiro ring systems, wherein the cycloalkyl is optionally substituted by one or more substituents selected from CF_3, $CONH_2$, CN, halogen, NH_2, NH-alkyl, alkyl, cycloalkyl or phenyl. Preferred examples of heterocycloalkyl are piperidine, piperazine and pyrrolidine.

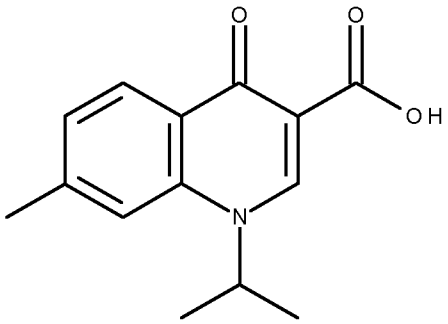
Embodiments of the invention that may be mentioned include those where cycloalkyl and/or heterocycloalkyl are unsubstituted.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

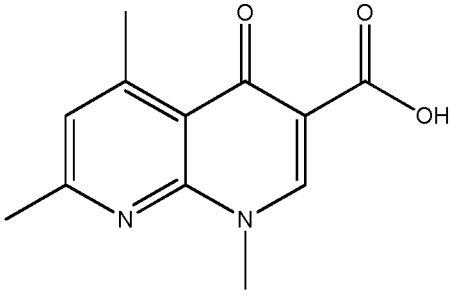
Compounds of formula (II) include some known quinolone antibiotics. Quinolone antibiotics are known to be broad spectrum antibiotics. They are chemotherapeutic bactericidal drugs and they work by preventing bacterial DNA from unwinding and duplicating. Known quinolone antibiotics include:

First-generation:	cinoxacin, flumequine, oxolinic acid, piromidic acid, pipemidic acid, rosoxacin.
Second-generation:	ciprofloxacin, enoxacin, fleroxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pefloxacin, rufloxacin.
Third-generation:	balofloxacin, grepafloxacin, levofloxacin, pazufloxacin, sparfloxacin, temafloxacin, tosufloxacin.
Fourth-generation:	clinafloxacin, gatifloxacin, gemifloxacin, moxifloxacin, sitafloxacin, trovafloxacin, prulifloxacin.
In development:	garenoxacin, delafloxacin.
Veterinary use:	danofloxacin, difloxacin, enrofloxacin, ibafloxacin, marbofloxacin, orbifloxacin, sarafloxacin.

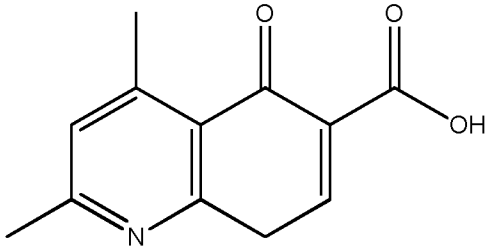
Compounds of formula (II) for use in the invention include (but are not limited to) known quinolone antibiotics as described above and novel compounds such as:



1-isopropyl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.



1,5,7-trimethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid



2,4-dimethyl-5-oxo-5,8-dihydroquinoline-6-carboxylic acid

It is understood that compounds for use in the invention include salts, e.g. sodium, potassium, ammonium, ethylenediamine, arginine, diethylamine, piperazine or N-Methylglucamide salts, but also extends to metabolites and pro-drugs thereof. Most aptly the free acid or salt is employed.

Compounds for use in the invention, or their pharmaceutically acceptable salts, may be chiral, and it will be understood that this invention includes any diastereomers and enantiomers of formula (II). It will also be understood that the invention includes any isotopic derivatives of the compound of formula (I) and/or formula (II).

For the avoidance of doubt, compounds of formula (I) and (II) may contain the stated atoms in any of their natural or non-natural isotopic forms. In this respect, embodiments of the invention that may be mentioned include those in which:

a) the compound of formula (I) and/or formula (II) is not isotopically enriched or labelled with respect to any atoms of the compound; and

b) the compound of formula (I) and/or formula (II) is isotopically enriched or labelled with respect to one or more atoms of the compound.

References herein to an "isotopic derivative" relate to the second of these two embodiments. In particular embodiments of the invention, the compound of formula (I) and/or formula (II) is isotopically enriched or labelled (with respect to one or more atoms of the compound) with one or more stable isotopes. Thus, the compounds of the invention that may be mentioned include, for example, compounds of formula (I) and/or formula (II) that are isotopically enriched or labelled with one or more atoms such as deuterium or the like.

Preferred examples of compounds of formula (II) include cinoxacin, flumequine, oxolinic acid, piromidic acid, pipemidic acid and rosoxacin.

Nalidixic acid or the compounds of formula (II), or their pharmaceutically acceptable salts, according to the invention are used to treat uveitis; dry eye; conjunctivitis such as allergic conjunctivitis, viral conjunctivitis, bacterial conjunctivitis and keratoconjunctivitis; ARMD; CNVM; CME; ERM; macular hole; retinopathies, including diabetic retinopathy; and as an adjunctive treatment to ophthalmic surgery.

The anti-inflammatory activity of the compounds of the invention can be demonstrated in appropriate in vitro or in vivo assays as described in the examples. Histamine (Example 1) and PGD2 (Example 2) released from IgE challenged human mast cells are both inhibited by Nalidixic acid treatment in a dose-related manner. In addition the release of Annexin-A1 (Example 3) is increased by treatment with Nalidixic acid in a dose-related manner.

The anti-inflammatory activity of the compounds of the present invention is not linked to their anti-bacterial activity and their anti-inflammatory effect can be observed at non anti-bacterial concentrations of Nalidixic acid or the analogues. Thus, according to another aspect of the invention, Nalidixic acid (I) or analogues of formula (II) or a pharmaceutically acceptable salt can be used in the treatment or prevention of inflammatory ophthalmic conditions when the amount, dose or concentration of Nalidixic Acid or analogue or salt thereof has no substantial antibiotic activity. In circumstances in which bacterial infection does not represent a component of the disease, the use of Nalidixic acid or analogue or salt thereof at

sub-antibiotic doses would avoid unnecessary exposure to antibacterial activity that may lead to the generation of bacterial resistance.

According to an additional aspect of the invention, Nalidixic acid (I) or a compound of formula (II) or a pharmaceutically acceptable salt of Nalidixic acid can be used to potentiate the anti-inflammatory action of glucocorticosteroids. This activity has been demonstrated by the use of the appropriate in vitro and in vivo assays. Thus the use of a compound of the invention with steroids allows the use of traditionally sub-therapeutic, and therefore non-harmful, doses of steroids with greatly potentiated anti-inflammatory activity. Nalidixic acid or the compounds of formula (II) or a pharmaceutically acceptable salt thereof may be used according to the invention when the patient is also administered one or more glucocorticosteroids or wherein the compound of the invention is provided in combination with one or more glucocorticosteroids. Glucocorticosteroids which can be used in the invention include, but are not limited to, beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, fluticasone, fluocinolone, fluromethalone, difluprednate, loteprednol, triamcinolone, meprednisone, mometasone, paramethasone and prednisolone. Particularly preferred is the use in combination with one or more of prednisolone, dexamethasone, fluocinolone, fluromethalone, difluprednate, loteprednol or triamcinolone.

Nalidixic acid, an analogue of formula (II) or a pharmaceutically acceptable salt may be used according to the invention when the patient is also administered another therapeutic agent or in combination with another therapeutic agent, wherein the therapeutic agent is selected from angiostatic peptides, such as angiostatin; angiostatic steroids, such as anecortave acetate; modulators of VEGF or FGF, such as zactima; non-steroidal anti-inflammatory drugs (NSAIDs) formulated for ocular use such as flurbiprofen, diclofenac and ketorolac; leukotriene modulators such as zilueton; anti-histamines such as cetirizine, loratidine, ketotifen and the like; antibiotics such as antibacterials, antivirals and antifungals, for example bactitracin, chloramphenicol, ciprofloxacin, fusidic acid, gentamycin, levofloxacin, neomycin alone and in combination with polymixin and gramicidin, propamide, dibromopropamide; and general cytokine / growth factor modulating agents such as cyclosporin A, phosphodiesterase inhibitors and the like. The compound of formula (1) or a salt thereof may also be administered before, during or after laser photocoagulation therapy. Laser photocoagulation therapy is used in the treatment of, for example, diabetic retinopathy and age related macular degeneration.

Nalidixic acid, an analogue of formula (II) or a salt thereof can be used to treat inflammatory conditions of the eye when administered in an amount that has

antibiotic activity or in an amount than has no antibiotic activity or substantially no antibiotic activity. No substantial antibiotic activity means that the concentration of the active agent would not have clinically relevant activity on the growth of pathogenic bacteria involved in infectious ocular conditions. For susceptible bacterial strains this would be less than approximately 1μg/ml.

The compounds described herein can be used as an anti-inflammatory agent to treat ocular inflammation. In some instances, the ocular inflammation or the ophthalmic diseases described above may be accompanied by a microbial infection of the eye. Such infection may be fungal, viral or bacterial. Nalidixic acid, an analogue of formula (II) or a salt thereof can be used to treat ocular inflammation in the presence or absence of a microbial infection. When an ocular microbial infection is present, the compounds of the invention may be administered in addition to or in combination with antibiotics. Preferred antibiotics include, but are not limited to, bactitracin, chloramphenicol, ciprofloxacin, fusidic acid, gentamycin, levofloxacin or neomycin alone or in combination with polymixin and gramicidin, propamide, dibromopropamide.

The route of administration of Nalidixic acid, an analogue of formula (II) or a salt thereof to the eye is local. This may be topical or by intraocular injection. A preferred route of delivery is by topical administration to the eye, such as administration to the surface of the eye. Another preferred route would be by injection into the structures of the eye.

Ophthalmic pharmaceutical compositions of Nalidixic acid, an analogue of formula (II) or a pharmaceutically acceptable salt thereof represent another aspect of the invention. An injectable composition suitable for intraocular injection typically comprises a solution of the drug or a fine particle suspension, which may enable sustained delivery to the eye. Formulations are usually aqueous based and may commonly include solubilisation enhancers such as, but not limited to, polyvinyl alcohol, Tween 80 solutol, cremophore and cyclodextrin. These solubilisation enhancers may be used in combination. The formulation would typically be in the pH range of 3-8 which would be regarded as acceptable for intravitreal formulations. To achieve an acceptable pH buffering systems are sometimes used. These include but are not limited to citrate and phosphate based buffering systems. The tonicity of the intravitreal formulation may be adjusted to remain within a desirable range which typically would be 250-360 mOsm/kg. Adjustment of tonicity may be achieved for example by addition of sodium chloride. Typically intravitreal formulations are produced by sterile manufacture for single use. Preserved formulations can be used, for example formulations containing a preservative such as benzoyl alcohol. The

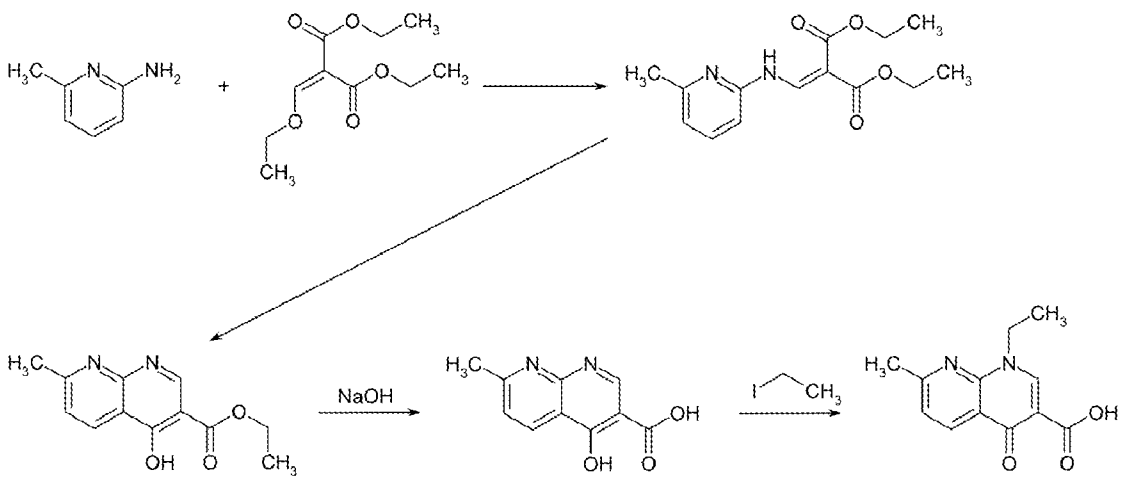
overall volume of the injectate would normally be limited such that it is equal to or less than 0.1ml per injection to avoid damage due to significantly increasing the volume of the vitreous humour of the eye. The dose of the active agent in the compositions of the invention will depend on the nature and degree of the condition, the age and condition of the patient and other factors known to those skilled in the art. A typical dose is 0.001-10 mg given either as a single injection with no further dosing or in multiple injections. Typically, multiple injections are given at a maximum frequency of once per week.

A topical formulation can either be an aqueous solution (eye drop), a non-aqueous solution (eye ointment) or a fine particulate suspension. Such formulations are typically made up in a manner well known to those skilled in the art. Preferred ophthalmic formulations for the topical delivery of the compounds of the invention are preservative free, however a preservative may be used. Typical preservatives include quaternary ammonium compounds such as benzylalkonium chloride or benzethonium chloride and the like; organomercurials such as phenylmercuric acetate or phenyl mercuric nitrate and the like; parahydroxybenzoates such as methylparaben, ethylparaben and the like; and chlorobutanol. Preservative agents can also act as penetration enhancers which might have the beneficial effect of increasing corneal epithelial permeability and further increasing ocular bioavailability. Tonicity and pH are important features of a topical ophthalmic formulation. In actual practice it has been found that the eye can tolerate a range of osmotic pressure values equivalent to 0.6 – 2% sodium chloride, without marked discomfort. In topical ophthalmic formulations EDTA or salts of EDTA are often used to modulate tonicity and also provide a preservative action. A preferred formulation has a pH close to the physiological pH of the tear duct (pH 6.5 - 7.5), minimising tearing and patient discomfort. However low pH is better tolerated than high pH so an acceptable pH range would be pH 4 - 7.5. Other agents which may be added to a topical ophthalmic formulation include viscosity modulators such as polyvinylalcohol (PVA), polyvinylpyrrolidone, methylcellulose, hydroxymethylcellulose and hydroxypropylmethylcellulose (HPMA) which increase the viscosity of the formulation. This has the advantage of minimising the drainage rate and increasing the corneal contact time.

The dose of the active agent in the compositions of the invention will depend on the nature and degree of the condition, the age and condition of the patient and other factors known to those skilled in the art. A typical dose is 0.001-100 mg given one to three times per day, for example 0.1 to 10 mg given one to three times a day.

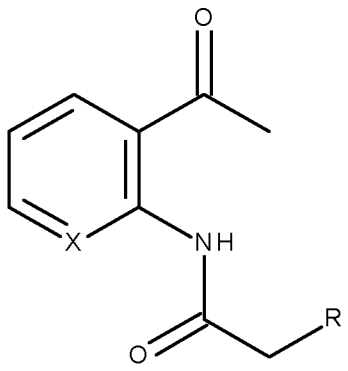
The compositions may further comprise one or more steroids and/or another therapeutic agent. Typically, a composition comprising Nalidixic acid or a compound of formula (II) or a pharmaceutically acceptable salt thereof and one or more steroids will comprise the steroid(s) in a range of 0.001% to 5% wt/wt of the formulation. Preferably the steroid is present in a normally sub-therapeutic dose of less than 1% wt/wt of the formulation, due to the synergistic effect of the compounds of the invention as described above, although the specific dose will depend on the particular steroid used. For example, when Nalidixic acid is used, it is present within the compositions in the range of 0.001% to 5% wt/wt of the formulation and the steroid is present in a therapeutic dose of less than 1% wt/wt of the formulation.

Nalidixic acid is generally prepared through a multi-step synthetic route, which lends itself to several modifications which allow for the synthesis of Nalidixic acid analogues, such as those of formula (II):



Nalidixic acid analogues of formula (II) for use in the invention may also be prepared by a multi-step synthetic procedure, as shown in the following Scheme.

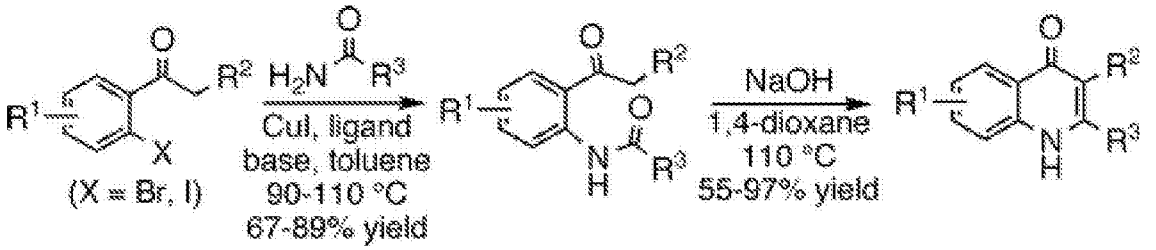
The synthesis proceeds by a cyclisation starting from a di-substituted benzene or pyridine compound of general formula (III):

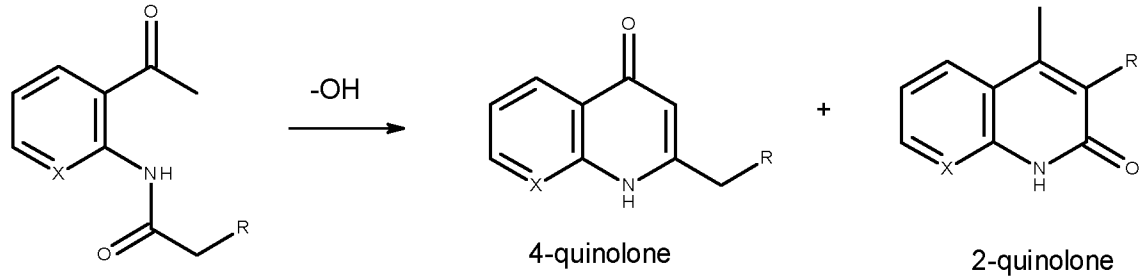


(III)

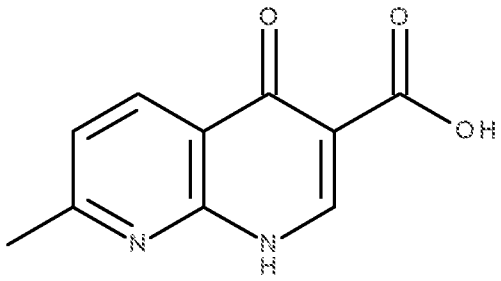
wherein R is any suitable group known to the skilled person, and X is CH or N.

The starting material is then cyclized through a Camps cyclisation to give compounds of general formula (IIIa) and (IIIb):





The 4-quinolone derivative of formula (IIIa) can then be isolated and further reacted to form 4-quinolone derivatives such as:



7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

The anti-inflammatory activity of the compounds of formula (II), or their pharmaceutically acceptable salts, can be determined by assessing their capability of inhibiting the release of histamine or PDG_2 from Human Mast Cells or promoting release of Annexin-A1

The following examples illustrate the invention

Examples

Example 1: The inhibition of histamine release from Human Mast Cells by Nalidixic acid

Protocol: Human derived cord mast cells were cultured using the following method. Commercially available $CD34^+$ stem cells were cultured for 2 weeks in StemSpan (StemCell Technologies, Grenoble, France) serum-free medium supplemented with 100ng/ml human SCF, 50ng/ml IL-6 and 1ng/ml IL-3, and 100µg/ml penicillin/streptomycin (Peprotech, London, UK). After eight weeks, cells were cultured in StemSpan with 10% FCS. The cells were passaged into new medium every week. Cells were used for experiments between 11 and 18 weeks following confirmation by microscopic examination, c-kit and FcRε1 staining (by FACS), of mast cell morphology. For assessment of drug effects, Nalidixic acid was incubated for 5 min with aliquots of $2x10^5$ CDMCs (cord derived mast cells) cultured in 10% FCS medium.

Measurement of histamine release

A commercially-available enzyme immunoassay was used to detect and quantify histamine released in the supernatant (SPI bio, Strasbourg, France). The assay was conducted following the manufacturer's standard protocols. A standard curve ranging from 0.39-50 nM histamine was prepared using the reagent provided and the optical density was then read within 60 min in a microplate reader (at 405 nm). In some cases, the total cell content of histamine was established by freeze thawing of cells prior to challenge.

The results from these experiments are shown in Figure 1. The data clearly demonstrates a dose related inhibition of the inflammatory mediator histamine by Nalidixic Acid.

Example 2: Inhibition of Prostaglandin D_2 release form human mast cells by Nalidixic acid

Human cord derived mast cells were cultured using the methodology described in Example 1.

Measurement of PGD_2 release

A commercially-available enzyme immunoassay (Cayman Chemical, Michigan, USA) was used to detect and quantify PGD_2 released in the supernatant. The assay was conducted following the manufacturer's standard protocols. A standard curve ranging from 78-10,000 pg/ml PGD_2 was prepared using the reagent provided and the optical density was then read within 60 min in a microplate reader (at 405 nm).

The results from these experiments are shown in Figure 2. The data illustrates a dose related inhibition by Nalidixic acid of the inflammatory prostanoid PGD_2.

Example 3: Nalidixic acid promotes the release of Annexin–A1 (Anx-A1) from human mast cells.

Human cord derived mast cells were cultured using the methodology described in Example 1.

Anx-A1 protein levels in conditioned medium were determined by ELISA. Briefly, 96-well flat-bottomed ELISA plates (Greiner, Gloucestershire, UK) were coated with 1µg anti-Anx-A1 mAb 1B in bicarbonate buffer (pH 9.6) and incubated overnight at 4°C. After washing in the bicarbonate buffer, potentially uncoated sites were blocked with 100µL of PBS containing 1% BSA for 1h at room temperature. Sample aliquots (100µL) or Anx-A1 standard solutions (prepared in 0.1% Tween-20 in PBS; concentration ranging between 10 and 0.001 µg/mL) were added for 1h at 37°C. After extensive washing in PBS/Tween-20, 100µL of a polyclonal rabbit anti-human Anx-A1 serum (Zymed, Invitrogen, Paisley, UK; diluted 1:1000 in PBS/Tween-20) was added (1h at 37°C) prior to incubation with donkey anti-rabbit 1gG conjugated to alkaline phosphatase (1:1000; Sigma). The colour was developed by addition of 100µL p-nitrophenyl phosphate (1mg/mL in bicarbonate buffer, pH 9.6).

Absorbance was read at 405nm (with a 620-nm reference filter) in a microplate reader (Titertek™, Vienna, Austria). Anx-A1 levels in the study samples were read against the standard curve and expressed as ng/ml.

The results, as shown in Figure 3, highlight the increase of the anti-inflammatory Annexin-A1 released from human mast cells in response to increasing concentrations of Nalidixic acid.

Example 4: Murine model of allergic conjunctivitis.

Mice (Balb/C strain) were sensitised to ragweed pollen by injection of the extract mixed with alum into the hind paw. A control group was immunised with alum alone. Five animals were used in each group.

Eleven days after the initial immunisation with ragweed pollen extract the mice were challenged daily with Ragweed pollen by application to the eye (150mg/ml antigen) and dosed twice daily (prior and after challenge with ragweed extract) with either Phosphate buffered saline (PBS, control) or 40µl of a 2% solution of Nalidixic acid. All applications were to the left eye with the right eye acting as a control.

Conjunctivitis was assessed on the 10th day 1 hour after the final application of the ragweed antigen. Assessment of the development of conjunctivitis was performed microscopically using the clinical scale shown in the table (Table 1) below. This assessment was performed by an operator unaware of the dosing protocol for the animals.

Table 1 Clinical scoring system for murine conjunctivitis model

Tissue	Symptoms	Score			
		0	1	2	3
Conjunctiva	Redness	Absent (same as control)	Some or faint	Moderate (easily detectable)	Severe
	Edema	Absent (same as control)	Minimal but different to right eye	Obvious swelling	Severe
Eyelid	Redness	Absent (same as control)	Some or faint	Moderate (easily detectable)	Severe
	Edema	Absent (same as control)	Minimal but different to right eye	Obvious swelling	Unable to open eye
Surface	Mucus	Absent (same as control)	Filaments	Patches	Severe
	Tears	Absent (same as control)	Slight film	Glistening	Tears shed

Clinical scores of each group were compared statistically using the non-parametric Kruskal –Wallis test with Dunns multiple comparison test correction applied (Figure 4). Assessment of clinical scores indicated that treatment with Nalidixic acid resulted in significant attenuation of the development of conjunctivitis, with only the immunised untreated group of animals displaying clinical signs of disease different from the unimmunised control group.

In addition, histological analysis of sections of the conjunctiva was used to assess the number of migrating eosinophils into the tissue, a key measure of the inflammatory process. No migrating cells were observed in tissue from non-immunised PBS treated (control) animals, whereas in tissue from immunised animals treated with PBS, migrating eosinophils were seen in sections from all animals (mean 3.75±0.48 S.E.M.). Treatment with Nalidixic acid resulted in the observation of no migrating eosinophils in conjunctival tissue a highly significant reduction compared to control ($p<0.001$). In addition histological examination of the conjunctival tissue to assess architectural changes revealed a normal well-ordered and polarised epithelial surface in the non-immunised challenge group. Whereas, repetitive challenge with ragweed and vehicle (PBS) treatment resulted in clear changes characteristic of conjunctivitis including a largely disordered cyto-architecture with many invading cells comprising but not limited to eosinophils and polymorphonuclear leukocytes.

These observations demonstrate the activity of topically applied Nalidixic acid in a murine model of allergic conjunctivitis.

Example 5: Murine model of endotoxin induced uveitis.

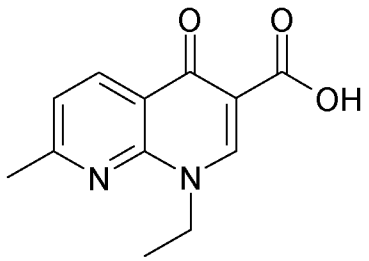
The efficacy of locally applied Nalidixic acid as a potential treatment for uveitis was explored. Experimental uveitis was induced in male C57BL/6 mice (n=5 animals per group) by the intravitreal injection of the endotoxin lipopolysaccharide (LPS 0.5ng/ml) co-injected with either vehicle (phosphate buffered saline) or Nalidixic acid at a final concentration of 0.1µg into alternate eyes. The other eye acting as control. The inflammatory response in this model is characterised by invasion of inflammatory cells and in particular invasion of neutrophils into the retina peaks at approximately 15 hours after endotoxin treatment at which time the animals were culled. Retinas from the animals were dissected and digested into a single cell suspension. Cell numbers from retinal tissue were measured by fluorescence-activated cell sorting (FACS) analysis.

Analysis of cell infiltration following induction of uveitis with endotoxin revealed a clear reduction in invading neutrophils following co-treatment with Nalidixic acid (treated group in Figure 5).

The ability of Nalidixic acid to attenuate neutrophil invasion, a key driver of disease, in this experiment is indicative of the potential for Nalidixic acid to treat human uveitis.

Claims

1. Nalidixic acid of formula (I) or an analogue or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of inflammatory ophthalmic diseases by local administration

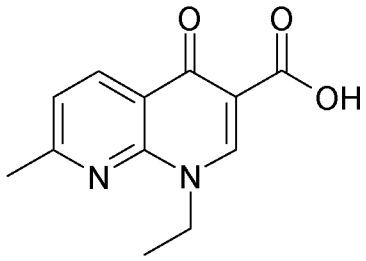


(I).

2. A compound for use according to claim 1 wherein the disease is characterised by ocular inflammation, dry eye disorders, pathological ocular angiogenesis and/or retinal or sub-retinal edema.
3. A compound for use according to claims 1 or 2 wherein the ophthalmic disease is conjunctivitis, such as allergic, viral or bacterial conjunctivitis.
4. A compound for use according to claims 1 or 2 wherein the ophthalmic disease is dry eye.
5. A compound for use according to claims 1 or 2 wherein the ophthalmic disease is inflammation or dry eye as a result of refractive eye surgery.
6. A compound for use according to claims 1 or 2 wherein the ophthalmic disease is uveitis.
7. A compound for use according to claims 1 or 2 wherein the ophthalmic disease is age related macular degeneration (ARMD).
8. A compound for use according to claims 1 or 2 wherein the ophthalmic disease is diabetic retinopathy.
9. A compound for use according to claims 1 or 2 wherein the ophthalmic disease is choroidal neovascular membrane (CNVM), cystoid macular edema (CME), epiretinal membrane (ERM) or macular hole.
10. A compound for use according to any preceding claim wherein the compound is formulated for topical application to the eye.
11. A compound for use according to claims 1 to 9 wherein the compound is formulated for intraocular injection.
12. A compound for use according to any preceding claim wherein the treatment comprises administration of said compound to a patient who is also administered one or more glucocorticosteroids such as beclomethasone, betamethasone,

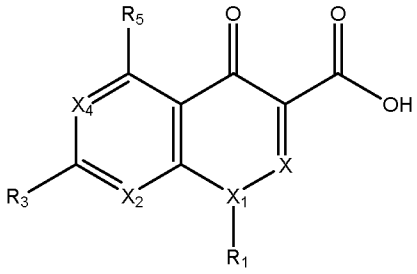
budesonide, cortisone, dexamethasone, hydrocortisone, fluticasone, meprednisone, mometasone, paramethasone and prednisolone.

13. A compound for use according to any preceding claim wherein the treatment comprises administration of said compound to a patient who is also administered another therapeutic agent selected from angiostatic peptides, such as angiostatin; angiostatic steroids, such as anecortave acetate; modulators of VEGF or FGF, such as zactima; non-steroidal anti-inflammatory drugs (NSAIDs) formulated for ocular use such as flurbiprofen, diclofenac and ketorolac; glucocorticosteroids, such as methylprednisolone; leukotriene modulators such as zilueton; anti-histamines such as cetirizine, loratidine, ketotifen and the like; and general cytokine / growth factor modulating agents such as cyclosporin A, phosphodiesterase inhibitors and the like.
14. A compound for use according to claims 1, 2, 7 or 8 wherein the compound is administered before, during or after laser photocoagulation therapy.
15. A compound for use according to claims 12 or 13 wherein the compound and said other agent are provided in combination.
16. A pharmaceutical composition comprising Nalidixic acid of formula (I), an analogue or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of inflammatory ophthalmic diseases by local administration



(I).

17. A pharmaceutical composition for use according to claim 16 wherein the disease is characterised by ocular inflammation, dry eye disorders, pathological ocular angiogenesis and /or retinal or sub-retinal edema.
18. A pharmaceutical composition according to claims 16 or 17 suitable for topical delivery to the eye or for intraocular injection.
19. A compound for use or a pharmaceutical composition for use according to any preceding claim wherein the compound is Nalidixic acid or a pharmaceutically acceptable salt thereof.
20. A compound for use or a pharmaceutical composition for use according to any of claims 1 to 18 wherein the Nalidixic acid analogue is a compound of formula (II)



(II)

wherein,

X and X_1 independently represent CH or N;

X_2 represents $C(R_2)$ or N;

X_4 represents $C(R_4)$ or N;

R_1 is H, CF_3, $CONH_2$, CN, halogen, NH_2, NH-alkyl, alkyl, cycloalkyl or phenyl and is optionally substituted with one or more R_6; wherein R_1 may form part of a cycle with R_2;

R_2 is H, CF_3, $CONH_2$, CN, halogen, NH_2, alkyl, O-alkyl or S-alkyl; wherein R_2 may form part of a cycle with R_1;

R_3 is H, CF_3, $CONH_2$, CN, halogen, NH_2, alkyl, O-alkyl, pyridyl, cycloalkyl or heterocycloalkyl and is optionally substituted with one or more R_6; wherein R_3 may form part of a cycle with R_4;

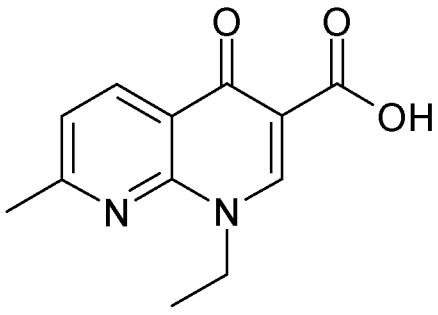
R_4 is H, F or O-alkyl; wherein R_4 may form part of a cycle with R_3;

R_5 is H, F, Cl, alkyl, O-alkyl or NH_2;

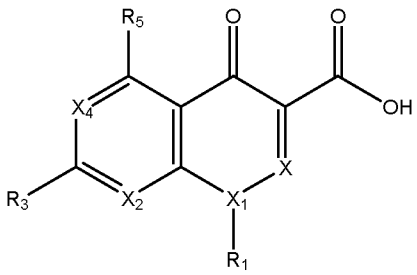
R_6 is F, alkyl, NH_2, NH-alkyl, CH_2NH_2 or OH;

or a pharmaceutically acceptable salt thereof.

21. A method for treating or preventing inflammatory ophthalmic diseases characterised by ocular inflammation, dry eye disorders, pathological ocular angiogenesis and/or retinal or sub-retinal edema by the local administration of a compound of Nalidixic acid of formula (I) or a Nalidixic acid analogue of formula (II)



(I)



(II)

wherein,

X and X_1 independently represent CH or N;

X_2 represents $C(R_2)$ or N;

X_4 represents $C(R_4)$ or N;

R_1 is H, CF_3, $CONH_2$, CN, halogen, NH_2, NH-alkyl, alkyl, cycloalkyl or phenyl and is optionally substituted with one or more R_6; wherein R_1 may form part of a cycle with R_2;

R_2 is H, CF_3, $CONH_2$, CN, halogen, NH_2, alkyl, O-alkyl or S-alkyl; wherein R_2 may form part of a cycle with R1;

R_3 is H, CF_3, $CONH_2$, CN, halogen, NH_2, alkyl, O-alkyl, pyridyl, cycloalkyl or heterocycloalkyl and is optionally substituted with one or more R_6; wherein R_3 may form part of a cycle with R_4;

R_4 is H, F or O-alkyl; wherein R_4 may form part of a cycle with R_3;

R_5 is H, F, Cl, alkyl, O-alkyl or NH_2;

R_6 is F, alkyl, NH_2, NH-alkyl, CH_2NH_2 or OH;

or a pharmaceutically acceptable salt thereof.

22. A compound for use, a composition for use or a method according to any preceding claim wherein the amount of (I) or (II) or a pharmaceutically acceptable salt thereof has no substantial antibacterial activity.

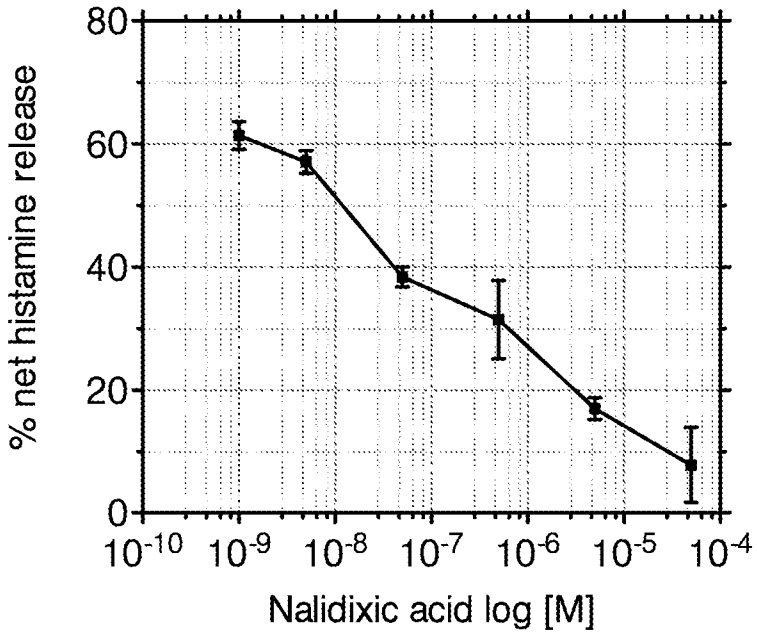


Figure 1

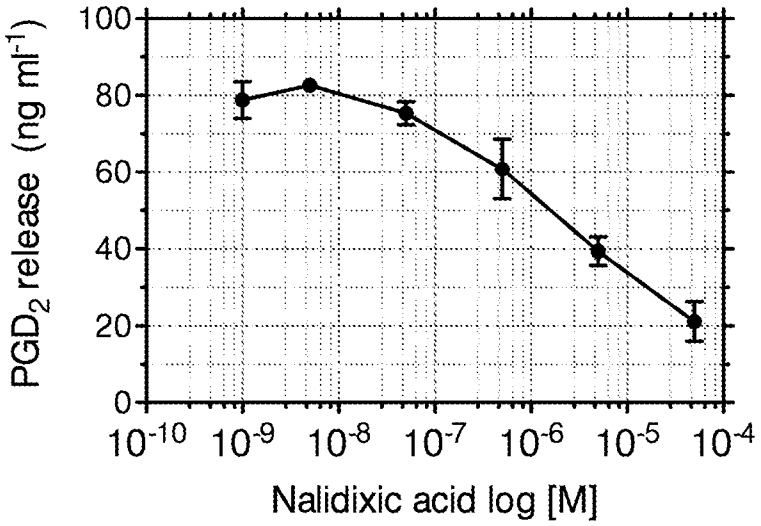


Figure 2

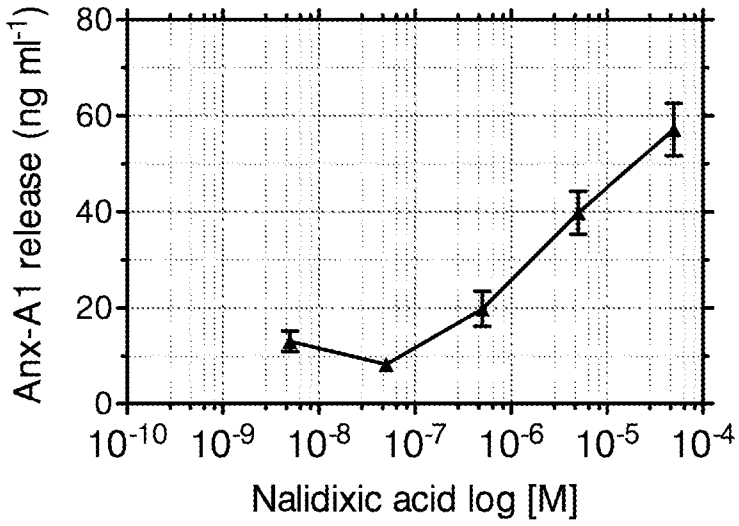


Figure 3

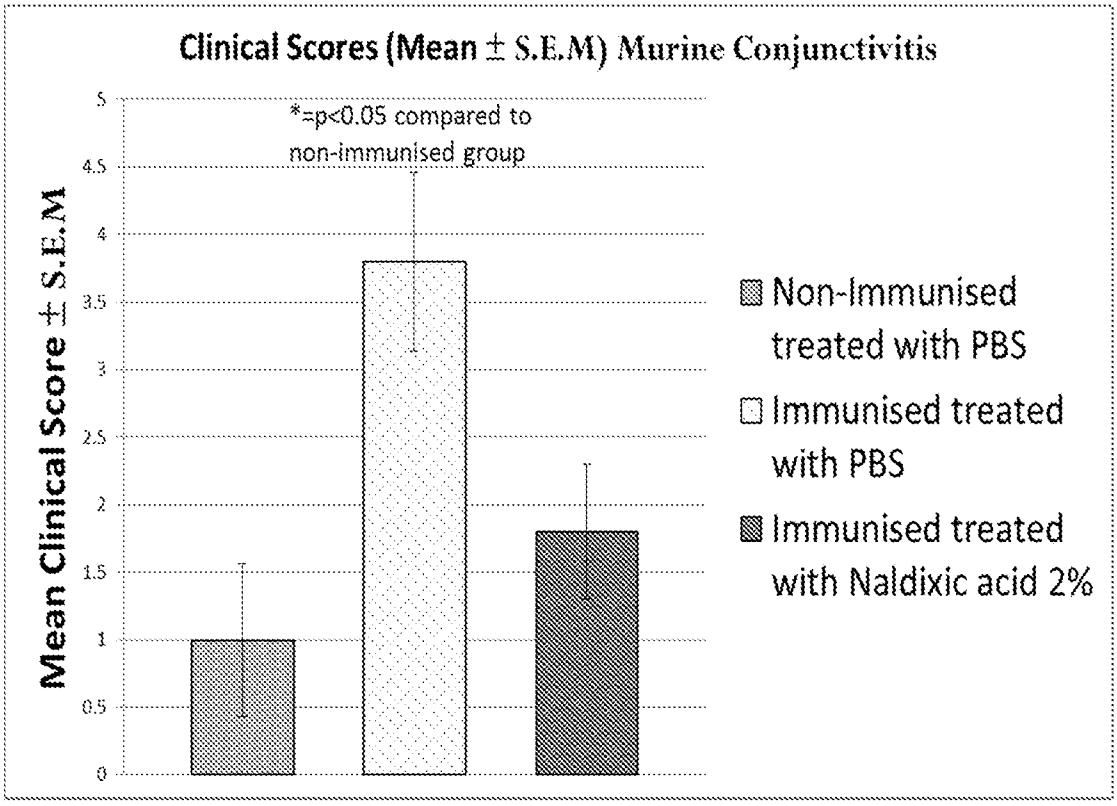


Figure 4

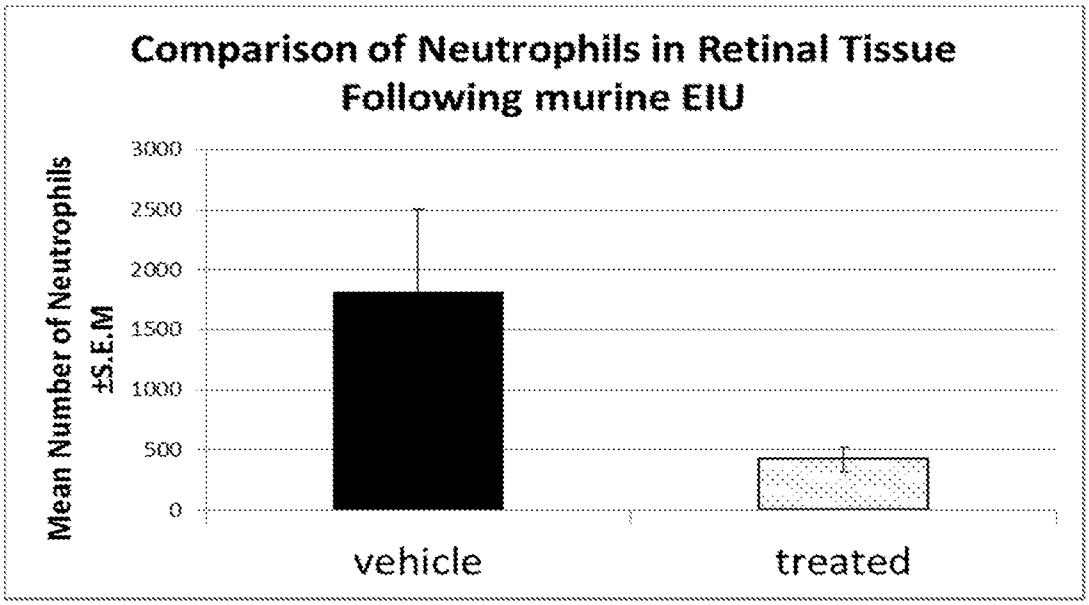

Comparison of Neutrophils in Retinal Tissue Following murine EIU
Mean Number of Neutrophils ±S.E.M
3000
2500
2000
1500
1000
500
0
vehicle
treated

Figure 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2014/051108

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P27/02 A61P29/00 A61K45/06 A61K9/00 A61K31/4375
A61K31/47 A61K31/4709 A61K31/473 A61K31/4741 A61K31/5025
A61K31/519

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/004098 A1 (SUCAMPO AG [CH]; UENO RYUJI [US]) 16 January 2003 (2003-01-16) page 2, lines 6-23 page 14, lines 28-32 page 17, paragraph 1-28 page 18, line 33 - page 20, line 3 examples 1,2 claims ----- -/--	1-3,5,6, 10-19, 21,22

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 2014	23/09/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gradassi, Giulia

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2014/051108

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

19(completely); 1-18, 21, 22(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 19(completely); 1-18, 21, 22(partially)

   Nalidixic acid of formula (I) or a pharmaceutical salt thereof for use in the treatment or prevention of inflammatory ophthalmic diseases by local administration.

   ---

2. claims: 20(completely); 1-18, 21, 22(partially)

   Nalidixic acid analogue of formula (II) or a pharmaceutical salt thereof for use in the treatment or prevention of inflammatory ophthalmic diseases by local administration, and wherein any embodiment falling within this definition and also pertaining to the earlier invention is considered to fall within invention 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2014/051108

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GALIN M A ET AL: "Experimental corneal infections. Evaluation of nalidixic acid in proteus and pseudomonas keratitis.", AMERICAN JOURNAL OF OPHTHALMOLOGY SEP 1968, vol. 66, no. 3, September 1968 (1968-09), pages 447-451, XP008169508, ISSN: 0002-9394 page 448, left-hand column, paragraph 2 page 448, left-hand column, last line - page 449, left-hand column, paragraph 2 page 449, right-hand column, paragraph 4-5 -----	1-3,10, 16-19, 21,22
A	WADA TOMOYUKI ET AL: "Immunomodulatory effect of gatifloxacin on mouse peritoneal macrophages in vitro and in models of endotoxin-induced rat conjunctivitis and rabbit bacterial keratitis", OPHTHALMIC RESEARCH, vol. 40, no. 2, 2008, pages 54-60, XP008169524, ISSN: 0030-3747 page 59, left-hand column, last paragraph; figures page 59, right-hand column, paragraphs 3,4 -----	1-19,21, 22
A	HIRSCHELMANN ROLF ET AL: "Antiinflammatorische Wirkung von Chemotherapeutika und Antibiotika. [Antiinflammatory action of chemotherapeutic agents and antibiotics]", ZEITSCHRIFT FUER DIE GESAMTE INNERE MEDIZIN UND IHRE GRENZGEBIETE, THIEME, LEIPZIG, DE, vol. 28, no. 24, 1 January 1973 (1973-01-01), pages 799-800, XP008169395, ISSN: 0044-2542 page 799; tables page 799, left-hand column, paragraph 2 - right-hand column, paragraph 1 page 799, right-hand column, paragraphs 3,4 page 800, left-hand column, paragraph 1 abstract -----	1-19,21, 22

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2014/051108

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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摘要

本发明提供了萘啶酸和萘啶酸类似物，其通过局部施用用于治疗炎症性眼科病症。