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(54) **Faciális amfifil polimerek és oligomerek szemészeti vagy fülészeti készítményei és alkalmazásuk**

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(54) **OPHTHALMIC AND OTIC COMPOSITIONS OF FACIALLY AMPHIPHILIC POLYMERS AND OLIGOMERS AND USES THEREOF**

ZUSAMMENSETZUNGEN FÜR AUGEN UND OHREN VON FAZIAL AMPHIPHILEN POLYMEREN UND OLIGOMEREN UND IHRE VERWENDUNGEN

COMPOSITIONS OPHTALMIQUES ET OTIQUES DE POLYMÈRES ET OLIGOMÈRES À FACE AMPHIPHILE ET LEURS UTILISATIONS

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(56) References cited:
WO-A2-2004/082634 **WO-A2-2005/072246**
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Description

Field of the Invention

[0001] The present invention relates to antimicrobial compositions of facially amphiphilic antimicrobial polymers and oligomers useful for the treatment or prevention of ophthalmic and otic infections. The present invention also relates to methods of using the compositions for treating and/or preventing ophthalmic and otic infections.

Background of the Invention

[0002] Bacterial drug resistance is a significant current health problem throughout the world. Multiple drug resistance is being commonly seen in a number of human pathogens (see, e.g., Hiramatsu et al., J. Antimicrob. Chemother., 1998, 40, 311-313 and Montecalvo et al., Antimicro. Agents Chemother., 1994, 38, 1363-1367, and the incidence of drug-resistant hospital infections is growing at a rapid rate. For example, in some U.S. hospitals, nosocomial pathogens, such as *E. faecium* and *Acinetobacter* species, have acquired multiple resistance determinants and are virtually untreatable with current antimicrobial agents. Bacterial resistance has now reached epidemic proportions and has been attributed to a variety of abuses of antibiotic treatments, including overuse (Monroe et al., Curr. Opin. Microbiol., 2000, 3, 496-501), inappropriate dosing at sub-therapeutic levels (Guillemot et al., JAMA, 1998, 279, 365-370), and misuse as antimicrobial growth promoters in animal food (Lathers, J. Clin. Pharmacol., 2002, 42, 587-600). Moreover, the threat of bio-terrorism has provided a further impetus to develop novel classes of antibiotics, particularly ones against which it will be difficult to develop resistant bacterial strains.

[0003] The pharmaceutical scientific community is responding to this challenge by focusing on the development of new antibiotic drugs. Much of this work, however, is directed to synthesizing analogs of known drugs, such as cephalosporins and quinolones, that, while potentially useful for a short time, will inevitably also encounter bacterial drug resistance and become ineffective. Thus, therapeutically effective antimicrobial drugs that act by novel mechanisms would provide an economic as well as a human health benefit.

[0004] A series of nonpeptidic mimics of the natural antimicrobial peptides have been developed that are polymers, oligomers and small molecules comprised of non-natural building blocks. See, Tew et al., Proc. Natl. Acad. Sci. U.S.A., 2002, 99, 5110-5116; Arnt et al., J. Polym. Sci., Part A, 2004, 42, 3860-3864; and Liu et al., Angew Chem. Int. Ed. Engl., 2004, 43, 1158-1162. Many of these compounds are significantly smaller and easier to prepare than the natural antimicrobial peptides and peptidic mimetics, with the shortest of these oligomers having molecular weights typical of small molecule drugs. They have the same mechanism of action as magainin, are highly potent and have a broad spectrum of activity, killing gram-positive, gram-negative and antibiotic-resistant pathogens. Relative to the antimicrobial peptides, the nonpeptidic mimetics are significantly less toxic towards human erythrocytes, much less expensive to prepare, and more stable.

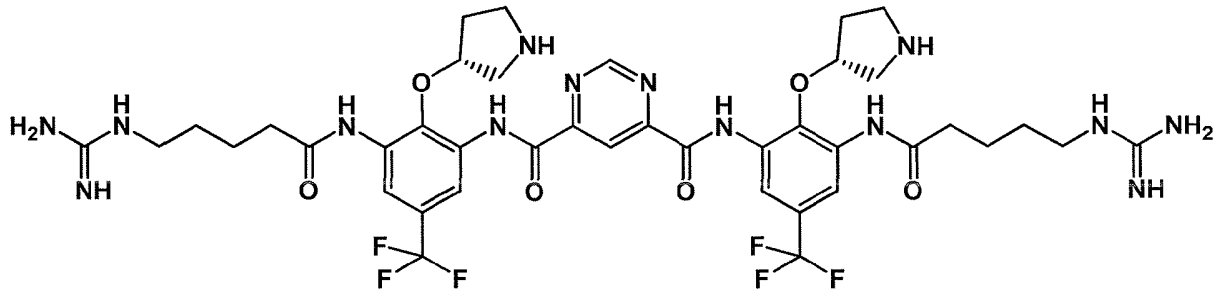
[0005] See, for example, U.S. Published Patent Appl. Nos. US 2006-0041023 A1, US 2004-0202639 A1, US 2005-0287108 A1, and US 2006-0024264 A1, and US Patent No. 7,173,102.

[0006] There is a great need for improved compositions and methods of treatment based on the use of antimicrobials that are more effective than existing agents against key ophthalmic and otic pathogens, and less prone to the development of resistance by those pathogens. In particular, there is a great need for effective compositions and methods for the treatment of otic infections, especially bacterial infections. The use of oral antibacterials to treat otic infections in children has limited efficacy and creates a serious risk of pathogen resistance to the orally administered antibacterial agent.

[0007] Thus, a need remains for improved ophthalmic and otic antimicrobial compositions, in particular, for broad-spectrum antimicrobial agents useful for the treatment of ophthalmic and otic infections that are not prone to the development of resistance by ophthalmic and/or otic pathogens and that are effective in the treatment of ophthalmic and otic pathogens that have already developed resistance to existing antimicrobial agents.

Summary of the Invention

[0008] The present invention provides ophthalmic or otic composition comprising a compound having the formula:



or a pharmaceutically acceptable salt thereof.

[0009] The present invention is also directed to an ophthalmic or otic composition which is in the form of a liquid or solid, or which is in the form of a solution, a suspension, an emulsion, a gel, or an ointment.

[0010] The present invention is also directed to an ophthalmic or otic composition of further comprising a preservative, a stabilizer, an antioxidant, a chelating agent, or a surfactant.

[0011] The present invention is also directed to an ophthalmic or otic composition further comprising an additional medicament. The additional medicament is chosen from an antibiotic, an anti-inflammatory agent, an anesthetic agent, an anti-allergic agent, an acetylcholine blocking agent, an adrenergic agonist, a beta-adrenergic blocking agent, an anti-glaucoma agent, and an anti-hypertensive agent.

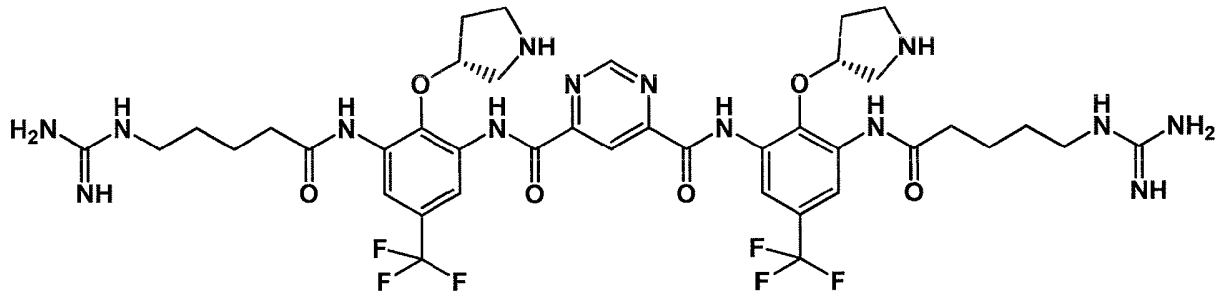
[0012] The antibiotic may be chosen from an aminoglycoside, a cephalosporin, a diaminopyridine, a fluoroquinolone, a sulfonamide, and a tetracycline. The antibiotic is particularely chosen from amikacin, azithromycin, cefixime, cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, chloramphenicol, ciprofloxacin, clindamycin, colistin, demeclocycline, doxycycline, erythromycin, gentamicin, mafenide, methacycline, minocycline, neomycin, norfloxacin, ofloxacin, oxytetracycline, polymyxin B, pyrimethamine, silver sulfadiazine, sulfacetamide, sulfisoxazole, tetracycline, tobramycin, and trimethoprim.

[0013] The anti-inflammatory agent may be a steroidal agent, particularly chosen from dexamethasone, rimexolone, prednisolone, fluorometholone, and hydrocortisone.

[0014] The anti-inflammatory agent may be a non-steroidal agent, particularly chosen from a cyclooxygenase type I or type II inhibitor, a PAF antagonist, a PDE IV inhibitor, and an inhibitor of cytokine production. The cyclooxygenase type I or type II inhibitor may be chosen from diclofenac, flurbiprofen, ketorolac, suprofen, nepafenac, amfenac, indomethacin, naproxen, ibuprofen, bromfenac, ketoprofen, meclofenamate, piroxicam, sulindac, mefanamic acid, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, tenoxicam, carprofen, vioxx, celecoxib, and etodolac. The PAF antagonist is preferably chosen from apafant, bepafant, minopafant, nupafant, and modipafant. The PDE IV inhibitor is preferably chosen from ariflo, torbafylline, rolipram, filaminast, piclamilast, cipamfylline, and roflumilast.

[0015] The anti-allergic agent is preferably pemirolast or olopatadine, or a corticosteroid. The corticosteroid is preferably chosen from prednisolone, fluorometholone, loteprenol, and dexamethasone.

[0016] The invention also concerns a compound having the formula:



[0017] The invention also concerns an ophthalmic or otic composition or a compound as defined above for use in the treatment of a bacterial infection in a mammal.

Description of Embodiments

[0018] In other aspects of the present invention, the oligomer in the ophthalmic or otic compositions is provided in the form of an acceptable salt (for example, a pharmaceutically acceptable salt) for treating microbial infections. Oligomer

salts can be provided for pharmaceutical use, or as an intermediate in preparing the pharmaceutically desired form of the oligomer. One oligomer salt that is considered to be acceptable is the hydrochloride acid addition salt. Since one or more of the disclosed oligomer may be polyionic, such as a polyamine, the acceptable oligomer salt can be provided in the form of a poly(amine hydrochloride). Examples of other acceptable salts include, but are not limited to, those having sodium, potassium, or ammonium cations, and/or those having chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, bisulfite, mesylate, esylate, napsydisylate, tosylate, besylate, orthophoshate, acetate, gluconate, glutamate, lactate, malonate, fumarate, tartrate, maleate, or trifluoroacetate anions. In some embodiments, acceptable salts are those having mesylate, chloride, sulfate, esylate, napsydisylate, tosylate, besylate, phosphate, orthophoshate, acetate, gluconate, glutamate, lactate, malonate, citrate, fumarate, tartrate, maleate, or trifluoroacetate anions. In other embodiments, acceptable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite, and ammonium sulfate.

[0019] In some aspects of the invention, the disclosed oligomer (such as the polymers and/or oligomers of Formulae I, II, IIa, IV, IVa, IVb, IVc, V, Va, and VI) are derivatives referred to as prodrugs. The expression "prodrug" denotes a derivative of a known direct acting drug, which derivative has enhanced delivery characteristics and therapeutic value as compared to the drug, and is transformed into the active drug by an enzymatic or chemical process.

[0020] The oligomer employed in the ophthalmic compositions of the present invention can be prepared as described in the following patents and patent publications: US Published Patent Appl. Nos. US 2006-0041023 A1, US 2004-0202639 A1, US 2005-0287108 A1, and US 2006-0024264 A1, as well as US Patent No. 7,173,102. oligomeroligomer

[0021] Examples of the design, synthesis, and testing of arylamide oligomersare also presented in Tew et al., Proc. Natl. Acad. Sci. USA, 2002, 99, 5110-5114 and in WIPO Publication No. WO 2004/082634.

[0022] The oligomers can be synthesized by solid-phase synthetic procedures well know to those of skill in the art. See, for example, Tew et al., Proc. Natl. Acad. Sci. USA, 2002, 99, 5110-5114; Barany et al., Int. J. Pept. Prot. Res., 1987, 30, 705-739; Solid-phase Synthesis: A Practical Guide, Kates, S.A., and Albericio, F., eds., Marcel Dekker, New York (2000); and Dörwald, F.Z., Organic Synthesis on Solid Phase: Supports, Linkers, Reactions, 2nd Ed., Wiley-VCH, Weinheim (2002).

[0023] The ophthalmic or otic compositions can be tested for anti-microbial activity by methods known to those of skill in the art. For example, anti-microbial assays suitable for testing the antimicrobial activity of the ophthalmic or otic compositions of the invention are described, for example, US Pat. Appl. Publ. No. US 2006-0041023 A1; Tew et al., Proc. Natl. Acad. Sci. USA, 2002, 99, 5110-5114; and Liu et al., J. Amer. Chem. Soc., 2001, 123, 7553-7559.

Compositions

[0024] The ophthalmic and otic compositions of the present invention can take the form of a liquid or solid, including, e.g., but not limited to, a solution, a suspension, an emulsion, a gel, an ointment, or a solid article that can be inserted in a suitable location in the eye.

[0025] In some embodiments, a composition of the present invention is in the form of a liquid wherein the active agent (*i.e.,* one of the facially amphiphilic polymers or oligomers disclosed herein) is present in solution, in suspension, as an emulsion, or as a "solution/suspension." The term "solution/suspension" as used herein refers to a liquid composition wherein a first portion of the active agent is present in solution and a second portion of the active agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, the liquid composition is in the form of a gel. In other embodiments, the liquid composition is aqueous. In other embodiments, the composition is in the form of an ointment.

[0026] In yet other embodiments, the composition is in the form of a solid article. For example, in some embodiments, the ophthalmic composition is a solid article that can be inserted in a suitable location in the eye, such as between the eye and eyelid or in the conjunctival sac, where it releases the active agent as described, for example, U.S. Pat. No. 3,863,633; U.S. Pat. No. 3,867,519; U.S. Pat. No. 3,868,445; U.S. Pat. No. 3,960,150; U.S. Pat. No. 3,963,025; U.S. Pat. No. 4,186,184; U.S. Pat. No. 4,303,637; U.S. Pat. No. 5,443,505; and U.S. Pat. No. 5,869,079. Release from such an article is usually to the cornea, either via the lacrimal fluid that bathes the surface of the cornea, or directly to the cornea itself, with which the solid article is generally in intimate contact. Solid articles suitable for implantation in the eye in such fashion are generally composed primarily of polymers and can be bioerodible or non-bioerodible. Bioerodible polymers that can be used in the preparation of ocular implants carrying one or more of the anti-microbial, facially amphiphilic oligomer active agents in accordance with the present invention include, but are not limited to, aliphatic polyesters such as polymers and copolymers of poly(glycolide), poly(lactide), poly(epsilon-caprolactone), poly-(hydroxybutyrate) and poly(hydroxyvalerate), polyamino acids, polyorthoesters, polyanhydrides, aliphatic polycarbonates and polyether lactones. Suitable non-bioerodible polymers include silicone elastomers.

[0027] The oligomer is typically present in the ophthalmic or otic composition in an "effective amount" or "effective concentration." The terms "effective amount," "effective concentration," or "amount effective," as used herein in reference to a oligomer in a composition of the present invention, refers to the amount of the oligomer sufficient to treat or prevent an ophthalmic infection in an eye of an animal, or to treat or prevent an otic infection in an ear of an animal.

[0028] The "effective amount" or concentration of the oligomer in the composition will vary and depends, among other factors, on the particular facially amphiphilic oligomer (active agent) being administered (e.g., on the relative antimicrobial activity of the specific oligomer); the mode of administration; the residence time provided by the particular formulation of the oligomer; the species, age and body weight of the subject; the intended use of the composition (e.g., treatment of existing infections or prevention of post-surgical infections); the particular condition for which treatment or prophylaxis is sought; and the severity of the condition.

[0029] The activity of antimicrobials is generally expressed as the minimum concentration of a compound (active agent) required to inhibit the growth of a specified pathogen. This concentration is also referred to as the "minimum inhibitory concentration" or "MIC." The term "MIC_{90}" refers to the minimum concentration of an antimicrobial active agent required to inhibit the growth of ninety percent (90%) of the tested isolates for one particular organism. The concentration of a compound required to totally kill a specified bacterial species is referred to as the "minimum bactericidal concentration" or "MCB."

[0030] The "effective amount" or concentration of the oligomer in the compositions of the invention will generally be an amount sufficient to provide a concentration on or in the affected eye or ear tissue equal to or greater than the MIC_{90} level for the selected oligomer, relative to the microbes commonly associated with the infection. Thus, the "effective amount" or concentration of the oligomer in the ophthalmic or otic composition will generally be the amount of the oligomer sufficient to provide a concentration on or in the eye or ear tissue(s) equal to or greater than the MIC_{90} level for the oligomer, relative to microbes commonly associated with the ophthalmic or otic infection.

[0031] Thus, for example, in the ophthalmic and otic compositions of the present invention, an effective concentration of the antimicrobial oligomer in the composition will generally be from about 0.01 % to about 20% by weight (*i.e.,* wt%) of the composition. More typically, it will be about 0.05% to about 10% by weight, about 0.1% to about 8.0% by weight, about 0.5% to about 5.0% by weight, about 1.0% to about 5.0% by weight, or about 2.0% to about 4.0% of the composition. For example, in ophthalmic compositions in the form of solid suspensions, such as ointments, an effective concentration of the antimicrobial oligomer will generally be from about 1% to about 5% by weight (wt%) of the composition.

[0032] The ophthalmic and otic compositions of the invention are preferably sterile and have physical properties (e.g., osmolality and pH) that are specially suited for application to ophthalmic or otic tissues, including tissues that have been compromised as the result of preexisting disease, trauma, surgery or other physical conditions. For example, aqueous compositions of the invention typically have a pH in the range of 4.5 to 8.0, more preferably, 6.0 to 8.0, or 6.5 to 8.0, or 7.0 to 8.0.

[0033] In addition to one or more of the polymers or oligomers disclosed herein, the ophthalmic or otic compositions of the invention can also comprise one or more ophthalmically or otically acceptable excipients.

[0034] The term "ophthalmically acceptable" as used herein means having no persistent detrimental effect on the treated eye or the functioning thereof, or on the general health of the subject being treated. However, it will be recognized that transient effects such as minor irritation or a "stinging" sensation are common with topical ophthalmic administration of drugs and the existence of such transient effects is not inconsistent with the composition, formulation, or ingredient (e.g., excipient) in question being "ophthalmically acceptable" as herein defined. However, preferred ophthalmically acceptable compositions, formulations, and excipients are those that cause no substantial detrimental effect, even of a transient nature.

[0035] Similarly, the term "otically acceptable," as used herein, means having no persistent detrimental effect on the treated ear or the functioning thereof, or on the general health of the subject being treated. Preferred otically acceptable compositions, formulations, and excipients are those that cause no substantial detrimental effect, even of a transient nature.

[0036] Ophthalmically and otically acceptable excipients include, but are not limited to, viscosity-enhancing agents, preservatives, stabilizers, antioxidants, suspending agents, solubilizing agents, buffering agents, lubricating agents, ophthalmically or otically acceptable salts, and combinations thereof.

[0037] For example, aqueous ophthalmic compositions of the present invention, when in suspension or solution form, are preferably viscous or mucoadhesive, or both viscous or mucoadhesive, and thus comprise a viscosity-enhancing agent. Examples of suitable viscosity-enhancing agents include, but are not limited to, glycerin, polyvinyl alcohol, polyvinyl pyrrolidone, methylcellulose, hydroxypropylmethylcellulose, hydroxyethyl-cellulose, carboxymethylcellulose, hydroxypropylcellulose, and/or various gelling agents. For example, in some embodiments, the viscosity-enhancing agent is selected from methylcellulose, hydroxypropyl-methylcellulose, polyvinyl alcohol, and glycerol. Such agents are generally employed in the compositions of the invention at a concentration of about 0.01% to about 3% by weight.

[0038] Thus, for ophthalmic compositions of the present invention, in some embodiments, the ophthalmically acceptable excipient is a viscosity-enhancing agent or a promoter of mucoadhesion, such as carboxymethylcellulose. In such embodiments, the concentration of carboxymethylcellulose in the aqueous suspension or solution is 0.1 % to 5% by weight or about 0.1% to about 2.5% by weight. The carboxymethylcellulose is preferably in the form of sodium carboxymethylcellulose substituted to a degree that the sodium content of the sodium carboxymethylcellulose is about 1% to about 20%.

[0039] In other embodiments, the ophthalmic composition is *an in situ* gellable aqueous composition, more preferably, an *in situ* gellable aqueous solution. Such a composition 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, enabling the composition to remain in the eye for a prolonged period without loss by lacrimal drainage. Suitable gelling agents non-restrictively include thermosetting polymers such as tetra-substituted ethylene diamine block copolymers of ethylene oxide and propylene oxide (e.g., poloxamine 1307); polycarbophil; and polysaccharides such as gellan, carrageenan (e.g., kappa-carrageenan and iota-carrageenan), chitosan and alginate gums.

[0040] The phrase *"in situ* gellable" as used herein is to be understood as embracing 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.

[0041] For example, in some embodiments of the present invention, the ophthalmic composition is an *in situ* gellable aqueous solution, suspension or solution/suspension, comprising about 0.1% to about 6.5%, preferably about 0.5% to about 4.5%, by weight, based on the total weight of the composition, of one or more lightly cross-linked carboxyl-containing polymers as gelling agents. A preferred gelling agent in this embodiment is polycarbophil. In other embodiments, the composition is an *in situ* gellable aqueous solution, suspension or solution/suspension, preferably a solution, comprising about 0.1 % to about 2% by weight of a polysaccharide that gels when it contacts an aqueous medium having the ionic strength of lacrimal fluid. A preferred polysaccharide is gellan gum, more preferably a low acetyl clarified grade of gellan gum such as that sold under the trademark Gelrite®. Suitable partially deacylated gellan gums are disclosed in U.S. Pat. No. 5,190,927.

[0042] In yet other embodiments, the composition is an *in situ* gellable aqueous solution, suspension or solution/suspension, comprising about 0.2% to about 3%, preferably about 0.5% to about 1%, by weight of a gelling polysaccharide, preferably selected from gellan gum, alginate gum and chitosan, and about 1% to about 50% of a water-soluble film-forming polymer, preferably selected from alkylcelluloses (e.g., methylcellulose, ethylcellulose), hydroxyalkylcelluloses (e.g., hydroxyethylcellulose, hydroxypropyl methylcellulose), hyaluronic acid and salts thereof, chondroitin sulfate and salts thereof, polymers of acrylamide, acrylic acid and polycyanoacrylates, polymers of methyl methacrylate and 2-hydroxyethyl methacrylate, polydextrose, cyclodextrins, polydextrin, maltodextrin, dextran, polydextrose, gelatin, collagen, natural gums (e.g., xanthan, locust bean, acacia, tragacanth and carrageenan gums and agar), polygalacturonic acid derivatives (e.g., pectin), polyvinyl alcohol, polyvinylpyrrolidone and polyethylene glycol. The composition can optionally contain a gel-promoting counterion such as calcium in latent form, for example encapsulated in gelatin.

[0043] In yet other embodiments, the composition is an *in situ* gellable aqueous solution, suspension or solution/suspension comprising about 0.1% to about 5% of a carrageenan gum, e.g., a carrageenan gum having no more than 2 sulfate groups per repeating disaccharide unit, such as e.g., kappa-carrageenan, having 18-25% ester sulfate by weight, iota-carrageenan, having 25-34% ester sulfate by weight, and mixtures thereof.

[0044] In still other embodiments, the composition comprises a bioerodible polymer substantially as disclosed in U.S. Pat. No. 3,914,402.

[0045] In some embodiments, the composition comprises an ophthalmically acceptable mucoadhesive polymer, selected, for example, from hydroxypropylmethylcellulose, carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, polyethylene oxide, acrylic acid/butyl acrylate copolymer, sodium alginate, and dextran.

[0046] Ophthalmic compositions of the invention preferably incorporate means to inhibit microbial growth, for example through preparation and packaging under sterile conditions and/or through inclusion of an antimicrobially effective amount of an ophthalmically acceptable preservative.

[0047] Suitable preservatives include, but are not limited to, mercury-containing substances such as phenylmercuric salts (e.g., phenylmercuric acetate, borate and nitrate) and thimerosal; stabilized chlorine dioxide; quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride; imidazolidinyl urea; parabens such as methylparaben, ethylparaben, propylparaben and butylparaben, and salts thereof; phenoxyethanol; chlorophenoxyethanol; phenoxypropanol; chlorobutanol; chlorocresol; phenylethyl alcohol; disodium EDTA; and sorbic acid and salts thereof.

[0048] Several preservatives may precipitate in the presence of other excipients in the composition and/or in the presence of the oligomer in the ophthalmic compositions of the present invention. For example, benzalkonium chloride can precipitate in a composition using iota-carrageenan as a gelling agent. Thus, in those embodiments of the invention in which a preservative is present, the preservative is one that does not precipitate but remains in solution in the composition.

[0049] Optionally one or more stabilizers can be included in the compositions of the invention to enhance chemical stability where required. Suitable stabilizers include, but are not limited to, chelating agents or complexing agents, such as, for example, the calcium complexing agent ethylene diamine tetraacetic acid (EDTA). For example, an appropriate amount of EDTA or a salt thereof, e.g., the disodium salt, can be included in the composition to complex excess calcium

ions and prevent gel formation during storage. EDTA or a salt thereof can suitably be included in an amount of about 0.01% to about 0.5%. In those embodiments containing a preservative other than EDTA, the EDTA or a salt thereof, more particularly disodium EDTA, can be present in an amount of about 0.025% to about 0.1% by weight.

[0050] One or more antioxidants can also be included in the ophthalmic compositions of the invention. Suitable antioxidants include ascorbic acid, sodium metabisulfite, polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, or other agents know to those of skill in the art. Such preservatives are typically employed at a level of from about 0.001% to about 1.0% by weight. In some embodiments of the present invention, the facially amphiphilic polymer(s) or oligomer(s) of the compositions are solubilized at least in part by an ophthalmically acceptable solubilizing agent. The term "solubilizing agent" herein includes agents that result in formation of a micellar solution or a true solution of the drug. Certain ophthalmically acceptable nonionic surfactants, for example polysorbate 80, can be useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, e.g., polyethylene glycol 400 (PEG-400), and glycol ethers.

[0051] Particularly preferred solubilizing agents for solution and solution/suspension compositions of the invention are cyclodextrins. Suitable cyclodextrins can be selected from α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, alkylcyclodextrins (e.g., methyl-β-cyclodextrin, dimethyl-β-cyclodextrin, diethyl-β-cyclodextrin), hydroxyalkylcyclodextrins (e.g., hydroxyethyl-P-cyclodextrin, hydroxypropyl-β-cyclodextrin), carboxy-alkylcyclodextrins (e.g., carboxymethyl-β-cyclodextrin), sulfoalkylether cyclodextrins (e.g., sulfobutylether-β-cyclodextrin), and the like. Ophthalmic applications of cyclodextrins have been reviewed in Rajewski et al., Journal of Pharmaceutical Sciences, 1996, 85, 1155-1159.

[0052] An ophthalmically acceptable cyclodextrin can optionally be present in an ophthalmic composition of the invention at a concentration of about 1 to about 200 mg/ml, preferably about 5 to about 100 mg/ml and more preferably about 10 to about 50 mg/ml.

[0053] In some embodiments, the ophthalmic composition optionally contains a suspending agent. For example, in those embodiments in which the ophthalmic composition is an aqueous suspension or solution/suspension, the composition can contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers, for example, hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. However, preferred ophthalmic compositions of the invention do not contain substantial amounts of solid particulate matter, whether of the anti-microbial oligomer active agent, an excipient, or both, as solid particulate matter, if present, can cause discomfort and/or irritation of a treated eye.

[0054] One or more ophthalmically acceptable pH adjusting agents and/or buffering agents can be included in the ophthalmic compositions of the invention, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an ophthalmically acceptable range.

[0055] One or more ophthalmically acceptable salts can be included in the compositions of the invention in an amount required to bring osmolality of the composition into an ophthalmically acceptable range. Such salts include, but are not limited to, those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; preferred salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate, with sodium chloride being especially preferred.

[0056] Optionally an ophthalmically acceptable xanthine derivative such as caffeine, theobromine or theophylline can be included in the compositions of the invention, e.g., as disclosed in U.S. Pat. No. 4,559,343. Inclusion of the xanthine derivative can reduce ocular discomfort associated with administration of the composition.

[0057] Optionally one or more ophthalmically acceptable surfactants, preferably nonionic surfactants, or co-solvents can be included in the compositions of the invention to enhance solubility of the components of the compositions or to impart physical stability, or for other purposes. Suitable nonionic surfactants include, but are not limited to, polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40; polysorbate 20, 60 and 80; polyoxyethylene/polyoxypropylene surfactants (e.g., Pluronic® F-68, F84 and P-103); cyclodextrin; or other agents known to those of skill in the art. Typically, such co-solvents or surfactants are employed in the compositions at a level of from about 0.01% to about 2% by weight.

[0058] One or more ophthalmic lubricating agents can also be included optionally in the compositions of the invention to promote lacrimation or as a "dry eye" medication. Such agents include, but are not limited to, polyvinyl alcohol, methylcellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, and the like. It will be understood that promotion of lacrimation is beneficial in the present invention only where lacrimation is naturally deficient, to restore a normal degree of secretion of lacrimal fluid. Where excessive lacrimation occurs, residence time of the composition in the eye can be reduced.

[0059] Ophthalmic compositions of the present invention typically include a combination of one or more of the optional excipients listed above. For example, in some embodiments of the invention, the ophthalmic composition can optionally

further comprise glycerin in an amount of about 0.5% to about 5%, more preferably about 1% to about 2.5%, for example about 1.5% to about 2%, by weight. Glycerin can be useful to increase viscosity of the composition and for adjustment of osmolality. Independently of the presence of glycerin, the composition can also further comprise a cyclodextrin, preferably hydroxypropyl-β-cyclodextrin, in an amount of about 0.5% to about 25% by weight, as a solubilizing agent, and an antimicrobially effective amount of a preservative, e.g., imidazolidinyl urea in an amount of about 0.03% to about 0.5%; methylparaben in an amount of about 0.015% to about 0.25%; propylparaben in an amount of about 0.005% to about 0.01%; phenoxyethanol in an amount of about 0.25% to about 1%; disodium EDTA in an amount of about 0.05% to about 0.2%; thimerosal in an amount of 0.001% to about 0.15%; chlorobutanol in an amount of about 0.1 % to about 0.5%; and/or sorbic acid in an amount of about 0.05% to about 0.2%; all by weight.

[0060] The otic compositions of the present invention also optionally comprise one or more otically acceptable excipients. Otically acceptable excipients include, but are not limited to, one or more of the preservatives, stabilizers, antioxidants, viscosity-enhancing agents, buffering agents, solubilizing agents, surfactants, lubricating agents, or acceptable salts described above, or combinations thereof, as described above for the ophthalmic compositions of the invention.

[0061] Thus, for example, in some embodiments, an otic composition of the present invention optionally comprises one or more buffering agents, solubilizing agents, and antioxidants, typically in an aqueous solution. In some embodiments, the otic composition further comprises glycerin (e.g., anhydrous glycerin) or propylene glycol as a viscosity-enhancing agent. The otic composition may also comprise a surfactant in combination with the glycerin or propylene glycol to aid in the removal of cerum (ear wax). Sodium bicarbonate may also be used if wax is to be removed from the ear.

[0062] Thus, e.g., in some embodiments, the otic composition of the present invention is a sterile aqueous solution comprising one or more of the disclosed polymers or oligomers, glycerin, sodium bicarbonate, and, optionally, a preservative, in purified water.

[0063] The ophthalmic and otic compositions of the present invention can be prepared by methods known in the art and described in patents and publications cited herein and incorporated herein by reference.

Methods of Treatment and Administration

[0064] The ophthalmic or otic compositions of the present invention possess anti-microbial activity and can be used in methods of treating or preventing ophthalmic infections in an eye of an animal, or otic infections in the ear of an animal.

[0065] The term "animal" as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. Preferably, the animal is a warm-blooded, mammalian subject, including, but not limited to, domestic, farm and exotic mammals, and humans. The methods of the present invention can be useful, for example, in the treatment of eye infections in dogs, cats, horses, cattle, sheep and/or pigs, but is more particularly useful where the subject is human.

[0066] The phrases "treating an ophthalmic infection" and "treatment of an ophthalmic infection" refer to both the prevention and the therapeutic treatment, e.g., the alleviation or amelioration, of an ophthalmic infection, wherein the object is to prevent or slow down (lessen) the progress of an ophthalmic infection, or obtain beneficial or desired clinical results. For example, "beneficial or desired clinical results" include, but are not limited to, alleviation of the symptoms of an ophthalmic infection; diminishment of the extent of an ophthalmic infection; stabilization (for example, not worsening) of the state of an ophthalmic infection; delay in the onset or the slowing of an ophthalmic infection or its progression; amelioration of an ophthalmic infection or remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of an ophthalmic infection. Treatment includes eliciting a clinically significant response without excessive levels of side effects.

[0067] Similarly, the phrases "treating an otic infection" and "treatment of an otic infection" refer to both the prevention and the therapeutic treatment, e.g., the alleviation or amelioration, of an otic infection, wherein the object is to prevent or slow down (lessen) the progress of an otic infection, or obtain beneficial or desired clinical results. For example, "beneficial or desired clinical results" include, but are not limited to, alleviation of the symptoms of an otic infection; diminishment of the extent of an otic infection; stabilization (for example, not worsening) of the state of an otic infection; delay in the onset or the slowing of an otic infection or its progression; amelioration of an otic infection or remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of an otic infection. Treatment includes eliciting a clinically significant response without excessive levels of side effects.

[0068] Ophthalmic infections for which the compositions and methods of the present invention are useful include, but are not limited to, infections of one or more tissues of the eye, including, for example, conjunctivitis, keratitis (including ulcerative keratitis with bacterial infection), keratoconjunctivitis (including, e.g., keratoconjunctivitis sicca (KCS) commonly found in dogs), blepharitis, blepharoconjunctivitis, dacyrocystitis, hordeolum, corneal ulcers, orbital and preseptal cellulitis, and endophthalmitis

[0069] In preferred methods of the invention, the infected tissue is one that is directly bathed by the lacrimal fluid, as in conjunctivitis, keratitis, keratoconjunctivitis, blepharitis, and blepharoconjunctivitis.

[0070] The ophthalmic compositions of the present invention may also be used prophylactically in connection with

various ophthalmic surgical procedures that create a risk of infection.

[0071] Otic infections for which the compositions and methods of the present invention are useful include, but are not limited to, otitis externa and otitis media. With respect to the treatment of otitis media, the compositions of the present invention are primarily useful in cases where the tympanic membrane has ruptured or tympanostomy tubes have been implanted. The otic compositions may also be used to treat infections associated with otic surgical procedures, such as tympanostomy, or to prevent such infections.

[0072] The ophthalmic and otic compositions of the invention are effective in killing or inhibiting the growth of a broad spectrum of pathogens or microbes often associated with ophthalmic and/or otic infections, including a range of bacteria (both gram-postive and gram-negative), fungi and viruses.

[0073] For example, the ophthalmic and otic compositions are useful in killing or inhibiting the growth of any of the following clinically relevant ocular or otic pathogens, and can be administered topically to treat and/or prevent ophthalmic or otic infections caused by the following pathogens or mixtures of the following pathogens: Staphylococcus spp. (e.g., *Staphylococcus aureus*, *Staphylococcus epidermidis*), Streptococcus spp. (e.g., *Streptococcus viridans*, *Streptococcus pneumoniae),* Enterococcus spp., Bacillus spp., Corynebacterium spp., Propionibacterium spp., Chlamydia spp., Moraxella spp. (e.g., *Moraxella lacunata* and *Moraxella catarrhalis*), Haemophilus spp. (e.g., *Haemophilus influenza* and *Haemophilus aegyptius*), Pseudomonas spp. (e.g., *Pseudomonas aeruginosa*, and, for otic infections, *Pseudomonas otitidis),* Serratia spp. (e.g., *Serratia marcescens*), Neisseria spp., and Mycoplasma spp., as well as Enterobacter spp. (e.g., *Enterobacter aerogenes*), Eschericia spp. (e.g., *Eschericia coli*), Klebsiella spp. (e.g., *Klebsiella pneumoniae*), Proteus spp. (e.g., *Proteus mirabillis* and *Proteus vulgaris),* Acinetobacter spp. (e.g., *Acinetobacter calcoaceticus),* Prevotella spp., Fusobacterium spp., Porphyromonas spp., and Bacteroides spp. (e.g., *Bacteroides fragilis).* This list of microbes is purely illustrative and is in no way to be interpreted as restrictive.

[0074] Thus, for example, the ophthalmic compositions of the present invention can be administered to treat or prevent a bacterial infection of the eye caused by one or more of the following species: *Staphylococcus aureus*, *Staphylococcus epidermidis, Streptococcus pneumoniae*, *Streptococcus pyogenes, Streptococcus viridans*, *Enterococcus faecalis*, Corynebacterium spp., Propionibacterium spp., *Moraxella catarrhalis* and *Haemophilus influenzae.*

[0075] For example, treatment of bacterial conjunctivitis by administering an ophthalmic composition of the present invention is appropriate where infection with one or more of the following species is present: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes, Streptococcus viridans, Enterococcus faecalis*, Corynebacterium spp., Propionibacterium spp., *Moraxella catarrhalis* and *Haemophilus influenzae.*

[0076] Similarly, treatment of bacterial blepharitis by administering an ophthalmic composition of the present invention is appropriate where infection with one or more of the following species is present: *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pneumoniae.* Treatment of bacterial keratitis by administering an ophthalmic composition of the present invention is also appropriate where infection with one or more of the following species is present: *Staphylococcus aureus*, *Staphylococcus epidermidis, Streptococcus pneumoniae* and *Streptococcus viridans.*

[0077] The otic compositions of the present invention, for example, can also be administered to treat or prevent a bacterial infection of the ear caused by one or more of the following species: *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis, Streptococcus pneumoniae*, *Moraxella catarrhalis, Pseudomonas otitidis,* and Proteus spp. (e.g., *Proteus mirabillis* and *Proteus vulgaris*), as well as one or more of the following anaerobes: Prevotella spp., Fusobacterium spp., Porphyromonas spp., and Bacteroides spp. (e.g., *Bacteroides fragilis).* Thus, for example, treatment of chronic suppurative otitis media by administering an otic composition of the present invention is appropriate where infection with one or more of the following species is present: *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Eschericia coli*, Klebsiella spp. (e.g., *Klebsiella pneumoniae*), Proteus spp. (e.g., *Proteus mirabillis* and *Proteus vulgaris),* Prevotella spp., Fusobacterium spp., Porphyromonas spp., and Bacteroides spp. (e.g., *Bacteroides fragilis*).

[0078] The ophthalmic or otic compositions are also useful in killing or inhibiting the growth of clinically relevant ocular or otic fungi, and can be administered topically to treat and/or prevent ophthalmic or otic infections caused by one or more species of fungi, or a mixture of species of fungi, including, but not limited to, Aspergillus spp. (e.g., *Aspergillus fumigatus, Aspergillus favus, Aspergillus niger* and *Aspergillus terreus),* Fusarium spp. (e.g., *Fusarium solani, Fusarium moniliforme* and *Fusarium proliferartum*), Malessezia spp. (e.g., *Malessezia pachydermatis*), and/or Candida spp. (e.g., *Candida albicans*), as well as *Chrysosporium parvum*, *Metarhizium anisopliae*, *Phaeoisaria clematidis,* and *Sarcopodium oculorum.* This list of microbes is purely illustrative and is in no way to be interpreted as restrictive.

[0079] Thus, the ophthalmic compositions of the present invention can be administered to treat or prevent a fungal infection of the eye caused by one or more of the following species: Aspegillus spp., Fusarium spp., *Chrysosporium parvum*, *Metarhizium anisopliae*, *Phaeoisaria clematidis,* and *Sarcopodium oculorum.* For example, the ophthalmic composition can be administered to treat fungal keratitis caused by one or more Aspergillus spp. and/or Fusarium spp.

[0080] The otic compositions of the present invention, for example, can also be administered to treat or prevent a fungal infection of the ear caused by one or more of the following species: Candida spp., Aspegillus spp., and/or Malessezia spp. (e.g., *Malessezia pachydermatis*).

[0081] The ophthalmic or otic compositions are also useful in killing or inhibiting the growth of clinically relevant ocular

or otic viruses and can be administered topically to treat and/or prevent ophthalmic or otic infections caused by one or more viruses, including, but not limited to, adenoviruses and herpes viruses (including, e.g., Herpes simplex 1 virus and/or varicellazoster virus), Eneroviruses and Cytomegaloviruses.

[0082] Thus, for example, the ophthalmic compositions of the present invention can be administered to treat or prevent a viral infection of the eye, e.g., Herpes keratitis, caused by Herpes simplex 1 virus.

[0083] In some embodiments, the ophthalmic or otic compositions of the invention are useful and effective in killing and/or preventing the growth of microbes that have developed significant levels of resistance to anti-microbial agents other than the disclosed oligomer. For example, in some embodiments, the ophthalmic compositions and otic compositions are especially effective in methods of treating ophthalmic infections or otic infections cased by bacterial strains that have developed resistance to ciprofloxacin, e.g., Ciprofloxacin Resistant (CR) *S. aureus* and CR *S. epidermidis,* or to fluoroquinolone, or bacterial strains that have developed resistance to penicillin.

[0084] In some embodiments, the compositions of the invention are administered topically to one or more tissues of the eye or ear to treat an existing microbial infection, or as a prophylactic measure to prevent a microbial infection.

[0085] Thus, for example, in some embodiments, an ophthalmic composition of the present invention is administered topically to one or more tissues of the eye to treat an existing microbial infection, e.g., conjunctivitis, keratitis, blepharitis, or blepharoconjunctivitis.

[0086] In other embodiments, an ophthalmic composition of the present invention is administered topically to one or more tissues of the eye as a prophylactic measure. That is, the compositions are administered for prophylactic uses, e.g., in connection with various ophthalmic surgical procedures that create a risk of infection. Thus, for example, a composition of the invention can be administered in a method of post-traumatic prophylaxis, especially post-surgical prophylaxis, to prevent infection after ocular surgery, or in a method of prophylaxis prior to ocular surgery, for example, administered prior to surgery to prevent infection as a consequence of surgery.

[0087] The ophthalmic and otic compositions of the present invention possess broad-spectrum anti-microbial activity due to the facially amphiphilic and cationic properties of the facially amphiphilic oligomer in the compositions. As a consequence, an ophthalmic infection or an otic infection can be treated or prevented by administering only one of the compositions of the present invention, rather than by administering two or more separate antimicrobial compositions or one antimicrobial composition containing a combination of antimicrobial agents.

[0088] For example, because the ophthalmic compositions of the invention can be used to treat or prevent both viral and bacterial ophthalmic infections in an eye, only one of the present compositions needs to be administered to the eye to treat a viral ophthalmic infection where there is a risk of a secondary bacterial infection. Similarly, for an eye infection caused by multiple strains of bacteria (e.g., by both gram-positive bacteria and gram-negative bacteria), only one composition containing one of the disclosed amphiphilic oligomers needs to be administered, rather than a composition containing multiple anti-microbial agents, or a combination of separate treatments administered concurrently.

[0089] In some embodiments, the ophthalmic or otic compositions of the present invention are administered with an additional anti-microbial agent, such as, e.g., an anti-bacterial, anti-fungal, or anti-viral agent. For example, the additional anti-microbial agent can be a second facially amphiphilic oligomer disclosed herein, or the additional anti-microbial agent can be another anti-microbial agent such as, for example, an antibiotic selected from the group consisting of aminoglycosides, cephalosporins, diaminopyridines, fluoroquinolones, sulfonamides and tetracyclines. Examples of useful antibiotics which can serve as additional anti-microbials include, but are not limited to, amikacin, azithromycin, cefixime, cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, chloramphenicol, ciprofloxacin, clindamycin, colistin, domeclocycline, doxycycline, erythromycin, gentamicin, mafenide, methacycline, minocycline, neomycin, norfloxacin, ofloxacin, oxytetracycline, polymyxin B, pyrimethamine, silver sulfadiazine, sulfacetamide, sulfisoxazole, tetracycline, tobramycin, and trimethoprim.

[0090] In those embodiments in which the ophthalmic or otic composition is administered with another anti-microbial agent, the present invention provides a method of treating or preventing multiple bacterial infections in an eye or an ear, the method comprising application to the eye or ear in co-therapy (including co-formulation) one or more facially amphiphilic polymers or oligomers disclosed herein and one or more additional anti-microbial agents. "Co-therapy" herein means administration to the eye or ear, at the same time or sequentially, of an ophthalmically or otically acceptable composition comprising one or more of the facially amphiphilic polymers or oligomers disclosed herein and a separate ophthalmically or otically acceptable composition of the additional anti-microbial agent, in a treatment regimen intended to provide a beneficial effect from co-action of the two types of antimicrobial agents. "Co-formulation" herein means that the facially amphiphilic oligomer active agent and the additional anti-microbial agent are administered to the eye or ear as components of a single ophthalmically or otically acceptable composition.

[0091] The ophthalmic or otic compositions of the present invention also can be used in co-therapy with one or more drugs, or medicaments, other than anti-microbial agents. Such medicaments other than anti-microbial agents can be co-administered to the eye or ear together with a composition of the invention. Thus, e.g., an ophthalmic composition of the present invention can further comprise, in co-formulation with the facially amphiphilic oligomer active agent, a therapeutically and/or prophylactically effective amount of one or more medicaments that are other than anti-microbial

agents.

[0092] These additional medicaments other than anti-microbial agents can cooperate with the anti-microbial facially amphiphilic oligomer active agent(s) in treating and/or preventing an infective disease of the eye or ear, or can be used to treat a related or unrelated condition simultaneously affecting the eye or ear.

[0093] Any medicament having utility in an ophthalmic or otic application can be used in co-therapy, co-administration or co-formulation with an ophthalmic or otic composition of the present invention as described above. Such additional medicaments include, but are not limited to, anti-inflammatory agents (e.g., steroidal anti-inflammatory agents, non-steroidal anti-inflammatory agents (NSAIDs), and selective cyclooxygenase-2 inhibitors); topical and/or regional anesthetic agents; anti-allergic agents (e.g., anti-histamines); demulcents; acetylcholine blocking agents; adrenergic agonists, beta-adrenergic blocking agents and other anti-glaucoma agents; anti-hypertensives; and anti-cataract agents.

[0094] For example, ophthalmic and otic infections are frequently accompanied by inflammation of the infected ophthalmic and/or otic tissues and surrounding tissues. In addition, ophthalmic and otic surgical procedures that create a risk of microbial infections frequently also causes inflammation of the affected tissues. Thus, the ophthalmic and otic compositions of the present invention can be co-formulated with an anti-inflammatory agent to combine the anti-infective activity of one or more antibiotics with the anti-inflammatory activity of one or more steroid or non-steroid agents in a single composition.

[0095] The anti-inflammatory agents can be steroidal or non-steroidal. Examples of suitable steroidal anti-inflammatory agents include, but are not limited to, dexamethasone; dexamethasone derivatives such as those disclosed in US pat. No. 5,223,492; rimexolone; prednisolone; fluorometholone; and hydrocortisone.

[0096] Examples of suitable non-steroidal anti-inflammatory agents include, but are not limited to, prostaglandin H synthetase inhibitors (Cos I or Cox II), also referred to as cyclooxygenase type I and type II inhibitors, such as diclofenac, flurbiprofen, ketorolac, suprofen, nepafenac, amfenac, indomethacin, naproxen, ibuprofen, bromfenac, ketoprofen, meclofenamate, piroxicam, sulindac, mefanamic acid, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, tenoxicam and carprofen; cyclooxygenase type II selective inhibitors, such as vioxx, celecoxib, etodolac; PAF antagonists, such as apafant, bepafant, minopafant, nupafant and modipafant; PDE IV inhibitors, such as ariflo, torbafylline, rolipram, filaminast, piclamilast, cipamfylline, and roflumilast; inhibitors of cytokine production, such as inhibitors of the NFkB transcription factor; or other anti-inflammatory agents know to those skilled in the art.

[0097] Examples of suitable topical or regional anesthetic agents include, but are not limited to, benzocaine.

[0098] Examples of suitable anti-allergic agents include, but are not limited to, pemirolast, olopatadine, and the corticosteroids (prednisolone, fluorometholone, loteprenol and dexamthasone).

[0099] The additional medicament can be administered in co-therapy (including co-formulation) with the one or more facially amphiphilic polymers of the ophthalmic or otic composition. For example, in some embodiments, an ophthalmic composition of the present invention comprising one of the anti-microbial oligomer disclosed herein is administered in co-therapy with an anti-inflammatory agent, e.g., a glucocorticoid. The glucocorticoid can be co-formulated with the oligomer in a single ophthalmically acceptable composition, which is administered to one or more tissues of an eye, to not only treat or prevent an ophthalmic infection but also to treat and/or prevent inflammation.

[0100] The ophthalmic or otic compositions can be administered by any appropriate route of administration. In some aspects of the invention, the ophthalmic and otic compositions are administered topically, for example, the composition is topically administered in an antimicrobially effective amount to one or more tissues of the eye of the animal, or to one or more tissues of the ear of an animal.

[0101] An appropriate dosage, frequency and duration of administration, for example, treatment regimen, to be used in any particular situation will be readily determined by one of skill in the art without undue experimentation, and will depend, among other factors, on the particular polymer(s) or oligomer(s) present in the composition, on the particular ophthalmic infection being treated, on the age, weight and general physical condition of the subject, and on other medication being administered to the subject. It is preferred that response of the ophthalmic or otic infection to treatment according to the present methods be monitored and the treatment regimen be adjusted if necessary in light of such monitoring.

[0102] Frequency of administration is typically such that the dosing interval, for example, the period of time between one dose and the next, during waking hours is about 2 to about 12 hours, more typically about 3 to about 8 hours, for example about 4 to about 6 hours. It will be understood by those of skill in the art that an appropriate dosing interval is dependent to some degree on the length of time for which the selected composition is capable of maintaining a concentration of the anti-microbial polymer(s) or oligomer(s) in the lacrimal fluid and/or in the target tissue (e.g., the conjunctiva) above the MIC_{90} (the minimum concentration of the oligomer or polymer which inhibits microbial growth by 90%). Ideally the concentration remains above the MIC_{90} for at least 100% of the dosing interval. Where this is not achievable it is desired that the concentration should remain above the MIC_{90} for at least about 60% of the dosing interval, in a worst case at least about 40% of the dosing interval.

[0103] For example, in some embodiments of the ophthalmic compositions of the invention, the ophthalmic composition

is formulated as an *in situ* gellable aqueous liquid and is administered as eye drops. Typically each drop, generated by a conventional dispensing means, has a volume of about 10 to about 40 μL. From 1 to about 6 such drops typically provides a suitable dose of the oligomer active agent in about 25-150 μL of the composition. For example, preferably no more than 3 drops, more preferably no more than 2 drops, and most preferably no more than 1 drop, should contain the desired dose of the active agent for administration to an eye. Where the composition is administered in a form other than eye drops, for example, as an ophthalmic ointment or as a solid implant, an equivalent dose is provided. Such a dose can be administered as needed, but typically administration to the eye 1 to about 6 times per day, in most cases 2 to 4 times a day, provides adequate continuing relief or prevention of the infective disease indicated.

[0104] The ophthalmic compositions of the invention, e.g., the aqueous suspension compositions, can be packaged in single-dose non-reclosable containers. Such containers can maintain the composition in a sterile condition and thereby eliminate need for preservatives such as mercury-containing preservatives, which can sometimes cause irritation and sensitization of the eye. Alternatively, multiple-dose reclosable containers can be used, in which case it is preferred to include a preservative in the composition.

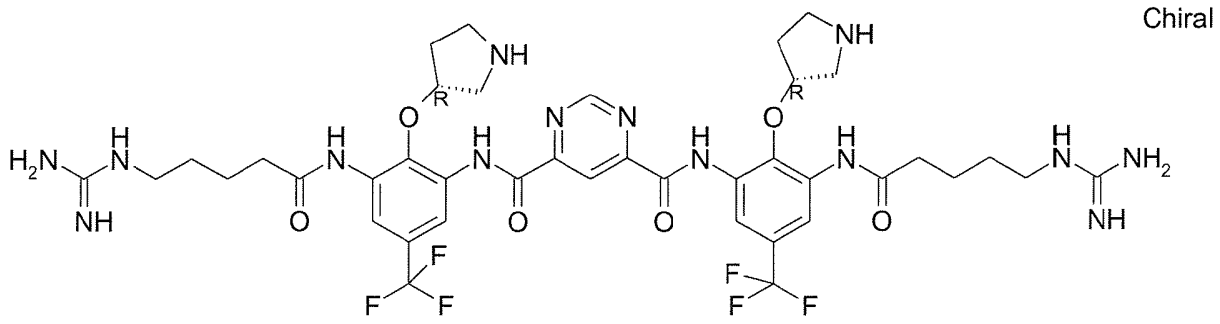
[0105] For example, in some embodiments, the ophthalmic composition is an aqueous solution, suspension or solution/suspension which is administered in the form of eye drops. In these embodiments, a desired dosage of the active agent can be administered by means of a suitable dispenser as a known number of drops into the eye. Examples of suitable dispensers are disclosed in International Patent Publication No. WO 96/06581.

[0106] The following examples will serve to further typify the nature of this invention but should not be construed as a limitation in the scope thereof, which scope is defined solely by the appended claims. In order that the invention disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the invention in any manner.

EXAMPLES

Example 1: Toxicity

[0107] The ocular toxicity of several formulations of Oligomer 4 with and without farnesol, using the Draize ocular toxicity scoring system, in the NZW rabbit ocular toxicity model was carried out.



Oligomer 4

[0108] Fifteen rabbits were received from Myrtles' Rabbitry, Thompson Station, TN and were divided into 8 groups:

Group	Formulation	N Rabbits	N Eyes	Rabbit Numbers
I	0.25% Oligomer 4 in Tris Buffered Saline (TBS)	2	4	1-2
II	0.5% Oligomer 4 Tris Buffered Saline (TBS)	2	4	3-4
III	100μM Farnesol in 1% Propylene Glycol (PG) and TBS	2	4	5-6
IV	200μM Farnesol in 1% Propylene Glycol (PG) and TBS	2	4	7-8
V	0.25% Oligomer 4 + 100μM Farnesol in 1% PG and TBS	2	4	9-10
VI	0.5% Oligomer 4 + 100μM Farnesol in 1% PG and TBS	2	4	11-12
VII	1% Propylene Glycol in TBS	2	4	13-14
VIII	Tris-Buffered Saline	1	2	15

Rabbits were treated in both eyes with (37 μl) topical drops every 30 minutes for 3 hours (7 total doses). One rabbit was treated with Tris-Buffered Saline and served as a negative control. Rabbits were evaluated in a masked fashion for ocular toxicity by an ophthalmologist with specialty training in corneal and external disease 30 minutes after the final dose. Ocular toxicity was evaluated using the Draize scoring system (see above) after treatment on Day 0 and on Day 2 post treatment for any delayed toxicity.

[0109] Formulations: 1) 0.25% Oligomer 4: Vial 1 of Oligomer 4 in powder form was stored at 4°C until use. The vial was removed from the refrigerator and 1.04 ml of sterile water for injection was added and vortexed until solid was completely dissolved. Then, 1.04 ml of Solution A (2X TBS) was added and vortexed for 10 seconds; 2) 0.5% Oligomer 4: Vial 2 of Oligomer 4 in powder form was stored at 4°C until use. The vial was removed from the refrigerator and 1.04 ml of sterile water for injection was added and vortexed until solid was completely dissolved. Then, 1.04 ml of Solution A (2X TBS) was added and vortexed for 10 seconds; 3) 100 μM Farnesol in 1% Propylene Glycol (PG) and TBS: Vial 3 containing about 2 ml of 100μM Farnesol in 1% Propylene Glycol (PG) and TBS was stored at 4°C until use; 4) 200 μM Farnesol in 1% Propylene Glycol (PG) and TBS: Vial 4 containing about 2 ml of 200μM Farnesol in 1% Propylene Glycol (PG) and TBS was stored at 4°C until use; 5) 0.25% Oligomer 4 + 100μM Farnesol in 1% PG and TBS: Vial 5 of Oligomer 4 in powder form was stored at 4°C until use; at the time of use, the vial was removed from the refrigerator and 1.016 ml of sterile water for injection was added and vortexed until solid was completely dissolved; then 1.016 ml of Solution B (2% PG, 2X TBS, 200 μM Farnesol) was added and vortexed for 10 seconds; 6) 0.5% Oligomer 4 + 100μM Farnesol in 1% PG and TBS: Vial 6 of Oligomer 4 in powder form was stored at 4°C until use; at the time of use, the vial was removed from the refrigerator and 1.02 ml of sterile water for injection was added and vortexed until solid was completely dissolved; then 1.02 ml of Solution B (2% PG, 2X TBS, 200 μM Farnesol) was added and vortexed for 10 seconds; 7) 1% Propylene Glycol in TBS: Vial 7 containing about 2 ml of 1% Propylene Glycol was stored at 4°C until use; and 8) Tris-Buffered Saline: Vial 8 containing about 2 ml of Tris-Buffered Saline (10mM TRIS, 150mM NaCl, pH=7.4) was stored at 4°C until use.

[0110] IACUC Protocol #0701145-1 "The In Vivo Evaluation of Biomimetics as Topical Ocular Antibiotics".

			Ocular Toxicity Evaluation			Drop Schedule				
Drop	Elapsed Time	Time of Day	Group I	Group II	Group III	Group IV	Group V	Group VI	Group VII	Group VIII
1	0	10:45	X	X	X	X	X	X	X	X
2	:30	11:15	X	X	X	X	X	X	X	X
3	1:00	11:45	X	X	X	X	X	X	X	X
4	1:30	12:15	X	X	X	X	X	X	X	X
5	2:00	12:45	X	X	X	X	X	X	X	X
6	2:30	1:15	X	X	X	X	X	X	X	X
7	3:00	1:45	X	X	X	X	X	X	X	X
Exam	3:30	2:15	X	X	X	X	X	X	X	X

Acute Ocular Toxicity Evaluation

[0111] Observations of Rabbit Behavior After Instillation of Test Drugs on Day 0

Group	Formulation
I	0.25% Oligomer 4 in Tris Buffered Saline (TBS)
II	0.5% Oligomer 4 Tris Buffered Saline (TBS)
III	100μM Farnesol in 1% Propylene Glycol (PG) and TBS
IV	200μM Farnesol in 1% Propylene Glycol (PG) and TBS
V	0.25% Oligomer 4 + 100μM Farnesol in 1% PG and TBS
VI	0.5% Oligomer 4 + 100μM Farnesol in 1% PG and TBS
VII	1% Propylene Glycol in TBS

(continued)

Group	Formulation
VIII	Tris-Buffered Saline

Drop 1 (10:45 am)
No adverse behavior observed after instillation of ALL test drugs.
Drop 2 (11:15 am)
No adverse behavior observed after instillation of ALL test drugs.
Drop 3 (11:45 am)
No adverse behavior observed after instillation of ALL test drugs.
Drop 4 (12:15 am)
No adverse behavior observed after instillation of ALL test drugs.
Drop 5 (12:45 pm)
No adverse behavior observed after instillation of ALL test drugs.
Drop 6 (1:15 pm)
No adverse behavior observed after instillation of ALL test drugs.
Drop 7 (1:45 pm)
No adverse behavior observed after instillation of ALL test drugs.
Group: I 0.25% Oligomer 4

	Day 0				Day 2			
Test/Eye	1L	1R	2L	2R	1L	1R	2L	2R
I. A.	0	0	0	0	0	0	0	0
I. B.	0	0	0	0	0	0	0	0
I. Tot	0	0	0	0	0	0	0	0
II. A.	0	0	0	0	0	0	0	0
II. Tot	0	0	0	0	0	0	0	0
III. A.	0	0	0	0	0	0	0	0
III. B.	0	0	0	0	0	0	0	0
III. C.	0	1	1	1	0	1	0	0
III. Tot	0	2	2	2	0	2	0	0
Score	0	2	2	2	0	2	0	0
MMTS	1.5 - PN Practically Non-Irritating				0.5-N Non-Irritating			

Group: II 0.5% Oligomer 4

	Day 0				Day 2			
Test/Eye	3L	3R	4L	4R	3L	3R	4L	4R
I. A.	0	0	0	0	0	0	0	0
I. B.	0	0	0	0	0	0	0	0
I. Tot	0	0	0	0	0	0	0	0
II. A.	0	0	0	0	0	0	0	0
II. Tot	0	0	0	0	0	0	0	0
III. A.	1	1	1	0	0	0	0	0
III. B.	1	1	1	0	0	0	0	0

(continued)

	Day 0				Day 2			
Test/Eye	3L	3R	4L	4R	3L	3R	4L	4R
III. C.	2	2	2	1	0	0	1	1
III. Tot	8	8	8	2	0	0	2	2
Score	8	8	8	2	0	0	2	2
MMTS	6.5 - M_1 Minimally Irritating				1.0 - N Practically Non-Irritating			

Group: III 100 μM Farnesol in 1% Propylene Glycol (PG) and TBS

	Day 0				Day 2			
Test/Eye	5L	5R	6L	6R	5L	5R	6L	6R
I. A.	0	0	0	0	0	0	0	0
I. B.	0	0	0	0	0	0	0	0
I. Tot	0	0	0	0	0	0	0	0
II. A.	0	0	0	0	0	0	0	0
II. Tot	0	0	0	0	0	0	0	0
III. A.	0	0	0	0	0	0	0	0
III. B.	0	0	0	0	0	0	0	0
III. C.	0	0	0	0	1	0	1	1
III. Tot	0	0	0	0	2	0	2	2
Score	0	0	0	0	2	0	2	2
MMTS	0.0-N Non-Irritating				1.5 - PN Practically Non-Irritating			

Group: IV 200 μM Farnesol in 1% Propylene Glycol (PG) and TBS

	Day 0				Day 2			
Test/Eye	7L	7R	8L	8R	7L	7R	8L	8R
I. A.	0	0	0	0	0	0	0	0
I. B.	0	0	0	0	0	0	0	0
I. Tot	0	0	0	0	0	0	0	0
II. A.	0	0	0	0	0	0	0	0
II. Tot	0	0	0	0	0	0	0	0
III. A.	0	0	0	0	0	0	0	0
III. B.	0	0	0	0	0	0	0	0
III. C.	0	0	0	1	0	0	0	1
III. Tot	0	0	0	2	0	0	0	2
Score	0	0	0	2	0	0	0	2
MMTS	0.5 - N Non-Irritating				0.5 - N Non-Irritating			

Group: V 0.25% Oligomer 4 + 100 μM Farnesol in 1% PG and TBS

	Day 0				Day 2			
Test/Eye	9L	9R	10L	10R	9L	9R	10L	10R
I. A.	0	0	0	0	0	0	0	0
I. B.	0	0	0	0	0	0	0	0
I. Tot	0	0	0	0	0	0	0	0
II. A.	0	0	0	0	0	0	0	0
II. Tot	0	0	0	0	0	0	0	0
III. A.	0	1	0	0	0	0	0	0
III. B.	0	1	0	0	0	0	0	0
III. C.	0	2	1	1	0	1	1	1
III. Tot	0	8	2	2	0	2	2	2
Score	0	8	2	2	0	2	2	2
MMTS	3.0 - M_1 Minimally Irritating				1.5 - PN Practically Non-Irritating			

Group: VI 0.5% Oligomer 4 + 100 μM Farnesol in 1% PG and TBS

	Day 0				Day 2			
Test/Eye	11L	11R	12L	12R	11L	11R	12L	12R
I. A.	0	0	0	0	0	0	0	0
I. B.	0	0	0	0	0	0	0	0
I. Tot	0	0	0	0	0	0	0	0
II. A.	0	0	0	0	0	0	0	0
II. Tot	0	0	0	0	0	0	0	0
III. A.	2	2	2	2	0	0	0	0
III. B.	1	2	1	1	0	0	0	0
III. C.	2	2	2	2	1	0	1	0
III. Tot	10	12	10	10	2	0	2	0
Score	10	12	10	10	2	0	2	0
MMTS	10.5 - M_1 Minimally Irritating				1.0-PN Practically Non-Irritating			

Group: VII 1% Propylene Glycol in TBS

	Day 0				Day 2			
Test/Eye	13L	13R	14L	14R	13L	13R	14L	14R
I. A.	0	0	0	0	0	0	0	0
I. B.	0	0	0	0	0	0	0	0
I. Tot	0	0	0	0	0	0	0	0
II. A.	0	0	0	0	0	0	0	0
II. Tot	0	0	0	0	0	0	0	0
III. A.	0	0	0	0	0	0	0	0

(continued)

	Day 0				Day 2			
Test/Eye	13L	13R	14L	14R	13L	13R	14L	14R
III. B.	0	0	0	0	0	0	0	0
III. C.	0	1	0	0	1	1	0	1
III. Tot	0	2	0	0	2	2	0	2
Score	0	2	0	0	2	2	0	1
MMTS	0.5 - N Non-Irritating				1.5 - PN Practically Non-Irritating			

Group: VIII TBS Treated Control

	Day 0		Day 2	
Test/Eye	15L	15R	15L	15R
I. A.	0	0	0	0
I. B.	0	0	0	0
I. Tot	0	0	0	0
II. A.	0	0	0	0
II. Tot	0	0	0	0
III. A.	0	0	0	0
III. B.	0	0	0	0
III. C.	1	1	1	1
III. Tot	2	2	2	2
Score	2	2	2	2
MMTS	2.0 - PN Practically Non-Irritating		2.0 - PN Practically Non-Irritating	

Summary of MMTS Results

[0112]

Group	Day 0	Day 2
0.25% Oligomer 4 in Tris Buffered Saline (TBS)	1.5 - PN Practically Non-Irritating	0.5 - N Non-Irritating
0.5% Oligomer 4 Tris Buffered Saline (TBS)	6.5 - M_1 Minimally Irritating	1.0 - N Practically Non-Irritating
100 μM Farnesol in 1% Propylene Glycol (PG) and TBS	0.0 - N Non-Irritating	1.5 - PN Practically Non-Irritating
200 μM Farnesol in 1% Propylene Glycol (PG) and TBS	0.5 - N Non-Irritating	0.5 - N Non-Irritating
0.25% Oligomer 4 + 100μM Farnesol in 1% PG and TBS	3.0 - M_1 Minimally Irritating	1.5-PN Practically Non-Irritating
0.5% Oligomer 4 + 100μM Farnesol in 1 % PG and TBS	10.5 - M_1 Minimally Irritating	1.0 - PN Practically Non-Irritating
1% Propylene Glycol in TBS	0.5 - N Non-Irritating	1.5-PN Practically Non-Irritating

(continued)

Group	Day 0	Day 2
Tris-Buffered Saline	2.0 - PN Practically Non-Irritating	2.0 - PN Practically Non-Irritating

[0113] Oligomer 4 demonstrated dose dependent ocular toxicity after 7 topical instillations (every 30 minutes for 3 hours) in the NZW rabbit ocular toxicity model. 0.5% Oligomer 4 was determined to be Mildly Irritating, while 0.25% was determined to be Practically Non-Irritating. The addition of 100 μM Farnesol in 1% Propylene Glycol to the Oligomer 4 concentrations increased the toxicity of both 0.5% and 0.25% Oligomer 4. Both formulations were determined to be Mildly Irritating. This was the same category as 0.5% Oligomer 4 alone, but the scores were higher. This classification was an increase for 0.25% Oligomer 4. 100 μM Farnesol, 200 μM Farnesol, and 1% Propylene Glycol individually were determined to be Non-Irritating. Tris-buffered Saline was determined to be Practically Non-Irritating. Rabbits demonstrated no adverse behavior upon instillation of any the test drugs. This indicates all of the test drugs did not sting upon instillation. There was really no prolonged or delayed toxicity (2 days after drops) demonstrated in any treatment group. The only finding on Day 2 was a slight discharge in some of the eyes which accounted for all of the scores. Although the complete formulations of 0.5% Oligomer 4 and 0.25% Oligomer 4 (including 100 μM Farnesol and 1% Propylene Glycol) were both classified as Mildly Irritating, the MMTS score for the 0.5% Oligomer 4 formulation was at the higher end of the classification whereas 0.25% Oligomer 4 formulation was at the lower end of the classification. It appears that the complete 0.5% Oligomer 4 formulation (including 100 μM Farnesol and 1% Propylene Glycol), though Mildly Irritating in uninfected eyes is probably not as suitable as other formulations for use in the efficacy studies in the *Staphylococcus aureus* keratitis model. The complete formulation of 0.25% Oligomer 4 (including 100 μM Farnesol and 1% Propylene Glycol) may be acceptable from a toxicity point of view. Experience with other formulations have generally shown that ocular toxicity can increase when instilled more frequently (21 drops vs. 7 drops) in infected eyes in the *Staphylococcus aureus* keratitis efficacy model.

Example 2: MIC

[0114] One purpose of the follwing experiments was to determine the MICs of two biomimetic compounds vs. 25 ocular isolates of *Staphylococcus aureus* fluoroquinolone-susceptible, *Staphylococcus aureus* fluoroquinolone-resistant, *Staphylococcus epidermidis* (Coagulase-negative *Staphylococcus*) fluoroquinolone-susceptible, *Staphylococcus epidermidis* (Coagulase-negative *Staphylococcus)* fluoroquinolone-resistant, *Serratia marcescens*, *Streptococcus pneumoniae*, *Streptococcus viridans* group, *Moraxella* species (including *Moraxella catarrhalis*) and *Pseudomonas aeruginosa* and *Haemophilus influenzae.*

General Procedures:

[0115] Mueller-Hinton Broth in tubes was inoculated with 25 ocular isolates of *Staphylococcus aureus* fluoroquinolone-susceptible, *Staphylococcus aureus* fluoroquinolone-resistant, *Staphylococcus epidermidis* (Coagulase-negative *Staphylococcus*) fluoroquinolone-susceptible, *Staphylococcus epidermidis* (Coagulase-negative *Staphylococcus)* fluoroquinolone-resistant, *Pseudomonas aeruginosa* and *Serratia marcescens*, plus two controls (*Staphylococcus aureus* and *E. coli)* and incubated at 37°C overnight on a shaker set at 250 rpm.

[0116] Mueller-Hinton Broth supplemented with 2% lysed horse blood in tubes was inoculated with 25 ocular isolates of *Streptococcus pneumoniae*, *Streptococcus viridans* group, and *Moraxella* species (including *Moraxella catarrhalis*) plus two controls (*Staphylococcus aureus* and *E. coli*) and incubated at 37°C overnight. Additionally, Mueller-Hinton Broth in tubes was inoculated with two controls (*Staphylococcus aureus* and *E. coli*) and incubated at 374°C overnight on a shaker set at 250 rpm.

[0117] HTM (*Haemophilus* Test Medium) in tubes was inoculated with 25 ocular isolates of *Haemophilus influenzae* plus two controls *(Staphylococcus aureus* and *E. coli)* and incubated at 37°C overnight. Additionally, Mueller-Hinton Broth in tubes was inoculated with two controls (*Staphylococcus aureus* and *E. coli*) and incubated at 37°C overnight on a shaker set at 250 rpm.

[0118] On the day of testing, a 640 μg/ml (1280 μg/ml for *Serratia marcescens* and *Pseudomonas aeruginosa*) concentration was prepared from a 1% stock solution in 0.01% acetic acid, 0.2% BSA in polypropylene tubes.

[0119] Serial doubling dilutions in 0.01% acetic acid, 0.2% BSA in 96 well polypropylene plates, which are used as reservoirs for the inoculation of the test plates, were carried out to obtain serial dilutions of test agents at 10 times the required test concentrations: 640, 320, 160, 80, 40, 20, 10, 5, 2.5, 1.25, and 0.625 μg/ml (1280, 640, 320, 160, 80, 40, 20, 10, 5, 2.5, and 1.25 μg/ml for *Serratia marcescens* and *Pseudomonas aeruginosa*).

[0120] Ten μl of diluted 10x test agents was added to each well of one row of the 96 well polypropylene plates from column 2 to column 12 (column 1 is a control for bacteria alone, with no peptide). Test agent concentrations in columns 2-12 were as follows: 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125, and 0.0625 μg/ml (128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, and 0.125 μg/ml for *Serratia marcescens* and *Pseudomonas aeruginosa*). The same peptide was in each of the 8 rows. One plate contained dilutions of one test agent and 8 bacterial isolates.

[0121] On the day of testing, the overnight bacterial broth cultures of *Staphylococcus aureus* fluoroquinolone-susceptible, *Staphylococcus aureus* fluoroquinolone-resistant, *Staphylococcus epidermidis* (Coagulase-negative *Staphylococcus)* fluoroquinolone-susceptible, *Staphylococcus epidermidis* (Coagulase-negative *Staphylococcus*) fluoroquinolone-resistant, *Serratia marcescens*, *and Pseudomonas aeruginosa*, plus two controls (*Staphylococcus aureus* and *E. coli)* were diluted in 5 ml of trypticase soy broth to yield turbidity equal to a 0.5 McFarland standard. The final inoculum for MIC testing for *Staphylococcus aureus* fluoroquinolone-susceptible, *Staphylococcus aureus* fluoroquinolone-resistant, *Staphylococcus epidermidis* (Coagulase-negative *Staphylococcus*) fluoroquinolone-susceptible, *Staphylococcus epidermidis* (Coagulase-negative *Staphylococcus*) fluoroquinolone-resistant, *Serratia marcescens*, *and Pseudomonas aeruginosa* was achieved by placing 0.05 ml of the turbidity adjusted sample to 5 ml of Mueller-Hinton broth.

[0122] Control Bacteria - The two control bacteria (*Staphylococcus aureus* and *E. coli)* were treated as above.

[0123] On the day of testing, the overnight bacterial broth cultures of *Streptococcus pneumoniae*, *Streptococcus viridans* and *Moraxella* species (including *Moraxella catarrhalis*) plus two controls (*Staphylococcus aureus* and *E. coli)* were diluted in 5 ml of trypticase soy broth to yield turbidity equal to a 0.5 McFarland standard. The final inoculum for MIC testing for *Streptococcus pneumoniae*, *Streptococcus viridans* and *Moraxella* species (including *Moraxella catarrhalis*) was achieved by placing 0.1 ml of the turbidity adjusted sample to 5 ml of Mueller-Hinton broth containing 2% lysed horse red blood cells.

[0124] Control Bacteria Set #1 - this set of control bacteria were treated as the *Streptococcus pneumoniae*, *Streptococcus viridans* and *Moraxella* species (including *Moraxella catarrhalis*) test isolates above; the control bacteria underwent the same conditions as the test *Streptococcus pneumoniae*, *Streptococcus viridans* and *Moraxella* species (including *Moraxella catarrhalis*) isolates. This set of control bacteria was to determine whether there was a difference in the MICs by performing the MIC determinations in 2% lysed horse red blood cells with the standard method performed in Mueller-Hinton broth.

[0125] Control Bacteria Set #2 - the control bacteria were added to 5 ml of Mueller-Hinton Broth without the 2% lysed horse red blood cells to achieve the standard inoculum concentration. This set of control bacteria is the normal control to determine whether the PMX compounds are at the target MICs.

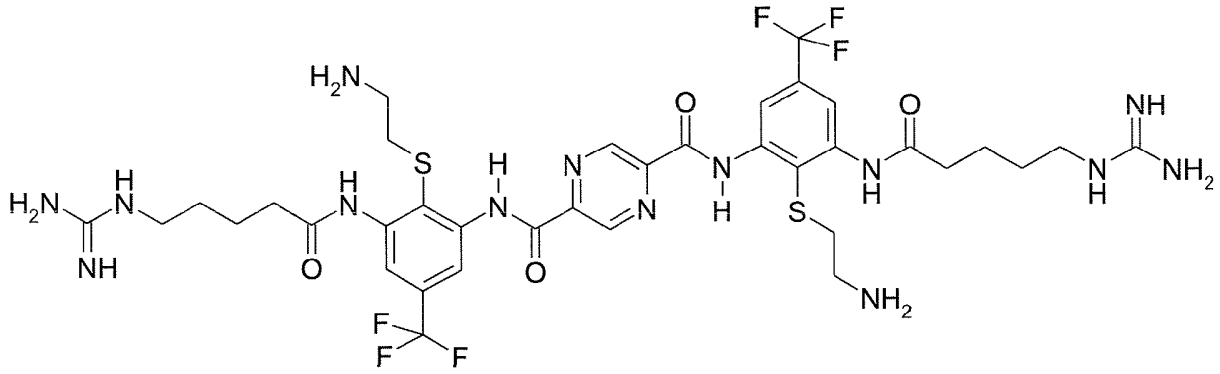
[0126] On the day of testing, the overnight bacterial broth cultures of *Haemophilus species* was diluted in 5 ml of trypticase soy broth to yield turbidity equal to a 0.5 McFarland standard. The final inoculum for MIC testing for *Haemophilus species* was achieved by placing 0.1 ml of the turbidity adjusted sample to 5 ml of HTM medium.

[0127] Control Bacteria Set #1 - this set of control bacteria were treated as the *Haemophilus influenzae* test isolates above; the control bacteria underwent the same conditions as the test *Haemophilus influenzae* isolates. This set of control bacteria is to determine whether there was a difference in the MICs by performing the MIC determinations in HTM broth with the standard method performed in Mueller-Hinton broth.

[0128] Control Bacteria Set #2 - the control bacteria were added to 5 ml of Mueller-Hinton Broth to achieve the standard inoculum concentration. This set of control bacteria is the normal control to determine whether the PMX compounds are at the target MICs.

[0129] Ninety μl of the bacterial suspensions was dispensed in each well from column 1 to column 12. Each bacterial isolate was placed in one row of a 96 well polypropylene plate containing the test agents. The plates were placed on shaker at 15 minutes at room temperature, and then incubated at 37°C overnight. MICs were determined visually as the lowest concentration of drug that inhibits visible bacterial growth.

[0130] The MICs of the 2 compounds Oligomer 4 and Oligomer 5 were compared statistically with the Kruskal-Wallis ANOVA with Duncan's Multiple Comparisons Test using True Epistat statistical software (True Epistat, Richardson, TX).



Oligomer 5 (comparative)

Oligomer	MIC (ug/mL)	
	E.coli D31	S.aureus ATCC27660
Oligomer 4	0.78	0.098
Oligomer 5	1.56	0.78

Compound	*E. coli* Lab Strain D31	*S. aureus* ATCC 27660	*E. faecalis* ATCC 29212	*P. aeruginosa* ATCC 10145	*K. pneumoniae* Lab Strain KP10
Oligomer 4	0.78	0.098	0.78	12.5	0.78
Oligomer 5	1.56	0.78	1.56	>100	1.56

[0131] Isolate numbers with a "K" before the number indicates they have been isolated from cases of Keratitis. Isolate numbers with an "E" before the number indicates they have been isolated from cases of Endophthalmitis. Isolate numbers with a "B" before the number indicates they have been isolated from cases of Blepharitis and or Conjunctivitis. Most *Streptococcus pneumoniae* isolates are from cases of conjunctivitis. "Fluoroquinolone-resistant" indicates the bacteria are resistant to the second generation fluoroquinolones ciprofloxacin and ofloxacin but, not necessarily resistant to the fourth generation fluoroquinolones gatifloxacin and moxifloxacin by CLSI serum standards.

S. aureus fluoroquinolone-susceptible	MICs μg/ml	
Isolate	Oligomer 4	Oligomer 5
1 - E402	0.25	0.5
2 - E1512	0.25	0.25
3 - E253	0.25	0.25
4 - K1518	0.25	0.125
5 - K1525	0.125	0.125
6 - K1663	0.5	0.125
7 - K1648	0.25	0.125
8 - K1646	0.25	0.25
9 - K1642	0.5	0.25
10 - K1638	0.5	0.25
11 - K1628	0.25	0.25
12 - K1618	0.5	0.125

(continued)

S. aureus fluoroquinolone-susceptible	MICs μg/ml	
Isolate	Oligomer 4	Oligomer 5
13 - K1617	0.25	0.25
14 - K1611	0.25	0.25
15 - K1607	0.25	0.25
16 - K1600	0.25	0.125
17 - K1591	0.25	0.5
18 - K1585	0.25	0.25
19 - K1583	0.25	0.25
20 - K1574	0.25	0.25
21 - K1566	0.25	0.25
22 - K1551	0.25	0.125
23 - K1545	0.25	0.25
24 - K1540	0.25	0.25
25 - K1530	0.25	0.5
***E. coli* D31**	1 (0.78)	16 (1.56)
***S. aureus* ATCC 27660**	2 (0.098)	16 (0.78)

[0132] MICs for Control Bacteria *(E. coli, S. aureus)* are within the parentheses.

S. aureus fluoroquinolone-susceptible
MIC_{50} and MIC_{90} Determinations and Statistics

Row	Oligomer 4 QSSA-A	Oligomer 5 QSSA-A	
1	0.125	0.125	
2	0.250	0.125	
3	0.250	0.125	
4	0.250	0.125	
5	0.250	0.125	
6	0.250	0.125	
7	0.250	0.125	
8	0.250	0.250	
9	0.250	0.250	
10	0.250	0.250	
11	0.250	0.250	
12	0.250	0.250	
13	0.250	0.250	MIC_{50}
14	0.250	0.250	
15	0.250	0.250	
16	0.250	0.250	
17	0.250	0.250	
18	0.250	0.250	
19	0.250	0.250	
20	0.250	0.250	
21	0.250	0.250	
22	0.500	0.250	MIC_{90}

(continued)

S. aureus fluoroquinolone-susceptible
MIC_{50} and MIC_{90} Determinations and Statistics

Row	Oligomer 4 QSSA-A	Oligomer 5 QSSA-A
23	0.500	0.500
24	0.500	0.500
25	0.500	0.500

Descriptive Statistics

[0133]

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Median	Maximum
Olig 4 QSSA	25	0	0.2850	0.0198	0.0990	0.1250	0.2500	0.5000
Olig 5 QSSA	25	0	0.2450	0.0222	0.1111	0.1250	0.2500	0.5000

Summary of Results

[0134]

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	0.25 μg/ml	0.25 μg/ml	0.25 μg/ml	0.125 - 0.5 μg/ml
Oligomer 5	0.25 μg/ml	0.5 μg/ml	0.25 μg/ml	0.125 - 0.5 μg/ml

Mann-Whitney Test and CI: Oligomer 4 QSSA, Oligomer 5 QSSA

[0135]

	N	Median
Olig 4 QSSA	25	0.2500
Olig 5 QSSA	25	0.2500

Point estimate for ETA1-ETA2 is 0.0000
95.2 Percent CI for ETA1-ETA2 is (-0.0000, 0.1250)
W = 712.5
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.1483
The test is significant at 0.0731 NS (adjusted for ties)

S. aureus fluoroquinolone-resistant	MICs μg/ml	
Isolate	Oligomer 4	Oligomer 5
1 - E504	0.25	0.5
2 - E475	0.25	0.25
3 - E442	0.25	0.25
4 - E427	0.5	0.5
5 - E425	0.25	0.25
6 - E424	0.25	0.25
7 - E417	1	0.25
8 - E407	0.25	0.125
9 - E401	0.25	0.25

(continued)

S. aureus fluoroquinolone-resistant	MICs μg/ml	
Isolate	Oligomer 4	Oligomer 5
10 - K1659	0.25	0.25
11 - E96	0.125	0.25
12 - E379	0.5	0.5
13 - E369	0.125	0.5
14 - E361	0.25	0.25
15 - E339	0.25	0.25
16 - E333	0.25	0.125
17 - E332	0.25	0.25
18 - E327	0.5	0.25
19 - E325	0.5	0.25
20 - K950	0.5	0.25
21 - K839	0.25	0.25
22 - K1679	0.25	0.25
23 - K1677	0.25	0.5
24 - K1672	0.25	0.25
25 - K1670	0.25	0.25
***E. coli* D31**	1 (0.78)	4 (1.56)
***S. aureus* ATCC 27660**	1 (0.098)	8 (0.78)

[0136] MICs for Control Bacteria *(E. coli, S. aureus)* are within the parentheses.

S. aureus fluoroquinolone-resistant

MIC_{50} and MIC_{90} Determinations and Statistics

Row	Oligomer 4 QRSA-A	Oligomer 5 QRSA-A	
1	0.125	0.125	
2	0.125	0.125	
3	0.250	0.250	
4	0.250	0.250	
5	0.250	0.250	
6	0.250	0.250	
7	0.250	0.250	
8	0.250	0.250	
9	0.250	0.250	
10	0.250	0.250	
11	0.250	0.250	
12	0.250	0.250	
13	0.250	0.250	MIC_{50}
14	0.250	0.250	
15	0.250	0.250	
16	0.250	0.250	
17	0.250	0.250	
18	0.250	0.250	

(continued)

S. aureus fluoroquinolone-resistant

MIC_{50} and MIC_{90} Determinations and Statistics

Row	Oligomer 4 QRSA-A	Oligomer 5 QRSA-A	
19	0.250	0.250	
20	0.500	0.250	
21	0.500	0.500	
22	0.500	0.500	MIC_{90}
23	0.500	0.500	
24	0.500	0.500	
25	1.000	0.500	

Descriptive Statistics

[0137]

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Median	Maximum
Olig 4 QRSA	25	0	0.3200	0.0361	0.1807	0.1250	0.2500	1.0000
Olig 5 QRSA	25	0	0.2900	0.0225	0.1125	0.1250	0.2500	0.5000

Summary of Results

[0138]

	MIC50	MIC90	Median MIC	Range of MICs
Oligomer 4	0.25 μg/ml	0.5 μg/ml	0.25 μg/ml	0.125 - 1.0 μg/ml
Oligomer 5	0.25 μg/ml	0.5 μg/ml	0.25 μg/ml	0.125 - 0.5 μg/ml

Mann-Whitney Test and CI: Oligomer 4 QRSA, Oligomer 5 QRSA

[0139]

	N	Median
Olig 4 QRSA	25	0.2500
Olig 5 QRSA	25	0.2500

Point estimate for ETA1-ETA2 is -0.0000
95.2 Percent CI for ETA1-ETA2 is (-0.0000, 0.0000)
W = 651.5
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.7934
The test is significant at 0.7450 NS (adjusted for ties)

Control Bacteria

[0140] During the first sets of MICs performed with the *S. aureus* fluoroquinolone-susceptible and *S. aureus* fluoroquinolone-resistant, the MICs for the control bacteria (*E. coli* D31, and *S. aureus* ATCC 27660) for both Oligomer 4 and Oligomer 5 were much higher than those shown below.

Control Isolate	Control for MIC Test	Oligomer 4	Oligomer 5
E. coli D31	SA-FQS	1 (0.78)	16 (1.56)
S. aureus ATCC 27660	SA-FQS	2 (0.098)	16 (0.78)
E. coli D31	SA-FQR	1 (0.78)	4 (1.56)

(continued)

Control Isolate	Control for MIC Test	Oligomer 4	Oligomer 5
S. aureus ATCC 27660	SA-FQR	1 (0.098)	8 (0.78)

MICs for Control Bacteria *(E. coli, S. aureus)* are within the parentheses.

[0141] A new set of MICs were performed with new batches of both Oligomer 4 and Oligomer 5, and control bacteria, in quadruplicate. The results from the experiment is as follows:

Control Isolate	Control for MIC Test	Oligomer 4	Oligomer 5
E. coli D31	Control Only 1	1 (0.78)	8 (1.56)
S. aureus ATCC 27660	Control Only 1	0.25 (0.098)	0.25 (0.78)
E. coli D31	Control Only 2	1 (0.78)	8 (1.56)
S. aureus ATCC 27660	Control Only 2	0.25 (0.098)	0.25 (0.78)
E. coli D31	Control Only 3	1 (0.78)	8 (1.56)
S. aureus ATCC 27660	Control Only 3	0.25 (0.098)	0.5 (0.78)
E. coli D31	Control Only 4	1 (0.78)	16 (1.56)
S. aureus ATCC 27660	Control Only 4	0.5 (0.098)	0.5 (0.78)

MICs for Control Bacteria *(E. coli, S. aureus)* are within the parentheses.

[0142] Although the MICs for Oligomer 5 for *E. coli* D31 remained high, the MICs for *S. aureus* ATCC 27660 were for both Oligomer 4 and Oligomer 5 and Oligomer 4 for *E. coli* D31 were within the acceptable range (1-2 doubling dilutions) of the MICs previously obtained. It was decided to continue with the MIC determinations using the new batches of Oligomer 4 and Oligomer 5 for all subsequent MIC determinations.

[0143] Since the MICs for both Oligomer 4 and Oligomer 5 with the *S. aureus* fluoroquinolone-susceptible and *S. aureus* fluoroquinolone-resistant were similar to that of the control *S. aureus* ATCC 27660 MIC performed previously, these MICs performed with the first batch of drugs would not be repeated using the new batches of compounds.

Staphylococcus epidermidis (Coagulase-negative *Staphylococcus)* fluoroquinolone-susceptible		MICs μg/ml
Isolate	Oligomer 4	Oligomer 5
1 - E511	0.25	0.25
2 - E489	0.125	0.125
3 - E491	0.125	0.125
4 - E476	0.25	0.25
5 - E473	0.25	0.125
6 - E462	0.125	0.125
7 - E460	0.125	0.125
8 - E453	0.125	0.125
9 - E448	0.125	0.125
1 - 443	<0.0625	<0.0625
11 - E441	<0.0625	0.125
12 - E438	0.125	0.125
13 - E437	0.125	0.125
14 - E434	0.125	0.125
15 - E433	0.125	0.125

(continued)

Staphylococcus epidermidis (Coagulase-negative *Staphylococcus)* fluoroquinolone-susceptible		MICs μg/ml
Isolate	Oligomer 4	Oligomer 5
16 - E430	<0.0625	0.125
17 - E420	0.125	0.125
18 - E419	0.125	0.125
19 - E403	0.125	0.125
20 - E394	0.125	0.125
21 - E393	0.125	0.125
22 - E328	0.25	0.25
23 - E382	0.125	0.125
24 - E381	0.125	0.25
25 - E372	0.25	<0.0625
E. coli D31	1 (0.78)	4 (1.56)
S. aureus ATCC 27660	0.25 (0.098)	0.25 (0.78)

MICs for Control Bacteria *(E. coli, S. aureus)* are within the parentheses.

Staphylococcus epidermidis (Coagulase-negative *Staphylococcus)* fluoroquinolone-susceptible MIC_{50} and MIC_{90} Determinations and Statistics

For Statistical Calculation Purposes, <0.0625 was Replaced with 0.03125.

Row	Oligomer 4 QSSE-A	Oligomer 5 QSSE-A	
1	0.03125	0.03125	
2	0.03125	0.03125	
3	0.03125	0.12500	
4	0.12500	0.12500	
5	0.12500	0.12500	
6	0.12500	0.12500	
7	0.12500	0.12500	
8	0.12500	0.12500	
9	0.12500	0.12500	
10	0.12500	0.12500	
11	0.12500	0.12500	
12	0.12500	0.12500	
13	0.12500	0.12500	MIC_{50}
14	0.12500	0.12500	
15	0.12500	0.12500	
16	0.12500	0.12500	
17	0.12500	0.12500	
18	0.12500	0.12500	
19	0.12500	0.12500	
20	0.12500	0.12500	
21	0.25000	0.12500	
22	0.25000	0.25000	MIC_{90}
23	0.25000	0.25000	
24	0.25000	0.25000	
25	0.25000	0.25000	

Descriptive Statistics

[0144]

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Median	Maximum
Olig 4 QSSE	25	0	0.1388	0.0129	0.0645	0.0313	0.1250	0.2500
Olig 5 QSSE	25	0	0.1375	0.0113	0.0563	0.0313	0.1250	0.2500

Summary of Results

[0145]

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	0.125 μg/ml	0.25 μg/ml	0.125 μg/ml	0.03125 - 0.25 μg/ml
Oligomer 5	0.125 μg/ml	0.25 μg/ml	0.125 μg/ml	0.03125 - 0.25 μg/ml

Mann-Whitney Test and CI: Oligomer 4 QSSE, Oligomer 5 QSSE

[0146]

	N	Median
Olig 4 QSSE	25	0.12500
Olig 5 QSSE	25	0.12500

Point estimate for ETA1-ETA2 is 0.00000
95.2 Percent CI for ETA1-ETA2 is (-0.00002,0.00000)
W = 638.5
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.9923
The test is significant at 0.9902 NS (adjusted for ties)

Staphylococcus epidermidis (Coagulase-negative *Staphylococcus)* fluoroquinolone-resistant		MICs μg/ml
Isolate	Oligomer 4	Oligomer 5
1 - E515	0.125	0.125
2 - E514	<0.0625	0.125
3 - E513	0.125	0.125
4 - E510	<0.0625	0.125
5 - E509	0.125	0.125
6 - E508	0.125	0.125
7 - E505	0.125	0.125
8 - E503	0.125	0.125
9 - E502	0.125	0.25
10 - E499	0.125	0.25
11 - E498	0.125	0.125
12 - E494	<0.0625	0.125
13 - E493	0.125	0.125
14 - E485	0.125	0.125
15 - E487	0.125	<0.0625
16 - E486	<0.0625	0.125

(continued)

Staphylococcus epidermidis (Coagulase-negative *Staphylococcus)* fluoroquinolone-resistant		MICs μg/ml
Isolate	Oligomer 4	Oligomer 5
17 - E480	0.125	0.125
18 - E475	0.25	0.125
19 - E471	0.125	0.125
20 - E458	0.125	0.125
21 - E452	0.25	0.5
22 - E450	0.125	0.125
23 - E440	0.25	0.125
24 - E446	0.125	<0.0625
25 - E444	0.25	0.25
E. coli D31	1 (0.78)	4 (1.56)
S. aureus ATCC 27660	0.25 (0.098)	0.25 (0.78)

MICs for Control Bacteria *(E. coli, S. aureus)* are within the parentheses.

Staphylococcus epidermidis (Coagulase-negative *Staphylococcus)* fluoroquinolone-resistant MIC_{50} and MIC_{90} Determinations and Statistics For Statistical Calculation Purposes, <0.0625 was Replaced with 0.03125.

	Oligomer 4	Oligomer 5	
Row	QRSE-A	QRSE-A	
1	0.03125	0.03125	
2	0.03125	0.03125	
3	0.03125	0.12500	
4	0.03125	0.12500	
5	0.12500	0.12500	
6	0.12500	0.12500	
7	0.12500	0.12500	
8	0.12500	0.12500	
9	0.12500	0.12500	
10	0.12500	0.12500	
11	0.12500	0.12500	
12	0.12500	0.12500	
13	0.12500	0.12500	MIC_{50}
14	0.12500	0.12500	
15	0.12500	0.12500	
16	0.12500	0.12500	
17	0.12500	0.12500	
18	0.12500	0.12500	
19	0.12500	0.12500	
20	0.12500	0.12500	
21	0.12500	0.12500	
22	0.25000	0.25000	MIC_{90}
23	0.25000	0.25000	
24	0.25000	0.25000	
25	0.25000	0.50000	

Descriptive Statistics

[0147]

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Median	Maximum
Olig 4 QRSE	25	0	0.1300	0.0127	0.0636	0.0313	0.1250	0.2500
Olig 5 QRSE	25	0	0.1475	0.0179	0.0895	0.0313	0.1250	0.5000

Summary of Results

[0148]

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	0.125 μg/ml	0.25 μg/ml	0.125 μg/ml	0.03125 - 0.25 μg/ml
Oligomer 5	0.125 μg/ml	0.25 μg/ml	0.125 μg/ml	0.03125 - 0.5 μg/ml

Mann-Whitney Test and CI: Oligomer 4 QRSE, Oligomer 5 QRSE

[0149]

	N	Median
Olig 4 QRSE	25	0.12500
Olig 5 QRSE	25	0.12500

Point estimate for ETA1-ETA2 is -0.00000
95.2 Percent CI for ETA1-ETA2 is (0.00001,-0.00002)
W = 614.5
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.6624
The test is significant at 0.5800 NS (adjusted for ties)

Serratia marcescens	MICs μg/ml	
Isolate	Oligomer 4	Oligomer 5
1 - K1681	32	>128
2 - K1674	32	>128
3 - K1558	4	>128
4 - K1538	16	>128
5 - K1503	32	>128
6 - K1216	4	>128
7 - K1496	8	>128
8 - K1481	2	>128
9 - K1470	32	>128
10 - K1468	2	>128
11 - K1467	32	>128
12 - K1462	16	>128
13 - K1461	8	128
14 - K1413	16	>128
15 - K1402	0.25	8
16 - K1357	1	>128

(continued)

Serratia marcescens	MICs μg/ml	
Isolate	Oligomer 4	Oligomer 5
17 - K1351	0.5	64
18 - K1327	8	>128
19 - K1321	8	>128
20 - K1315	16	>128
21 - K1306	8	>128
22 - K1290	8	>128
23 - K1265	8	>128
24 - K1263	8	>128
25 - K1239	8	>128
E. coli D31	0.5 (0.78)	4 (1.56)
S. aureus ATCC 27660	0.25 (0.098)	0.5 (0.78)

MICs for Control Bacteria *(E. coli, S. aureus)* are within the parentheses.

Serratia marcescens

MIC_{50} and MIC_{90} Determinations and Statistics

For Statistical Calculation Purposes, > 128 was Replaced with 256.

Row	Oligomer 4 SM-A	Oligomer 5 SM-A	
1	0.25	8	
2	0.50	64	
3	1.00	128	
4	2.00	256	
5	2.00	256	
6	4.00	256	
7	4.00	256	
8	8.00	256	
9	8.00	256	
10	8.00	256	
11	8.00	256	
12	8.00	256	
13	8.00	256	MIC_{50}
14	8.00	256	
15	8.00	256	
16	8.00	256	
17	16.00	256	
18	16.00	256	
19	16.00	256	
20	16.00	256	
21	32.00	256	
22	32.00	256	MIC_{90}
23	32.00	256	
24	32.00	256	
25	32.00	256	

Descriptive Statistics

[0150]

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Median	Maximum
Olig 4 SM	25	0	12.39	2.21	11.04	0.25	8.00	32.00
Olig 5 SM	25	0	233.3	13.0	65.1	8.0	256.0	256.0

Summary of Results

[0151]

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	8 μg/ml	32 μg/ml	8 μg/ml	0.25 - 32 μg/ml
Oligomer 5	256 μg/ml	256 μg/ml	256 μg/ml	8 - 256 μg/ml

Mann-Whitney Test and CI: Oligomer 4 SM, Oligomer 5 SM

[0152]

	N	Median
Olig 4 SM	25	8.00
Olig 5 SM	25	256.00

Point estimate for ETA1-ETA2 is -248.00
95.2 Percent CI for ETA1-ETA2 is (-247.98,-239.99)
W = 338.5
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.0000
The test is significant at 0.0000 (adjusted for ties)
Oligomer 4 > Oligomer 5 (More Potent > Less Potent)

Pseudomonas aeruginosa	MICs μg/ml	
Isolate	Oligomer 4	Oligomer 5
1 - K1673	2	32
2 - K1668	2	64
3 - K1662	2	64
4 - K1657	2	64
5 - K1651	4	128
6 - K1649	4	64
7 - K1564	8	>128
8 - K1636	0.5	4.0
9 - K1634	2	128
10 - K1633	4	64
11 - K1632	4	64
12 - K1631	8	64
13 - K1629	4	64
14 - K1627	2	64
15 - K1626	8	128

(continued)

Pseudomonas aeruginosa	MICs μg/ml	
Isolate	Oligomer 4	Oligomer 5
16 - K1625	4	64
17 - K1562	4	128
18 - K1613	4	32
19 - K1553	2	128
20 - K1594	2	64
21 - K1588	4	128
22 - K1554	4	128
23 - K1580	2	32
24 - K1577	2	64
25 - K1576	4	128
E. coli D31	0.5 (0.78)	8 (1.56)
S. aureus ATCC 27660	0.5 (0.098)	0.25 (0.78)

MICS for Control Bacteria (*E. coli*, *S. aureus*) are within the parentheses.

Pseudomonas aeruginosa

MIC_{50} and MIC_{90} Determinations and Statistics

For Statistical Calculation Purposes, > 128 was Replaced with 256.

Row	Oligomer 4 PA-A	Oligomer 5 PA-A	
1	0.5	4	
2	2.0	32	
3	2.0	32	
4	2.0	32	
5	2.0	64	
6	2.0	64	
7	2.0	64	
8	2.0	64	
9	2.0	64	
10	2.0	64	
11	2.0	64	
12	4.0	64	
13	4.0	64	MIC_{50}
14	4.0	64	
15	4.0	64	
16	4.0	64	
17	4.0	128	
18	4.0	128	
19	4.0	128	
20	4.0	128	
21	4.0	128	
22	4.0	128	MIC_0
23	8.0	128	
24	8.0	128	
25	8.0	256	

Descriptive Statistics

[0153]

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Median	Maximum
Olig 4 PA	25	0	3.540	0.398	1.989	0.500	4.000	8.000
Olig 5 PA	25	0	85.9	10.4	51.8	4.0	64.0	256.0

Summary of Results

[0154]

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	4 μg/ml	4 μg/ml	4 μg/ml	0.5 - 8 μg/ml
Oligomer 5	64 μg/ml	128 μg/ml	64 μg/ml	4 - 256 μg/ml

Mann-Whitney Test and CI: Oligomer 4 PA, Oligomer 5 PA

[0155]

	N	Median
Olig 4 PA	25	4.00
Olig 5 PA	25	64.00

Point estimate for ETA1-ETA2 is -62.00
95.2 Percent CI for ETA1-ETA2 is (-120.00,-60.00)
W = 333.5
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.0000
The test is significant at 0.0000 (adjusted for ties)
Oligomer 4 > Oligomer 5 (More Potent > Less Potent)

Streptococcus pneumoniae MICs μg/ml		
Isolate	Oligomer 4	Oligomer 5
1 - B1386	>64	>64
2 - B1380	1	4
3 - B1378	1	0.5
4 - B1377	2	8
5 - B1373	1	8
6 - B1367	1	16
7 - B1355	2	8
8 - B1353	1	4
9 - B1351	1	1
10 - B1339	1	2
11 - B1337	0.5	1
12 - B1335	2	1
13 - B1334	1	1
14 - B1333	1	1
15 - B1255	0.5	1

(continued)

Streptococcus pneumoniae MICs μg/ml		
Isolate	Oligomer 4	Oligomer 5
16 - B1288	1	8
17 - B1287	1	16
18 - B1272	0.5	1
19 - B1264	0.5	1
20 - B1252	1	16
21 - B1245	0.5	2
22 - B1211	1	8
23 - B1213	1	16
24 - B1208	0.5	8
25 - B1214	1	4
E. coli D31*	2	2
S. aureus ATCC 27660*	1	1
E. coli D31**	0.5 (0.78)	16 (1.56)
S. aureus ATCC 27660**	0.25 (0.098)	2 (0.78)
* Control Bacteria Set #1; ** Control Bacteria Set #2; (MICs for Control Bacteria *(E. coli, S. aureus*) are within the parentheses.)		

Streptococcus pneumoniae

MIC_{50} and MIC_{90} Determinations and Statistics

For Statistical Calculation Purposes, > 64 was Replaced with 128.

Row	Oligomer 4 SP-A	Oligomer 5 SP-A	
1	0.5	0.5	
2	0.5	1.0	
3	0.5	1.0	
4	0.5	1.0	
5	0.5	1.0	
6	0.5	1.0	
7	1.0	1.0	
8	1.0	1.0	
9	1.0	1.0	
10	1.0	2.0	
11	1.0	2.0	
12	1.0	4.0	
13	1.0	4.0	MIC_{50}
14	1.0	4.0	
15	1.0	8.0	
16	1.0	8.0	
17	1.0	8.0	
18	1.0	8.0	
19	1.0	8.0	
20	1.0	8.0	
21	1.0	16.0	

(continued)

Streptococcus pneumoniae

MIC_{50} and MIC_{90} Determinations and Statistics

For Statistical Calculation Purposes, > 64 was Replaced with 128.

Row	Oligomer 4 SP-A	Oligomer 5 SP-A	
22	2.0	16.0	MIC_{90}
23	2.0	16.0	
24	2.0	16.0	
25	128.0	128.0	

Descriptive Statistics

[0156]

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Median	Maximum
Olig 4 SP	25	0	6.08	5.08	25.40	0.50	1.00	128.00
Olig 5 SP	25	0	10.58	5.01	25.05	0.50	4.00	128.00

Summary of Results

[0157]

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	1 μg/ml	2 μg/ml	1 μg/ml	0.5 - 128 μg/ml
Oligomer 5	4 μg/ml	16 μg/ml	4 μg/ml	4 - 128 μg/ml

Mann-Whitney Test and CI: Oligomer 4 SP, Oligomer 5 SP

[0158]

	N	Median
Olig 4 SP	25	1.000
Olig 5 SP	25	4.000

Point estimate for ETA1-ETA2 is -3.000
95.2 Percent CI for ETA1-ETA2 is (-6.999,-0.499)
W = 457.5
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.0005
The test is significant at 0.0002 (adjusted for ties)
Oligomer 4 > Oligomer 5 (More Potent > Less Potent)

Streptococcus viridans group	MICs μg/ml	
Isolate	Oligomer 4	Oligomer 5
1 - K1684	2	8
2 - K1680	4	64
3 - E546	1	8
4 - E272	2	16
5 - E506	16	>64
6 - E496	1	0.5
7 - E456	4	16

(continued)

Streptococcus viridans group MICs μg/ml		
Isolate	Oligomer 4	Oligomer 5
8 - E432	4	8
9 - E423	4	>64
10 - E418	8	>64
11 - E412	2	8
12 - E409	8	32
13 - E405	4	>64
14 - E404	32	>64
15 - E396	16	32
16 - E262	1	4
17 - E362	4	16
18 - E359	4	32
19 - E348	8	16
20 - E344	4	4
21 - E308	4	4
22 - E294	4	2
23 - E292	4	0.5
24 - E285	4	0.5
25 - E265	1	8
E. coli D31 *	2	2
S. aureus ATCC 27660*	2	1
E. coli D31**	0.5 (0.78)	16 (1.56)
S. aureus ATCC 27660**	1 (0.098)	1 (0.78)
* Control Bacteria Set #1; ** Control Bacteria Set #2; (MICs for Control Bacteria (*E. coli, S. aureus)* are within the parentheses.)		

Streptococcus viridans group

MIC_{50} and MIC_{90} Determinations and Statistics

For Statistical Calculation Purposes, > 64 was Replaced with 128.

Row	Oligomer 4 SV-A	Oligomer 5 SV-A
1	1	0.5
2	1	0.5
3	1	0.5
4	1	2.0
5	2	4.0
6	2	4.0
7	2	4.0
8	4	8.0
9	4	8.0
10	4	8.0
11	4	8.0

(continued)

Streptococcus viridans group

MIC_{50} and MIC_{90} Determinations and Statistics

For Statistical Calculation Purposes, > 64 was Replaced with 128.

Row	Oligomer 4 SV-A	Oligomer 5 SV-A	
12	4	8.0	
13	4	16.0	MIC_{50}
14	4	16.0	
15	4	16.0	
16	4	16.0	
17	4	32.0	
18	4	32.0	
19	4	32.0	
20	8	64.0	
21	8	128.0	
22	8	128.0	MIC_{90}
23	16	128.0	
24	16	128.0	
25	32	128.0	

Descriptive Statistics

[0159]

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Median	Maximum
Olig 4 SV	25	0	5.84	1.34	6.72	1.00	4.00	32.00
Olig 5 SV	25	0	36.78	9.72	48.59	0.50	16.00	128.00

Summary of Results

[0160]

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	4 μg/ml	8 μg/ml	4 μg/ml	1 - 32 μg/ml
Oligomer 5	16 μg/ml	128 μg/ml	16 μg/ml	0.5 - 128 μg/ml

Mann-Whitney Test and CI: Oligomer 4 SV, Oligomer 5 SV

[0161]

	N	Median
Olig 4 SV	25	4.00
Olig 5 SV	25	16.00

Point estimate for ETA1-ETA2 is -7.00
95.2 Percent CI for ETA1-ETA2 is (-23.99,-3.01)
W = 487.5
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.0037
The test is significant at 0.0031 (adjusted for ties)
Oligomer 4 > Oligomer 5 (More Potent > Less Potent)

Moraxella species & *Moraxella catarrhalis* Combined MS = *Moraxella* species; MC = *Moraxella* (*Branhamella*) *catarrhalis*		
Isolate	Oligomer 4	Oligomer 5
1 - K1614 - MS	16	64
2 - K1661 - MS	32	16
3 - K1643 - MS	64	0.125
4 - K1640 - MS	8.0	8.0
5 - B1431 - MS	32	0.5
6 - B1429 - MS	1	1
7 - B1418 - MS	32	0.25
8 - K1784 - MS	64	0.25
9 - K1773 - MS	64	0.25
10 - K1369 - MS	2.0	2.0
11 - B1275 - MS	2.0	0.125
12 - B1221 - MS	2.0	0.125
13 - B1172 - MS	>64	>64
14 - E542 - MS	2.0	2.0
15 - K678 - MS	2.0	0.5
16 - K660 - MS	2.0	0.25
17 - K599 - MC	0.5	0.25
18 - K1650 - MC	64	0.25
19 - K1373 - MC	1.0	0.125
20 - K1553 - MC	4.0	2.0
21 - K1453 - MC	4.0	64
22 - K1227 - MC	2.0	1.0
23 - B1102 - MC	1.0	0.5
24 - K1819 - MC	4.0	32
25 - K1855 - MC	2.0	8.0
E. coli D31 *	4	2
S. aureus ATCC 27660*	1	1
E. coli D31**	1 (0.78)	16 (1.56)
S. aureus ATCC 27660**	0.5 (0.098)	0.5 (0.78)
* Control Bacteria Set #1; ** Control Bacteria Set #2; (MICs for Control Bacteria (*E. coli, S. aureus)* are within the parentheses.)		

Moraxella species & *Moraxella catarrhalis* Combined

MIC_{50} and MIC_{90} Determinations and Statistics

For Statistical Calculation Purposes, > 64 was Replaced with 128.

Row	Oligomer 4 MS-A	Oligomer 5 MS-A
1	0.5	0.125

(continued)

Moraxella species & *Moraxella catarrhalis* Combined

MIC_{50} and MIC_{90} Determinations and Statistics

For Statistical Calculation Purposes, > 64 was Replaced with 128.

Row	Oligomer 4 MS-A	Oligomer 5 MS-A	
2	1.0	0.125	
3	1.0	0.125	
4	1.0	0.125	
5	2.0	0.250	
6	2.0	0.250	
7	2.0	0.250	
8	2.0	0.250	
9	2.0	0.250	
10	2.0	0.250	
11	2.0	0.500	
12	2.0	0.500	
13	4.0	0.500	MIC_{50}
14	4.0	1.000	
15	4.0	1.000	
16	8.0	2.000	
17	16.0	2.000	
18	32.0	2.000	
19	32.0	8.000	
20	32.0	8.000	
21	64.0	16.000	
22	64.0	32.000	MIC_{90}
23	64.0	64.000	
24	64.0	64.000	
25	128.0	128.000	

Descriptive Statistics

[0162]

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Median	Maximum
Olig 4 MS	25	0	21.42	6.43	32.13	0.50	4.00	128.00
Olig 5 MS	25	0	13.26	6.00	30.00	0.13	0.50	128.00

Summary of Results

[0163]

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	4 μg/ml	64 μg/ml	4 μg/ml	0.5 - 128 μg/ml
Oligomer 5	0.5 μg/ml	32 μg/ml	0.5 μg/ml	0.125 - 128 μg/ml

Mann-Whitney Test and CI: Oligomer 4 MS, Oligomer 5 MS

[0164]

	N	Median
Olig 4 MS	25	4.00

(continued)

	N	Median
Olig 5 MS	25	0.50

Point estimate for ETA1-ETA2 is 1.75
95.2 Percent CI for ETA1-ETA2 is (0.75,6.00)
W = 785.0
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.0043
The test is significant at 0.0040 (adjusted for ties)
Oligomer 4 > Oligomer 5 (More Potent > Less Potent)

Haemophilus influenzae MICs μg/ml		
Isolate	Oligomer 4	Oligomer 5
1 - B1359	8	>64
2 - B1346	8	>64
3 - B1345	8	>64
4 - B1343	8	>64
5 - B1338	4	16
6 - B1332	8	64
7 - B1331	8	>64
8 - B1330	8	>64
9 - B1379	16	8
10 - B1378	8	4
11 - B1313	4	2
12 - B1477	8	4
13 - B1286	8	2
14 - B1282	32	8
15 - B1291	8	16
16 - B1280	8	16
17 - B1279	16	64
18 - B1260	8	16
19 - B1238	2	8
20 - B1209	4	8
21 - B1249	4	16
22 - B1248	8	4
23 - B1244	8	32
24 - B1419	4	32
25 - B1222	8	>64
E. coli D31	8	16
S. aureus ATCC 27660	4	4
E. coli D31	1 (0.78)	16 (1.56)

(continued)

Haemophilus influenzae MICs μg/ml		
Isolate	Oligomer 4	Oligomer 5
S. aureus ATCC 27660	0.5 (0.098)	0.5 (0.78)
* Control Bacteria Set #1; ** Control Bacteria Set #2; (MICs for Control Bacteria (*E. coli, S. aureus*) are within the parentheses.)		

Haemophilus influenzae

MIC_{50} and MIC_{90} Determinations and Statistics

For Statistical Calculation Purposes, > 64 was Replaced with 128.

	Oligomer 4	Oligomer 5	
Row	HI-A	HI-A	
1	2	2	
2	4	2	
3	4	4	
4	4	4	
5	4	4	
6	4	8	
7	8	8	
8	8	8	
9	8	8	
10	8	16	
11	8	16	
12	8	16	
13	8	16	MIC_{50}
14	8	16	
15	8	32	
16	8	32	
17	8	64	
18	8	64	
19	8	128	
20	8	128	
21	8	128	
22	8	128	MIC_{50}
23	16	128	
24	16	128	
25	32	128	

Descriptive Statistics

[0165]

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Median	Maximum
Olig 4 HI	25	0	8.56	1.16	5.82	2.00	8.00	32.00
Olig 5 HI	25	0	48.6	10.6	53.0	2.0	16.0	128.0

Summary of Results

[0166]

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	8 μg/ml	8 μg/ml	8 μg/ml	2 - 32 μg/ml
Oligomer 5	16 μg/ml	128 μg/ml	16 μg/ml	2 - 128 μg/ml

Mann-Whitney Test and CI: Oligomer 4 HI, Oligomer 5 HI

[0167]

	N	Median
Olig 4 HI	25	8.00
Olig 5 HI	25	16.00

Point estimate for ETA1-ETA2 is -8.00
95.2 Percent CI for ETA1-ETA2 is (-56.00,0.00)
W = 493.5
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.0054
The test is significant at 0.0038 (adjusted for ties)
Oligomer 4 > Oligomer 5 (More Potent > Less Potent)

Summary of Results

[0168]

MIC Determinations of Control Bacteria from Each Day of MIC Testing MICs [μg/ml]			
Control Isolate	Control for MIC Test	Oligomer 4	Oligomer 5
E. coli D31	SA-FQS	1 (0.78)	16 (1.56)
S. aureus ATCC 27660	SA-FQS	2 (0.098)	16 (0.78)
E. coli D31	SA-FQR	1 (0.78)	4 (1.56)
S. aureus ATCC 27660	SA-FQR	1 (0.098)	8 (0.78)
E. coli D31	Control Only 1	1 (0.78)	8 (1.56)
S. aureus ATCC 27660	Control Only 1	0.25 (0.098)	0.25 (0.78)
E. coli D31	Control Only 2	1 (0.78)	8 (1.56)
S. aureus ATCC 27660	Control Only 2	0.25 (0.098)	0.25 (0.78)
E. coli D31	Control Only 3	1 (0.78)	8 (1.56)
S. aureus ATCC 27660	Control Only 3	0.25 (0.098)	0.5 (0.78)
E. coli D31	Control Only 4	1 (0.78)	16 (1.56)
S. aureus ATCC 27660	Control Only 4	0.5 (0.098)	0.5 (0.78)
E. coli D31	SE-FQS	1 (0.78)	4 (1.56)
S. aureus ATCC 27660	SE-FQS	0.25 (0.098)	0.25 (0.78)
E. coli D31	SE-FQR	1 (0.78)	4 (1.56)
S. aureus ATCC 27660	SE-FQR	0.25 (0.098)	0.25 (0.78)
E. coli D31	SM	0.5 (0.78)	4 (1.56)
S. aureus ATCC 27660	SM	0.25 (0.098)	0.5 (0.78)
E. coli D31	PA	0.5 (0.78)	8 (1.56)
S. aureus ATCC 27660	PA	0.5 (0.098)	0.25 (0.78)

(continued)

MIC Determinations of Control Bacteria from Each Day of MIC Testing MICs [μg/ml]			
Control Isolate	Control for MIC Test	Oligomer 4	Oligomer 5
E. coli D31	SP	0.5 (0.78)	16 (1.56)
S. aureus ATCC 27660	SP	0.25 (0.098)	2 (0.78)
E. coli D31	SV	0.5 (0.78)	16 (1.56)
S. aureus ATCC 27660	SV	1 (0.098)	1 (0.78)
E. coli D31	MS	1 (0.78)	16 (1.56)
S. aureus ATCC 27660	MS	0.5 (0.098)	0.5 (0.78)
E. coli D31	HI	1 (0.78)	16 (1.56)
S. aureus ATCC 27660	HI	0.5 (0.098)	0.5 (0.78)

MICs for Control Bacteria *(E. coli, S. aureus)* are within the parentheses.

Summary of MIC Results (n = 25 per group)

S. aureus fluoroquinolone-susceptible

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	0.25 μg/ml	0.25 μg/ml	0.25 μg/ml	0.125 - 0.5 μg/ml
Oligomer 5	0.25 μg/ml	0.5 μg/ml	0.25 μg/ml	0.125 - 0.5 μg/ml

S. aureus fluoroquinolone-resistant

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	0.25 μg/ml	0.5 μg/ml	0.25 μg/ml	0.125 - 1.0 μg/ml
Oligomer 5	0.25 μg/ml	0.5 μg/ml	0.25 μg/ml	0.125 - 0.5 μg/ml

Staphylococcus epidermidis (Coagulase-negative *Staphylococcus)* FQ-susceptible

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	0.125 μg/ml	0.25 μg/ml	0.125 μg/ml	0.03125 - 0.25 μg/ml
Oligomer 5	0.125 μg/ml	0.25 μg/ml	0.125 μg/ml	0.03125 - 0.25 μg/ml

Staphylococcus epidermidis (Coagulase-negative *Staphylococcus)* FQ-resistant

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	0.125 μg/ml	0.25 μg/ml	0.125 μg/ml	0.03125 - 0.25 μg/ml
Oligomer 5	0.125 μg/ml	0.25 μg/ml	0.125 μg/ml	0.03125 - 0.5 μg/ml

Serratia marcescens

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	8 μg/ml	32 μg/ml	8 μg/ml	0.25 - 32 μg/ml
Oligomer 5	256 μg/ml	256 μg/ml	256 μg/ml	8 - 256 μg/ml

Pseudomonas aeruginosa

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	4 μg/ml	4 μg/ml	4 μg/ml	0.5 - 8 μg/ml
Oligomer 5	64 μg/ml	128 μg/ml	64 μg/ml	4 - 256 μg/ml

(continued)

Streptococcus pneumoniae

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	1 μg/ml	2 μg/ml	1 μg/ml	0.5 - 128 μg/ml
Oligomer 5	4 μg/ml	16 μg/ml	4 μg/ml	4 - 128 μg/ml

Streptococcus viridans group

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	4 μg/ml	8 μg/ml	4 μg/ml	1 - 32 μg/ml
Oligomer 5	16 μg/ml	128 μg/ml	16 μg/ml	0.5 - 128 μg/ml

Moraxella species (Including *Moraxella catarrhalis)*

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	4 μg/ml	64 μg/ml	4 μg/ml	0.5 - 128 μg/ml
Oligomer 5	0.5 μg/ml	32 μg/ml	0.5 μg/ml	0.125 - 128 μg/ml

Haemophilus influenzae

	MIC_{50}	MIC_{90}	Median MIC	Range of MICs
Oligomer 4	8 μg/ml	8 μg/ml	8 μg/ml	2 - 32 μg/ml
Oligomer 5	16 μg/ml	128 μg/ml	16 μg/ml	2 - 128 μg/ml

[0169] Oligomer 4 and Oligomer 5 demonstrated the lowest MICs for *Staphylococcus aureus* fluoroquinolone-susceptible, *Staphylococcus aureus* fluoroquinolone-resistant, *Staphylococcus epidermidis* (Coagulase-negative *Staphylococcus)* fluoroquinolone-susceptible, *Staphylococcus epidermidis* (Coagulase-negative *Staphylococcus)* fluoroquinolone-resistant. Median MIC determinations were less than or equal to 0.25 μg/ml for the compounds against the ocular isolates of these species. The median MICs for Oligomer 4 and Oligomer 5 against *Streptococcus pneumoniae* and *Moraxella* species (including *Moraxella catarrhalis)* were less than or equal to 4 μg/ml. The median MIC for Oligomer 4 against *Streptococcus viridans* group was 4 μg/ml whereas the median MIC for Oligomer 5 was 16 μg/ml. Oligomer 4 and Oligomer 5 demonstrated the highest MICs against the Gram-negative pathogens *Serratia marcescens, Pseudomonas aeruginosa,* and *Haemophilus influenzae.* The median MIC of Oligomer 4 to *Pseudomonas aeruginosa, Serratia marcescens* and *Haemophilus influenzae* were 4, 8, and 8 μg/ml respectively The median MICs of Oligomer 5 to *Pseudomonas aeruginosa, Serratia marcescens* and *Haemophilus influenzae* were 64, 128, and 16 μg/ml respectively. Overall, MICs for the Control Bacteria (*E. coli* D31 and *S. aureus* ATCC 27660) for each date on which MICs were performed were within the acceptable standard of a 1-2 dilution range in MICs from the MICs previously obtained for those compounds and between different preparation days. The addition of 2% lysed horse red blood cells to the Mueller-Hinton broth for MIC testing with *Streptococcus pneumoniae, Moraxella* species (including *Moraxella catarrhalis),* and *Streptococcus viridans* group appeared to decrease the activity of the Oligomer 4 against the Control Bacteria (*E. coli* D31 and *S. aureus* ATCC 27660) approximately 4 fold. It is unknown whether the 2% lysed horse red blood cells had the same effect on the test isolates. The addition of 2% lysed horse red blood cells to the Mueller-Hinton broth for MIC testing with *Streptococcus pneumoniae, Moraxella* species (including *Moraxella catarrhalis*), and *Streptococcus viridans* group generally appeared to increase or have no effect on the activity of the Oligomer 5 against the Control Bacteria (*E. coli* D31 and *S. aureus* ATCC 27660). It is unknown whether the 2% lysed horse red blood cells had the same effect on the test isolates. The use of HTM broth for the MIC testing of *Haemophilus influenzae* appeared to decrease the activity of the Oligomer 4 and Oligomer 5 against the Control Bacteria *S. aureus* ATCC 27660 approximately 8 fold. The use of HTM broth for the MIC testing of *Haemophilus influenzae* appeared to decrease the activity of the Oligomer 4 against the Control Bacteria *E. coli* D31 approximately 8 fold but appeared to have no effect on the activity of Oligomer 5 against the Control Bacteria *E. coli* D31.

[0170] Oligomer 4 and Oligomer 5 demonstrated the lowest MICs against a variety of Gram-positive ocular bacterial isolates and at least one Gram-negative ocular bacterial species *(Moraxella).* Oligomer 4 and Oligomer 5 demonstrated varying *in vitro* antibacterial activity against the three species that are the leading causes of conjunctivitis (*Staphylococcus aureus, Streptococcus pneumoniae,* and *Haemophilus influenzae).* The order of the lower MICs for Oligomer 4 and Oligomer 5 against the species was: *Staphylococcus aureus* < *Streptococcus pneumoniae* < *Haemophilus influenzae.* (< = lower MICs). Oligomer 4 demonstrated lower MICs than Oligomer 5 for all bacterial species tested except for the Staphylococcal species (equipotent) and for *Moraxella* species (less potent).

Example 3: Ker-3

[0171] One purpose of the following experiments was to determine the efficacy of 0.25% Oligomer 4, with and without

200 μM Farnesol, and 200 μM Farnesol in the treatment of a fluoroquinolone-resistant and methicillin-resistant *Staphylococcus aureus* infection in the NZW rabbit keratitis model with or without intact corneal epithelia. The 200 μM Farnesol has been added to try to increase the efficacy and penetration of 0.25% Oligomer 4 through the corneal epithelium.

[0172] Fifteen rabbits were received from Myrtles' Rabbitry, Thompson Station, TN. The clinical isolate of fluoroquinolone-resistant and methicillin-resistant (MRSA) *Staphylococcus aureus* (K950) was subcultured on 5% sheep blood agar and incubated at 37°C in 6% CO_2 overnight. The next morning, the MRSA strain was suspended in sterile trypticase soy broth to a 0.5 McFarland Standard, containing approximately 5 x 10^8 CFU/ml of bacteria. The absorbance of the suspension was measured at 650 nm using a Beckman DU-70 spectrophotometer. OD readings of 0.07 corresponded to 5 x 10^8 CFU/ml of bacteria. This concentration was appropriately diluted in sterile trypticase soy broth to provide the inoculum of approximately 1,000 (1.0 x 10^3) CFU/eye in 25 μl. Colony counts were performed on the inoculum to determine the actual CFU inoculated. Following general anesthesia with ketamine and xylazine and topical anesthesia with proparacaine and prior to bacterial inoculation in the left eyes, 6 mm areas of the corneal epithelia were removed centrally from the left eyes with an Amoils epithelial scrubber. Nothing was done to the right eyes. The 15 rabbits the were then inoculated intrastromally in both eyes with 25 μl of the bacterial dilution of approximately 10^3 cfu/eye of the bacteria. The bacterial inoculation of the left eyes was directly under the epithelial defect created by the Amoils epithelial scrubber. The epithelia were removed in the left corneas in order to determine whether this layer of the cornea is a barrier for drug penetration when compared to the right cornea with an intact epithelium. A colony count was done on the inoculum to determine the actual CFU inoculated. The rabbits were immediately treated with analgesia in the form of an intramuscular injection of ketoprofen, 1.5 mg/kg. After 4 hours, the 15 rabbits were divided into 4 treatment groups and one untreated control group sacrificed at the onset of therapy. Both eyes of each rabbit of the treatment groups were treated with one 37 μl drop of the PMX solutions or control Saline.

Groups:

[0173]

Group	Left Eye	Right Eye	Rx - Both Eyes	Treatment Regimen	Rabbit #
I	Abraded Epithelium	Intact Epithelium	0.25% Oligomer 4 (PMX)	Every 15 minutes for 5 hours (21 total doses)	1-3
II	Abraded Epithelium	Intact Epithelium	0.25% Oligomer 4 + 200 μM Farnesol (P+F)	Every 15 minutes for 5 hours (21 total doses)	4-6
III	Abraded Epithelium	Intact Epithelium	200 μM Farnesol (FARN)	Every 15 minutes for 5 hours (21 total doses)	7-9
IV	Abraded Epithelium	Intact Epithelium	Tris-Buffered Saline (CON)	Every 15 minutes for 5 hours (21 total doses)	10-12
V	Abraded Epithelium	Intact Epithelium	Sacrifice at Onset of Therapy (4 hours PI) (ONSET)	None	13-15

[0174] Treatment was scheduled for every 15 minutes for 5 hours (21 total doses). The 3 rabbits in group V were sacrificed 4 hours PI and large 9.5 mm buttons were removed from the corneas. These were placed in 1 ml of PBS and kept on ice. The corneal buttons were homogenized for 25 seconds on ice using the motorized homogenizer. After homogenization, colony counts were done on the homogenates using 5% sheep blood agar plates to determine the amount of bacteria contained in the corneas at the onset of therapy. Following the completion of therapy, the eyes were examined for clinical signs of infection. One hour after the final treatment, the treated rabbits (Groups I-IV) were sacrificed and large 9.5 mm buttons were removed from the corneas. These were placed in 1 ml of PBS and kept on ice. The corneal buttons were homogenized for 25 seconds on ice using the motorized homogenizer. After homogenization, colony counts were done on the homogenates using 5% sheep blood agar plates to determine the amount of bacteria contained in the corneas after treatment. The next morning, the plates were counted and the number of CFU/eye of *Staphylococcus aureus* was determined for each cornea.

[0175] Formulations: 1) 0.25% Oligomer 2 (PMX): Tube G1 of Oligomer 2 powder was stored at 4°C until use. Upon use, the tube was removed from the refrigerator and 3.28 ml of S1 (sterile water for injection) was added and vortexed until the solid was completely dissolved. Then 3.28 ml of S2 (2X TBS) was added and vortexed for 10 seconds. This solution was designated PMX. 37 μl drops were instilled were instilled using a Rainin EDP electronic pipet set in the multi-dispense mode; 2) 0.25% Oligomer 2 with 200 μM Farnesol (P+F): Tube G2 of Oligomer 2 powder was stored at

4°C until use. Upon use, the tube was removed from the refrigerator and 3.33 ml of S1 (sterile water for injection) was added and vortexed until the solid was completely dissolved. Then 3.33 ml of S3 (400 μM Farnesol + 2% Propylene Glycol in 2X TBS) was added and vortexed for 10 seconds. This solution was designated P+F. 37 μl drops were instilled were instilled using a Rainin EDP electronic pipet set in the multi-dispense mode; 3) 200 μM Farnesol (FARN): Tube G3 containing about 8 ml of 200μM Farnesol in 1% Propylene Glycol (PG) and TBS was stored at 4°C until use. This solution was designated FARN. 37 μl drops were instilled using a Rainin EDP electronic pipet set in the multi-dispense mode; 4) Control (Tris-Buffered Saline, CON): Tube G4 containing about 8 ml of Tris-Buffered Saline (10mM TRIS, 150mM NaCl, pH=7.4) was stored at 4°C until use. This solution was designated CON. 37 μl drops were instilled using a Rainin EDP electronic pipet set in the multi-dispense mode.

IACUC Protocol #0701145-1. "The *In Vivo* Evaluation of Biomimetics as Topical Ocular Antibiotics".

[0176]

MIC Characterization of Fluoroquinolone-Resistant, Methicillin-Resistant *Staphylococcus aureus* Strain K950

Antibiotic	MIC [μg/ml] (Minimum Inhibitory Concentration)	
Oligomer 4	0.5 μg/ml	
	Drop Schedule	
	Drop #	Time	Time of Day
	1	0	9:30
	2	:15	9:45
	3	:30	10:00
	4	:45	10:15
	5	1:00	10:30
	6	1:15	10:45
	7	1:30	11:00
	8	1:45	11:15
	9	2:00	11:30
	10	2:15	11:45
	11	2:30	12:00
	12	2:45	12:15
	13	3:00	12:30
	14	3:15	12:45
	15	3:30	1:00
	16	3:45	1:15
	17	4:00	1:30
	18	4:15	1:45
	19	4:30	2:00
	20	4:45	2:15
	21	5:00	2:30

[0177] Sacrifice rabbits 1 hour after final drop (3:30).

Definitions of Abbreviations

[0178]

PMX-IE	0.25% Oligomer 4 with Intact Epithelium
PMX-AE	0.25% Oligomer 4 with Abraded Epithelium
P+F-IE	0.25% Oligomer 4 + 200 μM Farnesol with Intact Epithelium
P+F-AE	0.25% Oligomer 4 + 200 μM Farnesol with Abraded Epithelium
FARN-IE	200 μM Farnesol with Intact Epithelium
FARN-AE	200 μM Farnesol with Abraded Epithelium
CON-AE	Tris-Buffered Saline Control with Abraded Epithelium

CON-IE Tris-Buffered Saline Control with Intact Epithelium

Clinical Evaluation - Results

[0179]

Eye	Group	Conj.	Chemosis	Discharge	Iritis	Corneal Edema	Corneal Infiltrate	Total Score
1R	PMX-IE	2.5	2.5	2.0	2.0	1.0	2.0	12.0
2R	PMX-IE	2.0	2.0	2.0	2.0	0.5	0.5	9.0
3R	PMX-IE	2.0	2.0	2.0	2.0	0.5	1.0	9.5
1L	PMX-AE	2.0	2.5	3.0	2.0	1.5	0	11.0
2L	PMX-AE	2.0	2.0	3.0	2.0	0.5	0	9.5
3L	PMX-AE	2.0	2.0	2.5	1.5	1.0	0	9.0
4R	P+F-IE	1.5	1.5	1.5	1.0	0.5	0.5	6.5
5R	P+F-IE	2.0	1.5	1.5	2.0	1.0	2.5	10.5
6R	P+F-IE	2.0	2.0	2.5	2.0	1.0	1.5	11.0
4L	P+F-AE	2.0	2.0	2.0	1.5	1.0	0	8.5
5L	P+F-AE	2.5	2.5	2.5	2.0	1.0	0	10.5
6L	P+F-AE	2.0	2.5	3.0	2.0	1.0	0	10.5
7R	FARN-IE	1.5	1.5	1.5	1.5	1.0	2.0	9.0
8R	FARN-IE	1.5	1.0	1.0	1.5	0.5	1.5	7.0
9R	FARN-IE	1.5	1.5	1.5	2.0	1.0	2.0	9.5
7L	FARN-AE	2.0	2.0	2.0	2.0	2.0	1.0	11.0
8L	FARN-AE	1.5	1.5	1.5	1.5	1.0	0.5	7.5
9L	FARN-AE	1.5	1.5	1.5	1.5	1.0	1.0	8.0
10R	CON-IE	1.5	1.0	1.0	1.0	1.0	1.0	6.5
11R	CON-IE	1.0	1.0	1.0	1.5	1.0	1.0	6.5
12R	CON-IE	1.5	1.5	1.0	2.0	1.0	2.0	9.0
10L	CON-AE	1.0	1.5	2.0	1.0	0.5	0	6.0
11L	CON-AE	1.5	1.5	2.0	1.5	1.5	1.0	9.0
12L	CON-AE	1.5	1.5	2.0	1.5	1.5	1.0	9.0
Scale 0 = Normal; 0.5 = Trace; 1.0 = Mild; 1.5 = Mild/Moderate; 2.0 = Moderate; 2.5 = Moderate/Severe; 3.0 = Severe								

Clinical Evaluation - Statistics

[0180]

Descriptive Statistics Total	Total Ocular Score						
Variable	Count	Mean	SE Mean	StDev	Minimum	Median	Maximum
PMX-IE Score	3	10.167	0.928	1.607	9.000	9.500	12.000
PMX-AE Score	3	9.833	0.601	1.041	9.000	9.500	11.000
P+F-IE Score	3	9.33	1.42	2.47	6.50	10.50	11.00
P+F-AE Score	3	9.833	0.667	1.155	8.500	10.500	10.500

(continued)

Descriptive Statistics Total	Total Ocular Score						
Variable	Count	Mean	SE Mean	StDev	Minimum	Median	Maximum
FARN-IE Score	3	8.500	0.764	1.323	7.000	9.000	9.500
FARN-AE Score	3	8.83	1.09	1.89	7.50	8.00	11.00
CON-IE Score	3	7.333	0.833	1.443	6.500	6.500	9.000
CON-AE Score	3	8.00	1.00	1.73	6.00	9.00	9.00

Duncan Multiple Comparisons Test		Total Score		
Row #	Group/Level	Mean Rank	C.I. Overlaps	
1	CON-IE Sco	5.8333	2, 3, 4, 5, 6, 7, 8,	
2	CON-AE Sco	8.0000	1, 3, 4, 5, 6, 7, 8,	
3	FARN-IE Sc	10.8333	1, 2, 4, 5, 6, 7, 8,	
4	FARN-AE Sc	11.6667	1, 2, 3, 5, 6, 7, 8,	P=0.05
5	P+F-IE Sco	14.6667	1, 2, 3, 4, 6, 7, 8,	
6	P+F-AE Sco	15.3333	1, 2, 3, 4, 5, 7, 8,	
7	PMX-AE Sco	16.5000	1, 2, 3, 4, 5, 6, 8,	
8	PMX-IE Sco	17.1667	1, 2, 3, 4, 5, 6, 7,	

N0 Differences Among the Groups

[0181]

Microbiological Results

Inoculum = 1098 CFU/cornea

Data Display			CFU/ml					
Row	PMX-IE	PMX-AE	P+F-IE	P+F-AE	FARN-IE	FARN-AE	CON-IE	CON-AE
1	1650000	0	50	9500	45200000	7750000	115000000	30500
2	12500	12500	13600000	50	18600000	6650000	253000000	69000000
3	92000	350	5200000	8050	21400000	8250000	15000000	176000000

Row	Onset-IE	Onset-AE
1	75000	118000
2	59000	61000
3	55500	2500

Data Display		Log_{10} CFU/ml				
Row	PMX-IE Log	PMX-AE Log	P+F-IE Log	P+F-AE Log	FARN-IE Log	FARN-AE Log
1	6.21748	0.00000	1.69897	3.97772	7.65514	6.88930
2	4.09691	4.09691	7.13354	1.69897	7.26951	6.82282
3	4.96379	2.54407	6.71600	3.90580	7.33041	6.91645

			Onset-IE	Onset-AE
Row	CON-IE Log	CON-AE Log	Log	Log
1	8.06070	4.48430	4.87506	5.07188
2	8.40312	7.83885	4.77085	4.78533
3	7.17609	8.24551	4.74429	3.39794

Descriptive Statistics Total Log_{10} CFU/ml

Variable	Count	Mean	SE Mean	StDev	Minimum	Median	Maximum
PMX-IE Log	3	5.093	0.616	1.066	4.097	4.964	6.217
PMX-AE Log	3	2.21	1.19	2.07	0.00	2.54	4.10
P+F-IE Log	3	5.18	1.75	3.02	1.70	6.72	7.13
P+F-AE Log	3	3.194	0.748	1.295	1.699	3.906	3.978
FARN-IE Log	3	7.418	0.120	0.207	7.270	7.330	7.655
FARN-AE Log	3	6.8762	0.0278	0.0482	6.8228	6.8893	6.9165
CON-IE Log	3	7.880	0.366	0.633	7.176	8.061	8.403
CON-AE Log	3	6.86	1.19	2.06	4.48	7.84	8.25
Onset-IE Log	3	4.7967	0.0399	0.0691	4.7443	4.7709	4.8751
Onset-AE Log	3	4.418	0.517	0.895	3.398	4.785	5.072

Microbiological Results - Intact Epithelium

[0182] Kruskal-Wallis ANOVA with Duncan Multiple Comparisons Test - Log_{10} CFU/ml

Row #	Group/Level	Mean Rank	C.I. Overlaps
1	Onset-IE L	4.0000	2,3,
2	PMX-IE Log	5.0000	1,3,
3	P+F-IE Log	6.0000	1,2, P=0.05
4	FARN-IE Lo	12.0000	5,
5	CON-IE Log	13.0000	4,

ONSET = PMX = P+F < FARN = CON

Microbiological Results - Abraded Epithelium

Kruskal-Wallis ANOVA with Duncan Multiple Comparisons Test - Log_{10} CFU/ml

Row #	Group/Level	Mean Rank	C.I. Overlaps
1	PMX-AE Log	3.6667	2,3,
2	P+F-AE Log	4.3333	1,3,
3	Onset-AE L	7.6667	1, 2, P=0.05
4	FARN-AE Lo	12.0000	5,
5	CON-AE Log	12.3333	4,

PMX = P+F = ONSET < FARN = CON

Microbiological Results - 0.25% Oligomer 4 w/o FARN vs. w/ FARN - Intact Epithelium

Mann-Whitney Test and CI: PMX-IE Log, P+F-IE Log

	N	Median
PMX-IE Log	3	4.964
P+F-IE Log	3	6.716

Point estimate for ETA1-ETA2 is -0.916
91.9 Percent CI for ETA1-ETA2 is (-3.034,4.518)
W = 9.0
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.6625 NS

Microbiological Results - 0.25% Oligomer 4 w/o FARN vs. w/ FARN - Abraded Epithelium

Mann-Whitney Test and CI: PMX-AE Log, P+F-AE Log

	N	Median
PMX-AE Log	3	2.544
P+F-AE Log	3	3.906

Point estimate for ETA1-ETA2 is -1.362
91.9 Percent CI for ETA1-ETA2 is (-3.977,2.399)
W = 10.0
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 1.0000 NS

Microbiological Results - Intact vs. Abraded Epithelium

Mann-Whitney Test and CI: PMX-IE Log, PMX-AE Log

	N	Median
PMX-IE Log	3	4.964
PMX-AE Log	3	2.544

Point estimate for ETA1-ETA2 is 2.420
91.9 Percent CI for ETA1-ETA2 is (0.001,6.218)
W = 14.5
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.1266
The test is significant at 0.1212 NS (adjusted for ties)

Mann-Whitney Test and CI: P+F-IE Log, P+F-AE Log

	N	Median
P+F-IE Log	3	6.716
P+F-AE Log	3	3.906

Point estimate for ETA1-ETA2 is 2.810
91.9 Percent CI for ETA1-ETA2 is (-2.277,5.436)
W = 12.5
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.5127
The test is significant at 0.5066 NS (adjusted for ties)

Mann-Whitney Test and CI: FARN-IE Log, FARN-AE Log

	N	Median
FARN-IE Log	3	7.3304
FARN-AE Log	3	6.8893

Point estimate for ETA1-ETA2 is 0.4467
91.9 Percent CI for ETA1-ETA2 is (0.3532,0.8323)
W = 15.0
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.0809 NS

Mann-Whitney Test and CI: CON-IE Log, CON-AE Log

	N	Median
CON-IE Log	3	8.061
CON-AE Log	3	7.839

Point estimate for ETA1-ETA2 is 0.222
91.9 Percent CI for ETA1-ETA2 is (-1.070,3.917)
W = 12.0
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.6625 NS

Mann-Whitney Test and CI: Onset-IE Log, Onset-AE Log

	N	Median
Onset-IE Log	3	4.771
Onset-AE Log	3	4.785

Point estimate for ETA1-ETA2 is -0.015
91.9 Percent CI for ETA1-ETA2 is (-0.328,1.477)
W = 10.0
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 1.0000 NS

Summary of Statistical Comparisons for Microbiological Data

< = Significantly Fewer Colony Counts

[0183]

Effect of Abraded Epithelium on Effectiveness of Each Test Solution or Onset Control	
PMX	Abraded = Intact
P+F	Abraded = Intact
FARN	Abraded = Intact
Saline Control	Abraded = Intact
Onset of Therapy Control	Abraded = Intact

Effect of Test Solutions on Corneas with Intact Epithelium

[0184] ONSET = PMX = P+F < FARN = CON

Effect of Test Solutions on Corneas with Abraded Epithelium

[0185] PMX = P+F = ONSET < FARN = CON

Effect of Farnesol on 0.25% Oligomer 4 on Corneas with Intact Epithelium

[0186] PMX = P+F

Effect of Farnesol on 0.25% Oligomer 4 on Corneas with Abraded Epithelium

[0187] PMX = P+F

Summary of Results

[0188] 0.25% Oligomer 4 (PMX) and 0.25% Oligomer 4 with 200 mM Farnesol (P+F) were effective in reducing fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* colony counts compared with the Saline Control in the NZW rabbit keratitis model when the corneal epithelium was intact or removed from the corneas. 0.25% Oligomer 4 (PMX) and 0.25% Oligomer 4 with 200 mM Farnesol (P+F) were not effective in reducing fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* colony counts compared with the Onset of Therapy Control in the NZW rabbit keratitis model when the corneal epithelium was intact or removed from the corneas. There was no difference in fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* colony counts in the NZW rabbit keratitis model between 0.25% Oligomer 4 (PMX) and 0.25% Oligomer 4 with 200 mM Farnesol (P+F) with intact or abraded corneal epithelium. 200 mM Farnesol alone was NOT effective in reducing colony counts fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* colony counts compared with the Saline Control in the NZW rabbit keratitis model. 0.25% Oligomer 4 (PMX) and 0.25% Oligomer 4 with 200 mM Farnesol (P+F) and 200 mM Farnesol alone did not induce statistically greater toxicity (as manifested by higher Total Ocular Scores) compared with the Saline treated eyes in eyes with intact or abraded corneal epithelia.

[0189] The biomimetic Oligomer 4 alone or in combination with 200 mM Farnesol were effective in reducing the number

fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* colony counts in the NZW rabbit keratitis model compared with the Saline Control compared with the Saline Control. However, Oligomer 4 alone or in combination with 200 mM Farnesol were not effective in reducing fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* colony counts whether when the corneal epithelium was intact or removed compared with the Onset of Therapy Control in the fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* NZW rabbit keratitis model indicating the compounds did not significantly reduce the bacterial load present at the onset of therapy. The addition of 200 mM Farnesol did not appear aid in the penetration of 0.25% Oligomer 4 through the intact corneal epithelium to the site of the infection in the corneal stroma nor enhance its antibacterial efficacy in the fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* NZW rabbit keratitis model. In the current study, Oligomer 4 alone or in combination with 200 mM Farnesol did not induced significantly greater toxicity in infected rabbit eyes compared with the Saline treated Control in the fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* NZW rabbit keratitis model. The results from this study essentially reproduce those obtained in previous studies.

Example 4: Ker-4

Definitions of Abbreviations

[0190]

PMX-IE	0.25% Oligomer 4 with Intact Epithelium
PMX-AE	0.25% Oligomer 4 with Abraded Epithelium
P+F-IE	0.25% Oligomer 4 + 200 μM Farnesol with Intact Epithelium
P+F-AE	0.25% Oligomer 4 + 200 μM Farnesol with Abraded Epithelium
FARN-IE	200 μM Farnesol with Intact Epithelium
FARN-AE	200 μM Farnesol with Abraded Epithelium
CON-AE	Tris-Buffered Saline Control with Abraded Epithelium
CON-IE	Tris-Buffered Saline Control with Intact Epithelium

Clinical Evaluation - Statistics

[0191]

Data Display	Total Ocular Score								
Row	PMX-IE	PMX-AE	P+F-IE	P+F-AE	FARN-IE	FARN-AE	CON-IE	CON-AE	
1	6.5	9.5	13.0	9.5	10.0	11.0	9.5	10.0	
2	13.0	10.5	8.0	8.5	10.0	8.5	11.0	14.0	Ker-3
3	16.5	12.0	12.5	10.0	8.5	8.5	9.5	10.5	
4	12.0	11.0	6.5	8.5	9.0	11.0	6.5	6.0	
5	9.0	9.5	10.5	10.5	7.0	7.5	6.5	9.0	Ker-4
6	9.5	9.0	11.0	10.5	9.5	8.0	9.0	9.0	

Descriptive Statistics	Total Ocular Score						
Variable	Total Count	Mean	SE Mean	StDev	Minimum	Median	Maximum
PMX-IE Score	6	11.08	1.43	3.51	6.50	10.75	16.50
PMX-AE Score	6	10.250	0.461	1.129	9.000	10.000	12.000
P+F-IE Score	6	10.25	1.04	2.54	6.50	10.75	13.00
P+F-AE Score	6	9.583	0.375	0.917	8.500	9.750	10.500
FARN-IE Score	6	9.000	0.465	1.140	7.000	9.250	10.000
FARN-AE Score	6	9.083	0.625	1.530	7.500	8.500	11.000
CON-IE Score	6	8.667	0.738	1.807	6.500	9.250	11.000
CON-AE Score	6	9.75	1.06	2.60	6.00	9.50	14.00

Duncan Multiple Comparisons Test			Total Score	
Row #	Group/Level	Mean Rank	C.I. Overlaps	
1	CON-IE Sco	18.5833	2, 3, 4, 5, 6, 7, 8,	
2	FARN-AE Sc	19.5833	1, 3, 4, 5, 6, 7, 8,	
3	FARN-IE Sc	19.7500	1, 2, 4, 5, 6, 7, 8,	
4	P+F-AE Sco	24.2500	1, 2, 3, 5, 6, 7, 8,	P=0.05
5	CON-AE Sco	24.4167	1, 2, 3, 4, 6, 7, 8,	
6	P+F-IE Sco	29.0833	1, 2, 3, 4, 5, 7, 8,	
7	PMX-IE Sco	30.1667	1, 2, 3, 4, 5, 6, 8,	
8	PMX-AE Sco	30.1667	1, 2, 3, 4, 5, 6, 7,	

No Differences Among the Groups

Microbiological Results

[0192]

Data Display			CFU/ml				
Row	PMX-IE	PMX-AE	P+F-IE	P+F-AE	FARN-IE	FARN-AE	
1	0	0	11950000	255	15200000	7500000	
2	16750000	0	415000	1100000	18150000	1285000	Ker-3
3	5800000	995000	16650000	35500	30100000	1400000	
4	1650000	0	50	9500	45200000	7750000	
5	12500	12500	13600000	50	18600000	6650000	Ker-4
6	92000	350	5200000	8050	21400000	8250000	

Row	CON-IE	CON-AE	Onset-IE	Onset-AE	
1	467000000	1650000	15000	1635000	
2	221500000	23500000	107000	130000	PMX-Ker-3
3	202000000	5400000	132500	133000	
4	115000000	30500	75000	118000	
5	253000000	69000000	59000	61000	PMX-Ker-4
6	15000000	176000000	55500	2500	

Data Display			Log_{10} CFU/ml				
Row	PMX-IE	Log PMX-AE	Log P+F-IE Log	P+F-AE Log	FARN-IE Log	FARN-AE	Log
1	0.00000	0.00000	7.07737	2.40654	7.18184	6.87506	
2	7.22401	0.00000	5.61805	6.04139	7.25888	6.10890	K-3
3	6.76343	5.99782	7.22141	4.55023	7.47857	6.14613	
4	6.21748	0.00000	1.69897	3.97772	7.65514	6.88930	
5	4.09691	4.09691	7.13354	1.69897	7.26951	6.82282	K-4
6	4.96379	2.54407	6.71600	3.90580	7.33041	6.91645	

Row	CON-IE Log	CON-AE Log	Onset-IE Log	Onset-AE Log	
1	8.66932	6.21748	4.17609	6.21352	
2	8.34537	7.37107	5.02938	5.11394	PMX-Ker-3

(continued)

Row	CON-IE Log	CON-AE Log	Onset-IE Log	Onset-AE Log	
3	8.30535	6.73239	5.12222	5.12385	
4	8.06070	4.48430	4.87506	5.07188	
5	8.40312	7.83885	4.77085	4.78533	PMX-Ker-4
6	7.17609	8.24551	4.74429	3.39794	

Descriptive Statistics		Log_{10} CFU/ml					
Variable	Total Count	Mean	SE Mean	StDev	Minimum	Median	Maximum
PMX-IE Log	6	4.88	1.08	2.66	0.00	5.59	7.22
PMX-AE Log	6	2.11	1.04	2.55	0.00	1.27	6.00
p+F-IE Log	6	5.911	0.876	2.147	1.699	6.897	7.221
p+F-AE Log	6	3.763	0.632	1.548	1.699	3.942	6.041
FARN-IE Log	6	7.3624	0.0712	0.1744	7.1818	7.3000	7.6551
FARN-AE Log	6	6.626	0.158	0.388	6.109	6.849	6.916
CON-IE Log	6	8.160	0.212	0.520	7.176	8.325	8.669
CON-AE Log	6	6.815	0.554	1.356	4.484	7.052	8.246
Onset-IE Log	6	4.786	0.136	0.333	4.176	4.823	5.122
Onset-AE Log	6	4.951	0.370	0.906	3.398	5.093	6.214

Microbiological Results - Intact Epithelium

[0193] Kruskal-Wallis ANOVA with Duncan Multiple Comparisons Test - Log_{10} CFU/ml

Row #	Group/Level	Mean Rank	C.I. Overlaps	
1	Onset-IE L	6.8333	2, 3,	
2	PMX-IE Log	9.6667	1, 3,	
3	P+F-IE Log	12.6667	1, 2,	P=0.05
4	FARN-IE Lo	22.1667	5,	
5	CON-IE Log	26.1667	4,	
ONSET = PMX = P+F < FARN = CON				

Microbiological Results - Abraded Epithelium

Kruskal-Wallis ANOVA with Duncan Multiple Comparisons Test - Log_{10} CFU/ml

[0194]

Row #	Group/Level	Mean Rank	C.I. Overlaps	
1	PMX-AE Log	6.5000	2,	
2	P+F-AE Log	9.3333	1,	
3	Onset-AE L	14.3333		P=0.05
4	FARN-AE Lo	23.5000	5,	
5	CON-AE Log	23.8333	4,	
PMX = P+F < ONSET < FARN = CON				

Microbiological Results - 0.25% Oligomer 4 w/o FARN vs. w/ FARN - Intact Epithelium

Mann-Whitney Test and CI: PMX-IE Log, P+F-IE Log

[0195]

	N	Median
PMX-IE Log	6	5.591
P+F-IE Log	6	6.897

Point estimate for ETA1-ETA2 is -0.757
95.5 Percent CI for ETA1-ETA2 is (-3.124,1.607)
W = 34.0
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.4712 NS

Microbiological Results - 0.25% Oligomer 4 w/o FARN vs. w/ FARN - Abraded Epithelium

Mann-Whitney Test and CI: PMX-AE Log, P+F-AE Log

[0196]

	N	Median
PMX-AE Log	6	1.272
P+F-AE Log	6	3.942

Point estimate for ETA1-ETA2 is -1.822
95.5 Percent CI for ETA1-ETA2 is (-4.549,1.690)
W = 32.0
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.2980
The test is significant at 0.2946 NS (adjusted for ties)

Microbiological Results - Intact vs. Abraded Epithelium

Mann-Whitney Test and CI: PMX-IE Log, PMX-AE Log

[0197]

	N	Median
PMX-IE Log	6	5.591
PMX-AE Log	6	1.272

Point estimate for ETA1-ETA2 is 3.400
95.5 Percent CI for ETA1-ETA2 is (0.001,6.764)
W = 50.0
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.0927
The test is significant at 0.0864 NS (adjusted for ties)

Mann-Whitney Test and CI: P+F-IE Log, P+F-AE Log

[0198]

	N	Median
P+F-IE Log	6	6.897
P+F-AE Log	6	3.942

Point estimate for ETA1-ETA2 is 2.705
95.5 Percent CI for ETA1-ETA2 is (-0.423,4.727)
W = 50.5
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.0782
The test is significant at 0.0776 NS (adjusted for ties)

Mann-Whitney Test and CI: FARN-IE Log, FARN-AE Log

[0199]

	N	Median	
FARN-IE Log	6	7.3000	
FARN-AE Log	6	6.8489	FARN-AE < FARN-IE

Point estimate for ETA1-ETA2 is 0.5964
95.5 Percent CI for ETA1-ETA2 is (0.3588,1.1843)
W = 57.0
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.0051

Mann-Whitney Test and CI: CON-IE Log, CON-AE Log

[0200]

	N	Median	
CON-IE Log	6	8.325	
CON-AE Log	6	7.052	CON-AE < CON-IE

Point estimate for ETA1-ETA2 is 1.003
95.5 Percent CI for ETA1-ETA2 is (0.100,2.691)
W = 53.0
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.0306

Mann-Whitney Test and CI: Onset-IE Log, Onset-AE Log

[0201]

	N	Median
Onset-IE Log	6	4.823
Onset-AE Log	6	5.093

Point estimate for ETA1-ETA2 is -0.218
95.5 Percent CI for ETA1-ETA2 is (-1.091,0.778)
W = 32.0
Test of ETA1 = ETA2 vs ETA1 not = ETA2 is significant at 0.2980 NS

Summary of Statistical Comparisons for Microbiological Data

< = Significantly Fewer Colony Counts

Effect of Abraded Epithelium on Effectiveness of Each Test Solution or Onset Control

[0202]

PMX	Abraded = Intact
P+F	Abraded = Intact

(continued)

FARN	Abraded < Intact
Saline Control	Abraded < Intact
Onset of Therapy Control	Abraded = Intact

Effect of Test Solutions on Corneas with Intact Epithelium

[0203] ONSET = PMX = P+F < FARN = CON

Effect of Test Solutions on Corneas with Abraded Epithelium

[0204] PMX = P+F < ONSET < FARN = CON

Effect of Farnesol on 0.25% Oligomer 4 on Corneas with Intact Epithelium

[0205] PMX = P+F

Effect of Farnesol on 0.25% Oligomer 4 on Corneas with Abraded Epithelium

[0206] PMX = P+F

Summary of Results

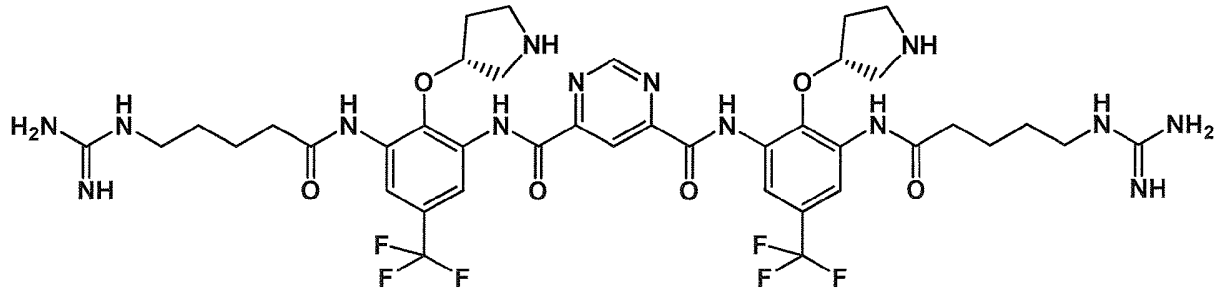
[0207] 0.25% Oligomer 4 (PMX) and 0.25% Oligomer 4 with 200 mM Farnesol (P+F) were effective in reducing fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* colony counts compared with the Saline Control in the NZW rabbit keratitis model when the corneal epithelium was intact or removed from the corneas. 0.25% Oligomer 4 (PMX) and 0.25% Oligomer 4 with 200 mM Farnesol (P+F) were effective in reducing fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* colony counts compared with the Onset of Therapy Control in the NZW rabbit keratitis model when the corneal epithelium was removed but not when the epithelium was intact. There was no difference in fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* colony counts in the NZW rabbit keratitis model between 0.25% Oligomer 4 (PMX) and 0.25% Oligomer 4 with 200 mM Farnesol (P+F) with intact or abraded corneal epithelium. 200 mM Farnesol alone was not effective in reducing colony counts fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* colony counts compared with the Saline Control in the NZW rabbit keratitis model. Eyes treated with 200 mM Farnesol alone and Saline demonstrated significantly fewer colony counts in eyes with the corneal epithelium removed compared to those with intact epithelium. 0.25% Oligomer 4 (PMX) and 0.25% Oligomer 4 with 200 mM Farnesol (P+F) and 200 mM Farnesol alone did not induce statistically greater toxicity (as manifested by higher Total Ocular Scores) compared with the Saline treated eyes in eyes with intact or abraded corneal epithelia.

[0208] The biomimetic Oligomer 4 was effective in significantly reducing colony counts in a fluoroquinolone-resistant, methicillin-resistant *Staphylococcus aureus* NZW rabbit keratitis model. Oligomer 4 formulations were effective when the corneal epithelium was removed suggesting that epithelium appears to be barrier for penetration of Oligomer 4 to the site of infection in the corneal stroma. The addition of 200 mM Farnesol did nothing to promote penetration Oligomer 4 through intact corneal epithelium, nor did it enhance its antibacterial efficacy. In fact, a trend toward antagonism was observed. Mechanical abrasion of the corneal epithelium alone reduced the bacterial colony counts in the control eyes. Therefore, the lower colony counts observed in the Oligomer 4-treated abraded eyes does not necessarily indicate greater drug efficacy. No significant ocular toxicity was observed for any formulation in this rabbit keratitis model.

[0209] Having now fully described this invention, it will be understood to those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All documents, e.g., scientific publications, patents, patent applications, and patent publications recited herein are hereby referred to in their entirety. Where the document cited only provides the first page of the document, the entire document is intended, including the remaining pages of the document.

Claims

1. An ophthalmic or otic composition comprising a compound having the formula:



or a pharmaceutically acceptable salt thereof.

2. The ophthalmic or otic composition of claim 1 which is in the form of a liquid or solid.

3. The ophthalmic or otic composition of claim 1 which is in the form of a solution, a suspension, an emulsion, a gel, or an ointment.

4. The ophthalmic or otic composition of claim 1 further comprising a preservative, a stabilizer, an antioxidant, a chelating agent, or a surfactant.

5. The ophthalmic or otic composition of claim 1 further comprising an additional medicament.

6. The ophthalmic or otic composition of claim 5 wherein the additional medicament is chosen from an antibiotic, an anti-inflammatory agent, an anesthetic agent, an anti-allergic agent, an acetylcholine blocking agent, an adrenergic agonist, a beta-adrenergic blocking agent, an anti-glaucoma agent, and an anti-hypertensive agent.

7. The ophthalmic or otic composition of claim 6 wherein the antibiotic is chosen from an aminoglycoside, a cephalosporin, a diaminopyridine, a fluoroquinolone, a sulfonamide, and a tetracycline.

8. The ophthalmic or otic composition of claim 6 wherein the antibiotic is chosen from amikacin, azithromycin, cefixime, cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, chloramphenicol, ciprofloxacin, clindamycin, colistin, domeclocycline, doxycycline, erythromycin, gentamicin, mafenide, methacycline, minocycline, neomycin, norfloxacin, ofloxacin, oxytetracycline, polymyxin B, pyrimethamine, silver sulfadiazine, sulfacetamide, sulfisoxazole, tetracycline, tobramycin, and trimethoprim.

9. The ophthalmic or otic composition of claim 6 wherein the anti-inflammatory agent is a steroidal agent.

10. The ophthalmic or otic composition of claim 9 wherein the steroidal agent is chosen from dexamethasone, rimexolone, prednisolone, fluorometholone, and hydrocortisone.

11. The ophthalmic or otic composition of claim 6 wherein the anti-inflammatory agent is a non-steroidal agent.

12. The ophthalmic or otic composition of claim 11 wherein the non-steroidal agent is chosen from a cyclooxygenase type I or type II inhibitor, a PAF antagonist, a PDE IV inhibitor, and an inhibitor of cytokine production.

13. The ophthalmic or otic composition of claim 12 wherein the cyclooxygenase type I or type II inhibitor is chosen from diclofenac, flurbiprofen, ketorolac, suprofen, nepafenac, amfenac, indomethacin, naproxen, ibuprofen, bromfenac, ketoprofen, meclofenamate, piroxicam, sulindac, mefanamic acid, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, tenoxicam, carprofen, vioxx, celecoxib, and etodolac.

14. The ophthalmic or otic composition of claim 12 wherein the PAF antagonist is chosen from apafant, bepafant, minopafant, nupafant, and modipafant.

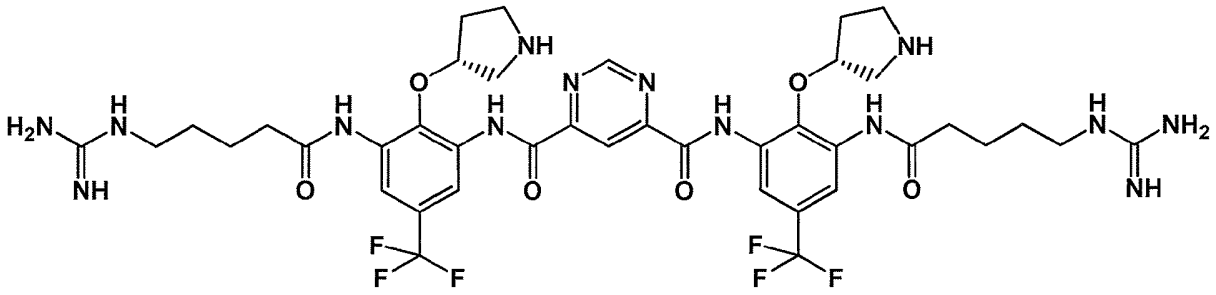
15. The ophthalmic or otic composition of claim 12 wherein the PDE IV inhibitor is chosen from ariflo, torbafylline, rolipram, filaminast, piclamilast, cipamfylline, and roflumilast.

16. The ophthalmic or otic composition of claim 6 wherein the anti-allergic agent is pemirolast or olopatadine.

17. The ophthalmic or otic composition of claim 6 wherein the anti-allergic agent is a corticosteroid.

18. The ophthalmic or otic composition of claim 17 wherein the corticosteroid is chosen from prednisolone, fluorometholone, loteprenol, and dexamethasone.

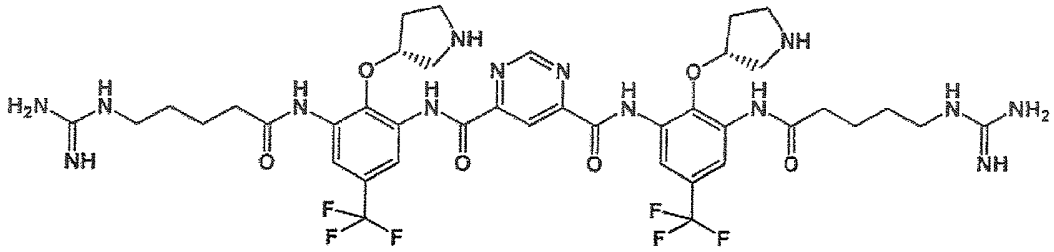
19. A compound having the formula:



20. An ophthalmic or otic composition according to any of claims 1 to 18 or a compound according to claim 19 for use in the treatment of a bacterial ophthalmic or otic infection in a mammal.

Patentansprüche

1. Ophthalmische oder aurikulare Zusammensetzung, umfassend eine Verbindung mit der Formel:



oder ein pharmazeutisch verträgliches Salz davon.

2. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 1, die in der Form einer Flüssigkeit oder eines Feststoffes ist.

3. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 1, die in der Form einer Lösung, einer Suspension, einer Emulsion, eines Gels oder einer Salbe ist.

4. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 1, des Weiteren umfassend ein Konservierungsmittel, einen Stabilisator, ein Antioxidations-mittel, ein Chelatisierungsmittel oder ein oberflächenaktives Mittel.

5. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 1, des Weiteren umfassend ein zusätzliches Medikament.

6. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 5, wobei das zusätzliche Medikament ausgewählt ist aus einem Antibiotikum, einem anti-inflammatorischen Mittel, einem Anästhetikum, einem anti-allergenen Mittel, einem Acetylcholin blockierenden Mittel, einem adrenergischen Antagonisten, einem beta-adrenergisch blockierendem Mittel, einem anti-Glaukom-Mittel, und einem blutdrucksenkenden Mittel.

7. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 6, wobei das Antibiotikum ausgewählt ist aus

einem Aminoglycosid, einem Cephalosporin, einem Diaminopyridin, einem Fluorchinolon, einem Sulfonamid und einem Tetra-cyclin.

8. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 6, wobei das Antibiotikum ausgewählt ist aus Amikacin, Azithromycin, Cefixim, Cefoperazon, Cefotaxim, Ceftazidim, Ceftizoxim, Ceftriaxon, Chloramphenicol, Ciprofloxacin, Clindamycin, Colistin, Domeclocyclin, Doxycyclin, Erythromycin, Gentamicin, Mafenid, Methacyclin, Minocyclin, Neomycin, Norfloxacin, Ofloxacin, Oxytetra-cyclin, Polymyxin B, Pyrimethamin, Silbersulfadiazin, Sulfacetamid, Sulfisoxazol, Tetracyclin, Tobramycin und Trimethoprim.

9. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 6, wobei das anti-inflammatorische Mittel ein steroidales Mittel ist.

10. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 9, wobei das steroidale Mittel ausgewählt ist aus Dexamethason, Rimexolon, Prednisolon, Fluorometholon und Hydrocortison.

11. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 6, wobei das anti-inflammatorische Mittel ein nicht-steroidales Mittel ist.

12. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 11, wobei das nicht-steroidale Mittel ausgewählt ist aus Cyclooxygenase Typ I oder Typ II-Inhibitor, einem PAF-Antagonisten, einem PDE IV-Inhibitor und einem Inhibitor der Cytokinproduktion.

13. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 12, wobei der Cyclooxygenase Typ I oder Typ II-Inhibitor ausgewählt ist aus Diclofenac, Flurbiprofen, Ketorolac, Suprofen, Nepafenac, Amfenac, Indomethacin, Napro-xen, Ibuprofen, Bromfenac, Ketoprofen, Meclofenamat, Piroxicam, Sulindac, Mefenaminsäure, Diflunisal, Oxaprozin, Tolmetin, Fenoprofen, Benoxaprofen, Nabumeton, Phenylbutazon, Aspirin, Oxyphenbutazon, Tenoxicam, Carprofen, Vioxx, Celecoxib, und Etodolac.

14. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 12, wobei der PAF-Antagonist ausgewählt ist aus Apafant, Bepafant, Minopafant, Nupafant und Modipafant.

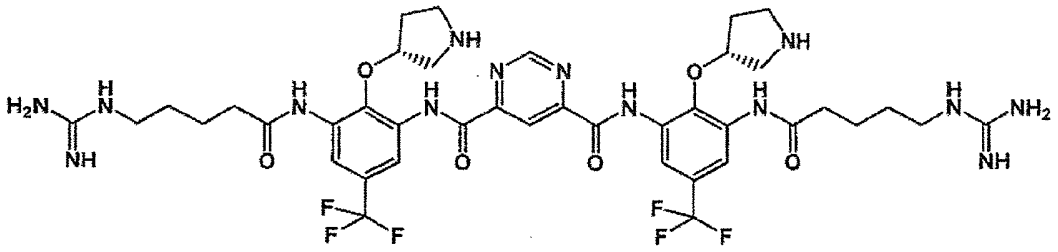
15. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 12, wobei der PDE IV-Inhibitor ausgewählt ist aus Ariflo, Torbafyllin, Rolipram, Filaminast, Piclamilast, Cipamfyllin und Roflumilast.

16. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 6, wobei das anti-allergene Mittel Pemirolast oder Olopatadin ist.

17. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 6, wobei das anti-allergene Mittel ein Corticosteroid ist.

18. Ophthalmische oder aurikulare Zusammensetzung nach Anspruch 17, wobei das Corticosteroid ausgewählt ist aus Prednisolon, Fluorometholon, Loteprednol und Dexamethason.

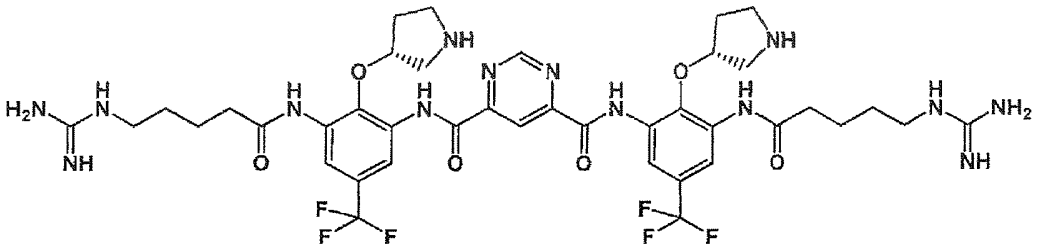
19. Verbindung mit der Formel:



20. Ophthalmische oder aurikulare Zusammensetzung gemäß einem beliebigen der Ansprüche 1 bis 18, oder eine Verbindung gemäß Anspruch 19, zur Verwendung in der Behandlung einer ophthalmischen oder aurikularen bakteriellen Infektion in einem Säuger.

Revendications

1. Composition ophtalmique ou otique comprenant un composé ayant la formule :



ou un sel pharmaceutiquement acceptable de celui-ci.

2. Composition ophtalmique ou otique selon la revendication 1, qui est sous la forme d'un liquide ou d'un solide.

3. Composition ophtalmique ou otique selon la revendication 1, qui est sous la forme d'une solution, d'une suspension, d'une émulsion, d'un gel, ou d'une pommade.

4. Composition ophtalmique ou otique selon la revendication 1, comprenant en outre un conservateur, un stabilisant, un antioxydant, un agent chélateur, ou un surfactant.

5. Composition ophtalmique ou otique selon la revendication 1, comprenant en outre un médicament supplémentaire.

6. Composition ophtalmique ou otique selon la revendication 5, dans laquelle le médicament supplémentaire est choisi parmi un antibiotique, un agent anti-inflammatoire, un agent anesthésique, un agent antiallergique, un agent bloqueur de l'acétylcholine, un agoniste adrénergique, un agent bloquant bêta-adrénergique, un agent anti-glaucome, et un agent antihypertenseur.

7. Composition ophtalmique ou otique selon la revendication 6, dans laquelle l'antibiotique est choisi parmi un aminoglycoside, une céphalosporine, une diaminopyridine, une fluoroquinolone, un sulfonamide, et une tétracycline.

8. Composition ophtalmique ou otique selon la revendication 6, dans laquelle l'antibiotique est choisi parmi l'amikacine, l'azithromycine, le céfixime, la céfopérazone, le céfotaxime, le ceftazidime, le ceftizoxime, la ceftriaxone, le chloramphénicol, la ciprofloxacine, la clindamycine, la colistine, la doméclocycline, la doxycycline, l'érythromycine, la gentamicine, le mafénide, la méthacycline, la minocycline, la néomycine, la norfloxacine, l'ofloxacine, l'oxytétracycline, la polymyxine B, la pyriméthamine, la sulfadiazine d'argent, le sulfacétamide, le sulfisoxazole, la tétracycline, la tobramycine, et le triméthoprime.

9. Composition ophtalmique ou otique selon la revendication 6, dans laquelle l'agent anti-inflammatoire est un agent stéroïdien.

10. Composition ophtalmique ou otique selon la revendication 9, dans laquelle l'agent stéroïdien est choisi parmi la dexaméthasone, la rimexolone, la prednisolone, la fluorométholone, et l'hydrocortisone.

11. Composition ophtalmique ou otique selon la revendication 6, dans laquelle l'agent anti-inflammatoire est un agent non stéroïdien.

12. Composition ophtalmique ou otique selon la revendication 11, dans laquelle l'agent non stéroïdien est choisi parmi un inhibiteur de la cyclooxygénase de type I ou de type II, un antagoniste du PAF, un inhibiteur de la PDE IV, et un inhibiteur de la production de cytokines.

13. Composition ophtalmique ou otique selon la revendication 12, dans laquelle l'inhibiteur de la cyclooxygénase de type I ou de type II est choisi parmi le diclofénac, le flurbiprofène, le kétorolac, le suprofène, le népafénac, l'amfénac, l'indométacine, le naproxène, l'ibuprofène, le bromfénac, le kétoprofène, le méclofénamate, le piroxicam, le sulindac, l'acide méfénamique, le diflunisal, l'oxaprozine, la tolmétine, le fénoprofène, le bénoxaprofène, la nabumétone,

l'étodolac, la phénylbutazone, l'aspirine, l'oxyphenbutazone, le ténoxicam, le carprofène, le Vioxx, le célécoxib, et l'étodolac.

14. Composition ophtalmique ou otique selon la revendication 12, dans laquelle l'antagoniste du PAF est choisi parmi l'apafant, le bépafant, le minopafant, le nupafant, et le modipafant.

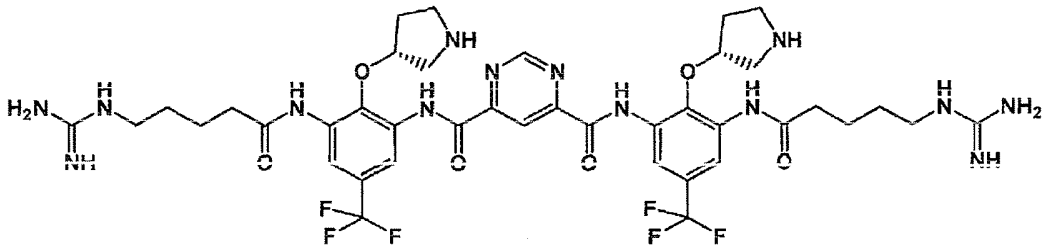
15. Composition ophtalmique ou otique selon la revendication 12, dans laquelle l'inhibiteur de la PDE IV est choisi parmi l'ariflo, la torbafylline, le rolipram, le filaminast, le piclamilast, la cipamfylline, et le roflumilast.

16. Composition ophtalmique ou otique selon la revendication 6, dans laquelle l'agent antiallergique est le pémirolast ou l'olopatadine.

17. Composition ophtalmique ou otique selon la revendication 6, dans laquelle l'agent antiallergique est un corticostéroïde.

18. Composition ophtalmique ou otique selon la revendication 17, dans laquelle le corticostéroïde est choisi parmi la prednisolone, la fluorométholone, le lotéprénol, et la dexaméthasone.

19. Composé ayant la formule :



20. Composition ophtalmique ou otique selon l'une quelconque des revendications 1 à 18 ou composé selon la revendication 19 pour une utilisation dans le traitement d'une infection bactérienne ophtalmique ou otique chez un mammifère.

REFERENCES CITED IN THE DESCRIPTION

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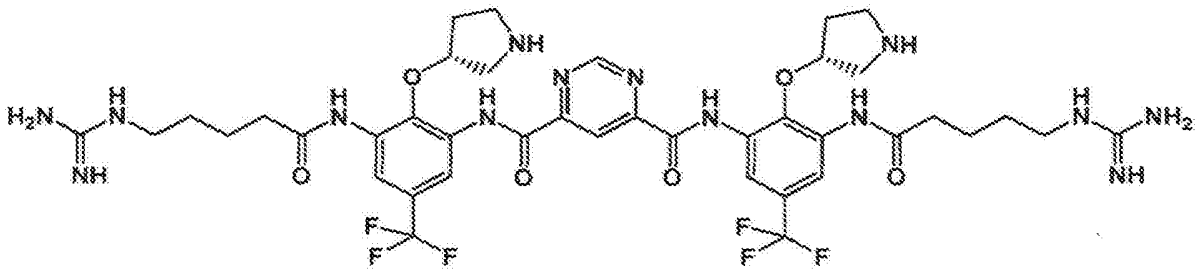
Szabadalmi igénypontok

1. Egy szemészeti vagy fülészeti készítmény, amely egy alábbi képletű vegyületet:



vagy egy gyógyászatilag elfogadható sóját tartalmazza.

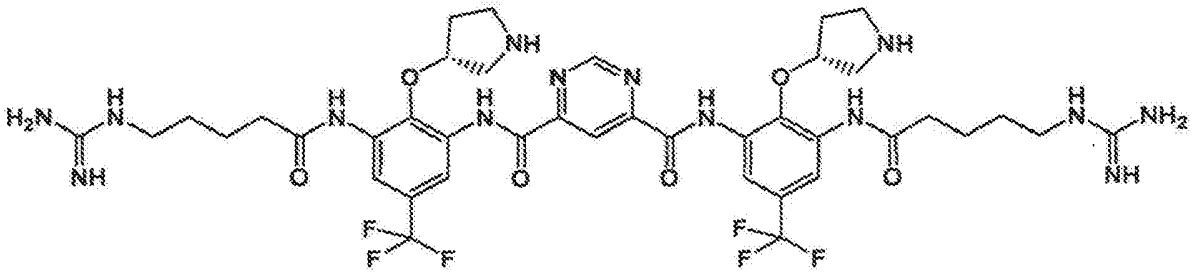
2. Az 1. igénypont szerinti szemészeti vagy fülészeti készítmény, amely egy folyadék vagy szilárdanyag formájában van.
3. Az 1. igénypont szerinti szemészeti vagy fülészeti készítmény, amely egy oldat, egy szuszpenzió, egy emulzió, egy gél vagy egy kenőcs formájában van.
4. Az 1. igénypont szerinti szemészeti vagy fülészeti készítmény, amely tartalmaz továbbá egy prezerváló szert, egy stabilizáló szert, egy antioxidánst, egy kelátképző szert vagy egy felületaktív anyagot.
5. Az 1. igénypont szerinti szemészeti vagy fülészeti készítmény, amely tartalmaz még egy további gyógyszert.
6. Az 5. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben a további gyógyszer a következőkből kerül kiválasztásra: egy antibiotikum, egy gyulladáscsökkentő szer, egy érzéstelenítő szer, egy allergia ellenes szer, egy acetilkolin-blokkoló szer, egy adrenerg agonista, egy béta-adrenerg blokkoló szer, egy glaukóma-elleni szer és egy vérnyomáscsökkentő szer.
7. A 6. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben az antibiotikum egy aminoglikozid, egy cefalosporin, egy diamino-piridin, egy fluorokinolon, egy szulfonamid és egy tetraciklin közül kerül kiválasztásra.
8. A 6. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben az antibiotikum a következőkből kerül kiválasztásra: amikacin, azitromicin, cefixim, cefoperazon, cefotaxim, ceftazidim, ceftizoxim, ceftriaxon, kloramfenikol, ciprofloxacin, clindamicin, colistin, domeklociklin, doxiciklin,

eritromicin, gentamicin, mafenid, metaciklin, minociklin, neomicin, norfloxacin, ofloxacin, oxitetraciklin, polimixin B, pirimetamin, ezüst-szulfadiazin, szulfacetamid, szulfizoxazol, tetraciklin, tobramicin és trimetoprim.

9. A 6. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben a gyulladáscsökkentő szer egy szteroid szer.
10. A 9. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben a szteroid szer dexametazon, rimexolon, prednizolon, fluorometolon és hidrokortizon közül kerül kiválasztásra.
11. A 6. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben a gyulladáscsökkentő szer egy nem-szteroid szer.
12. A 11. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben a nem-szteroid szer egy ciklooxigenáz I-típusú vagy II-típusú inhibitor, egy PAF antagonista, egy PDE IV inhibitor és a citokin-termelés egy inhibitora közül kerül kiválasztásra.
13. A 12. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben a ciklooxigenáz I-típusú vagy II-típusú inhibitor az alábbiakból kerül kiválasztásra: diclofenac, flurbiprofen, ketorolac, suprofen, nepafenac, amfenac, indometacin, naproxen, ibuprofen, bromfenac, ketoprofen, meclofenamat, piroxicam, sulindac, mefanaminsav, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetom, etodolac, fenilbutazon, aszpirin, oxifenbutazon, tenoxicam, carprofen, vioxx, celecoxib és etodolac.
14. A 12. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben a PAF antagonista apafant, bepafant, minopafant, nupafant és modipafant közül kerül kiválasztásra.
15. A 12. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben a PDE IV inhibitor ariflo, torbafillin, rolipram, filaminast, piclamilast, cipamfillin és roflumilast közül kerül kiválasztásra.
16. A 6. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben az allergia-ellení szer pemirolast vagy olopatadin.
17. A 6. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben az allergia ellenes szer egy kortikoszteroid.

18. A 17. igénypont szerinti szemészeti vagy fülészeti készítmény, amelyben a kortikoszteroid a prednizolon, fluorometolon, loteprenol és dexametazon közül kerül kiválasztásra.

19. Egy alábbi képletű vegyület:



20. Az 1-18. igénypontok bármelyike szerinti szemészeti vagy fülészeti készítmény vagy egy 19. igénypont szerinti vegyület egy bakteriális szem- vagy fül-fertőzés kezelésében történő alkalmazásra egy emlősben.

A meghatalmazott:

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