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(54) Title: COMBINATIONS COMPRISING A FLUOROQUINOLONE FOR TREATING, REDUCING, AMELIORATING, OR PREVENTING INFECTIONS

(57) Abstract: Compositions for treating, reducing, ameliorating, or preventing infections comprise a fluoroquinolone having Formulae I-VIII and an additional anti-infective agent. Methods for treating, reducing, ameliorating, or preventing such infection use such compositions. Such compositions and methods can be effective against mixed types of pathogens including certain antibiotic-resistant microbial pathogens found in such infections.

COMPOSITIONS AND METHODS FOR TREATING, REDUCING, AMELIORATING, OR PREVENTING INFECTIONS

BACKGROUND OF THE INVENTION

The present invention relates to compositions and methods for treating, reducing, ameliorating, or preventing infections. In particular, the present invention relates to such compositions comprising a quinolone carboxylic acid or a derivative thereof, and an additional anti-infective medicament; and to methods of using such compositions. More particularly, the present invention relates to such compositions comprising a fluoroquinolone carboxylic acid or a derivative thereof, and an additional anti-infective medicament; and to methods of using such compositions.

Pathogens continue to pose a serious threat to public health as indicated by a worldwide resurgence of diseases caused by bacteria, fungi, and/or viruses. Infections by pathogenic microorganisms affect a large number of patients every year. Common infections include those of the ear, respiratory system, and eye. An experienced medical practitioner often can determine the etiology of an infection and, therefore, prescribe an effective treatment. However, infections are often caused by mixed types of microorganisms that may not be immediately obvious on presentation. Consequently, an initial treatment regimen may not be immediately effective and must be replaced with another. In cases where the patients are especially vulnerable, such as those with a compromised immune system, a delayed onset of a beneficial effect of the treatment may lead to increased risk of more serious complications.

Otitis media, an infection of the middle ear, is a major worldwide infection in children. By the age of 2 years, seventy percent of children have experienced at least one episode of acute otitis media ("AOM"). T. Heikkinen et al., *Clin. Microbiol. Rev.*, Vol. 16, No. 2, 230 (2003). Otitis media can also occur in adults. AOM is generally considered a bacterial infection that is treated with antibiotics. The three most common bacteria isolated from the middle ear fluid ("MEF") are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. See; e.g., J.T. Kirchener, *American Family Physician*, April 15, 1999. However, since the 1980s, viruses have also been detected in the MEF of children with AOM in approximately twenty percent of the cases.

T. Heikkinen et al., *supra.* The common respiratory viruses such as human rhinovirus, respiratory syncytial virus, influenza viruses, and coronavirus, have been found in children MEF. In addition, in a recent study, fungal DNA was detected in MEF of some patients with recurrent AOM and serous otitis media.

In cases of otitis externa, an infection of the external ear canal, mixed bacteria and fungi have often been found. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most common bacteria species, and *Aspergillus* and *Candida* fungus species account for over ninety percent of the cases in which fungi are present. However, fungus is occasionally the primary pathogen in otitis externa, especially in the presence of moisture and heat. R. Sander, *American Family Physician*, Vol. 63, No.5, 927 (2001).

Infections of the upper respiratory system are also common. The common cold is mostly of viral etiology. However, bacteria and fungi have also often caused other infections of the upper respiratory system. Bacteria are the most common infectious agents in sinusitis. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* have been found in most of cases of sinusitis. Other possible bacterial culprits include other streptococcal strains and *Staphylococcus aureus*. While fungi are an uncommon cause of sinusitis, the incidence of such infections is increasing. The most common fungi involved in sinusitis are *Asperillus* species; in particular, *Asperillus fumigatus*. Other fungi that can cause sinusitis include *Curvularia* (in particular, *Curvularia lunata*), *Bipolaris*, *Exserohilum*, and *Mucomycosis*. See, Sinusitis, at http://adam.about.com (visited on February 20, 2007). While fungal sinusitis is mostly non-invasive and does not lead to serious complications, rare cases of invasive fungal sinusitis caused by the fungus *Scopulariopsis acremonium* have been reported. Invasive fungal sinusitis is potentially fatal for immunocompromised patients. M.D. Ellison et al., *Arch. Otolaryngol. Head Neck Surg.*, Vol. 124, 1014 (1998). It can lead to tissue invasion and destruction of adjacent structures (e.g., orbit, central nervous system). Therefore, early detection and treatment are vital for these patients.

Keratitis and conjunctivitis, two common ocular infections, are caused mostly by bacteria, fungi, and/or viruses. Numerous cocci (*Staphylococcus,*

Streptococcus, and *Neisseria* species) and bacilli (*Corynebacterium*, *Propionobacterium*, *Clostridium*, *Pseudomonas*, *Klebsiella*, *Hemophilus*, *Moraxella*, *Proteus*, *Serratia*, *Escherichia*, and *Enterobacter* species) have been isolated from cases of ocular infections. Among the fungi causing ocular infections are *Aspergillus*, *Fusarium*, and *Candida* species. *Herpes simplex* virus ("HSV"), *Varicella zoster* virus, *Andenovirus*, and *Molluscum contagiosum* have been found in cases of viral ocular infections. See; e.g., G.M. Bohigian and Shailaja Valluri, in *Handbook of Ocular Infections, Inflammation, and External Diseases*, Chapter 2. Moreover, several studies have identified mixed microorganism types in ocular infections, such as mixtures of bacteria and HSV, bacteria and *Andenovirus*, or bacteria and fungi. See; e.g., M.J. Bharathi et al., *Br. J. Ophthalmol.*, 90, 1271 (2006); S.K. Basak, *Indian J. Ophthalmol.*, Vol. 53, No. 1, 17 (2005).

An additional challenge in the treatment of infections is the emergence of bacterial resistance to antibiotics. Such resistance may be attributed to prior widespread, and largely effective, therapeutic and prophylactic use of antibiotics, which, unfortunately, over time has also selected for resistant strains of various bacterial pathogens. Of particular concern to the public health have been the emergence and proliferation of bacterial strains that are resistant to multiple antibiotics in the current arsenal of antimicrobial agents. Therefore, a condition may not respond to an initially prescribed therapy, and, in such a case, another medicament must be given, resulting in delayed control of the pathogen.

Therefore, there is a continued need to develop improved pharmaceutical compositions that can begin to provide benefits to patients in combating infections that do not have clear etiology, soon after being administered to the patients. It is also very desirable to provide pharmaceutical compositions that minimize the risk of complications of the primary infection due to the delayed onset of effectiveness of the treatment.

SUMMARY OF THE INVENTION

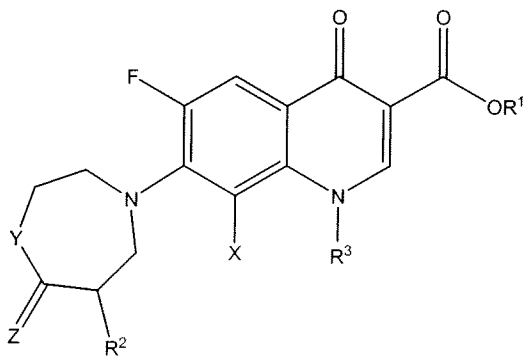
In general, the present invention provides pharmaceutical compositions and methods using such compositions for the treatment, reduction, amelioration, or prevention of infections.

In one aspect, the present invention provides pharmaceutical compositions and methods using such compositions for the treatment, reduction, amelioration, or prevention of infections of an eye, an ear, a portion of a respiratory system, or a combination thereof.

In another aspect, an etiology of such infections is not readily ascertainable upon presentation.

In still another aspect, such infections are caused by mixed types of microorganisms.

In still another aspect, such compositions comprise: (a) at least one member of a family of fluoroquinolones that have Formula I or salts thereof; and (b) an additional anti-infective medicament; wherein



(I)

wherein R^1 is selected from the group consisting of hydrogen, unsubstituted lower alkyl groups, substituted lower alkyl groups, cycloalkyl groups, unsubstituted C_5-C_{24} aryl groups, substituted C_5-C_{24} aryl groups, unsubstituted C_5-C_{24} heteroaryl groups,

substituted C_5-C_{24} heteroaryl groups, and groups that can be hydrolyzed in living bodies; R^2 is selected from the group consisting of hydrogen, unsubstituted amino group, and amino groups substituted with one or two lower alkyl groups; R^3 is selected from the group consisting of hydrogen, unsubstituted lower alkyl groups, substituted lower alkyl groups, cycloalkyl groups, unsubstituted lower alkoxy groups, substituted lower alkoxy groups, unsubstituted C_5-C_{24} aryl groups, substituted C_5-C_{24} aryl groups, unsubstituted C_5-C_{24} heteroaryl groups, substituted C_5-C_{24} heteroaryl groups, unsubstituted C_5-C_{24} aryloxy groups, substituted C_5-C_{24} aryloxy groups, unsubstituted C_5-C_{24} heteroaryloxy groups, substituted C_5-C_{24} heteroaryloxy groups, and groups that can be hydrolyzed in living bodies; X is selected from the group consisting of halogen atoms; Y is selected from the group consisting of CH_2, O, S, SO, SO_2, and NR^4, wherein R^4 is selected from the group consisting of hydrogen, unsubstituted lower alkyl groups, substituted lower alkyl groups, and cycloalkyl groups; and Z is selected from the group consisting of oxygen and two hydrogen atoms; and wherein the compositions are capable of inhibiting a growth or survival of mixed types of microorganisms causing said infections.

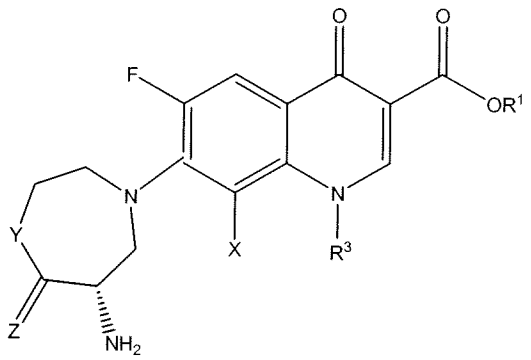
In still another aspect, said additional anti-infective medicament comprises a quinolone other than those represented by Formula I.

In still another aspect, said additional anti-infective medicament comprises a quinolone other than those represented by Formula I, and another agent selected from the group consisting of antiviral agents, antifungal agents, antiprotozoal agents, and combinations thereof.

In yet another aspect, said additional anti-infective medicament is selected from the group consisting of antifungal agents, antiviral agents, and combinations thereof.

In a further aspect, a composition of the present invention comprises a single enantiomer of a compound having Formula I, and an additional anti-infective medicament.

In still another aspect, a composition of the present invention comprises: (a) a member of a family of fluoroquinolones having Formula II or salts thereof; and (b) an additional anti-infective medicament; wherein



(II)

wherein R^1, R^3, X, Y, and Z have the meanings as disclosed above; and wherein the composition is capable of inhibiting a growth or survival of mixed types of microorganisms causing an infection.

In still another aspect, the present invention provides a method for treating, reducing, ameliorating, or preventing an infection of an ear, a portion of a respiratory system, an eye, or a combination thereof. The method comprises administering a composition comprising: (a) a fluoroquinolone having Formula I or II; and (b) an additional anti-infective medicament, to a site of infection to treat, reduce, or ameliorate said infection.

In one embodiment, the method comprises topically administering such a composition. In another embodiment, the method comprises orally administering such a composition.

In yet another aspect, said infection comprises infections of an ear, a portion of an upper respiratory system, an eye, or a combination thereof.

Other features and advantages of the present invention will become apparent from the following detailed description and claims.

DETAILED DESCRIPTION

As used herein, the term "lower alkyl" or "lower alkyl group" means a C_1-C_{15} linear- or branched-chain saturated aliphatic hydrocarbon monovalent group, which may be unsubstituted or substituted. The group may be partially or completely substituted with halogen atoms (F, Cl, Br, or I). Non-limiting examples of lower alkyl groups include methyl, ethyl, n-propyl, 1-methylethyl (or isopropyl), n-butyl, n-pentyl, 1,1-dimethylethyl (or t-butyl), and the like. It may be abbreviated as "Alk".

As used herein, the term "lower alkoxy" or "lower alkoxy group" means a C_1-C_{15} linear- or branched-chain saturated aliphatic alkoxy monovalent group, which may be unsubstituted or substituted. The group may be partially or completely substituted with halogen atoms (F, Cl, Br, or I). Non-limiting examples of lower alkoxy groups include methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, n-pentoxy, t-butoxy, and the like.

The term "cycloalkyl" or "cycloalkyl group" means a stable aliphatic saturated 3- to 15-membered monocyclic or polycyclic monovalent radical consisting solely of carbon and hydrogen atoms which may comprise one or more fused or bridged ring(s), preferably a 3- to 7-membered monocyclic rings. Other exemplary embodiments of cycloalkyl groups include 7- to 10-membered bicyclic rings. Unless otherwise specified, the cycloalkyl ring may be attached at any carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable carbon atom which results in a stable structure. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, norbornyl, adamantyl, tetrahydronaphthyl (tetralin), 1-decalinyl, bicyclo[2.2.2]octanyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the like.

As used herein, the term "aryl" or "aryl group" means an aromatic carbocyclic monovalent or divalent radical. In some embodiments, the aryl group has a number of carbon atoms from 5 to 24 and has a single ring (e.g., phenyl or phenylene), multiple condensed rings (e.g., naphthyl or anthranyl), or multiple bridged rings (e.g., biphenyl). Unless otherwise specified, the aryl ring may be attached at any suitable

carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable carbon atom which results in a stable structure. Non-limiting examples of aryl groups include phenyl, naphthyl, anthryl, phenanthryl, indanyl, indenyl, biphenyl, and the like. It may be abbreviated as "Ar".

The term "heteroaryl" or "heteroaryl group" means a stable aromatic monocyclic or polycyclic monovalent or divalent radical, which may comprise one or more fused or bridged ring(s). In some embodiments, the heteroaryl group has 5-24 members, preferably a 5- to 7-membered monocyclic or 7- to 10-membered bicyclic radical. The heteroaryl group can have from one to four heteroatoms in the ring(s) independently selected from nitrogen, oxygen, and sulfur, wherein any sulfur heteroatoms may optionally be oxidized and any nitrogen heteroatom may optionally be oxidized or be quaternized. Unless otherwise specified, the heteroaryl ring may be attached at any suitable heteroatom or carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable heteroatom or carbon atom which results in a stable structure. Non-limiting examples of heteroaryls include furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolizinyl, azaindolizinyl, indolyl, azaindolyl, diazaindolyl, dihydroindolyl, dihydroazaindoyl, isoindolyl, azaisoindolyl, benzofuranyl, furanopyridinyl, furanopyrimidinyl, furanopyrazinyl, furanopyridazinyl, dihydrobenzofuranyl, dihydrofuranopyridinyl, dihydrofuranopyrimidinyl, benzothienyl, thienopyridinyl, thienopyrimidinyl, thienopyrazinyl, thienopyridazinyl, dihydrobenzothienyl, dihydrothienopyridinyl, dihydrothienopyrimidinyl, indazolyl, azaindazolyl, diazaindazolyl, benzimidazolyl, imidazopyridinyl, benzthiazolyl, thiazolopyridinyl, thiazolopyrimidinyl, benzoxazolyl, benzoxazinyl, benzoxazinonyl, oxazolopyridinyl, oxazolopyrimidinyl, benzisoxazolyl, purinyl, chromanyl, azachromanyl, quinolizinyl, quinolinyl, dihydroquinolinyl, tetrahydroquinolinyl, isoquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, cinnolinyl, azacinnolinyl, phthalazinyl, azaphthalazinyl, quinazolinyl, azaquinazolinyl, quinoxalinyl, azaquinoxalinyl, naphthyridinyl, dihydronaphthyridinyl, tetrahydronaphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl, and the like.

In general, the present invention provides a pharmaceutical composition and a method for treating, reducing, or ameliorating an infection.

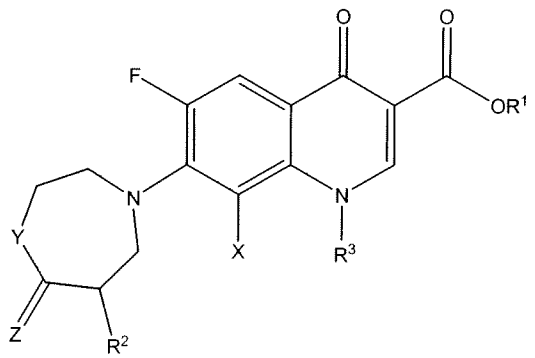
In one aspect, said infection has an etiology that is not readily ascertainable upon presentation.

In another aspect, said infection is caused by mixed types of microorganisms.

In still another aspect, said infection comprises an infection of an ear, a portion of a respiratory system, an eye, or a combination thereof.

In one aspect, said infection is selected from the group consisting of otitis, sinusitis, nasophrayngitis, orophrayngitis, epiglottitis, laryngotracheitis, bronchitis, bronchiolitis, pneumonia, keratitis, conjunctivitis, blepharitis, hordeolum, phlyctenulosis, endophthalmitis, preseptal and orbital cellulites, dacryocystitis, and combinations thereof.

In another aspect, a composition of the present invention comprises: (a) at least one member of a family of fluoroquinolones that have Formula I or salts thereof; and (b) an additional anti-infective medicament; wherein



(I)

wherein R^1 is selected from the group consisting of hydrogen, unsubstituted lower alkyl groups, substituted lower alkyl groups, cycloalkyl groups, unsubstituted C_5-C_{24} aryl groups, substituted C_5-C_{24} aryl groups, unsubstituted C_5-C_{24} heteroaryl groups, substituted C_5-C_{24} heteroaryl groups, and groups that can be hydrolyzed in living bodies;

R^2 is selected from the group consisting of hydrogen, unsubstituted amino group, and amino groups substituted with one or two lower alkyl groups; R^3 is selected from the group consisting of hydrogen, unsubstituted lower alkyl groups, substituted lower alkyl groups, cycloalkyl groups, unsubstituted lower alkoxy groups, substituted lower alkoxy groups, unsubstituted C_5-C_{24} aryl groups, substituted C_5-C_{24} aryl groups, unsubstituted C_5-C_{24} heteroaryl groups, substituted C_5-C_{24} heteroaryl groups, unsubstituted C_5-C_{24} aryloxy groups, substituted C_5-C_{24} aryloxy groups, unsubstituted C_5-C_{24} heteroaryloxy groups, substituted C_5-C_{24} heteroaryloxy groups, and groups that can be hydrolyzed in living bodies; X is selected from the group consisting of halogen atoms; Y is selected from the group consisting of CH_2, O, S, SO, SO_2, and NR^4, wherein R^4 is selected from the group consisting of hydrogen, unsubstituted lower alkyl groups, substituted lower alkyl groups, and cycloalkyl groups; and Z is selected from the group consisting of oxygen and two hydrogen atoms; and wherein the composition is capable of inhibiting a growth or survival of mixed types of microorganisms causing said infection.

In one aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_5 (or alternatively, C_1-C_3) substituted and unsubstituted alkyl groups, C_3-C_{10} (or alternatively, C_3-C_5) cycloalkyl groups, C_5-C_{14} (or alternatively, C_6-C_{14}, or C_5-C_{10}, or C_6-C_{10}) substituted and unsubstituted aryl groups, C_5-C_{14} (or alternatively, C_6-C_{14}, or C_5-C_{10}, or C_6-C_{10}) substituted and unsubstituted heteroaryl groups, and groups that can be hydrolyzed in living bodies. In one embodiment, R^1 is selected from the group consisting of C_1-C_5 (or alternatively, C_1-C_3) substituted and unsubstituted alkyl groups.

In another aspect, R^2 is selected from the group consisting of unsubstituted amino group and amino groups substituted with one or two C_1-C_5 (or alternatively, C_1-C_3) alkyl groups.

In still another aspect, R^3 is selected from the group consisting of hydrogen, C_1-C_5 (or alternatively, C_1-C_3) substituted and unsubstituted alkyl groups, C_3-C_{10} (or alternatively, C_3-C_5) cycloalkyl groups, C_1-C_5 (or alternatively, C_1-C_3) substituted and unsubstituted alkoxy groups, C_5-C_{14} (or alternatively, C_6-C_{14}, or C_5-C_{10}, or C_6-C_{10}) substituted and unsubstituted aryl groups, C_5-C_{14} (or alternatively, C_6-C_{14}, or C_5-C_{10}, or C_6-C_{10}) substituted and unsubstituted heteroaryl groups, and C_5-C_{14} (or alternatively, C_6-

C_{14}, or C_5-C_{10}, or C_6-C_{10}) substituted and unsubstituted aryloxy groups. In one embodiment, R^3 is selected from the group consisting of C_3-C_{10} (or alternatively, C_3-C_5) cycloalkyl groups.

In yet another aspect, X is selected from the group consisting of Cl, F, and Br. In one embodiment, X is Cl. In another embodiment, X is F.

In a further aspect, Y is CH_2 and Z comprises two hydrogen atoms.

In still another aspect, Y is NH, Z is O, and X is Cl.

Some non-limiting members of the family of compounds having Formula I are shown in Table 1. Other compounds of the family not listed in Table 1 are also suitable in selected situations.

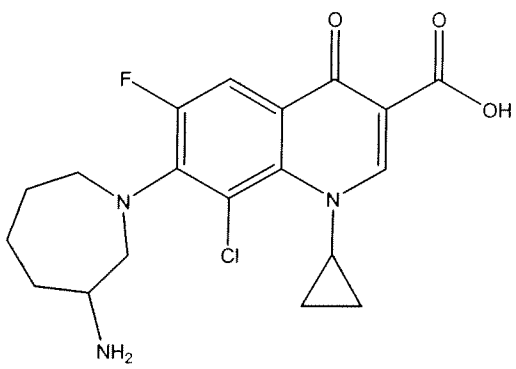
Table 1

Some Selected Fluoroquinolones

Compound	R^1	R^2	R^3	X	Y	Z
1	H	H	CH_3	Cl	CH_2	2 H
2	H	NH_2	CH_3	Cl	CH_2	2 H
3	H	NH_2	cyclopropyl	Cl	CH_2	2 H
4	H	$NH(CH_3)$	cyclopropyl	Cl	CH_2	2 H
5	H	$N(CH_3)_2$	cyclopropyl	Cl	CH_2	2 H
6	CH_3	NH_2	cyclopropyl	Cl	CH_2	2 H
7	C_2H_5	NH_2	cyclopropyl	Cl	CH_2	2 H
8	H	NH_2	cyclopropyl	F	CH_2	2 H
9	H	NH_2	cyclopropyl	Br	CH_2	2 H
10	H	$NH(C_3H_5)$	cyclopropyl	Cl	CH_2	2 H

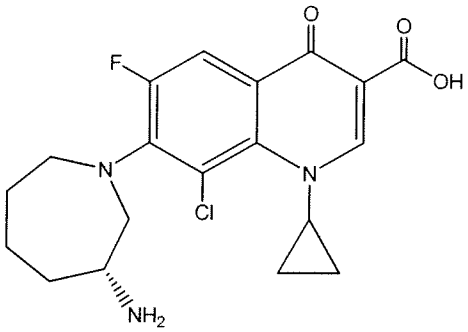
11	H	$NH(C_3H_5)$	cyclopropyl	F	CH_2	2 H
12	H	NH_2	cyclopentyl	Cl	CH_2	2 H
13	H	NH_2	cyclopropyl	Cl	CH_2	O
14	H	NH_2	cyclopropyl	F	CH_2	O
15	H	NH_2	cyclopropyl	Br	CH_2	O
16	H	NH_2	cyclopropyl	Cl	$CH(C_3H_5)$	O
17	CH_3	NH_2	cyclopropyl	Cl	CH_2	O
18	CH_3	$NH(CH_3)$	cyclopropyl	Cl	CH_2	O
19	CH_3	$N(CH_3)_2$	cyclopropyl	Cl	CH_2	O
20	CH_3	$NH(C_3H_5)$	cyclopropyl	Cl	CH_2	O
21	CH_3	$NH(C_3H_5)$	cyclopropyl	Cl	CH_2	O
22	CH_3	$N(CH_3)(C_2H_5)$	cyclopropyl	Cl	CH_2	O
23	H	NH_2	cyclopropyl	Cl	NH	O
24	CH_3	$NH(CH_3)$	cyclopropyl	Cl	NH	O
25	H	2H	cyclopropyl	Cl	NH	O

In one embodiment, the fluoroquinolone carboxylic acid included in a composition of the present invention has Formula III.

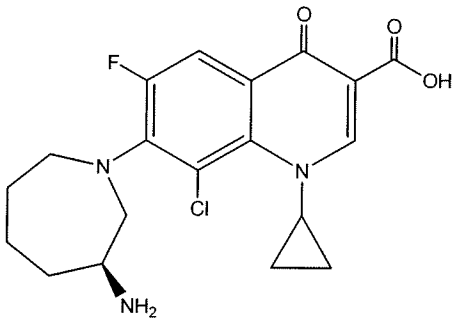


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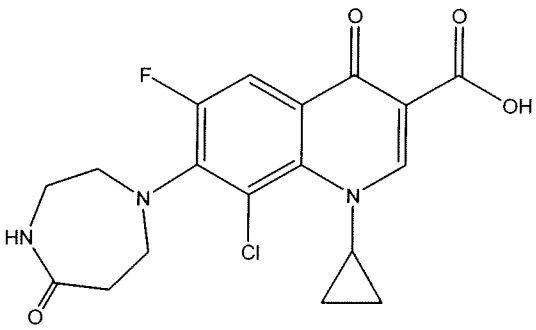
In another embodiment, the fluoroquinolone carboxylic acid included in a composition of the present invention has Formula IV, V, or VI.



(IV)

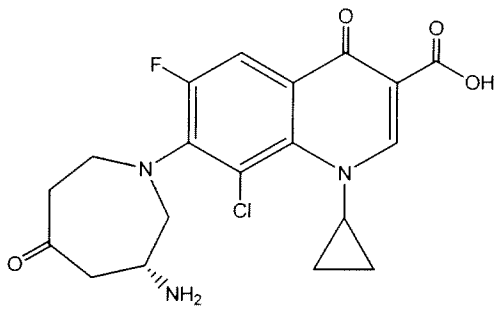


(V)

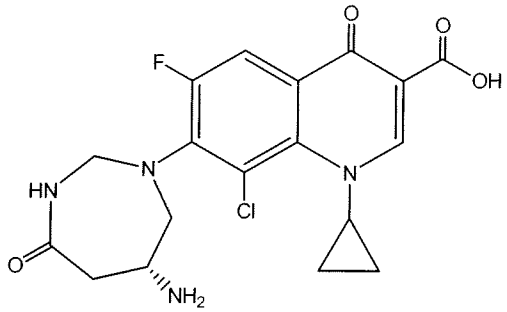


(VI)

In still other embodiments, the fluoroquinolone carboxylic acid included in a composition of the present invention has Formula VII or VIII.



(VII)



(VIII)

In still another aspect, a composition of the present invention comprises an enantiomer of one of the compounds having Formula I, II, or III.

In still another aspect, a composition of the present invention comprises a mixture of enantiomers of one of the compounds having Formula I, II, or III.

In a further aspect, the additional anti-infective medicament is selected from the group consisting of an antibacterial agent other than the quinolones having Formulae I, II, III, IV, V, VI, VII, and VIII; an antifungal agent; an antiviral agent; an antiprotozoal agent; and combinations thereof.

In another aspect, the additional antibacterial agent other than the quinolones having Formulae I, II, III, IV, V, VI, VII, and VIII comprises another quinolone.

In still another aspect, said another quinolone is selected from the group consisting of cinoxacin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, fleroxacin, gatifloxacin, grepafloxacin, levofloxacin, lomefloxacin, miloxacin, moxifloxacin, nadifloxacin, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, sitafloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin, mixtures thereof, and combinations thereof.

In yet another aspect, said another quinolone has a MIC_{90} value for a Gram-negative bacterium that is lower than that of the fluoroquinolone having Formula I, II, III, IV, V, VI, VII, or VIII for the same bacterium, said fluoroquinolone being included in the composition. MIC_{90} is the minimum concentration of the active compound required to inhibit ninety percent of the growth of a specified pathogen, in μg/ml.

Non-limiting examples of antibacterial agents other than the quinolones having antibacterial agent other than the quinolones having Formulae I, II, III, IV, V, VI, VII, and VIII include biologically-derived antibacterial agents such as aminoglycosides (e.g., amikacin, apramycin, arbekacin, bambermycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin(s), gentamicin, isepamicin, kanamycin, micronomicin, neomycin, neomycin undecylenate, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin), amphenicols (e.g., azidamfenicol, chloramphenicol, florfenicol, thiamphenicol), ansamycins (e.g., rifamide, rifampin, rifamycin sv, rifapentine, rifaximin), β-lactams (e.g., carbacephems (e.g., loracarbef), carbapenems (e.g., biapenem, imipenem, meropenem, panipenem), cephalosporins (e.g., cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefcapene pivoxil, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefinenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cefpimizole, cefpiramide, cefpirome, cefpodoxime proxetil, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalexin, cephaloglycin, cephaloridine, cephalosporin, cephalothin, cephapirin sodium, cephradine, pivcefalexin), cephamycins (e.g., cefbuperazone, cefinetazole, cefininox, cefotetan, cefoxitin), monobactams (e.g., aztreonam, carumonam, tigemonam), oxacephems, flomoxef, moxalactam), penicillins (e.g., amdinocillin, amdinocillin pivoxil, amoxicillin, ampicillin, apalcillin, aspoxicillin, azidocillin, azlocillin, bacampicillin, benzylpenicillinic acid, benzylpenicillin sodium, carbenicillin, carindacillin, clometocillin, cloxacillin, cyclacillin, dicloxacillin, epicillin, fenbenicillin, floxacillin, hetacillin, lenampicillin, metampicillin, methicillin sodium, mezlocillin, nafcillin sodium, oxacillin, penamecillin, penethamate hydriodide, penicillin G benethamine, penicillin G benzathine, penicillin G benzhydrylamine, penicillin G calcium, penicillin G hydrabamine, penicillin G potassium, penicillin G procaine,

penicillin N, penicillin O, penicillin V, penicillin V benzathine, penicillin V hydrabamine, penimepicycline, phenethicillin potassium, piperacillin, pivampicillin, propicillin, quinacillin, sulbenicillin, sultamicillin, talampicillin, temocillin, ticarcillin), ritipenem, lincosamides (e.g., clindamycin, lincomycin), macrolides (e.g., azithromycin, carbomycin, clarithromycin, dirithromycin, erythromycin, erythromycin acistrate, erythromycin estolate, erythromycin glucoheptonate, erythromycin lactobionate, erythromycin propionate, erythromycin stearate, josamycin, leucomycins, midecamycins, miokamycin, oleandomycin, primycin, rokitamycin, rosaramicin, roxithromycin, spiramycin, troleandomycin), polypeptides (e.g., amphomycin, bacitracin, capreomycin, colistin, enduracidin, enviomycin, fusafungine, gramicidin s, gramicidin(s), mikamycin, polymyxin, pristinamycin, ristocetin, teicoplanin, thiostrepton, tuberactinomycin, tyrocidine, tyrothricin, vancomycin, viomycin, virginiamycin, zinc bacitracin), tetracyclines (e.g., apicycline, chlortetracycline, clomocycline, demeclocycline, doxycycline, guamecycline, lymecycline, meclocycline, methacycline, minocycline, oxytetracycline, penimepicycline, pipacycline, rolitetracycline, sancycline, tetracycline), cycloserine, mupirocin, and tuberin.

Non-limiting examples of synthetic antibacterial agents include 2,4-diaminopyrimidines (e.g., brodimoprim, tetroxoprim, trimethoprim), nitrofurans (e.g., furaltadone, furazolium chloride, nifuradene, nifuratel, nifurfoline, nifurpirinol, nifurprazine, nifurtoinol, nitrofuirantoin), quinolones and analogs (e.g., cinoxacin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, fleroxacin, flumequine, gatifloxacin, grepafloxacin, levofloxacin, lomefloxacin, miloxacin, moxifloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, oxolinic acid, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rosoxacin, rufloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin, sulfonamides (e.g., acetyl sulfamethoxypyrazine, benzylsulfamide, chloramines B, chloramines T, dichloramine T, n^2-formylsulfisomidine, n^4-β-D-glucosylsulfanilamide, mafenide, 4'-(methylsulfamoyl)sulfanilanilide, noprylsulfamide, phthalylsulfacetamide, phthalylsulfathiazole, salazosulfadimidine, succinylsulfathiazole, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanol, sulfalene, sulfaloxic acid, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole,

sulfamethoxypyridazine, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 4-sulfanilamidosalicylic acid, n^4-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfanitran, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfatolamide, sulfisomidine, sulfisoxazole) sulfones (e.g., acedapsone, acediasulfone, acetosulfone sodium, dapsone, diathymosulfone, glucosulfone sodium, solasulfone, succisulfone, sulfanilic acid, p-sulfanilylbenzylamine, sulfoxone sodium, thiazolsulfone), clofoctol, hexedine, methenamine, methenamine anhydromethylene citrate, methenamine hippurate, methenamine mandelate, methenamine sulfosalicylate, nitroxoline, taurolidine, and xibomol. In one embodiment, a compostion of the present invention comprises an anti-infective agent selected from the group consisting of cinoxacin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, fleroxacin, flumequine, gatifloxacin, grepafloxacin, levofloxacin, lomefloxacin, miloxacin, moxifloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, oxolinic acid, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rosoxacin, rufloxacin, sparfloxacin, temafloxacin, tosufloxacin, and trovafloxacin.

Non-limiting examples of antiviral agents include rifampin, ribavirin, pleconaryl, cidofovir, acyclovir, pencyclovir, gancyclovir, valacyclovir, famciclovir, foscarnet, vidarabine, amantadine, zanamivir, oseltamivir, resquimod, adenosine arabinoside, cytosine arabinoside, antiproteases, PEGylated interferon (Pegasys™), anti HIV proteases (e.g. lopinivir, saquinivir, amprenavir, HIV fusion inhibitors, nucleotide HIV RT inhibitors (e.g., AZT, lamivudine, abacavir), non-nucleotide HIV RT inhibitors, doconosol, interferons, butylated hydroxytoluene (BHT), and hypericin.

Non-limiting examples of biologically-derived antifungal agents include polyenes (e.g., amphotericin B, candicidin, dermostatin, filipin, fungichromin, hachimycin, hamycin, lucensomycin, mepartricin, natamycin, nystatin, pecilocin, perimycin), azaserine, griseofulvin, oligomycins, neomycin undecylenate, pyrrolnitrin, siccanin, tubercidin, and viridin.

Non-limiting examples of synthetic antifungal agents include allylamines (e.g., butenafine, naftifine, terbinafine), imidazoles (e.g., bifonazole, butoconazole,

chlordantoin, chlormidazole, cloconazole, clotrimazole, econazole, enilconazole, fenticonazole, flutrimazole, isoconazole, ketoconazole, lanoconazole, miconazole, omoconazole, oxiconazole nitrate, sertaconazole, sulconazole, tioconazole), thiocarbamates (e.g., tolciclate, tolindate, tolnaftate), triazoles (e.g., fluconazole, itraconazole, saperconazole, terconazole), acrisorcin, amorolfine, biphenamine, bromosalicylchloranilide, buclosamide, calcium propionate, chlorphenesin, ciclopirox, cloxyquin, coparaffinate, diamthazole dihydrochloride, exalamide, flucytosine, halethazole, hexetidine, loflucarban, nifuratel, potassium iodide, propionic acid, pyrithione, salicylanilide, sodium propionate, sulbentine, tenonitrozole, triacetin, ujothion, undecylenic acid, and zinc propionate.

Non-limiting examples of antiprotozoal agents include polymycin B sulfate, bacitracin zinc, neomycine sulfate (e.g., Neosporin®), imidazoles (e.g., clotrimazole, miconazole, ketoconazole), aromatic diamidines (e.g., propamidine isethionate, brolene), polyhexamethylene biguanide ("PHMB"), chlorhexidine, pyrimethamine (Daraprim®), sulfadiazine, folinic acid (leucovorin), clindamycin, and trimethoprim-sulfamethoxazole.

The amount of a fluoroquinolone compound having Formula I, II, III, IV, V, VI, VII, or VIII that is incorporated into a composition of the present invention is not critical; the concentration should be within a range sufficient to permit ready application of the composition to the affected tissue area in an amount which will deliver the desired amount of compound to the desired treatment site and to provide the desired therapeutic effect. In some embodiments of the present invention, compositions comprise a fluoroquinolone having Formula I, II, III, IV, V, VI, VII, or VIII in a concentration in a range from about 0.0001% to 10% by weight (or alternatively, from about 0.001% to about 5%, or from about 0.01% to about 5%, or from about 0.01% to about 2%, or from about 0.01% to about 1%, or from about 0.01% to about 0.7%, or from about 0.01% to about 0.5%, by weight).

In another aspect, the concentration of said additional anti-infective medicament in a composition of the present invention can be in the range from about 0.0001% to 10% by weight (or alternatively, from about 0.001% to about 5%, or from about 0.01% to about 5%, or from about 0.01% to about 2%, or from about 0.01% to

about 1%, or from about 0.01% to about 0.7%, or from about 0.01% to about 0.5%, by weight).

In still another aspect, a composition of the present invention further comprises a pharmaceutically acceptable carrier.

A fluoroquinolone compound and an additional anti-infective medicament that are disclosed herein can be formulated into a pharmaceutical composition for topical, oral, or systemic administration for the treatment, reduction, amelioration, or prevention of an. In an embodiment, such infection comprises an infection of an ear, a portion of a respiratory system, an eye, or a combination thereof. Such a composition comprises a fluoroquinolone compound having Formula I, II, III, IV, V, VI, VII, or VIII, an additional anti-infective medicament, and a pharmaceutically acceptable carrier for the administration, which carrier can be determined by a person having skill in the art of pharmaceutical formulation for the applications disclosed above. For example, various pharmaceutically acceptable carriers known in the art can be used to formulate a solution, suspension, dispersion, ointment, gel, capsule, or tablet. A fluoroquinolone compound having Formula I, II, III, IV, V, VI, VII, or VIII disclosed herein is particularly suitable for a treatment, reduction, amelioration, or prevention of infections of an ear, a portion of a respiratory system, an eye, or a combination thereof, which infections are caused by bacteria, fungi, viruses, protozoans, or combinations thereof, including, but not being limited to, the bacteria, fungi, viruses, and protozoans disclosed above. In one embodiment, such infections are caused by mixed microorganisms comprising at least one bacterium. In another embodiment, such a fluroquinolone and an additional anti-infective medicament or agent are formulated into a solution, ointment, suspension, dispersion, or gel.

In one embodiment, a topical composition of the present invention comprises an aqueous solution or suspension. Typically, purified or deionized water is used. The pH of the composition is adjusted by adding any physiologically and otically acceptable pH adjusting acids, bases, or buffers to within the range of about 3 to about 8.5 (or alternatively, or from about 4 to about 7.5, or from about 4 to about 6.5, or from about 5 to about 6.5). Examples of acids include acetic, boric, citric, lactic, phosphoric,

hydrochloric, and the like, and examples of bases include sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate, tromethamine, THAM (trishydroxymethylamino-methane), and the like. Salts and buffers include citrate/dextrose, sodium bicarbonate, ammonium chloride and mixtures of the aforementioned acids and bases. pH buffers are introduced into the composition to maintain a stable pH and to improve product tolerance by the user. In some embodiments, the pH is in the range from about 4 to about 7.5. Biological buffers for various pHs are available, for example, from Sigma-Aldrich. A composition of the present invention can have a viscosity in the range from about 5 to about 100,000 centipoise ("cp") or mPa.s (or alternatively, from about 10 to about 50,000, or from about 10 to about 20,000, or from about 10 to about 10,000, or from about 10 to about 1,000, or from about 100 to about 10,000, or from about 100 to about 20,000, or from about 100 to about 50,000 or from about 500 to about 10,000, or from about 500 to about 20,000 cp).

In another embodiment, a topical composition of the present invention comprises an ointment, emulsion or cream (such as oil-in-water emulsion), or gel.

Ointments generally are prepared using either (1) an oleaginous base; i.e., one consisting of fixed oils or hydrocarbons, such as white petrolatum or mineral oil, or (2) an absorbent base; i.e., one consisting of an anhydrous substance or substances which can absorb water, for example anhydrous lanolin. Customarily, following formation of the base, whether oleaginous or absorbent, the active ingredient (compound) is added to an amount affording the desired concentration.

Creams are oil/water emulsions. They consist of an oil phase (internal phase), comprising typically fixed oils, hydrocarbons, and the like, such as waxes, petrolatum, mineral oil, and the like, and an aqueous phase (continuous phase), comprising water and any water-soluble substances, such as added salts. The two phases are stabilized by use of an emulsifying agent, for example, a surface active agent, such as sodium lauryl sulfate, hydrophilic colloids, such as acacia colloidal clays, veegum, and the like. Upon formation of the emulsion, the active ingredient (compound) customarily is added in an amount to achieve the desired concentration.

Gels comprise a base selected from an oleaginous base, water, or an emulsion-suspension base. To the base is added a gelling agent which forms a matrix in the base, increasing its viscosity. Examples of gelling agents are hydroxypropyl cellulose, acrylic acid polymers, and the like. Customarily, the active ingredient (compound) is added to the formulation at the desired concentration at a point preceding addition of the gelling agent.

Moreover, a topical composition of the present invention can contain one or more of the following: preservatives, surfactants, adjuvants including additional medicaments, antioxidants, tonicity adjusters, viscosity modifiers, and the like.

Preservatives may be used to inhibit microbial contamination of the product when it is dispensed in single or multidose containers, and can include: quaternary ammonium derivatives, (benzalkonium chloride, benzylammonium chloride, cetylmethyl ammonium bromide, cetylpyridinium chloride), benzethonium chloride, organomercury compounds (Thimerosal, phenylmercury acetate, phenylmercury nitrate), methyl and propyl p-hydroxy-benzoates, betaphenylethyl alcohol, benzyl alcohol, phenylethyl alcohol, phenoxyethanol, and mixtures thereof. These compounds are used at effective concentrations, typically from about 0.005% to about 5% (by weight), depending on the preservative or preservatives selected. The amount of the preservative used should be enough so that the solution is physically stable; i.e., a precipitate is not formed, and antibacterially effective.

The solubility of the components, including a fluoroquinolone having Formula I, II, III, IV, V, VI, VII, or VIII of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition or solubility enhancing agents like cyclodextrins such as hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α-, β-, and γ-cyclodextrin. In one embodiment, the composition comprises 0.1% to 20% hydroxypropyl- β-cyclodextrin; alternatively, 1% to 15% (or 2% to 10%) hydroxypropyl- β-cyclodextrin. Co-solvents include polysorbates (for example, polysorbate 20, 60, and 80), polyoxyethylene/polyoxypropylene surfactants (e.g., Pluronic® F68, F84, F127, and P103), cyclodextrin, fatty-acid triglycerides, glycerol, polyethylene glycol, other solubility agents such as octoxynol 40

and tyloxapol, or other agents known to those skilled in the art and mixtures thereof. The amount of solubility enhancer used will depend on the amount of fluoroquinolone in the composition, with more solubility enhancer used for greater amounts of fluoroquinlones. Typically, solubility enhancers are employed at a level of from 0.01% to about 20% (alternatively, from about 0.1% to about 10%, from about 0.1% to about 5%, or from about 0.1% to about 2%) by weight depending on the ingredient.

The use of viscosity enhancing agents to provide the compositions of the invention with viscosities greater than the viscosity of simple aqueous solutions may be desirable to increase absorption of the active compounds by the target tissues or to increase the retention time in the ear. Such viscosity enhancing agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents know to those skilled in the art. Such agents are typically employed at a level of from about 0.01% to about 10% (alternatively, from about 0.1% to about 5%, or from about 0.1% to about 2%) by weight.

Suitable surfactants include polyvinyl pyrolidone, polyvinyl alcholol, polyethylene glycol, ethylene glycol, and propylene glycol. Other surfactants are polysorbates (such as polysorbate 80 (polyoxyethylene sorbitan monooleate), polysorbate 60 (polyoxyethylene sorbitan monostearate), polysorbate 20 (polyoxyethylene sorbitan monolaurate), commonly known by their trade names of Tween® 80, Tween® 60, Tween® 20), poloxamers (synthetic block polymers of ethylene oxide and propylene oxide, such as those commonly known by their trade names of Pluronic®; e.g., Pluronic® F127 or Pluronic® F108)), or poloxamines (synthetic block polymers of ethylene oxide and propylene oxide attached to ethylene diamine, such as those commonly known by their trade names of Tetronic®; e.g., Tetronic® 1508 or Tetronic® 908, etc., other nonionic surfactants such as Brij®, Myrj®, and long chain fatty alcohols (i.e., oleyl alcohol, stearyl alcohol, myristyl alcohol, docosohexanoyl alcohol, etc.) with carbon chains having about 12 or more carbon atoms (e.g., such as from about 12 to about 24 carbon atoms). The surfactant helps a topical formulation to spread on the surface of narrow passages.

It is often that an infection is followed by inflammation. Therefore, in another aspect, a composition of the present invention further comprises an anti-inflammatory agent. Anti-inflammatory agents include the well-known glucocorticosteroids and the non-steroidal anti-inflammatory drugs ("NSAIDs").

Non-limiting examples of the glucocorticosteroids are: 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino-acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, their physiologically acceptable salts, combinations thereof, and mixtures thereof.

The preferred glucocorticoids for otic use include dexamethasone, loteprednol, rimexolone, prednisolone, fluorometholone, hydrocortisone, and their derivatives. The preferred glucocorticoids for nasal use include mometasone, fluticasone, beclomethasone, flunisolide, triamcinolone, budesonide, and their derivatives.

Non-limiting examples of the NSAIDs are: aminoarylcarboxylic acid derivatives (e.g., enfenamic acid, etofenamate, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, niflumic acid, talniflumate, terofenamate, tolfenamic acid), arylacetic acid derivatives (e.g., aceclofenac, acemetacin, alclofenac, amfenac, amtolmetin guacil, bromfenac, bufexamac, cinmetacin, clopirac, diclofenac sodium, etodolac, felbinac, fenclozic acid, fentiazac, glucametacin, ibufenac, indomethacin,

isofezolac, isoxepac, lonazolac, metiazinic acid, mofezolac, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, tropesin, zomepirac), arylbutyric acid derivatives (e.g., bumadizon, butibufen, fenbufen, xenbucin), arylcarboxylic acids (e.g., clidanac, ketorolac, tinoridine), arylpropionic acid derivatives (e.g., alminoprofen, benoxaprofen, bermoprofen, bucloxic acid, carprofen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, indoprofen, ketoprofen, loxoprofen, naproxen, oxaprozin, piketoprolen, pirprofen, pranoprofen, protizinic acid, suprofen, tiaprofenic acid, ximoprofen, zaltoprofen), pyrazoles (e.g., difenamizole, epirizole), pyrazolones (e.g., apazone, benzpiperylon, feprazone, mofebutazone, morazone, oxyphenbutazone, phenylbutazone, pipebuzone, propyphenazone, ramifenazone, suxibuzone, thiazolinobutazone), salicylic acid derivatives (e.g., acetaminosalol, aspirin, benorylate, bromosaligenin, calcium acetylsalicylate, diflunisal, etersalate, fendosal, gentisic acid, glycol salicylate, imidazole salicylate, lysine acetylsalicylate, mesalamine, morpholine salicylate, 1-naphthyl salicylate, olsalazine, parsalmide, phenyl acetylsalicylate, phenyl salicylate, salacetamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalate, sulfasalazine), thiazinecarboxamides (e.g., ampiroxicam, droxicam, isoxicam, lornoxicam, piroxicam, tenoxicam), ε-acetamidocaproic acid, S-(5'-adenosyl)-L-methionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, α-bisabolol, bucolome, difenpiramide, ditazol, emorfazone, fepradinol, guaiazulene, nabumetone, nimesulide, oxaceprol, paranyline, perisoxal, proquazone, superoxide dismutase, tenidap, zileuton, their physiologically acceptable salts, combinations thereof, and mixtures thereof. In one embodiment, the NSAID is diclofenac, furbiprofen, or ketorolac.

Other non-steroidal anti-inflammatory agents include the cyclooxygenase type II selective inhibitors, such as celecoxib, and etodolac; platelet activating factor ("PAF") antagonists, such as apafant, bepafant, minopafant, nupafant, and modipafant; phosphodiesterase ("PDE") IV inhibitors, such as ariflo, torbafylline, rolipram, filaminast, piclamilast, cipamfylline, and roflumilast; inhibitors of cytokine production, such as inhibitors of the NF-κB transcription factor; or other anti-inflammatory agents known to those skilled in the art.

The concentrations of the anti-inflammatory agents contained in the compositions of the present invention will vary based on the agent or agents selected and the type of inflammation being treated. The concentrations will be sufficient to reduce inflammation in the targeted tissues following topical application of the compositions to those tissues. Such concentrations are typically in the range from about 0.0001 to about 3% by weight (or alternatively, from about 0.01 to about 2%, or from about 0.05% to about 1%, by weight).

Bacterial pathogens that have been isolated from cases of ear infection include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyrogenes, Streptococcus faecalis*, *Haemophilus influenzae*, *Moraxella catarahalis*, *Escherichia coli*, *Proteus* species, *Klebsiella* species, and *Enterococcus* species. Several of these species from the isolates have been found to be resistant to a number of antimicrobial drugs. For example, a published study of antimicrobial-resistant pathogens in middle-ear fluid of children with acute otitis media shows that thirty percent of the *S. pneumoniae* isolates were intermediately or fully resistant, and eight percent fully resistant, to penicillin; ten percent of the isolates were resistant to amoxicillin or amoxicillin-clavulanate. M.R. Jacobs et al., *Antimicrobial Agents and Chemotherapy*, Vol. 42, No. 3, 589 (1998). The same study shows that thirty percent of *H. influenzae* isolates produced β-lactamase, and thus, were expected to be resistant to penicillin.

Bacterial pathogens that have been isolated from cases of upper respiratory infection include *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus pyrogenes*, *Haemophilus influenzae*, *Peptostreptococcus* species, and *Bacteroides* species. Some of these strains have been found to be resistant to commonly used antibiotics, as mentioned above.

Anti-bacterial activity of the compound having Formula IV was tested against several Gram-negative reference bacteria strains and compared to the anti-bacterial activity of three commercially available antibiotics (nadifloxacin, ofloxacin, and sparfloxacin). The results are shown in Table 2 as MIC_{90} values (minimum

concentration of the active compound required to inhibit ninety percent of the growth of a specified pathogen, in μg/ml).

Table 2

Comparison of *In vitro* Anti-bacterial Activity of Compound Having Formula IV, Nadifloxacin, Ofloxacin, and Sparfloxacin Against Some Gram-Negative Bacteria

Strain	MIC_{90} (μg/ml)			
	Compound Having Formula IV	Nadifloxacin	Ofloxacin	Sparfloxacin
Escherichia coli (O-1)	0.1	0.2	0.05	0.012
Klebsiella pneumoniae (IFO 13541)	0.024	0.1	0.024	0.012
Salmonella typhimurium (TD)	0.05	0.2	0.05	0.012
Shigella flexneri (2b)	0.006	0.006	0.006	0.006
Enterobacter aerogenes (IFO 13534)	0.39	1.56	0.2	0.1
Serratia marcenscens (NHL)	0.2	1.56	0.1	0.2
Proteus mirabilis (IFO 13300)	0.1	0.1	0.05	0.1
Proteus rettgeri	0.39	0.39	0.2	0.2
Acinetobacter calcoaceticus (IFO 12552)	0.39	0.78	0.39	0.024
Pseudomonas aeruginosa (IFO 13736)	1.56	3.13	1.56	0.78
Pseudomonas aeruginosa (ATCC 27853)	1.56	6.25	3.13	0.78

Anti-bacterial activity of the compound having Formula IV was tested against several Gram-positive reference bacteria strains and compared to the anti-

bacterial activity of three commercially available antibiotics (nadifloxacin, ofloxacin, and sparfloxacin). The results are shown in Table 3 as MIC_{90} values.

Table 3

Comparison of *In vitro* Anti-bacterial Activity of Compound Having Formula IV, Nadifloxacin, Ofloxacin, and Sparfloxacin Against Some Gram-Positive Bacteria

Strain	MIC_{90} (μg/mL)			
	Compound Having Formula IV	Nadifloxacin	Ofloxacin	Sparfloxacin
Bacillis subtilis (ATCC 6633)	0.012	0.006	0.05	0.024
Staphylococcus aureus (ATCC 25933)	0.05	0.05	0.39	0.1
Staphylococcus aureus (FDA 209P)	0.012	0.024	0.2	0.024
Staphylococcus aureus (Smith)	0.006	0.024	0.2	0.05
Staphylococcus epidermidis (ATCC 12228)	0.05	0.1	0.78	0.2
Sarcina lutea (ATCC 9341)	0.1	0.39	3.13	1.56
Streptococcus faecalis (IFO 12964)	0.1	0.78	1.56	0.78
Streptococcus faecalis (ATCC 29212)	0.2	0.78	1.56	0.39
Streptococcus pyogenes (Cook)	0.1	0.78	0.78	0.39
Streptococcus pyogenes (IID 698)	0.1	0.1	0.39	0.2

Streptococcus pneumoniae (IID 553)	0.1	0.78	1.56	0.39
Streptococcus pneniae (IID 554)	0.2	0.78	1.56	0.39

Anti-bacterial activity of the compound having Formula IV was tested against some methicillin-resistant *Staphylococcus aureus* bacteria strains and compared to the anti-bacterial activity of three commercially available antibiotics (nadifloxacin, ofloxacin, and sparfloxacin). The results are shown in Table 4 as MIC_{90} values.

Table 4

Comparison of *In vitro* Anti-bacterial Activity of Compound Having Formula IV, Nadifloxacin, Ofloxacin, and Sparfloxacin Against Some Methicillin-Resistant *Staphylococcus aureus* Isolates

Strain	MIC_{90} (μg/mL)			
	Compound Having Formula IV	Nadifloxacin	Ofloxacin	Sparfloxacin
Staphylococcus aureus (ATCC 33591)	0.012	0.006	0.05	0.024
Staphylococcus aureus (ATCC 33592)	0.05	0.05	0.39	0.1
Staphylococcus aureus (ATCC 33593)	0.012	0.024	0.2	0.024
Staphylococcus aureus (No. 395)	0.006	0.024	0.2	0.05
Staphylococcus aureus (No. 415)	0.05	0.1	0.78	0.2
Staphylococcus aureus (No. 419)	0.1	0.39	3.13	1.56

Staphylococcus aureus (No. 420)	0.1	0.78	1.56	0.78
Staphylococcus aureus (No. 421)	0.2	0.78	1.56	0.39

Anti-bacterial activity of the compound having Formula IV was tested against selected anaerobic reference bacteria and compared to the anti-bacterial activity of three commercially available antibiotics (nadifloxacin, ofloxacin, and sparfloxacin). The results are shown in Table 5 as MIC_{90} values.

Table 5

Comparison of *In vitro* Anti-bacterial Activity of Compound Having Formula IV, Nadifloxacin, Ofloxacin, and Sparfloxacin Against Some Common Anaerobic Bacteria

Strain	MIC_{90} (μg/mL)			
	Compound Having Formula IV	Nadifloxacin	Ofloxacin	Sparfloxacin
Clostridium perfringens (KZ 210)	0.2	0.2	0.78	0.39
Peptostreptococcus micros (GIFU 7824)	0.2	0.39	0.78	0.78
Peptostreptococcus magnum (GAI 0664)	0.05	0.2	0.39	0.1
Propionibacterium acnes (GAI 5419)	0.2	0.2	0.78	0.39
Propionibacterium acnes (ATCC 6919)	0.2	0.2	0.78	0.39
Propionibacterium acnes (ATCC 11828)	0.39	0.78	1.56	0.78

Bacteroides fragillis (GAI 0675)	0.1	1.56	1.56	0.78
Bacteroides thetaiotaomicron (GAI 0659)	0.2	1.56	3.13	0.78
Bacteroides vulgatus (GAI 0673)	0.1	0.78	3.13	0.78
Veillonella parvula (GAI 5602)	0.1	0.78	0.39	0.2

Anti-bacterial activity of the compound having Formula IV was tested against some ophthalmologic clinical bacteria isolates and compared to the anti-bacterial activity of three commercially available antibiotics (nadifloxacin, ofloxacin, and ciprofloxacin). As disclosed above, most of these bacteria strains are also relevant to infections of the ear and upper respiratory tract. The results are shown in Table 6 as MIC_{90} values.

Table 6

Comparison of *In vitro* Anti-bacterial Activity of Compound Having Formula IV, Nadifloxacin, Ofloxacin, and Ciprofloxacin Against Some Clinical Bacteria Isolates

Strain	MIC_{90} (μg/mL)			
	Compound Having Formula IV	Norfloxacin	Ofloxacin	Ciprofloxacin
Gram-negative				
Moraxella species	0.13	0.25	0.13	≤ 0.06
Pseudomonas aeruginosa	4	4	4	0.5
Haemophilus influenzae	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06

Gram-positive				
Staphylococcus aureus	1	> 128	32	64
Coagulase-negative *Staphylococcus*	0.5	128	8	16
Streptococcus pneumoniae	0.13	8	2	1
Corynebacterium species	2	16	32	8
Propionibacterium acnes	0.25	4	1	0.5
Antibiotic-resistant Organisms				
Ofloxacin-resistant *Enterobacteriaceae*	16	128	64	32
Ofloxacin –resistant *Staphylococcus aureus*	8	> 128	> 128	> 128
Gentamycin-resistant *Staphylococcus aureus*	4	128	128	128
Gentamycin-resistant *Pseudomonas aeruginosa*	32	128	64	32
Penicillin-resistant *Streptococcus pneumoniae*	0.13	8	2	1

The results show that the compound having Formula IV is effective against bacteria, including some antibiotic-resistant strains, which have been found in cases of infection of the eye, ear, or upper respiratory tract. Although the applicants do not wish to be bound by any particular theory, they believe that the unique moieties on the fluoroquinolones disclosed herein provide their advantageous antibacterial property and are effective for the treatment, reduction, amelioration, or prevention of infection of the

ear, including otitis externa and otitis media, and infection of the upper respiratory tract, including sinusitis, nasopharyngitis, and oropharyngitis.

The following examples are provided to further illustrate non-limiting compositions of the present invention, and methods of preparing such composition, for the treatment, reduction, amelioration, or prevention of infections.

EXAMPLE 1: Antibacterial Solution

Ingredient	Amount (% by weight)
Compound having Formula IV	0.2
Tobramycin	0.3
Hydroxypropylmethyl cellulose ("HPMC")	0.5
Benzakonium chloride ("BAK")	0.01
Pluronic® F127	0.1
EDTA	0.1
NaCl	0.25
Phosphate buffer (0.05M, pH = 5.0)	q.s. to 100

An appropriate proportion (shown in the above table) of Pluronic® F127 is added to phosphate buffer in a sterilized stainless steel jacketed vessel equipped with a stirring mechanism, at a temperature in the range from 50 to 60° C. The resulting buffer solution is heated to 61 to 75° C. At a temperature of about 66° C, an appropriate amount of BAK is added to the buffer solution while mixing three to ten minutes. At a temperature of 75° C, appropriate amounts of the compound having Formula IV and tobramycin are added to the contents of the vessel over a period of three to fifteen minutes while mixing continues. EDTA and NaCl are then added to the mixture while mixing continues for five to fifteen more minutes at 75° C. The resulting mixture is cooled to 25 to 30° C. The final composition is packaged in appropriate containers.

EXAMPLE 2: Antibacterial Solution

A procedure similar to that of Example 1 is used to produce this solution.

Ingredient	Amount (% by weight)
Compound having Formula IV	0.35
Trimethoprim	0.3
Mannitol	4.5
Benzakonium chloride ("BAK")	0.005
Polysorbate 80	0.1
EDTA	0.05
Sodium acetate	0.03
Acetic acid	0.04
Purified water	q.s. to 100

EXAMPLE 3: Antibacterial and Anti-inflammatory Solution

A procedure similar to that of Example 1 is used to produce this solution having the following composition.

Ingredient	Amount (% by weight)
Compound having Formula IV	0.2
Neomycin	0.25
Dexamethasone	0.1
Hydroxypropylmethyl cellulose ("HPMC")	0.5
Alexidine	0.01
Brij® surfactant	0.1
EDTA	0.1
Citrate buffer (0.02M sodium citrate, pH = 5)	q.s. to 100

EXAMPLE 4: Antibacterial, Anti-fungal, and Anti-inflammatory Solution

A procedure similar to that of Example 1 is used to produce this solution having the following composition.

Ingredient	Amount (% by weight)
Compound 8 of Table 1	0.3
Chlormidazole	0.2
Colecoxib	0.15
Propylene glycol	0.5
Alexidine	0.01
Tyloxapol	0.1
EDTA	0.1
Citrate buffer (0.02M sodium citrate, pH = 5)	q.s. to 100

EXAMPLE 5: Antibacterial, Antiviral, and Anti-inflammatory Suspension

A procedure similar to that of Example 1 is used to produce this solution having the following composition.

Ingredient	Amount (% by weight)
Compound having Formula VI	0.3
Rifampin	0.25
Triamcinolone, micronized USP	0.2
Hydroxyethyl cellulose	0.25
BAK	0.01
Tyloxapol	0.05
EDTA	0.01
NaCl	0.3
Na_2SO_4	1.2
Sulfuric acid and/or NaOH	q.s. for pH adjustment to 5.5
Citrate buffer (0.02M sodium citrate, pH = 5)	q.s. to 100

EXAMPLE 6: Antibacterial and Anti-inflammatory Emulsion

A modification of the procedure of Example 1 is used to produce this emulsion having the composition shown in the table immediately below.

Polysorbate 60 (Tween 60) is added to water in a first sterilized stainless steel jacketed vessel, equipped with a stirring mechanism, at a temperature of 50° C to 60° C in amounts corresponding the proportions shown in the table below. The resulting aqueous solution is heated to 61° C to 75° C. At a temperature of 66° C, benzyl alcohol (a preservative) is added to the aqueous solution while mixing three to ten minutes. At a temperature of 75° C, appropriate amounts of the compound having Formula IV and loteprednole etabonate are added to Mygliol oil in a second sterilized vessel, also equipped with a stirring mechanism, over a period of three to five minutes while stirring continues. Sorbitan monostearate and cetyl stearyl alcohol are added to the oil mixture. The resulting oil mixture is heated to a temperature in the range from 62° C to 75° C. The oil mixture is then added with vigorous mixing to the aqueous solution in the first vessel at a temperature of 66° C over a period of three to five minutes. Sodium sulfate and sulfuric acid and/or sodium hydroxide are added to the mixture to adjust pH to 5.5. The resulting composition is cooled to 35° C to 45° C and homogenized by mixing with a high shear emulsifier or running through a homogenizer. The composition is further cooled to 25° C to 30° C. The final composition is packaged in appropriate containers.

Ingredient	Amount (% by weight)
Compound having Formula IV	0.5
Loteprednol etabonate	0.2
Polysorbate 60	1
Sorbitan monostearate (an emulsifier)	1.5
Cetyl stearyl alcohol (an emulsion stabilizer)	1.5
Benzyl alcohol	0.5
Miglyol oil	14.5
Na_2SO_4	1.2
Sulfuric acid and/or NaOH	q.s. for pH adjustment to 5.5
Purified water	q.s. to 100

Typically, the oil used in an emulsion is a non-irritating emollient oil. Illustrative but non-limiting examples thereof include a mineral oil, vegetable oil, and a reformed vegetable oil of known composition. More specific but non-limiting examples of the oil can be selected from the group consisting of peanut oil, sesame seed oil, cottonseed oil, and a medium chain (C_6 to C_{12}) triglycerides (e.g., Miglyol Neutral Oils 810, 812, 818, 829, 840, etc., available from Huls America Inc.). Typical emulsifiers employed can be selected from the group consisting of sorbitan monostearate and Tween 60 (also known as Polysorbate 60). Preferably, the emulsifiers are nonionic. The emulsifiers can be employed in an amount of 1.5 to 6.5% by weight of the composition, and preferably, 3 to 5% by weight of the composition. The hydrophobic phase of the emulsion can be in an amount of 15 to 25% by weight of the composition, and preferably, 18 to 22% by weight of the composition.

EXAMPLE 7: Antibacterial, Antifungal, and Anti-inflammatory Emulsion

A procedure similar to that of Example 6 is used to produce this emulsion having the following composition.

Ingredient	Amount (% by weight)
Compound 13 of Table 1	0.5
Butoconazole	0.2
Triamcinolone, micronized USP	0.2
Polysorbate 60	1
Sorbitan monostearate	1.5
Cetyl stearyl alcohol	1.5
Benzyl alcohol	0.5
Miglyol oil	14.5
Na_2SO_4	1.2
Sulfuric acid and/or NaOH	q.s. for pH adjustment to 5.5
Purified water	q.s. to 100

EXAMPLE 8: Antibacterial Ointment

A procedure similar to that of Example 1 is used to produce this solution having the following composition.

Ingredient	Amount (% by weight)
Compound having Formula VI	0.3
Apramycin	0.2
White petrolatum USP	50
Propylene glycol	5
Glycerin	5
Tween® 20	2
Vitamin E	1
BAK	0.1
Mineral oil	q.s. to 100

EXAMPLE 9: Antibacterial and Anti-inflammatory Ointment

A procedure similar to that of Example 1 is used to produce this solution having the following composition.

Ingredient	Amount (% by weight)
Compound having Formula IV	0.3
Gatifloxacin	0.1
Dexamethasone	0.15
White petrolatum USP	50
Propylene glycol	5
Glycerin	5
Tween® 20	2
Vitamin E	1
Vitamin D	0.5
BAK	0.1
Mineral oil	q.s. to 100

EXAMPLE 10: Antibacterial and Antiviral Solution

A procedure similar to that of Example 1 is used to produce this solution.

Ingredient	Amount (% by weight)
Compound having Formula IV	0.35
Mannitol	4.5
Adenine arabinoside	0.3
Benzakonium chloride ("BAK")	0.005
Polysorbate 80	0.1
EDTA	0.05
Sodium acetate	0.03
Acetic acid	0.04
Purified water	q.s. to 100

EXAMPLE 11: Antibacterial and Antifungal Solution

A procedure similar to that of Example 1 is used to produce this solution.

Ingredient	Amount (% by weight)
Compound having Formula IV	0.2
Compound having Formula VI	0.2
Amphotericin B	0.3
Mannitol	4.5
Benzakonium chloride ("BAK")	0.005
Polysorbate 80	0.1
EDTA	0.05
Sodium acetate	0.03
Acetic acid	0.04
Purified water	q.s. to 100

EXAMPLE 12: Antibacterial Emulsion

The procedure of Example 6 is used to produce this emulsion having the composition shown in the table immediately below.

Ingredient	Amount (% by weight)
Compound having Formula IV	0.5
Moxifloxacin	0.2
Polysorbate 60	1
Sorbitan monostearate (an emulsifier)	1.5
Cetyl stearyl alcohol (an emulsion stabilizer)	1.5
Benzyl alcohol	0.5
Miglyol oil	14.5
Na_2SO_4	1.2
Sulfuric acid and/or NaOH	q.s. for pH adjustment to 5.5
Purified water	q.s. to 100

EXAMPLE 13: Antibacterial Composition Comprising Compound Having Formula IV and Ciprofloxacin

Compositions having various combinations of concentrations of compound having Formula IV and cirprofloxacin were tested systematically against *S. aureus*, *P. aeruginosa*, and *E. coli*. The MICs (in μg/ml) of each drug alone and in combination are shown in Table 7.

Table 7

MICs of Compound Having Formula IV and Ciprofloxacin Alone and in Combination

Organism	Compound Having Formula IV Alone	Ciprofloxacin Alone	Compound Having Formula IV in Combination	Ciprofloxacin in Combination
S. aureus (ATCC 29213)	0.03	0.5	0.015	0.25
			0.0005 – 0.001	0.5
P. aeruginosa (ATCC 27853)	4	0.5	1	0.25
			1 – 2	0.012
			2	0.06
E. coli (ATCC 25922)	0.12	0.015 - 0.030	≤ 0.03	0.015
			0.015 – 0.06	0.008
			0.03 – 0.06	0.004
			0.03 – 0.06	0.002
			0.015 – 0.03	0.008
			0.06	0.004

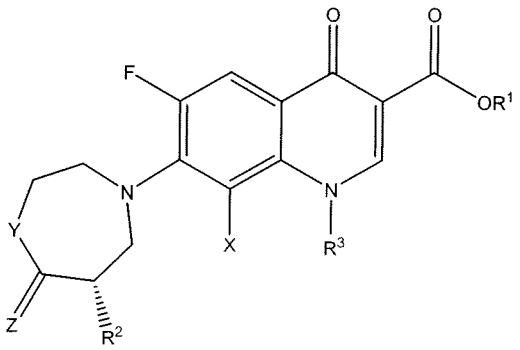
Data of Table 7 show that although ciprofloxacin alone is effective against *S. aureus*, combinations of the compound having Formula IV and ciprofloxacin can be more effective than either drug alone against *P. aeruginosa* and *E. coli* as MIC of at least one drug in the combination is less than one-half that of the same drug used alone.

The present invention also provides a method for treating, reducing, ameliorating, or preventing infection of the eye, ear, or upper respiratory tract. In one aspect, such an infection is caused by mixed types of microorganisms including at least a bacterium. In another aspect, said at least a bacterium is one that is resistant to at least a commonly used antibiotic. In still another aspect, the method comprises administering one or more drops of a composition of the present invention to the ear canal, nasal cavity, or back of the throat of a subject who has indication of infection or whose risk of infection is indicated. A composition of the present invention can also be formulated into a spray, which can be administered into the otic or nasal cavity of such a subject.

While specific embodiments of the present invention have been described in the foregoing, it will be appreciated by those skilled in the art that many equivalents, modifications, substitutions, and variations may be made thereto without departing from the spirit and scope of the invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A composition for treating, reducing, ameliorating, or preventing an infection in a subject, the composition comprising: (a) a fluoroquinolone having Formula I or salts thereof; and (b) an additional anti-infective agent; wherein the fluoroquinolone and the additional anti-infective agent are present in amounts effective to treat, reduce, ameliorate, or prevent said infection,



(I)

wherein R^1 is selected from the group consisting of hydrogen, unsubstituted lower alkyl groups, substituted lower alkyl groups, cycloalkyl groups, unsubstituted C_5-C_{24} aryl groups, substituted C_5-C_{24} aryl groups, unsubstituted C_5-C_{24} heteroaryl groups, substituted C_5-C_{24} heteroaryl groups, and groups that can be hydrolyzed in living bodies; R^2 is selected from the group consisting of hydrogen, unsubstituted amino group, and amino groups substituted with one or two lower alkyl groups; R^3 is selected from the group consisting of hydrogen, unsubstituted lower alkyl groups, substituted lower alkyl groups, cycloalkyl groups, unsubstituted lower alkoxy groups, substituted lower alkoxy groups, unsubstituted C_5-C_{24} aryl groups, substituted C_5-C_{24} aryl groups, unsubstituted C_5-C_{24} heteroaryl groups, substituted C_5-C_{24} heteroaryl groups, unsubstituted C_5-C_{24} aryloxy groups, substituted C_5-C_{24} aryloxy groups, unsubstituted C_5-C_{24} heteroaryloxy groups, substituted C_5-C_{24} heteroaryloxy groups, and groups that can be hydrolyzed in living bodies; X is selected from the group consisting of halogen atoms; Y is selected from the group consisting of CH_2, O, S, SO, SO_2, and NR^4, wherein R^4 is selected from the group consisting of hydrogen, unsubstituted lower alkyl groups, substituted lower alkyl groups, and cycloalkyl groups; and Z is selected from the group consisting of

oxygen and two hydrogen atoms; and wherein the composition is capable of inhibiting a growth or survival of mixed types of microorganisms causing said infection.

2. The composition of claim 1, wherein R^1 is selected from the group consisting of hydrogen, C_1-C_5 substituted and unsubstituted alkyl groups, C_3-C_{10} cycloalkyl groups, C_6-C_{14} substituted and unsubstituted aryl groups, C_5-C_{14} substituted and unsubstituted heteroaryl groups, and groups that can be hydrolyzed in living bodies; R^2 is selected from the group consisting of unsubstituted amino group and amino groups substituted with one or two C_1-C_5 alkyl groups; R^3 is selected from the group consisting of hydrogen, C_1-C_5 substituted and unsubstituted alkyl groups, C_3-C_{10} cycloalkyl groups, C_1-C_5 substituted and unsubstituted alkoxy groups, C_5-C_{14} substituted and unsubstituted aryl groups, C_5-C_{14} substituted and unsubstituted heteroaryl groups, and C_5-C_{14} substituted and unsubstituted aryloxy groups; and X is selected from the group consisting of Cl, F, and Br.

3. The composition of claim 1, wherein R^1 is selected from the group consisting of hydrogen, C_1-C_5 substituted and unsubstituted alkyl groups and groups that can be hydrolyzed in living bodies; R^2 is selected from the group consisting of unsubstituted amino group and amino groups substituted with one or two C_1-C_5 alkyl groups; R^3 is selected from the group consisting of C_3-C_{10} cycloalkyl groups; X is selected from the group consisting of Cl and F; Y comprises hydrogen; and Z comprises two hydrogen atoms.

4. The composition of claim 1, wherein the fluoroquinolone is present in an amount from 0.0001 to 10% by weight.

5. The composition of claim 1, wherein the fluoroquinolone is present in an amount from 0.01 to 5% by weight.

6. The composition of claim 1, wherein the additional anti-infective agent is selected from the group consisting of antiviral agents, antifungal agents, antiprotozoal agents, antibacterial agents other than the fluoroquinolones having Formula I, and mixtures thereof.

7. The composition of claim 6, further comprising an anti-inflammatory agent.

8. The composition of claim 7, wherein said anti-inflammatory agent is selected from the group consisting of glucocorticosteroids, non-steroidal anti-inflammatory drugs, inhibitors of cytokine production, and mixtures thereof.

9. The composition of claim 4, further comprising a material selected from the group consisting of buffers, surfactants, viscosity modifiers, tonicity adjusting agents, preservatives, antioxidants, additional medicaments, and combinations thereof.

10. The composition of claim 8, further comprising a material selected from the group consisting of buffers, surfactants, viscosity modifiers, tonicity adjusting agents, preservatives, antioxidants, additional medicaments, and combinations thereof.

11. The composition of claim 4, wherein the fluoroquinolone has Formula IV.

12. The composition of claim 7, wherein the fluoroquinolone has Formula IV.

13. The composition of claim 1, comprising a single enantiomer of the fluoroquinolone having Formula I.

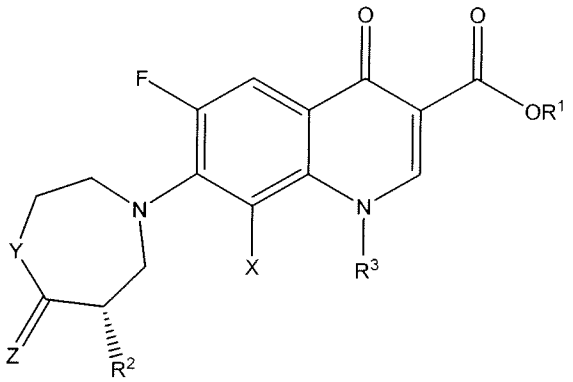
14. The composition of claim 4, wherein the fluoroquinolone has Formula VI.

15. The composition of claim 4, wherein the fluoroquinolone comprises a racemic mixture of a compound having Formula III.

16. The composition of claim 4, wherein the composition is in a form of a solution, cream, emulsion, suspension, ointment, or gel.

17. The composition of claim 4, further comprising a quinolone other than the fluoroquinolones having Formula I, and wherein the additional anti-infective agent is selected from the group consisting of antiviral agents, antifungal agents, antiprotozoal agents, and mixtures thereof.

18. A method for treating, reducing, ameliorating, or preventing an infection in a subject, the method comprising administering to a subject in need thereof, a composition comprising: (a) a fluoroquinolone having Formula I or salts thereof; and (b) an additional anti-infective agent; wherein the fluoroquinolone is present in an amount effective to treat, reduce, ameliorate, or prevent said infection,



(I)

wherein R^1 is selected from the group consisting of hydrogen, unsubstituted lower alkyl groups, substituted lower alkyl groups, cycloalkyl groups, unsubstituted C_5-C_{24} aryl groups, substituted C_5-C_{24} aryl groups, unsubstituted C_5-C_{24} heteroaryl groups, substituted C_5-C_{24} heteroaryl groups, and groups that can be hydrolyzed in living bodies; R^2 is selected from the group consisting of hydrogen, unsubstituted amino group, and amino groups substituted with one or two lower alkyl groups; R^3 is selected from the group consisting of hydrogen, unsubstituted lower alkyl groups, substituted lower alkyl groups, cycloalkyl groups, unsubstituted lower alkoxy groups, substituted lower alkoxy groups, unsubstituted C_5-C_{24} aryl groups, substituted C_5-C_{24} aryl groups, unsubstituted C_5-C_{24} heteroaryl groups, substituted C_5-C_{24} heteroaryl groups, unsubstituted C_5-C_{24} aryloxy groups, substituted C_5-C_{24} aryloxy groups, unsubstituted C_5-C_{24} heteroaryloxy groups, substituted C_5-C_{24} heteroaryloxy groups, and groups that can be hydrolyzed in living bodies; X is selected from the group consisting of halogen atoms; Y is selected from the group consisting of CH_2, O, S, SO, SO_2, and NR^4, wherein R^4 is selected from the group consisting of hydrogen, unsubstituted lower alkyl groups, substituted lower alkyl groups, and cycloalkyl groups; and Z is selected from the group consisting of oxygen and two hydrogen atoms; and wherein the composition is capable of inhibiting a growth or survival of mixed types of microorganisms causing said infection.

19. The method of claim 17, wherein the composition is administered topically, orally, or systemically.

20. The method of claim 18, wherein the composition is administered topically.

21. The method of claim 19, wherein the infection is an infection of an eye, an ear, a portion of a respiratory system, or a combination thereof.

22. The method of claim 17, wherein the additional anti-infective agent is selected from the group consisting of antiviral agents, antifungal agents, antiprotozoal agents, antibacterial agents other than the fluoroquinolones having Formula I, and combinations thereof.

23. The method of claim 21, wherein at least one of the microorganism is a bacterium that is resistant to an antibacterial agent.

24. The method of claim 22, wherein said infection is caused by a bacterium and a fungus, and said additional anti-infective agent is an antifungal drug.

25. The method of claim 22, wherein said infection is caused by a bacterium and a virus, and said additional anti-infective agent is an antiviral drug.

26. The method of claim 22, wherein said infection is caused by a bacterium and a protozoa, and said additional anti-infective agent is an antiprotozoal drug.

27. The method of claim 18, wherein the composition further comprises a quinolone other than the fluoroquinolones having Formula I, and wherein the additional anti-infective agent is selected from the group consisting of antiviral agents, antifungal agents, antiprotozoal agents, and mixtures thereof.

28. A method for treating, reducing, ameliorating, or preventing an infection in a subject, the method comprising administering to the subject in need thereof, a composition comprising: (a) a fluoroquinolone having Formula III or salts thereof; and an additional anti-infective agent.

29. The method of claim 26, wherein the fluoroquinolone is a single enantiomer of the fluoroquinolone having Formula III.

30. The method of claim 26, wherein the composition is administered topically, orally, or systemically.

31. The method of claim 27, wherein the composition is administered topically.

32. The method of claim 29, wherein the infection is an infection of an eye, an ear, a portion of a respiratory tract, or a combination thereof.

33. The method of claim 32, wherein the composition further comprises a quinolone other than the fluoroquinolones having Formula III, and wherein the additional anti-infective agent is selected from the group consisting of antiviral agents, antifungal agents, antiprotozoal agents, and mixtures thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/063624

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/55 A61P11/00 A61P27/16 A61P31/04

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 385 900 A (KONNO FUJIKO [JP] ET AL) 31 January 1995 (1995-01-31) tables	1-33
X	US 2002/187193 A1 (ROY SAMIR [US] ET AL) 12 December 2002 (2002-12-12) paragraphs [0006] - [0011], [0053]	1-33
X	BRUNNER ET AL: "P1679 In vitro activity of SS734, a novel fluoroquinolone, against pathogens associated with bacterial conjunctivitis" INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, AMSTERDAM, NL, vol. 29, 1 March 2007 (2007-03-01), pages S475-S476, XP022038868 ISSN: 0924-8579 the whole document	1-33

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 August 2008	05/09/2008

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/063624

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with Indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BRUNNER ET AL: "P1680 Bactericidal activity of SS734, a novel fluoroquinolone, against pathogens associated with bacterial conjunctivitis" INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, AMSTERDAM, NL, vol. 29, 1 March 2007 (2007-03-01), page S476, XP022038869 ISSN: 0924-8579 the whole document	1-33
X	CAMBAU ET AL: "P1665 Mode of action and resistance of the new fluoroquinolone BOL-303224-A" INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, AMSTERDAM, NL, vol. 29, 1 March 2007 (2007-03-01), page S471, XP022038854 ISSN: 0924-8579 the whole document	1-33
A	DHOPLE ET AL: "IN VITRO ACTIVITY OF KRM - 1648 , EITHER SINGLY OR IN COMBINATION WITH OFLOXACIN, AGAINST MYCOBACTERIUM ULCERANS" INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, AMSTERDAM, NL, vol. 17, no. 1, 1 January 2001 (2001-01-01), pages 57-61, XP008079269 ISSN: 0924-8579 the whole document	1-33
A	BASSETTI ET AL: "Efficacy of the combination of levofloxacin plus ceftazidime in the treatment of hospital-acquired pneumonia in the Intensive Care Unit" INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, AMSTERDAM, NL, vol. 28, no. 6, 22 November 2006 (2006-11-22), pages 582-585, XP005775404 ISSN: 0924-8579 the whole document	1-33

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 18-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

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

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

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

Although claims 18-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

see FURTHER INFORMATION sheet PCT/ISA/210

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

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

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

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

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

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

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

Remark on Protest

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

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/063624

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5385900 A	31-01-1995	NONE	
US 2002187193 A1	12-12-2002	NONE	