COMPOSITIONS COMPRISING QUINOLONE AND METHODS FOR TREATING OR CONTROLLING INFECTIONS

BACKGROUND OF THE INVENTION

The present invention relates to compositions and methods for treating or controlling infections. In particular, the present invention relates to such compositions comprising a quinolone carboxylic acid or a derivative thereof, 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 eye, ear, and respiratory system. 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. In cases of otitis externa, the most common bacteria are *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Fungi have also been found to a lesser extent in cases of otic infections.

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*.

Keratitis and conjunctivitis, two common ocular infections, are caused mostly by bacteria, fungi, and/or viruses. Among these microorganisms, 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.

Quinolones comprise a family of newer antibacterial agents, some of which have been used for the foregoing conditions. However, quinolones typically have low solubility, and thus, extra measures have been used to increase their availability at the target sites.

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 for combating infections. It is also very desirable to provide pharmaceutical compositions that can overcome at least some of the shortcomings of prior-art antimicrobial agents.

SUMMARY OF THE INVENTION

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

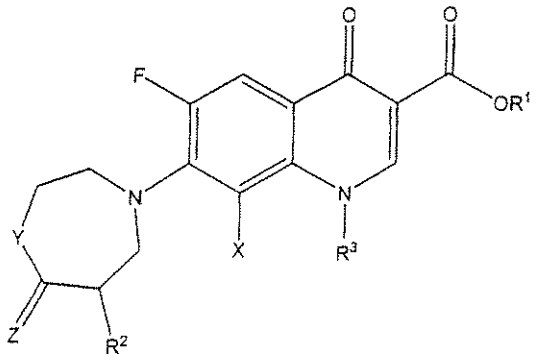
In one aspect, the present invention provides pharmaceutical compositions and methods using such compositions for the treatment or control of infections of an eye, an ear, a portion of a respiratory system, or a combination thereof.

In another aspect, a pharmaceutical composition comprises a high concentration of a quinolone soluble in a pharmaceutically acceptable vehicle.

In still another aspect, the pharmaceutical composition comprises an aqueous solution.

In yet another aspect, the pharmaceutical composition is effective against at least a bacterium that is resistant to at least a prior-art antibacterial agent.

In a further aspect, such quinolone comprises at least one member of a family of fluoroquinolones that have Formula I or salts thereof,

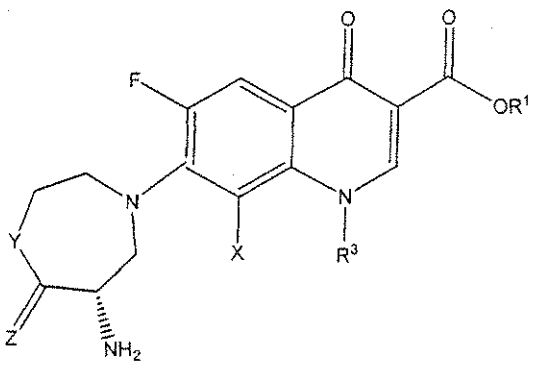


(I)

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 quinolone comprises a member of a family of fluoroquinolones having Formula II or salts thereof,



(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 or controlling an infection of an eye, an ear, a portion of a respiratory system, or a combination thereof. The method comprises administering a composition comprising a

fluoroquinolone having Formula I or II soluble therein at a high concentration to a site of infection to treat or control 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 eye, an ear, a portion of an upper respiratory system, or a combination thereof.

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

BRIEF DESCIRPTION OF THE FIGURE

Figure 1 shows the solubility of the compound having Formula IV in USP water.

DETAILED DESCRIPTION

As used herein, the term "control" includes alleviation, reduction, amelioration, and prevention.

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 or controlling an infection.

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

In another aspect, a pharmaceutical composition comprises a high concentration of a quinolone soluble in a pharmaceutically acceptable vehicle.

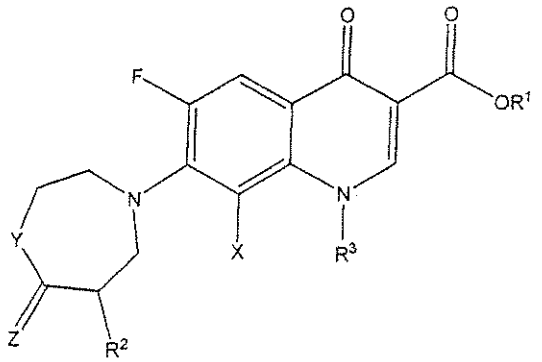
In a still another aspect, said concentration is greater than about 0.05 percent by weight (or, alternatively, greater than about 0.1, or 1 percent by weight) of the total composition.

In still another aspect, said concentration is in the range from about 0.05 percent to about 2 percent by weight (or, alternatively, from about 0.05 percent to about 1 percent by weight) of the total composition.

In yet another aspect, the pharmaceutical composition comprises an aqueous solution.

In yet another aspect, the pharmaceutical composition is effective against at least a bacterium that is resistant to at least a prior-art antibacterial agent.

In a further aspect, such quinolone comprises at least one member of a family of fluoroquinolones that have Formula I or salts thereof,



(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 another aspect, said infection is caused by mixed types of bacteria.

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 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.

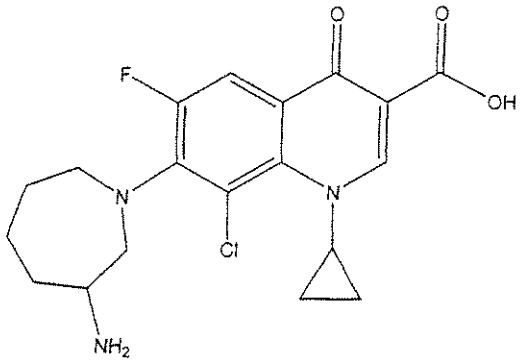
Table 1

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

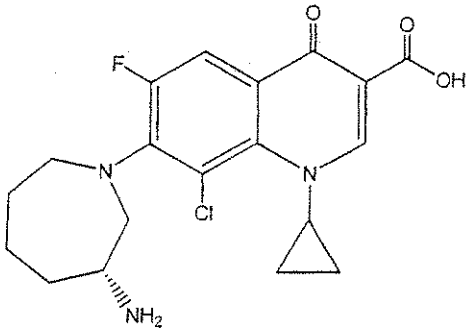
8	H	NH_2	cyclopropyl	F	CH_2	2 H
9	H	NH_2	cyclopropyl	Br	CH_2	2 H
10	H	$NH(C_2H_5)$	cyclopropyl	Cl	CH_2	2 H
11	H	$NH(C_2H_5)$	cyclopropyl	F	CH_2	2 H
12	H	NH_2	cyclopentyl	Cl	CH_2	2 H
13	H	NH_2	cyclopropyl	Cl	CH_2	O
14	H	NH_2	cyclopropyl	F	CH_2	O
15	H	NH_2	cyclopropyl	Br	CH_2	O
16	H	NH_2	cyclopropyl	Cl	$CH(C_3H_5)$	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	$NH(C_2H_5)$	cyclopropyl	Cl	CH_2	O
21	CH_3	$NH(C_3H_7)$	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.

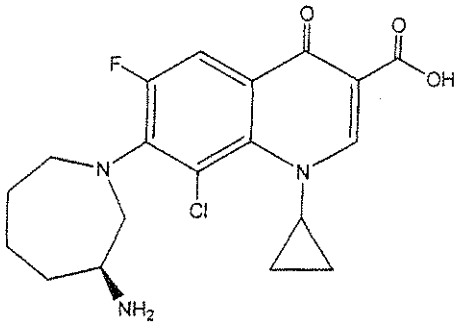


(III)

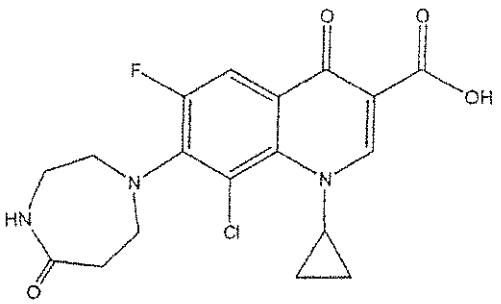
In another embodiment, the fluoroquinolone carboxylic acid included in a composition of the present invention has Formula IV, V, or VI.



(IV)

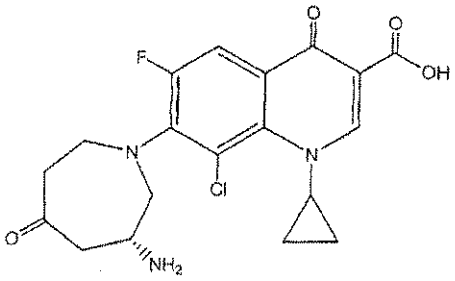


(V)

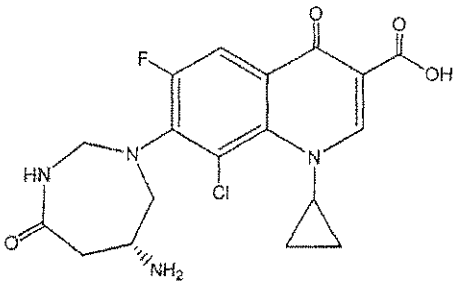


(VI)

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 yet another aspect, a composition of the present invention has a pH in the range from about 3.5 to about 5.5 (or, alternatively, from about 3.5 to 5, or from about 4 to 5, or from about 4 to 5.5), or from about 10.5 to about 12 (or, alternatively, from about 10.5 to 11, or from about 11 to 12).

In a further aspect, a composition of the present invention further comprises an additional anti-infective medicament that 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 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 percent to 10 percent by weight (or alternatively, from about 0.001 percent to about 5 percent, or from about 0.01 percent to about 5 percent, or from about 0.01 percent to about 2 percent, or from about 0.01 percent to about 1 percent, or from about 0.01 percent to about 0.7 percent, or from about 0.01 percent to about 0.5 percent, by weight).

In a still another aspect, said concentration is greater than about 0.05 percent by weight (or, alternatively, greater than about 0.1, or 1 percent by weight) of the total composition.

In still another aspect, said concentration is in the range from about 0.05 percent to about 2 percent by weight (or, alternatively, from about 0.05 percent to about 1 percent by weight) of the total composition.

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 percent to 10 percent by weight (or alternatively, from about 0.001 percent to about 5 percent, or from about 0.01 percent to about 5 percent, or from about 0.01 percent to about 2 percent, or from about 0.01 percent to about 1 percent, or from about 0.01 percent to about 0.7 percent, or from about 0.01 percent to about 0.5 percent, or

from about 0.05 percent to about 0.5 percent, or from about 0.05 percent to about 1 percent, by weight).

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

A fluoroquinolone compound and, optionally, 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 or control of an infection. In an embodiment, such infection comprises an infection of an eye, an ear, a portion of a respiratory system, or a combination thereof. Such a composition comprises a fluoroquinolone compound having Formula I, II, III, IV, V, VI, VII, or VIII, an optionally 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. In one embodiment, the fluoroquinolone compound is dissolved in the carrier of these dosage forms. A fluoroquinolone compound having Formula I, II, III, IV, V, VI, VII, or VIII disclosed herein is particularly suitable for a treatment or control of infections of an eye, an ear, a portion of a respiratory system, or a combination thereof. In a preferred embodiment, the composition is an aqueous solution.

In one embodiment, such infections are caused by at least one bacterium. When the additional anti-infective agent is an antifungal agent, an antiviral agent, or an antiprotozoal agent, a composition of the present invention can be used to treat or control mixed types of microorganisms comprising at least a bacterium and a fungus, at least a bacterium and a virus, or at least a bacterium and a protozoa, respectively. In another embodiment, such a fluoroquinolone 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 acceptable pH adjusting acids, bases, or buffers to within the range from about 3.5 to about 5.5 (or, alternatively, from about 3.5 to 5, or from about 4 to 5, or from about 4 to 5.5), or from about 10.5 to about 12 (or, alternatively, from about 10.5 to 11, or from about 11 to 12).

Non-limiting 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 or to improve product tolerance by the user. 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 1 to about 100,000 centipoise ("cp") or mPa.s (or alternatively, from about 5 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 percent to about 5 percent (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 percent to 20 percent hydroxypropyl- β-cyclodextrin; alternatively, 1 percent to 15 percent (or 2 percent to 10 percent) 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 percent to about 20 percent (alternatively, from about 0.1 percent to about 10 percent, from about 0.1 percent to about 5 percent, or from about 0.1 percent to about 2 percent) 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 percent to about 10 percent (alternatively, from about 0.1 percent to about 5 percent, or from about 0.1 percent to about 2 percent) 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 ocular use include dexamethasone, prednisolone, methasone, fluorometholone, loteprednol, medrysone, and rimesolone. 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 percent by weight (or alternatively, from about 0.01 to about 2 percent, or from about 0.05 percent to about 1 percent, by weight).

Bacterial pathogens that have been isolated from cases of eye infection include gram-negative bacteria (such as *Neisseria* species, *Moraxella* species, *Brucella* species, *Enterobacter* species, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*), gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus mitis*, *Streptococcus faecalis*, *Bacillus subtilis*, *Clostridium tetani*, *Corynebacterium diphtheriae*, *Propionibacterium acnes*, and *Actinomyces israelii*.

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.

Solubility and Stability of Solution Containing Compound Having Formula IV

The solubility of the compound having Formula IV in USP water is shown in Figure 1. Compositions of the present invention having pH in the ranges from about 3.5 to about 5.5 or from about 10.5 to about 12 can contain a high concentration of the compound and, thus, can deliver an effective amount of the drug to the affected site.

The stability of the compound having Formula IV in solution is shown in Table 7, as the remaining amount (expressed as the percentage of the initial amount) of the compound after selected times. The compound is stable in the pH range of most interest for the present invention.

Table 7

Stability of the Compound Having Formula IV (Initial Concentration of 100 μg/ml)

Time (week)		0	2	4
pH	3.5	100	99.0	98.8
	4.0	100	98.5	98.4
	4.5	100	98.4	98.4
	5.0	100	98.2	98.8
	5.5	100	96.8	96.8
	6.0	100	96.3	98.0
	6.5	100	95.3	95.6

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 (percent by weight)
Compound having Formula IV	0.3
Hydroxypropylmethyl cellulose ("HPMC"), medium viscosity ("MV")	0.5
Benzakonium chloride ("BAK")	0.01
Pluronic® F127	0.1
EDTA	0.1
NaCl	0.25
Succinate buffer (0.05M, pH = 4.0)	q.s. to 100

An appropriate amount of succinate buffer is placed 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, an appropriate amount of the compound having Formula IV is 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 then sterilized, for example by autoclaving at a temperature of about 121° C for about 30 minutes. The sterilized 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 (percent by weight)
Compound having Formula IV	0.5
Carboxymethyl cellulose (CMC) MV	1
Benzakonium chloride ("BAK")	0.01
Pluronic® F68	0.1
EDTA	0.1
Sodium chloride	0.25
Acetate buffer (0.05 M, pH = 4.5)	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 (percent by weight)
Compound having Formula IV	0.4
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 (percent 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 (percent 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 loteprednol etabonate are added to the first vessel. An appropriate amount of Mygliol oil is charged into 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. 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 then sterilized, for example by autoclaving at a temperature of about 120° C. The sterilized composition is further cooled to 25° C to 30° C. The final composition is packaged in appropriate containers.

Ingredient	Amount (percent by weight)
Compound having Formula IV	0.1
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
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 percent by weight of the composition, and preferably, 3 to 5 percent by weight of the composition. The hydrophobic phase of the emulsion can be in an amount of 15 to 25 percent by weight of the composition, and preferably, 18 to 22 percent 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 (percent by weight)
Compound 13 of Table 1	0.2
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
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 (percent 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 (percent 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 (percent 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 (percent 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 (percent by weight)
Compound having Formula IV	0.2
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
Purified water	q.s. to 100

EXAMPLE 13: Antibacterial Solution Containing Compound Having Formula IV

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

Ingredient	Amount (percent by weight)
Compound having Formula IV	0.6
CMC MV	1
Pluronic® F68	0.1
EDTA	0.1
Sodium chloride	0.25
Potassium chloride	0.1
Formate buffer (0.05 M, pH = 4)	q.s. to 100

EXAMPLE 14: Antibacterial Solution Containing Compound Having Formula IV

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

Ingredient	Amount (percent by weight)
Compound having Formula IV	0.2
Povidone	3
Triton 100	0.1
EDTA	0.1
Benzalkonium chloride	0.01
Sodium chloride	0.25
Sorbitol	3
Phosphate buffer (0.05 M, pH = 5)	q.s. to 100

EXAMPLE 15: Antibacterial Solution Containing Compound Having Formula IV

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

Ingredient	Amount (percent by weight)
Compound having Formula IV	0.2
CMC MV	1
Benzakonium chloride ("BAK")	0.01
Pluronic® F127	0.1
EDTA	0.1
Sodium chloride	0.15
Mannitol	2.5
Phosphate buffer (0.03 M) and citrate buffer (0.02 M), pH = 4	q.s. to 100

EXAMPLE 16: Antibacterial Solution Containing Compound Having Formula IV and Anti-inflammatory Drug

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

Ingredient	Amount (percent by weight)
Compound having Formula IV	0.3
Loteprednol etabonate	0.1
CMC MV	1
Pluronic® F127	0.2
EDTA	0.1
Sodium chloride	0.1
Citrate buffer (0.05 M, pH = 4)	q.s. to 100

EXAMPLE 17: 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 8.

Table 8

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

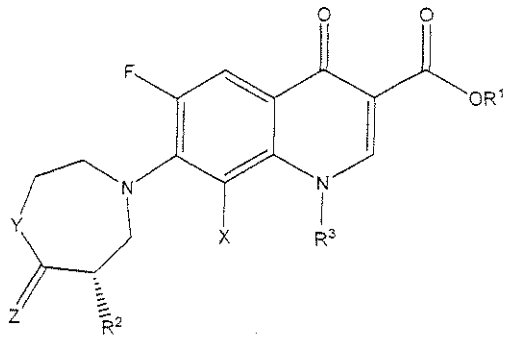
Data of Table 8 show that although ciprofloxacin alone is effective against *S. aureus*, combinations of the compound having Formula IV and ciprofloxacin can be more effective than either drug alone against *P. aeruginosa* and *E. coli* as MIC of at least one drug in the combination is less than one-half that of the same drug used alone.

The present invention also provides a method for treating or controlling 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.

CLAIMS

1. A composition for treating or controlling an infection in a subject, the composition comprising a fluoroquinolone having Formula I or salts thereof, wherein the composition is an emulsion and has a pH of at most 5.5, and the fluoroquinolone is present in an amount effective to treat or control the 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; 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, and substituted C_5-C_{24} heteroaryloxy groups; 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.

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, and C_5-C_{14} substituted and unsubstituted heteroaryl groups; 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 the emulsion has a pH of at least 3.5.

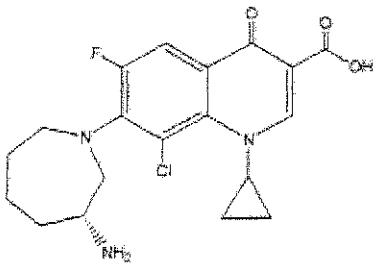
4. The composition of claim 1, wherein the fluoroquinolone is present in a concentration from 0.01 to 1 percent by weight.

5. The composition of claim 1, further comprising an 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.

6. The composition of claim 1, further comprising an anti-inflammatory agent.

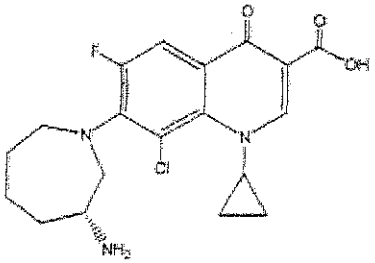
7. The composition of claim 6, wherein said anti-inflammatory agent is selected from the group consisting of glucocorticosteroids, non-steroidal anti-inflammatory drugs, inhibitors of cytokine production, and mixtures thereof.

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



(IV)

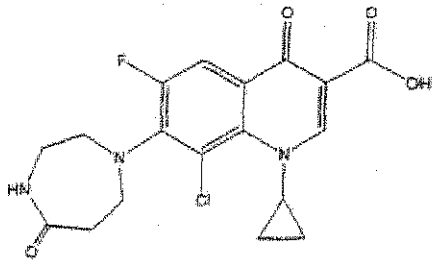
9. The composition of claim 6, wherein the fluoroquinolone has Formula IV



(IV)

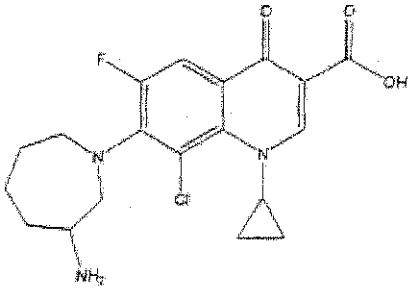
10. The composition of claim 1, comprising a single enantiomer of the fluoroquinolone having Formula I.

11. The composition of claim 1, wherein the fluoroquinolone has Formula VI



(VI)

12. The composition of claim 1, wherein the fluoroquinolone comprises a racemic mixture of a compound having Formula III



(III)

13. The composition of claim 1, wherein the emulsion has a pH of 5 to 5.5.

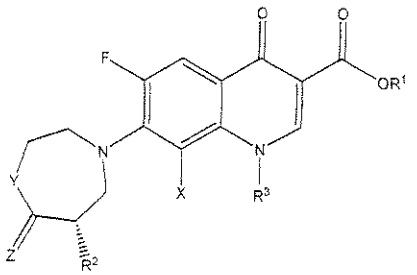
14. The composition of claim 5, further comprising a quinolone other than the fluoroquinolones having Formula I, and wherein the additional anti-infective agent is selected from the group consisting of antiviral agents, antifungal agents, antiprotozoal agents, and mixtures thereof.

15. A composition for treating or controlling an infection in a subject, the composition comprising a fluoroquinolone having Formula I or salts thereof, wherein the composition has a pH of at most 5.5, and the fluoroquinolone is present at a concentration from 0.01 to 1 percent by weight of the total composition, wherein the composition is an emulsion.

16. The composition of claim 15, wherein the emulsion has a pH of at least 3.5.

17. The composition of claim 15, wherein the emulsion has a pH of 5 to 5.5.

18. Use of a fluoroquinolone having Formula I or salts thereof for preparing a medicament for treating or controlling an infection in a subject, wherein the medicament is an emulsion having a pH of at most 5.5, and the fluoroquinolone is present in an amount effective to treat or control 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; 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, and substituted C_5-C_{24} heteroaryloxy groups; 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.

19. The use of claim 18, wherein the medicament is administered topically.

20. The use of claim 18, wherein the emulsion has a pH of at least 3.5.

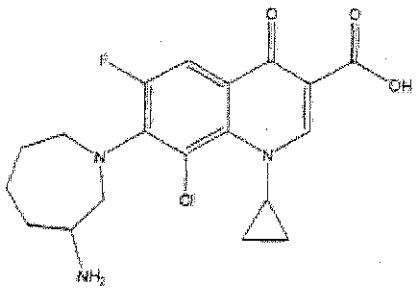
21. The use of claim 18, wherein the emulsion has a pH of 5 to 5.5.

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

23. The use of claim 18, wherein a microorganism causing the infection is a bacterium that is resistant to an antibacterial agent.

24. The use of claim 18, wherein the medicament 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.

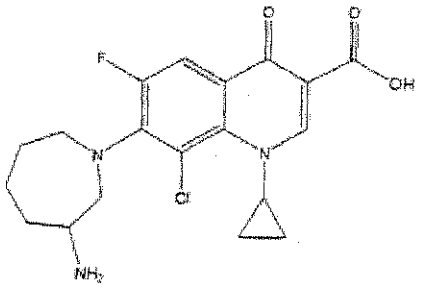
25. Use of a combination of (a) a fluoroquinolone having Formula III or salts thereof; and (b) an additional anti-infective agent for preparing a medicament for treating or controlling an infection in a subject,



(III)

wherein the medicament is an emulsion having a pH of at most 5.5, and the fluoroquinolone has a concentration of from 0.01 to 1 percent by weight.

26. The use of claim 25, wherein the fluoroquinolone is a single enantiomer of the fluoroquinolone having Formula III



(III)

27. The use of claim 25, wherein the infection is an infection of an eye, an ear, a portion of a respiratory tract, or a combination thereof.

28. The use of claim 25, wherein the emulsion has a pH of at least 3.5.

29. The use of claim 25, wherein the emulsion has a pH of 5 to 5.5.