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# ANTIMICROBIAL QUINOLONES, THEIR COMPOSITIONS AND USES

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## FIELD OF THE INVENTION

The subject invention relates to novel antimicrobial compounds, their compositions and their uses.

## CROSS REFERENCE

This application claims priority under Title 35, United States Code 119(e) from Provisional Application Serial No. 60/058,891, filed September 15, 1997.

## BACKGROUND

The chemical and medical literature describes compounds that are said to be antimicrobial, i.e., capable of destroying or suppressing the growth or reproduction of microorganisms, such as bacteria. For example, such antibacterials and other antimicrobials are described in Antibiotics, Chemotherapeutics, and Antibacterial Agents for Disease Control (M. Grayson, editor, 1982), and E. Gale et al., The Molecular Basis of Antibiotic Action 2d edition (1981).

The mechanism of action of these antibacterials vary. However, they are generally believed to function in one or more of the following ways: by inhibiting cell wall synthesis or repair; by altering cell wall permeability; by inhibiting protein synthesis; or by inhibiting synthesis of nucleic acids. For example, beta-lactam antibacterials act through inhibiting the essential penicillin binding proteins (PBPs) in bacteria, which are responsible for cell wall synthesis. As another example, quinolones act, at least in part, by inhibiting synthesis of DNA, thus preventing the cell from replicating.

The pharmacological characteristics of antimicrobials, and their suitability for any given clinical use, vary. For example, the classes of antimicrobials (and members within a class) may vary in 1) their relative efficacy against different types of microorganisms, 2) their susceptibility to development of microbial resistance and 3) their pharmacological characteristics, such as their bioavailability, and biodistribution. Accordingly, selection of an appropriate antibacterial (or other antimicrobial) in a given clinical situation requires analysis of many factors, including the type of organism involved, the desired method of administration, the location of the infection to be treated and other considerations.

However, many such attempts to produce improved antimicrobials yield equivocal results. Indeed, few antimicrobials are produced that are truly clinically-acceptable in terms of their spectrum of antimicrobial activity, avoidance of microbial resistance, and

pharmacology. Thus there is a continuing need for broad spectrum antimicrobials, which are effective against resistant microbes.

Some 1,4-dihydroquinolone, naphthyridine or related heterocyclic moieties are known in the art to have antimicrobial activity and are described in the following references: R. Albrecht, Prog. Drug Research, Vol. 21, p. 9 (1977); J. Wolfson et al., "The Fluoroquinolones: Structures, Mechanisms of Action and Resistance, and Spectra of Activity In Vitro", Antimicrob. Agents and Chemother., Vol. 28, p. 581 (1985); G. Klopman et al., Antimicrob. Agents and Chemother., Vol. 31, p. 1831 (1987); M. P. Wentland et al., Ann. Rep. Med. Chem., Vol. 20, p. 145 (1986); J. B. Cornett et al., Ann. Rep. Med. Chem., Vol. 21, p. 139 (1986); P. B. Fernandes et al., Ann. Rep. Med. Chem., Vol. 22, p. 117 (1987); A. Koga, et al., "Structure-Activity Relationships of Antibacterial 6,7- and 7,8-Disubstituted 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids", J. Med. Chem., Vol. 23, pp. 1358-1363 (1980); J.M. Domagala et al., J. Med. Chem., Vol. 31, p. 991 (1988); T. Rosen et al., J. Med. Chem., Vol. 31, p. 1586 (1988); T. Rosen et al., J. Med. Chem., Vol. 31, p. 1598 (1988); B. Ledoussal et al., "Non 6-Fluoro Substituted Quinolone Antibacterials: Structure and Activity", J. Med Chem., Vol. 35, p. 198-200 (1992); J. M. Domagala et al., "Quinolone Antibacterials Containing the New 7-[3-(1-Aminoethyl)-1-pyrrolidinyl] Side Chain: The Effects of the 1-Aminoethyl Moiety and Its Stereochemical Configurations on Potency and in Vivo Efficacy", J. Med. Chem., Vol. 36, pp. 871-882 (1993); Hagen et al., "Synthesis and Antibacterial Activity of New Quinolones Containing a 7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl] Moiety. Gram Positive Agents with Excellent Oral Activity and Low Side-Effect Potential", J. Med. Chem. Vol. 37, pp. 733-738 (1994); V. Cecchetti et al., "Studies on 6-Aminoquinolines: Synthesis and Antibacterial Evaluation of 6-Amino-8-methylquinolones", J. Med. Chem., Vol. 39, pp. 436-445 (1996); V. Cecchetti et al., "Potent 6-Desfluoro-8-methylquinolones as New Lead Compounds in Antibacterial Chemotherapy", J. Med. Chem., Vol. 39, pp. 4952-4957 (1996); Hong et al., "Novel 5-Amino-6-methylquinolone Antibacterials: a New Class of Non-6-fluoroquinolones", Bioorg. of Med. Chem. Let., Vol. 7, pp. 1875-1878 (1997); U.S. Pat. No. 4,844,902 to Grohe on July 4, 1989; U.S. Pat. No. 5,072,001 to Hagen & Suto on Dec. 10, 1991; U. S. Pat. No. 5,328,908 to Demuth & White on July 12, 1994; U. S. Pat. No. 5,457,104 to Bartel et al. on Oct. 10, 1995; U.S. Pat. No. 5,556,979 to Philipps et al. on Sept. 17, 1996; European Patent Appl. 572,259 of Ube Ind. pub. Dec. 1, 1993; European Patent Appl. 775,702 of Toyama Chem. Co. pub. May 28, 1997; Japanese Patent Pub. 62/255,482 of Kyorin Pharm. Co. pub. Mar. 1, 1995.

Structure activity relationships of the quinolones have been the subject of detailed study for more than a decade. As a result of these studies, it has been determined by those

in the art that certain structures, with specific sites on the quinolone ring functionalized, have distinct advantages over others. For example, A. Koga, et al., "Structure-Activity Relationships of Antibacterial 6,7- and 7,8-Disubstituted 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids", J. Med. Chem, Vol. 23, pp. 1358-1363 (1980) (Koga) discloses the non-equivalence of the 6- and 8-quinolonyl position, and the importance of the substitution at the 6-quinolonyl position. Koga appears to demonstrate by examples that 6-fluoro, 8-hydrogen substitution is superior to 6-hydrogen, 8-fluoro or halo. Perhaps as a result of this early structure activity work in this area, the art has focused on the 6-fluorinated structures to provide the next generation of quinolones. Despite the work in this area, the full promise of the quinolones as antibacterials has not yet been exploited.

Examples of bacterial infections resistant to antibiotic therapy have been reported in the past; they are now a significant threat to public health in the developed world. The development of microbial resistance (perhaps as a result of the intense use of antibacterials over extended periods of time) is of increasing concern in medical science. "Resistance" can be defined as existence of organisms, within a population of a given microbial species, that are less susceptible to the action of a given antimicrobial agent. This resistance is of particular concern in environments such as hospitals and nursing homes, where relatively high rates of infection and intense use of antibacterials are common. See, e.g., W. Sanders, Jr. et al., "Inducible Beta-lactamases: Clinical and Epidemiologic Implications for Use of Newer Cephalosporins", Reviews of Infectious Diseases p. 830 (1988).

Pathogenic bacteria are known to acquire resistance via several distinct mechanisms including inactivation of the antibiotic by bacterial enzymes (e.g., b-lactamases hydrolyzing penicillin and cephalosporins); removal of the antibiotic using efflux pumps, modification of the target of the antibiotic via mutation and genetic recombination (e.g., penicillin-resistance in *Neiserria gonorrhoeae*); and acquisition of a readily transferable gene from an external source to create a resistant target (e.g., methicillin-resistance in *Staphylococcus aureus*). There are certain Gram positive pathogens, such as vancomycin-resistant *Enterococcus faecium*, which are resistant to virtually all commercially available antibiotics.

Hence existing antibacterials have limited capacity in overcoming the threat of resistance. Thus it would be advantageous to provide a quinolone with useful properties that can be used commercially against resistant microbes.

## Objects of the Invention

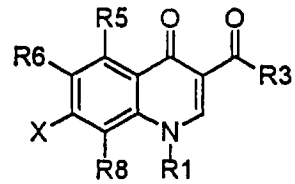
It is an object of the subject invention to provide quinolone and quinolonyl antimicrobial compounds that are useful against a broad spectrum of microbes, and especially against bacteria.

It is a further object of the invention to provide such antimicrobials which are effective against quinolone-resistant microbes.

## SUMMARY OF THE INVENTION

We have found a novel series of quinolone and quinolonyl compounds that are effective against resistant microbes, and provide significant activity advantages over the art. Furthermore, we have found that these quinolone and quinolonyl compounds defy the art accepted structure/activity relationships.

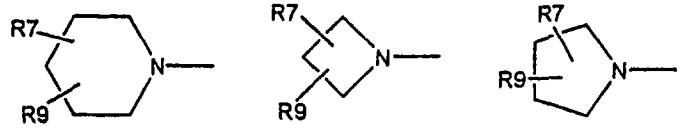
The invention relates to compounds of formula




Formula 1

wherein:

(a) X is selected from




;

(b) R1 is selected from $C_3$ to about $C_5$ cycloalkyl, $C_1$ to about $C_2$ alkanyl, $C_2$ to about $C_3$ linear alkenyl, $C_3$ to about $C_4$ branched alkanyl or alkenyl, all such alkyl or cycloalkyl moieties being unsubstituted or substituted with from 1 to about 3 fluoro; and phenyl, unsubstituted or substituted with from 1 to about 3 fluoro, or with one hydroxy in the 4-position;

(c) R3 is hydrogen or hydroxy;

(d) R5 is selected from hydrogen, hydroxy, amino, halo, $C_1$ to about $C_2$ alkanyl, $C_2$ alkenyl, and methoxy, all alkyl moieties being unsubstituted or substituted with from 1 to about 3 fluoro;

(e) R6 is selected from hydrogen, hydroxy, aminocarbonyl, bromo, cyano, $C_1$ to about $C_2$ alkanyl, $C_2$ to about $C_4$ alkenyl or alkynyl, all such alkyl moieties being

unsubstituted or substituted with from 1 to about 3 fluoro, or such methyl or ethyl moieties being optionally substituted with one hydroxy or one amino;

(f) R8 is selected from chloro, bromo, methoxy, $C_1$ to about $C_2$ alkanyl, $C_2$ to about $C_4$ alkenyl, all such alkyl moieties being unsubstituted or substituted with from 1 to about 3 fluoro;

(g) R7 is amino which is attached to a ring carbon of X which is not adjacent to the ring nitrogen, the amino being unsubstituted or substituted with one or two $C_1$ to about $C_3$ alkanyl; or aminoalkanyl which is attached to any ring carbon of X and is $C_1$ to about $C_3$ alkanyl substituted with one amino, the amino being unsubstituted or substituted with one or two $C_1$ to about $C_3$ alkanyl; and

(h) each R9 is independently selected from hydrogen, $C_1$ to about $C_4$ alkanyl, $C_2$ to about $C_6$ alkenyl or alkynyl, and a $C_3$ to about $C_6$ fused or spirocycle alkyl ring, all such alkyl moieties being unsubstituted or substituted with from 1 to about 3 fluoro;

(j) a R7 moiety described in (g) and a R9 moiety described in (h) may optionally be connected thus forming a fused or spirocycle ring with the N-containing ring shown in (a), the fused or spirocycle ring comprising from 2 to about 5 ring carbons and 0 or 1 ring nitrogen, but if such rings are fused, R8 is preferably other than chloro or bromo;

or an optical isomer, diastereomer or enantiomer thereof; a pharmaceutically-acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof. In addition, compounds incorporating the compounds of the invention, or using compounds of the invention as starting materials are also contemplated in this invention.

It has been found that the compounds of this invention, and compositions containing these compounds, are effective antimicrobial agents against a broad range of pathogenic microorganisms with advantages in low susceptibility to microbial resistance, reduced toxicity, and improved pharmacology.

## DESCRIPTION OF THE INVENTION

The present invention encompasses certain compounds, dosage forms, and methods of administering the compounds to a human or other animal subject. Specific compounds and compositions to be used in the invention must, accordingly, be pharmaceutically acceptable. As used herein, such a "pharmaceutically-acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

### Glossary of Terms

Unless otherwise specified, the following terms have the indicated meanings when used in this application.

"Alkanyl" is an unsubstituted or substituted, linear or branched, saturated hydrocarbon chain radical having from 1 to 8 carbon atoms, preferably from 1 to 4 carbon atoms. Preferred alkanyl groups include (for example) methyl, ethyl, propyl, isopropyl, and butyl.

"Alkenyl" is an unsubstituted or substituted, linear or branched, hydrocarbon chain radical having from 2 to 8 carbon atoms, preferably from 2 to 4 carbon atoms, and having at least, preferably only one, one carbon-carbon double bond.

"Alkynyl" is an unsubstituted or substituted, linear or branched, hydrocarbon chain radical having from 2 to 8 carbon atoms, preferably from 2 to 4 carbon atoms, and having at least, preferably only one, one carbon-carbon triple bond.

"Alkyl" includes alkanyl, alkenyl, and alkynyl as defined above, unless specifically limited otherwise to only one or two of them or by other restrictions. Alkyl retains this meaning when it is used as part of another word; examples are provided below (e.g., alkylene, haloalkyl). In such words, alkyl can be replaced by any of alkanyl, alkenyl, or alkynyl to narrow the meaning of such words accordingly.

"Alkylene" is a hydrocarbon diradical. Preferred alkylene includes ethylene and methylene.

"Amino" is an unsubstituted or substituted $-NH_2$.

"Haloalkyl" is an alkyl with one or more halogens (fluoro, chloro, bromo, iodo) on the alkyl. Hence, fluoroalkyl is an example of a subgenus of haloalkyl.

"Heteroatom" is a nitrogen, sulfur or oxygen atom. Groups containing one or more heteroatoms may contain different heteroatoms.

"Heteroalkyl" is an unsubstituted or substituted chain radical having from 2 to 8 members comprising carbon atoms and at least one heteroatom.

"Carbocyclic ring" is an unsubstituted or substituted, saturated, unsaturated or aromatic, hydrocarbon ring radical. Carbocyclic rings are monocyclic or are fused, bridged or spiro polycyclic ring systems. Monocyclic rings contain from 3 to 9 carbon atoms, preferably 3 to 6 carbon atoms. Polycyclic rings contain from 7 to 17 carbon atoms, preferably from 7 to 13 carbon atoms.

"Cycloalkyl" is a saturated or unsaturated, but not aromatic, carbocyclic ring radical. Preferred cycloalkyl groups are saturated, and include cyclopropyl, cyclobutyl and cyclopentyl, especially cyclopropyl.

"Heterocyclic ring" is an unsubstituted or substituted, saturated, unsaturated or aromatic ring radical comprised of carbon atoms and one or more heteroatoms in the ring

Heterocyclic rings are monocyclic or are fused, bridged or spiro polycyclic ring systems. Monocyclic rings contain from 3 to 9 carbon and heteroatoms, preferably 3 to 6 carbon and heteroatoms. Polycyclic rings contain from 7 to 17 carbon and heteroatoms, preferably from 7 to 13 carbon and heteroatoms.

"Aryl" is an unsubstituted or substituted aromatic carbocyclic ring radical. Preferred aryl groups include (for example) phenyl, 2,4-difluorophenyl, 4-hydroxyphenyl, tolyl, xylyl, cumenyl and naphthyl. Preferred substituents for aryl include fluoro and hydroxy.

"Heteroaryl" is an unsubstituted or substituted aromatic heterocyclic ring radical. Preferred heteroaryl groups include (for example) thienyl, furyl, pyrrolyl, pyridinyl, pyrazinyl, thiazolyl, quinolinyl, pyrimidinyl and tetrazolyl.

"Alkoxy" is an oxygen radical having a hydrocarbon chain substituent, where the hydrocarbon chain is an alkyl (i.e., -O-alkyl or -O-alkanyl). Preferred alkoxy groups are saturated, and include (for example) methoxy, ethoxy, propoxy and allyloxy.

"Alkylamino" is an amino radical having one or two alkyl substituents (e.g., -NH-alkyl). The alkyl groups are preferably saturated, and include (for example) methyl and ethyl.

"Arylalkyl" is an alkyl radical substituted with an aryl group. Preferred arylalkyl groups include benzyl and phenylethyl.

"Arylamino" is an amino radical substituted with an aryl group (e.g., -NH-phenyl).

"Aryloxy" is an oxygen radical having a aryl substituent (e.g., -O-phenyl).

"Acyl" or "carbonyl" is a radical formed by removal of the hydroxy from a carboxylic acid (e.g., R-C(O)-). Preferred groups include (for example) formyl, and alkylacyl moieties such as acetyl and propionyl.

"Acyloxy" is an oxygen radical having an acyl substituent (i.e., -O-acyl); for example, -O-C(O)-alkyl.

"Acylamino" is an amino radical having an acyl substituent (e.g., -NH-acyl); for example, -NH-C(O)-alkyl.

"Halo", "halogen", or "halide" is a chloro, bromo, fluoro or iodo radical.

Also, as referred to herein, a "lower" hydrocarbon moiety (e.g., "lower" alkyl) is a hydrocarbon chain comprised of 1 to 4, preferably from 1 to 2, carbon atoms.

A "pharmaceutically-acceptable salt" is a cationic salt formed at any acidic (e.g., carboxyl) group, or an anionic salt formed at any basic (e.g., amino, alkylamino, dialkylamino, morphylino, and the like) group on the compound of the invention. Since many of the compounds of the invention are zwitterionic, either salt is possible and acceptable. Many such salts are known in the art. Preferred cationic salts

include the alkali metal salts (such as sodium and potassium), alkaline earth metal salts (such as magnesium and calcium) and organic salts, such as ammonio. Preferred anionic salts include halides, sulfonates, carboxylates, phosphates, and the like. Clearly contemplated in such salts are addition salts that may provide an optical center, where once there was none. For example, a chiral tartrate salt may be prepared from the compounds of the invention, and this definition includes such chiral salts. Salts contemplated are nontoxic in the amounts administered to the patient-animal, mammal or human.

The compounds of the invention are sufficiently basic to form acid-addition salts. The compounds are useful both in the free base form and the form of acid-addition salts, and both forms are within the purview of the invention. The acid-addition salts are in some cases a more convenient form for use. In practice, the use of the salt form inherently amounts to the use of the base form of the active. Acids used to prepare acid-addition salts include preferably those which produce, when combined with the free base, medicinally acceptable salts. These salts have anions that are relatively innocuous to the animal organism, such as a mammal, in medicinal doses of the salts so that the beneficial property inherent in the free base are not vitiated by any side effects ascribable to the acid's anions.

Examples of appropriate acid-addition salts include, but are not limited to hydrochloride, hydrobromide, hydroiodide, sulfate, hydrogensulfate, acetate, trifluoroacetate, nitrate, citrate, fumarate, formate, stearate, succinate, maleate, malonate, adipate, glutarate, lactate, propionate, butyrate, tartrate, methanesulfonate, trifluoromethanesulfonate, p-toluenesulfonate, dodecyl sulfate, cyclohexanesulfamate, and the like. However, other appropriate medicinally acceptable salts within the scope of the invention are those derived from other mineral acids and organic acids. The acid-addition salts of the basic compounds are prepared by several methods. For example, the free base can be dissolved in an aqueous alcohol solution containing the appropriate acid and the salt is isolated by evaporation of the solution. Alternatively, they may be prepared by reacting the free base with an acid in an organic solvent so that the salt separates directly. Where separation of the salt is difficult, it can be precipitated with a second organic solvent, or can be obtained by concentration of the solution.

Although medicinally acceptable salts of the basic compounds are preferred, all acid-addition salts are within the scope of the present invention. All acid-addition salts are useful as sources of the free base form, even if the particular salt per se is desired only as an intermediate product. For example, when the salt is formed only for purposes of purification or identification, or when it is used as an intermediate in preparing a

medicinally acceptable salt by ion exchange procedures, these salts are clearly contemplated to be a part of this invention.

"Host" is a substrate capable of sustaining a microbe, preferably it is a living organism, more preferably an animal, more preferably a mammal, more preferably still a human.

"Biohydrolyzable amides" are aminoacyl, acylamino, or other amides of the compounds of the invention, where the amide does not essentially interfere, preferably does not interfere, with the activity of the compound, or where the amide is readily converted in vivo by a host to yield an active compound.

"Biohydrolyzable imides" are imides of compounds of the invention, where the imide does not essentially interfere, preferably does not interfere, with the activity of the compound, or where the imide is readily converted in vivo by a host to yield an active compound. Preferred imides are hydroxyimides.

"Biohydrolyzable esters" are esters of compounds of the invention, where the ester does not essentially interfere, preferably does not interfere, with the antimicrobial activity of the compound, or where the ester is readily converted in a host to yield an active compound. Many such esters are known in the art, as described in U.S. Patent No. 4,783,443, issued to Johnston and Mobashery on November 8, 1988 (incorporated by reference herein). Such esters include lower alkyl esters, lower acyloxy-alkyl esters (such as acetoxymethyl, acetoxyethyl, aminocarbonyloxymethyl, pivaloyloxymethyl and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxycarbonyloxymethyl, ethoxycarbonyloxyethyl and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters and alkylacylaminoalkyl esters (such as acetamidomethyl esters).

The illustration of specific protected forms and other derivatives of the Formula 1 compounds is not intended to be limiting. The application of other useful protecting groups, salt forms, etc. is within the ability of the skilled artisan.

"Optical isomer", "stereoisomer", "diastereomer" as referred to herein have the standard art recognized meanings (Cf., Hawley's Condensed Chemical Dictionary, 11th Ed.).

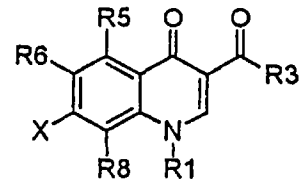
The compounds of the invention may have one or more chiral centers. As a result, one may selectively prepare one optical isomer, including diastereomer and enantiomer, over another, for example by use of chiral starting materials, catalysts or solvents, one may prepare both stereoisomers or both optical isomers, including diastereomers and enantiomers at once (a racemic mixture). Since the compounds of the invention may exist as racemic mixtures, mixtures of optical isomers, including diastereomers and

enantiomers, or stereoisomers, they may be separated using known methods, such as chiral resolution, chiral chromatography and the like.

In addition, it is recognized that one optical isomer, including diastereomer and enantiomer, or stereoisomer may have favorable properties over the other. Thus when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

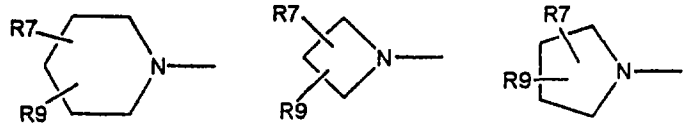
As used herein, a quinolone derivative includes prodrugs of a quinolone, or an active drug made from a quinolone. Preferably, such derivatives include lactams (e.g., cephems, carbacephems, penems, monolactams, etc.) covalently linked to the quinolone optionally via a spacer. Such derivatives and methods to make and use them are apparent to the skilled artisan, given the teaching of this specification.

Compounds of the Invention




Formula 1

In Formula 1, X is selected from




;

Preferred X include the pyrrolidinyl ring above or the piperidinyl ring above or the azetidinyl ring above; more preferred is the pyrrolidinyl ring.

In Formula 1, R1 includes certain alkyl, cycloalkyl, and aryl moieties. R1 cycloalkyl moieties include from about 3 to about 5 carbon atoms in the ring, preferably 3 carbon atoms in the ring. R1 cycloalkyl moieties are preferably saturated or unsaturated with one double bond; more preferably R1 cycloalkyl are saturated (cycloalkanyl). R1 linear alkanyl contain from 1 to about 2 carbon atoms; methyl and ethyl are preferred, especially ethyl. R1 linear alkenyl contain from 2 to about 3 carbon atoms; ethenyl is preferred. R1 branched alkanyl and alkenyl contain from 3 to about 4 carbon atoms; branched alkanyl are preferred; isopropyl, isopropenyl, isobutyl, isobutenyl, and t-butyl are also preferred. All of the foregoing alkyl (alkanyl, alkenyl, and alkynyl) or cycloalkyl moieties aforementioned in this paragraph are unsubstituted or substituted with from 1 to about 3

fluoro moieties. R1 aryl moieties include phenyl, unsubstituted or substituted with from 1 to about 3 fluoro, or with one hydroxy in the 4-position; substituted phenyl are preferred. Preferred R1 is selected from cyclopropyl, ethyl, phenyl substituted with 1 to 3 fluoro, and 4-hydroxyphenyl; more preferred is 2,4-difluorophenyl, and especially cyclopropyl or ethyl.

In Formula 1, R3 is hydrogen or hydroxy; preferably R3 is hydroxy. When R3 is hydroxy, it and the carbonyl to which it is attached are a carboxylic acid moiety. As such, it is a potential point of formation for the subject compounds of pharmaceutically-acceptable salts, and biohydrolizable esters, aminoacyls, and amides, as described herein. Compounds having any such variations at the R3 position are included in the subject invention.

In Formula 1, R5 includes hydrogen, amino, halo, hydroxy, methoxy, and certain alkyl. R5 alkanyl moieties have from 1 to about 2 carbon atoms, preferably 1 carbon atom. R5 alkenyl moieties preferably have 2 carbon atoms. All R5 alkyl and methoxy moieties are unsubstituted or substituted with from 1 to about 3 fluoro moieties. Preferred R5 is selected from hydrogen, hydroxy, chloro, bromo, amino, methyl, monofluoromethyl, difluoromethyl, and trifluoromethyl. More preferred R5 is selected from hydrogen, hydroxy, amino, and methyl, especially hydrogen.

In Formula 1, R6 includes hydrogen, hydroxy, aminocarbonyl, bromo, cyano, and certain alkyl. R6 alkanyl moieties have from 1 to about 2 carbon atoms; preferred are methyl and ethyl; more preferred is methyl. R6 alkenyl and alkynyl moieties have from 2 to about 4 carbon atoms, preferably 2 carbon atoms, with one double or triple, preferably double, bond; ethenyl is preferred. All R6 alkyl moieties are unsubstituted or substituted with from 1 to about 3 fluoro. R6 methyl or ethyl moieties are optionally substituted with one hydroxy moiety or one amino moiety. Preferred R6 is selected from hydrogen, hydroxy, methyl, monofluoromethyl, difluoromethyl, and trifluoromethyl. More preferred R6 is hydrogen.

In Formula 1, R8 includes chloro, bromo, methoxy, methylthio, and certain alkyl. R8 alkanyl moieties have from 1 to about 2 carbon atoms; methyl is preferred. R8 alkenyl moieties have from 2 to about 4 carbon atoms; ethenyl is preferred. All R8 alkyl moieties are unsubstituted or substituted with from 1 to about 3 fluoro moieties. Preferred R8 is selected from chloro, methyl, methoxy, methylthio, monofluoromethyl, difluoromethyl, trifluoromethyl, monofluoromethoxy, difluoromethoxy, and trifluoromethoxy. More preferred R8 is selected from methyl substituted with from 1 to 3 fluoro, methoxy, methylthio, and chloro; especially either methoxy or methylthio or chloro.

In X of Formula 1, R7 includes amino which is attached to a ring carbon which is not adjacent to the ring nitrogen. Such R7 amino is unsubstituted or substituted with one or two alkanyl having from 1 to about 3 carbon atoms, preferably methyl or ethyl, more preferably methyl; preferred amino R7 is unsubstituted or substituted with one such alkanyl moiety. When X comprises the piperidinyl ring, R7 is preferably an unsubstituted or substituted amino moiety. More preferred R7, especially when X comprises the piperidinyl ring, is amino or methylamino.

R7 also includes aminoalkanyl, the alkanyl having from 1 to about 3 carbon atoms, preferably methyl, ethyl, or isopropyl, the alkanyl being substituted with one amino, such amino being unsubstituted or substituted with 1 or 2, preferably 1, alkanyl having from 1 to about 3 carbon atoms, preferably ethyl or especially methyl. Such aminoalkanyl can be attached to any carbon of the ring of X; preferably it is attached to a carbon not adjacent to the ring nitrogen. R7 is preferably such aminoalkanyl, especially if R8 is any unsubstituted alkyl, also particularly if X comprises the pyrrolidinyl ring. Preferred R7, especailly when X comprises the pyrrolidinyl ring, is selected from aminomethyl, methylaminomethyl, 1-aminoethyl, 1-methylaminoethyl, 1-amino-1-methylethyl, and 1-methylamino-1-methylethyl; more preferred is aminomethyl, and especially 1-aminoethyl.

The amino moiety of R7 is a potential point of formation for the subject compounds of a pharmaceutically-acceptable anionic salt; such salts are included in the subject invention compounds. Preferred salts are acid addition salts with, for example, HCl, $CH_3SO_3H$, HCOOH, or $CF_3COOH$.

In X of Formula 1, R9 represents all the moieties other than R7 on the ring carbons of the piperidinyl, pyrrolidinyl, and azetidinyl rings of X shown above; such moieties include hydrogen or certain alkyl. Non-hydrogen R9 may be mono- or disubstituents on each ring carbon atom to which R7 is not attached or monosubstitutents on the ring carbon to which R7 is attached (i.e., each ring carbon of X has two hydrogens, one hydrogen and R7, one hydrogen and one alkyl, one alkyl and R7, or two alkyls bonded to it). Preferably no more than two ring carbons have alkyl R9 substituents; more preferably only one ring carbon has alkyl R9 substituents; also preferably all R9 are hydrogen.

Alkyl R9, especially dialkyl R9, are preferably attached to a carbon of the ring of X which is adjacent to the ring nitrogen, especially when X comprises the pyrrolidinyl ring. Non-hydrogen R9 includes linear, branched or cyclic alkanyl, preferably linear or branched, more preferably linear, having from 1 to about 4 carbon atoms; methyl and ethyl are preferred; methyl is more preferred. Non-hydrogen R9 includes linear, branched or cyclic alkenyl and alkynyl, preferably linear or branched, more preferably linear, having

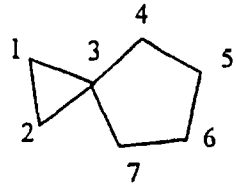
from 2 to about 6 carbon atoms, preferably from 2 to about 4 carbon atoms; ethenyl is preferred.

Two alkyl R9 can be attached together thus forming a fused or a spirocycle alkyl ring with the N-containing ring of X, the fused or spirocycle ring having from about 3 to about 6 carbon atoms. Such fused or spirocycle alkyl ring is preferably saturated or unsaturated with one double bond, more preferably saturated. A spirocyclopropyl ring is particularly preferred.

All such R9 alkyl moieties are unsubstituted or substituted with from 1 to about 3 fluoro moieties, preferably unsubstituted. More preferred R9 is selected from hydrogen, methyl, dimethyl, spirocyclopropyl, and ethyl; more preferred are ethyl, dimethyl, and spirocyclopropyl; and especially hydrogen.

Optionally, a R9 can be connected to R7 thus forming a fused or a spirocycle ring with the N-containing ring of X, the fused or spirocycle ring having from 2 to about 5 ring carbon atoms and 0 or 1 ring nitrogen atom (from R7). Such fused or spirocycle ring may be a hydrocarbon ring with an amino or aminoalkyl substituent, the amino being from R7; or it may be a heterocyclic ring with the R7 amino nitrogen being a ring nitrogen. Such ring may have one or two alkanyl substituents. Such fused or spirocycle ring is preferably saturated or unsaturated with one double bond; more preferably it is saturated. If such ring is fused, R8 is other than chloro, preferably other than chloro and bromo, more preferably is methoxy or methylthio or methyl, more preferably still methoxy or methylthio, especially methoxy.

Subject compounds having R7 or R9 spirocycles are named according to the following numbering system: the numbering starts at the smaller ring, completing around the larger ring which forms a spiro junction, e.g., at carbon 3 when the smaller ring is cyclopropyl as for the following example:




The aza nomenclature used herein follows the conventional nomenclature and is the position where the ring nitrogen is attached to the quinolone nucleus.

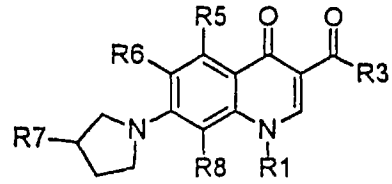
As used herein, any radical is independently selected each time it is used (e.g., R1 and R5 need not be the same in all occurrences in defining a given compound of this invention).

The compounds of the invention may contain chiral center(s), thus any such compound includes and contemplates each optical isomer, diastereomer or enantiomer

thereof, in purified or substantially purified form, and mixtures thereof, including racemic mixtures.

The following exemplary compounds are made using the procedures described herein and variations thereof which are within the purview of the skilled artisan's practice. The examples below do not limit the invention, but rather serve to illustrate some of the embodiments of the invention.

Preferred examples of the quinolones of the subject invention with structures of Formula 2 are provided in the table below:




Formula 2

In the following examples, $R_1$ is cyclopropyl, $R_3$ is hydroxy, and z represents the preferred chirality of the R7 radical's attachment on the pyrrolidine ring, although other chirality is also envisioned. In compounds where R7 is $-CH(CH_3)NH_2$, it is preferred that the configuration of this radical be R.

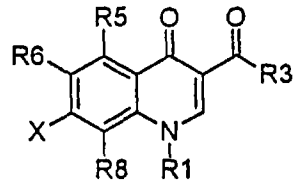
| Example | R5 | R6 | R7 | R8 | z |
|---|---|---|---|---|---|
| 1 | -NH2 | H | -NH2 | Cl | S |
| 2 | $-NH_2$ | H | $-CH_2NH_2$ | Cl | S |
| 3 | $-NH_2$ | H | $-CH(CH_3)NH_2$ | Cl | R |
| 4 | F | H | $-NH_2$ | Cl | S |
| 5 | F | H | $-CH_2NH_2$ | Cl | S |
| 6 | F | H | $-CH(CH_3)NH_2$ | Cl | R |
| 7 | $-OCH_3$ | H | $-NH_2$ | Cl | S |
| 8 | H | H | $-CH_2NH_2$ | $CH_3$ | S |
| Example | R5 | R6 | R7 | R8 | z |
| 9 | H | H | $-CH(CH_3)NH_2$ | $CH_3$ | R |
| 10 | -OH | H | $-NH_2$ | Cl | S |
| 11 | -OH | H | $-CH_2NH_2$ | Cl | S |
| 12 | -OH | H | $-CH(CH_3)NH_2$ | Cl | R |
| 13 | H | H | $-NH_2$ | Cl | S |
| 14 | H | H | $-CH_2NH_2$ | Cl | S |
| 15 | H | H | $-CH(CH_3)NH_2$ | Cl | R |
| 16 | H | H | $-NH_2$ | $OCH_3$ | S |
| 17 | H | H | $-CH_2NH_2$ | $OCH_3$ | S |

| | | | | | |
|---|---|---|---|---|---|
| 18 | H | H | $-CH(CH_3)NH_2$ | $OCH_3$ | R |
| 19 | H | Br | $-NH_2$ | Cl | S |
| 20 | H | Br | $-CH_2NH_2$ | Cl | S |
| 21 | H | Br | $-CH(CH_3)NH_2$ | Cl | R |
| 22 | H | $-CH_3$ | $-NH_2$ | Cl | S |
| 23 | H | $-CH_3$ | $-CH_2NH_2$ | Cl | S |
| 24 | H | $-CH_3$ | $-CH(CH_3)NH_2$ | Cl | R |
| 25 | H | $-CHCH_2$ | $-NH_2$ | Cl | S |
| 26 | H | $-CHCH_2$ | $-CH_2NH_2$ | Cl | S |
| 27 | H | $-CHCH_2$ | $-CH(CH_3)NH_2$ | Cl | R |
| 28 | H | -OH | $-NH_2$ | Cl | S |
| 29 | H | -OH | $-CH_2NH_2$ | Cl | S |
| 30 | H | -OH | $-CH(CH_3)NH_2$ | Cl | R |
| 31 | H | -CN | $-NH_2$ | Cl | S |
| 32 | H | -CN | $-CH_2NH_2$ | Cl | S |
| 33 | H | -CN | $-CH(CH_3)NH_2$ | Cl | R |
| 34 | H | $-CH_2OH$ | $-NH_2$ | Cl | S |
| 35 | H | $-CH_2OH$ | $-CH_2NH_2$ | Cl | S |
| 36 | H | $-CH_2OH$ | $-CH(CH_3)NH_2$ | Cl | R |
| 37 | H | $-CH_2NH_2$ | $-NH_2$ | Cl | S |
| 38 | H | $-CH_2NH_2$ | $-CH_2NH_2$ | Cl | S |
| 39 | H | $-CH_2NH_2$ | $-CH(CH_3)NH_2$ | Cl | R |
| 40 | H | $-CONH_2$ | $-NH_2$ | Cl | S |
| 41 | H | $-CONH_2$ | $-CH_2NH_2$ | Cl | S |
| 42 | H | $-CONH_2$ | $-CH(CH_3)NH_2$ | Cl | R |
| 43 | H | H | $-C(CH_3)_2NH_2$ | Cl | R |
| 44 | H | H | $-C(CH_3)_2NH_2$ | $OCH_3$ | R |

| Example | R5 | R6 | R7 | R8 | z |
|---|---|---|---|---|---|
| 45 | H | H | $-CH(CH_3)NHCH_3$ | $OCH_3$ | R |
| 46 | H | H | $C(CH_3)_2NHCH_3$ | $OCH_3$ | R |
| 47 | H | H | $-C(CH_3)_2NH_2$ | $OCH_3$ | R |
| 48 | H | H | $-C(CH_3)_2NH_2$ | Cl | R |
| 49 | H | H | $-CH(CH_3)NHCH_3$ | Cl | R |
| 50 | H | H | $C(CH_3)_2NHCH_3$ | Cl | R |
| 51 | H | H | $-CH(CH_3)NH_2$ | $SCH_3$ | R |
| 52 | H | H | $-C(CH_3)_2NH_2$ | $SCH_3$ | R |

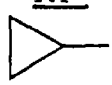
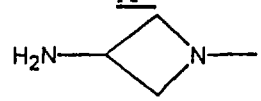
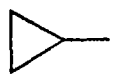
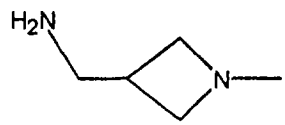
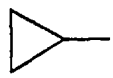
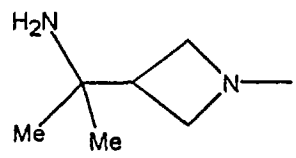
| | | | | | |
|---|---|---|---|---|---|
| 53 | H | H | $-CH_2NH_2$ | $SCH_3$ | R |
| 54 | H | H | $-NH_2$ | $SCH_3$ | S |

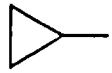
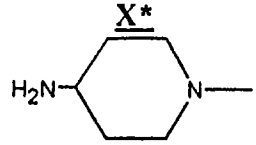
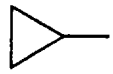
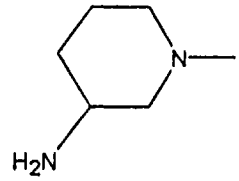
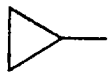
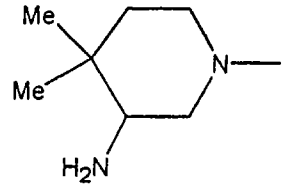
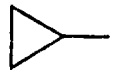
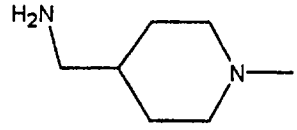
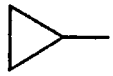
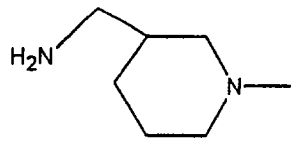
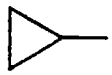
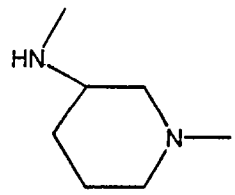
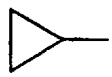
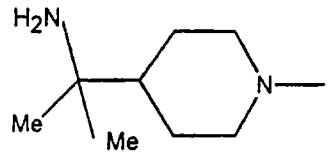
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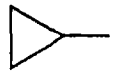
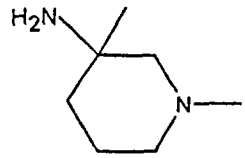


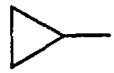
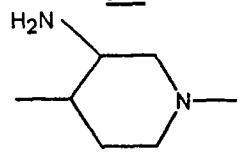
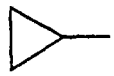
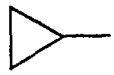
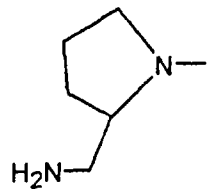
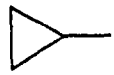
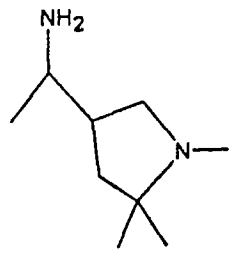
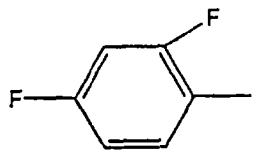
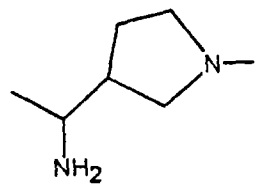
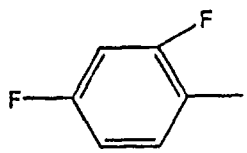
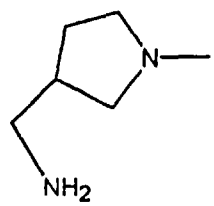

Formula 1

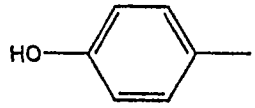
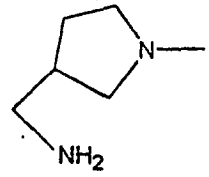
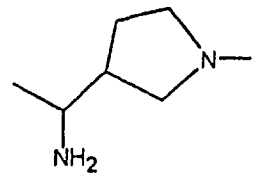
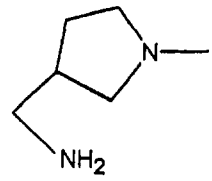
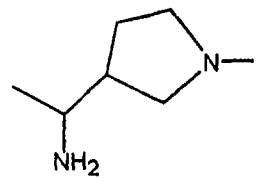
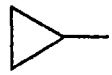
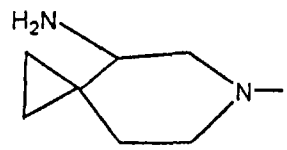
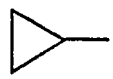
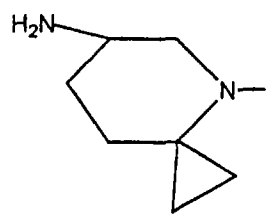
In the following examples, R3 is hydroxy, R5 and R6 are both hydrogen, and z represents the preferred chirality, if any, of attachment of the R7 radical to the respective pyrrolidine or piperidine ring, although other chirality is also envisioned.

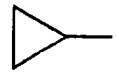
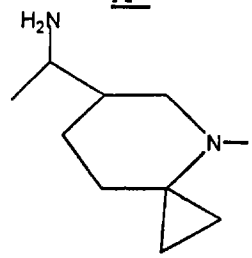
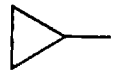
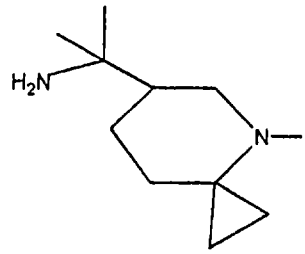
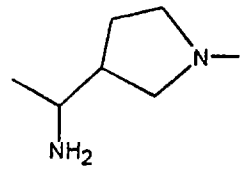
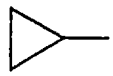
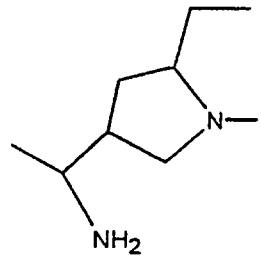
| Example | R8 | R1* | X* | z |
|---|---|---|---|---|
| 55 | $-OCH_3$ |  |  | - |
| 56 | -Cl | | | - |
| 57 | $-OCH_3$ |  |  | - |
| 58 | -Cl | | | - |
| 59 | $-OCH_3$ |  |  | - |
| 60 | -Cl | | | - |

| Example | R8 | R1* | X* | z |
|---|---|---|---|---|
| 61 | -$OCH_3$ |  |  | - |
| 62 | -Cl | | | - |
| 63 | -$OCH_3$ |  |  | S |
| 64 | -Cl | | | S |
| 65 | -$SCH_3$ | | | S |
| 66 | -$OCH_3$ |  |  | S |
| 67 | -Cl | | | S |
| 68 | -$OCH_3$ |  |  | - |
| 69 | -Cl | | | - |
| 70 | -$OCH_3$ |  |  | - |
| 71 | -Cl | | | - |
| 72 | -$OCH_3$ |  |  | S |
| 73 | -Cl | | | S |
| 74 | -$OCH_3$ |  |  | - |
| 75 | -Cl | | | - |

| | | | | |
|---|---|---|---|---|
| 76 | $-OCH_3$ |  |  | S |
| 77 | -Cl | | | S |

| Example | R8 | R1* | X* | z |
|---|---|---|---|---|
| 78 | -$OCH_3$ |  |  | S |
| 79 | -Cl | | | S |
| 80 | -$OCH_3$ |  |  | - |
| 81 | -Cl | | | - |
| 82 | -$OCH_3$ |  |  | - |
| 83 | -Cl | | | - |
| 84 | -$OCH_3$ |  |  | R |
| 85 | -Cl | | | R |
| 86 | -$SCH_3$ | | | R |
| 87 | -$OCH_3$ |  |  | R |
| 88 | -Cl | | | R |
| 89 | -$OCH_3$ |  |  | R |
| 90 | -Cl | | | R |

| Example | R8 | R1* | X* | z |
|---|---|---|---|---|
| 91 | -$OCH_3$ |  |  | R |
| 92 | -Cl | | | R |
| 93 | -$OCH_3$ | $CH_3CH_2$- |  | R |
| 94 | -Cl | $CH_3CH_2$- | | R |
| 95 | -$SCH_3$ | $CH_3CH_2$- | | R |
| 96 | -$OCH_3$ | $CH_3CH_2$- |  | R |
| 97 | -Cl | $CH_3CH_2$- | | R |
| 98 | -$OCH_3$ | $CH_3$- |  | R |
| 99 | -Cl | $CH_3$- | | R |
| 100 | -$OCH_3$ |  |  | S |
| 101 | -Cl | | | S |
| 102 | -$OCH_3$ |  |  | S |
| 103 | -Cl | | | S |

| Example | R8 | R1* | X* | z |
|---|---|---|---|---|
| 104 | $-OCH_3$ |  |  | R |
| 105 | -Cl | | | R |
| 106 | $-OCH_3$ |  |  | R |
| 107 | -Cl | | | R |
| 108 | $-OCH_3$ | $CFH_2CH_2-$ |  | R |
| 109 | -Cl | $CFH_2CH_2-$ | | R |
| 110 | $-OCH_3$ |  |  | R |
| 111 | -Cl | | | R |

* Each structure depicted in this column generally pertains to the two or three different Examples with which it is grouped.

In addition, it is recognized that for purification, administration and the like, salts and other derivatives of the above compounds are often used. Thus, a pharmaceutically-acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof is contemplated as part of the subject invention.

The subject invention compounds above are also useful precursors for compounds of formula Q-L-B, wherein Q is a compound of Formula 1, L is a linking moiety, and B is a lactam containing moiety. This formula includes optical isomers, disatereomers or enantiomers thereof; pharmaceutically-acceptable salts, hydrates, or biohydrolyzable esters, amides and imides thereof. These compounds and their uses are disclosed in U.S. Patent 5,180,719 issued January 19, 1993; U S. Patent 5,387,748 issued February 7, 1995; U.S. Patent 5,491,139 issued February 13, 1996; U.S. Patent 5,530,116 issued June 25, 1996; and EPO publications 0366189 published May 2, 1990 and 0366640 published

May 2, 1990, all incorporated herein by reference. For compositions and methods of use, the compounds of formula Q-L-B are useful in the same way as compound of Formula 1. Thus, they can be interchanged in the composition examples herein.

Biological activities of the invention compounds can be compared to ciprofloxacin and the other known antimicrobial quinolone compounds. Compounds of the subject invention provide better antibacterial properties against certain quinolone resistant bacteria compared to ciprofloxacin and certain other prior art compounds. When tested against quinolone-resistant bacteria such as *S. aureus, S. saprophyticus, E. faecalis, S. pyogenes, S. pneumoniae, S. viridans, E. coli, P. aeruginosa, P. mirabilis, K. pneumoniae, E. cloacae,* certain compounds of the subject invention have been found to have MIC values (μg/ml) that are up to about 500 times lower than ciprofloxacin.

Methods of Making the Compounds

In making the compounds of the invention, the order of synthetic steps may be varied to increase yield of desired product. In addition, the skilled artisan will also recognize the judicious choice of reactants, solvents, and temperatures is an important component in successful synthesis. While the determination of optimal conditions, etc. is routine, it will be understood that a variety of compounds can be generated in a similar fashion, using the guidance of the scheme below.

The starting materials used in preparing the compounds of the invention are known, made by known methods, or are commercially available as a starting material.

It is recognized that the skilled artisan in the art of organic chemistry can readily carry out standard manipulations of organic compounds without further direction; that is, it is well within the scope and practice of the skilled artisan to carry out such manipulations. These include, but are not limited to, reduction of carbonyl compounds to their corresponding alcohols, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic, etherifications, esterification and saponification and the like. Examples of these manipulations are discussed in standard texts such as March, Advanced Organic Chemistry (Wiley), Carey and Sundberg, Advanced Organic Chemistry (Vol. 2), Fieser & Feiser, Reagents for Organic Synthesis (16 volumes), L. Paquette, Encyclopedia of Reagents for Organic Synthesis (8 volumes), Frost & Fleming, Comprehensive Organic Synthesis (9 volumes) and the like.

The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus avoiding any undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within

the scope of the skilled artisan. Examples of many of these manipulations can be found for example in T. Greene, Protecting Groups in Organic Synthesis. Of course, amino acids used as starting materials with reactive side chains are preferably blocked to prevent undesired side reactions.

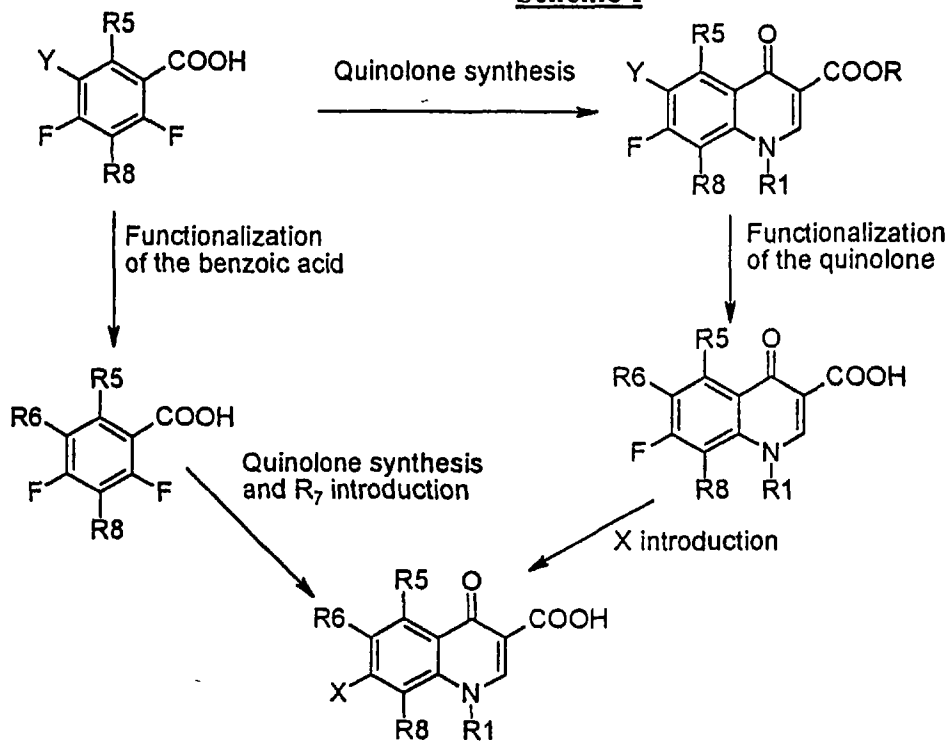
General procedures for preparing quinolone moieties useful in making the compounds of the subject invention are described in the following references, all incorporated by reference herein (including articles listed within these references); Progress in Drug Research, Vol. 21, pp. 9-104 (1977); J. Med. Chem., Vol. 23, pp. 1358-1363 (1980); J. Med. Chem., Vol. 29, pp. 2363-2369 (1986); J. Med. Chem., Vol. 31, p. 503 (1988); J. Med. Chem., Vol. 31, pp. 503-506 (1988); J. Med. Chem., Vol. 31, pp. 983-991 (1988); J. Med. Chem., Vol. 31, pp. 991-1001 (1988); J. Med. Chem., Vol. 31, pp. 1586-1590 (1988); J. Med. Chem., Vol. 31, pp. 1598-1611 (1988); J. Med. Chem., Vol. 32, pp. 537-542 (1989); J. Med. Chem., Vol. 32, p. 1313 (1989); J. Med. Chem., Vol. 32, pp. 1313-1318 (1989); Drugs Exptl. Clin. Res., Vol. 14, pp. 379-383 (1988); J. Pharm. Sci., Vol. 78, pp. 585-588 (1989); J. Het. Chem., Vol. 24, pp. 181-185 (1987); J. Het. Chem., Vol. 25, pp. 479-485 (1988); Chem. Pharm. Bull., Vol. 35, pp. 2281-2285 (1987); Chem. Pharm. Bull., Vol. 36, pp. 1223-1228 (1988); U.S. Patent No. 4,594,347, June 10, 1986; U.S. Patent No. 4,599,334, July 8, 1986; U.S. Patent No. 4,687,770, Aug. 1, 1987; U.S. Patent No. 4,689,325, Aug. 25, 1987; U.S. Patent No. 4,767,762, Aug. 30, 1988; U.S. Patent No. 4,771,055, Sept. 13, 1988; U.S. Patent No. 4,795,751, Jan. 3, 1989; U.S. Patent No. 4,822,801, Apr. 18, 1989; U.S. Patent No. 4,839,355, June 13, 1989; U.S. Patent No. 4,851,418, July 25, 1989; U.S. Patent No. 4,886,810, Dec. 12, 1989; U.S. Patent No. 4,920,120, Apr. 24 1990; U.S. Patent No. 4,923,879, May 8, 1990; U.S. Patent No. 4,954,507, Sept. 4, 1990; U.S. Patent No. 4,956,465, Sept. 11, 1990; U.S. Patent No. 4,977,154, Dec. 11, 1990; U.S. Patent No. 4,980,470, Dec. 25, 1990; U.S. Patent No. 5,013,841, May 7, 1991; U.S. Patent No. 5,045,549, Sept. 3, 1991; U.S. Patent No. 5,290,934, Mar. 1, 1994; U.S. Patent No. 5,328,908, July 12, 1994; U.S. Patent No. 5,430,152, July 4, 1995; European Patent Publication 172,651, Feb. 26, 1986; European Patent Publication 230,053, July 29, 1987; European Patent Publication 230,946, Aug. 5, 1987; European Patent Publication 247,464, Dec. 2, 1987; European Patent Publication 284,935, Oct. 5, 1988; European Patent Publication 309,789, Apr. 5, 1989; European Patent Publication 332,033, Sept. 13, 1989; European Patent Publication 342,649, Nov. 23, 1989; and Japanese Patent Publication 09/67,304 (1997).

The compounds are generally made by methods which include those disclosed in the references above. A preferred method is to prepare the quinolone moiety with a suitable

leaving group at the 7 position and have that leaving group displaced by the heterocycle - X as a last step. Examples of these methods follow.

The quinolone compounds of the subject invention may be prepared several ways. Versatile methodologies for providing the compounds of the invention are shown in Scheme I below:

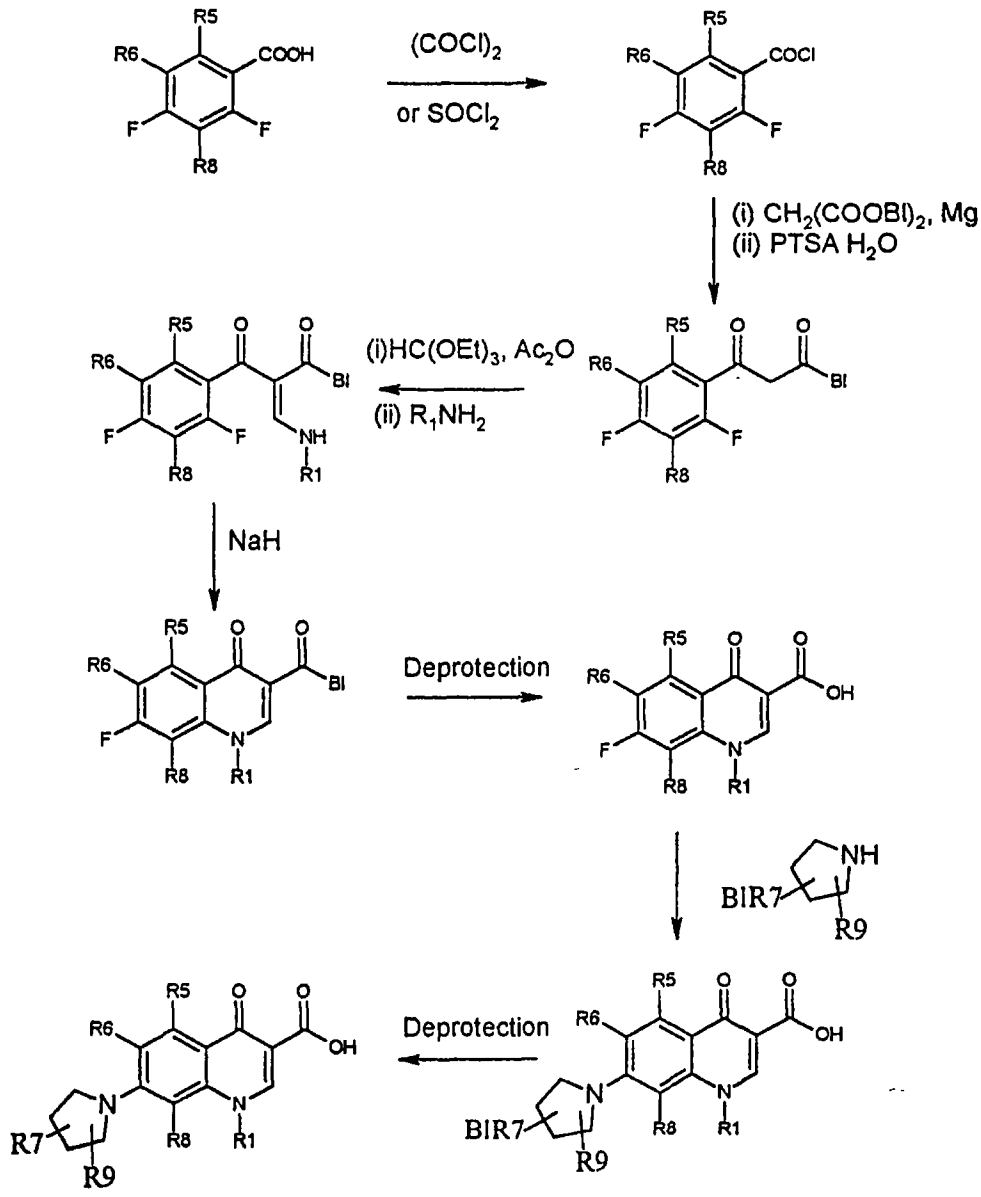
**Scheme I**




In Scheme I, Y can be bromo, iodo, nitro, amino, acetyl, or like moieties known to the skilled chemist; preferred Y is bromo or nitro.

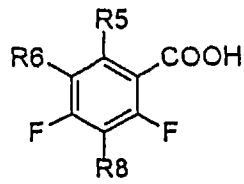
Alternatively, the general methodology of Scheme II can be used to make certain subject compounds.

## Scheme II

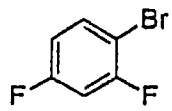



Bl = Blocking group.

A preferred process for preparing the benzoic acid precursors of Schemes I and II is described and exemplified herein below. These benzoic acid derivatives have the formula:

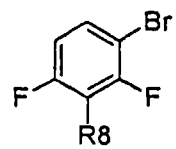



In this process, 2,4-difluoro-bromobenzene:




is treated with a strong, non-nucleophilic base. This base may be any base useful in permutational hydrogen-metal exchange. Preferred bases include lithium diisopropylamide (LDA), lithium 2,2,6,6-tetramethylpiperidide (LiTMP), lithium bis(trimethylsilyl)amide (LTSA), t-butoxide, or other known bases for this purpose. Suitable bases are known in the literature, and can be found in common reference texts as non-nucleophilic bases. Most preferred is LDA, which produces intermediates that are reasonably stable over a range of times and temperatures. It is preferred that the temperature of this reaction is from about -80$^0$C up to about 40$^0$C, more preferably up to about room temperature, most preferably to about -40$^0$C. Temperature may vary with the base used, for example the most preferred reaction temperature is about -65$^0$C with LDA. Reaction times may be up to about 24 hours, preferably about 2 hours, most preferably the process is carried on as soon as it is apparent that the resulting benzene derivative may proceed to the next step in the process. It is also preferred that this reaction take place under an inert atmosphere.

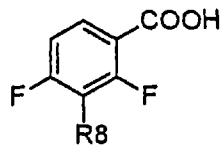
After the base has reacted with the 1-bromo-2,4-fluorobenzene, an electrophilic reagent provides the desired R8 substituent or a functional group which can be transformed into the desired R8 substituent, thus producing a compound of formula:




Solvents suitable for this reaction are typically aprotic. Preferably these solvents are compatible with the bases used in the step above. More preferred solvents include the ethers and glymes, most preferably tetrahydrofuran (THF). Such solvents are known in the art, and suitable substitutions are made depending on the base, electrophile, and the polarity and solubility characteristics of the reactants and resulting compound.

This 3-R8-2,4-difluoro-bromobenzene compound is useful in making the corresponding benzoic acid and related intermediates for the eventual synthesis of the quinolone or quinolone derivatives of the subject invention. This benzoic acid is prepared by treating the above R8-benzene compound with an equivalent of a reagent useful in permutational halogen-metal exchange. Preferred reagents include n-butyllithium, magnesium, lithium or other known reagents for this purpose. Suitable reagents are known in the literature, and can be found in common reference texts. The most preferred base is n-butyllithium, which produces intermediates that are reasonably stable over a range of times and temperatures. It is preferred that the temperature for this reaction is at least -80$^0$C up to about 40$^0$C, more preferably up to about room temperature, most preferably to about -40$^0$C. Temperature may vary with the base used, for example the most preferred reaction temperature is about -70$^0$C with n-butyllithium. Reaction times may be up to about 24 hours, preferably about 15 min, most preferably the process is carried on as soon as it is apparent that the resulting intermediate derivative may proceed to the next step in the process. It is also preferred that this reaction take place in an inert atmosphere.

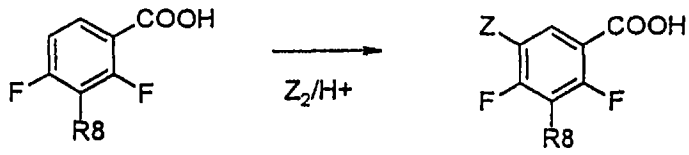
The intermediate resulting from the last reaction above is treated with carbon dioxide or N,N-dimethylformamide (DMF), most preferably carbon dioxide. Often these reactions are exothermic, so it is preferred that the temperature be maintained by cooling the reaction to prevent side reactions, and the like. If carbon dioxide is used, the resulting benzoic acid compound is useful without further purification after a typical work up:




If DMF or a similar formylating compound is used, the resulting benzaldehyde compound is oxidized to the corresponding benzoic acid via oxidation. This reaction may occur in the presence of air, or by using any other known oxidizing reagents. The same resulting benzoic acid compound is useful without further purification after a typical work up.

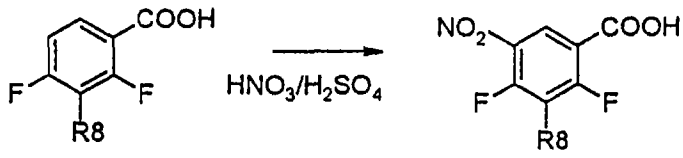
The benzoic acid compound prepared by the above method is amenable to derivatization of the R6 position as well. If derivatization of this position is desired, the reactions chosen depend on the desired functionality, for example

Halogenation:



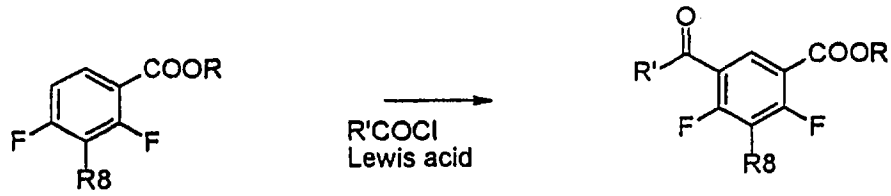

Where Z is a halide, preferably bromine. This reaction occurs under acidic conditions, such as in acetic acid, preferably with a halide activating reagent, such as a silver reagent (e.g., $AgNO_3$).

Nitration:




Nitration occurs via treatment with activated nitric acid, such as in a mixture of nitric and sulfuric acids. Reduction of the nitro compound to the corresponding amine may be performed via any appropriate reduction process.

Acylation:




Preparation of acyl compounds is accomplished by introducing an acylating reagent, for example R'COCl (where R' is an alkyl or aryl), preferably in the presence of a Lewis acid, for example $AlCl_3$. The compound formed as a result is amenable to Baeyer-Villiger chemistry to provide a R6 hydroxyl, that may optionally be etherified.

R5 may be derivatized using similar methodologies described for R6.

For illustration, the following examples of making the benzoic acid precursors are provided; the examples are not meant to be limiting.

Precursor Example A

3-Chloro-2,4-difluoro-bromobenzene

To a solution of 19 ml (0.135 mole) of diisopropylamine in 125 ml of tetrahydrofuran (THF) cooled at -20°C is added 80 ml of n-butyllithium (1.6 M in hexane). The temperature is raised to 0°C for 5 minutes and lowered to -78°C. Then 25 g (0.129 mole) of 2,4-difluoro-bromobenzene is then added and the reaction is stirred at -65°C for 2 hours. Then, 25 ml (0.164 mole) of hexachloroacetone is added and the solution is

warmed to room temperature. After evaporation of the solvent, the residue is distilled under vacuum to give the desired product.

3-Chloro-2,4-difluorobenzoic acid

To a solution of 21.5 g (0.0945 mole) of 3-chloro-2.4-difluoro-bromobenzene in 220 ml of ether at -78°C is added 59 ml of 1.6 M n-butyllithium diluted in 60 ml of ether keeping the temperature below -70°C. After 15 minutes, $CO_2$ is bubbled in the reaction keeping the temperature below -70°C. After warming to room temperature, water and hydrochloric acid are added and the organic phase is separated, and dried. Removal of the solvent affords the desired product.

Precursor Example B

3-Methyl-2,4-difluoro-bromobenzene

Diisoproplylamine (11.9 ml, 85 mmol) is dissolved in 50 ml of anhydrous THF and cooled in a dry ice/acetone bath. n-Butyllithium (34 ml of a 2.5 M solution in hexanes, 85 mmol) is added dropwise. After 15 minutes, a solution of 1-bromo-2,4-difluorobenzene (16 g, 83 mmol) in 8 ml of THF is added at a rate to keep the temperature below -65°C. The reaction is stirred for 2.5 hours then a solution of iodomethane (10.3 ml, 166 mmol) in 8 ml of THF is added to the reaction. The ice bath is removed and the reaction is allowed to warm to room temperature. After 2 hours the reaction is quenched with water and 1N HCl. The aqueous layer is extracted twice with ether. The combined organics are washed with brine and dried over $Na_2SO_4$. Removal of the solvent affords the desired product.

3-Methyl-2,4-difluorobenzoic acid

3-Methyl-2,4-difluoro-bromobenzene (16.07 g 77.6 mmol) is dissolved in 120 ml anhydrous ether and cooled in a dry ice/acetone bath. A solution of butyllithium (20.5 ml of a 2.5 M solution in hexanes, 76.2 mmol) in 15 ml of ether is added dropwise at a rate to keep the temperature below -65°C. After 45 minutes, $CO_2$ is bubbled through the solution keeping the temperature below -65°C. After the temperature stabilized, $CO_2$ bubbling is continued as the reaction is allowed to warm to room temperature. The mixture is quenched with 30 ml of water and acidified to pH 2 with 1N HCl. The layers are separated and the aqueous layer is extracted with ether. The combined organics are washed with brine and saturated sodium bicarbonate. The bicarbonate layer is then acidified with 1N HCl to pH 3. The resulting solid is filtered, washed with water, and dried under vacuum.

Precursor Example C

3-Hydroxy-2,4-difluoro-bromobenzene

A quantity of 40.2 ml of 2.0 M lithium diisopropylamine (LDA) is dissolved in 80 ml of THF at -78°C and 15.4 g of 2,4-difluorobromobenzene is added keeping the temperature below -65°C. The reaction is stirred at -65°C for 2 hours and 6.6 ml of 6 M anhydrous t-

butyl hydroperoxide is added. After warming to room temperature, 100 ml of water is added and the mixture acidified. The solvent is removed by evaporation and the aqueous layer extracted with ether. The extracts are dried and then concentrated to give the desired product.

3-Methoxy-2,4-difluoro-bromobenzene

A quantity of 3.7 g of 3-hydroxy-2,4-difluoro-bromobenzene is dissolved in 25 ml of acetone and 2.5 g of potassium carbonate is added followed by 2.2 ml of methyl iodide. The mixture is stirred at 20°C for 6 hours and the solvent evaporated. After addition of dichloromethane, the suspension is filtered. Evaporation of the solvent affords the desired product.

3-Methoxy-2,4-difluorobenzoic acid

A procedure analogous to the 3-chloro-2,4-difluorobenzoic acid preparation is used starting from 3-methoxy-2,4-difluoro-bromobenzene.

Precursor Example D

5-Bromo-3-chloro-2,4-difluorobenzoic acid

In a mixture of 50 ml of acetic acid, 10 ml of water and 13 ml of nitric acid is dissolved 2 g (0.014 mole) of 3-chloro-2,4-difluorobenzoic acid and 3.64 ml (0.028 mole) of bromine. A solution of 3.52 g (0.0208 mole) of silver nitrate in 10 ml of water is then added slowly. After 14 hours at 20°C, the precipitate is filtered and rinsed with ether. The organic phase is washed with sodium bisulfite, then water and dried. Removal of the solvent affords the desired product.

Precursor Example E

5-Nitro-3-chloro-2,4-difluorobenzoic acid

An amount of 1 g of 3-chloro-2,4-difluorobenzoic acid is added to a mixture of 1 ml of fuming nitric acid and 1.3 ml of sulfuric acid at 0°C. The suspension is then stirred at room temperature for 30 minutes and poured on ice. Filtration affords the desired product.

The following is an example of the functionalization of a quinolone as depicted in Scheme I above.

Precursor Example F

5-Bromo-3-chloro-2,4-difluorobenzoyl chloride

A quantity of 5.2 g of 5-bromo-3-chloro-2,4-difluorobenzoic acid is suspended in 30 ml of dichloromethane; then 2.92 g of oxalyl chloride is added, and 3 drops of dry DMF are added. The mixture is stirred at room temperature for 3 hours and the desired compound is isolated after evaporation of the solvent.

Ethyl 5-bromo-2,4-difluoro-3-chloro-benzoyl acetate

A quantity of 0.475 g of magnesium is suspended in 1.5 ml of ethanol and 0.16 ml of carbon tetrachloride is added. A solution of 3 ml of diethylmalonate in 15 ml of ethanol is added dropwise and the mixture is stirred at 60°C until complete dissolution of the magnesium. The mixture is cooled at -5°C and 5.5 g of 5-bromo-3-chloro-2,4-difluorobenzoyl chloride is added dropwise. The mixture is stirred at room temperature for 1 hour and 50 ml of diethyl ether, 20 ml of water are added; then the mixture is acidified with concentrated hydrochloric acid. After separation of the organic phase and removal of the solvent, the residue is suspended in 40 ml of water and 0.1 g of PTSA is added. The suspension is refluxed for 2 hours, cooled at room temperature and extracted with diethyl ether. The desired product is obtained after evaporation of the solvent.

Ethyl 3-cyclopropylamino-2-(5-bromo-2,4-difluoro-3-chloro-benzoyl) acrylate

A quantity of 6.2 g of ethyl 5-bromo-2,4-difluoro-3-chloro-benzoyl acetate is dissolved in a mixture of 4.4 ml of acetic anhydride and 4.5 ml of triethyl orthofomate. After 2 hours of reflux, excess reagent is evaporated, the residue is dissolved in 20 ml of ethanol and the resulting solution cooled at 0°C. A volume of 2 ml of cyclopropylamine is added and after 30 minutes the desired product is isolated by filtration and air dried.

Ethyl 6-bromo-1-cyclopropyl-1,4-dihydro-7-fluoro-8-chloro-4-oxo-quinoline-3-carboxylate

A quantity of 2.48 g of ethyl 3-cyclopropylamino-2-(5-bromo-2,4-difluoro-3-chloro-benzoyl) acrylate is dissolved in 15 ml of THF and 0.27 g of 60% sodium hydride is added portionwise. After 1 hour at room temperature, the suspension is poured into 100 ml of water and the desired product isolated by filtration and air dried.

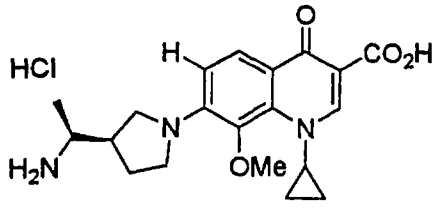
Ethyl 1-cyclopropyl-1,4-dihydro-7-fluoro-8-chloro-6-methyl-4-oxoquinoline-3-carboxyate

6-Bromo-8-chloro-1-cyclopropyl-7-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxyate (100 mg, 0.26 mmol), lithium chloride (0.033 g, 0.77 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.024 g, 0.026 mmol), tetramethyltin (0.093 g, 0.52 mmol) and 5 mg of butylated hydroxytoluene (2,6-di-tert-butyl-4-methyl-phenol-BHT) were combined in 8 ml of dimethyl formamide (DMF) and heated to 70-75°C for 18 hours. The solvent is then removed *in vacuo*. The residue is triturated with hexanes and then chromatographed with 1% methanol in chloroform on silica to afford the desired product.

The following are examples of typical synthesis of an 8-methoxy and 8-chloro quinolone of the subject invention as depicted in Scheme II. The last two steps allow variation at R7 by using a different amine.

Example G

Preparation of:




3-Methoxy-2-4-difluorobenzoyl chloride

A quantity of 43.9 g of 3-methoxy-2-4-difluorobenzoic acid is suspended in 300 mL of dichloromethane and 25 mL of oxalyl chloride are added followed by 4 drops of dry DMF. The mixture is stirred at room temperature for 6 hours and the solvent removed by evaporation to afford the desired product.

Ethyl 2,4-difluoro-3-methoxy-benzoyl acetate

A quantity of 26.4 g of monoethyl malonate is dissolved in 700 mL of THF. The solution is cooled at -50°C and 160 mL of 2.5 M n-butyllithium is added keeping the temperature below -50°C. The temperature is initially raised to 0°C and cooled back to -50°C. An amount of 20.6 g of 3-methoxy-2-4-difluorobenzoyl chloride is added keeping the temperature at -50°C, then the reaction mixture is warmed to room temperature. Hydrochloric acid is added until the pH becomes acidic. The organic phase is washed with sodium bicarbonate and dried, evaporation of the solvent affords the desired product.

Ethyl 3-cyclopropylamino-2-(2,4-difluoro-3-methoxy-benzoyl) acrylate

To a mixture of 50 mL of acetic anhydride and 50 mL of triethyl orthoformate is added 52.94 g of ethyl 2,4-difluoro-3-methoxy-benzoyl acetate. The mixture is refluxed for 2 hours, then cooled to room temperature. The excess reagent is removed by evaporation to provide a thick oil which is dissolved in 150 mL of ethanol. A quantity of 17.1 g of cyclopropylamine is then added while keeping the temperature about 20°C. The desired product is isolated by filtration and air dried.

Ethyl 1-cyclopropyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylate

A quantity of 30.3 g of ethyl 3-cyclopropylamino-2-(2,4-difluoro-3-methoxy-benzoyl) acrylate is added to 230 mL of dry THF. An amount of 4.1 g of 60% sodium hydride in oil is added portionwise keeping the temperature below 40°C. The solution is stirred at room temperature for 2 hours and then poured into 1.5 L of water. The desired product is isolated by filtration and air dried.

1-Cyclopropyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid

A quantity of 28.6 g of ethyl-1-cyclopropyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylate and 300 mL of a mixture of acetic acid, water, sulfuric acid (8/6/1) are refluxed for 2 hours. The reaction mixture is cooled at 0°C and the desired product collected by filtration.

1-Cyclopropyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid boron difluoride complex

A quantity of 1.0 g of 1-cyclopropyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid is dissolved in 10 mL of THF and 1.76 mL of boron trifluoride etherate is added. The mixture is stirred at 60°C for 2 hours then cooled to room temperature. The desired product is collected by filtration and air dried.

7-[(3R)-(1S-*tert*-Butoxycarbonylaminoethyl)-1-pyrrolidinyl]-1-cyclopropyl-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

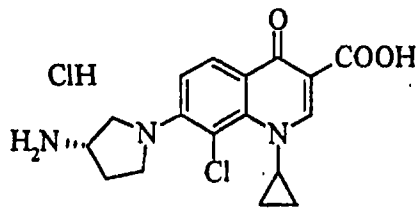
A quantity of 0.1 g of 1-cyclopropyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid boron difluoride complex is dissolved in 2 mL of acetonitrile; then, 0.16 mL of diisopropylethylamine and 0.08 g of 3R-(1S-*tert*-butoxycarbonylaminoethyl)pyrrolidine are added. The mixture is stirred at 60°C for 24 hours, and then the solvent is removed by evaporation. The residue is dissolved in 5 mL of ethanol and 2 mL of triethylamine. The solution is stirred at 80°C for 4 hours, then evaporated to dryness. The desired compound is isolated by column chromatography.

7-[(3R)-(1S-Aminoethyl)-1-pyrrolidinyl]-1-cyclopropyl-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride

A quantity of 54 mg of 7-[(3R)-(1S-*tert*-butoxycarbonylaminoethyl)-1-pyrrolidinyl]-1-cyclopropyl-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid is dissolved in 2 mL of ethanol and 0.5 mL of concentrated hydrochloric acid. After half an hour at room temperature the desired compound is collected by filtration after cooling the mixture in an ice bath.

Example H

Preparation of:



3-Chloro-2,4-difluorobenzoyl chloride

A quantity of 6.0 g of 3-chloro-2,4-difluorobenzoic acid is suspended in 20 ml of dichloromethane. A quantity of 2.99 ml of oxalyl chloride and 2 drops of DMF are then added. The suspension is stirred at room temperature overnight and the desired product is collected after evaporation of the solvent.

Ethyl 2,4-difluoro-3-chloro-benzoyl acetate

A quantity of 0.728 g of magnesium is suspended in 5 ml of ethanol and 0.1 ml of carbon tetrachloride is added. A solution of 4.6 ml of diethyl malonate in 20 ml of ethanol is added and the reaction is stirred at 60°C until complete dissolution of the magnesium. Then 6.1 g of 3-chloro-2,4-difluorobenzoyl chloride are added and the reaction stirred overnight. After evaporation of the solvent, the residue is treated with hydrochloric acid and the organic extracted by ethyl acetate. After evaporation of the solvent the residue is suspended in 50 ml of water and 100 mg of PTSA is added. The suspension is refluxed for 4 hours then cooled to room temperature. The desired compound is extracted with ethyl acetate and recovered by evaporation of the solvent.

Ethyl 3-cyclopropylamino-2-(2,4-difluoro-3-chloro-benzoyl) acrylate

To a mixture of 7.03 ml of triethyl orthoformate and 6.65 ml of acetic anhydride is added 7.6 g of ethyl 2,4-difluoro-3-chloro-benzoyl acetate. The solution is refluxed for 4 hours and the excess of reagent removed by evaporation. The residual thick oil is dissolved in a mixture of 10 ml of ethanol and 2 ml of diethyl ether and cooled in an ice bath. Cyclopropylamine (1.3 ml) is then added. After 30 minutes at room temperature the desired product is isolated by filtration.

Ethyl 1-cyclopropyl-1,4-dihydro-7-fluoro-8-chloro-4-oxo-quinoline-3-carboxylate

A quantity of 2.8 g of ethyl 3-cyclopropylamino-2-(2,4-difluoro-3-chlorobenzoyl) acrylate is dissolved in 25 ml of THF and 0.37 g of 60% sodium hydride is added portion wise. After 30 minutes, the solvent is evaporated; the residue is redissolved in ethyl acetate and washed with water. The desired product is collected by removal of the solvent.

1-Cyclopropyl-1,4-dihydro-7-fluoro-8-chloro-4-oxo-quinoline-3-carboxylic acid

A quantity of 1.93 g of ethyl-1-cyclopropyl-1,4-dihydro-7-fluoro-8-chloro-4-oxo-quinoline-3-carboxylate is dissolved in 30 ml of a mixture of acetic acid, water and sulfuric acid (8/6/1). the mixture is refluxed for 3 hours and cooled to room temperature. The desired compound is collected by filtration and air dried.

7-[(3R)-(1S-*tert*-Butoxycarbonylaminoethyl)-1-pyrrolidinyl]-1-cyclopropyl-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

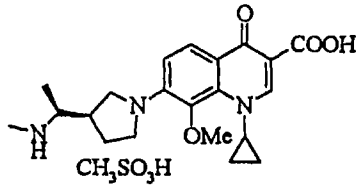
A quantity of 0.1 g of 1-cyclopropyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid boron difluoride complex is dissolved in 2 mL of acetonitrile; then 0.16 mL of diisopropylethylamine and 0.08 g of 3R-(1S-*tert*-butoxycarbonylaminoethyl)pyrrolidine are added. The mixture is stirred at 60°C for 24 hours, and then the solvent removed by evaporation. The residue is dissolved in 5 mL of ethanol and 2 mL of triethylamine. The solution is stirred at 80°C for 4 hours, then evaporated to dryness. The desired compound is isolated by column chromatography.

7-[(3R)-(1S-Aminoethyl)-1-pyrrolidinyl]-1-cyclopropyl-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride

A quantity of 54 mg of 7-[(3R)-(1S-*tert*-butoxycarbonylaminoethyl)-1-pyrrolidinyl]-1-cyclopropyl-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid is dissolved in 2 mL of ethanol and 0.5 mL of concentrated hydrochloric acid. After half an hour at room temperature, the mixture is cooled in an ice bath, and the desired compound is collected by filtration.

Example J

Preparation of:



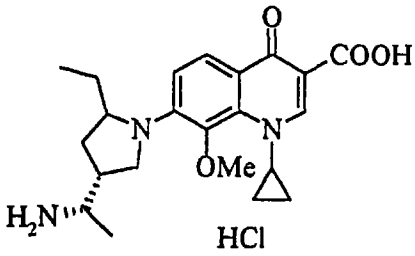

7-[3R-(1S-Methylaminoethyl)-1-pyrrolidinyl]-1-cyclopropyl-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid methanesulfonate

A quantity of 1.775 g of 1-cyclopropyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid boron difluoride ester is dissolved in 12 ml of dimethylformamide; then 3.35 ml of triethylamine and 1.050 g of 3R-(1S-methylaminoethyl)-1-pyrrolidine are added. The mixture is stirred at 50°C for 18 hours and the solvent removed by evaporation. The residue is redissolved in 20 ml of ethanol and 7 ml of triethylamine. The solution is refluxed at 80°C for 24 hours, and then evaporated to dryness. The desired material is isolated by recrystallization from isopropanol and methanol. This material is

suspended in 15 mL of ethanol and warmed slightly. The suspension is treated with 0.3 mL of methanesulfonic acid and stirred for 2 hours at room temperature. The mixture is cooled in an ice bath, and the desired compound is collected by filtration.

Example K

Preparation of:




1-Benzyl-4R-(1S-*tert*-butoxycarbonylaminoethyl)-2-pyrrolidinone

Sodium hydride (60% dispersion in mineral oil, 1.06 g, 26.4 mmol) is suspended in DMF. 4R-(1S-*tert*-butoxycarbonylaminoethyl)-2-pyrrolidinone (5.04 g, 22.0 mmol) is added as a solution in DMF over the course of five minutes. The solution is allowed to stir for one hour after which benzyl bromide (3.76 g, 22.0 mmol) is added, and the solution is allowed to stir overnight. The DMF is removed under reduced pressure and the remaining solid partitioned between water and ethyl acetate. The organic layer is removed and the water layer is extracted twice with ethyl acetate. The combined organic layers are washed once with brine, dried over sodium sulfate and evaporated to yield a white solid.

1-Benzyl-4R-(1S-aminoethyl)-2-pyrrolidinone

1-Benzyl-4R-(1S-*tert*-butoxycarbonylaminoethyl)-2-pyrrolidinone (6.57 g, 20.6 mmol) is dissolved in 40 ml of absolute ethanol and 10 ml of 12N HCl is added with stirring. The solution is stirred for two hours, at which time the solution is brought to greater than pH 12 by addition of ammonium hydroxide. The solution is extracted three times with 300 ml of dichloromethane. The organic portions are dried over sodium sulfate and evaporated to yield an amber oil

1-Benzyl-4-(2',2',5',5'-tetramethyl-2',5'-disila-1'-azacyclopentyl)ethyl-2-pyrrolidinone

1-Benzyl-4R-(1S-aminoethyl)-2-pyrrolidinone (2.47 g, 11.3 mmol) is dissolved in 25 ml of dichloromethane and 12 ml of diisopropylethylamine. Bis(chlorodimethylsilyl)ethane (4.88 g, 22.6 mmol) is added, and the reaction is stirred under argon for three hours. The reaction is quenched by addition of saturated ammonium chloride and washed twice with water. The dichloromethane is removed and the residue redissolved in ether and any solid filtered away. The ether is removed in vacuo to yield a reddish oil.

4-Benzyl-6-(2',2',5',5'-tetramethyl-2',5'-disila-1'-azacyclopentyl)ethyl-4-azaspiro[2.4]heptane

A mixture of 160 ml of THF and 38 ml of 1M ethylmagnesium bromide in THF (38.0 mmol) is brought to -70°C. Titanium isopropoxide (4.85 g, 17.1 mmol) is added quickly and the solution turns a light orange. After two minutes, 1-benzyl-4-(2',2',5',5'-tetramethyl-2',5'-disila-1'-azacyclopentyl)ethyl-2-pyrrolidinone (3.85 g, 10.7 mmol) in THF is added dropwise. The resulting mixture is stirred for 15 minutes at -70°C and then allowed to warm to room temperature for two hours. The reaction is quenched by addition of 200 ml of half saturated ammonium chloride; the resulting slurry is filtered. The filtrate is extracted three times with 150 ml of ether. The combined organic layers are washed with brine, dried over sodium sulfate, and evaporated to yield a light yellow oil.

4-Benzyl-6R-(1S-*t*-butoxycarbonylaminoethyl)-4-azaspiro[2.4]heptane

4-Benzyl-6-(2',2',5',5'-tetramethyl-2',5'-disila-1'-azacyclopentyl)ethyl-4-azaspiro[2.4]heptane (0.89 g, 2.4 mmol) is dissolved in 10 ml of absolute ethanol and 5 ml of glacial acetic acid. After stirring for an hour, the solvent is removed in vacuo, and the sample is redissolved in ethanol and treated with di-*tert*-butyl dicarbonate (1.05 g, 4.8 mmol) and triethylamine (0.49 g, 4.8 mmol). The mixture is allowed to stir overnight. Solvent and excess triethylamine are evaporated off and the residue is subjected to flash chromatography (3:2 hexane/ethyl acetate v/v) to obtain the desired compound.

3R-(1S-*tert*-Butoxycarbonylaminoethyl)-5-ethylpyrrolidine

4-Benzyl-6R-(1S-*t*-butoxycarbonylaminoethyl)-4-azaspiro[2.4]heptane (0.31 g, 0.9 mmol) is dissolved in 5 ml of methanol is mixed with palladium hydroxide on carbon (0.10 g) and palladium on activated carbon (0.05 g). The mixture is placed under a hydrogen atmosphere at 44 psi and shaken overnight. The solution is then filtered to remove catalyst, and the filtrate is concentrated to yield 3-*tert*-butoxycarbonylaminoethyl-5-ethylpyrrolidine as a clear oil.

7-[3R-(1S-*tert*-Butoxycarbonylaminoethyl)-5-ethyl-1-pyrrolidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid, boron difluoride ester

3R-(1S-*tert*-butoxycarbonylaminoethyl)-5-ethylpyrrolidine (0.17 g, 0.7 mmol) is dissolved in DMF and stirred in the presence of 1-cyclopropyl-7-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid, boron difluoride ester (0.13 g, 0.4 mmol) and triethylamine at 40°C for several hours until the reaction is complete. The solvent is removed in vacuo and the residue triturated with water to yield the targeted compound as a solid.

7-[3R-(1S-*tert*-Butoxycarbonylaminoethyl)-5-ethyl-1-pyrrolidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

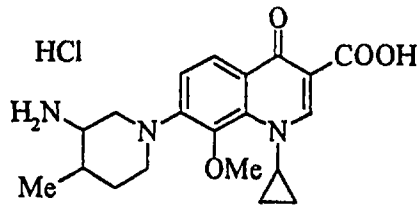
7-[3R-(1S-*tert*-Butoxycarbonylaminoethyl)-5-ethyl-1-pyrrolidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid, boron difluoride ester (0.20 g, 0.4 mmol) is stirred in a solution of 1:1 ethanol/triethylamine for several hours until the removal of the boronate ester is complete. The solvent is evaporated in vacuo and the residue triturated with water to yield the desired product.

7-[3R-(1S-Aminoethyl)-5-ethyl-1-pyrrolidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid hydrochloride

7-[3R-(1S-*tert*-Butoxycarbonylaminoethyl)-5-ethyl-1-pyrrolidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (0.18 g, 0.4 mmol) is stirred in a 1:1 mixture of ethanol and concentrated HCl until the reaction is complete. The solvent is removed in vacuo and the residue purified by recrystallization from ethanol.

Example L

Preparation of:




3-Amino-4-methylpiperidine

A quantity of 5.0 g of 3-nitro-4-methylpyridine, 0.5 g of ruthenium oxide, 0.5 g of rhodium on aluminia, and 0.5 g of platinum oxide are suspended in 20 ml of ammonia solution and 10 ml of methanol. The mixture is subjected to high temperature and high pressure hydrogen gas. The desired product is obtained by an aqueous work up.

7-[3-Amino-4-methylpiperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylic acid boron difluoride complex

Quantities of 2.62 g of 1-cyclopropyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid boron difluoride complex and 1.38 g of 3-amino-4-methylpiperidine are dissolved in 48.0 mL of dimethylformamide and 4.50 mL of triethylamine. After overnight at room temperature, the solution is evaporated to dryness. The desired product is isolated by recrystallization.

7-[3-Amino-4-methylpiperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylic acid

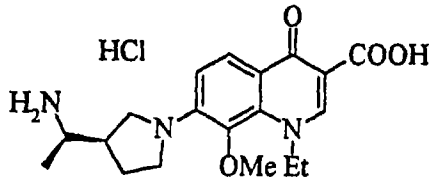
A quantity of 0.263 g of 7-[3-amino-4-methylpiperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylic acid boron difluoride complex is dissolved in 6 mL of ethanol, and 1.75 mL of triethylamine is added. The solution is heated to reflux for 2 hours, then cooled to room temperature. The solution is evaporated to dryness, and the desired product is isolated by recrystallization.

7-[3-Amino-4-methylpiperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylic acid hydrochloride salt

A quantity of 0.20 g of 7-[3-amino-4-methylpiperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylic acid is suspended in 1.0 mL of ethanol. Its pH is adjusted to 2 with hydrogen chloride to obtain the desired product after the evaporation of solvent.

Example M

Preparation of:




Ethyl 2-(2,4-difluoro-3-methoxy benzoyl)-3-ethylaminoacrylate

To a mixture of 3.7 ml of acetic anhydride and 4.3 ml of triethyl orthoformate (26 mmol) is added 4.15 g of ethyl 2,4-difluoro-3-methoxy-benzoyl acetate (16 mmol). The mixture is refluxed for 4 hours, cooled to room temperature and the excess reagent is removed under reduced pressure to provide a thick oil. The product is used without further purification by dissolving it in 12 ml of absolute ethanol. A quantity of 8 ml of ethylamine (2.0 M solution in THF) is then added at 0°C and stirred overnight at room temperature. The desired product is isolated by filtration and washing with cold ethanol.

Ethyl 1-ethyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-3-quinolinecarboxylate

Ethyl 2-(2,4-difluoro- 3-methoxy)-3-ethylaminoacrylate (1.75 g, 5.6 mmol) is added to anhydrous THF under nitrogen atmosphere. The mixture is cooled to 0°C in an ice bath. Sodium hydride (335 mg, 8.3 mmol) is added portionwise over 2 minutes maintaining the temperature of the reaction below 10°C. The reaction is warmed to room temperature and stirred for additional 50 minutes and cooled to 0°C. Careful addition of water quenches the reaction, which is extracted with dichloromethane. The organic layer is washed twice with brine, dried over $MgSO_4$, and concentrated under reduced pressure to yield the desired compound as a solid.

1-Ethyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

Ethyl 1-ethyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-3-quinolinecarboxylate (1.37 g, 4.7 mmol) is suspended in a mixture of acetic acid water: sulfuric acid (8:6:1). The mixture is refluxed for 3 hours, and then cooled to room temperature. The crystals are filtered and rinsed with cold water.

1-Ethyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-3-quinolinecarboxylic acid, boron difluoride ester

To 1-ethyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (985 mg, 3.7 mmol) dissolved in anhydrous THF (10 ml) is added boron trifuloride ethrate (940 ml, 7.4 mmol). The mixture is heated to 65°C for 4 hours and allowed to cool to room temperature overnight. The filtered crystals are washed with hexanes to afford the desired product.

7-[3R-(1S-*tert*-Butoxycarbonylaminoethyl)-1-pyrrolidinyl]-1-ethyl-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

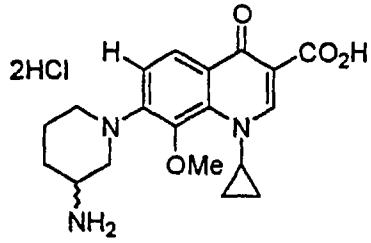
1-Ethyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid boron difluoride ester (0.17 g, 0.5 mmol), 3R-(1S-*tert*-butoxycarbonylaminoethyl)-pyrrolidine 0.11 g, 0.5 mmol) and triethylamine (0.3 ml, 2.0 mmol) are dissolved in 5 ml of DMF. The mixture is stirred at 60°C for 24 hours, and the solvent is removed under reduced pressure. The solid obtained from the filtration is washed with small amount of water and re-dissolved in 5 ml of methanol with 1 ml of triethylamine. The solution is heated at 70°C for 6 hours and then evaporated to dryness to afford the desired product.

7-[3R-(1S-Aminoethyl)-1-pyrrolidinyl]-1-ethyl-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride

A quantity of 110 mg of 7-[3R-(1S-*tert*-butoxycarbonylaminoethyl)-1-pyrrolidinyl]-1-ethyl-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid is dissolved in 2 ml of ethanol and 2 ml of concentrated hydrochloric acid. After two hours at room temperature, the solid is obtained after the evaporation of the solvent and recrystallization in ethanol.

Example N

Preparation of:




7-[3-Aminopiperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylic acid boron difluoride complex

Quantities of 2.62 g of 1-cyclopropyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid boron difluoride complex and 2.08 g of 3-aminopiperidine dihydrochloride salt are mixed in 48.0 mL of dimethylformamide and 4.50 mL of triethylamine. After overnight stirring at room temperature, the solution is cooled and filtered to give the desired product.

7-[3-Aminopiperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylic acid

A quantity of 0.253 g of 7-[3-aminopiperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylic acid boron difluoride complex is dissolved in 6 mL of ethanol, and 1.75 mL of triethylamine is added. The solution is heated to reflux for 2 hours and the mixture is evaporated to dryness under reduced pressure. The desired product is isolated by recrystallization.

7-[3-Aminopiperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylic acid dihydrochloride salt

A quantity of 0.19 g of 7-[3-aminopiperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylic acid is suspended in 1.0 mL of ethanol. The pH of the solution is adjusted to 2 with the addition of hydrogen chloride. The desired product is obtained by evaporation of the solvent.

Compositions of the Invention

The compositions of this invention comprise:

(a) a safe and effective amount of the compound of the invention

(b) a pharmaceutically-acceptable excipient.

It may also optionally comprise other antimicrobials or other actives, which may or may not act synergystically with the invention.

A "safe and effective amount" of a quinolone is an amount that is effective, to inhibit microbial growth at the site of an infection to be treated in a host, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will vary with such factors as the particular condition being treated, the physical condition of the patient, the duration of treatment, the nature of concurrent therapy (if any), the specific dosage form to be used, the excipient employed, the solubility of the quinolone therein, and the dosage regimen desired for the composition.

The compositions of this invention are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition of this invention containing an amount of a quinolone that is suitable for administration to a human or lower animal subject, in a single dose, according to good medical practice. These compositions preferably contain from about 30 mg, more preferably from about 50 mg, more preferably still from about 100 mg, preferably to about 20,000 mg, more preferably to about 7,000 mg, more preferably still to about 1,000 mg, most preferably to about 500 mg, of a quinolone.

The compositions of this invention may be in any of a variety of forms, suitable (for example) for oral, rectal, topical or parenteral administration. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable excipients well-known in the art may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the antimicrobial activity of the quinolone. The amount of excipient employed in conjunction with the quinolone is sufficient to provide a practical quantity of material for administration per unit dose of the quinolone. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references, all incorporated by reference herein: Modern Pharmaceutics, Vol. 7, Chapters 9 and 10 (Banker & Rhodes, editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2d Edition (1976).

In particular, pharmaceutically-acceptable excipients for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers,

isotonic saline, and pyrogen-free water. Preferred excipients for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the pharmaceutically-acceptable excipient, in compositions for parenteral administration, comprises at least about 90% by weight by the total composition.

In addition, dosages for injection may be prepared in dried or lyophilized form. Such forms can be reconstituted with water or saline solution, depending on the preparation of the dosage form. Such forms may be packaged as individual dosages or multiple dosages for easier handling. Where lyophilized or dried dosages are used, the reconstituted dosage form is preferably isotonic, and at a physiologically compatible pH.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50%, of the quinolone. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents, such are well known to the skilled artisan. Preferred excipients for oral administration include gelatin, propylene glycol, cottonseed oil and sesame oil.

The compositions of this invention can also be administered topically to a subject, i.e., by the direct laying on or spreading of the composition on the epidermal or epithelial tissue of the subject. Such compositions include, for example, lotions, creams, solutions, gels and solids. These topical compositions preferably comprise a safe and effective amount, usually at least about 0.1%, and preferably from about 1% to about 5%, of the quinolone. Suitable excipients for topical administration preferably remain in place on the skin as a continuous film, and resist being removed by perspiration or immersion in water. Generally, the excipient is organic in nature and capable of having dispersed or dissolved therein the quinolone. The excipient may include pharmaceutically-acceptable emolients, emulsifiers, thickening agents, and solvents and the like; these are well known to the skilled artisan.

Methods of Using the Compounds

This invention also provides methods of treating or preventing an infectious disorder in a human or other animal subject, by administering a safe and effective amount of a quinolone to said subject. As used herein, an "infectious disorder" is any disorder characterized by the presence of a microbial infection. Preferred methods of this invention are for the treatment of bacterial infections. Such infectious disorders include (for example) central nervous system infections, external ear infections, infections of the middle ear (such as acute otitis media), infections of the cranial sinuses, eye infections, infections of the oral cavity (such as infections of the teeth, gums and mucosa), upper respiratory tract infections, lower respiratory tract infections, including pneumonia, genitourinary infections, gastrointestinal infections, gynecological infections, septicemia, sepsis, peritonitis, bone and joint infections, skin and skin structure infections, bacterial endocarditis, burns, antibacterial prophylaxis of surgery, and antibacterial prophylaxis in post-operative patients or in immunosuppressed patients (such as patients receiving cancer chemotherapy, or organ transplant patients).

The quinolone derivatives and compositions of this invention can be administered topically or systemically. Systemic application includes any method of introducing the quinolone into the tissues of the body, e.g., intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, sublingual, rectal, and oral administration. The specific dosage of antimicrobial to be administered, as well as the duration of treatment, are mutually dependent. The dosage and treatment regimen will also depend upon such factors as the specific quinolone used, the resistance pattern of the infecting organism to the quinolone used, the ability of the quinolone to reach minimum inhibitory concentrations at the site of the infection, the nature and extent of other infections (if any), the personal attributes of the subject (such as weight), compliance with the treatment regimen, the age and health status of the patient, and the presence and severity of any side effects of the treatment.

Typically, for a human adult (weighing approximately 70 kilograms), from about 75 mg, more preferably from about 200 mg, most preferably from about 500 mg to about 30,000 mg, more preferably to about 10,000 mg, most preferably to about 3,500 mg, of quinolone is administered per day. Treatment regimens preferably extend from about 1, preferably from about 3 to about 56 days, preferably to about 20 days, in duration. Prophylactic regimens (such as avoidance of opportunistic infections in immunocompromised patients) may extend 6 months, or longer, according to good medical practice.

A preferred method of parenteral administration is through intravenous injection. As is known and practiced in the art, all formulations for parenteral administration must be sterile. For mammals, especially humans, (assuming an approximate body weight of 70 kilograms) individual doses of from about 100 mg, preferably from about 500 mg to about 7,000 mg, more preferably to about 3,500 mg, is acceptable.

In some cases, such as generalized, systemic infections or in immune-compromised patients, the invention may be dosed intravenously. The dosage form is generally isotonic and at physiological pH. The dosage amount will depend on the patient and severity of condition, as well as other commonly considered parameters. Determination of such doses is well within the scope of practice for the skilled practitioner using the guidance given in the specification.

A preferred method of systemic administration is oral administration. Individual doses of from about 20 mg, more preferably from about 100 mg to about 2,500 mg, more preferably to about 500 mg.

Topical administration can be used to deliver the quinolone systemically, or to treat a local infection. The amounts of quinolone to be topically administered depends upon such factors as skin sensitivity, type and location of the tissue to be treated, the composition and excipient (if any) to be administered, the particular quinolone to be administered, as well as the particular disorder to be treated and the extent to which systemic (as distinguished from local) effects are desired.

The following non-limiting examples illustrate the compounds, compositions, processes, and uses of the present invention.

Composition Example P

A tablet composition for oral administration, according to the present invention, is made comprising:

| Component | Amount |
|---|---|
| Compound of Example 15 | 150 mg |
| Lactose | 120 mg |
| Maize Starch | 70 mg |
| Talc | 4 mg |
| Magnesium Stearate | 1 mg |

Other compounds having a structure according to Formula 1 are used with substantially similar results.

Composition Example Q

A capsule containing 200 mg of active for oral administration, according to the present invention, is made comprising:

| Component | Amount (%w/w) |
|---|---|
| Compound of Example 18 | 15% |
| Hydrous Lactose | 43% |
| Microcrystalline Cellulose | 33% |
| Crosspovidone | 3.3% |
| Magnesium Stearate | 5.7% |

Other compounds having a structure according to Formula 1 are used with substantially similar results.

Composition Example R

A saline-based composition for ocular administration, according to the present invention, is made comprising:

| Component | Amount (%w/w) |
|---|---|
| Compound of Example 63 | 10% |
| Saline | 90% |

Other compounds having a structure according to Formula 1 are used with substantially similar results.

Composition Example S

A intranasal composition for local administration, according to the present invention, is made comprising:

| Component | Composition (% w/v) |
|---|---|
| Compound of Example 24 | 0.20 |
| Benzalkonium chloride | 0.02 |
| EDTA | 0.05 |
| Glycerin | 2.0 |
| PEG 1450 | 2.0 |
| Aromatics | 0.075 |
| Purified water | q.s. |

Other compounds having a structure according to Formula 1 are used with substantially similar results.

Composition Example T

A inhalation aerosol composition, according to the present invention, is made comprising:

| Component | Composition (% w/v) |
|---|---|
| Compound of Example 84 | 5.0 |
| Ascorbic acid | 0.1 |
| Menthol | 0.1 |

| | |
|---|---|
| Sodium Saccharin | 0.2 |
| Propellant (F12, F114) | q.s. |

Other compounds having a structure according to Formula 1 are used with substantially similar results.

Composition Example U

A topical opthalmic composition, according to the present invention, is made comprising:

| Component | Composition (% w/v) |
|---|---|
| Compound of Example 47 | 0.10 |
| Benzalkonium chloride | 0.01 |
| EDTA | 0.05 |
| Hydroxyethylcellulose | 0.5 |
| Acetic acid | 0.20 |
| Sodium metabisulfite | 0.10 |
| Sodium chloride (0.9%) | q.s. |

Other compounds having a structure according to Formula 1 are used with substantially similar results.

Composition Example V

An antimicrobial composition for parenteral administration, according to this invention, is made comprising:

| Component | Amount |
|---|---|
| Compound of Example 93 | 30 mg/ml excipient |
| Excipient: | |
| 50 mm phosphate buffer pH 5 buffer with lecithin | 0.48% |
| carboxymethylcellulose | 0.53 |
| povidone | 0.50 |
| methyl paraben | 0.11 |
| propyl paraben | 0.011 |

The above ingredients are mixed, forming a suspension. Approximately 2.0 ml of the suspension is systemically administered, via intramuscular injection, to a human subject suffering from a lower respiratory tract infection, with Streptococcus pneumoniae present. This dosage is repeated twice daily, for approximately 14 days. After 4 days, symptoms of the disease subside, indicating that the pathogen has been substantially eradicated. Other compounds having a structure according to Formula 1 are used with substantially similar results.

Composition Example W

An enteric coated antimicrobial composition for oral administration, according to this invention, is made comprising the following core tablet:

| Component | Amount (mg) |
|---|---|
| Compound of Example 17 | 350.0 |
| Maltodextrine | 30.0 |
| Magnesium Stearate | 5.0 |
| Microcrystalline Cellulose | 100.0 |
| Colloidal Silicon Dioxide | 2.5 |
| Povidone | 12.5 |

The components are admixed into a bulk mixture. Compressed tablets are formed, using tabletting methods known in the art. The tablet is then coated with a suspension of methacrylic acid/methacrylic acid ester polymer in isopropanol/acetone. A human subject, having a urinary tract infection with Escherichia coli present, is orally administered two of the tablets, every 8 hours, for 4 days. Symptoms of the disease then subside, indicating substantial eradication of the pathogen. Other compounds having a structure according to Formula 1 are used with substantially similar results.

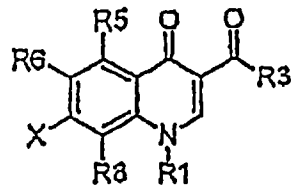
All references described herein are hereby incorporated by reference.

While particular embodiments of the subject invention have been described, it will be obvious to those skilled in the art that various changes and modifications of the subject invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

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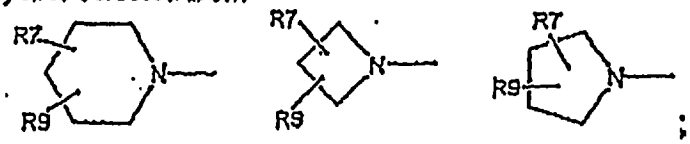
What is claimed is:

1. A compound having the following formula;



wherein:

(a) X is selected from



;

(b) R1 is selected from $C_3$ to $C_5$ cycloalkyl, $C_1$ to $C_2$ alkanyl, $C_2$ to $C_3$ linear alkenyl, $C_3$ to $C_4$ branched alkanyl or alkenyl, all such alkyl or cycloalkyl moieties being unsubstituted or substituted with from 1 to 3 fluoro; and phenyl, unsubstituted or substituted with from 1 to 3 fluoro, or with one hydroxy in the 4-position;

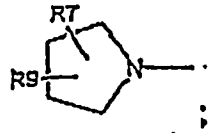
(c) R3 is hydrogen or hydroxy;

(d) R5 is selected from hydrogen, hydroxy, amino, halo, $C_1$ to $C_2$ alkanyl, $C_2$ alkenyl, and methoxy, all such alkyl and methoxy moieties being unsubstituted or substituted with from 1 to 3 fluoro;

(e) R6 is selected from hydrogen, hydroxy, aminocarbonyl, bromo, cyano, $C_1$ to $C_2$ alkanyl, $C_2$ to $C_4$ alkenyl or alkynyl, all such alkyl moieties being unsubstituted or substituted with from 1 to 3 fluoro, or such methyl or ethyl moieties being optionally substituted with one hydroxy or amino;

(f) R8 is selected from chloro, bromo, methoxy, methylthio, $C_1$ to $C_2$ alkanyl, $C_2$ to $C_4$ alkenyl, all such alkyl, methoxy and methylthio moieties being unsubstituted or substituted with from 1 to 3 fluoro;

(g) R7 is amino which is attached to a ring carbon of X which is not adjacent to the ring nitrogen, the amino being unsubstituted or substituted with one or two $C_1$ to $C_3$ alkanyl; or aminoalkanyl which is attached to any ring carbon of X and is $C_1$ to $C_3$ alkanyl substituted with one amino, the amino being unsubstituted or substituted with one or two $C_1$ to $C_3$ alkanyl; with the proviso that R7 is aminoalkanyl if X comprises



;

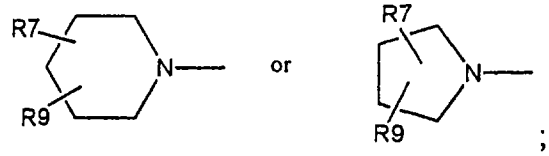
(h) each R9 is independently selected from hydrogen, $C_1$ to $C_4$ alkanyl, $C_2$ to $C_6$ alkenyl or alkynyl, and a $C_3$ to $C_6$ fused or spirocycle alkyl ring, all such alkyl moieties being unsubstituted or substituted with from 1 to 3 fluoro; and

(j) a R7 moiety described in (g) and a R9 moiety described in (h) may optionally be connected thus forming a fused or spirocycle ring with the N-containing ring shown in (a), the fused or spirocycle ring comprising from 2 to 5 ring carbons and 0 or 1 ring nitrogen, but if such rings are fused, R8 is other than chloro or bromo;

an optical isomer, diastereomer or enantiomer thereof; a pharmaceutically-acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof.

2. The compound of Claim 1 wherein:

(a) X is




;

(b) R3 is hydroxy;

(c) R1 is selected from $C_3$ to $C_5$ cycloalkanyl, methyl, ethyl, ethenyl, isopropyl, isopropenyl, isobutyl, isobutenyl, t-butyl, all such alkyl or cycloalkanyl moieties being unsubstituted or substituted with from 1 to 3 fluoro; and phenyl, unsubstituted or substituted with from 1 to 3 fluoro, or with one hydroxy in the 4-position; preferably from cyclopropyl, ethyl, phenyl substituted with 1 to 3 fluoro, and 4-hydroxyphenyl;

(d) R5 is selected from hydrogen, hydroxy, amino, fluoro, chloro, bromo, and methyl, the methyl being unsubstituted or substituted with from 1 to 3 fluoro; preferably from hydrogen, hydroxy, chloro, bromo, amino, and methyl, the methyl being unsubstituted or substituted with from 1 to 3 fluoro;

(e) R6 is selected from hydrogen, hydroxy, amino-carbonyl, bromo, cyano, methyl, and ethenyl, the ethenyl being unsubstituted or substituted with from 1 to 3 fluoro, the methyl being unsubstituted or substituted with one hydroxy or amino or from 1 to 3 fluoro; preferably from hydrogen, hydroxy, and methyl, the methyl being unsubstituted or substituted with from 1 to 3 fluoro;

(f) R8 is selected from chloro, bromo, methoxy or methylthio unsubstituted or substituted with from 1 to 3 fluoro, and methyl unsubstituted or substituted with from 1 to 3 fluoro; preferably from chloro, methoxy, methylthio, monofluoromethyl, difluoromethyl, and trifluoromethyl;

(g) R7 is amino unsubstituted or substituted with one $C_1$ to $C_3$ alkanyl or two methyl, or aminoalkanyl which is methyl or ethyl or isopropyl substituted with one amino unsubstituted or substituted with one methyl or ethyl or dimethyl; preferably R7 is selected from amino, methylamino, aminomethyl, methylaminomethyl, 1-aminoethyl, 1-methylaminoethyl, 1-amino-1-methylethyl and 1-methyamino-1-methylethyl; and

(h) no more than two ring carbons of X have non-hydrogen R9 attached thereto; preferably any non-hydrogen R9 are methyl, ethyl, dimethyl or spirocyclopropyl.

3. The compound of Claim 1 or 2 wherein:

(a) R1 is cyclopropyl or ethyl, unsubstituted or substituted with from 1 to 3 fluoro; preferably cyclopropyl;

(b) R5 is selected from hydrogen, hydroxy, amino, and methyl; preferably hydrogen;

(c) R6 is selected from hydrogen and hydroxy;

(d) R8 is methoxy or methylthio or chloro, preferably methoxy or methylthio; and

(e) only one ring carbon of X has non-hydrogen R9, such non-hydrogen R9 preferably being methyl or dimethyl or spirocyclopropyl; preferably all R9 are hydrogen.

4. The compound of any of Claims 1-3 wherein R8 is methoxy.

5. The compound of any of Claims 1-4 wherein X comprises the pyrrolidinyl ring, and R7 is aminoalkanyl, preferably selected from aminomethyl, methylaminomethyl, 1-aminoethyl, 1-methylaminoethyl, 1-amino-1-methylethyl and 1-methyamino-1-methylethyl.

6. The compound of any of Claims 1-4 wherein X comprises the piperidinyl ring, and R7 is unsubstituted or substituted amino, preferably amino or methylamino.

7. The compound of any of Claims 1-6 wherein wherein all R9 are hydrogen or, if X comprises the pyrrolidinyl ring, any non-hydrogen R9 are attached to a ring carbon adjacent to the ring nitrogen.

8. A compound selected from:

7-[3R-(1S-aminoethylpyrrolidinyl)]-1-ethyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1S-aminoethylpyrrolidinyl)]-1-(2-fluoroethyl)-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1S-aminoethylpyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1S-methylaminoethylpyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1-amino-methylethylpyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1-methylamino-methylethylpyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1S-aminoethyl-5-methyl-pyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1S-aminoethyl-5,5-dimethyl-pyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1-aminomethylethyl-5,5-dimethyl-pyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1S-methylaminoethyl-5,5-dimethyl-pyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1-methylaminomethylethyl-5,5-dimethyl-pyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1S-aminoethyl-5-ethyl-pyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1-aminomethylethyl-5-ethyl-pyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1S-methylaminoethyl-5-ethyl-pyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3R-(1-methylaminomethylethyl-5-ethyl-pyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[(3R-(1-amino-1-cyclopropyl-methylpyrrolidinyl)]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[6R-(1S-aminoethyl)-4-azaspiro[2.4]heptanyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[6R-(1S-methylaminoethyl)-4-azaspiro[2.4]heptanyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[6R-(1S-amino-methylethyl)-4-azaspiro[2.4]heptanyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[6R-(1S-methylamino-methylethyl)-4-azaspiro[2.4]heptanyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3-aminopiperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3-methylaminopiperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3-amino-4-methyl-piperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3-amino-4-ethyl-piperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3-amino-6,6-dimethyl-piperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[3-amino-6-methyl-piperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[6-amino-4-azaspiro[2.5]-octanyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[7-amino-5-azaspiro[2.5]-octanyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid;

7-[4-amino-6-azaspiro[2.5]-octanyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid; or

a pharmaceutically-acceptable salt thereof.

9. A pharmaceutical composition comprising:

(a) a safe and effective amount of a compound of any of Claims 1-8; and

(b) a pharmaceutically-acceptable excipient.

10. Use of a compound of any of Claims 1-8 for the manufacture of a medicament for preventing or treating microbial infection.