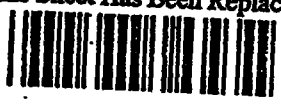
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ANTIMICROBIAL QUINOLONE THIOUREAS

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This application is a continuation-in-part of U.S. Patent Application Serial Number 416,645, filed October 10, 1989, which is a continuation-in-part of U.S. Patent Application Serial Number 261,948, filed October 24, 1988 (abandoned).

BACKGROUND OF THE INVENTION

This invention relates to novel antimicrobial compounds and compositions. In particular, the compounds of this invention contain a quinolone or related heterocyclic moiety.

The chemical and medical literature describes a myriad of compounds that are said to be antimicrobial, i.e., capable of destroying or suppressing the growth or reproduction of microorganisms, such as bacteria. In particular, antibacterials include a large variety of naturally-occurring (antibiotic), synthetic, or semi-synthetic compounds. They may be classified (for example) as the aminoglycosides, ansamacrolides, beta-lactams (including penicillins and cephalosporins), lincosaminides, macrolides, nitrofurans, nucleosides, oligosaccharides, peptides and polypeptides, phenazines, polyenes, polyethers, quinolones, tetracyclines, and sulfonamides. 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), both incorporated by reference herein.

The mechanism of action of these antibacterials vary. However, each can be generally classified as functioning in one or more of four 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



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essential penicillin binding proteins (PBPs) in bacteria, which are responsible for cell wall synthesis. On the other hand, quinolones act by inhibiting synthesis of bacterial DNA, thus preventing the bacteria from replicating.

Not surprisingly, the pharmacological characteristics of antibacterials and other antimicrobials, and their suitability for any given clinical use, also vary considerably. For example, the classes of antimicrobials (and members within a class) may vary in their relative efficacy against different types of microorganisms, and their susceptibility to development of microbial resistance. These antimicrobials may also differ in their pharmacological characteristics, such as their bioavailability, and biodistribution. Accordingly, selection of an appropriate antibacterial (or other antimicrobial) in any given clinical situation can be a complicated analysis of many factors, including the type of organism involved, the desired method of administration, and the location of the infection to be treated.

The pharmaceutical literature is replete with attempts to develop improved antimicrobials (i.e., compounds that have a broader scope of activity, greater potency, improved pharmacology, and/or less susceptibility to resistance development.) For example, one group of antimicrobials that has been developed relatively recently for clinical use is the quinolones. These compounds include, for example, nalidixic acid, difloxacin, enoxacin, fleroxacin, norfloxacin, lomefloxacin, ofloxacin, ciprofloxacin, and pefloxacin. See, C. Marchbanks and M. Dudley, "New Fluoroquinolones", 7 Hospital Therapy 18 (1988); P. Shah, "Quinolones", 31 Prog. Drug Res. 243 (1987); Quinolones - Their Future in Clinical Practice, (A. Percival, editor, Royal Society of Medical Services, 1986); and M. Parry, "Pharmacology and Clinical Uses of Quinolone Antibiotics", 116 Medical Times 39 (1988).

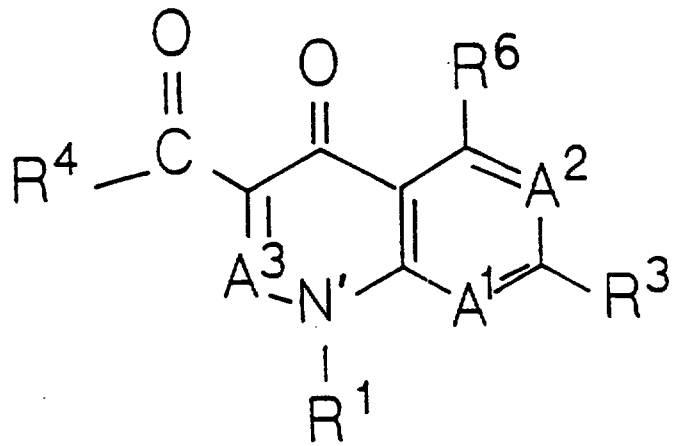
However, many such attempts to produce improved antimicrobials have produced equivocal results. Indeed, few antimicrobials are developed that are truly clinically-acceptable

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in terms of their spectrum of antimicrobial activity, avoidance of microbial resistance, and pharmacology. For example, the quinolones often show reduced effectiveness against certain clinically important pathogens (for example, gram positive bacteria and/or anaerobic bacteria). The quinolones also have limited water solubility limiting their bioavailability and suitability for parenteral dosing. They may also produce adverse side effects, such as gastrointestinal disturbance and central nervous system effects (such as convulsions). See, M. Neuman and A. Esanu, "Gaps and Perspectives of New Fluoroquinolones", 24 Drugs Exptl. Clin. Res. 385 (1988); W. Christ et al., "Specific Toxicologic Aspects of the Quinolones", 10 Rev. Infectious Diseases S141 (1988); H. Neu, "Clinical Use of the Quinolones", Lancet 1319 (1987); and "Ciprofloxacin: Panacea or Blunder Drug?", J. South Carolina Med. Assoc 131 (March 1989).

SUMMARY OF THE INVENTION

The present invention provides compounds of the general structure:



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wherein

(A) (1) A^1 is N or $C(R^7)$; where

(i) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $N(R^8)(R^9)$, and

(ii) R^8 and R^9 are, independently, R^{8a}; where R^{8a} is hydrogen, alkyl, alkenyl, carbocyclic ring, or heterocyclic ring substituents; or R^8 and R^9

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together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is $C(R^2)$; where R^2 is hydrogen or halogen;

(3) A^3 is N or $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, $N(R^8)(R^9)$, or X;

(5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, a heterocyclic ring, or X;

(6) R^4 is hydroxy; and

(7) R^6 is hydrogen, alkyl, halogen, nitro, $N(R^8)(R^9)$, or $S(R^{8a})$;

(B) except that

(1) when A^1 is $C(R^7)$, R^1 and R^7 may together comprise a heterocyclic ring including N' and A^1;

(2) R^2 and R^3 may together comprise $-O-(CH_2)_n-O-$, where n is from 1 to 4;

(3) when A^3 is $C(R^5)$, R^4 and R^5 may together comprise a heterocyclic ring including the carbon atoms to which R^4 and R^5 are bonded and the carbon atom of Formula (I) to which said carbon atoms are bonded; and

(4) when A^3 is $C(R^5)$, R^1 and R^5 may together comprise a heterocyclic ring including N' and the adjacent carbon to which R^5 is bonded;

(C) and

(1) R^1 is X, R^3 is X, or both R^1 and R^3 are X; and

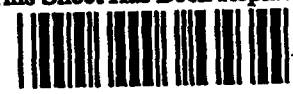
(2) X is $-R^{15}-N(R^{16})(R^{17})$ or $-R^{15}-R^{18}-N(R^{19})(R^{17})$, where

(a) (1) R^{15} is nil, alkyl, a carbocyclic ring, or a heterocyclic ring; and

(2) R^{16} is hydrogen; alkyl; alkenyl; a carbocyclic ring; a heterocyclic ring; or

(3) when X is $R^{15}-N(R^{16})(R^{17})$, R^{16} and R^{15} may together comprise a heterocyclic ring including the nitrogen atom to which R^{15} and R^{16} are bonded;

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(b) R^{17} is $C(=S)-NR^{20}R^{21}$; where R^{20} is hydrogen, alkyl, alkenyl, a carbocyclic ring or a heterocyclic ring; and R^{21} is R^{20} or $N(R^{20})(R^{20})$; or R^{20} and R^{21}, together with the nitrogen to which they are bonded, form a heterocyclic ring; and

(c) (1) R^{18} is alkyl, a carbocyclic ring, or a heterocyclic ring; and

(2) R^{19} is hydrogen; alkyl; alkenyl; a carbocyclic ring; a heterocyclic ring; or

(3) R^{18} and R^{19} may together comprise a heterocyclic ring including the nitrogen atom to which R^{18} and R^{19} are bonded;

and pharmaceutically-acceptable salts and biohydrolyzable esters thereof, and hydrates thereof.

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. These compounds provide advantages versus antimicrobial agents among those known in the art, including (for example) the spectrum of antimicrobial activity, potency, and improved pharmacology.

DESCRIPTION OF THE INVENTION

The present invention encompasses certain novel quinolones, methods for their manufacture, dosage forms, and methods of administering the dithiocarbamoyl quinolones 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.

Quinolone Thioureas

The compounds of this invention, herein referred to as "quinolone thioureas", encompass any of a variety of quinolones

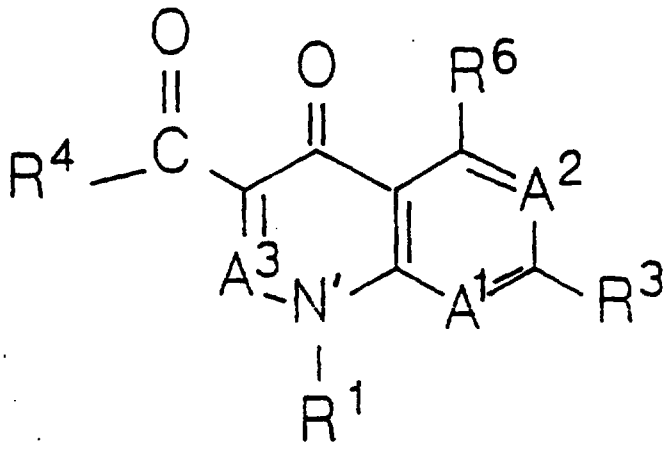
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(and related heterocyclic moieties) having a thiourea-containing substituent at the 1- and/or 7-position of the quinolone moiety.

The quinolone thioureas of this invention include compounds of the general structure:



wherein

(A) (1) A^1 is N or $C(R^7)$; where

(i) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $N(R^8)(R^9)$ (preferably hydrogen or halogen), and

(ii) R^8 and R^9 are, independently, R^{8a}; where R^{8a} is hydrogen, alkyl, alkenyl, carbocyclic ring, or heterocyclic ring substituents; or R^8 and R^9 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is $C(R^2)$; where R^2 is hydrogen or (preferably) halogen;

(3) A^3 is N or (preferably) $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, $N(R^8)(R^9)$ (preferably alkyl or a carbocyclic ring); or X;

(5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, a heterocyclic ring (preferably a heterocyclic ring); or X;

(6) R^4 is hydroxy; and

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(7) R^6 is hydrogen, alkyl, halogen, nitro, $N(R^8)(R^9)$, or $S(R^{8a})$ (preferably hydrogen);

(B) except that

(1) when A^1 is $C(R^7)$, R^1 and R^7 may together comprise a heterocyclic ring including N' and A^1;

(2) R^2 and R^3 may together comprise $-O-(CH_2)_n-O-$, where n is from 1 to 4;

(3) when A^3 is $C(R^5)$, R^4 and R^5 may together comprise a heterocyclic ring including the carbon atoms to which R^4 and R^5 are bonded and the carbon atom of Formula (I) to which said carbon atoms are bonded; and

(4) when A^3 is $C(R^5)$, R^1 and R^5 may together comprise a heterocyclic ring including N' and the adjacent carbon to which R^5 is bonded;

(C) and

(1) R^1 is X, R^3 is X, or both R^1 and R^3 are X; and

(2) X is $-R^{15}-N(R^{16})(R^{17})$ or $-R^{15}-R^{18}-N(R^{19})(R^{17})$, where

(a) (1) R^{15} is nil, alkyl, a carbocyclic ring, or a heterocyclic ring; and

(2) R^{16} is hydrogen; alkyl; alkenyl; a carbocyclic ring; a heterocyclic ring; or

(3) when X is $R^{15}-N(R^{16})(R^{17})$, R^{16} and R^{15} may together comprise a heterocyclic ring including the nitrogen atom to which R^{15} and R^{16} are bonded;

(b) R^{17} is $C(=S)-NR^{20}R^{21}$; where R^{20} is hydrogen, alkyl, alkenyl, a carbocyclic ring or a heterocyclic ring; and R^{21} is R^{20} or $N(R^{20})(R^{20})$; or R^{20} and R^{21}, together with the nitrogen to which they are bonded, form a heterocyclic ring; and

(c) (1) R^{18} is alkyl, a carbocyclic ring, or a heterocyclic ring; and

(2) R^{19} is hydrogen; alkyl; alkenyl; a carbocyclic ring; a heterocyclic ring; or

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(3) R^{18} and R^{19} may together comprise a heterocyclic ring including the nitrogen atom to which R^{18} and R^{19} are bonded;

and pharmaceutically-acceptable salts and biohydrolyzable esters thereof, and hydrates thereof.

Definitions and Usage of Terms:

The following is a list of definitions for terms used herein.

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

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

"Heteroalkyl" is an unsubstituted or substituted saturated chain radical having from 3 to 8 members comprising carbon atoms and one or two heteroatoms.

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

"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 atoms, preferably 3 to 6 atoms. Polycyclic rings contain from 7 to 17 atoms, preferably from 7 to 13 atoms.

"Cycloalkyl" is a saturated carbocyclic ring radical. Preferred cycloalkyl groups include (for example) cyclopropyl, cyclobutyl and cyclohexyl.

"Heterocyclic ring" is an unsubstituted or substituted, saturated, unsaturated or aromatic ring radical comprised of

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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 atoms, preferably 3 to 6 atoms. Polycyclic rings contain from 7 to 17 atoms, preferably from 7 to 13 atoms.

"Aryl" is an aromatic carbocyclic ring radical. Preferred aryl groups include (for example) phenyl, tolyl, xylyl, cumenyl and naphthyl.

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

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

"Alkylamino" is an amino radical having one or two alkyl substituents (i.e., -N-alkyl).

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

"Arylamino" is an amine radical substituted with an aryl group (i.e., -NH-aryl).

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

"Acyl" or "carbonyl" is a radical formed by removal of the hydroxy from an carboxylic acid (i.e., R-C(=O)-). Preferred alkylacyl groups include (for example) acetyl, formyl, and priopionyl.

"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 (i.e., -N-acyl); for example, -NH-C(=O)-alkyl.

"Halo", "halogen", or "halide" is a chloro, bromo, fluoro or iodo atom radical. Chloro and fluoro are preferred halides.

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Also, as referred to herein, a "lower" hydrocarbon moiety (e.g., "lower" alkyl) is a hydrocarbon chain comprised of from 1 to 6, preferably from 1 to 4, 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) group. Many such salts are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein). Preferred cationic salts include the alkali metal salts (such as sodium and potassium), and alkaline earth metal salts (such as magnesium and calcium). Preferred anionic salts include the halides (such as chloride salts).

A "biohydrolyzable ester" is an ester of a quinolone thiourea that does not essentially interfere with the antimicrobial activity of the compounds, or that are readily metabolized by a human or lower animal subject to yield an antimicrobially-active quinolone thiourea. Such esters include those that do not interfere with the biological activity of quinolone antimicrobials. Many such esters are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987, (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 alkyl acylamino alkyl esters (such as acetamidomethyl esters).

As defined above and as used herein, substituent groups may themselves be substituted. Such substitution may be with one or more substituents. Such substituents include those listed in C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology (1979), incorporated by

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reference herein. Preferred substituents include (for example) alkyl, alkenyl, alkoxy, hydroxy, oxo, nitro, amino, aminoalkyl (e.g., aminomethyl, etc.), cyano, halo, carboxy, alkoxyaceyl (e.g., carboethoxy, etc.), thiol, aryl, cycloalkyl, heteroaryl, heterocycloalkyl (e.g., piperidinyl, morpholinyl, pyrrolidinyl, etc.), imino, thioxo, hydroxyalkyl, aryloxy, arylalkyl, and combinations thereof.

Also, as used in defining the structure of the compounds of this invention, a particular radical may be defined for use as a substituent in multiple locations. For example, the R^8 substituent is defined as a potential substituent of R^7, but is also incorporated into the definition of other substituents (such as R^1, and R^6). As used herein, such a radical is independently selected each time it is used (e.g., R^8 need not be alkyl in all occurrences in defining a given compound of this invention).

Groups A^1, A^2, A^3, R^1, R^3, R^4 and R^6 form any of a variety of quinolone, naphthyridine or related heterocyclic moieties known in the art to have antimicrobial activity. Such moieties are well known in the art, as described in the following articles, all incorporated by reference herein: J. Wolfson et al., "The Fluoroquinolones: Structures, Mechanisms of Action and Resistance, and Spectra of Activity In Vitro", 28 Antimicrobial Agents and Chemotherapy 581 (1985); and T. Rosen et al., 31 J. Med Chem. 1586 (1988); T. Rosen et al., 31 J. Med. Chem. 1598 (1988); G. Klopman et al., 31 Antimicrob. Agents Chemother. 1831 (1987); 31:1831-1840; J. P. Sanchez et al., 31 J. Med. Chem. 983 (1988); J. M. Domagalia et al., 31 J. Med. Chem. 991 (1988); M. P. Wentland et al., in 20 Ann. Rep. Med. Chem. 145 (D. M. Baily, editor, 1986); J. B. Cornett et al., in 21 Ann. Rep. Med. Chem. 139 (D. M. Bailey, editor, 1986); P. B. Fernandes et al., in 22 Ann. Rep. Med. Chem. 117 (D. M. Bailey, editor, 1987); R. Albrecht, 21 Prog. Drug Research 9 (1977); and P. B. Fernandes et al., in 23 Ann. Rep. Med. Chem. (R. C. Allen, editor, 1987).

Preferred quinolone moieties include those where A^1 is $C(R^7)$, and A^3 is $C(R^5)$ (i.e., quinolones); A^1 is nitrogen, and A^3 is $C(R^5)$ (i.e., naphthyridines); and where A^1 is $C(R^7)$, and A^3 is

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nitrogen (i.e., cinnoline acid derivatives). More preferred quinolone moieties are those where A^1 is $C(R^7)$, and A^3 is $C(R^5)$ (i.e., quinolones); and where A^1 is nitrogen, and A^3 is $C(R^5)$ (i.e., naphthyridines). Particularly preferred quinolone moieties are where A^1 is $C(R^7)$, and A^3 is $C(R^5)$ (i.e., quinolones).

R^1 is preferably alkyl, aryl, cycloalkyl and alkylamino. More preferably, R^1 is ethyl, 2-fluoroethyl, 2-hydroxyethyl, t-butyl, 4-fluorophenyl, 2,4-difluorophenyl, methylamino and cyclopropyl. Cyclopropyl is a particularly preferred R^1 group. Preferred quinolone moieties also include those where A^1 is $C(R^7)$ and R^1 and R^7 together comprise a 6-membered heterocyclic ring containing an oxygen or sulfur atom.

R^2 is preferably chlorine or fluorine. Fluorine is a particularly preferred R^2 group.

Preferred R^3 groups include nitrogen-containing heterocyclic rings. Particularly preferred are nitrogen-containing heterocyclic rings having from 5 to 8 members. The heterocyclic ring may contain additional heteroatoms, such as oxygen, sulfur, or nitrogen, preferably nitrogen. Such heterocyclic groups are described in U.S. Patent 4,599,334, Petersen et al., issued July 8, 1986; and U.S. Patent 4,670,444, Grohe et al., issued June 2, 1987 (both incorporated by reference herein). Preferred R^3 groups include unsubstituted or substituted pyridine, piperidine, morpholine, diazabicyclo[3.1.1]heptane, diazabicyclo[2.2.1]heptane, diazabicyclo[3.2.1]octane, diazabicyclo[2.2.2]octane, thiazolidine, imidazolidine, pyrrole and thiamorpholine, as well as the following particularly preferred R^3 groups include piperazine, 3-methylpiperazine, 3-aminopyrrolidine, 3-aminomethylpyrrolidine, N,N-dimethylaminomethylpyrrolidine, N-methylaminomethylpyrrolidine, N-ethylaminomethylpyrrolidine, pyridine, N-methylpiperazine and 3,5-dimethylpiperazine.

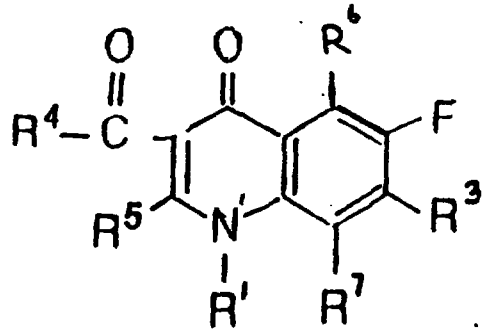
Preferred quinolone thioureas include those having a 6-fluoroquinolone moiety or an 8-halo-6-fluoroquinolone moiety, of formula:

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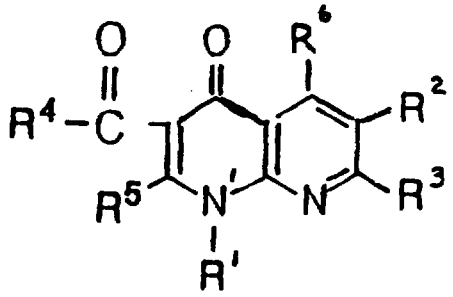
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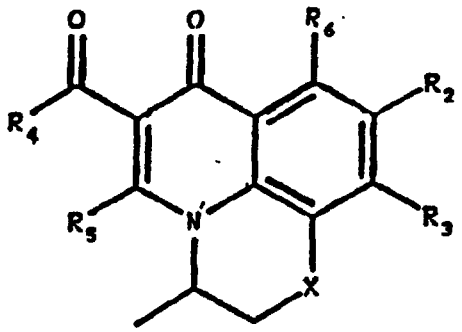
wherein, referring to formula (I), R^2 is F; A^3 is $C(R^5)$; and A^1 is $C(R^7)$ where R^7 is hydrogen, fluorine or chlorine.

Also preferred are quinolone thioureas having a 1,8-naphthyridine moiety, of formula:



wherein, referring to formula (I), A^1 is N; and A^3 is $C(R^5)$.

Also preferred are quinolone thioureas having a pyridobenzoxazine or pyridobenzthiazine moiety, of formula:

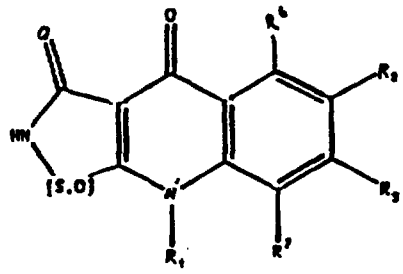


wherein, referring to formula (I), A^1 is $C(R^7)$; A^3 is $C(R^5)$; and R^7 and R^1 together comprise a linking moiety between N' and A^1 to

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form a 6-membered heterocyclic ring where X (in this formula) is oxygen or sulfur.

Also preferred are quinolone thioureas having an isothiazoloquinolinedione or isoxazoloquinolinedione moiety, of formula:



wherein, referring to formula (I), wherein A^1 is $C(R^7)$; A^3 is $C(R^5)$; and R^4 and R^5 together comprise a moiety forming a 5-membered, substituted, heterocyclic ring.

The compounds of this invention are also useful as intermediates in the synthesis of novel lactam-quinolones. Such compounds are disclosed in U.S. Patent Application Serial No. 416,645, filed October 10, 1989 (Norwich Eaton Case N-529R), incorporated by reference herein. Lactam-quinolones encompass any of a variety of lactam moieties linked, by a linking moiety, to a quinolone moiety at positions other than the 3-carboxy position.

Lactam-quinolones include compounds having the general structure:

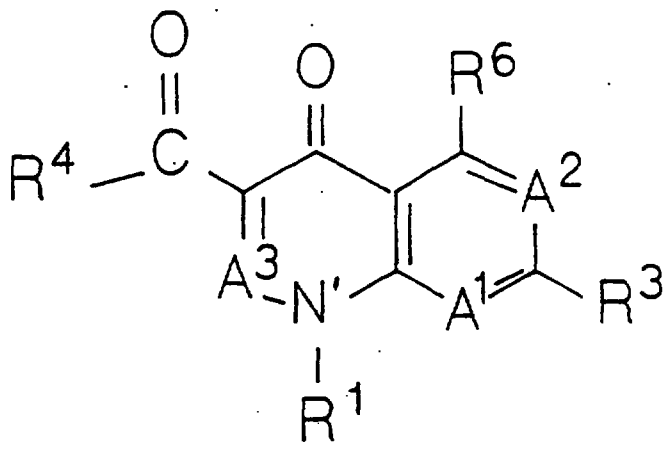
Q - L - B

wherein Q, L and B are defined as follows:

(I) Q is a structure according to Formula (I)

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(I) 

wherein

(A) (1) A^1 is N or $C(R^7)$; where

(i) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $N(R^8)(R^9)$ (preferably hydrogen or halogen), and

(ii) R^8 and R^9 are, independently, R^{8a}, where R^{8a} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring substituent; or R^8 and R^9 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is N or $C(R^2)$ (preferably $C(R^2)$); where R^2 is hydrogen or halogen;

(3) A^3 is N or (preferably) $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen or R^{15}, where R^{15} is (for this formula, only) alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or $N(R^8)(R^9)$ (preferably alkyl or a carbocyclic ring);

(5) R^3 is hydrogen, halogen, or R^{16}, where R^{16} (for this formula, only) is alkyl, a carbocyclic ring, or a heterocyclic ring (preferably a heterocyclic ring);

(6) R^4 is hydroxy; and

(7) R^6 is hydrogen, halogen, nitro, or $N(R^8)(R^9)$ (preferably hydrogen);

(B) except that

(1) when A^1 is $C(R^7)$, R^1 and R^7 may together comprise a heterocyclic ring including N' and A^1;

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(2) when A^2 is $C(R^2)$, R^2 and R^3 may together comprise $-O-(CH_2)_n-O-$, where n is an integer from 1 to 4;

(3) when A^3 is $C(R^5)$, R^4 and R^5 may together comprise a heterocyclic ring including the carbon atoms to which R^4 and R^5 are bonded and the carbon atom of Formula (I) to which said carbon atoms are bonded; and

(4) when A^3 is $C(R^5)$, R^1 and R^5 may together comprise a heterocyclic ring including N' and the adjacent carbon to which R^5 is bonded;

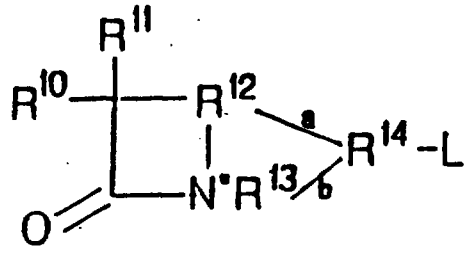
(C) and either

(1) R^1 is R^{15} and is a substituent moiety of L; or

(2) R^3 is R^{16} and is a substituent moiety of L;

(II) B is a structure according to Formula (II), where L is bonded to R^{14}:

(II)



wherein

(A) R^{10} is hydrogen, halogen, alkyl, alkenyl, heteroalkyl, a carbocyclic ring, a heterocyclic ring, $R^{8a}-O-$, $R^{8a}CH=N-$, $(R^8)(R^9)N-$, $R^{17}-C(=CHR^{20})-C(=O)NH-$, or (preferably) $R^{17}-C(=NO-R^{19})-C(=O)NH-$, or $R^{18}-(CH_2)_m-C(=O)NH-$; where

(1) m is an integer from 0 to 9 (preferably from 0 to 3);

(2) R^{17} is (for this formula, only) hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring (preferably alkyl, a carbocyclic ring, or a heterocyclic ring);

(3) R^{18} is (for this formula, only) R^{17}, $-Y^1$, or $-CH(Y^2)(R^{17})$;

(4) R^{19} is (for this formula, only) R^{17}, arylalkyl, heteroarylalkyl, $-C(R^{22})(R^{23})COOH$, $-C(=O)O-R^{17}$, or $-C(=O)NH-R^{17}$, where R^{22} and R^{23} are, independently, R^{17}

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or together comprise a carbocyclic ring or a heterocyclic ring including the carbon atom to which R^{22} and R^{23} are bonded (preferably R^{17} or $-C(R^{22})(R^{23})COOH$)

(5) R^{20} is R^{19}, halogen, $-Y^1$, or $-CH(Y^2)(R^{17})$ (preferably R^{19} or halogen);

(6) Y^1 is $-C(=O)OR^{21}$, $-C(=O)R^{21}$, $-N(R^{24})R^{21}$, or (preferably) $-S(O)_pR^{29}$ or $-OR^{29}$; and Y^2 is Y^1 or -OH, -SH, or $-SO_3H$;

(a) p is an integer from 0 to 2 (preferably 0);

(b) R^{24} is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbocyclic ring; a heterocyclic ring; $-SO_3H$; $-C(=O)R^{25}$; or, when R^{18} is $-CH(Y\text{-}R^{21})(R^{17})$, R^{24} may comprise a moiety bonded to R^{21} to form a heterocyclic ring; and

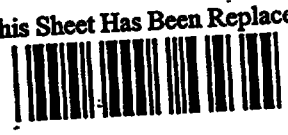
(c) R^{25} is R^{17}, $NH(R^{17})$, $N(R^{17})(R^{26})$, $O(R^{26})$, or $S(R^{26})$ (preferably R^{17}, $NH(R^{17})$ or $N(R^{17})(R^{26})$); where R^{26} is alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring or (preferably) when R^{25} is $N(R^{17})(R^{26})$, R^{26} may comprise a moiety bonded to R^{17} to form a heterocyclic ring; and

(7) R^{21} is R^{29} or hydrogen; where R^{29} is alkyl; alkenyl; arylalkyl; heteroalkyl; heteroalkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Y is $N(R^{24})$ and R^{21} is R^{29}, R^{21} and R^{24} may together comprise a carbocyclic ring or a heterocyclic ring including the nitrogen atom to which R^{29} is bonded (preferably hydrogen, alkyl, a carbocyclic ring or a heterocyclic ring);

(B) R^{11} is hydrogen, halogen, alkoxy, or $R^{27}C(=O)NH$- (preferably hydrogen or alkoxy), where R^{27} is hydrogen or alkyl (preferably hydrogen);

(C) bond "a" is a single bond or is nil; and bond "b" is a single bond, a double bond, or is nil; except bond "a" and bond "b" are not both nil;

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(D) R^{12} is $-C(R^{8a})-$, or $-CH_2-R^{28}-$ (preferably $-C(R^{8a})-$); where R^{28} is $-C(R^8)$, $-O-$, or $-N-$, and R^{28} is directly bonded to N" in Formula (II) to form a 5-membered ring;

except, if bond "a" is nil, then R^{12} is

(1) (preferably) $-C(R^{8a})(X^1)-$, where

(i) X^1 is $-R^{21}$; $-OR^{30}$; $-S(O)_rR^{30}$, where r is an integer from 0 to 2 (preferably 0); $-OC=O)R^{30}$; or $N(R^{30})R^{31}$; and

(ii) R^{30} and R^{31} are, independently, alkyl, alkenyl, carbocyclic ring or heterocyclic ring substituents; or R^{30} and R^{31} together comprise a heterocyclic ring including the nitrogen atom to which R^{30} and R^{31} are bonded; or

(2) $-CH_2-R^{32}-$; where R^{32} is $-C(R^8)(R^{21})$, $-O-$, or $-NR^8$, and R^{32} is directly bonded to N" in Formula (II) to form a 5-membered ring;

(E) (1) if bond "b" is a single bond, R^{13} is preferably $-CH(R^{33})-$; or, $-C(O)NHSO_2-$, if bond "a" is nil; or $-C^*(R^{33})-$, if R^{14} contains a R^{36} moiety; where R^{33} is hydrogen or COOH (preferably COOH), and C^* is linked to R^{36} to form a 3-membered ring;

(2) if bond "b" is a double bond, R^{13} is $-C(R^{33})=$; or

(3) if bond "b" is nil, R^{13} is hydrogen, $-SO_3H$, $-PO(OR^{34})OH$, $-C(O)NHSO_2N(R^{34})(R^{35})$, $-OSO_3H$, $-CH(R^{35})COOH$, or $-OCH(R^{34})COOH$ (preferably $-SO_3H$, or $-C(O)NHSO_2N(R^{34})(R^{35})$; where R^{34} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and R^{35} is hydrogen, alkyl, alkenyl, or $-NHR^{8a}$; or (preferably), if R^{13} is $-C(O)NHSO_2N(R^{34})(R^{35})$, R^{34} and R^{35} may together comprise a heterocyclic ring including the nitrogen to which R^{34} and R^{35} are bonded; and

(F) (1) if bond "a" or bond "b" is nil, then R^{14} is nil and L is bonded directly to R^{12} or R^{13};

(2) if bond "a" and "b" are single bonds, R^{14} is $-W-C"'=C(R^{8a})-R^{37}-$, or $-W-C"'(R^{36})-R^{37}-$; or

(3) (preferably) if bond "a" is a single bond and bond "b" is a double bond, R^{14} is $-C(R^{8a})(R^{38})-W-C"'-R^{37}-$; or

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(preferably) -W-C(R^{8a})(R^{38})-C"'-R^{37}-, or -W-C"'-R^{37}-; where

(a) W is O; $S(O)_s$, where s is an integer from 0 to 2 (preferably 0); or C(R^{38}), where R^{38} is hydrogen, alkyl or alkoxy;

(b) R^{36} hydrogen; alkyl; alkenyl; -COOH; or, if R^{13} is -C*(R^{33}), R^{36} may be linked to C* to form a 3-membered carbocyclic ring;

(c) R^{37} is nil, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and

(d) C"' is directly bonded to R^{13} to form a 5- or 6-membered ring,

and

(III) L links Q to B; and L is L', -X^2_r-R^{39}-L', or -X^3_r-R^{39}-L'; where L' is -X^4-C(=Y^3)-Z-Q";

(1) R^{39} is alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring (preferably alkyl or alkenyl);

(2) X^2 is oxygen, or $S(O)_v$, where v is an integer from 0 to 2 (preferably 0);

(3) X^3 is nitrogen; N(R^{40}); N$^+$(R^{41})(R^{42}); or R^{43}-N(R^{41}); and is linked to R^{14} by a single or double bond; or, if R^{14} is nil, X^3 is linked to B by a single or double bond (preferably X^3 is nitrogen, N(R^{40}) or N$^+$(R^{41})(R^{42})); where

(a) R^{40} is R^{8a}; -OR^{8a}; or -C(=O)R^{8a}; (preferably R^8);

(b) R^{41} and R^{42} are, independently, hydrogen; alkyl; alkenyl; carbocyclic rings; heterocyclic rings; or, (preferably) together with Q", comprise a heterocyclic ring as R^{15} or R^{16};

(c) R^{43} is N(R^{41}), oxygen or sulfur;

(4) X^4 is sulfur;

(5) Y^3 is N$^+$(R^{41})(R^{42});

(6) Z is nitrogen;

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(7) Q" is R^{15} or R^{16}; or together with Z, is an R^{15} or R^{16} group;

and pharmaceutically-acceptable salts and biohydrolyzable esters thereof, and hydrates thereof.

Preferred lactam-containing moieties include cephems, isocephems, iso-oxacephems, oxacephems, carbacephems, penicillins, penems, carbapenems, and monocyclic beta-lactams. Particularly preferred are cephems, penems, carbapenems and monocyclic beta-lactams.

R^{10}, in formula (II), is any radical that may be substituted at the active stereoisomeric position of the carbon adjacent to the lactam carbonyl of an antimicrobially-active lactam. (As used herein, the term "antimicrobially-active lactam" refers to a lactam-containing compound, without a quinolonyl substituent moiety, which has antimicrobial activity.) This "active" position is beta (i.e., 7-beta) for cephems, oxacephems and carbacephems (for example). The active position is alpha for penems, carbapenems, clavems and clavams. Appropriate R^{10} groups will be apparent to one of ordinary skill in the art.

Procedures for preparing quinolones and quinolone intermediates useful in the methods of this invention are described in the following references, all incorporated by reference herein (including articles listed within these references); 21 Progress in Drug Research, 9-104 (1977); 31 J. Med. Chem., 503-506 (1988); 32 J. Med. Chem., 1313-1318 (1989); 1987 Liebigs Ann. Chem., 871-879 (1987); 14 Drugs Exptl. Clin. Res., 379-383 (1988); 31 J. Med. Chem., 983-991 (1988); 32 J. Med. Chem., 537-542 (1989); 78 J. Pharm. Sci., 585-588 (1989); 26 J. Het. Chem., (1989); 24 J. Het. Chem., 181-185 (1987); U.S. Patent 4,599,334, 35 Chem. Pharm. Bull., 2281-2285 (1987); 29 J. Med. Chem., 2363-2369 (1986); 31 J. Med. Chem., 991-1001 (1988); 25 J. Het. Chem., 479-485 (1988); European Patent Publication 266,576; European Patent Publication 251,308, 36 Chem. Pharm. Bull., 1223-1228 (1988); European Patent Publication 227,088; European Patent Publication 227,039; European Patent Publication 228,661; 31

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J. Med. Chem., 1586-1590 (1988); 31 J. Med. Chem., 1598-1611 (1988); and 23 J. Med. Chem., 1358-1363 (1980).

In general, quinolone thioureas can be prepared by the following procedure:

Quin-NH + XC(=S)Y ---> [Quin-NC(=S)X] + RR'NH ---> QuinNC(=S)NRR'

where X and Y are reactive leaving groups (such as halo or an activated ester or anhydride) and Quin-NH represents an appropriately protected, amino-containing quinolone. The reaction sequence can be envisioned as acylation of the quinolone amino substituent with thiophosgene or equivalent synthon, followed by the subsequent addition of an amino containing nucleophile to form the quinolone thiourea. Alternatively, quinolone thioureas can be prepared by the following procedure:

Quin-NH + S=C=NR ---> Quin-NC(=S)NHR

where S=C=NR is an appropriately substituted isothiocyanate and Quin-NH represents an appropriately protected, amino-containing quinolone. The reaction sequence involves the acylation of the quinolone amino substituent with the isothiocyanate or equivalent synthon to form the quinolone thiourea.

Compositions

The compositions of this invention comprise:

(a) a safe and effective amount of a quinolone thiourea; and

(b) a pharmaceutically-acceptable carrier.

A "safe and effective amount" of a quinolone thiourea is an amount that is effective, to inhibit microbial growth at the site of an infection to be treated in a human or lower animal subject, 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.

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The specific "safe and effective amount" will, obviously, 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 carrier employed, the solubility of the quinolone thiourea 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 thiourea 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 to about 20,000 mg, more preferably from about 50 mg (milligrams) to about 7000 mg, more preferably from about 500 mg to about 3500 mg, of a quinolone thiourea.

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 carriers 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 thiourea. The amount of carrier employed in conjunction with the quinolone thiourea is sufficient to provide a practical quantity of material for administration per unit dose of the quinolone thiourea. 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: 7 Modern Pharmaceutics, 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).



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In particular, pharmaceutically-acceptable carriers 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 carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight by the total composition.

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 thiourea. 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. Preferred carriers 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 thiourea. Suitable carriers for topical administration preferably remain in place on the skin as

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a continuous film, and resist being removed by perspiration or immersion in water. Generally, the carrier is organic in nature and capable of having dispersed or dissolved therein the quinolone thiourea. The carrier may include pharmaceutically-acceptable emolients, emulsifiers, thickening agents, and solvents.

Methods of Administration

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 thiourea 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, genitourinary infections, gastrointestinal infections, gynecological infections, septicemia, bone and joint infections, skin and skin structure infections, bacterial endocarditis, burns, antibacterial prophylaxis of surgery, and antibacterial prophylaxis in immunosuppressed patients (such as patients receiving cancer chemotherapy, or organ transplant patients).

The quinolone thioureas and compositions of this invention can be administered topically or systemically. Systemic application includes any method of introducing the quinolone thiourea 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

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upon such factors as the specific quinolone thiourea used, the resistance pattern of the infecting organism to the quinolone thiourea used, the ability of the quinolone thiourea 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, 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 to about 30,000 mg, more preferably from about 100 mg to about 20,000 mg, more preferably from about 500 mg to about 3500 mg, of quinolone thiourea are administered per day. Treatment regimens preferably extend from about 1 to about 56 days, preferably from about 7 to about 28 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 systemic administration is oral. Individual doses of from about 100 mg to about 2500 mg, preferably from about 250 mg to about 1000 mg are preferred.

Topical administration can be used to deliver the quinolone thiourea systemically, or to treat a local infection. The amounts of quinolone thiourea to be topically administered depends upon such factors as skin sensitivity, type and location of the tissue to be treated, the composition and carrier (if any) to be administered, the particular quinolone thiourea 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.

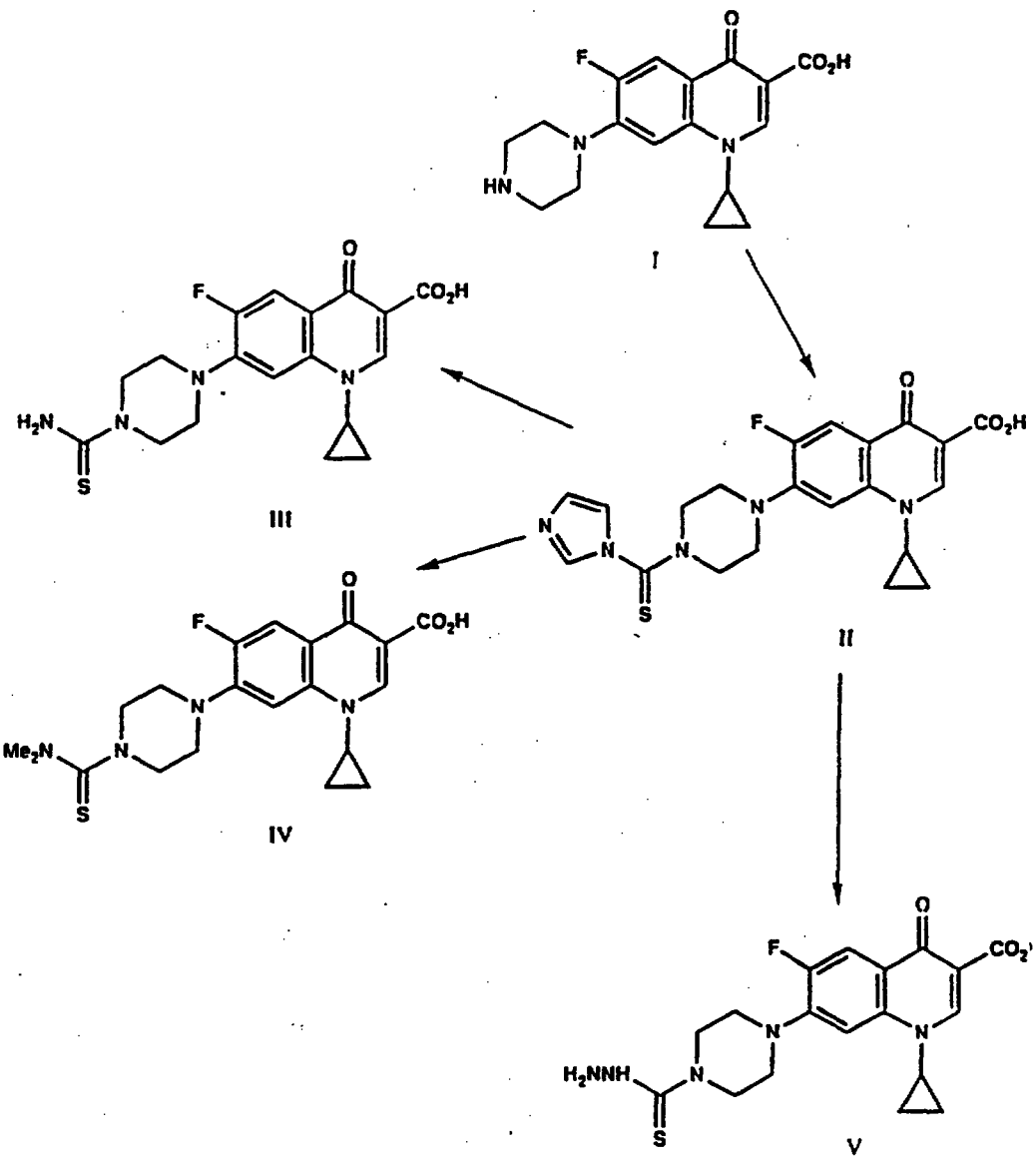
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EXAMPLE 1

Quinolone thioureas are made according to the following general procedure.



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Specifically, 7-(4-aminothioxomethyl-1-piperazinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (Compound III) is made by slowly adding 10.0 gm of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinoline-3-carboxylic acid (Compound I, prepared according to K. Grohe, et al., US Patent 4,670,444 (1987)) to a solution of 6.57 gm 1,1'-thiocarbonyl di-imidazole (90%) in approximately 300 ml DMF, at about 0°C. After 1 hr, a heavy precipitate is collected by filtration. The resultant solid is triturated in ether, filtered and dried in vacuo at room temperature to yield 11.68 gm Compound II.

Compound II (7.0 gm) is added at about 0°C to a saturated solution of ammonia in DMF (140 ml) and the reaction is allowed to warm to room temperature. Stirring is continued overnight. A precipitate forms which is collected and dried at about 100°C in vacuo to yield 4.55 gm Compound III.

Similarly, 1-cyclopropyl-7-[4-[(dimethylamino)-thioxomethyl]-1-piperazinyl]-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (Compound IV) is made, in 95% yield, from Compound II under similar conditions as for the synthesis of Compound III, using a saturated dimethylamine/DMF solution.

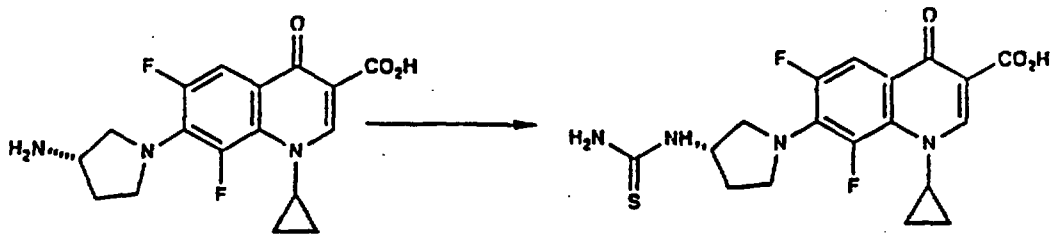
Similarly, 1-cyclopropyl-6-fluoro-7-[4-(hydrazinothioxomethyl)-1-piperazinyl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (Compound V) is made, in 85% yield, from Compound II under similar conditions as for the synthesis of Compound III, using approximately a 20-fold excess of hydrazine monohydrate in a DMF solution.

EXAMPLE 2

7-[3-(aminothioxomethyl)amino-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (Compound II) is made according to the following general procedure.

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I II

To a solution of 6.23 gm 1,1'-thiocarbonyl di-imidazole (90%) in approximately 300 ml DMF is slowly added 10.0 gm 7-(3-amino-1-pyrollidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (Compound I, prepared according to J.P. Sanchez, et al., 31 J. Med. Chem. 983-991 (1988)) at about 0°C. After 3 hr, the reaction mixture is transferred in portions at about 0°C to a saturated solution of ammonia in DMF (140 ml) and the reaction is allowed to warm to room temperature. Stirring is continued overnight. The resulting precipitate is collected by filtration and dried in vacuo to yield 6.82 gm Compound II.

EXAMPLE 3

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

Component	Amount (mg)
compound (III) of Example 1	350.0
starch	30.0
magnesium stearate	5.0
microcrystalline cellulose	100.0
colloidal silicon dioxide	2.5
povidone	12.5
flavor	5.0

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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 14 days. Symptoms of the disease then subside, indicating substantial eradication of the pathogen.

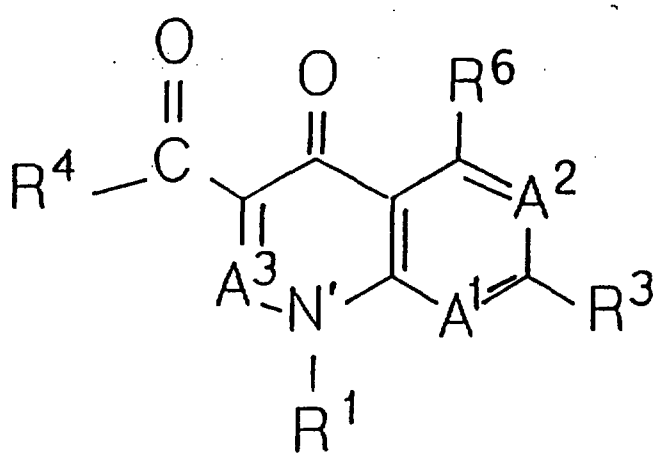
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What is claimed is:

1. Compounds of the general structure:



wherein

(A) (1) A^1 is N or $C(R^7)$; where

(i) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $N(R^8)(R^9)$, and

(ii) R^8 and R^9 are, independently, R^{8a}; where R^{8a} is hydrogen, alkyl, alkenyl, carbocyclic ring, or heterocyclic ring substituents; or R^8 and R^9 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is $C(R^2)$; where R^2 is hydrogen or halogen;

(3) A^3 is N or $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, $N(R^8)(R^9)$, or X;

(5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, a heterocyclic ring, or X;

(6) R^4 is hydroxy; and

(7) R^6 is hydrogen, alkyl, halogen, nitro, $N(R^8)(R^9)$, or $S(R^{8a})$;

(B) except that

(1) when A^1 is $C(R^7)$, R^1 and R^7 may together comprise a heterocyclic ring including N' and A^1;

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(2) R^2 and R^3 may together comprise -O-$(CH_2)_n$-O-, where n is from 1 to 4;

(3) when A^3 is $C(R^5)$, R^4 and R^5 may together comprise a heterocyclic ring including the carbon atoms to which R^4 and R^5 are bonded and the carbon atom of Formula (I) to which said carbon atoms are bonded; and

(4) when A^3 is $C(R^5)$, R^1 and R^5 may together comprise a heterocyclic ring including N' and the adjacent carbon to which R^5 is bonded;

(C) and

(1) R^1 is X, R^3 is X, or both R^1 and R^3 are X; and

(2) X is $-R^{15}-N(R^{16})(R^{17})$ or $-R^{15}-R^{18}-N(R^{19})(R^{17})$, where

(a) (1) R^{15} is nil, alkyl, a carbocyclic ring, or a heterocyclic ring; and

(2) R^{16} is hydrogen; alkyl; alkenyl; a carbocyclic ring; a heterocyclic ring; or

(3) when X is $R^{15}-N(R^{16})(R^{17})$, R^{16} and R^{15} may together comprise a heterocyclic ring including the nitrogen atom to which R^{15} and R^{16} are bonded;

(b) R^{17} is $C(=S)-NR^{20}R^{21}$; where R^{20} is hydrogen, alkyl, alkenyl, a carbocyclic ring or a heterocyclic ring; and R^{21} is R^{20} or $N(R^{20})(R^{20})$; or R^{20} and R^{21}, together with the nitrogen to which they are bonded, form a heterocyclic ring; and

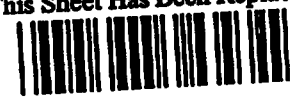
(c) (1) R^{18} is alkyl, a carbocyclic ring, or a heterocyclic ring; and

(2) R^{19} is hydrogen; alkyl; alkenyl; a carbocyclic ring; a heterocyclic ring; or

(3) R^{18} and R^{19} may together comprise a heterocyclic ring including the nitrogen atom to which R^{18} and R^{19} are bonded;

and pharmaceutically-acceptable salts and biohydrolyzable esters thereof, and hydrates thereof.

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2. A compound according to Claim 1, wherein: A^1 is nitrogen or $C(R^7)$, preferably nitrogen, and A^3 is $C(R^5)$.

3. A compound, according to Claim 2, wherein R^1 is alkyl, aryl, cycloalkyl or alkylamino, preferably ethyl, 2-fluoroethyl, 2-hydroxyethyl, t-butyl, 4-fluorophenyl, 2,4-difluorophenyl, methylamino or cyclopropyl; and R^7 is hydrogen or halogen, preferably hydrogen, chlorine or fluorine.

4. A compound, according to Claim 3, wherein R^3 is X.

5. A compound, according to Claim 4, wherein X is $-R^{15}-N(R^{16})(R^{17})$; R^{16} is hydrogen; and R^{15} is a heterocyclic ring, preferably pyrrolidine.

6. A compound, according to Claim 4, wherein X is $-R^{15}-N(R^{16})(R^{17})$; and R^{16} and R^{15} together comprise a heterocyclic ring including the nitrogen atom to which R^{15} and R^{16} are bonded.

7. A compound, according to Claim 6, wherein said heterocyclic ring is is piperazine, 3-methylpiperazine, or 3,5-dimethylpiperazine, preferably piperazine.

8. A compound, according to Claim 3, wherein X is $-R^{15}-R^{18}-N(R^{19})(R^{17})$; R^{18} is alkyl; and R^{15} is a heterocyclic ring.

9. A compound, according to any of Claims 2 through 8, wherein R^1 is cyclopropyl, and R^2 is fluorine.

10. A composition for treating or preventing an infectious disorder in a human or other animal subject, comprising:

(1) a safe and effective amount of a compound of any of Claims 1 through 9; and

(2) a pharmaceutically-acceptable carrier.

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11. The use, for the manufacture of a medicament for preventing or treating an infectious disorder in a human or other animal subject, of a compound of any of Claims 1 through 9.

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