

Antimicrobial 5-hydrazino-quinolone derivatives

5

BACKGROUND OF THE INVENTION

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

10 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),
15 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,
20 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
25 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
30 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. On the other hand, quinolones act by inhibiting synthesis of bacterial DNA, thus
35 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).

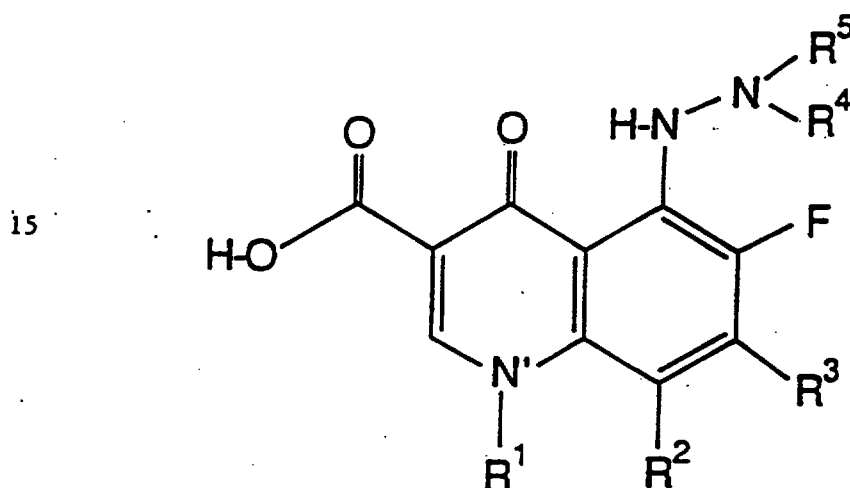
However, many such attempts to produce improved antimicrobials have produced equivocal results. Indeed, few antimicrobials are developed that are truly clinically-acceptable in terms of their spectrum of antimicrobial activity, avoidance of microbial resistance, and pharmacology. For example, the quinolones 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
 5 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

10 The present invention provides compounds of the general structure:



wherein

- 20 (A){1}(a) R¹ is alkyl; alkenyl; a carbocyclic ring; a heterocyclic ring; or -N(R⁶)(R⁷), where R⁶ and R⁷ are, independently, hydrogen, alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or R⁶ and R⁷ together comprise a heterocyclic ring that
 25 includes the nitrogen to which they are bonded; and
- (b) R² is hydrogen, halogen, lower alkyl, or lower alkoxy; or
- (2) R¹ and R² may together comprise a six-membered
 30 heterocyclic ring that includes N' and the carbon atom to which R² is bonded;
- (B) R³ is a heterocyclic ring or a carbocyclic ring; and



(C)(1) R⁴ and R⁵ are, independently, hydrogen; lower alkyl; cycloalkyl; heteroalkyl; or -C(=O)-X-R⁸, where X is a covalent bond, N, O, or S, and R⁸ is lower alkyl, lower alkenyl, arylalkyl, a carbocyclic ring, or a heterocyclic ring; or

(2) R⁴ and R⁵ together comprise a heterocyclic ring that includes the nitrogen to which they are bonded;

and pharmaceutically-acceptable salts and biohydrolyzable esters thereof, and solvates 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. Applicants have also discovered that, surprisingly, compounds of this invention offer significantly increased water solubility at physiological pH in comparison to related antimicrobials known in the art. This surprising property may allow for, among other things, improved pharmacology, including increased serum levels upon administration, ease of formulation, and a more flexible dosing regimen.

DESCRIPTION OF THE INVENTION

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

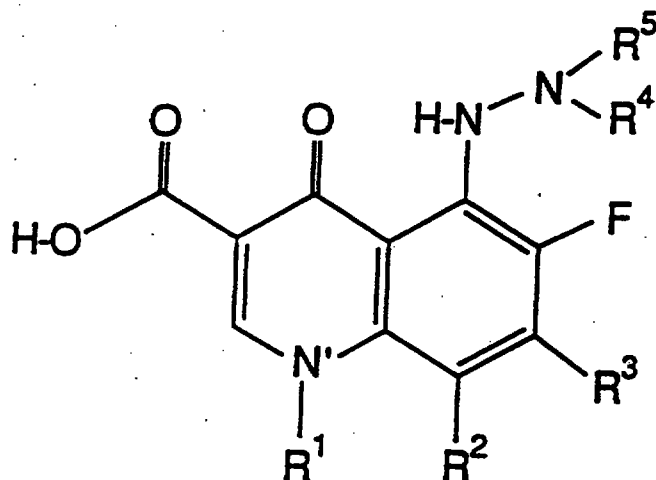
5-(N-heterosubstituted amino) quinolones

The compounds of this invention, herein referred to as "5-(N-heterosubstituted amino) quinolones", encompass any of a variety of quinolones (and related heterocyclic moieties) having an N-heteroamino substituent at the 5-position of the quinolone moiety.

The 5-(N-heterosubstituted amino) quinolones of this invention include compounds of the general structure:

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wherein

(A)(1)(a) R^1 is alkyl; alkenyl, a carbocyclic ring; a heterocyclic ring; or $-N(R^6)(R^7)$ (preferably alkyl or a carbocyclic ring), where R^6 and R^7 are, independently, hydrogen, alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or R^6 and R^7 together comprise a heterocyclic ring that includes the nitrogen to which they are bonded; and

(b) R^2 is hydrogen, halogen, lower alkyl, or lower alkoxy (preferably halogen); or

(2) (Preferably) R^1 and R^2 may together comprise a six-membered heterocyclic ring that includes N' and the carbon atom to which R^2 is bonded;

(B) R^3 is a heterocyclic ring or a carbocyclic ring (preferably a heterocyclic ring); and

(C)(1) R^4 and R^5 are, independently, hydrogen; lower alkyl; cycloalkyl; heteroalkyl; or $-C(=O)-X-R^8$ (preferably hydrogen or lower alkyl), where X is a covalent bond, N, O, or S, and R^8 is lower alkyl, lower alkenyl, arylalkyl, a carbocyclic ring, or a heterocyclic ring; or

(2) (Preferably) R^4 and R^5 together comprise a heterocyclic ring that includes the nitrogen to which they are bonded;

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

Definitions and Usage of Terms:

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

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

10 "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.

15 "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 (including, for example, vinyl, allyl and butenyl).

20 "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.

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

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

35 "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.

5 "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.

10 "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).

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

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

20 "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.

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

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.

30 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
35 (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).

5 A "biohydrolyzable ester" is an ester of a 5-(N-hetero-substituted amino) quinolone that does not essentially interfere with the antimicrobial activity of the compounds, or that are readily converted *in vivo* by a human or lower animal subject to yield an antimicrobially-active 5-(N-heterosubstituted amino) quinolone. Such esters include those that do not interfere with the biological activity of quinolone antimicrobials. Many such
10 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
15 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
20 acetamidomethyl esters).

A "solvate" is a complex formed by the combination of a solute (e.g., a 5-(N-heterosubstituted amino) quinolone) and a solvent (e.g., water). See J. Honig et al., The Van Nostrand Chemist's Dictionary, p. 650 (1953). Pharmaceutically-acceptable
25 solvents used according to this invention include those that do not interfere with the biological activity of the quinolone antimicrobials (e.g., water, ethanol, acetic acid, N,N-dimethylformamide).

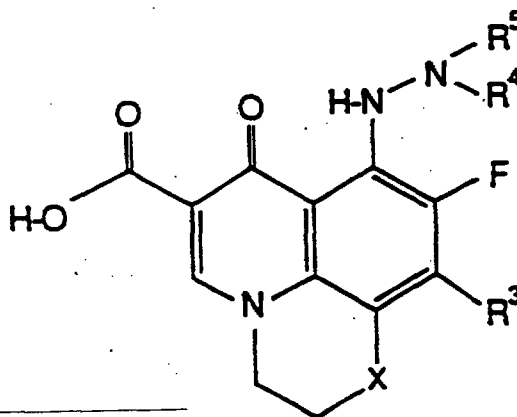
As defined above and as used herein, substituent groups may
30 themselves be substituted. Such substitution may be with one or more substituents. Such substituents include those listed in C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology (1979), incorporated by reference herein. Preferred substituents include (for example)
35 alkyl, alkenyl, alkoxy, hydroxy, oxo, nitro, amino, aminoalkyl (e.g., aminomethyl, etc.), cyano, halo, carboxy, alkoxyacyl (e.g., carboethoxy, etc.), thiol, aryl, cycloalkyl, heteroaryl, heterocycloalkyl (e.g., piperidinyl, morpholinyl, pyrrolidinyl,



etc.), imino, thioxo, hydroxyalkyl, aryloxy, arylalkyl, and combinations thereof.

Groups R^1 , R^2 , and R^3 form any of a variety of quinolone 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).

R^1 is preferably alkyl, alkenyl, aryl, cycloalkyl, a heterocyclic ring, or alkylamino. More preferably, R^1 is ethyl, 2-fluoroethyl, 2-hydroxyethyl, t-butyl, 4-fluorophenyl, 2,4-difluorophenyl, methylamino, 3-oxetanyl, 2-fluorocyclopropyl, bicyclo [1.1.1] pentane, vinyl, or cyclopropyl. Cyclopropyl, 2-fluorocyclopropyl, t-butyl, 2-fluorocyclopropyl, and 2,4-difluorophenyl are particularly preferred R^1 groups. Preferred 5-(N-heterosubstituted amino) quinolones also include those where R^1 and R^2 together comprise a 6-membered heterocyclic ring, according to the formula:



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where X is O, S, or CH₂.

R² is preferably chlorine, fluorine, methoxy, or methyl. Fluorine and chlorine are particularly preferred R² groups.

Preferred R³ 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 R³ 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, imidazolidine, and 5-amino-3-azabicyclo[4.2.0]heptane, as well as particularly preferred R³ groups which include piperazine, 3-methylpiperazine, 3-aminopyrrolidine, 3-aminomethylpyrrolidine, N,N-dimethylaminomethylpyrrolidine, N-ethylaminomethylpyrrolidine, 3,5-dimethylpyridine, N-methylpiperazine and 3,5-dimethylpiperazine.

Preferred R⁴ and R⁵ groups include those where R⁴ and R⁵ together comprise a heterocyclic ring containing the nitrogen atom to which they are bonded, those where both R⁴ and R⁵ are lower alkyl, those where one of R⁴ or R⁵ is hydrogen and the other is lower alkyl, and those where both R⁴ and R⁵ are hydrogen. More preferred groups are where one of R⁴ or R⁵ is hydrogen and the other is alkyl and those where both R⁴ and R⁵ are hydrogen. Particularly preferred groups are where both R⁴ and R⁵ are hydrogen.

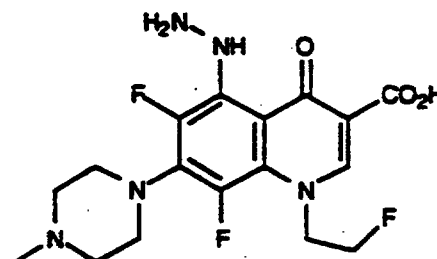
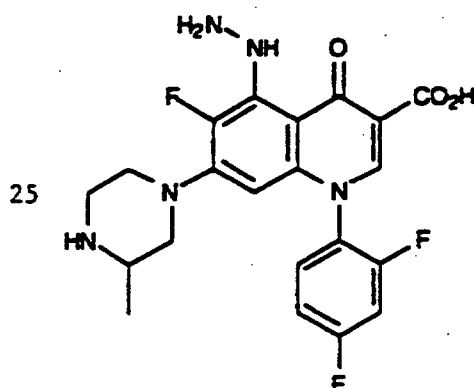
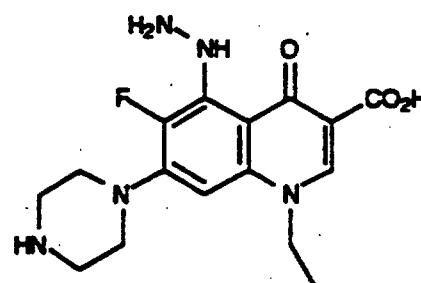
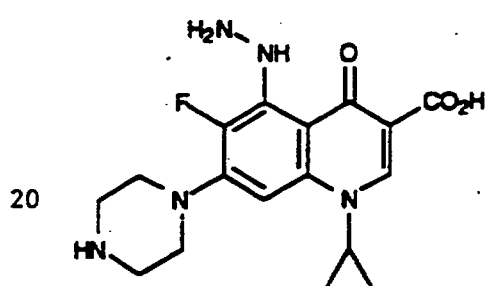
Preferred compounds of the present invention include those having both an R³ group that contains a basic nitrogen atom (including, for example, pyridine, piperidine, diazabicyclo[3.1.1]heptane, diazabicyclo[2.2.1]heptane, diazabicyclo[3.2.1]octane, diazabicyclo[2.2.2]octane, and imidazolidine) and R⁴ and R⁵ groups that allow the nitrogen atom to which they are bonded to be basic (including, e.g., where R⁴ and R⁵ together comprise a heterocyclic ring containing the nitrogen to which they



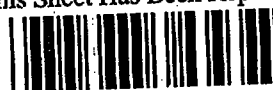
are bonded, both R^4 and R^5 are lower alkyl, one of R^4 and R^5 are lower alkyl and the other is hydrogen, or both R^4 and R^5 are hydrogen). Particularly preferred compounds are those where the R^3 group is one of piperazine, 3-methylpiperazine, 3-amino-
5 pyrrolidine, 3-aminomethylpyrrolidine, N,N-dimethylamino-
pyrrolidine, N-ethylaminomethylpyrrolidine, N-methylpiperazine, or 3,5-dimethylpiperazine; and both R^4 and R^5 are hydrogen.

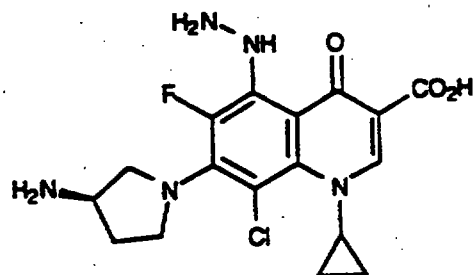
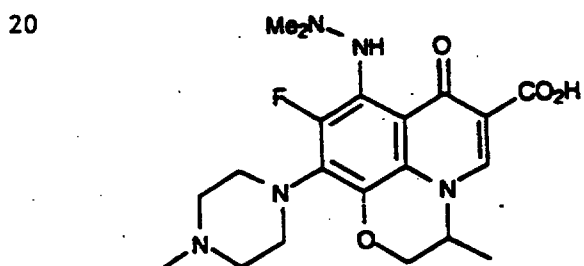
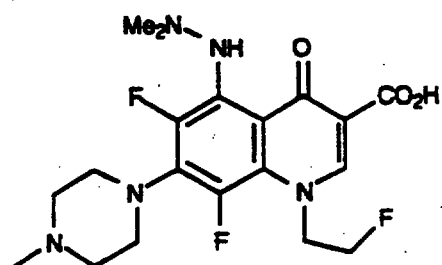
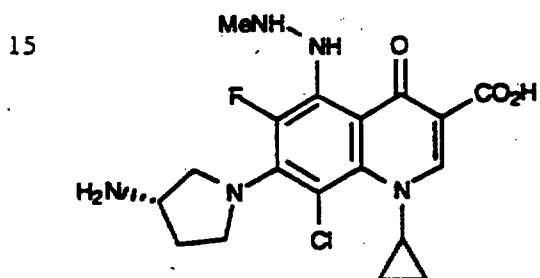
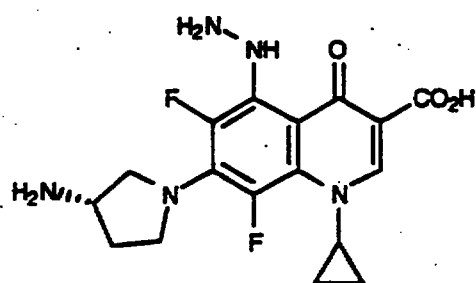
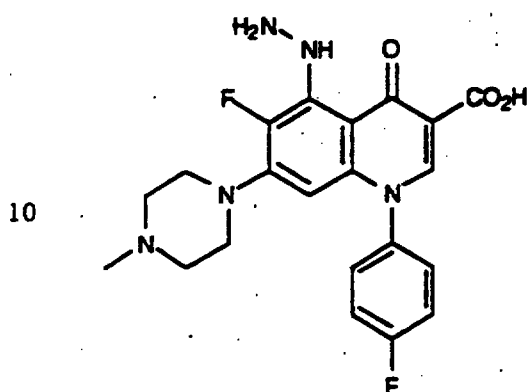
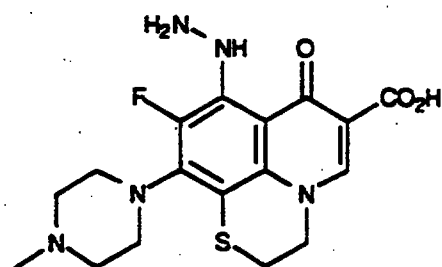
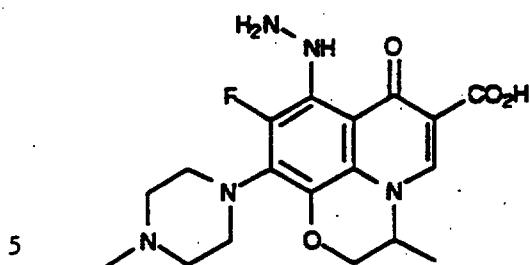
As used herein, a "basic nitrogen atom" is one where the nitrogen atom possesses a lone pair of electrons that can be
10 involved in ionic bonding with any of a variety of cations. It is understood in the art that the basicity of a nitrogen atom of a given moiety will depend on the nature of that nitrogen atom's covalent bonding. See, e.g., A. Streitwieser and C. Heathcock, Introduction to Organic Chemistry, 2d edition, pp. 734-40 (1981),
15 incorporated by reference herein.

Preferred 5-(N-heterosubstituted amino) quinolones include:



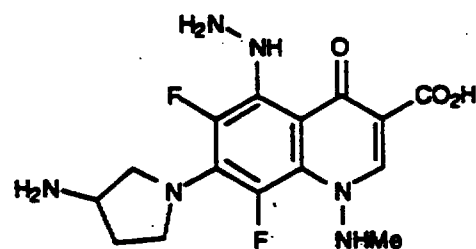
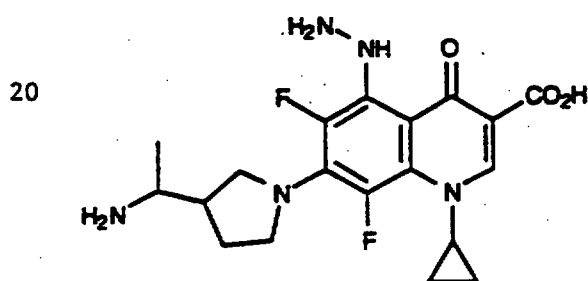
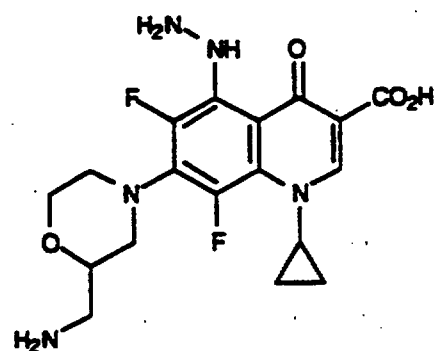
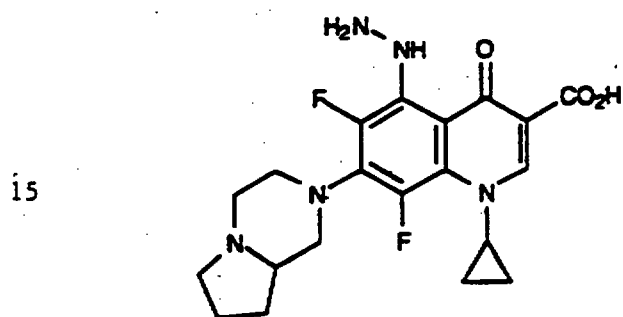
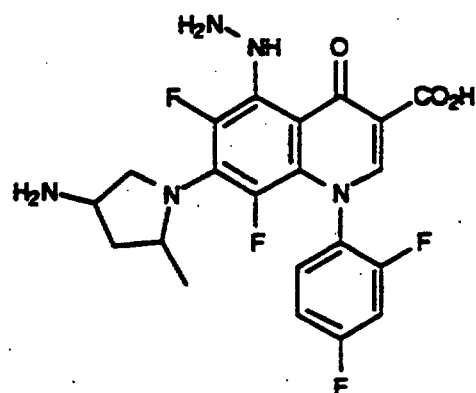
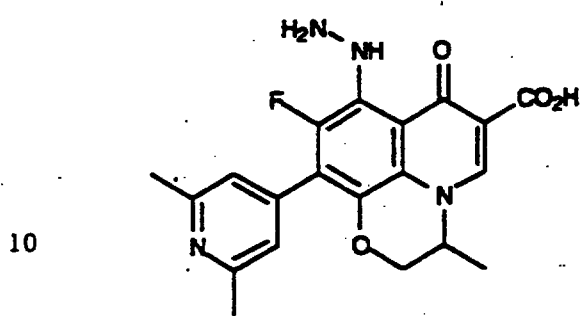
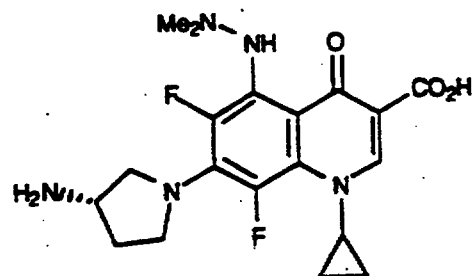
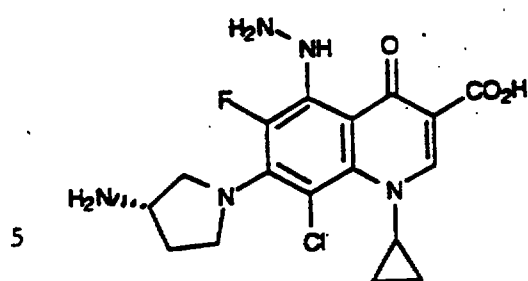
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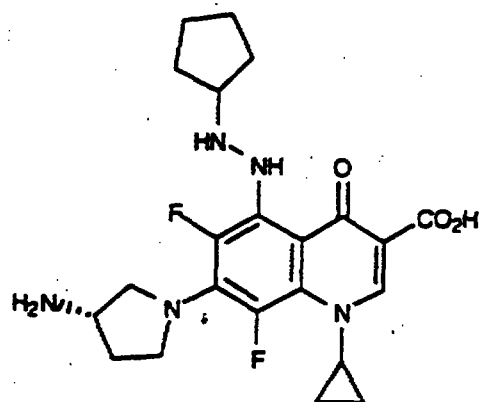
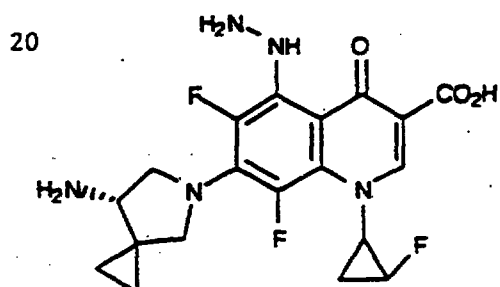
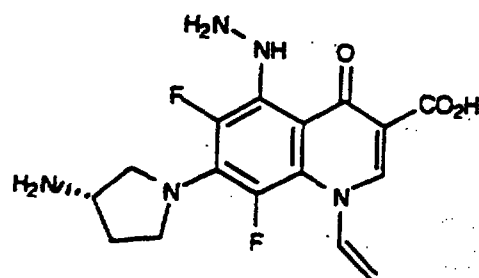
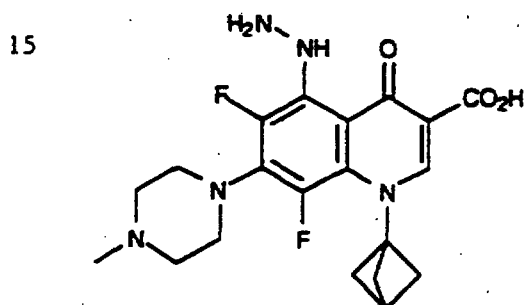
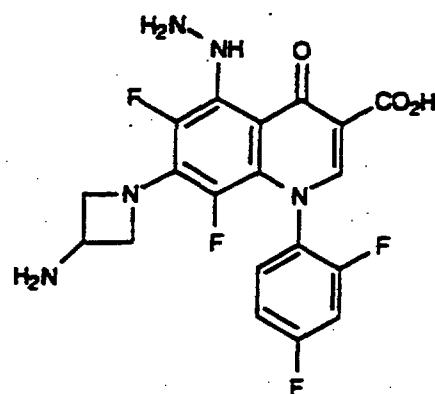
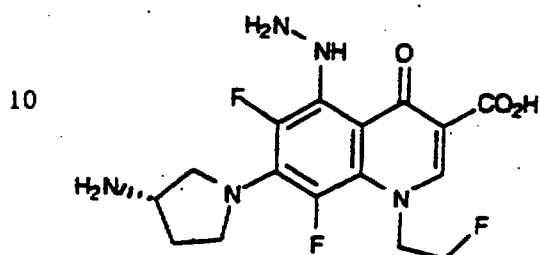
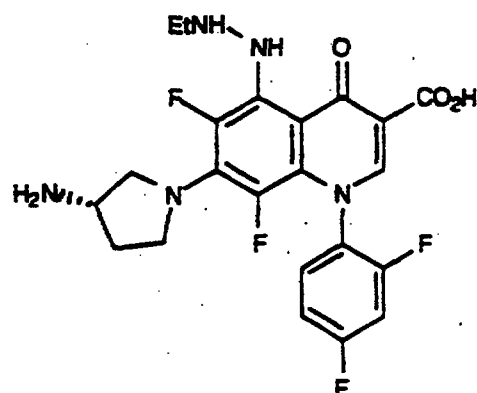
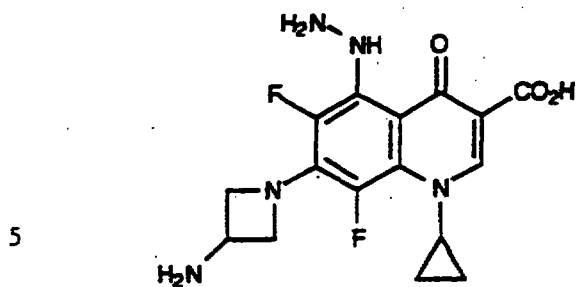
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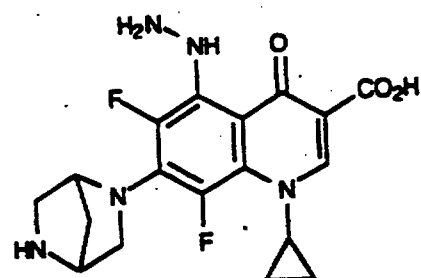
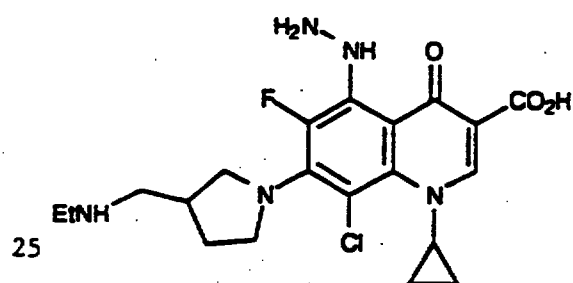
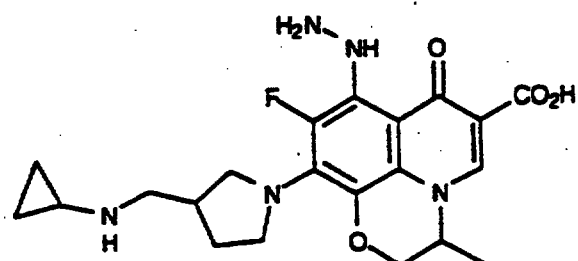
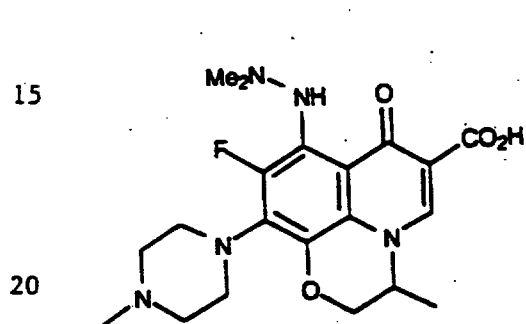
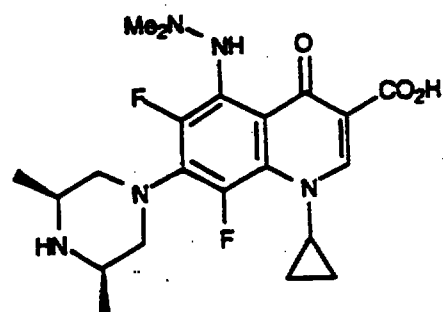
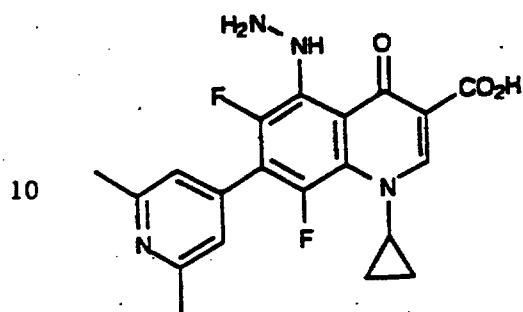
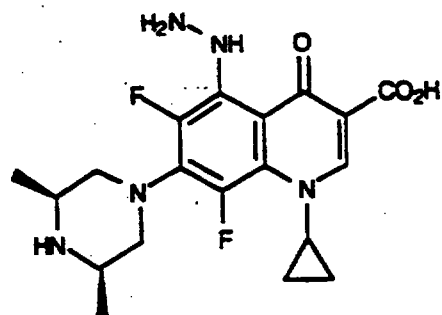
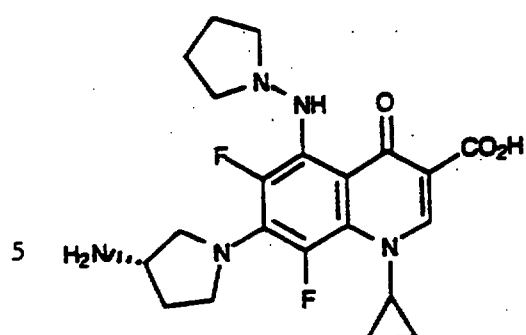
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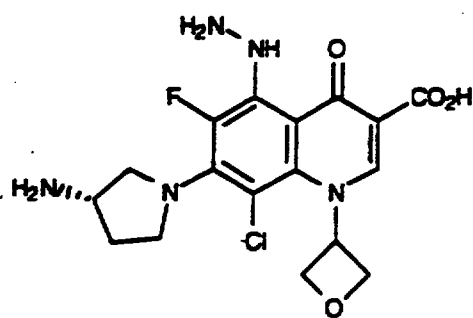




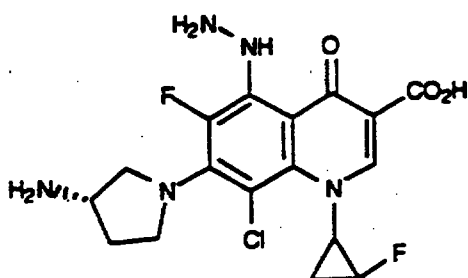
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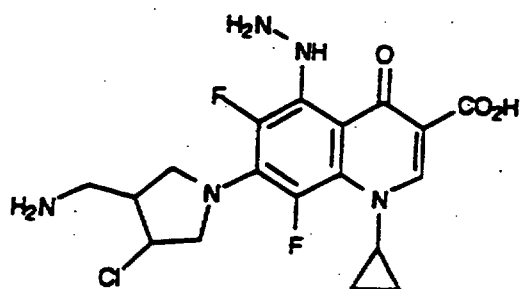
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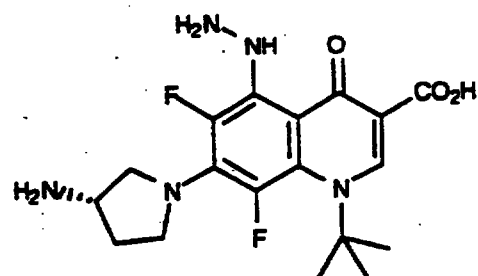
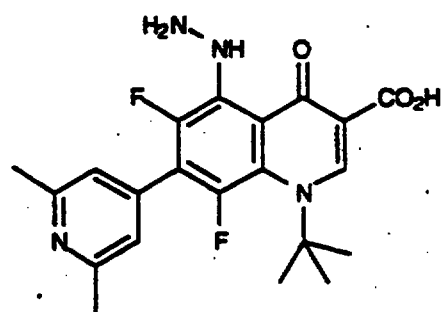
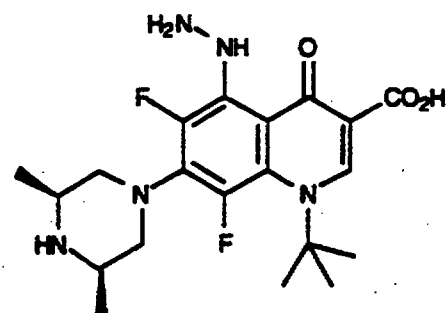
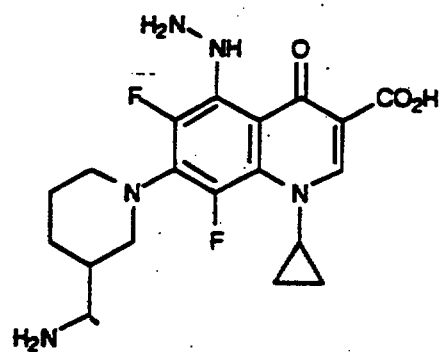
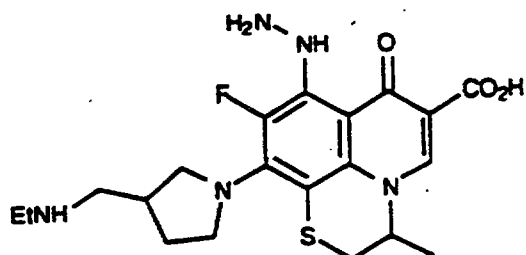
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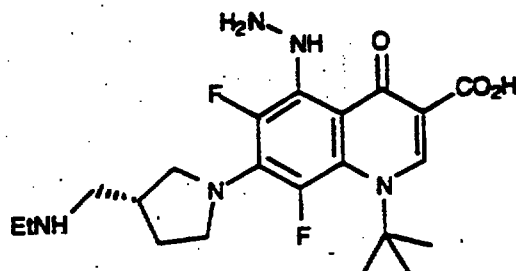
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The compounds of this invention are also useful as intermediates in the synthesis of novel lactam-quinolones. Such compounds are disclosed in International Publication No. WO 91/16327, published October 31, 1991, incorporated by reference herein. Lactam-quinolones encompass any of a variety of lactam moieties linked, by a linking moiety, to a quinolone moiety at the 5-position of the quinolone.

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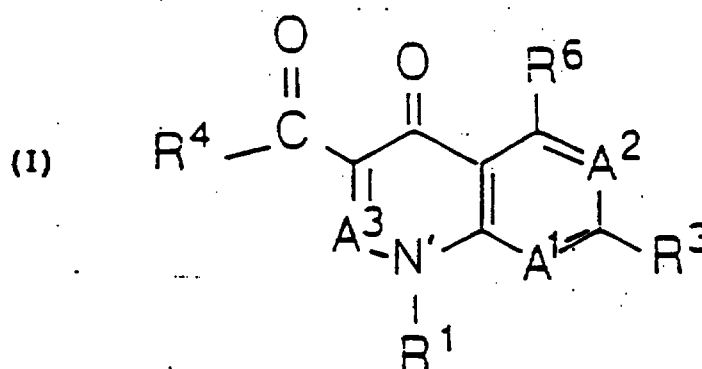
Lactam-quinolones include compounds having the general structure:

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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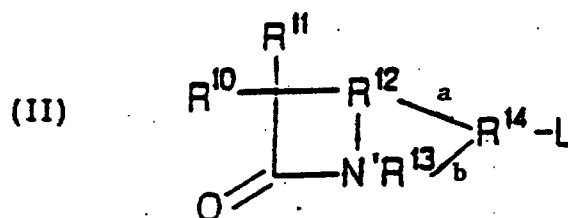
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- (A) (1) A^1 is N or C(R^7); where
- (i) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or N(R^8)(R^9) (preferably hydrogen or halogen), and
- 5 (ii) R^8 and R^9 are, independently, R^{8a} , where R^{8a} is hydrogen, alkyl, alkenyl, 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;
- 10 (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, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or N(R^8)(R^9) (preferably alkyl or a carbocyclic ring);
- 15 (5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring (preferably a heterocyclic ring);
- (6) R^4 is hydroxy; and
- (7) R^6 is R^{15} or $R^{16}X$; where R^{15} is a substituent moiety of L and is nil, alkyl, heteroalkyl, or alkenyl; R^{16} is a substituent moiety of L and is alkyl, alkenyl, a carbocyclic ring or a heterocyclic ring; and X is alkyl, heteroalkyl, alkenyl, oxygen, sulfur, or NH;
- 20 (B) except that
- 25 (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) when A^2 is C(R^2), R^2 and R^3 may together comprise -O-(CH₂)_n-O-, where n is an integer from 1 to 4;
- 30 (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;
- 35 (II) B is a structure according to Formula (II), where L is bonded to R^{14} :





wherein

- (A) R¹⁰ is hydrogen, halogen, heteroalkyl, a carbocyclic ring, a heterocyclic ring, R^{8a}-O-, R^{8a}CH=N-, (R⁸)(R⁹)N-, R¹⁷-C(=CHR²⁰)-C(=O)NH-, or (preferably) alkyl, alkenyl, R¹⁷-C(=NO-R¹⁹)-C(=O)NH-, or R¹⁸-(CH₂)_m-C(=O)NH-; where
- (1) m is an integer from 0 to 9 (preferably from 0 to 3);
 - (2) R¹⁷ is hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring (preferably alkyl, a carbocyclic ring, or a heterocyclic ring);
 - (3) R¹⁸ is R¹⁷, -Y¹, or -CH(Y²)(R¹⁷);
 - (4) R¹⁹ is R¹⁷, arylalkyl, heteroarylalkyl, -C(R²²)(R²³)COOH, -C(=O)O-R¹⁷, or -C(=O)NH-R¹⁷, where R²² and R²³ are, independently, R¹⁷ or together comprise a carbocyclic ring or a heterocyclic ring including the carbon atom to which R²² and R²³ are bonded (preferably R¹⁷ or -C(R²²)(R²³)COOH)
 - (5) R²⁰ is R¹⁹, halogen, -Y¹, or -CH(Y²)(R¹⁷) (preferably R¹⁹ or halogen);
 - (6) Y¹ is -C(=O)OR²¹, -C(=O)R²¹, -N(R²⁴)R²¹, or -S(O)_pR²⁹ or -OR²⁹; and Y² is Y¹ or -OH, -SH, or -SO₃H;
 - (a) p is an integer from 0 to 2 (preferably 0);
 - (b) R²⁴ is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbocyclic ring; a heterocyclic ring; -SO₃H; -C(=O)R²⁵; or, when R¹⁸ is -CH(N(R²⁴)R²¹)(R¹⁷), R²⁴ may comprise a moiety bonded to R²¹ to form a heterocyclic ring; and
 - (c) R²⁵ is R¹⁷, NH(R¹⁷), N(R¹⁷)(R²⁶), O(R²⁶), or S(R²⁶) (preferably R¹⁷, NH(R¹⁷) or N(R¹⁷)(R²⁶)); where R²⁶ is alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring or (preferably) when R²⁵ is N(R¹⁷)(R²⁶), R²⁶ may

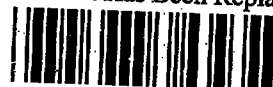


comprise a moiety bonded to R¹⁷ to form a heterocyclic ring; and

- 5 (7) R²¹ is R²⁹ or hydrogen; where R²⁹ is alkyl; alkenyl; arylalkyl; heteroalkyl; heteroalkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Y¹ is N(R²⁴)R²¹ and R²¹ is R²⁹, R²¹ and R²⁴ may together comprise a heterocyclic ring including the nitrogen atom to which R²⁴ is bonded (preferably hydrogen, alkyl, a carbocyclic ring or a heterocyclic ring);
- 10 (B) R¹¹ is hydrogen, halogen, alkoxy, or R²⁷C(=O)NH- (preferably hydrogen or alkoxy), where R²⁷ 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;
- 15 (D) R¹² is -C(R^{8a})-, or -CH₂-R²⁸- (preferably -C(R^{8a})-); where R²⁸ is -C(R^{8a}), -O-, or -N-, and R²⁸ is directly bonded to N" in Formula (II) to form a 5-membered ring; except, if bond "a" is nil, then R¹² is
- 20 (1) (preferably) -C(R^{8a})(X¹)-, where
- (i) X¹ is -R²¹; -OR³⁰; -S(O)_rR³⁰, where r is an integer from 0 to 2 (preferably 0); -O(C=O)R³⁰; or N(R³⁰)R³¹; and
- (ii) R³⁰ and R³¹ are, independently, alkyl, alkenyl, carbocyclic ring or heterocyclic ring substituents; or R³⁰ and R³¹ together comprise a heterocyclic ring including the nitrogen atom to which R³⁰ and R³¹ are bonded; or
- 25 (2) -CH₂-R³²-; where R³² is -C(R^{8a})(R²¹), -O-, or -NR^{8a}, and R³² is directly bonded to N" in Formula (II) to form a 5-membered ring;
- 30 (E) (1) if bond "b" is a single bond, R¹³ is preferably -CH(R³³)-; or, -C(O)NHSO₂-, if bond "a" is nil; or -C*(R³³)-, if R¹⁴ contains a R³⁶ moiety; where R³³ is hydrogen or COOH (preferably COOH), and C* is linked to R³⁶ to form a 3-membered ring;
- 35 (2) if bond "b" is a double bond, R¹³ is -C(R³³)=; 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 (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' , $-X^2_t-R^{39}-L'$, or $-X^3_t-R^{39}-L'$, where L' is Q' , $-X^2-Q''$, $-X^3-Q''$, or $-X^4_t-C(=Y^3_u)-Z-Q''$ (preferably $-X^2-Q''$, $-X^3-Q''$, $-X^4_t-C(=Y^3_u)-Z-Q''$);
- (1) t and u are, independently, 0 or 1;
- (2) R^{39} is alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring (preferably alkyl or alkenyl);
- (3) X^2 is oxygen, or $S(O)_v$, where v is an integer from 0 to 2 (preferably 0);



- (4) 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
- 5 (a) R^{40} is R^{8a} ; $-OR^{8a}$; or $-C(=O)R^{8a}$; (preferably R^{8a});
- (b) R^{41} and R^{42} are, independently, hydrogen; alkyl; alkenyl; carbocyclic rings; heterocyclic rings; or, if R^6 is R^{16X} , then R^{41} and R^{42} together with Q'' , may comprise a heterocyclic ring as R^{16} ;
- 10 (c) R^{43} is $N(R^{41})$, oxygen or sulfur;
- (5) X^4 is oxygen, sulfur, NR^{40} , or $R^{43}-NR^{41}$ (preferably oxygen, sulfur or NR^{40});
- 15 (6) Y^3 is oxygen, sulfur, NR^{40} or $N^+(R^{41})(R^{42})$;
- (7) Y^4 is oxygen or NR^{41} (preferably oxygen);
- (8) Z is nil, oxygen, sulfur, nitrogen, NR^{40} , or $N(R^{41})-R^{43}$ (preferably oxygen, sulfur, nitrogen or NR^{40});
- (9) Q' is said R^6 substituent of Q; and
- 20 (10) Q'' is Q' ; or together with X^2 , X^3 , Z or Z' , is said R^6 substituent of Q;

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

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

25

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 cepheids, oxacephems and carbacephems (for example). The active position is alpha for penems, carbapenems, clavams and clavams. Appropriate R^{10} groups will be apparent to one of ordinary skill in the art.

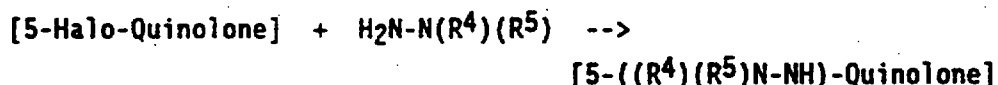
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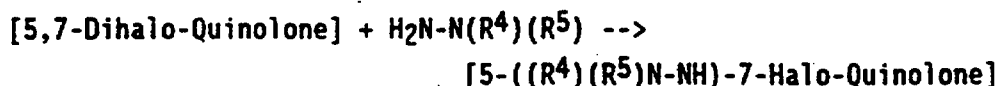
Procedures for preparing quinolones and quinolone intermediates useful in the methods of this invention are described in the following references, all incorporated by reference herein (including articles listed within these references); 21 Progress in Drug Research, 9-104 (1977); 31 J. Med. Chem., 503-506 (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 J. Med. Chem., 1586-1590 (1988); 31 J. Med. Chem., 1598-1611 (1988); and 23 J. Med. Chem., 1358-1363 (1980).

In general, 5-(N-heterosubstituted amino) quinolones can be prepared by the following procedure:



where R^4 and R^5 are previously defined and [5-Halo-Quinolone] is an appropriately protected 5-halogen substituted quinolone where the halogen is preferably chloro or fluoro (preferably fluoro). The reaction sequence can be envisioned as a nucleophilic aromatic displacement of the quinolone 5-halogen substituted by $(\text{R}^4)(\text{R}^5)\text{N-NH}_2$ to form the 5-(N-heterosubstituted amino)quinolones.

Alternatively, 5-(N-heterosubstituted amino)quinolones can be prepared by the following procedure:



where R^4 and R^5 are previously defined and [5,7-Dihalo-Quinolone] is an appropriately protected 5- and 7- halogen substituted



quinolone where the halogen at positions 5 and 7 is independently a chloro or fluoro (preferably fluoro). The reaction sequence can be envisioned as a selective nucleophilic aromatic displacement of the quinolone 5-halogen substituent by (R⁴)(R⁵)N-NH₂ to form the 5-(N-heterosubstituted amino)quinolones. The reaction can preferably be carried out in a nonpolar aprotic solvent, preferably benzene, toluene, xylene, etc., at an elevated temperature, preferably 50°C to reflux.

Compositions

The compositions of this invention comprise:

- (a) a safe and effective amount of a 5-(N-heterosubstituted amino) quinolone; and
- (b) a pharmaceutically-acceptable carrier.

A "safe and effective amount" of a 5-(N-heterosubstituted amino) quinolone 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. 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 5-(N-heterosubstituted amino) 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 5-(N-heterosubstituted amino) 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 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 5-(N-heterosubstituted amino) 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 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 5-(N-heterosubstituted amino) quinolone. The amount of carrier employed in conjunction with the 5-(N-heterosubstituted amino) quinolone is sufficient to provide a practical quantity of material for administration per unit dose of the 5-(N-heterosubstituted amino) quinolones. 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).

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 5-(N-heterosubstituted amino) 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, 5 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 10 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 5-(N-hetero- 15 substituted amino) quinolone. Suitable carriers 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 carrier is organic in nature and capable of having dispersed or dissolved therein the 20 5-(N-heterosubstituted amino) quinolone. The carrier may include pharmaceutically-acceptable emollients, emulsifiers, thickening agents, and solvents.

Methods of Administration

This invention also provides methods of treating or preventing 25 an infectious disorder in a human or other animal subject, by administering a safe and effective amount of a 5-(N-hetero-substituted amino) 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 30 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 35 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).

5 The 5-(N-heterosubstituted amino) quinolones and compositions of this invention can be administered topically or systemically. Systemic application includes any method of introducing the 5-(N-heterosubstituted amino) quinolone into the tissues of the body, e.g., intrathecal, epidural, intramuscular, transdermal,
10 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 5-(N-heterosubstituted
15 amino) quinolone used, the resistance pattern of the infecting organism to the 5-(N-heterosubstituted amino) quinolone used, the ability of the 5-(N-heterosubstituted amino) quinolone to reach minimum inhibitory concentrations at the site of the infection, the nature and extent of other infections (if any), the personal
20 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
25 from about 100 mg to about 20,000 mg, more preferably from about 500 mg to about 3500 mg, of 5-(N-heterosubstituted amino) quinolone 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
30 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 intramuscular injection. As is known and practiced in the art,
35 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 to



about 7000 mg, preferably from about 500 mg to about 3500 mg, are acceptable.

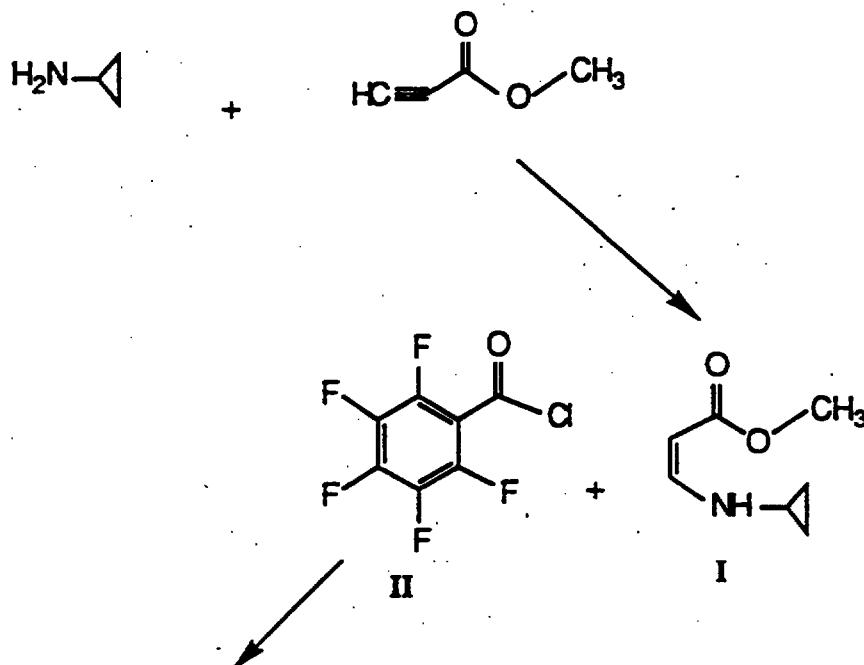
A preferred method of systemic administration is oral. Individual doses of from about 100 mg to about 2500 mg, preferably from about 250 mg to about 1000 mg are preferred.

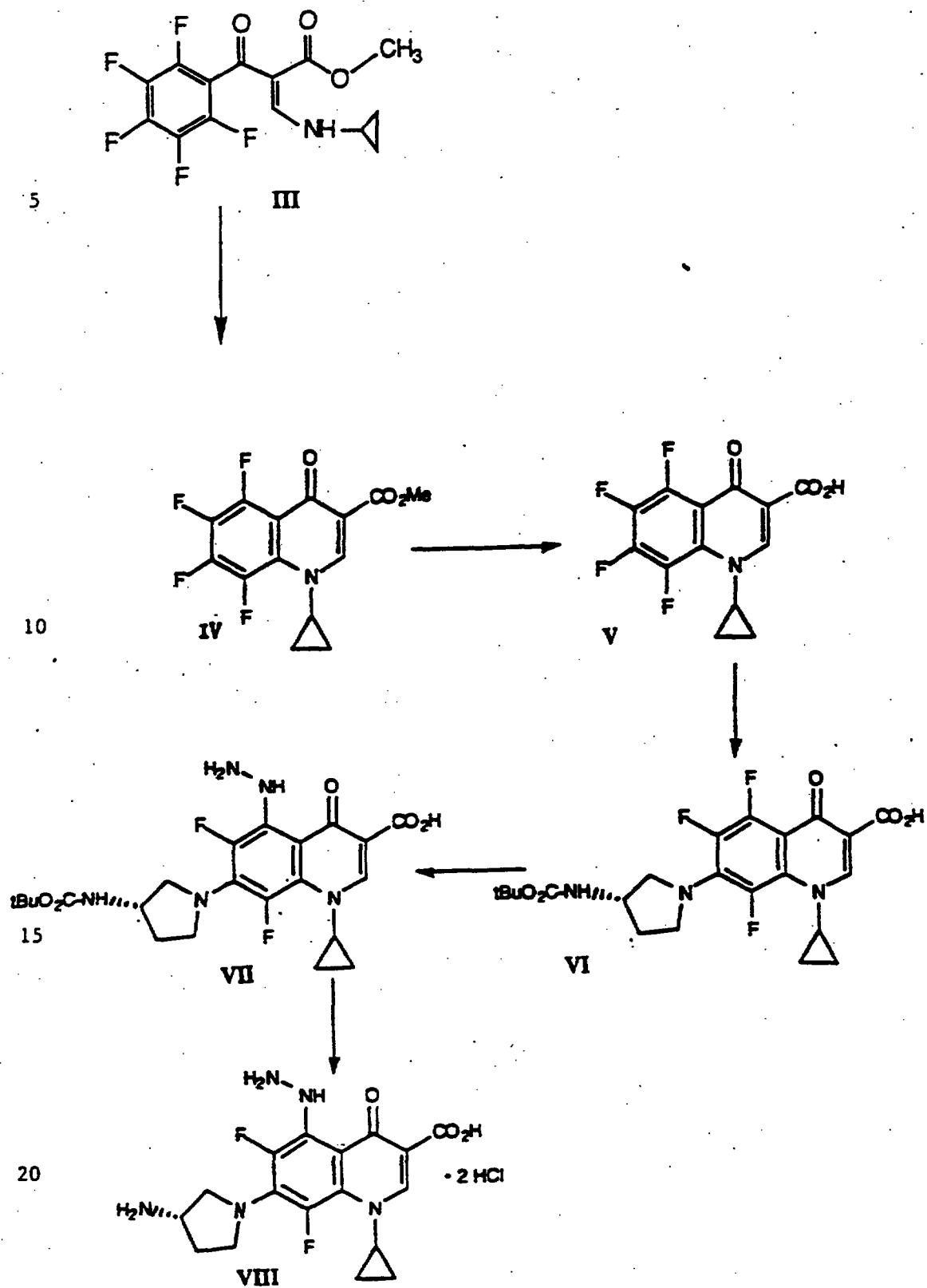
Topical administration can be used to deliver the 5-(N-hetero-substituted amino) quinolone systemically, or to treat a local infection. The amounts of 5-(N-heterosubstituted amino) quinolone to be topically administered depends upon such factors as skin sensitivity, type and location of the tissue to be treated, the composition and carrier (if any) to be administered, the particular 5-(N-heterosubstituted amino) 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.

EXAMPLE 1

(S)-7-(3-Aminopyrrolidiny)-1-cyclopropyl-6,8-difluoro-5-hydrazino-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Dihydrochloride





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5 A mixture of methyl propiolate (983 g, 11.7 mole) and 500 ml of tetrahydrofuran is cooled to 5°C and cyclopropylamine (667 g, 11.7 mole) dissolved in 1000 ml of tetrahydrofuran is added over approximately one hour from an addition funnel at a rate to keep the temperature at 3-7°C. The mixture is stirred for an additional hour at 5°C and the ice bath is removed. The reaction is stirred for approximately one hour at 20-25°C at room temperature for 3 hours and is allowed to stand for about 2.5 days at room temperature. The solvent is removed under reduced pressure and the residue is vacuum distilled to give I.

10 A solution of approximately 207 g of pentafluorobenzoyl chloride II (0.90 mole) and 250 ml of dioxane is cooled to 15-20°C with an ice water bath and a solution of approximately 126 g of I and 90.9 g of triethylamine (0.90 mole) in 300 ml of dioxane is added dropwise over 5.5 hours. The addition funnel is rinsed with an additional 50 ml of dioxane and the reaction is stirred at 20°C overnight. The mixture is then vacuum filtered and the precipitate is washed twice with 100 ml portions of dioxane. The filtrate is vacuum stripped at 25°C and 1000 ml of hexane is added to the residue. More precipitate is collected and added to the first batch. The combined product is then resuspended in 1500 ml of hexane, stirred briefly, filtered and vacuum dried to give III.

20 In a 5 L three-necked round-bottom flask equipped with thermometer, argon inlet, mechanical stirrer, and an addition funnel is placed approximately 14.9 g (0.621 mole) NaH (from hexane-washed NaH/mineral oil) and 1000 ml of dimethylformamide. This mixture is cooled to 15-20°C and approximately 181.5 g of III (0.542 mole) dissolved in 2 L of dimethylformamide is added dropwise over 3.5 hours while keeping the temperature at 15-20°C. Stirring is continued for 1.5 hours at this temperature and then the mixture is further cooled to 10° and 500 ml of ice and 1 L of water is added. The mixture is neutralized to pH 7 with approximately 5 ml of acetic acid and is extracted three times with chloroform. The dried chloroform extracts are evaporated to give a slurry which is triturated with 400 ml of boiling ethanol. The resulting solids are filtered at room temperature. An additional wash with 100 ml of cold ethanol followed by vacuum drying gives IV.



A mixture of methyl propiolate (983 g, 11.7 mole) and 500 ml of tetrahydrofuran is cooled to 5°C and cyclopropylamine (667 g, 11.7 mole) dissolved in 1000 ml of tetrahydrofuran is added over approximately one hour from an addition funnel at a rate to keep the temperature at 3-7°C. The mixture is stirred for an additional hour at 5°C and the ice bath is removed. The reaction is stirred for approximately one hour at 20-25°C at room temperature for 3 hours and is allowed to stand for about 2.5 days at room temperature. The solvent is removed under reduced pressure and the residue is vacuum distilled to give I.

A solution of approximately 207 g of pentafluorobenzoyl chloride II (0.90 mole) and 250 ml of dioxane is cooled to 15-20°C with an ice water bath and a solution of approximately 126 g of I and 90.9 g of triethylamine (0.90 mole) in 300 ml of dioxane is added dropwise over 5.5 hours. The addition funnel is rinsed with an additional 50 ml of dioxane and the reaction is stirred at 20°C overnight. The mixture is then vacuum filtered and the precipitate is washed twice with 100 ml portions of dioxane. The filtrate is vacuum stripped at 25°C and 1000 ml of hexane is added to the residue. More precipitate is collected and added to the first batch. The combined product is then resuspended in 1500 ml of hexane, stirred briefly, filtered and vacuum dried to give III.

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A stirred mixture of 1-cyclopropyl-5,6,7,8-tetrafluoro-4-oxo-3-carboxylic acid, methyl ester (compound IV) (8.2g), triethylamine (4 ml), t-butyl carbazate (3.8g), and toluene is refluxed for approximately one hour and concentrated to dryness under reduced pressure. The residue is dissolved in CH₂Cl₂ (200 ml) and washed with water (200 ml) and brine (200 ml). The organic phase is dried over Na₂SO₄, filtered and the filtrate is concentrated to dryness under reduced pressure. The residue is purified by flash chromatography (silica gel) with 5% MeOH/CH₂Cl₂ to give the desired C-5 substituted product V.

A mixture of approximately 3.5 g of V, tetrahydrofuran (THF) (30 ml) and 17 ml of 1 N NaOH is heated at 80°C for approximately 1.5 hours. The reaction is cooled in an ice bath and water (200 ml) is added, followed by the addition of glacial acetic acid (2.3 ml). The precipitate is filtered, washing with water and ether to give compound VI.

A mixture of approximately 2.6 g of VI, 1.3 g of 1-(t-butoxycarbonyl)piperazine, and pyridine (20 ml) is heated at 80°C for approximately one hour and the reaction mixture is concentrated to dryness under reduced pressure. The residue is dissolved in CH₂Cl₂ (100 ml) and washed with water, 5% citric acid, water, and brine. The organic layer is dried over Na₂SO₄, filtered and the filtrate is concentrated to dryness. The residue is purified by flash chromatography (silica gel) with 5% MeOH/CH₂Cl₂ to afford compound of VII.

To a mixture of VII (2.3 g) and CH₂Cl₂ (40 ml) at room temperature is added slowly approximately 28 ml of saturated ethanol/HCl. The mixture is stirred at room temperature for approximately 4.5 hours and the product is collected by filtration. The solid is heated in CHCl₃ (50 ml) and methanol (10 ml) is added. The mixture is cooled to room temperature and the product is collected by filtration to give compound VIII.

EXAMPLE 4

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

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	<u>Component</u>	<u>Amount</u>
5	(S)-7-(3-Aminopyrrolidine)-1-cyclopropyl-6,8-difluoro-5-hydrazino-1,4-dihydro-4-oxo-3-quinoline carboxylic acid ¹	100 mg/ml carrier

Carrier:

	sodium citrate buffer with (percent by weight of carrier):	
10	lecithin	0.48%
	carboxymethylcellulose	0.53
	povidone	0.50
	methyl paraben	0.11
	propyl paraben	0.011

15

1: a 5-(N-heterosubstituted amino) quinolone made according to Example I

20 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 pneumonia present. This dosage is repeated twice daily, for approximately 14 days. After 4 days, symptoms of the

25 disease subside, indicating that the pathogen has been substantially eradicated.

EXAMPLE 5

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

	<u>Component</u>	<u>Amount (mg)</u>
35	(S)-7-(3-Aminopyrrolidine)-1-cyclopropyl-6,8-difluoro-5-hydrazino-1,4-dihydro-4-oxo-3-quinoline carboxylic acid ¹	350.0
	starch	30.0
	magnesium stearate	5.0
	microcrystalline cellulose	100.0



colloidal silicon dioxide
povidone

2.5
12.5

5 1: a 5-(N-heterosubstituted amino) quinolone made according to Example I

10 The components are admixed into a bulk mixture. Compressed tablets are formed, using tableting 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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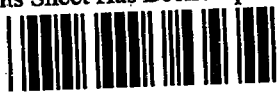
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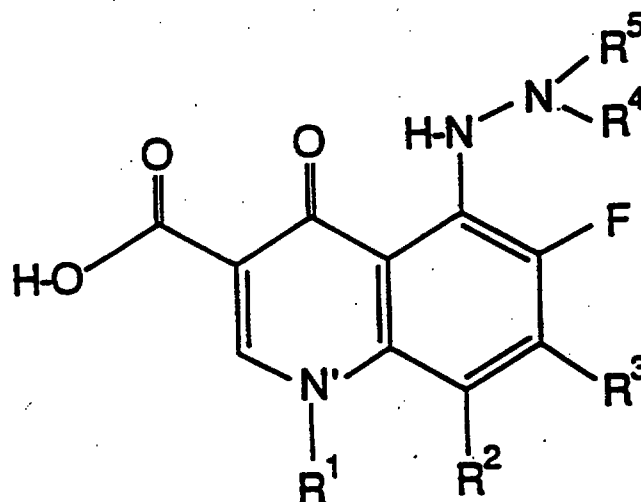
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WHAT IS CLAIMED IS:

1. Compounds of the general structure:



wherein

(A)(1)(a) R^1 is alkyl; alkenyl; a carbocyclic ring; a heterocyclic ring; or $-N(R^6)(R^7)$, where R^6 and R^7 are, independently, hydrogen, alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or R^6 and R^7 together comprise a heterocyclic ring that includes the nitrogen to which they are bonded; and

(b) R^2 is hydrogen; halogen, lower alkyl, or lower alkoxy; or

(2) R^1 and R^2 may together comprise a six-membered heterocyclic ring that includes N' and the carbon atom to which R^2 is bonded;

(B) R^3 is a heterocyclic ring or a carbocyclic ring; and

(C)(1) R^4 and R^5 are, independently, hydrogen; lower alkyl; cycloalkyl; heteroalkyl; or $-C(=O)-X-R^8$, where X is a covalent bond, N, O, or S, and R^8 is lower alkyl, lower alkenyl, arylalkyl, a carbocyclic ring, or a heterocyclic ring; or

(2) R^4 and R^5 together comprise a heterocyclic ring that includes the nitrogen to which they are bonded;

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





2. A compound, according to Claim 1, wherein R^1 is ethyl, 2-fluoroethyl, 2-hydroxyethyl, t-butyl, 4-fluorophenyl, 2,4-difluorophenyl, methylamino, cyclopropyl, or 2-fluorocyclopropyl.

3. A compound, according to Claim 1, wherein R^2 is chlorine or fluorine.

4. A compound, according to Claim 1, wherein R^4 is hydrogen and R^5 is hydrogen or lower alkyl.

5. A compound, according to Claim 4, wherein both R^4 and R^5 are hydrogen.

6. A compound, according to Claim 5, wherein R^3 is a heterocyclic ring.

7. A compound, according to Claim 6, wherein said heterocyclic ring is 3-aminopyrrolidine.

8. A compound, according to Claim 7, wherein R^1 is cyclopropyl and R^2 is fluorine.

9. A compound, according to Claim 7, wherein R^1 is 2,4-difluorophenyl and R^2 is fluorine.

10. A compound, according to Claim 6, wherein said heterocyclic ring is piperazine.

11. A compound, according to Claim 10, wherein R^1 is cyclopropyl and R^2 is fluorine.

12. A compound, according to Claim 4, wherein R^5 is lower alkyl.

13. A compound, according to Claim 12, wherein R^3 is a heterocyclic ring.





* C L H S *

14. A compound, according to Claim 13, wherein said heterocyclic ring is 3-aminopyrrolidine.

15. A compound, according to Claim 14, wherein R¹ is cyclopropyl and R² is fluorine.

16. A compound, according to Claim 13, wherein said heterocyclic ring is piperazine.

17. A compound, according to Claim 16, wherein R¹ is cyclopropyl and R² is fluorine.

18. A compound selected from the group consisting of
(3S)-7-(3-amino-1-pyrrolidinyl)-1-(2,4-difluorophenyl)-6,8-difluoro-5-hydrazino-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid;
(3S)-7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-5-hydrazino-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid; and
1-cyclopropyl-6,8-difluoro-5-hydrazino-1,4-dihydro-4-oxo-7-piperazinyl-3-quinolinecarboxylic acid; and
pharmaceutically-acceptable salts, biohydrolyzable esters, and solvates thereof.

19. 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 Claim 1;
and
- (2) a pharmaceutically-acceptable carrier.

20. A method for preventing or treating an infectious disorder in a human or other animal subject, by administering to said subject a safe and effective amount of a compound of Claim 1.

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