7-Amino Alkylidenyl-Heterocyclic Quinolones and Naphthyridones

Cross-Reference to Related Application

This application is a continuation-in-part of Application Serial Number 10/937238, filed September 9, 2004.

Field of Invention

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

Background

The chemical and medical literature describes compounds that are said to be antimicrobial, i.e., capable of destroying or suppressing the growth or reproduction of microorganisms, such as bacteria. For example, such antibacterial agents are described in Antibiotics, Chemotherapeutics, and Antibacterial Agents for Disease Control (M. Greyson, editor, 1982), E. Gale et al., The Molecular Basis of Antibiotic Action 2d edition (1981), Recent Research Developments in Antimicrobial Agents & Chemotherapy (S. G. Pandalai, Editor, 2001), Quinolone Antimicrobial Agents (John S Wolfson., David C Hooper, Editors, 1989), and F. O'Grady, H. P. Lambert, R. G. Finch, D. Greenwood, Martin Dedicoat, "Antibiotic and Chemotherapy, 7th edn." (1997).

The mechanisms of action of these antibacterial agents vary. However, they are generally believed to function in one or more ways: by inhibiting cell wall synthesis or repair; by altering cell wall permeability; by inhibiting protein synthesis; or by inhibiting the synthesis of nucleic acids. For example, beta-lactam antibacterial agents act through inhibiting essential penicillin binding proteins (PBPs) in bacteria, which are responsible for cell wall synthesis. As

another example, quinolones act, at least in part by inhibiting synthesis of DNA, thus preventing the cell from replicating.

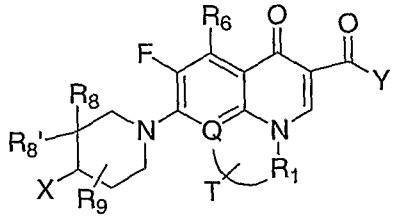
The pharmacological characteristics of antimicrobial agents, and their suitability for any given clinical use, vary. For example, the classes of antimicrobial agents (and members within a class) may vary in 1) their relative efficacy against different types of microorganisms, 2) their susceptibility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

However, many such attempts to produce improved antimicrobial agents yield equivocal results. Indeed, few antimicrobial agents are produced that are truly clinically acceptable in terms of their spectrum of antimicrobial activity, avoidance of microbial resistance, and pharmacology. Thus there is a continuing need for broad-spectrum antimicrobial agents, which are effective against resistant microbes.

Some 1,4-dihydroquinolone, naphthyridine or related heterocyclic moieties are known in the art to have antimicrobial activity and are described in the following references: R. Albrecht Prog. Drug Research, Vol. 21, p. 9 (1977); J. Wolfson et al., "The Fluoroquinolones: Structures, Mechanisms of Action and Resistance, and Spectra of Activity In Vitro", Antimicrob. Agents and Chemother., Vol. 28, p. 581 (1985); G. Klopman et al. Antimicrob. Agents and Chemother., Vol. 31, p. 1831 (1987); M. P. Wentland et al., Ann. Rep. Med. Chem., Vol. 20, p. 145 (1986); J. B. Cornett et al., Ann. Rep. Med. Chem., Vol. 21, p. 139 (1986); P. B. Fernandes et al. Ann. Rep. Med. Chem., Vol. 22, p. 117 (1987); A. Koga, et al. "Structure-Activity Relationships of Antibacterial 6,7- and 7,8-Disubstituted 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids" J. Med. Chem. Vol. 23, pp. 1358-1363 (1980); J. M. Domagala et al., J. Med. Chem. Vol. 31, p. 991 (1988); T. Rosen et al., J. Med. Chem. Vol. 31, p. 1598 (1988); B. Ledoussal et al., "Non 6-Fluoro Substituted Quinolone Antibacterials: Structure and Activity", J. Med. Chem.

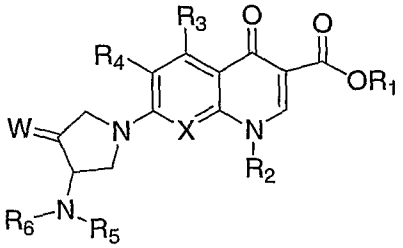
Vol. 35, p. 198-200 (1992); U. S. Patent 6329391; A. M Emmerson et al., "The quinolones: Decades of development and use", J. Antimicrob. Chemother., Vol 51, pp 13-20 (2003); J. Ruiz, "Mechanisms of resistance to quinolones: target alterations, decreased accumulation and DNA gyrase protection" J. Antimicrob. Chemother. Vol. 51, pp 1109-1117 (2003); Y. Kuramoto et al., "A Novel Antibacterial 8-Chloroquinolone with a Distorted Orientation of the N1-(5-Amino-2,4-difluorophenyl) Group" J. Med. Chem. Vol. 46, pp 1905-1917 (2003); Japanese Patent Publication 06263754; European Patent Publication 487030; International Patent Publication WO0248138; International Patent Publication WO9914214; U.S. Patent Publication 2002/0049192; International Patent Publication WO02085886; European Patent Publication 572259; International Patent Publication WO0136408; U.S. Patent 5677456; European Patent Publication 362759; U.S. Patent 5688791; U.S. Patent 4894458; European Patent Publication 677522; U.S. Patent 4822801; U.S. Patent 5256662; U.S. Patent 5017581; European Patent Publication 304087; International Patent Publication WO0136408; International Patent Publication WO02085886; Japanese Patent Publication 01090184; International Patent Publication WO9209579; International Patent Publication WO0185728; European Patent Publication 343524; Japanese Patent Publication 10130241; European Patent Publication 413455; International Patent Publication WO0209758; International Patent Publication WO0350107; International Patent Publication WO9415933; International Patent Publication WO9222550; Japanese Patent Publication 07300472; International Patent Publication WO0314108; International Patent Publication WO0071541; International Patent Publication WO0031062; and U.S. Patent 5869670.

WO03050107 describes a series of dihydroquinolone, naphthyridine and related heterocyclic antibacterial agents. Of particular interest is the disclosure of compounds of the formula,



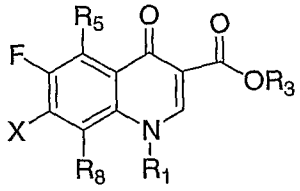
wherein R_8 and $R_{8'}$ are hydrogen, alkyl, substituted alkyl, alkylamino, or arylalkyl, R_9 is hydrogen, alkyl, alkylamino, dialkylamino, aryl, arylalkyl, or trihaloalkyl, and X is hydroxy, alkoxy, acyloxy, amino or substituted amino.

European Patent Publication 362759 discloses 1,4-dihydroquinolone and naphthyridine antibacterial agents of the formula,

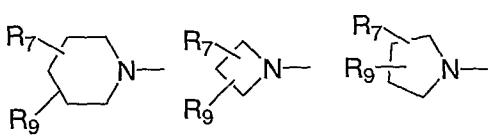


wherein W is C1-3 alkylidene and R_5 and R_6 are hydrogen or alkyl.

International Patent Publication WO 99/14214 and US Patent 6329391 disclose quinolone antibacterial agents with C_7-piperdinyl, C_7-azetidinyl, or C_7-pyrrolidinyl substituents of the formula,



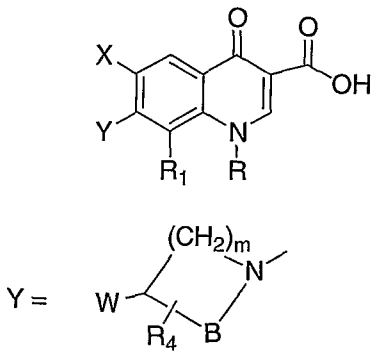
X =



Of particular interest are those compounds wherein R_7 is amino, aminoalkyl, or substituted aminoalkyl and R_9 is selected from hydrogen, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or a C_3-C_6 fused or spirocyclic alkyl ring. For compounds with a substituted piperidine at the 7-position of the

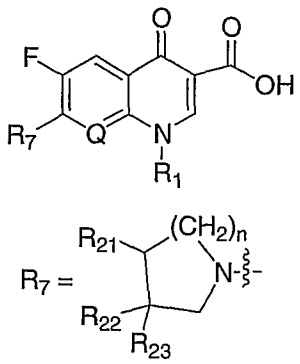
quinolonecarboxylic acid, among the preferred substituents are 3-amino-4-methyl, 3-amino-4,4-dimethyl, 3-amino-4-spirocyclopropyl, 3-amino-6-cyclopropyl, 3-aminomethyl, 4-aminomethyl and 3-methylamino. For compounds with a substituted pyrrolidine at the 7-position of the quinolonecarboxylic acid nucleus, preferred substituents include 3-(1-aminoethyl), 3-aminomethyl, 4-(1-aminoethyl)-2,2-dimethyl, and 2-aminomethyl. For compounds with an azetidine substituent at the 7-position of the quinolonecarboxylic acid, the compounds having the substituents, 3-amino, 3-aminomethyl and 3-(1-amino-1-methyl)ethyl, are included among the preferred examples.

European Patent Publication 241206A2 discloses compounds of the formula,



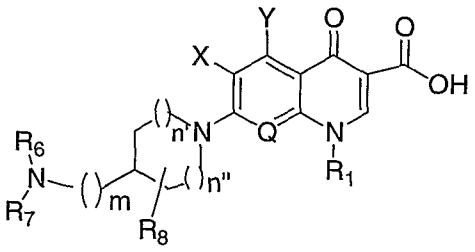
wherein B is $-CH_2-$, $-(CH_2)_2-$, or $-(CH_2)_3-$, R_4 is hydrogen, C_1-C_3 alkyl, hydroxy, or C_1-C_3 alkoxy, W is hydroxy, C_1-C_3 alkoxy, or a group of the formula $R_5R_6N-(CH_2)_n-$ in which n is 0 or 1 and R_5 and R_6 are the same or different and each represents a hydrogen atom, a C_1-C_3 alkyl group or an arylalkyl group, and m is 1 or 2. each symbol is as defined in the specification of the above mention publication. For the piperidine substituent at the 7-position of the quinolonecarboxylic acid, the compounds having substituents of 4-amino-3-methyl, 4-methylamino-3-methyl, 4-hydroxy-3methyl are included in the preferred examples therein.

European Patent Publication 0394553B1 discloses anti-viral compounds of the formula,



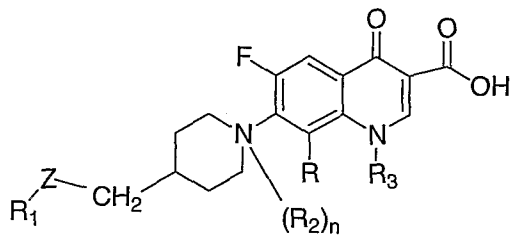
wherein R_{21}, R_{22} and R_{23} are each independently is a hydrogen atom, a halogen atom, amino, C_1-C_6 alkyl, C_1-C_8 alkoxy, or amino C1-C8 alkyl and two of them may be combined with each other to form a spiro ring, and n is 1 or 2.

European Patent Publication 0572259A1 discloses anti-viral compounds of the formula,



wherein R_6 and R_7 may be the same or different and each represents a hydrogen atom or a lower alkyl group, m is 0 or 1, n' is 1 or 2, n" is 1, 2, 3 or 4, and R8 is a hydrogen atom, a lower alkyl group, a hydroxy group or a lower alkoxy group.

International Patent Publication WO9324479 discloses compounds of the formula,



wherein Z is an amino radical, R_1 is hydrogen, an (optionally hydroxylated lower alkyl) radical, an acyl radical derived from a carboxylic acid, an alkyl carbonic acid or an arylsulfonic acid or an arylamino carbonyl radical, R_2 is an oxygen atom, and n is 0 or 1.

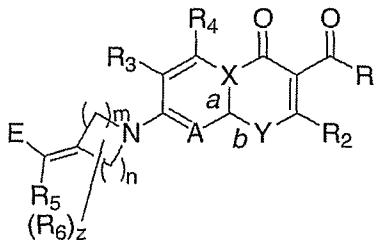
Examples of bacterial infections resistant to antibiotic therapy have been reported in the past; they are now a significant threat to public health in the developed world. The development of microbial resistance (perhaps as a result of the intense use of antibacterial agents over extended periods of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

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

Hence existing antibacterial agents have limited capacity in overcoming the threat of resistance. Thus it would be advantageous to provide new antibacterial agents that can be used against resistant microbes.

Summary of Invention

Applicants have found a novel series of quinolones and related compounds that are effective against resistant microbes, and provide significant activity advantages over the art. In particular, the invention relates to compounds having a structure according to Formula (I)



Formula I

wherein:

n is an integer from 1 to 3;

m is an integer from 1 to 3;

z is an integer from 0 to 3;

R is selected from hydrogen, hydroxy, and alkoxy;

$\mathbf{R_2}$ is hydrogen;

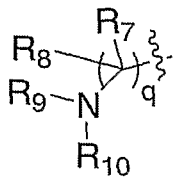
$\mathbf{R_3}$ and $\mathbf{R_4}$ are independently selected from hydrogen, halogen, amino, hydroxy, alkoxy, alkylthio, alkyl, alkenyl and alkynyl;

$\mathbf{R_5}$ is selected from hydrogen, halogen, alkyl, aryl, alkoxy, and alkylthio;

$\mathbf{R_6}$ is independently selected from alkyl, hydroxy, alkoxy, alkylthio, alkenyl, alkynyl, aryl, alkoxyimino, and halogen; or $\mathbf{R_5}$ and $\mathbf{R_6}$ join to form a 4- to 7-

membered carbocyclic ring wherein each carbon atom of the ring can be optionally substituted with R_{12}, wherein R_{12} is selected from the group consisting of halogen, amino, hydroxy, alkoxy, alkylthio, alkyl, alkenyl, alkynyl, oxo, alkoxyimino and hydroxyimino;

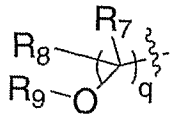
E is selected from the group consisting of:

1)  wherein,

q is an integer from 1 to 3;

R_7 and R_8 are each independently selected from hydrogen and alkyl, or R_7 and R_8 join to form a 3- to 6-membered carbocyclic ring, or either of R_7 or R_8 can be joined independently to either of R_9 or R_{10} to form a heterocyclic ring containing the nitrogen atom to which R_9 or R_{10} are bonded, wherein

R_9 and R_{10} are each independently selected from hydrogen, alkyl, acyl, alkoxycarbonyl, or sulfonyl, or alternatively R_9 and R_{10} join to form a heterocyclic ring containing the nitrogen atom to which they are bonded;

2)  wherein,

q is as defined above;

R_7 and R_8 are each independently selected from hydrogen and alkyl, or R_7 and R_8 join to form a 3- to 6-membered carbocyclic ring, and R_9 is selected from hydrogen, alkyl, acyl, alkoxycarbonyl, or sulfonyl;

and

3) alkenyl;

A is selected from N and C(R_{11}), wherein R_{11} is selected from hydrogen, alkyl, halogen, hydroxy, alkoxy, alkylthio, and cyano;

X is selected from C and N, where if **X** is C, ***a*** is a double bond and ***b*** is a single bond, and if **X** is N, ***a*** is a single bond and ***b*** is a double bond; and

Y is selected from N(R_1) and C(R_1), with the proviso that when **Y** is N(R_1), **X** is C and when **Y** is C(R_1), **X** is N, wherein R_1 is selected from C3 to C6

cycloalkyl, C4 to C6 heterocycloalkyl, alkyl, alkene, a 6-membered aryl and a 6-membered heteroaryl; provided that

if **A** is C(R_{11}), **X** is C and **Y** is N(R_1), then R_{11} and R_1 can join to form a 6-membered heterocyclic ring, or

if **A** is C(R_{11}), **X** is C and **Y** is N(R_1), then R_2 and R_1 can join to form a monocyclic or bicyclic heterocyclic ring, or

if **A** is C(R_{11}), **X** is C and **Y** is N(R_1), then R_2 and **R** can join to form a 5-membered heterocyclic ring;

or an optical isomer, diastereomer or enantiomer thereof; a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

In addition, methods of using compounds of the invention as starting materials are also contemplated in this invention.

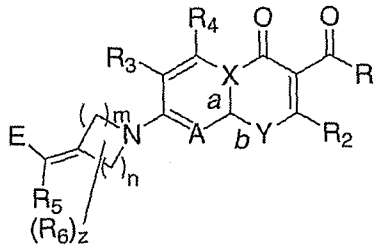
It has been found that the compounds of this invention, and compositions containing these compounds, are effective antimicrobial agents against a broad range of pathogenic microorganisms with advantages of activity against resistant microbes.

Accordingly, the present invention is also directed to a method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said mammal a therapeutically effective amount of the compound of Formula 1.

The present invention is further directed to a method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a prophylactically effective dose of the pharmaceutical composition of a compound of Formula 1.

Detailed Description

The subject invention provides compounds of Formula (I)



Formula I

wherein:

a, b, n, m, z, R, R_2, R_3, R_4, R_5, R_6, A, E, X and **Y** are as defined in the Summary of the Invention section above.

Relative to the above description, certain definitions apply as follows.

Unless otherwise noted, under standard nomenclature used throughout this disclosure the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment.

Unless specified otherwise, the terms "alkyl", "alkenyl", and "alkynyl," whether used alone or as part of a substituent group, include straight and branched chains having 1 to 8 carbon atoms, or any number within this range. The term "alkyl" refers to straight or branched chain hydrocarbons. "Alkenyl" refers to a straight or branched chain hydrocarbon with at least one carbon-carbon double bond. "Alkynyl" refers to a straight or branched chain hydrocarbon with at least one carbon-carbon triple bound. For example, alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, n-hexyl, 2-hexyl and 2-methylpentyl. "Alkoxy" radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. "Cycloalkyl" groups contain 3 to 8 ring carbons and preferably 5 to 7 ring carbons. The alkyl, alkenyl, alkynyl, cycloalkyl group and alkoxy groups may be independently substituted with one or more members of the group including, but not limited to, hydroxyimino, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, oxo, alkoxyimino aryl, heteroaryl, heterocyclo, CN, nitro, $-OCOR_{13}$, $-OR_{13}$, $-SR_{13}$, $-SOR_{13}$, $-SO_2R_{13}$, $-COOR_{13}$, $-NR_{13}R_{14}$, $-CONR_{13}R_{14}$, $-OCONR_{13}R_{14}$, $-NHCOR_{13}$, $-NHCOOR_{13}$, and $-NHCONR_{13}R_{14}$, wherein R_{13} and

R_{14} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, and heterocycloalkyl, or alternatively R_{14} and R_{15} may join to form a heterocyclic ring containing the nitrogen atom to which they are attached.

The term "acyl" as used herein, whether used alone or as part of a substituent group, means an organic radical having 2 to 6 carbon atoms (branched or straight chain) derived from an organic acid by removal of the hydroxyl group. The term "Ac" as used herein, whether used alone or as part of a substituent group, means acetyl.

The term "halo" or "halogen" means fluoro, chloro, bromo or iodo. (Mono-, di-, tri-, and per-)halo-alkyl is an alkyl radical substituted by independent replacement of the hydrogen atoms thereon with halogen.

"Aryl" or "Ar," whether used alone or as part of a substituent group, is a carbocyclic aromatic radical including, but not limited to, phenyl, 1- or 2-naphthyl and the like. The carbocyclic aromatic radical may be substituted by independent replacement of 1 to 3 of the hydrogen atoms thereon with aryl, heteroaryl, halogen, OH, CN, mercapto, nitro, amino, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_1-C_8-alkoxyl, C_1-C_8-alkylthio, C_1-C_8-alkyl-amino, di (C_1-C_8-alkyl)amino, (mono-, di-, tri-, and per-)halo-alkyl, formyl, carboxy, alkoxycarbonyl, C_1-C_8-alkyl-CO-O-, C_1-C_8-alkyl-CO-NH-, or carboxamide. Illustrative aryl radicals include, for example, phenyl, naphthyl, biphenyl, fluorophenyl, difluorophenyl, benzyl, benzoyloxyphenyl, carboethoxyphenyl, acetylphenyl, ethoxyphenyl, phenoxyphenyl, hydroxyphenyl, carboxyphenyl, trifluoromethylphenyl, methoxyethylphenyl, acetamidophenyl, tolyl, xylyl, dimethylcarbamylphenyl and the like. "Ph" or "PH" denotes phenyl. "Bz" denotes benzoyl.

Whether used alone or as part of a substituent group, "heteroaryl" refers to a cyclic, fully unsaturated radical having from five to ten ring atoms of which one ring atom is selected from S, O, and N; 0-2 ring atoms are additional heteroatoms independently selected from S, O, and N; and the remaining ring atoms are carbon. The radical may be joined to the rest of the molecule via any of the ring atoms. Exemplary heteroaryl groups include, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, triazolyl, triazinyl, oxadiazolyl, thienyl,

furanyl, quinolinyl, isoquinolinyl, indolyl, isothiazolyl, N-oxo-pyridyl, 1,1-dioxothienyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl-N-oxide, benzimidazolyl, benzopyranyl, benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, indazolyl, indolizinyl, benzofuryl, cinnolinyl, quinoxalinyl, pyrrolopyridinyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl, or furo[2,3-b]pyridinyl), imidazopyridinyl (such as imidazo[4,5-b]pyridinyl or imidazo[4,5-c]pyridinyl), naphthyridinyl, phthalazinyl, purinyl, pyridopyridyl, quinazolinyl, thienofuryl, thienopyridyl, and thienothienyl. The heteroaryl group may be substituted by independent replacement of 1 to 3 of the hydrogen atoms thereon with aryl, heteroaryl, halogen, OH, CN, mercapto, nitro, amino, C_1-C_8-alkyl, C_1-C_8-alkoxyl, C_1-C_8-alkylthio, C_1-C_8-alkyl-amino, di(C_1-C_8-alkyl)amino, (mono-, di-, tri-, and per-)halo-alkyl, formyl, carboxy, alkoxycarbonyl, C_1-C_8-alkyl-CO-O-, C_1-C_8-alkyl-CO-NH-, or carboxamide.

Heteroaryl may be substituted with a mono-oxo to give for example a 4-oxo-1H-quinoline.

The terms "heterocycle," "heterocyclic," and "heterocyclo" refer to an optionally substituted, fully saturated, partially saturated, or non-aromatic cyclic group which is, for example, a 4- to 7-membered monocyclic, 7- to 11-membered bicyclic, or 10- to 15-membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, or 3 heteroatoms selected from nitrogen atoms, oxygen atoms, and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized. The nitrogen atoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom. The heterocyclic group may be substituted by independent replacement of 1 to 3 of the hydrogen atoms thereon with aryl, heteroaryl, halogen, OH, CN, mercapto, nitro, amino, C_1-C_8-alkyl, C_1-C_8-alkoxyl, C_1-C_8-alkylthio, C_1-C_8-alkyl-amino, di(C_1-C_8-alkyl)amino, (mono-, di-, tri-, and per-)halo-alkyl, formyl, carboxy, alkoxycarbonyl, C_1-C_8-alkyl-CO-O-, C_1-C_8-alkyl-CO-NH-, or carboxamide.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl; oxetanyl; pyrazolinyl; imidazolinyl; imidazolidinyl; oxazolinyl; oxazolidinyl; isoxazolinyl; thiazolidinyl; isothiazolidinyl; tetrahydrofuryl; piperidinyl; piperazinyl; 2-

oxopiperazinyl; 2-oxopiperidinyl; 2-oxopyrrolidinyl; 4-piperidonyl; tetrahydropyranyl; tetrahydrothiopyranyl; tetrahydrothiopyranyl sulfone; morpholinyl; thiomorpholinyl; thiomorpholinyl sulfoxide; thiomorpholinyl sulfone; 1,3-dioxolane; dioxanyl; thietanyl; thiiranyl; 2-oxazepinyl; azepinyl; and the like. Exemplary bicyclic heterocyclic groups include quinuclidinyl; tetrahydroisoquinolinyl; dihydroisoindolyl; dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl); dihydrobenzofuryl; dihydrobenzothienyl; benzothiopyranyl; dihydrobenzothiopyranyl; dihydrobenzothiopyranyl sulfone; benzopyranyl; dihydrobenzopyranyl; indolinyl; chromonyl; coumarinyl; isochromanyl; isoindolinyl; piperonyl; tetrahydroquinolinyl; and the like.

The term "carbocyclic" refers to a saturated or unsaturated, non-aromatic, monocyclic, hydrocarbon ring of 3 to 7 carbon atoms.

Substituted aryl, substituted heteroaryl, and substituted heterocycle may also be substituted with a second substituted aryl, a second substituted heteroaryl, or a second substituted heterocycle to give, for example, a 4-pyrazol-1-yl-phenyl or 4-pyridin-2-yl-phenyl.

Designated numbers of carbon atoms (e.g., C_1-C_8 or C_{1-8}) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

Unless specified otherwise, it is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

The term "hydroxy protecting group" refers to groups known in the art for such purpose. Commonly used hydroxy protecting groups are disclosed, for example, in T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), which is incorporated herein by reference. Illustrative hydroxyl protecting groups include but are not limited to tetrahydropyranyl; benzyl; methylthiomethyl;

ethylthiomethyl; pivaloyl; phenylsulfonyl; triphenylmethyl; trisubstituted silyl such as trimethylsilyl, triethylsilyl, tributylsilyl, tri-isopropylsilyl, t-butyldimethylsilyl, tri-t-butylsilyl, methyldiphenylsilyl, ethyldiphenylsilyl, t-butyldiphenylsilyl; acyl and aroyl such as acetyl, benzoyl, pivaloylbenzoyl, 4-methoxybenzoyl, 4-nitrobenzoyl and arylacyl.

Where the compounds according to this invention have at least one stereogenic center, they may accordingly exist as enantiomers. Where the compounds possess two or more stereogenic centers, they may additionally exist as diastereomers. Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

Some of the compounds of the present invention may have trans and cis isomers. In addition, where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared as a single stereoisomer or in racemic form as a mixture of some possible stereoisomers. The non-racemic forms may be obtained by either synthesis or resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation. The compounds may also be resolved by covalent linkage to a chiral auxiliary, followed by chromatographic separation and/or crystallographic separation, and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using chiral chromatography.

The phrase "a pharmaceutically acceptable salt" denotes one or more salts of the free base or free acid which possess the desired pharmacological activity of the free base or free acid as appropriate and which are neither biologically nor otherwise undesirable. These salts may be derived from inorganic or organic acids. Examples of inorganic acids are hydrochloric acid, nitric acid, hydrobromic acid, sulfuric acid, or phosphoric acid. Examples of

organic acids are acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, salicyclic acid and the like. Suitable salts are furthermore those of inorganic or organic bases, such as KOH, NaOH, $Ca(OH)_2$, $Al(OH)_3$, piperidine, morpholine, ethylamine, triethylamine and the like.

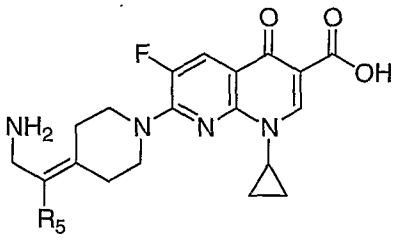
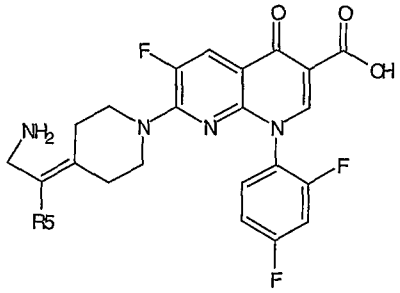
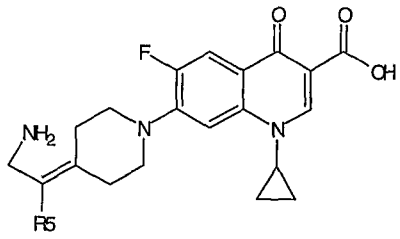
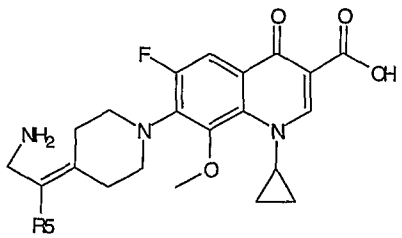
Included within the scope of the invention are the hydrated forms of the compounds that contain various amounts of water, for instance, the hydrate, hemihydrate, and sesquihydrate forms. The present invention also includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds that are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

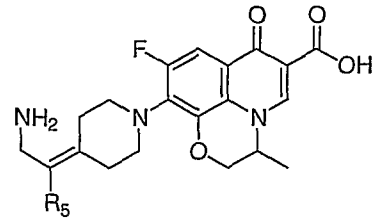
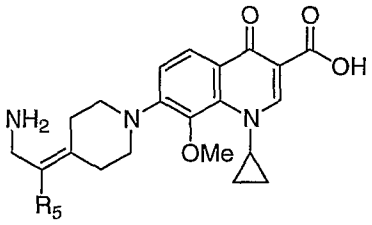
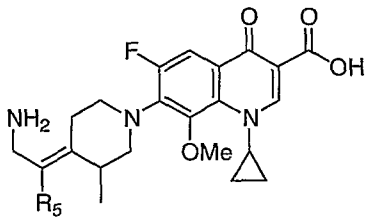
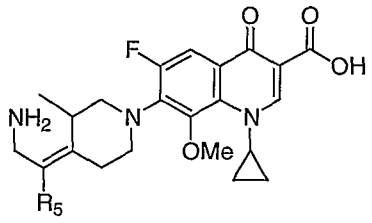
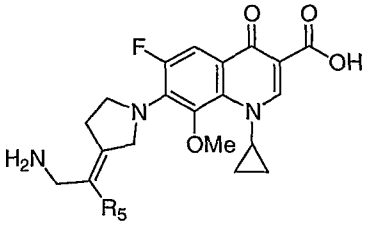
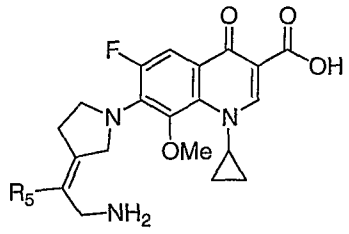
The term "subject" includes, without limitation, any animal or artificially modified animal. As a particular embodiment, the subject is a human.

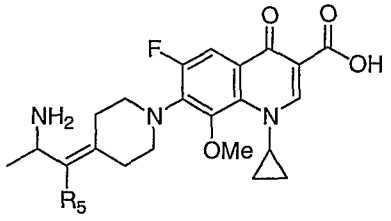
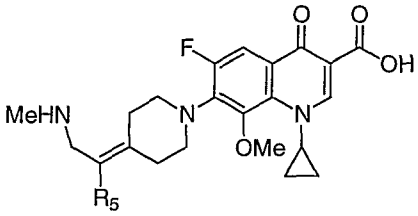
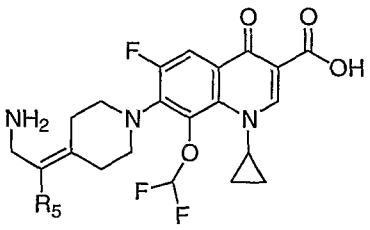
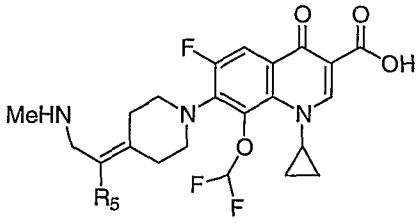
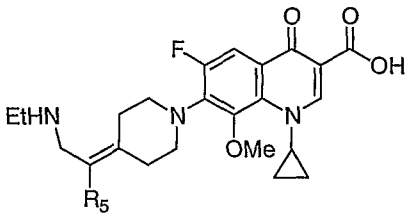
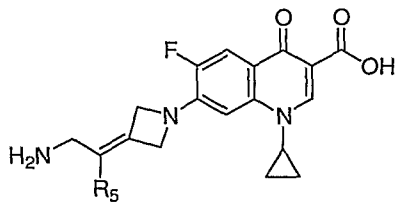
The term "drug-resistant" or "drug-resistance" refers to the characteristics of a microbe to survive in the presence of a currently available antimicrobial agent such as an antibiotic at its routine, effective concentration.

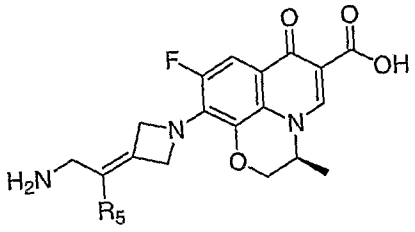
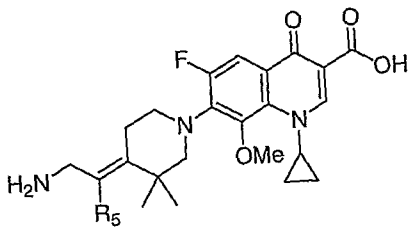
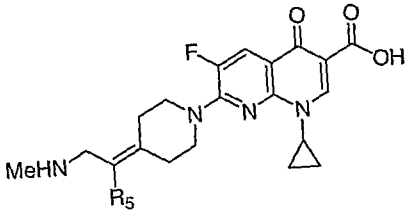
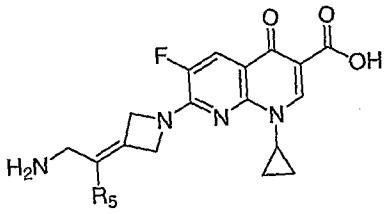
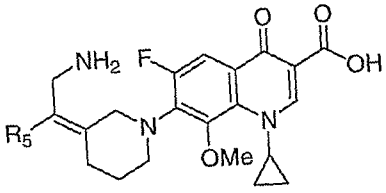
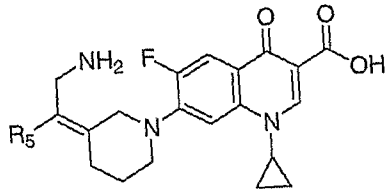
Table 1 contains a non-limiting list of preferred compounds of Formula I.

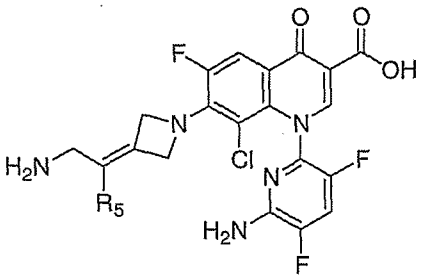
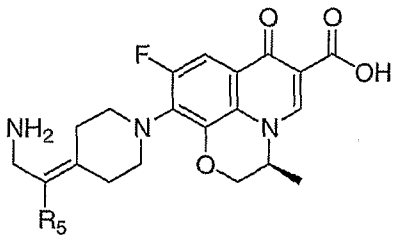
Table 1

Structure	R5 Substituent	Compound Number
	F	**1**
	CH_3	**2**
	Cl	**3**
	CH_3CH_2	**69**
	F	**4**
	F	**5**
	Cl	**65**
	F	**6**
	Cl	**7**
	CH_3	**70**
	CH_3CH_2	**71**

	F	**8**
	CH_3	**9**
	F	**10**
	F	**11**
	F	**12**
	Cl	**13**
	Cl	**14**

	Cl	**15**
	Cl	**72**
	Cl	**73**
	Cl	**74**
	Cl	**75**
	Cl	**76**

	Cl	**77**
	F	**78**
	F	**79**
	F	**80**
	Cl	**81**
	F	**303**
	Cl	**261**
	CH_3	**302**
	Cl	**257**

	F	269
	Cl	268
	Cl	277

General Reaction Scheme for Compound Preparation

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

The starting materials used in preparing the compounds of the invention are known, made by published synthetic methods or available from commercial vendors.

It is recognized that the skilled artisan in the art of organic chemistry can readily carry out standard manipulations of the organic compounds without further direction; that is, it is well within the scope and practice of the skilled artisan to carry out such manipulations. These include, but are not limited to, reductions of carbonyl compounds to their corresponding alcohols, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic,

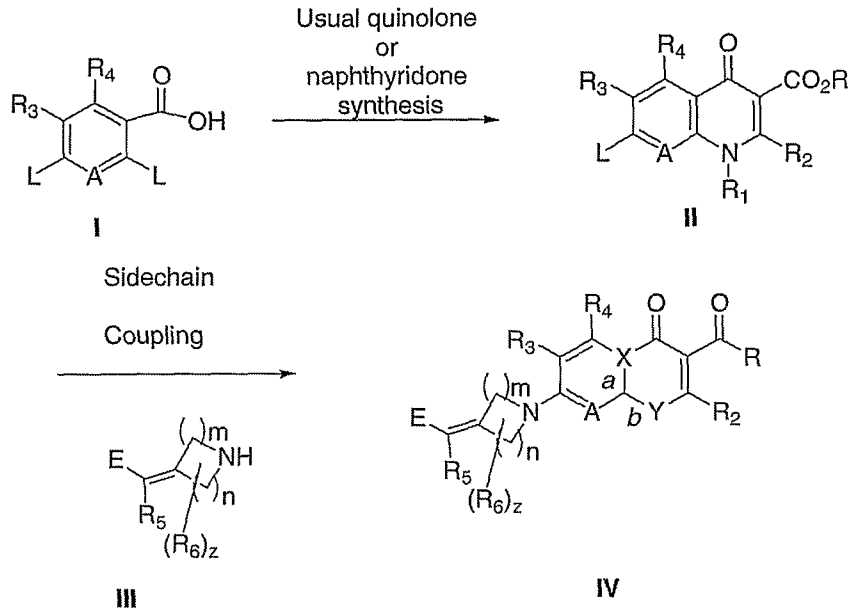
etherifications, esterification and saponification and the like. Examples of these manipulations are discussed in standard texts such as March, Advanced Organic Chemistry (Wiley), Carey and Sundberg, Advanced Organic Chemistry (Vol. 2), Feiser & Feiser, Reagents for Organic Synthesis (16 volumes), L. Paquette, Encyclopedia of Reagents for Organic Synthesis (8 volumes), Frost & Fleming, Comprehensive Organic Synthesis (9 volumes) and the like.

The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus avoiding any undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. Examples of these manipulations can be found for example in T. Greene, Protecting Groups in Organic Synthesis.

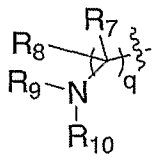
General procedures for preparing heterocyclic nuclei useful in making the compounds of the invention are described in the following references, all incorporated by reference herein (including articles listed within the references): U.S. Patent 6329391, European Patent Publication 342849, International Patent Publication WO9711068, European Patent Publication 195316, European Patent Publication 1031569, U.S. Patent 6025370, European Patent Publication 153828, European Patent Publication 191451, European Patent Publication 153163, European Patent Publication 230053, European Patent Publication 976749, International Patent Publication WO0118005, International Patent Publication WO9407873, U.S. Patent 4777253, European Patent Publication 421668, International Patent Publication WO0248138, European Patent Publication 230295, International Patent Publication WO9914214, U.S. Patent Publication 20020049223, International Patent Publication WO9921849, International Patent Publication WO9729102, International Patent Publication WO0334980, International Patent Publication WO0209758, International Patent Publication WO9619472, German Patent Publication DE 3142854, International Patent Publication WO0334980, International Patent Publication WO0328665, European Patent Publication 47005, International Patent Publication WO0311450, and European Patent Publication 688772.

The compounds of the subject invention may be prepared in several ways. Versatile methodologies for preparation of the compounds of the invention are shown in Scheme I below, where L is a leaving group such as fluoro or chloro:

Scheme I

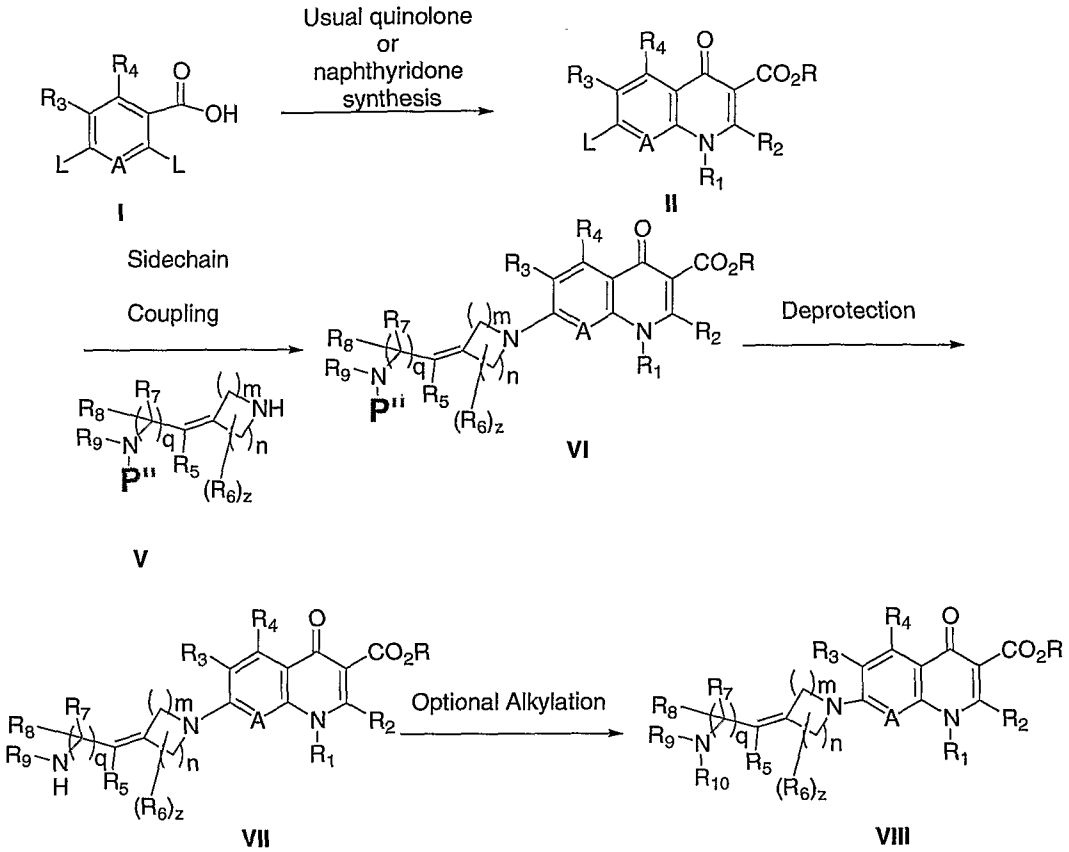


In the case where E is



and at least one of R_9 and R_{10} is hydrogen, it may be necessary to protect the terminal nitrogen to effect selective conversion to the desired product (Scheme II). In such case, standard amine protecting groups known to those skilled in the art, such as t-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), benzyl (Bn), 9-fluorenylmethoxycarbonyl (Fmoc), allyloxycarbonyl (Alloc), 2-trimethylsilylethoxycarbonyl (Teoc), N-formyl, N-acetyl, N-benzoyl, or phthalimide, may be used to mask the terminal amine, as in compound **V**. Following side chain coupling, the protecting group may be removed under standard conditions known to those skilled in the art to obtain the desired product **VII**. **VII** may be further elaborated, for example by alkylation, to other compounds of the invention **VIII**.

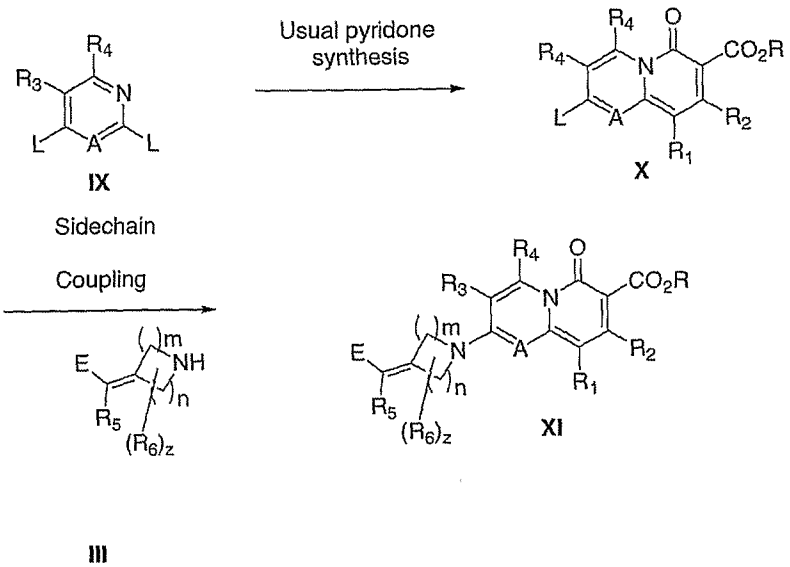
Scheme II

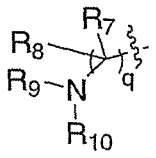


P^n = protecting group

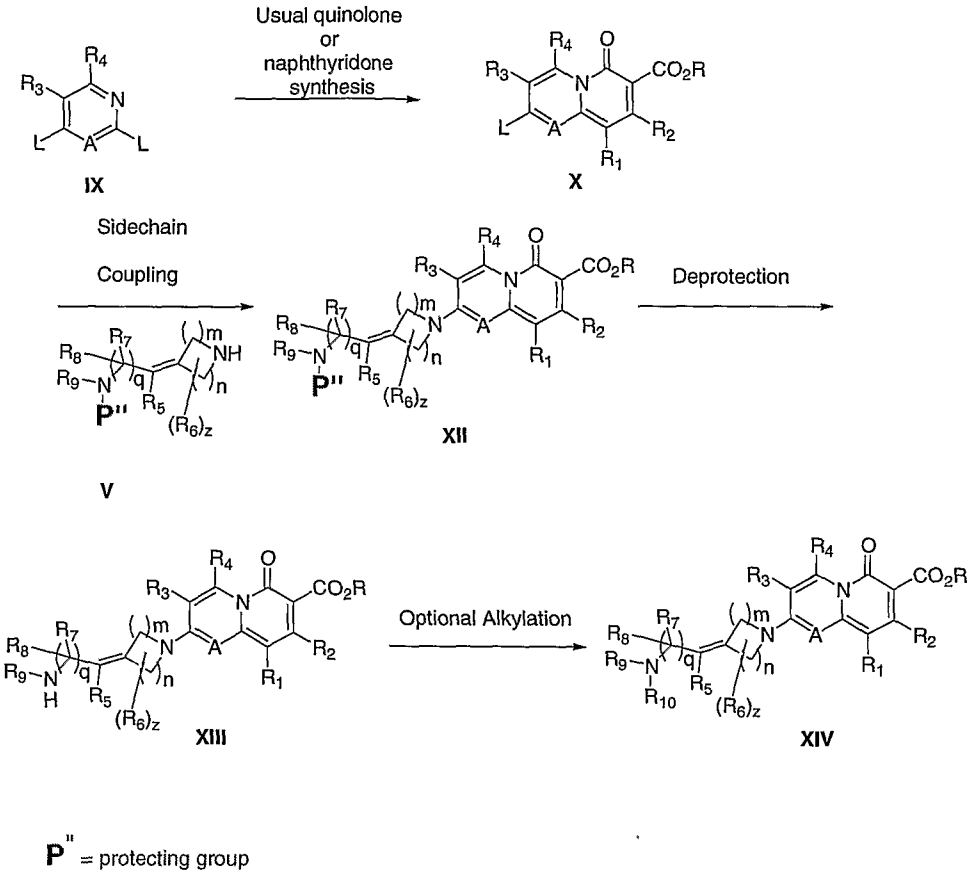
Methodologies for providing the compounds of the invention where X is N and Y is C(R_1) are shown in Scheme III below:

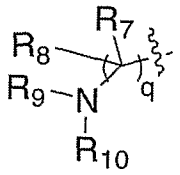
Scheme III



As before, where E is  and at least one of R_9 and R_{10} is hydrogen, it may be necessary to protect the terminal nitrogen to effect selective conversion to the desired product (Scheme IV). In such case, standard amine protecting groups known to those skilled in the art, such as *t*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), benzyl (Bn), 9-fluorenylmethoxycarbonyl (Fmoc), allyloxycarbonyl (Alloc), 2-trimethylsilylethoxycarbonyl (Teoc), N-formyl, N-acetyl, N-benzoyl, or phthalimide, may be used to mask the terminal amine, as in compound **V**. Following side chain coupling, the protecting group may be removed under standard conditions known to those skilled in the art to obtain the desired product **XIII**. **XIII** may be further elaborated, for example by alkylation, to other compounds of the invention **XIV**.

Scheme IV

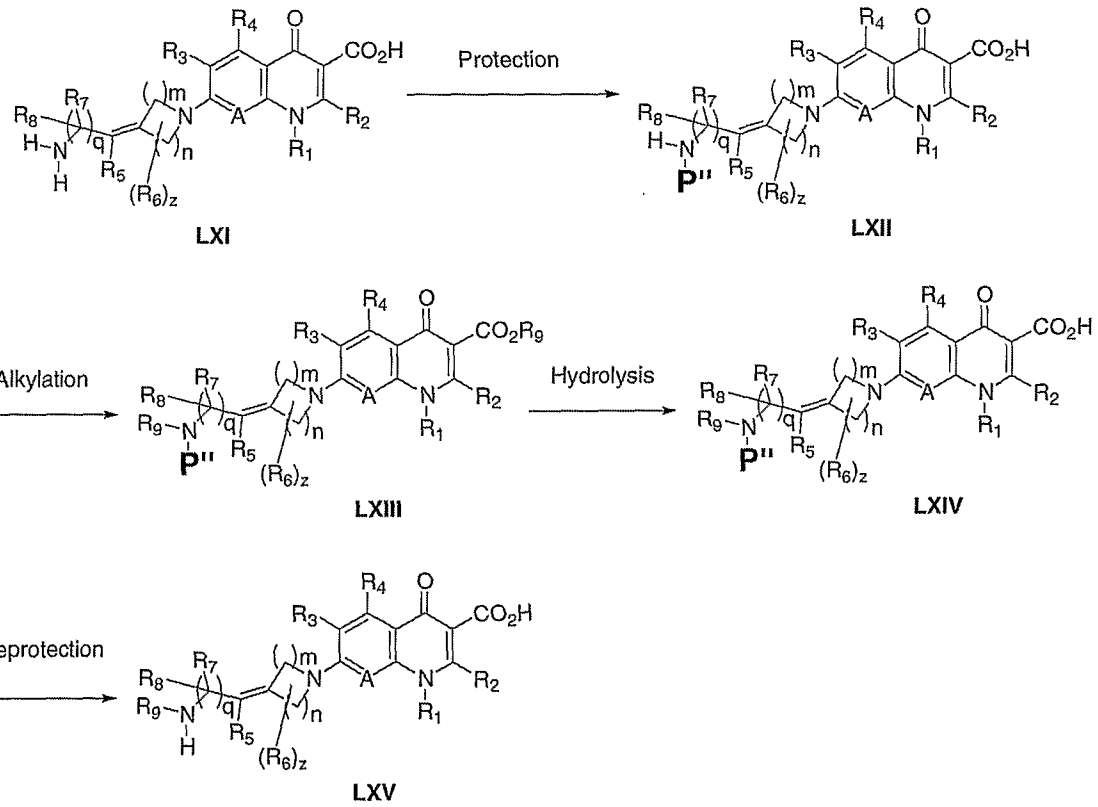


In the case where E is 

and both R_9 and R_{10} are hydrogen, selective alkylation of the side chain amine of **LXI** may also be accomplished by protection of the amine with a standard protecting group, such as Boc, utilizing reagents and conditions apparent to those skilled in the art to give **LXII** (Scheme XXXVI). The protected amine (**LXII**) is then treated with an excess (>2 equivalents) of a base, such as, but not limited to, sodium hydride, in an appropriate inert solvent, such as dimethylformamide or tetrahydrofuran, followed by the appropriate alkylating agent R_9X to yield the boc-protected secondary amine as the corresponding ester **LXIII**. Typically, the reaction is run at temperatures ranging from –20°C

to 60°C for from 1 to 48 hours depending on the reactivity of the alkylating agent. Typical alkylating agents including alkyl iodides (such as methyl iodide), alkyl bromides and alkyl sulfonates. The ester **LXIII** may be hydrolyzed under basic conditions to afford the corresponding carboxylic acid **LXIV**. Ester hydrolysis may be conducted by methods familiar to those skilled in the art, in particular, by employing a base such as an alkali metal hydroxide (for example, sodium hydroxide) or an alkali metal carbonate in a suitable solvent, such as water, methanol, ethanol, or aqueous alcohol mixtures, at a temperature ranging from 20°C to 100°C for from 1 to 48 hours. Removal of the amine-protecting group under conditions apparent to one skilled in the art affords the secondary amine **LXV**. In the case where the protecting group is Boc, for example, reagents such as with trifluoroacetic acid, optionally with methylene chloride as co-solvent, or hydrochloric acid in dioxane, may be used for deprotection.

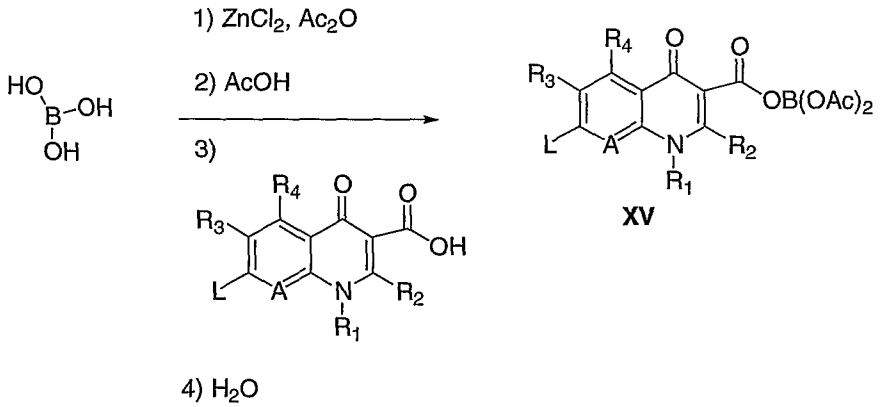
Scheme XXXVI



$P^{''}$ = protecting group

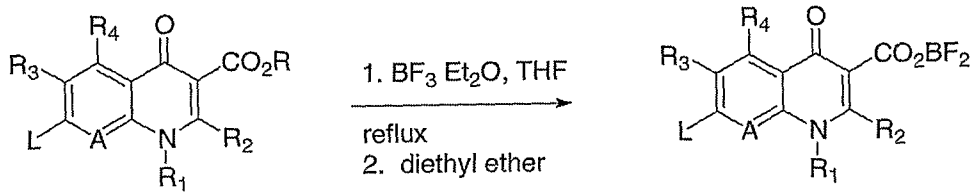
Occasionally, side chain amines are insufficiently reactive to add efficiently to the heterocyclic nuclei (**II** or **X**) under the conditions illustrated in Schemes I-IV, particularly when A is $C(R_{11})$, wherein R_{11} is alkoxy. The nucleus can be activated towards nucleophilic attack by the addition of a Lewis acid such as, but not limited to, boron trifluoride, triacetoxyborate, and lithium chloride. The preferred method of activation is described in U.S. Patent 5,157,117. The quinolone nucleus is treated with triacetoxyborate, prepared in situ, in solvent such as, but not limited to, acetic acid or propionic acid and is heated for 1 to 24 h at a temperature between 60°C and 120°C. The diacyl quinolinylborate (**XV**) is isolated by filtration after removal of the solvent. Scheme V illustrates this preferred method of activation.

Scheme V



Another preferred method for activating the heterocyclic nucleus toward nucleophilic attack is illustrated in Scheme XXXVII. In this method, a quinolone carboxylic acid or ester derivative (i.e., compound **II** wherein R is hydrogen or lower alkyl and L is a leaving group) is treated with boron trifluoride etherate, preferably in a suitable solvent, such as THF, for from 1 hour to 48 hours at temperatures ranging from 0°C to 60°C. After cooling, the product **LXVI** may be precipitated from the reaction mixture by the addition of a suitable solvent, such as diethyl ether, and the chelate isolated by filtration of the resulting solid.

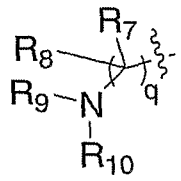
Scheme XXXVII



II **LXVI**

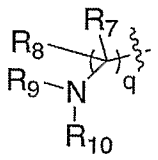
Precursor Preparation – Side chain amine III

Scheme VI illustrates the synthesis of the side chain amine **III** wherein E is



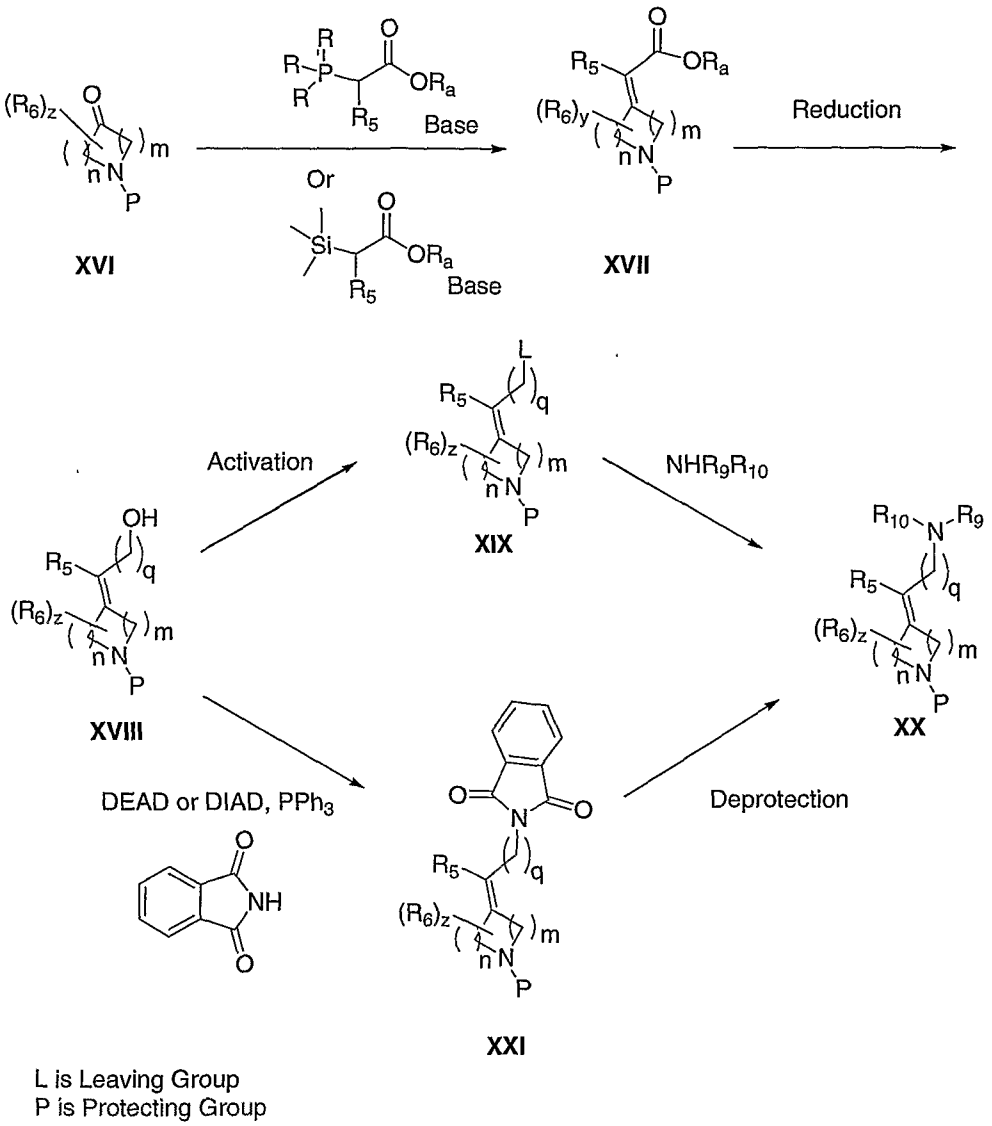
R_7 and R_8 are hydrogen, and q is 1. The trisubstituted or tetrasubstituted alkylidenes **XX** can be prepared by a Peterson, Wittig or Wadsworth-Horner-Emmons olefination of an appropriately substituted ketone (**XVI**) in a solvent such as, but not limited to, tetrahydrofuran, dimethylsulfoxide, or methylene chloride for 1 to 24 h at a temperature between -78°C to 120°C in the presence of a base such as, but not limited to *n*-butyl lithium, sodium hydride or potassium carbonate. The resulting ester (**XVII**) can be reduced with a reducing agent such as, but not limited to, diisobutylaluminum hydride, lithium

triethylborohydride or sodium borohydride in a solvent such as, but not limited to, toluene, methylene chloride, or tetrahydrofuran for 1 to 24 h at a temperature between 0°C and 120°C to afford the corresponding alcohol **XVIII**, where q = 1. Converting the alcohol **XVIII** to leaving group **XIX**, such as, but not limited to, chloride, bromide, mesylate or tosylate under standard conditions and displacing the leaving group with an appropriately substituted amine in a solvent such as, but not limited to, dimethylformamide, dimethylsulfoxide, or tetrahydrofuran for 1 to 24 h at a temperature between 0°C and 120°C converts the alcohol **XVIII** to an amine **XX**. Removal of the protecting group, P, under standard conditions known to those skilled in the art affords amine **III**, wherein E is



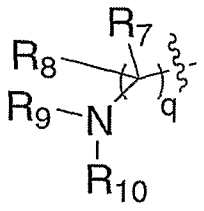
R_7 and R_8 are hydrogen, and q is 1. Alternatively, direct replacement of the alcohol **XVIII** can be accomplished via a Mitsunobu reaction with phthalimide and dialkyl azodicarboxylate to afford **XXI**. Deprotection of the phthalimide (**XXI**) with hydrazine in a solvent such as methanol or ethanol affords the amine (**XX**), wherein R_9 and R_{10} are hydrogen. Alternative methods of deprotection include treatment with methylamine in methanol or with 6N hydrochloric acid. The protecting group, P, may be removed from **XXI** under standard conditions known to those skilled in the art to provide the amine **V**, wherein R_7 and R_8 are hydrogen and R_9 and P" together with the nitrogen to which they are attached form a phthalimide group.

Scheme VI



It will be apparent to one skilled in the art that the conversion of ketone **XVI** to olefin **XVII** may lead to geometrical isomers (Scheme VI), specifically in the case where **XVI** is asymmetric (i.e., the value of m is not equal to n). In such a case, the geometrical isomers may be separated by a number of methods known to those skilled in the art, including selective recrystallization, flash chromatography, high-performance liquid chromatography, and the like. It should also be apparent that separation may be achieved at various stages in the synthetic process, including at intermediates **XVII**, **XVIII**, **XIX**, or **XXI**, or alternatively at the final product stage **XX**.

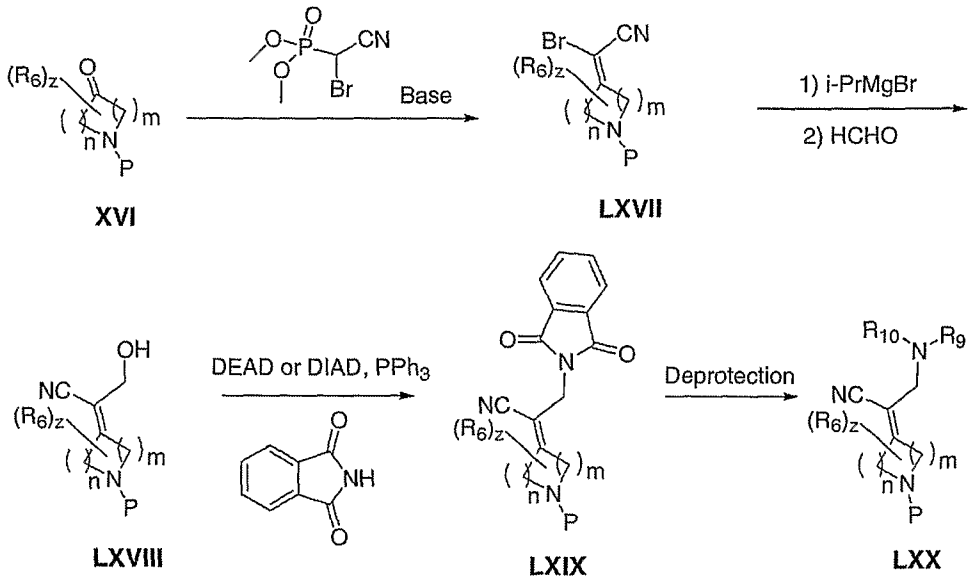
Scheme XXXVIII illustrates the synthesis of the side chain amine **LXX** wherein E is



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R_5 is cyano, R_7 and R_8 are hydrogen, and q is 1. The tetrasubstituted alkylidenes **LXVII** can be prepared by a Wadsworth-Horner-Emmons olefination of an appropriately substituted ketone (**XVI**) in a solvent such as, but not limited to, tetrahydrofuran, dimethylsulfoxide, or methylene chloride for from 1 to 24 h at a temperature between –78 °C to 120 °C in the presence of a base such as, but not limited to *n*-butyl lithium, sodium hydride or potassium carbonate. The cyano-substituted alkenyl bromides can undergo bromine-magnesium exchange with i-PrMgBr in an inert solvent, such as THF, at temperatures ranging from –78°C to –20°C. The resulting organomagnesium species, as a solution in a suitable solvent such as THF, may be treated with an electrophile such as formaldehyde, optionally stabilized with methylaluminum bis(2,6-diphenylphenoxide), in a suitable solvent, such as methylene chloride, for from 1 to 24 hours at temperatures ranging from –20°C to 37°C to give the alcohol **LXVIII**. Direct replacement of the alcohol **LXVIII** can be accomplished via a Mitsunobu reaction with phthalimide and a dialkyl azodicarboxylate to afford **LXIX**. Deprotection of the phthalimide (**LXIX**) with hydrazine in a solvent such as methanol or ethanol affords the amine (**LXX**), wherein R_9 and R_{10} are hydrogen. Alternative methods of deprotection include treatment with methylamine in methanol or heating with 6N hydrochloric acid. The protecting group, P, may be removed from **LXX** under standard conditions known to those skilled in the art to provide the amine **V**, wherein R_5 is cyano, R_7 and R_8 are hydrogen and R_9 and P" together with the nitrogen to which they are attached form a phthalimide group.

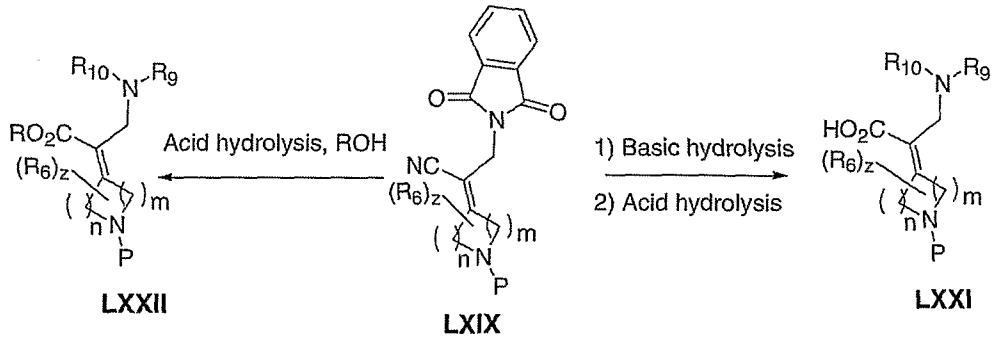
Scheme XXXVIII



P is Protecting Group

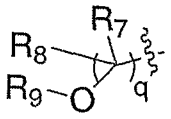
The cyano group of compound **LXIX** may also be converted to alternate functionalities, such as carboxy or alkoxycarbonyl, to afford amines **LXXI** or **LXXII** (Scheme XXXIX). For example, basic hydrolysis of nitrile **LXIX** with an alkali metal hydroxide, such as potassium hydroxide, in a suitable solvent, such as water, methanol, ethanol, or aqueous alcohol mixtures, at a temperature ranging from 20°C to 100°C for from 1 to 48 hours, followed by acid hydrolysis of the phthalamido group, with, for example, 6N hydrochloric acid at a temperature ranging from 60°C to 100°C for from 1 to 48 hours affords the corresponding amino acid derivative **LXXI** where R_9 and R_{10} are hydrogen. Alternatively, acid hydrolysis of nitrile **LXIX** with a mineral acid in the presence of an alcohol at a temperature ranging from 20°C to 200°C for from 30 minutes to 48 hours, optionally under microwave irradiation, provides the corresponding amino ester derivative **LXXII** where R_9 and R_{10} are hydrogen. Suitable mineral acids include, but are not limited to, sulfuric acid. Suitable alcohols include, but are not limited to, ethanol. Although Scheme XXXIX illustrates the conversion of nitrile **LXIX** to amino acid derivative **LXXI** and amino ester derivative **LXXII** with the ring nitrogen attached to a protecting group, the ring nitrogen may also be bound to the quinolone or naphthyridine nucleus as in compound **VIII** while performing the above transformations.

Scheme XXXIX

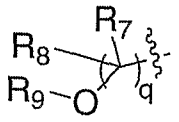


P is Protecting Group

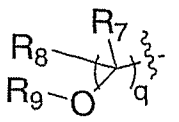
Scheme XXII illustrates the conversion of alcohols of formula **XVIII** to compounds of formula **III**, wherein E is alkenyl (**LVIII**). In addition, the Scheme outlines the synthesis of compounds of formula **III**, wherein E is



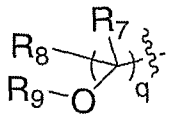
R_7 and R_8 are hydrogen and R_9 is acyl, alkoxycarbonyl, or sulfonyl (**LX**). Oxidation of alcohol **XVIII** with any of a number of suitable oxidizing agents, such as Dess-Martin periodinane, the Corey-Kim reagent, or the Swern reagent, affords the corresponding aldehyde (**LVI**). The aldehyde may be subjected to a base promoted olefination reaction, such as, but not limited to, the Wittig reaction to give **LVII**, wherein R_c is hydrogen or alkyl. Removal of the protecting group, P, from **LVII** under standard conditions known to those skilled in the art affords amine **III**, wherein E is alkenyl (**LVIII**). Scheme XX also illustrates the conversion of alcohols of formula **XVIII** to compounds of formula III, wherein E is

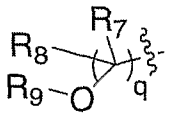


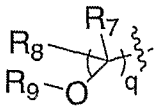
R_7 and R_8 are hydrogen, and R_9 is acyl, alkoxycarbonyl, or sulfonyl (**LX**). Reaction of alcohol **XVIII** with an acylating agent in the presence of an amine base, such as pyridine, in an inert solvent such as dichloromethane, tetrahydrofuran or toluene at temperatures ranging from –20°C to 60°C for from 1-48 hours provides compounds of formula **III**, wherein E is



R_7 and R_8 are hydrogen and R_9 is acyl (**LIX**). Acylating agents include acid halides, acid anhydrides, and acids in the presence of an activating agent such as dicyclohexylcarbodiimide, EDCI, BOP-Cl, BOP, PyBOP, and the like. Alcohols of formula **XVIII** may be converted into compounds of formula **III**, wherein E is

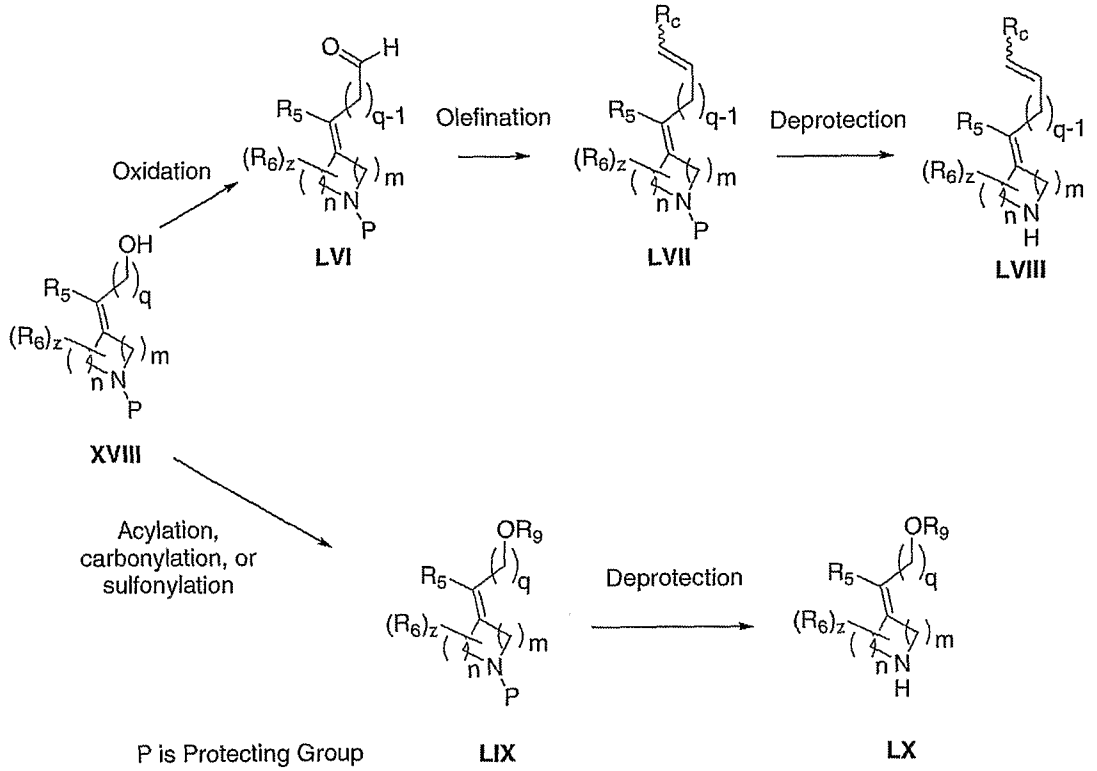


R_7 and R_8 are hydrogen and R_9 is alkoxycarbonyl (**LIX**) by reaction with a carbonylating agent in the presence of an amine base, such as pyridine, in an inert solvent such as dichloromethane, tetrahydrofuran or toluene at temperatures ranging from –20°C to 60°C for from 1-48 hours. Carbonylating agents include chloroformates, fluoroformates, azidoformates, and pyrocarbonates. Alcohols of formula **XVIII** may be converted into compounds of formula **III**, wherein E is 

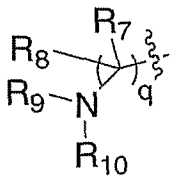
R_7 and R_8 are hydrogen and R_9 is sulfonyl (**LIX**) by reaction with a sulfonyl chloride or sulfonic anhydride in the presence of an amine base, such as pyridine, in an inert solvent such as dichloromethane, tetrahydrofuran or toluene at temperatures ranging from –20°C to 60°C for from 1-48 hours. Removal of the protecting group, P, from **LIX** under standard conditions known to those skilled in the art affords amine **III**, wherein E is 

R_7 and R_8 are hydrogen, and R_9 is acyl, alkoxycarbonyl, or sulfonyl (**LX**).

Scheme XXII

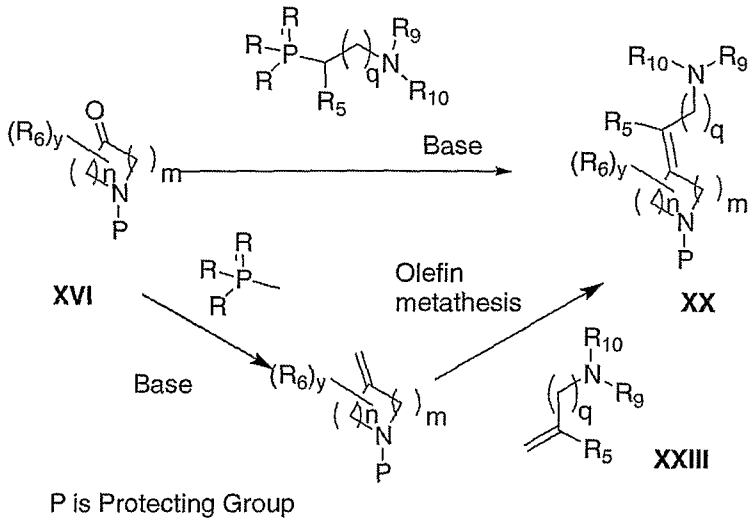


Scheme VII illustrates a direct conversion of ketone **XVI** to olefin **XX** using a base promoted olefination reaction such as, but not limited to, the Wittig, Wadsworth-Horner-Emmons, or Peterson olefination procedures. Alternatively, amine **XX** could be prepared by an olefin metathesis procedure from terminal olefin **XXII** using an appropriately substituted amine **XXIII**. Removal of the protecting group, P, from **XX** under standard conditions known to those skilled in the art affords amine **III**, wherein E is



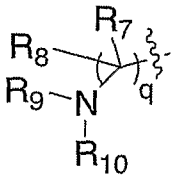
and R_7 and R_8 are hydrogen.

Scheme VII



XXII

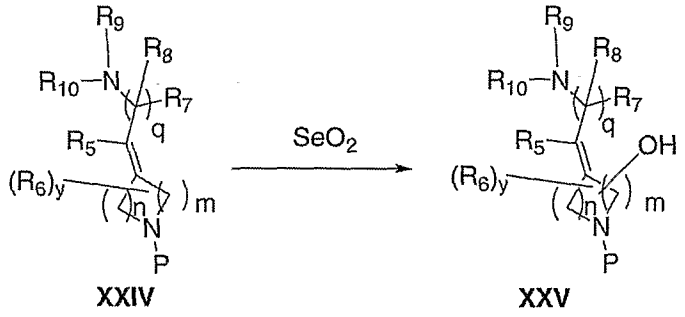
Scheme VIII illustrates the hydroxylation of **XXIV** with selenium dioxide to afford the allylic alcohol **XXV**. The transformation is performed in a solvent such as, but not limited to, methylene chloride, toluene or tetrahydrofuran at a temperature between 25°C and 150°C, optionally in the presence of a co-oxidant such as tert-butyl hydroperoxide. Removal of the protecting group, P, from **XXV** under standard conditions known to those skilled in the art affords amine **III**, wherein E is



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and one of R_6 is hydroxy.

Scheme VIII

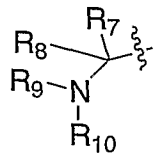


XXIV XXV

P is Protecting Group

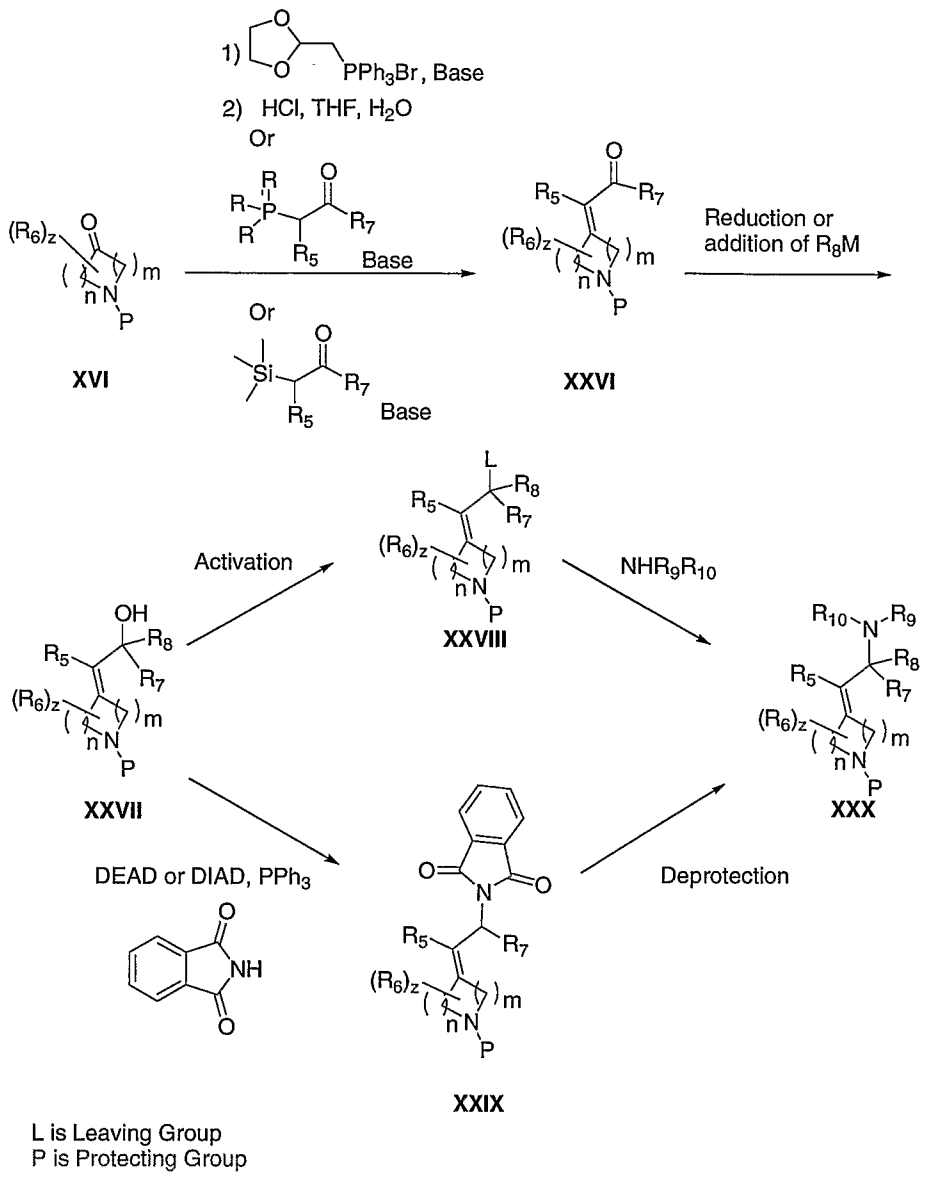
Scheme IX illustrates the preparation of α,β-unsaturated carbonyl compound **XXVI**, where R_7 is as defined previously, using a Peterson, Wittig or Wadsworth-Horner-Emmons olefination procedure of an appropriately substituted ketone (**XVI**) in a solvent such as, but not limited to, tetrahydrofuran, dimethylsulfoxide, or methylene chloride for from 1 to 24 h at a temperature between -78°C to 120°C in the presence of a base such as, but not limited to, *n*-butyl lithium, sodium hydride or potassium carbonate. The resulting carbonyl compound (**XXVI**) can be reduced with a reducing agent such as, but not limited to, diisobutylaluminum hydride, lithium triethylborohydride or sodium borohydride in a solvent such as, but not limited to, toluene, methylene chloride, or tetrahydrofuran for from 1 to 24 h at a temperature between 0°C and 120°C to afford the corresponding alcohol **XXVII**. Alternatively, the carbonyl compound may undergo nucleophilic addition with an appropriately substituted organometallic agent (R_8M, wherein M is a metal), such as an organolithium species or a Grignard reagent, to afford the corresponding alcohol **XXVII**, where R_8 is alkyl. Suitable solvents for the latter transformation include, diethyl ether, tetrahydrofuran, or toluene, at temperatures ranging from –78°C to 20°C for from 30 minutes to 48 hours. Where one of R_7 or R_8 are hydrogen, converting the alcohol functionality in **XXVII** to a leaving group, such as, but not limited to, bromide, mesylate or tosylate as in **XXVIII** under standard conditions and displacing the leaving group with an appropriately substituted amine in a solvent such as, but not limited to, dimethylformamide, dimethylsulfoxide, or tetrahydrofuran for from 1

to 24 h at a temperature between 0°C and 120°C converts the alcohol **XXVII** to an amine **XXX**. Removal of the protecting group, P, from **XXX** under standard conditions known to those skilled in the art affords amine **III**, wherein E is



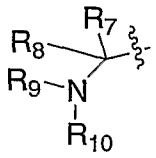
and one of R_7 and R_8 is hydrogen. Alternatively, where one of R_7 or R_8 is hydrogen, direct replacement of the alcohol **XXVII** can be accomplished via a Mitsunobu reaction with phthalimide and a dialkyl azodicarboxylate followed by deprotection of the phthalimide with hydrazine in a solvent such as methanol or ethanol to afford amine **XXX**. The protecting group, P, may be removed from **XXIX** under standard conditions known to those skilled in the art to provide the amine **V**, wherein R_8 is hydrogen and R_9 and P" together with the nitrogen to which they are attached form a phthalimide group.

Scheme IX



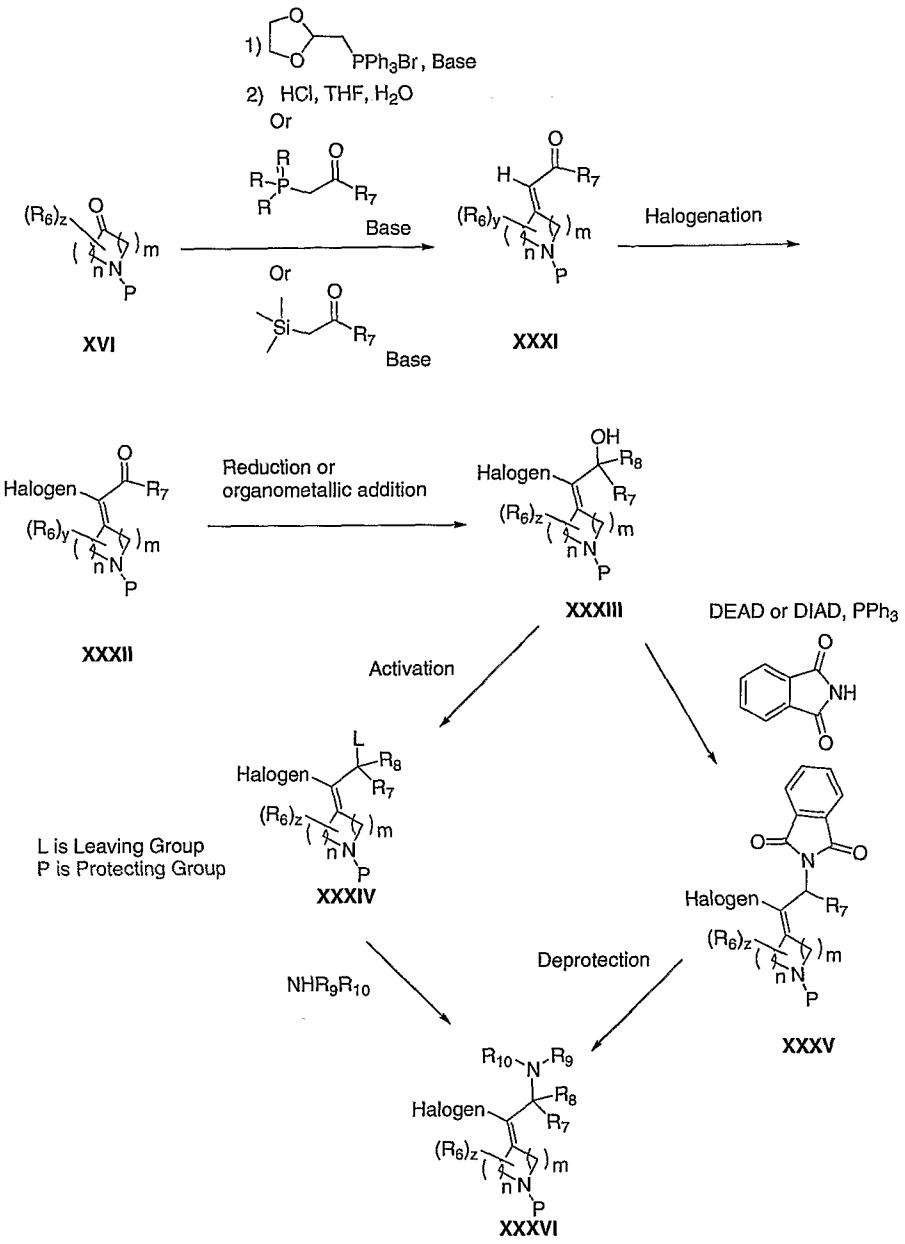
Scheme X depicts the preparation of **XXXVI**, wherein R_5 is halogen. Alkylidenes **XXXI**, wherein R_5 is hydrogen, can be halogenated with an appropriate halogenating agent such as, but not limited to, 1-bromo-2,5-pyrrolidinedione, 1,1,1-tris(acetyloxy)-1,1-dihydro-2-benziodoxol-3(1H)-one and a tetraalkylammonium bromide, or thionyl chloride to provide **XXXII.** Alkylidene **XXXII** can be reduced with a reducing agent such as, but not limited to, diisobutylaluminum hydride, lithium triethylborohydride or sodium borohydride in a solvent such as, but not limited to, toluene, methylene chloride, or

tetrahydrofuran for from 1 to 24 h at a temperature between 0°C and 120°C to afford the corresponding alcohol **XXXIII**. Alternatively, the carbonyl compound may undergo nucleophilic addition with an appropriately substituted organometallic agent, such as an organolithium species or a Grignard reagent, to afford the corresponding alcohol **XXXIII**, where R_8 is alkyl. Suitable solvents for the latter transformation include, diethyl ether, tetrahydrofuran, or toluene, at temperatures ranging from –78°C to 20°C for from 30 minutes to 48 hours. Where one of R_7 or R_8 is hydrogen, converting the alcohol functionality in **XXXIII** to a leaving group, such as, but not limited to, bromide, mesylate or tosylate as in **XXXIV** under standard conditions and displacing the leaving group with an appropriately substituted amine in a solvent such as, but not limited to, dimethylformamide, dimethylsulfoxide, or tetrahydrofuran for from 1 to 24 h at a temperature between 0°C and 120°C converts **XXXIV** to an amine **XXXVI**. Removal of the protecting group, P, from **XXXVI** under standard conditions known to those skilled in the art affords amine **III**, wherein E is

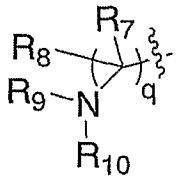


and one of R_7 and R_8 is hydrogen. Alternatively, where one of R_7 or R_8 is hydrogen, direct replacement of the alcohol **XXXIII** can be accomplished via a Mitsunobu reaction with phthalimide and a dialkyl azodicarboxylate followed by deprotection of the phthalimide with hydrazine in a solvent such as methanol or ethanol to afford the amine **XXXVI**. The protecting group, P, may be removed from **XXXV** under standard conditions known to those skilled in the art to provide the amine **V**, wherein R_8 is hydrogen and R_9 and P" together with the nitrogen to which they are attached form a phthalimide group.

Scheme X



Scheme XI illustrates the synthesis of the side chain amine **III** wherein E is

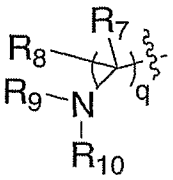


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R_7 and R_8 are hydrogen and R_5 is substituted or branched-chain alkyl. In Scheme XI, halogenated carbonyl compound **XXXVII**, wherein R_a is

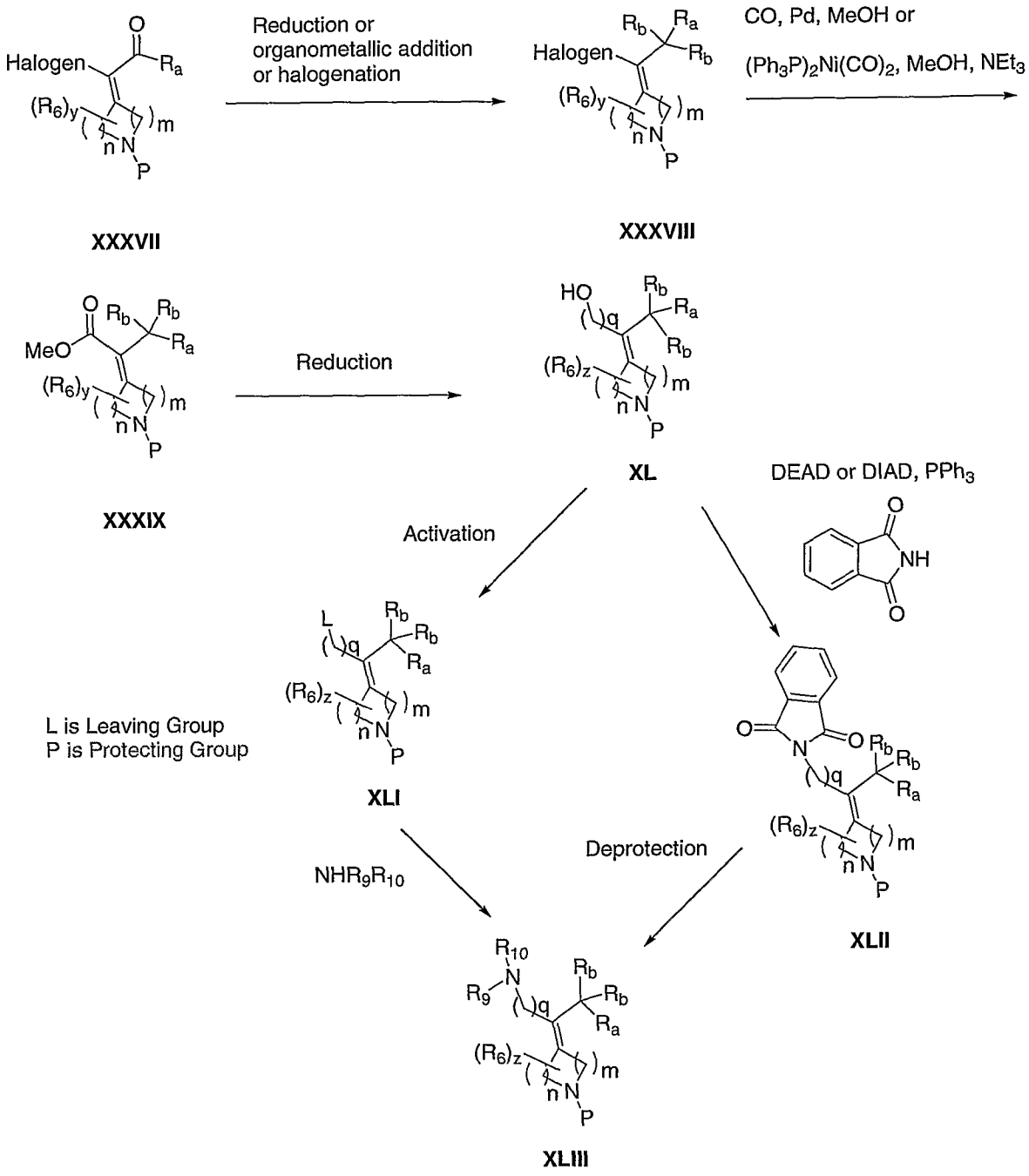
hydrogen or alkyl, may be prepared in a similar fashion as halogenated carbonyl compound **XXXII.** Carbonyl compound **XXXVII**, wherein Ra is hydrogen or alkyl, may be reduced with a reducing agent such as, but not limited to, diisobutylaluminum hydride, lithium triethylborohydride or sodium borohydride in a solvent such as, but not limited to, toluene, methylene chloride, or tetrahydrofuran for from 1 to 24 h at a temperature between 0°C and 120°C to afford the corresponding alcohol **XXXVIII** where R_a is hydrogen or alkyl, one of R_b is hydrogen, and the other R_b is hydroxyl. Alternatively, the carbonyl compound **XXXVII**, wherein R_a is alkyl, may undergo nucleophilic addition with an appropriately substituted organometallic agent, such as an organolithium species or a Grignard reagent, to afford the corresponding alcohol **XXXVIII** where R_a is alkyl, one of R_b is alkyl, and the other R_b is hydroxyl. Finally, carbonyl compound **XXXVII**, wherein R_a is hydrogen or alkyl, or alcohol **XXXVIII**, wherein R_a is hydrogen or alkyl, one of R_b is hydrogen, and the other R_b is hydroxyl, may be fluorinated using a nucleophilic fluorinating reagent, such as but not limited to, (N-ethylethanaminato)trifluorosulfur (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor), in a suitable solvent, such as methylene chloride, for from 1 to 24 h at a temperature between 0°C and 60°C to afford **XXXVIII**, where in the case of the carbonyl compound **XXXVII** as substrate, R_a is hydrogen or alkyl and R_b is fluorine, and where in the case of the alcohol **XXXVIII** as substrate, R_a is hydrogen or alkyl, one of R_b is hydrogen, and the other R_b is fluorine. Halogenated alkylidene **XXXVIII** may be carbonylated in the presence of a transition metal catalyst, such as but not limited to palladium acetate, dicarbonylbis(triphenylphosphine)nickel, or tetrakis (triphenylphosphine)palladium, under an atmosphere of carbon monoxide in the presence of a second additive such as methanol, optionally as solvent, or in a solvent such as, but not limited to, dimethylsulfoxide or tetrahydrofuran, for 1 to 24 h at a temperature between 0°C and 120°C to afford ester **XXXIX**. **XXXIX** may be reduced with a reducing agent such as, but not limited to, diisobutylaluminum hydride, lithium triethylborohydride or sodium borohydride in a solvent such as, but not limited to, toluene, methylene chloride, or tetrahydrofuran for 1 to 24 h at a temperature between 0°C and 120°C to afford the corresponding alcohol **XL**, where q = 1. Converting the alcohol **XL** to

leaving group **XLI**, such as, but not limited to, bromide, mesylate or tosylate, under standard conditions and displacing the leaving group with an appropriately substituted amine in a solvent such as, but not limited to, dimethylformamide, dimethylsulfoxide, or tetrahydrofuran for from 1 to 24 h at a temperature between 0°C and 120°C converts the alcohol **XL** to an amine **XLIII**. Removal of the protecting group, P, from **XLIII** under standard conditions known to those skilled in the art affords amine **III**, wherein E is

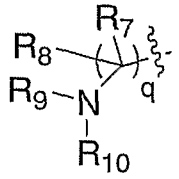


R_7 and R_8 are hydrogen and R_5 is $CR_aR_aR_b$. Alternatively, direct replacement of the alcohol **XL** may be accomplished via a Mitsunobu reaction with phthalimide and dialkyl azodicarboxylate to afford **XLII**. Deprotection of the phthalimide **XLII** with hydrazine in a solvent such as methanol or ethanol affords the amine **XLIII**. The protecting group, P, may be removed from **XLII** under standard conditions known to those skilled in the art to provide the amine **V**, wherein R_7 and R_8 are hydrogen, R_9 and P" together with the nitrogen to which they are attached form a phthalimide group, and R_5 is $CR_aR_aR_b$.

Scheme XI

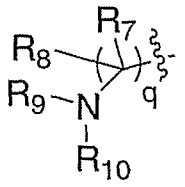


Scheme XII illustrates the synthesis of the side chain amine **III** wherein E is



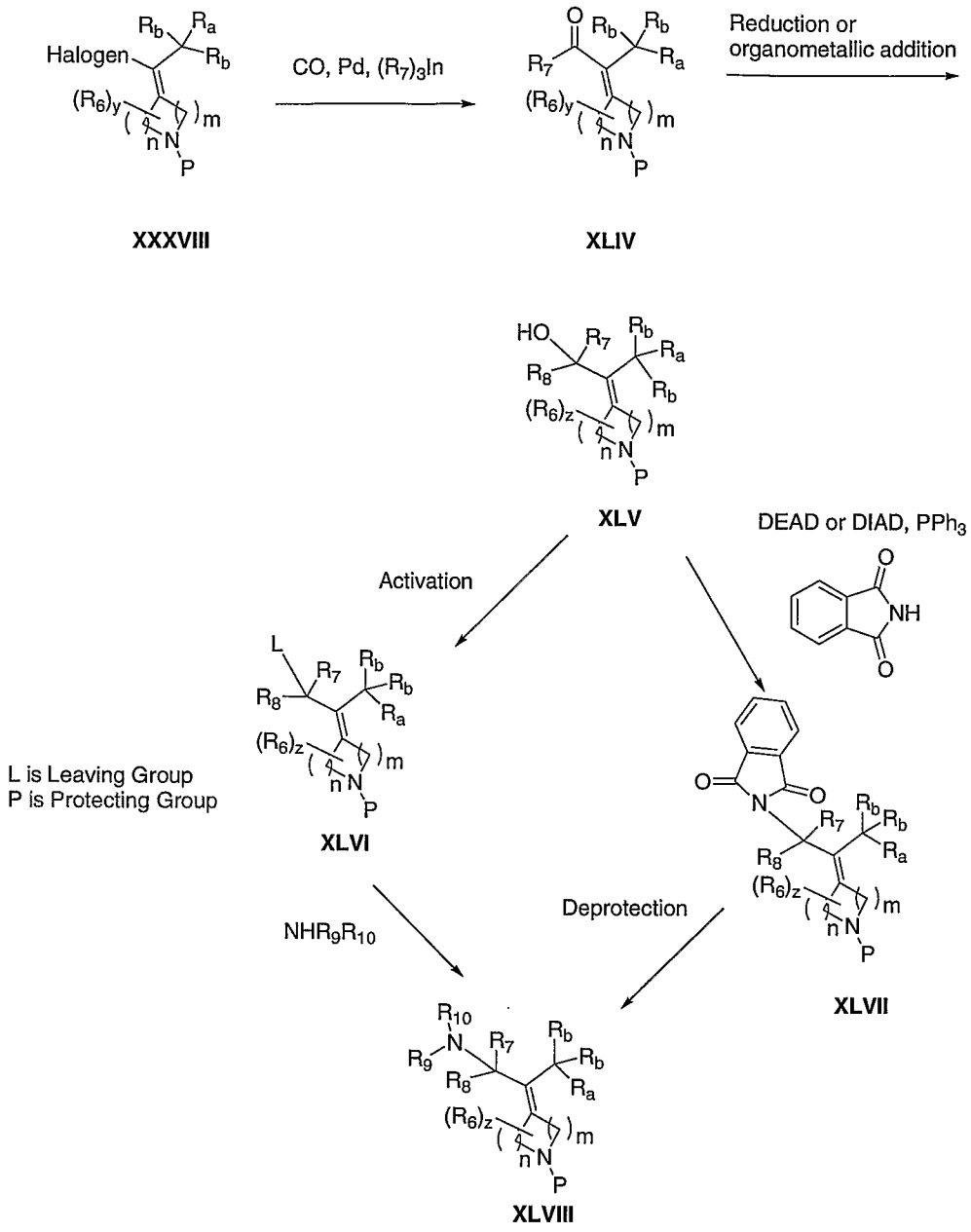
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one of R_7 or R_8 is hydrogen and the other is alkyl, R_5 is substituted or branched-chain alkyl, and q is 1. Compound **XXXVIII**, prepared as described above, may be carbonylated in the presence of a transition metal catalyst, such as but not limited to palladium acetate, dicarbonylbis(triphenylphosphine)nickel, or tetrakis (triphenylphosphine)palladium, under an atmosphere of carbon monoxide in the presence of an organometallic reagent R_7M, wherein R_7 is defined previously and includes reagents such as tributyltinhydride or alkyl indium agents (Organic Letters 2003, 5(7), 1103-1106), in a solvent such as, but not limited to, methanol, dimethylsulfoxide, or tetrahydrofuran for 1 to 24 h at a temperature between 0°C and 120°C to afford **XLIV**, where R_7 is as previously defined. Carbonyl compound **XLIV** may be reduced with a reducing agent such as, but not limited to, diisobutylaluminum hydride, lithium triethylborohydride or sodium borohydride in a solvent such as, but not limited to, toluene, methylene chloride, or tetrahydrofuran for from 1 to 24 h at a temperature between 0°C and 120°C to afford the corresponding alcohol **XLV**. Alternatively, the carbonyl compound may undergo nucleophilic addition with an appropriately substituted organometallic reagent, such as an organolithium species or a Grignard reagent, to afford the corresponding alcohol **XLV**, where R_8 is alkyl. Suitable solvents for the latter transformation include, diethyl ether, tetrahydrofuran, or toluene, at temperatures ranging from –78°C to 20°C for from 30 minutes to 48 hours. Where one of R_7 or R_8 are hydrogen, converting the alcohol functionality in **XLV** to a leaving group, such as, but not limited to, bromide, mesylate or tosylate as in **XLVI** under standard conditions and displacing the leaving group with an appropriately substituted amine in a solvent such as, but not limited to, dimethylformamide, dimethylsulfoxide, or tetrahydrofuran for from 1 to 24 h at a temperature between 0°C and 120°C converts the alcohol **XLV** to an amine **XLVIII**. Removal of the protecting group, P, from **XLVIII** under standard conditions known to those skilled in the art affords amine **III**, wherein E is



one of R_7 and R_8 is hydrogen and the other is alkyl, R_5 is substituted or branched-chain alkyl, and q is 1. Alternatively, where one of R_7 or R_8 is hydrogen, direct replacement of the alcohol **XLV** can be accomplished via a Mitsunobu reaction with phthalimide and a dialkyl azodicarboxylate followed by deprotection of the phthalimide with hydrazine in a solvent such as methanol or ethanol to afford amine **XLVIII**. The protecting group, P, may be removed from **XLVIII** under standard conditions known to those skilled in the art to provide the amine **V**, wherein one of R_7 and R_8 is hydrogen and the other is alkyl, R_9 and P" together with the nitrogen to which they are attached form a phthalimide group, R_5 is substituted or branched-chain alkyl, and q is 1.

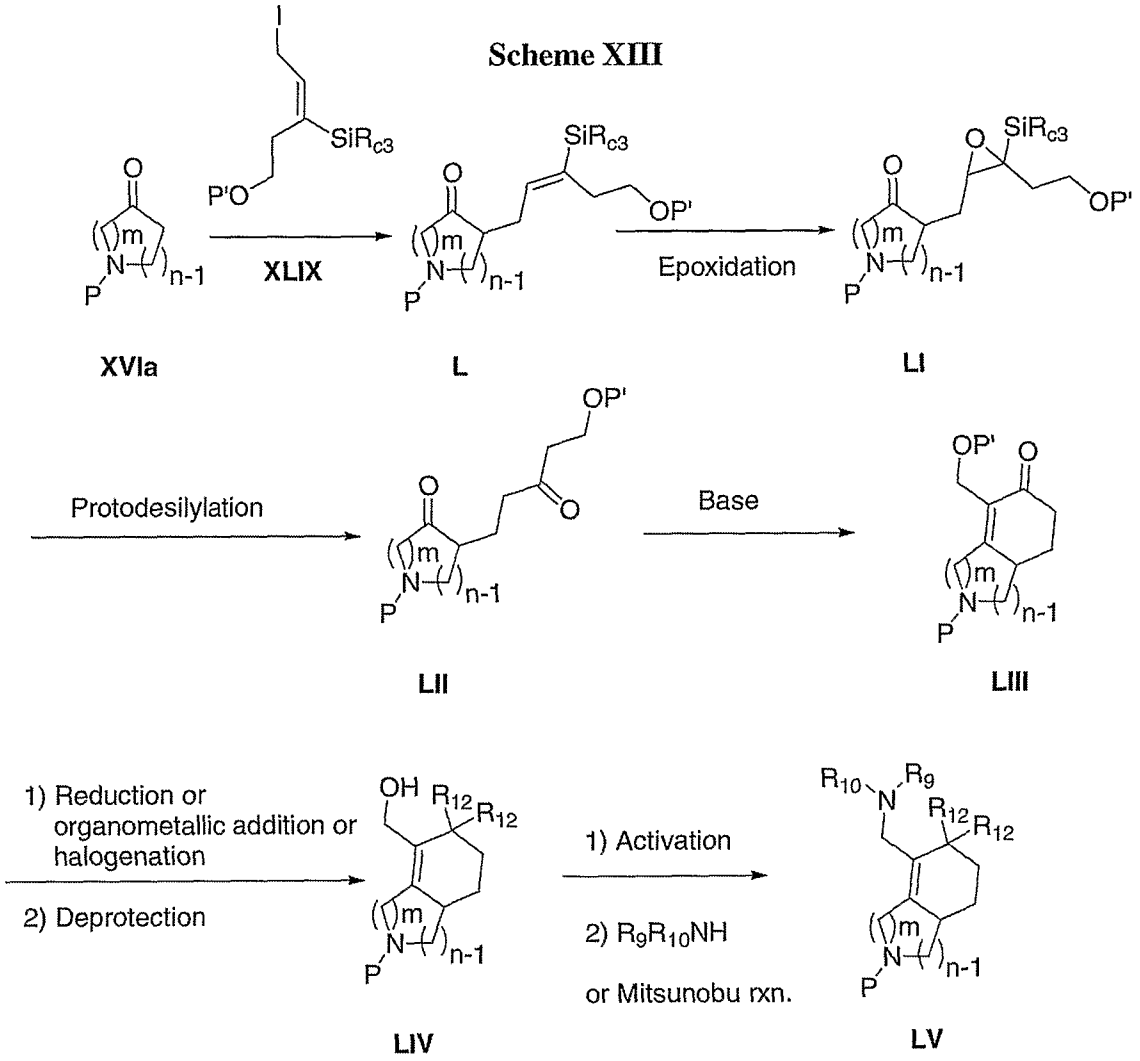
Scheme XII



Scheme XIII illustrates the conversion of ketone **XVIa** to olefin **LIII** using a base promoted Stork-Jung vinylsilane Robinson annulation protocol (Tetrahedron Letters, **2001**, 42, 9123). Condensation of ketone **XVIa** with allyl iodide **XLIX** , wherein R_c is an alkyl group and P' is a hydroxy protecting group, (Tetrahedron Letters, **2001**, 42, 9123) affords alkylated ketone **L**. Epoxidation of ketone **L** with epoxidizing agents such as, but not limited to, dimethyl dioxirane or m-chloroperbenzoic acid, affords oxirane **LI**. Protodesilylation of

LI with agents such as, but not limited to, tetra-n-butylammonium fluoride or pyridinium poly(hydrogen fluoride) and aqueous acid, with concomitant epoxide ring opening affords ketone **LII**. Ring annulation of **LII** may be accomplished by treatment of **LII** with a base, such as but not limited to, sodium methoxide to afford **LIII**. α,β-Unsaturated ketone **LIII** may be reduced with a reducing agent such as, but not limited to, diisobutylaluminum hydride, lithium triethylborohydride or sodium borohydride in a solvent such as, but not limited to, toluene, methylene chloride, or tetrahydrofuran for from 1 to 24 h at a temperature between 0°C and 120°C to afford, following removal of the hydroxy protecting group, the corresponding alcohol **LIV**, wherein one of R_{12} is hydrogen and the other R_{12} is hydroxy. Alternatively, **LIII** may undergo nucleophilic addition with an appropriately substituted organometallic reagent, such as an organolithium species or a Grignard reagent, to afford, following removal of the hydroxy protecting group, the corresponding alcohol **LIV**, where one of R_{12} is alkyl and the other R_{12} is hydroxy. Suitable solvents for the latter transformation include, diethyl ether, tetrahydrofuran, or toluene, at temperatures ranging from –78°C to 20°C for from 30 minutes to 48 hours. Finally, carbonyl compound **LIII**, may be fluorinated using a nucleophilic fluorinating reagent, such as but not limited to, (N-ethylethanaminato)trifluorosulfur (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor), in a suitable solvent, such as methylene chloride, for from 1 to 24 h at a temperature between 0°C and 60°C to afford, following removal of the hydroxy protecting group, alcohol **LIV**, where R_{12} is fluorine.

Scheme XIII



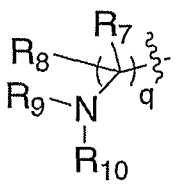
XVIa L LI

LII LIII

LIV LV

P is Protecting Group

Alcohol **LIV** may be converted to leaving group, such as, but not limited to, bromide, mesylate or tosylate under standard conditions. Displacement of the leaving group with an appropriately substituted amine in a solvent such as, but not limited to, dimethylformamide, dimethylsulfoxide, or tetrahydrofuran for from 1 to 24 h at a temperature between 0°C and 120°C converts **LIV** to amine **LV**. Removal of the protecting group, P, from **LV** under standard conditions known to those skilled in the art affords the corresponding secondary amine **III,** wherein E is



,

R_7 and R_8 are hydrogen, and R_5 and R_6 join to form a 6-membered carbocyclic ring, and q is 1.

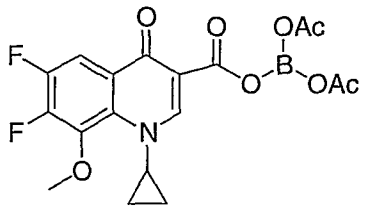
. Alternatively, direct replacement of the hydroxyl group of alcohol **LIV** can be accomplished via a Mitsunobu reaction with phthalimide and a dialkyl azodicarboxylate, followed by deprotection of the phthalimide with hydrazine in a solvent such as methanol or ethanol, to afford the amine **LV**, wherein R_9 and R_{10} are hydrogen.

Experimental Section

Precursor Preparation – Heterocyclic Nuclei

All heterocyclic nuclei such as 1-cyclopropyl-1,4-dihydro-6,7-difluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid, 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-naphthpyridine-3-carboxylic acid, 9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, 1-cyclopropyl-1,4-dihydro-6,7-difluoro-4-oxo-quinoline-3-carboxylic acid, 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid, 1-cyclopropyl-1,4-dihydro-6,7-difluoro-5-methyl-4-oxo-quinoline carboxylic acid, 1-[(1R,2S)-2-fluorocyclopropy]l-1,4-dihydro-6,7-difluoro-5-methyl-4-oxo-quinoline carboxylic acid, 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6,7-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid and 1-cyclopropyl-1,4-dihydro-7-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid were prepared according to literature methods (see above discussion about general procedures for preparing heterocyclic nuclei) or were purchased from commercial sources.

Precursor Preparation A - Preparation of Diacyl Quinolinyl Borates



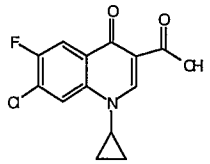
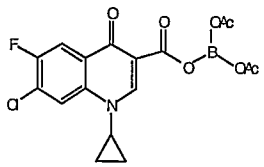
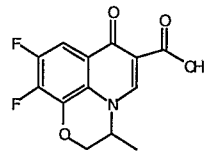
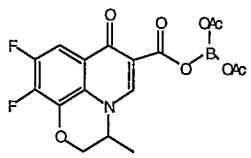
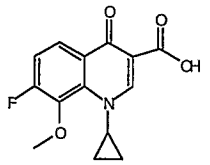
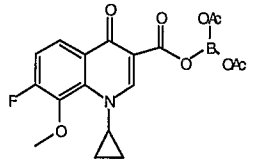
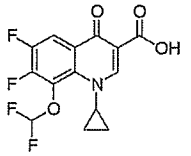
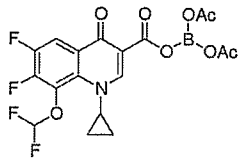
19

Compound **19** (Formula XV: L = F, A = C-OMe, R_1 = Cyclopropyl, R_2 = H, R_3 = F, R_4 =H)

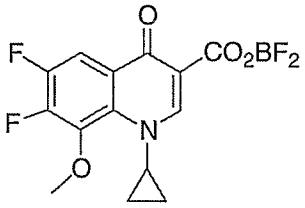
The diacyl quinolinyl borates were prepared by the procedure reported in U. S. patent 5,157,117. A mixture of boric acid (2.4 g, 38.7 mmol), acetic anhydride (13.8 mL, 146 mmol) and zinc chloride (52 mg, 0.38 mmol) was warmed to 110°C for 1.5 h, treated with acetic acid (51 mL) and was allowed to stir an additional hour at 110°C. The resulting mixture was allowed to cool to 60°C, treated with 1-cyclopropyl-1,4-dihydro-6,7-difluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid (**18**) (7.3 g, 25.9 mmol) and acetic acid (26 mL). The resulting solution was warmed to 60°C for 5 h, cooled to room temperature, and was concentrated in vacuo. The residue was treated with water (50 mL) and the solid was collected by filtration. The resulting solid was washed with water (3 x 50 mL), and dried to afford the title compound as a white solid, which was used as such in the next reaction.

The same procedure as above was used to convert each of the respective heterocyclic carboxylic acids listed in Table 2 to the corresponding diacylborate derivative (**17**, **21**, **23**, and **83**).

Table 2

Compound	Quinolone	Compound	Diacyl Quinonyl Borate
16		17	
20		21	
22		23	
82		83	

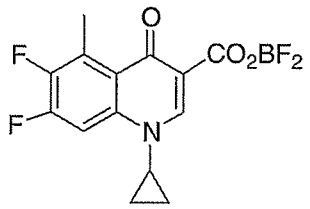
Precursor Preparation C - Preparation of Difluoro Quinolinyl Borates



223

1-Cyclopropyl-1,4-dihydro-6,7-difluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid difluoroborate ester (**223**).

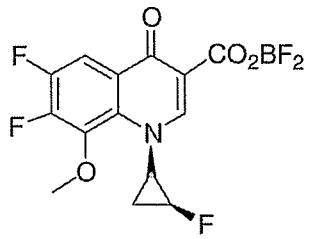
1-Cyclopropyl-1,4-dihydro-6,7-difluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid (**18**) (10.08 g; 34.14 mmol) and boron trifluoride etherate (30 mL; 236 mmol) in anhydrous THF (150 mL) were heated at reflux temperature under a nitrogen atmosphere for 36 hours. After cooling, ether (250 mL) was added. The resulting white solid was collected by filtration, washed with ether and dried to give 1-cyclopropyl-1,4-dihydro-6,7-difluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid difluoroborate ester (**223**) as a white solid (7.29 g; 63% yield). MS 344 (M + H).



224

1-Cyclopropyl-1,4-dihydro-6,7-difluoro-5-methyl-4-oxo-quinoline carboxylic acid difluoroborate ester (**224**).

This was prepared in a manner analogous to 1-cyclopropyl-1,4-dihydro-6,7-difluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid difluoroborate ester (**223**) but starting with 1-cyclopropyl-1,4-dihydro-6,7-difluoro-5-methyl-4-oxo-quinoline carboxylic acid (prepared as described in *Bioorganic and Medicinal Chemistry* **1995**, *3*, 1699) to afford (**224**) as a white powder (58%). MS 328 (M + H).



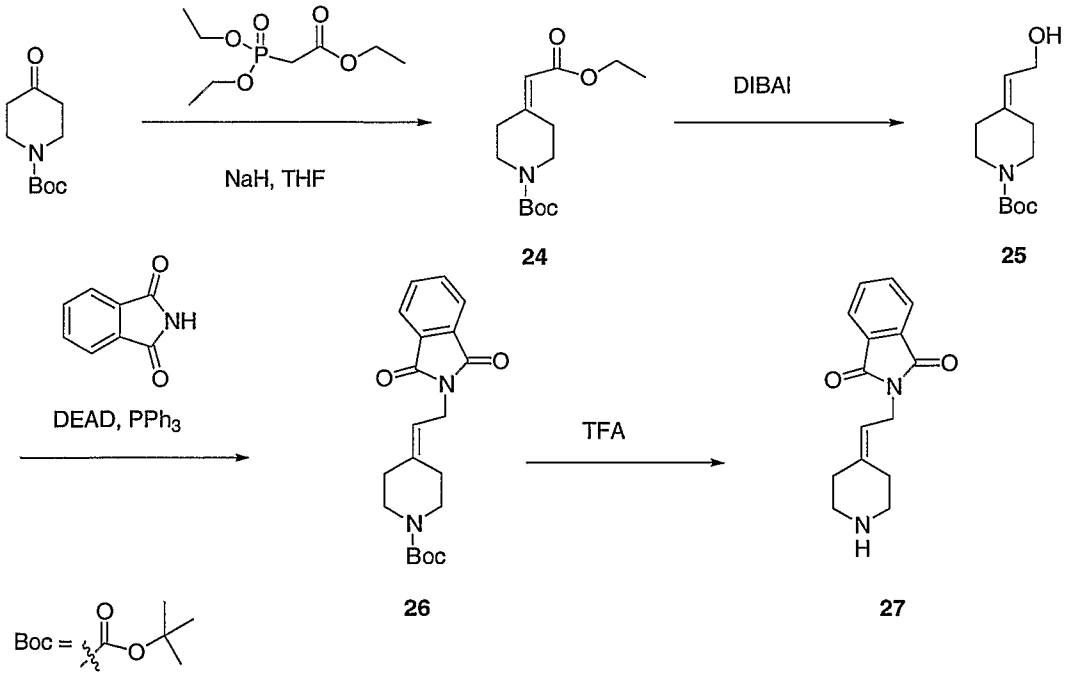
225

1-[(1R,2S)-2-Fluorocyclopropyl]-1,4-dihydro-6,7-difluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid difluoroborate ester (**225**).

This was prepared in a manner analogous to 1-cyclopropyl-1,4-dihydro-6,7-difluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid difluoroborate ester (**223**) but starting with 1-[(1R,2S)-2-fluorocyclopropy]l-1,4-dihydro-6,7-difluoro-5-methyl-4-oxo-quinoline carboxylic acid (prepared as described in WO 01/072738) to afford (**225**) as a grey solid (49%). MS 362 (M + H).

Precursor Preparation B – Side Chain **III**

Scheme XIV



Compound **27** of Scheme XIV:

t-Butyl 4-(2-Ethoxy-2-oxoethylidene)piperidinyl-1-carboxylate (**24**) was prepared according the procedure described in Sato et al. *Heterocycles*, **2001**, *54*, 747.

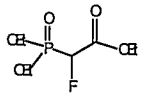
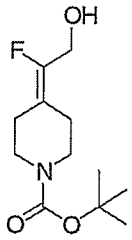
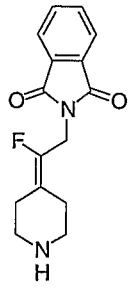
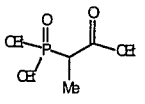
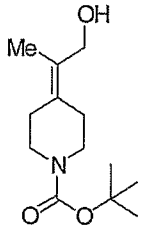
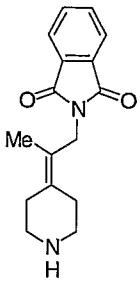
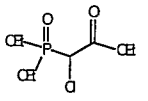
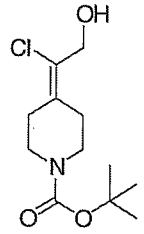
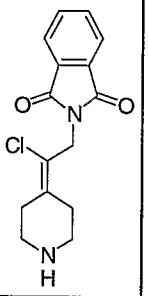
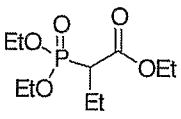
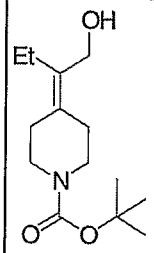
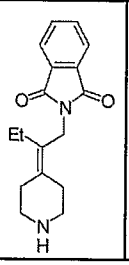
t-Butyl 4-(2-Hydroxyethylidene)piperidinyl-1-carboxylate (**25**) was prepared according the procedure described in Sato et. al *Heterocycles*, **2001**, *54*, 747.

t-Butyl 4-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethylidene]-piperidinyl-1-carboxylate (**26**) was prepared by a procedure adapted from *Synthesis* **1995**, 756. A solution of **25** (250 mg, 1.10 mmol), phthalimide (208 mg, 1.40 mmol), and triphenylphosphine (366 mg, 1.40 mmol) in dry THF (10 mL) was treated with diethyl azodicarboxylate (0.25 mL, 1.40 mmol) added via syringe in the dark under nitrogen. After 5 h, the reaction mixture was treated with water (10 mL), diluted with ethyl acetate (50 mL), washed with 10% aqueous sodium bicarbonate (2 x 25 mL), and dried ($MgSO_4$). Purification by flash chromatography (0-30% ethyl acetate/hexanes) afforded the title compound (389 mg, 78%) as a white foam. MS 357 (M+H).

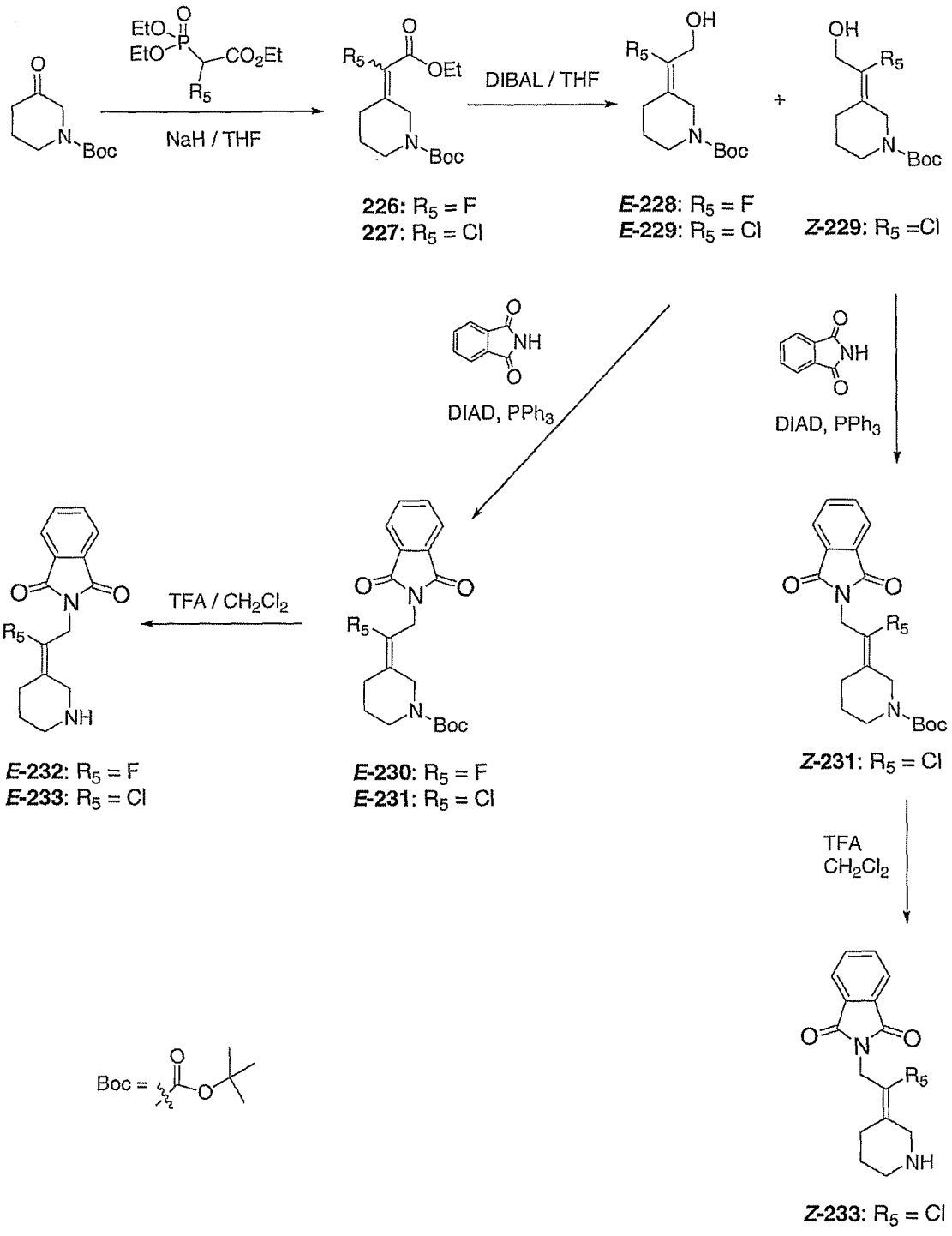
4-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)ethylidene]-1-piperidine trifluoroacetate (**27**). A solution of **26** (380 mg, 1.03 mmol) was dissolved in CH_2Cl_2 (50 mL) and was treated with trifluoroacetic acid (1 mL) at room temperature. After 1h, the reaction mixture was concentrated in vacuo to afford the title compound **27** (363 mg, 100%) as an oil. MS 257 (M+H).

1-(tert-Butoxycarbonyl)-4-piperidinone was reacted with each of the respective phosphonoacetates listed in Table 3, and the products subjected to analogous procedures as in the synthesis of **27**, to prepare the corresponding alcohols (**28-30, 84**) and the derived amines (**31-33, 85**).

Table 3

Phosphonoacetates	Compound	Alcohols	(M+H)	Compound	Amines	(M+H)
	28		246	31		275
	29		242	32		271
	30		262	33		291
	84		256	85		285

Scheme XL



Compounds ***E*-232**, ***E*-233**, and ***Z*-233** of Scheme XL:

(E/Z)-*t*-Butyl 3-(1-fluoro-2-ethoxy-2-oxoethylidene)-piperidinyl-1-carboxylate (**226**; R_5 = F).

This was prepared by the same procedure as in the synthesis of **24** except that 1-(*tert*-butoxycarbonyl)-3-piperidinone was used in place of 1-(*tert*-butoxycarbonyl)-4-piperidinone and triethyl 2-fluorophosphonoacetate was used in place of triethyl 2-chlorophosphonoacetate. MS 310 (M+Na).

(E/Z)-*t*-Butyl 3-(1-chloro-2-ethoxy-2-oxoethylidene)-piperidinyl-1-carboxylate (**227**; R_5 = Cl).

This was prepared by the same procedure as in the synthesis of **24** except that 1-(*tert*-butoxycarbonyl)-3-piperidinone was used in place of 1-(*tert*-butoxycarbonyl)-4-piperidinone. MS 326 (M+Na).

(E/Z)-*t*-Butyl 3-(1-chloro-2-hydroxyethylidene)-piperidinyl-1-carboxylate (***E*-229** and ***Z*-229**; R_5 = Cl).

A 1.0 M solution of DIBAL-H in toluene (8.2 mL, 8.23 mmol) was added to a solution of **227** (1.0 g, 3.29 mmol) in tetrahydrofuran (10 mL) at -78 °C under nitrogen and the mixture was stirred at the same temperature for 5h, then warmed to room temperature and stirred overnight. 0.5 M Rochelle's salt solution (40 mL) and EtOAc (80 mL) was added to the reaction at 0°C. The resulting mixture was stirred at rt for 3h. After phase separation the organic layer was concentrated. The E/Z isomers were separated by flash chromatography (0-40% ethyl acetate/hexanes) to afford ***E*-229** [200 mg, 23%, MS 284 (M+Na)] as a yellow oil and ***Z*-229** [250 mg, 29%, MS 284 (M+Na)] as a white solid.

(E)-*t*-Butyl 3-(1-fluoro-2-hydroxyethylidene)-piperidinyl-1-carboxylate (***E*-228**; R_5 = F).

This was prepared in a similar manner to the procedure described above except that **226** was used in place of **227**. MS 268 (M+Na). Although ***Z*-228** was present in the crude reaction mixture, it was not isolated in pure form by flash chromatography.

(E)-*t*-Butyl 3-[1-fluoro-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-ethylidene]-piperidinyl-1-carboxylate (***E*-230**; R_5 = F).

This was prepared by a similar procedure as in the synthesis of **26** except that ***E*-228** was used in place of **25**. MS 397 (M+Na).

(E)-*t*-Butyl 3-[1-chloro-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-ethylidene]-piperidinyl-1-carboxylate (***E*-231**; R_5 = Cl).

This was prepared by a similar procedure as in the synthesis of **26** except that ***E*-229** was used in place of **25**. MS 413 (M+Na).

(Z)-*t*-Butyl 3-[1-chloro-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-ethylidene]-piperidinyl-1-carboxylate (***Z*-231**; R_5 = Cl).

This was prepared by a similar procedure as in the synthesis of **26** except that ***Z*-229** was used in place of **25**. MS 413 (M+Na).

(E)-3-[1-fluoro-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-ethylidene]-piperidine trifluoroacetate (***E*-232**; R_5 = F).

This was prepared by the same procedure as in the synthesis of **135** except that ***E*-230** was used in place of **133**. MS 275 (M+H).

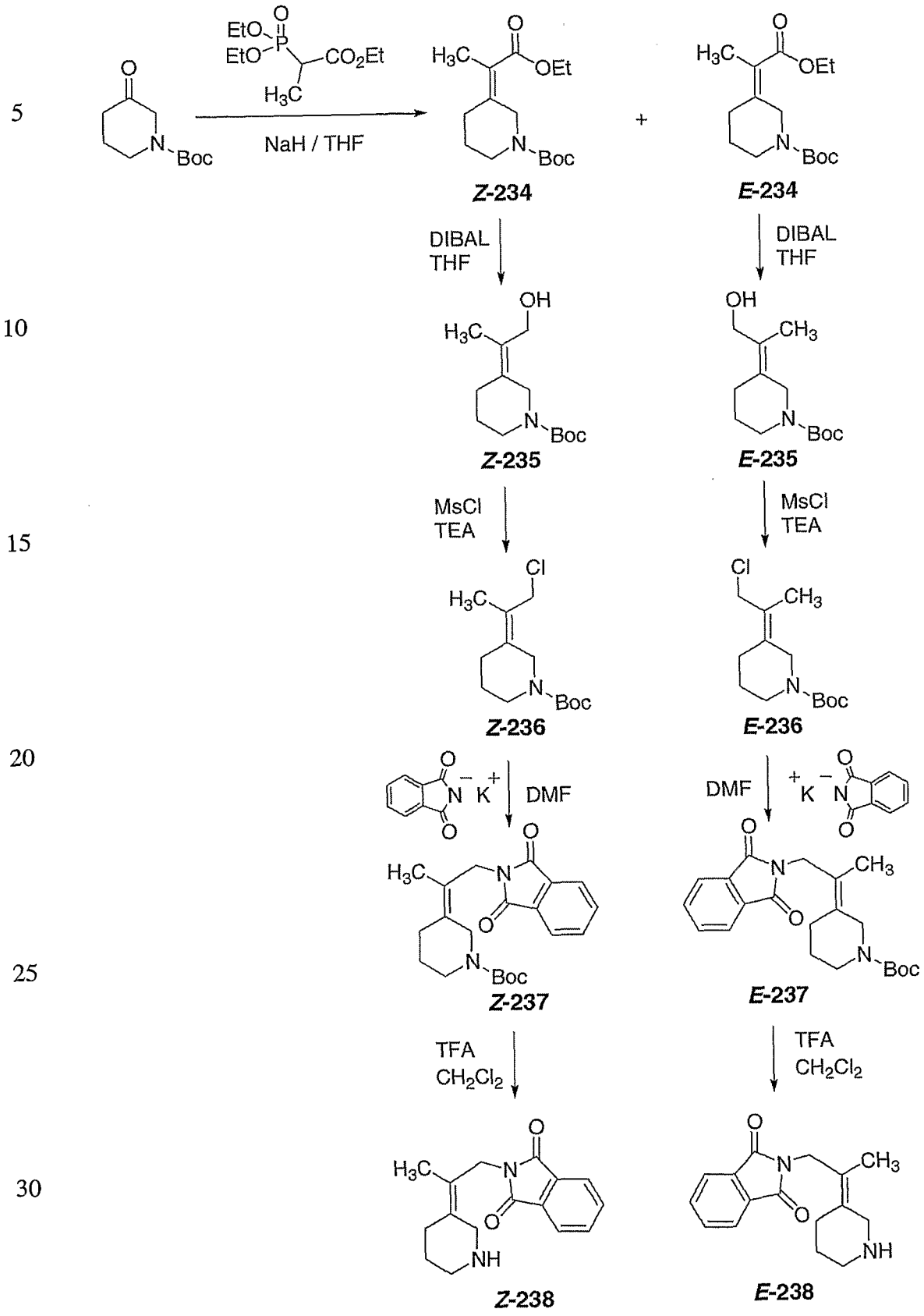
(E)-3-[1-chloro-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-ethylidene]-piperidine trifluoroacetate (***E*-233**; R_5 = Cl).

This was prepared by the same procedure as in the synthesis of **135** except that ***E*-231** was used in place of **133**. MS 291 (M+H).

(Z)-3-[1-chloro-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-ethylidene]-piperidine trifluoroacetate (***Z*-233**; R_5 = Cl).

This was prepared by the same procedure as in the synthesis of **135** except that ***Z*-231** was used in place of **133**. MS 291 (M+H).

Scheme XLI


EtO
EtO
O
P
CO2Et
H3C
NaH / THF
N
Boc
H3C
OEt
Z-234
E-234
DIBAL
THF
OH
CH3
Z-235
E-235
MsCl
TEA
Cl
Z-236
E-236
K
DMF
Z-237
E-237
TFA
CH2Cl2
NH
Z-238
E-238

(Compounds ***Z*-238** and ***E*-238** of Scheme XLI:

(Z)-*t*-Butyl 3-(1-ethoxy-1-oxo-2-propylidene)-piperidinyl-1-carboxylate (***Z*-234**) and (E)-*t*-Butyl 3-(1-ethoxy-1-oxo-2-propylidene)-piperidinyl-1-carboxylate (***E*-234**).

To sodium hydride (1.10 g, mmol) (60% in oil) in tetrahydrofuran (50 mL) at 0°C was added triethyl-2-phosphonopropionate (7.00 mL, 32.0 mmols) and the resulting mixture was stirred for 20 min whereupon 1-(*tert*-butoxycarbonyl)-3-piperdinone carboxylate (5.00 g, mmol) was added and stirred a further 5 hours at room temperature. The mixture was concentrated, diluted with half saturated aq. $NaHCO_3$ (200 mL) and extracted with ethyl acetate (6 X 40 mL). The organic extracts were dried over Na_2SO_4, concentrated and chromatographed on silica gel using 10% ethyl acetate/hexanes as eluent. The geometric isomers were isolated as clear oils. The reaction provided 1.66 g (23%) of the higher R_f *E*-isomer and 3.71 g (50%) of the lower R_f *Z*-isomer. Both: MS 284 (M+H).

(Z)-*t*-Butyl 3-(1-hydroxy-2-propylidene)-piperidinyl-1-carboxylate (***Z*-235**).

To ***Z*-234** from the above reaction (0.4982 g, 1.758 mmols) in tetrahydrofuran (6 mL) at –78°C was added DIBAL (4.0 mL, 1.0 M in toluene). The mixture was stirred for 5 hours at –78°C and then 30 min at room temperature. After concentrating and cooling to 0°C, 0.5M aq. Rochelle's Salt (50 mL) and ethyl acetate (20 mL) were added and the mixture stirred for 3 hours. The mixture was extracted with ethyl acetate (5 X 20 mL), dried over Na_2SO_4, concentrated and chromatographed on silica gel with 30% ethyl acetate/hexanes as eluent. The product was obtained as a clear oil (0.3163 g, 74% yield). MS 242 (M+H).

(Z)-*t*-Butyl 3-(1-chloro-2-propylidene)-piperidinyl-1-carboxylate (***Z*-236**).

To ***Z*-235** from the above reaction (0.1607 g, 0.6658 mmol) in CH_2Cl_2 (3 mL) was added triethylamine (0.28 mL, 2.0 mmols) and then methanesulfonyl chloride (0.08 mL, 1.0 mmol), and the resulting mixture stirred for 2 hours. This mixture was treated with sat. aq. NH_4Cl, extracted with CH_2Cl_2 (4 X 7 mL), dried over Na_2SO_4, concentrated, and chromatographed on silica gel (0-100%

ethyl acetate/hexanes gradient as eluent) to give 0.1118 g (65%) of a clear oil. MS 260 (M+H).

(Z)-*t*-Butyl 3-[1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-propylidene]-piperidinyl-1-carboxylate (***Z*-237**).

To ***Z*-236** from the above reaction (0.0859 g, 0.331 mmol) in dimethylformamide (3 mL) was added potassium phthalimide (0.075g, 4.0 mmols). The mixture was stirred for 3 days at 50°C. Water (10 mL) and brine (10 mL) were added and the mixture was extracted with CH_2Cl_2 (4 X 8 mL), dried over Na_2SO_4, concentrated, and chromatographed on silica gel (0-40% ethyl acetate/hexanes gradient as eluent) to give ***Z*-237** as a white solid (0.0459 g, 38%). MS 371 (M+H).

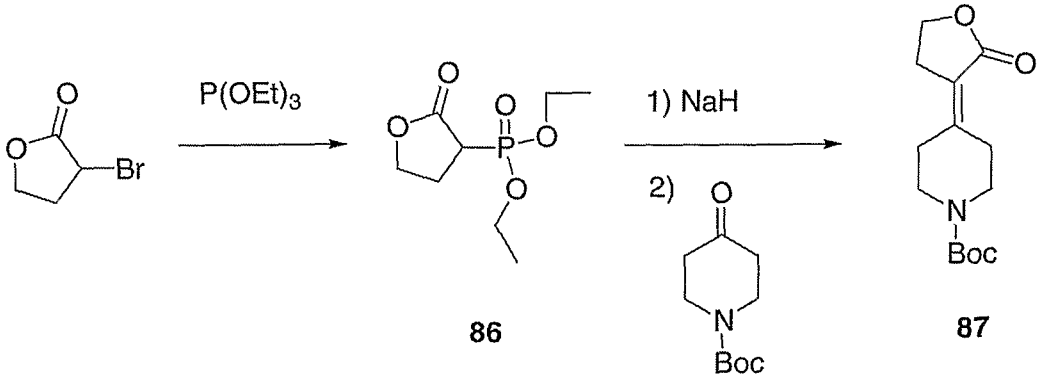
(Z)-3-[1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-propylidene]-piperidinyl-1-carboxylate (***Z*-238**).

This was prepared by the same procedure as in the synthesis of **135** except that ***Z*-237** was used in place of **133**. MS 271 (M+H).

(E)-3-[1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-propylidene]-piperidinyl-1-carboxylate (***E*-238**).

This geometrical isomer was prepared from ***E*-234** through an analogous series of reactions as for the conversion of ***Z*-234** to ***Z*-238**. MS 271 (M+H).

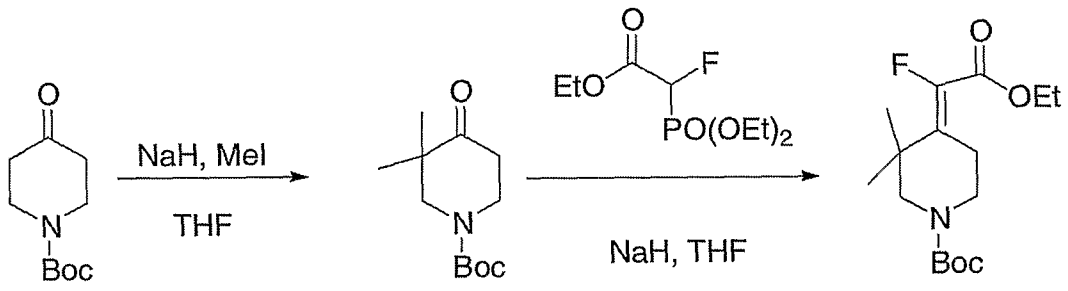
Scheme XXIII



(2-Oxo-tetrahydro-furan-3-yl)-phosphonic acid diethyl ester (**86**; Scheme XXIII) was prepared according the procedure described in Murphy et al. *Chemical Communications* **1996**, *6*, 737-8.

4-(2-Oxo-dihydrofuran-3-ylidene)piperidine-1-carboxylic acid *tert*-butyl ester (**87**; Scheme XXIII) was prepared by an analogous procedure to that described in Sato et al. *Heterocycles*, **2001**, *54*, 747; MS = 267 (M + H).

Scheme XXIV

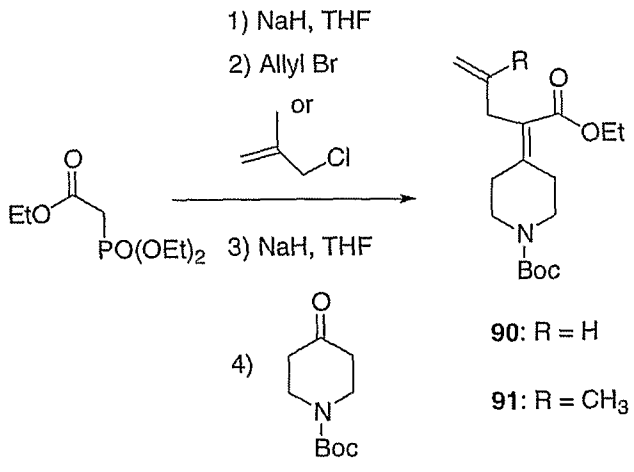


88 **89**

3,3-Dimethyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester (**88**; Scheme XXIV) was prepared according the procedure described in Vice et al. *J. Org. Chem.* **2001**, *66*, 2487-2492.

4-(2-Ethoxy-1-fluoro-2-oxoethylidene)-3,3-dimethylpiperidine-1-carboxylic acid tert-butyl ester (**89**; Scheme XXIV) was prepared by a procedure analogous to that described in Sato et al. *Heterocycles*, **2001**, *54*, 747.

Scheme XXV



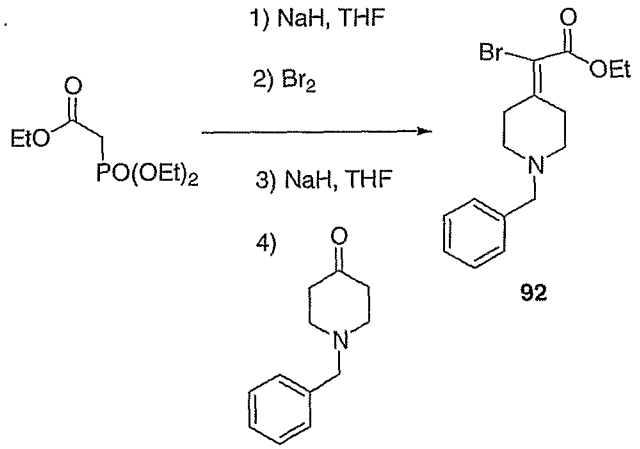
90: R = H

91: R = CH_3

4-(1-Ethoxycarbonyl-but-3-enylidene)piperidine-1-carboxylic acid tert-butyl ester (**90**; Scheme XXV). A slurry of sodium hydride (1.50 g, 37.6 mmol) in THF (100 mL) at 0°C under nitrogen was carefully treated with triethyl phosphonoacetate (8.12 mL, 37.6 mmol) via a syringe. After 30 min, the reaction mixture was treated with allyl bromide (3.3 mL, 37.6 mmol) and the resulting mixture was allowed to warm to 25°C over 12 h. The resulting mixture was recooled to 0°C, treated with sodium hydride (1.50 g, 37.6 mmol), and the resulting slurry was allowed to stir for 30 min at 0°C. A solution of 1-(tert-butoxycarbonyl)-4-piperidinone (5.0 g, 25 mmol) in THF (50 mL) was added via a cannula over 10 min and the resulting solution was allowed to warm to 25°C over 12 h. The reaction was quenched by the addition of 15% aqueous sodium bicarbonate (50 mL) and the resulting mixture was diluted with ethyl acetate (100 mL), washed with 15% aqueous sodium bicarbonate (2 x 100mL), and concentrated in vacuo. Purification by chromatography (0-50% EtOAc/hexanes) afforded title compound (1.93g, 25%) as a yellow oil: MS (M+H) = 310.

4-(1-Ethoxycarbonyl-3-methyl-but-3-enylidene)piperidine-1-carboxylic acid tert-butyl ester (**91**; Scheme XXV) was prepared according to the procedure described for **90** except methylallyl chloride was used instead of allyl bromide.

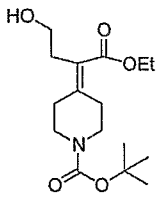
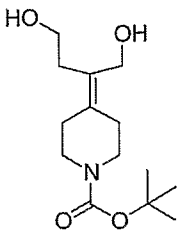
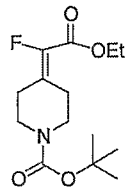
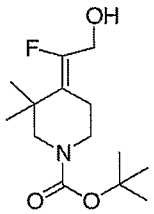
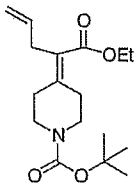
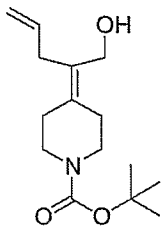
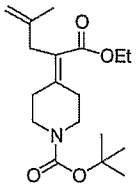
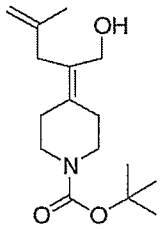
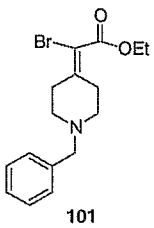
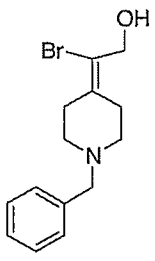
Scheme XXVI



(1-Benzyl-piperidin-4-ylidene)bromoacetic acid ethyl ester (**92**; Scheme XXVI). A slurry of sodium hydride (1.50 g, 37.6 mmol) in THF (100 mL) at 0°C under nitrogen was carefully treated with triethyl phosphonoacetate (8.12 mL, 37.6 mmol) via a syringe. After 30 min, the reaction mixture was treated with bromine (1.95 mL, 37.6 mmol) via a dropping funnel over 10 min and the resulting mixture was allowed to stir for 3 h. The reaction mixture was treated with sodium hydride (1.50 g, 37.6 mmol) and the resulting slurry was allowed to stir for 30 min at 0°C. A solution of 1-benzylpiperidin-4-one (5.0 g, 25 mmol) in THF (50 mL) was added via a cannula over 10 min and the resulting solution was allowed to warm to 25°C over 12 h. The reaction was quenched by the addition of 15% aqueous sodium bicarbonate (50 mL) and the resulting mixture was diluted with ethyl acetate (100 mL), washed with 15% aqueous sodium bicarbonate (2 x 100mL), and concentrated in vacuo. Purification by chromatography (0-50% EtOAc/hexanes) afforded the title compound (6.35g, 74%) as a red-orange oil: MS (M^+=H) = 339.

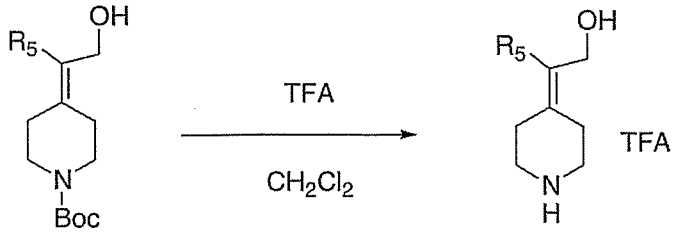
The alcohols listed in Table 6 were prepared in a similar fashion as described for t-butyl 4-(2-hydroxyethylidene)piperidinyl-1-carboxylate (**25**), except the corresponding ethylidene carboxylate was used instead of t-butyl 4-(2-ethoxy-2-oxoethylidene)piperidinyl-1-carboxylate (**24**).

Table 6

Ethylidine Carboxylate	Alcohols	Compound	(M+H)
 93		**94**	272
 95		**96**	274
 97		**98**	268
 99		**100**	282
 101		**102**	297

5

Scheme XXVII



25: $R_5 = H$
28: $R_5 = F$
29: $R_5 = CH_3$

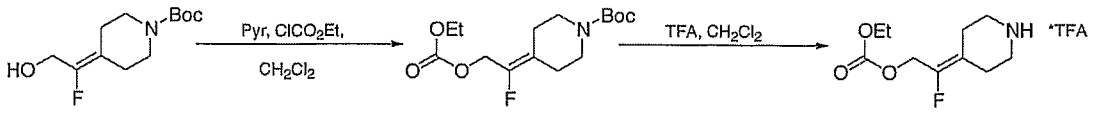
103: $R_5 = H$
104: $R_5 = F$
105: $R_5 = CH_3$

2-Piperidin-4-ylidene-ethanol trifluoroacetate (**103**; Scheme XXVII). A solution of **25** (191 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (10 mL) and was treated with trifluoroacetic acid (0.5 mL) at room temperature. After 1h, the reaction mixture was concentrated in vacuo to afford the title compound (64 mg, 100%) as an oil. MS 129 (M+H).

2-Piperidin-4-ylidene-propan-1-ol trifluoroacetate (**105**; Scheme XXVII) was prepared according the procedure described for **103** except **29** was used. MS 142 (M+H).

2-Fluoro-2-piperidin-4-ylidene-ethanol trifluoroacetate (**104**; Scheme XXVII) was prepared according the procedure described for **103** except **28** was used. MS 146 (M+H).

Scheme XXVIII



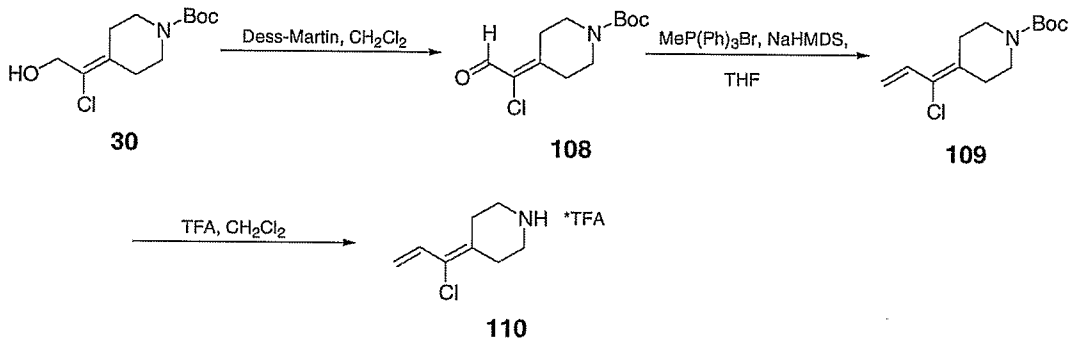
28 **106** **107**

t-Butyl 4-(2-ethoxycarbonyloxy-1-fluoroethylidene)piperidine-1-carboxylate (**106**; Scheme XXVIII). To alcohol **28** (0.5064 g, 2.064 mmols) in CH_2Cl_2 (10 mL) at RT was added pyridine (0.23 mL, 2.8 mmols) and then ethyl chloroformate (0.22 mL, 2.2 mmols). After stirring overnight, sat. aq. NH_4Cl (10 mL) was added and the mixture extracted with CH_2Cl_2 (5 X 10 mL), dried over

Na_2SO_4, concentrated and chromatographed on silica (20% EtOAc/hexane as eluent) to provide the title compound **106** (0.4546 g, 69%) as a clear oil. MS 318 (M + H).

4-(2-Ethoxycarbonyloxy-1-fluoro-ethylidene)-piperidine (**107**; Scheme XXVIII). To compound **106** (0.1787 g, 0.5631 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.56 mL, 7.3 mmols) and the mixture stirred for 3hrs whereupon all volatile materials were removed in vacuo to provide the crude title compound, which was used without further purification. MS 218 (M + H).

Scheme XXIX



t-Butyl 4-(1-chloro-2-oxoethylidene)-piperidine-1-carboxylate (**108**; Scheme XXIX) To alcohol **30** (6.01 g, 23.0 mmols) in CH_2Cl_2 at RT and open to the air was added the Dess-Martin reagent (21.17g, 49.9 mmols) and the reaction mixture stirred overnight whereupon the mixture was washed with sat. aq. $Na_2S_2O_3$ (60 mL) and sat. aq. $NaHCO_3$ (3 X 30 mL). The organic layer was dried over Na_2SO_4, concentrated and chromatographed on silica (25% EtOAc/Hexane as eluent) to provide the title compound **108** (5.22 g, 88%) as a white crystalline solid. MS 260 (M + H).

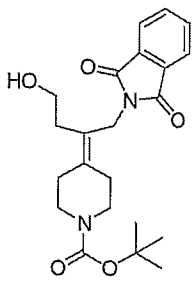
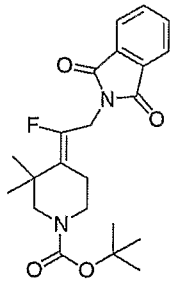
t-Butyl 4-(1-Chloro-2-propenylidene)piperidine-1-carboxylate (**109**; Scheme XXIX) Methyltriphenylphosphonium bromide (5.51 g, 15.4 mmols) in THF (40 mL) at 0^0C was treated with sodium bis(trimethylsilyl)amide (15.4 mL, 1.0 M in THF) and stirred for 20 min whereupon compound **108** (2.05 g, 7.89 mmols) in THF (15 mL) was added via cannula and the mixture stirred for 3hrs, warming to RT. The mixture was quenched by adding sat. aq. NH_4Cl (20 mL) and the

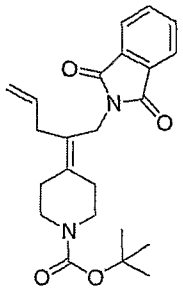
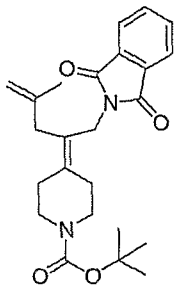
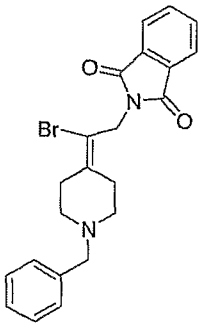
aqueous layer was extracted with EtOAc (6 X 20 mL). The combined organic layers were dried over Na_2SO_4, concentrated and chromatographed on silica (gradient elution with 0-10% MeOH/ CH_2Cl_2) to provide the title compound **109** (1.94 g, 96%) as a white crystalline solid. MS 258 (M + H).

4-(1-Chloro-2-propenylidene)piperidine TFA salt (**110**; Scheme XXIX) To compound **109** (0.1415 g, 0.5489 mmol) in CH_2Cl_2 (5 mL) was added TFA (0.55 mL, 7.1 mmols) and the mixture stirred for 3hrs whereupon all volatile materials were removed in vacuo. The crude title compound so obtained was used without further purification. MS 158 (M + H).

The protected amines listed in Table 7 were prepared in a similar fashion as described for t-butyl 4-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)ethylidene]-piperidinyl-1-carboxylate (**26**), except the corresponding alcohol was used instead of t-butyl 4-(2-hydroxyethylidene)piperidinyl-1-carboxylate (**25**).

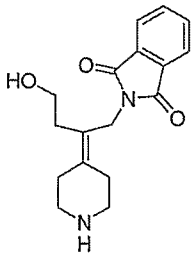
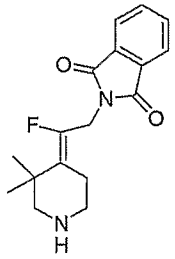
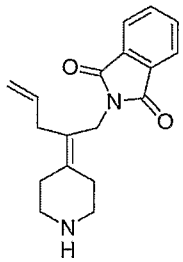
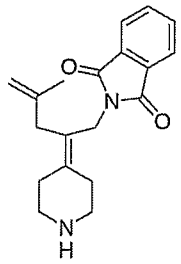
Table 7

Alcohol	Protected Amine	Compound	(M+H)
94		**111**	401
96		**112**	403

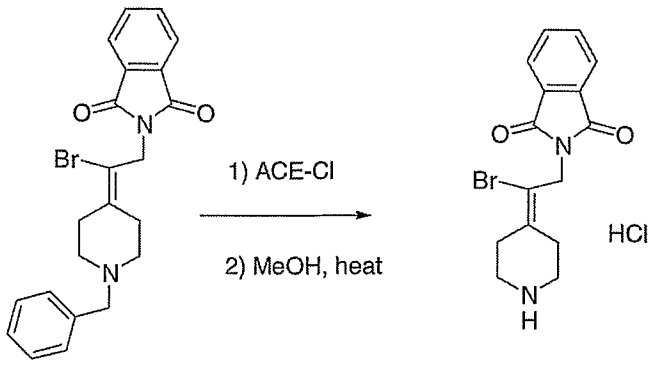
98		**113**	397
100		**114**	411
102		**115**	426

The amines listed in Table 8 were prepared in a similar fashion as described for 4-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)ethylidene]-1-piperidine trifluoroacetate (**27**), except the corresponding protected amine was used instead of t-butyl 4-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)ethylidene]-piperidinyl-1-carboxylate (**26**).

Table 8

Protected Amine	Amine	Compound	(M+H)
111		**116**	301
112		**117**	303
113		**118**	297
114		**119**	311

Scheme XXX



102 **120**

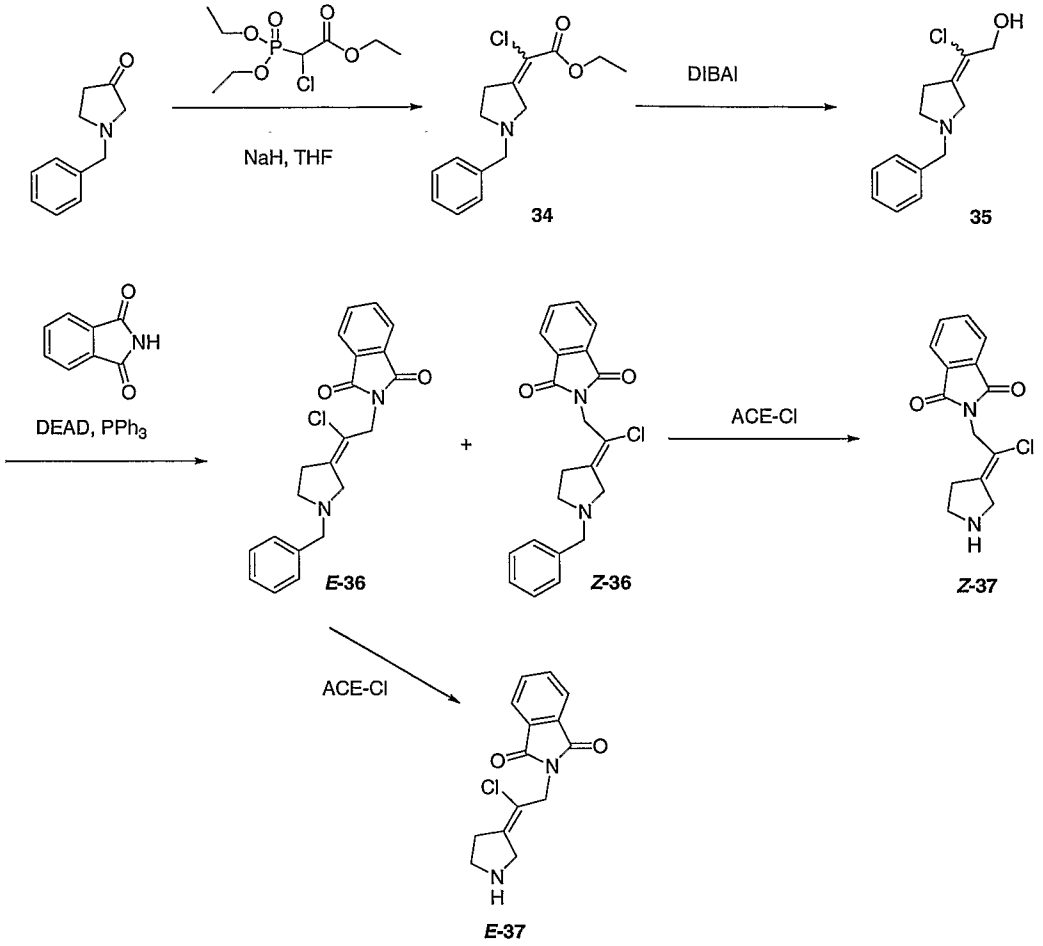
2-(2-Bromo-2-piperidin-4-ylidenylethyl)isoindole-1,3-dione hydrochloride (**120**: Scheme XXX). A mixture of **102** (0.50 g, 1.17 mmol) and 1-chloroethyl chloroformate (0.7 mL, 6.2 mmol) in dichloroethane (10 mL) was warmed to reflux temperature for 2h. The resulting solution was allowed to cool to room temperature and concentrated in vacuo. The residue was dissolved in methanol (50 mL) and warmed to reflux temperature for 2h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo to afford a white solid. The residue was washed with diethyl ether (2x) and dried to afford title compound (432 mg, 100%) as an orange oil. MS 336 (M + H).

Compounds *Z*-**37** and *E*-**37** of Scheme XV:

(E/Z)-Ethyl chloro(1-benzyl-3-pyrrolidinylidene)acetate (**34**). Prepared by the same procedure as in the synthesis of **24** except that 1-benzyl-pyrrolidin-3-one was used in place of 1-(tert-butoxycarbonyl)-4-piperidinone and triethyl 2-chlorophosphonoacetate was used in place of triethyl phosphonoacetate. MS 280 (M + H).

(E/Z)-2-(1-Benzyl-3-pyrrolidinylidene)-2-chloroethanol (**35**). Prepared by the same procedure as in the synthesis of **25** except that **34** was used in place of **24**. MS 283 (M + H).

Scheme XV



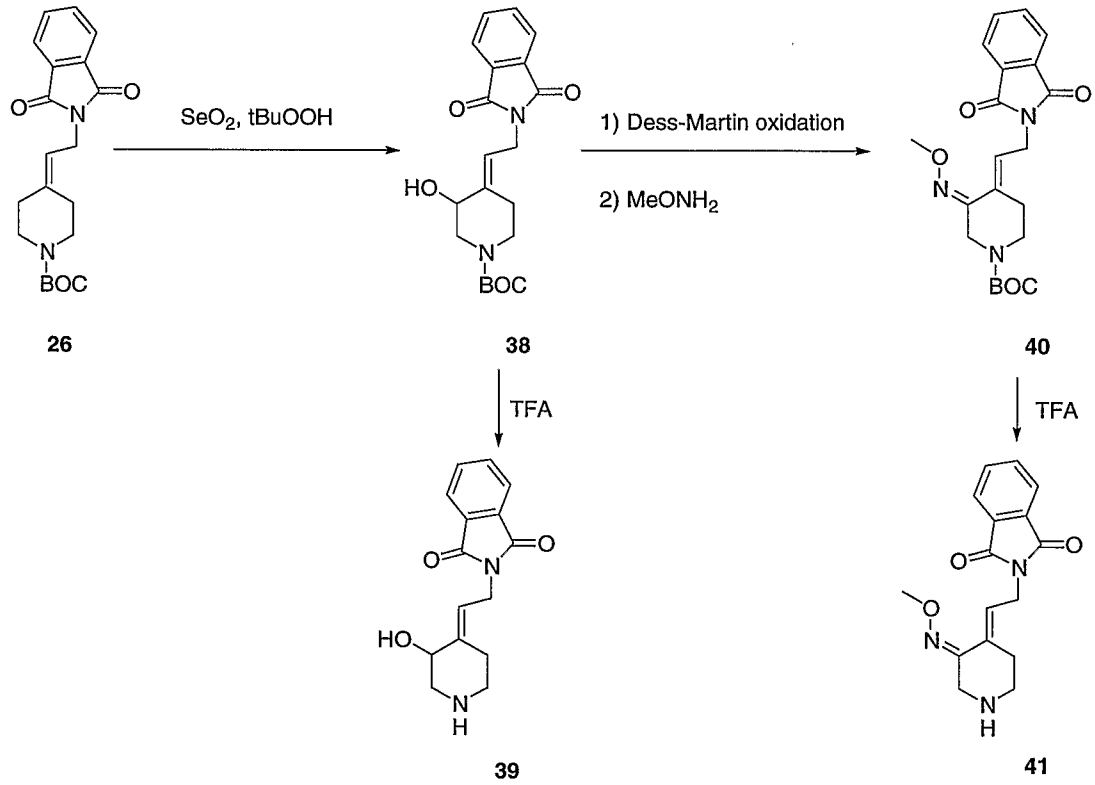
(E/Z)-2-[2-(1-Benzyl-3-pyrrolidinylidene)-2-chloroethyl]-1H-isoindole-1,3(2H)-dione (*E*-**36** and *Z*-**36**). Prepared by the same procedure as in the synthesis of **26** except that **35** (1.58g) was used in place of **25**. The E/Z isomers were separated by MPLC (0-45% ethyl acetate/hexanes) to afford Z-**36** (430 mg, MS 367 (M + H)) as a reddish oil and E-**36** (420 mg, MS 367 (M + H)) as a reddish oil.

(E)-2-[2-Chloro-2-(3-pyrrolidinylidene)ethyl]-1H-isoindole-1,3(2H)-dione hydrochloride (***E*-37**). A mixture of ***E*-36** (0.430 g, 1.45 mmol) and 1-chloroethyl chloroformate (0.7 mL, 6.2 mmol) in dichloroethane (10 mL) was warmed to reflux temperature for 2h. The resulting solution was allowed to cool to room temperature, and concentrated in vacuo. The residue was dissolved in methanol (50 mL) and warmed to reflux temperature for 2h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo to

afford a white solid. The residue was washed with diethyl ether (2x) and dried to afford ***E*-37** (200 mg, 50%) as a brown oil. MS 277 (M + H).

(Z)-2-[2-Chloro-2-(3-pyrrolidinylidene)ethyl]-1H-isoindole-1,3(2H)-dione hydrochloride (***Z*-37**). Prepared by the same procedure as in the synthesis of ***E*-37** except that ***Z*-36** was used in place of *E*-**36**. MS 277 (M + H).

Scheme XVI



Compounds **39** and **41** of Scheme XVI:

t-Butyl (*E*)-4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethylidene]-3-hydroxy-piperidinyl-1-carboxylate (**38**). A slurry of SeO_2 (0.5g, 6.06 mmol) in CH_2Cl_2 (5 mL) at 0°C was treated with *tert*-butyl hydroperoxide (2.5 mL, 9.09 mmol, 5-6 M, 10% in undecane) via a syringe. After 20 min, the reaction mixture was treated with a solution of ethylidene **26** (1.44g, 4.04 mmol) in CH_2Cl_2 (15 mL) and the resulting mixture was allowed to stir for 12h at room temperature. The reaction was carefully quenched by the addition of 15% aqueous sodium

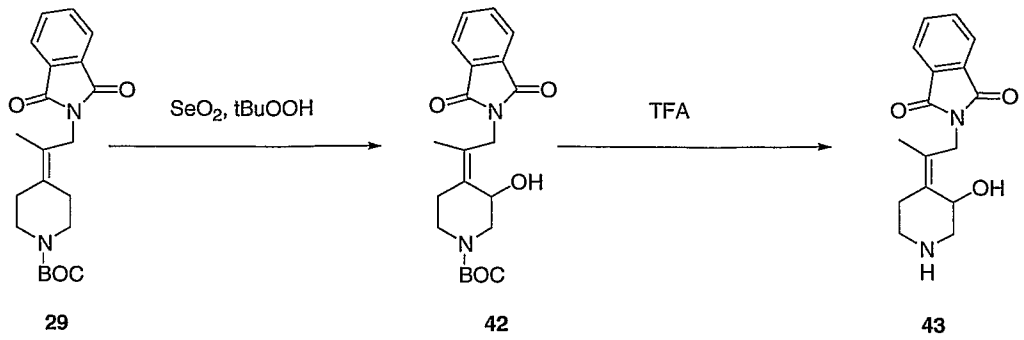
thiosulfate (15 mL), and the reaction mixture was diluted with CH_2Cl_2 (25 mL). The layers are separated, and the organic layer was washed with 15% aqueous sodium thiosulfate (15 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 0-75% ethyl acetate/hexanes) afforded the title compound **38** (0.51g, 33%) as a white solid. MS 373 (M + H).

(*E*)-4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethylidene]-3-hydroxypiperidine (**39**). Prepared by the same procedure as in the synthesis of **27** except that **38** was used in place of **26**. MS 273 (M + H).

(*E*)-*t*-Butyl 4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethylidene]-3-methoxyimino-piperidinyl-1-carboxylate (**40**). A solution of **38** (0.51 g, 1.37 mmol) in CH_2Cl_2 (15 mL) at 25°C was treated with Dess-Martin periodinane (0.254 g, 0.60 mmol). After 1 h, the reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with 10% aqueous $NaHCO_3$ (3 x 25 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was used in the next step without further purification. A solution of the residue in pyridine (6 mL) in methanol (36 mL) at 25°C was treated with methoxyamine hydrochloride (0.835 g, 6.0 mmol). After 2 min, the reaction mixture was warmed to reflux for 5h, diluted with ethyl acetate (25 mL), washed with 10% aqueous $NaHCO_3$ (3 x 25 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford **40** (230 mg, 42%) as an orange residue. The residue was used in the next step without further purification. MS 400 (M + H).

(*E*)-4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethylidene]-3-methoxyimino-piperidine (**41**). Prepared by the same procedure as in the synthesis of **27** except that **40** was used in place of **26**. MS 300 (M + H).

Scheme XVII



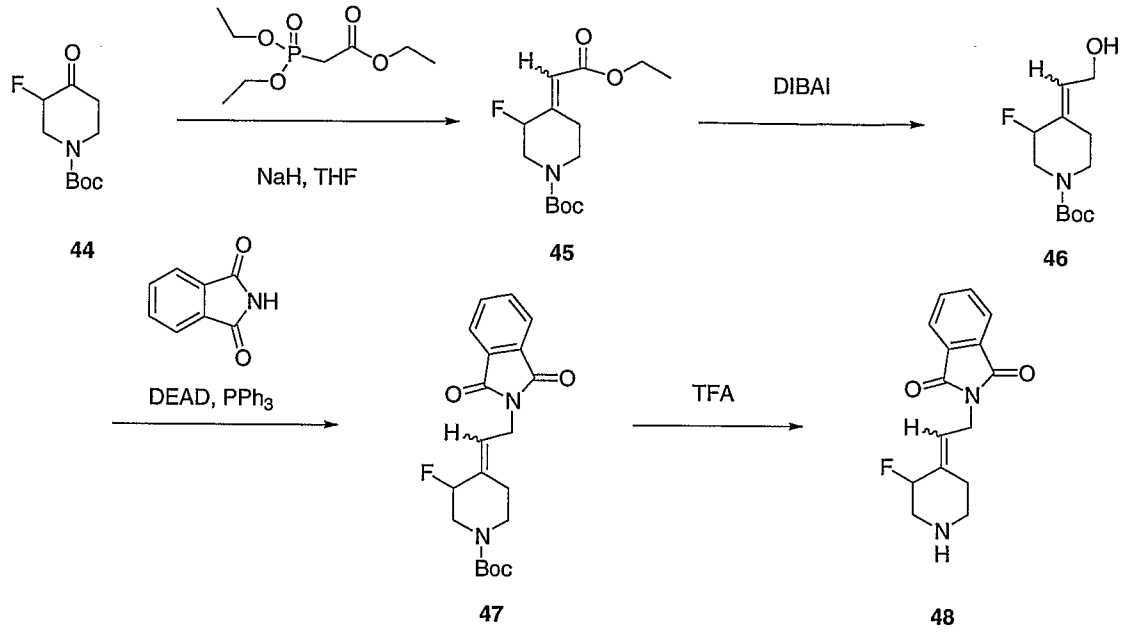
29 42 43

Compound **43** of Scheme XVII:

(*Z*)-*t*-Butyl 4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-methylethylidene]-3-hydroxy-piperidinyl-1-carboxylate (**42**). A slurry of SeO_2 (1.3 g, 11.4 mmol) in CH_2Cl_2 (15 mL) at 0°C was treated with *tert*-butyl hydroperoxide (4 mL, 22 mmol, 5-6 M, 10% in undecane) via a syringe. After 20 min, the reaction mixture was treated with a solution of ethylidene **29** (3.4 g, 9.1 mmol) in CH_2Cl_2 (15 mL) and the resulting mixture was allowed to stir for 12h at room temperature. The reaction was carefully quenched by the addition of 15% aqueous sodium thiosulfate (15 mL), and the reaction mixture was diluted with CH_2Cl_2 (25 mL). The layers were separated, and the organic layer was washed with 15% aqueous sodium thiosulfate (15 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 0-75% ethyl acetate/hexanes) afforded the title compound **42** (1.2 g, 34%) as a white solid. MS 387 (M + H).

(*Z*)-4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)1-methyl-ethylidene]-3-hydroxy-piperidine (**43**). Prepared by the same procedure as in the synthesis of **27** except that **42** was used in place of **26**. MS 287 (M + H).

Scheme XVIII



Compound **48** of Scheme XVIII:

t-Butyl-3-fluoro-4-oxopiperidinyl-1-carboxylate (**44**) was prepared according to U.S. Patent 5837715.

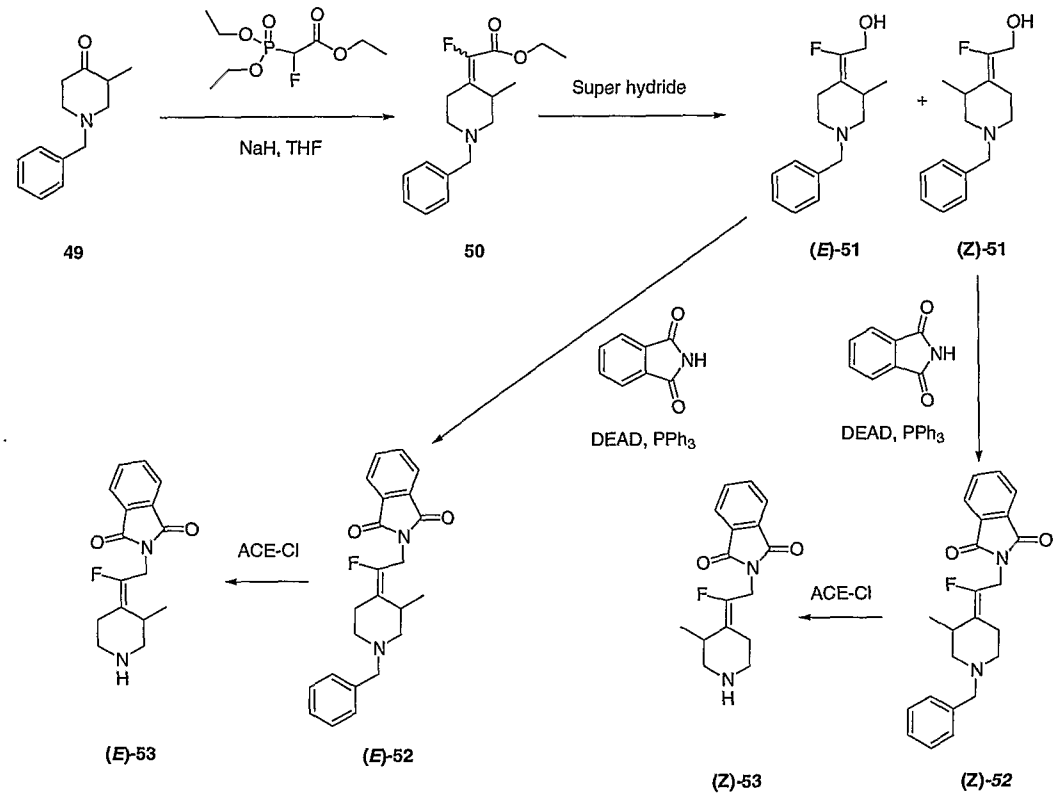
(*E/Z*)-*t*-Butyl 4-(2-ethoxy-2-oxoethylidene)-3-fluoropiperidinyl-1-carboxylate (**45**) Prepared by the same procedure as in the synthesis of **24** except that **44** was used in place of 1-(tert-butoxycarbonyl)-4-piperidinone. MS 288 (M + H).

(*E/Z*)-*t*-Butyl 4-(2-hydroxyethylidene)-3-fluoropiperidinyl-1-carboxylate (**46**) Prepared by the same procedure as in the synthesis of **25** except that **45** was used in place of **24**. MS 246 (M + H).

(*E/Z*)-*t*-Butyl 4-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)ethylidene]-3-fluoro-piperidinyl-1-carboxylate (**47**) Prepared by the same procedure as in the synthesis of **26** except that **46** was used in place of **25**. MS 375 (M + H).

(*E/Z*)-4-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)ethylidene]-3-fluoropiperidine trifluoroacetate (**48**). Prepared by the same procedure as in the synthesis of **27** except **47** was used in place of **26**. MS 275 (M + H).

Scheme XIX



Compounds *Z*-**53** and *E*-**53** of Scheme XIX:

Ethyl 1-[3-methyl-1-(phenylmethyl)-4-piperidinylidenyl]-1-fluoroacetate (**50**). Prepared by the same procedure as in the synthesis of **24** except that **49** was used in place of 1-(tert-butoxycarbonyl)-4-piperidinone and triethyl 2-fluorophosphonoacetate was used in place of triethyl phosphonoacetate. MS 292 (M + H).

2-[3-methyl-1-(phenylmethyl)-4-piperidinylidenyl]-2-fluoroethanol (***E*-51** and ***Z*-51**). A solution of **50** (2.68 g, 9.19 mmol) in tetrahydrofuran (50 mL) at 0°C was treated with a solution of Super-Hydride™ (23 mL, 23 mmol, 1.0 M in tetrahydrofuran, Aldrich) under nitrogen. After 1 h, the reaction mixture was carefully treated with methanol (10 mL), diluted with ethyl acetate (50 mL),

washed with 10% aqueous $NaHCO_3$ (3 x 50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by MPLC (silica gel, 0-50% ethyl acetate/hexanes) afforded the Z–isomer **51** (0.84 g, 37%) (MS 250 (M + H)) as a colorless oil and the E–isomer **51** (0.97 g, 42%) (MS 250 (M + H)) as a colorless oil.

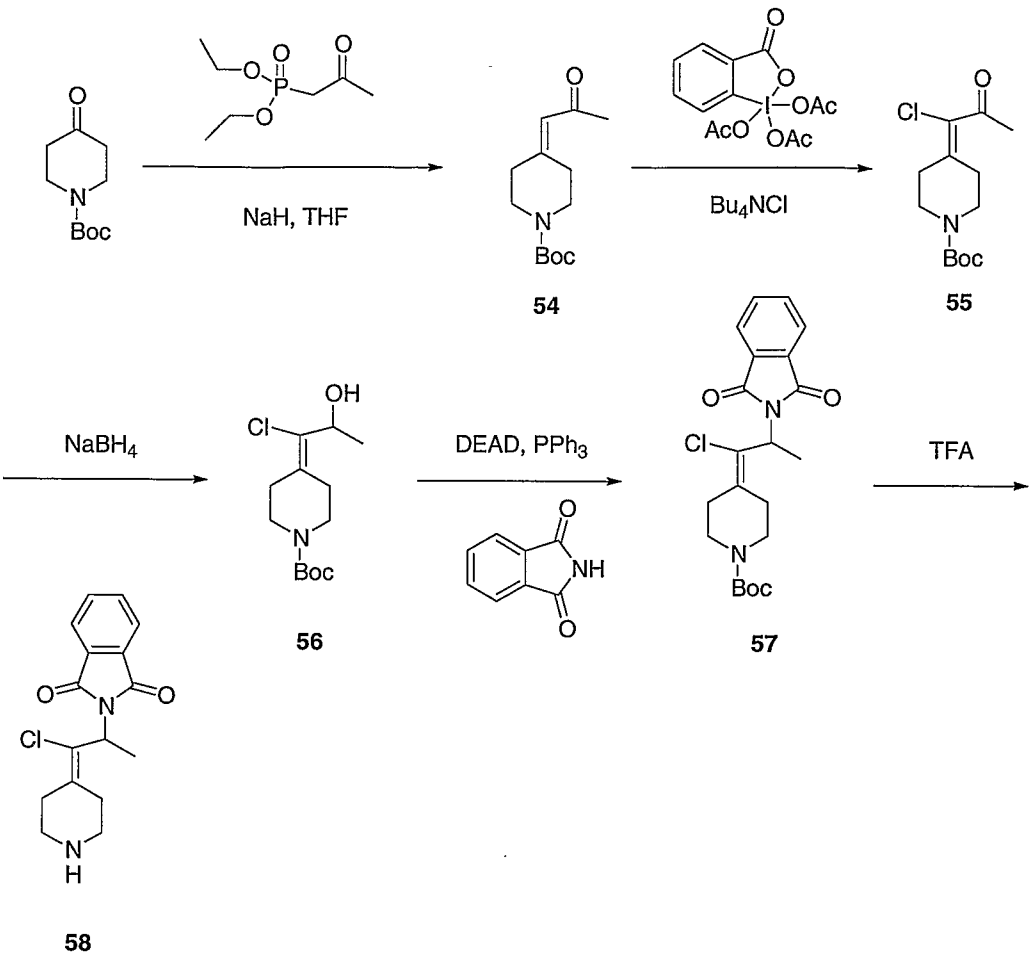
(*Z*)-2-[2-(3-methyl-1-(phenylmethyl)-4-piperidinylidenyl)-2-fluoroethyl]-1H-isoindole-1,3(2H)-dione (*Z*-**52**). Prepared by the same procedure as in the synthesis of **26** except that *Z*-**51** was used in place of **25**. MS 379 (M + H).

(*E*)-2-[2-(3-methyl-1-(phenylmethyl)-4-piperidinylidenyl)-2-fluoroethyl]-1H-isoindole-1,3(2H)-dione (*E*-**52**). Prepared by the same procedure as in the synthesis of **26** except that *E*-**51** was used in place of **25**. MS 379 (M + H).

(*Z*)-2-[2-fluoro-2-(3-methyl-4-piperidinylidenyl)-ethyl]-1H-isoindole-1,3(2H)-dione hydrochloride (***Z*-53**). A mixture of ***Z*-52** (0.550 g, 1.45 mmol) and 1-chloroethyl chloroformate (0.63 mL, 5.8 mmol) in dichloroethane (15 mL) was warmed to reflux temperature for 2h. The resulting solution was allowed to cool to room temperature, and concentrated in vacuo. The residue was dissolved in methanol (50 mL) and warmed to reflux temperature for 2h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo to afford a white solid. The residue was washed with diethyl ether (2x) and dried to afford ***Z*-53** (260 mg, 55%) as a white solid. MS 289 (M + H).

(*E*)-2-[2-fluoro-2-(3-methyl-4-piperidinylidenyl)-ethyl]-1H-isoindole-1,3(2H)-dione hydrochloride (*E*-**53**). Prepared by the same procedure as in the synthesis of ***Z*-52** except that ***E*-52** was used in place of *Z*-**52**. MS 289 (M + H).

Scheme XX



4-(2-Oxo-propylidene)piperidine-1-carboxylic acid tert-butyl ester (**54**). Prepared by the same procedure as described in International Patent Publication WO0285901.

4-(1-Chloro-2-oxo-propylidene)piperidine-1-carboxylic acid tert-butyl ester (**55**). A slurry of tetrabutylammonium chloride (11.1 g, 40.1 mmol) in CH_2Cl_2 (50 mL) at 25°C was treated with 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one (17.0g, 40.1 mmol) and the resulting light yellow solution was allowed to stir for 10 min. The reaction mixture was treated with a solution of **54** in CH_2Cl_2 (50 mL) and the resulting solution was allowed to stir for 3 h. The light yellow solution was carefully poured into a 10% aqueous solution of sodium bicarbonate (100 mL), diluted with CH_2Cl_2 (50 mL), to induce precipitation, filtered, and the precipitate was discarded. The resulting clear

solution was washed with a 10% aqueous solution of sodium bicarbonate (1 x 100 mL), brine (1 x100 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by MPLC (0-40% ethyl acetate / hexanes) afforded **55** (1.24g, 34%) as a colorless oil. MS 274 (M + H).

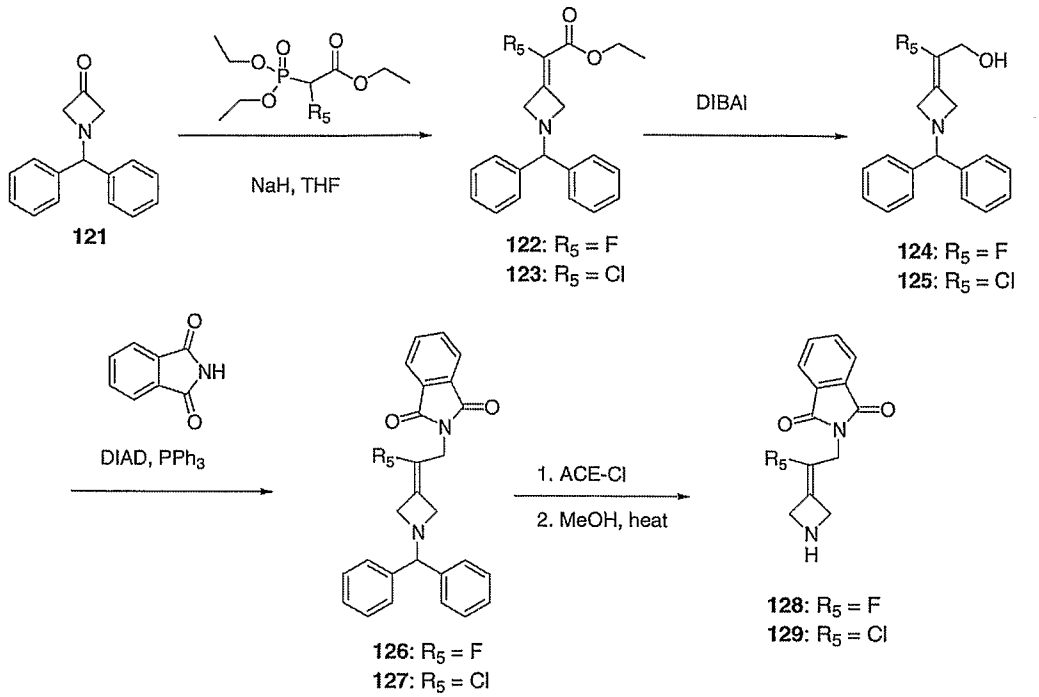
4-(1-Chloro-2-hydroxypropylidene)piperidine-1-carboxylic acid tert-butyl ester (**56**)

A solution of **55** (1.24 g, 4.53 mmol) in ethanol (25 mL) was treated with sodium borohydride (102 mg, 2.72 mmol) at 25°C. After 1 h, the reaction mixture was concentrated in vacuo, diluted with ethyl acetate (40 mL), carefully treated with 5% aqueous hydrochloric acid (1 x 25 mL), the layers separated, and dried ($MgSO_4$). The resulting solution was concentrated in vacuo to afford **56** (902.1 mg, 72%) as a colorless residue that was used without further purification. MS 298 (M + Na).

4-[1-Chloro-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propylidene]piperidine-1-carboxylic acid tert-butyl ester (**57**). Prepared by the same procedure as in the synthesis of **26** except that **56** was used in place of **25**. MS 427 (M + Na).

2-[(2-Chloro-1-methyl-2-(4-piperidinylidene)ethyl]-1H-isoindole-1,3(2H)-dione (**58**) Prepared by the same procedure as in the synthesis of **27** except that **56** was used in place of **26**. MS 305 (M + H).

Scheme XXXI



121

122: R_5 = F
123: R_5 = Cl

124: R_5 = F
125: R_5 = Cl

126: R_5 = F
127: R_5 = Cl

128: R_5 = F
129: R_5 = Cl

1-Benzhydrylazetidin-3-one (**XX**) was prepared according to the procedure described in Claiborne, et al WO 01/01988.

Ethyl 1-[1-diphenylmethylazetidin-3-ylidene]-1-fluoroacetate (**122**; R_5 = F).

Triethyl 2-fluoro-2-phosphonoacetate (0.63 mL, 3.10 mmol) was added to NaH (60% in oil, 115 mg, 2.87 mmol) in anhydrous THF (6 mL) at 0°C. After stirring for 15 minutes, a solution of ketone **121** (562 mg, 2.37 mmol) in anhydrous THF (6 mL) was added. The reaction was warmed to room temperature and stirred overnight. The reaction was diluted with ethyl acetate (100 mL), washed with saturated $NaHCO_3$ (2 x 100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was chromatographed (100% CH_2Cl_2) to afford ester **122** (R_5 = F) as a yellow oil (392 mg, 66%). MS 326 (M + H).

Ethyl 1-[1-diphenylmethylazetidin-3-ylidene]-1-chloroacetate (**123**; R_5 = Cl).

This was prepared in a similar manner to the procedure described above except that triethyl 2-chloro-2-phosphonoacetate was utilized in place of triethyl 2-fluoro-2-phosphonoacetate in the reaction. Ester **123** (R_5 = Cl) was isolated as a white solid (77%). MS 342, 344 (M + H).

2-(1-Diphenylmethylazetidin-3-ylidene)-2-fluoroethanol (**124**; R_5 = F). DIBAL (1M in toluene, 4.2 mL, 4.2 mmol) was added to a solution of ester **122** (R_5 = F) (510 mg, 1.56 mmol) in toluene (8 mL) at –78°C over several minutes. The reaction was stirred for 5 hours and then quenched by the slow addition of a solution of methanol in toluene. The reaction was diluted with ethyl acetate (100 mL), washed with NaOH (1N, 2 x 50 mL), water (50 mL), dried ($MgSO_4$) and concentrated in vacuo to afford alcohol **124** (R_5 = F, 289 mg, 65%) as a pale yellow solid after trituration with ether/hexanes. MS 284 (M + H).

2-(1-Diphenylmethylazetidin-3-ylidene)-2-chloroethanol (**125**; R_5= Cl). This was prepared in a similar manner to the procedure described above except that ester **123** (R_5 = Cl) was used in place of ester **122** (R_5 = F). Alcohol **125** (R_5 = Cl) was isolated by chromatography (20% ethyl acetate/hexanes) as a white solid (53%). MS 300, 302 (M + H).

2-[2-(1-Diphenylmethylazetidin-3-ylidene)-2-fluoroethyl]isoindole-1,3-dione (**126**; R_5 = F). DIAD (0.89 mL, 4.489 mmol) was added to a solution of alcohol **124** (R_5 = F) (1.00 g, 3.533 mmol), triphenyl phosphine (1.14 g, 4.34 mmol) and phthalimide (0.648 g, 4.527 mmol) in anhydrous THF (30 mL) at 0°C. The reaction was warmed to room temperature and stirred for 36 hours. The volatiles were evaporated and the residue chromatographed on silica gel (5% ethyl acetate/hexanes) to afford phthalimide **126** (R_5 = F) (952 mg, 65%) as a white solid. MS 413 (M + H).

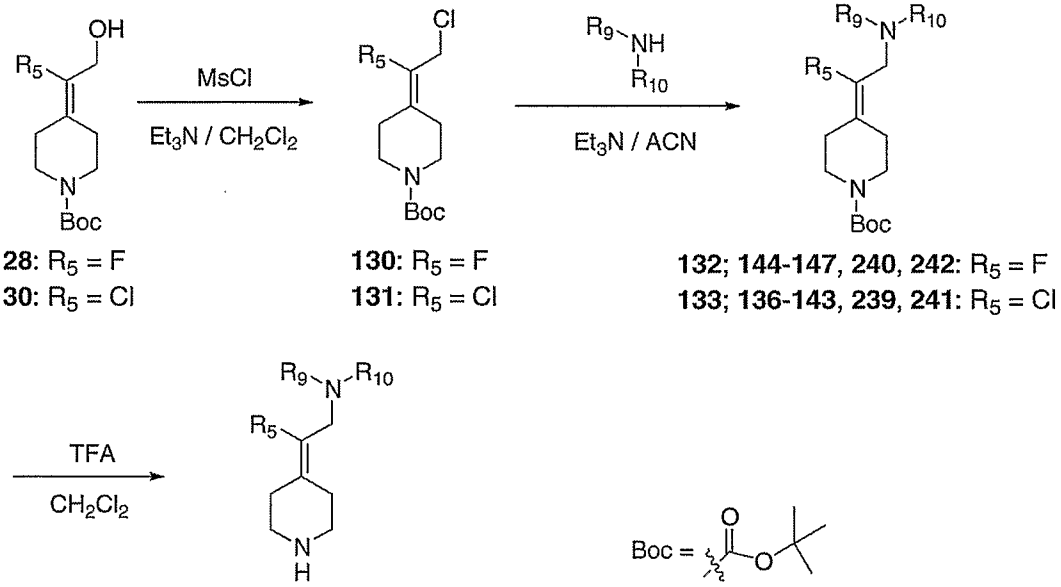
2-[2-(1-Diphenylmethylazetidin-3-ylidene)-2-chloroethyl]isoindole-1,3-dione (**127**; R_5 = Cl). This was prepared in a similar manner to the procedure described above except that alcohol **125** (R_5 = Cl) was used in place of alcohol **124** (R_5 = F) in the Mitsunobu reaction. Phthalimide **127** (R_5 = Cl) was isolated by chromatography (15% ethyl acetate/hexanes) as a white solid (68%). MS 429, 431 (M + H).

2-(2-Azetidin-3-ylidene-2-fluoroethyl)isoindole-1,3-dione Hydrochloride (**128**; R_5 = F). Phthalimide **126** (R_5 = F) (350 mg, 0.8491 mmol) and ACE-Cl (0.50 mL,

4.65 mmol) in 1,2-dichloroethane (20 mL) were heated at reflux temperature under a nitrogen atmosphere for 24 hours. After cooling, the volatiles were evaporated and methanol (25 mL) was added to the resulting residue. This was heated at reflux temperature for 3 hours after which the methanol was evaporated to afford **128** (R_5 = F) as a beige powder (230 mg, 96%). MS 247 (M + H).

2-(2-Azetidin-3-ylidene-2-chloroethyl)isoindole-1,3-dione Hydrochloride (**129**; R_5 = Cl). This was prepared in a similar manner to the procedure described above except that phthalimide **127** (R_5 = Cl) was used in place of phthalimide **126** (R_5 = F) in the reaction. The compound was isolated as a white powder (86%). MS 263, 265 (M + H).

Scheme XXXII



28: R_5 = F
30: R_5 = Cl

130: R_5 = F
131: R_5 = Cl

132; 144-147, 240, 242: R_5 = F
133; 136-143, 239, 241: R_5 = Cl

134; 156-159, 244, 246: R_5 = F
135; 148-155, 243, 245: R_5 = Cl

t-Butyl 4-(1,2-dichloroethylidene)piperidinyl-1-carboxylate (**131**; R_5 = Cl).
A solution of **30** (R_5 = Cl) (4.24 g, 16.20 mmol)) and triethylamine (6.8 mL, 48.60 mmol) in CH_2Cl_2 (120 mL) was treated with methanesulfonyl chloride (1.9 mL, 24.30 mmol) at 0°C, then warmed to rt and stirred over night. The resulting mixture was quenched by addition of saturated aq. $NaHCO_3$ (100 mL) and the product was extracted into CH_2Cl_2. Purification by flash

chromatography (0-20% ethyl acetate/hexanes) afforded the title compound (3.1 g, 68%) as a white solid.

t-Butyl 4-(2-chloro-1-fluoroethylidene)piperidinyl-1-carboxylate (**130**; R_5 = F).

This was prepared in a similar manner to the procedure described above except that alcohol **28** (R_5 = F) was used in place of alcohol **30** (R_5 = Cl).

t-Butyl 4-[2-(N-benzyl-N-methylamino)-1-chloroethylidene]piperidinyl-1-carboxylate (**133**; R_5 = Cl; R_9 = methyl; R_{10} = benzyl).

A solution of **131** (R_5 = Cl) (600 mg, 2.14 mmol)) and triethylamine (1.5 mL, 10.71 mmol) in acetonitrile (18 mL) was treated with N-benzylmethylamine (0.45 mL, 3.43 mmol) at rt and stirred overnight. The resulting mixture was concentrated in vacuo, and the residue was diluted with ethyl acetate (20 mL), washed with water (2 x 10 mL), and dried ($MgSO_4$). Purification by flash chromatography (0-15% ethyl acetate/hexanes) afforded the title compound (690 mg, 88%) as a white solid. MS 365 (M+H).

t-Butyl 4-[2-(N-benzyl-N-methylamino)-1-fluoroethylidene]piperidinyl-1-carboxylate (**132**; R_5 = F; R_9 = methyl; R_{10} = benzyl).

This was prepared in a similar manner to the procedure described above except that chloride **130** (R_5 = F) was used in place of chloride **131** (R_5 = Cl). MS 349 (M+H).

N-Benzyl-N-methyl-(2-chloro-2-piperidin-4-ylidene)ethylamine (**135**; R_5 = Cl; R_9 = methyl; R_{10} = benzyl).

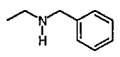
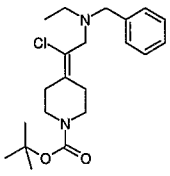
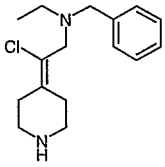
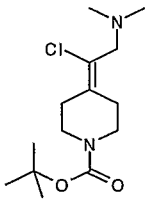
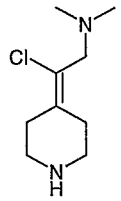
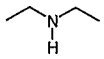
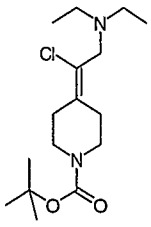
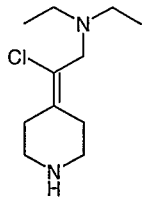
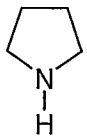
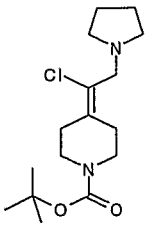
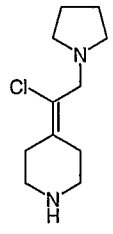
A solution of **133** (R_5 = Cl) (690 mg, 1.89 mmol) was dissolved in CH_2Cl_2 (15 mL) and was treated with trifluoroacetic acid (1.5 mL) at rt. After 5h, the reaction mixture was concentrated in vacuo to afford the title compound (quant.) as an oil, which was used in the next step without further purification. MS 265 (M+H).

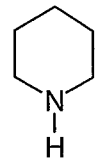
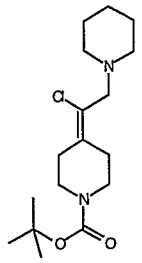
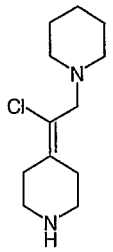
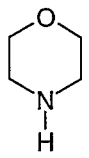
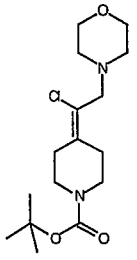
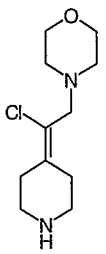
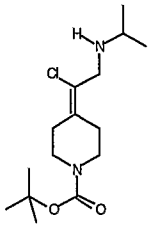
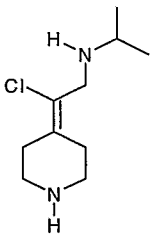
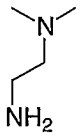
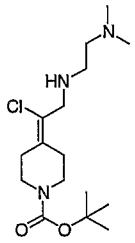
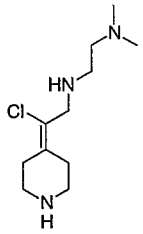
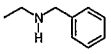
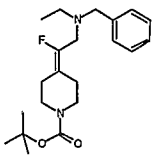
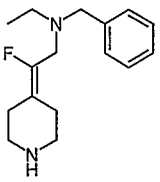
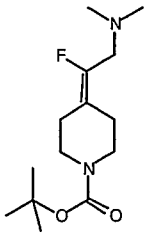
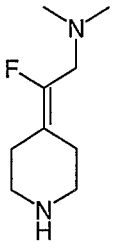
N-Benzyl-N-methyl-(2-fluoro-2-piperidin-4-ylidene)ethylamine (**134**; R_5 = F; R_9 = methyl; R_{10} = benzyl).

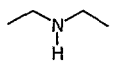
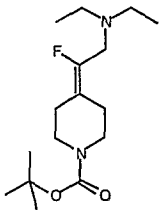
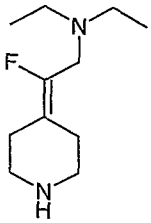
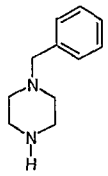
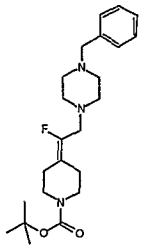
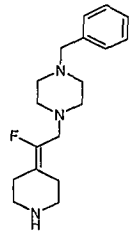
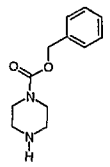
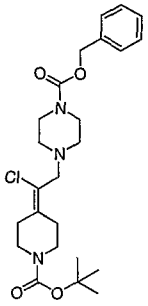
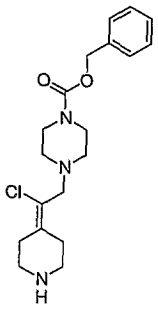
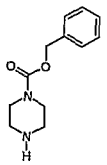
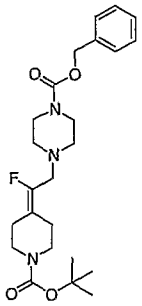
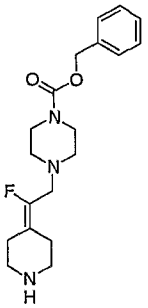
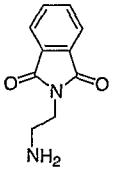
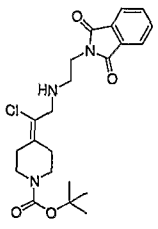
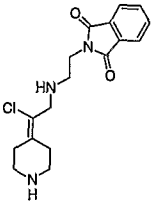
This was prepared in a similar manner to the procedure described above except that amine **132** (R_5 = F) was used in place of amine **133** (R_5 = Cl). MS 249 (M+H).

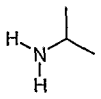
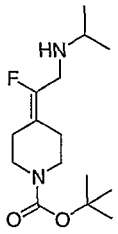
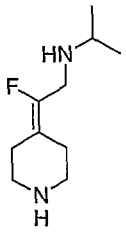
Table 9 lists the Boc-protected amines (**136-147**) and the derived amines (**148-159**) prepared by analogous procedures to those detailed above. The 2-(2-aminoethyl)-1H-isoindole-1,3(2H)-dione used in the preparation of **241** was synthesized by a similar procedure as that described in *Tetrahedron: Asymmetry* **2000**, *11*, 1907.

Table XX

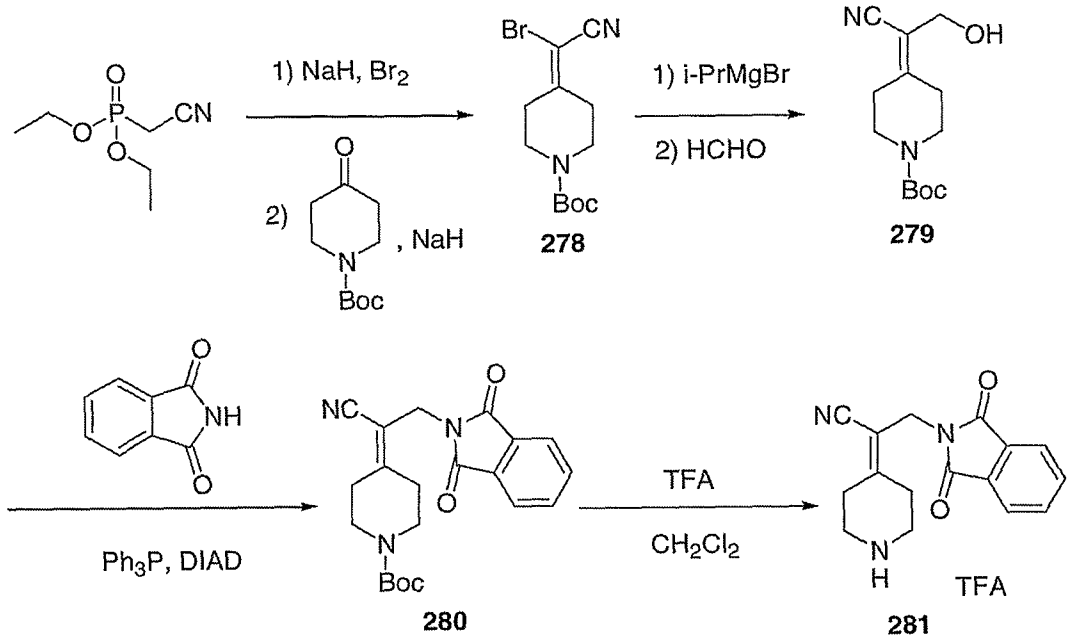
NHR_9R_{10}	Cmpd. Number	Boc-protected Amine	(M+H)	Cmpd. Number	Amine	(M+H)
	**136**		379	**148**		279
	**137**		289	**149**		189
	**138**		317	**150**		217
	**139**		315	**151**		215

	**140**		329	**152**		229
	**141**		331	**153**		231
	**142**		303	**154**		203
	**143**		332	**155**		232
	**144**		363	**156**		263
	**145**		373	**157**		273

	**146**		301	**158**		201
	**147**		404	**159**		304
	**239**		464	**243**		364
	**240**		448	**244**		348
	**241**		434	**245**		334

	**242**		287	**246**		187

Scheme XLIII



4-(bromo-cyano-methylidene)-piperidine-1-carboxylic acid *tert*-butyl ester (**278**). A slurry of sodium hydride (0.76 g, 19.0 mmol) in THF (75 mL) at 0 °C under nitrogen was carefully treated with diethyl cyanomethylphosphonate (3.4 g, 19.0 mmol) via a syringe. After gas evolution ceased, the reaction mixture was treated with bromine (3.04 g, 19.0 mmol) via a dropping funnel over 10 min., and the resulting mixture was allowed to stir for 2 h. The reaction mixture was treated with sodium hydride (0.76 g, 19.0 mmol) and the resulting slurry was allowed to stir for 30 min. at 0 °C. A solution of 1-(*tert*-butoxycarbonyl)-4-piperidinone (2.52 g, 12.7 mmol) in THF (10 mL) was added dropwise over 10 min. and the resulting solution was allowed to stir at room temperature overnight. The reaction was quenched by the addition of water (50 mL) and the resulting mixture was diluted with ethyl acetate (100 mL), washed with sat.

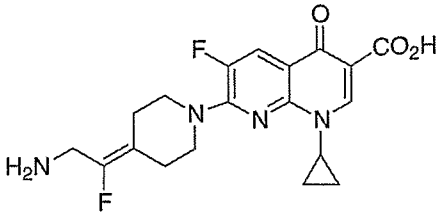
NH_4Cl (100 mL), brine (100 mL), and concentrated in vacuo. Purification by chromatography (EtOAc/hexanes = 1:4) yielded the title compound (2.8 g, 74%) as a white solid. MS 301 (M+H).

4-(1-cyano-2-hydroxy-ethylidene)-piperidine-1-carboxylic acid *tert*-butyl ester (**279**). To a solution of 2,6-diphenylphenol (10.5 g, 42 mmol) in 60 mL CH_2Cl_2 at room temperature was added $AlMe_3$ (2.0 M in hexane, 10.5 mL, 21 mmol). Gas evolution was observed and the mixture was stirred at room temperature for 30 min. The solution was cooled to 0 °C and 1,3,5-trioxane (630 mg, 7 mmol) in 6 mL CH_2Cl_2 was added dropwise and the solution was stirred for 1 h. In a separate flask 4-(bromo-cyano-methylidene)-piperidine-1-carboxylic acid *tert*-butyl ester (2.1 g, 7 mmol) was dissolved in 20 mL THF at –40 °C and to this solution was added isopropylmagnesium bromide (1M in THF, 8.4 mL, 8.4 mmol) dropwise. The mixture was stirred at –40 °C to –30 °C for 1.5 h. The above freshly prepared Grignard reagent was added dropwise to the formaldehyde solution and the mixture was stirred at 0 °C for 1 h. Water was carefully added and the mixture was extracted with ethyl acetate. Purification by chromatography (EtOAc/hexanes = 1:1) yielded the title compound (800 mg, 45%) as a white solid. MS 253 (M+H).

4-[1-cyano-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethylidene]-piperidine-1-carboxylic acid *tert*-butyl ester (**280**). This compound was prepared in a similar manner as in the synthesis of **26** except that **279** was used in place of **25**. MS 382 (M+H).

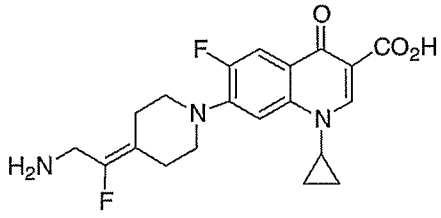
3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-piperidin-4-ylidene-propionitrile (**281**). This compound was prepared in a similar manner as in the synthesis of **27** except that **280** was used in place of **26**. MS 282 (M+H).

Final Product Preparation



1

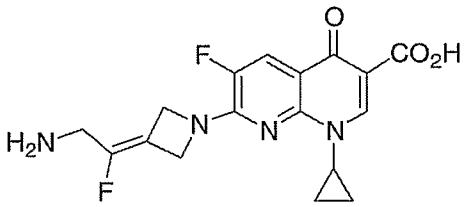
7-[4-(2-Amino-1-fluoro-ethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (**1**) A solution of amine **31** (612 mg, 1.57 mmol) and triethylamine (0.7 mL, 5.0 mmol) in acetonitrile (4 mL) was treated with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-naphthpyridine-3-carboxylic acid (222 mg, 0.787 mmol) under nitrogen and the reaction mixture was allowed to stir for 12 h. The resulting mixture was concentrated in vacuo, and the residue was washed with water (3 x 10 mL). The residue was allowed to dry for 15 min. The solid was collected, resuspended in methanol (5 mL) and the reaction mixture was treated with hydrazine (1 mL). After 5 min, the reaction mixture was warmed to reflux and the resulting mixture was allowed to stir for 1 h. The reaction mixture was concentrated in vacuo, diluted with water and the solids were collected by filtration. The off white product was washed with water (3 x 20 mL), allowed to dry overnight to afford the title compound **1** (40.4 mg, 13%). MS 391 (M+H).



5

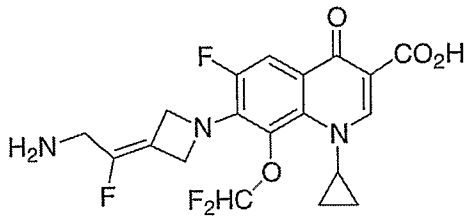
7-[4-(2-Amino-1-fluoro-ethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid trifluoroacetic acid salt (**5**) A solution of amine **31** (311 mg, 0.80 mmol) and triethylamine (0.55 mL, 4.0 mmol) in acetonitrile (4 mL) was treated with diacetyl quinolinyl borate **17** (300 mg, 0.60 mmol) under nitrogen. After 5 min, the reaction mixture was warmed to reflux and the reaction mixture was allowed to stir for 12 h. The resulting mixture was

allowed to cool to room temperature, concentrated in vacuo, and the residue was washed with water (3 x 10 mL). The residue was dissolved in tetrahydrofuran (3 mL) and treated with 10% aqueous hydrochloric acid (5 mL) at room temperature. After 30 min, the reaction mixture was concentrated in vacuo, diluted with water (10 min) and the solid collected by filtration. The solid residue was washed with water (3 x 5 mL) and allowed to dry for 15 min. The solid was collected and resuspended in methanol (5 mL) and the reaction mixture was treated with hydrazine (1 mL). After 5 min, the reaction mixture was warmed to reflux temperature and the resulting mixture was allowed to stir for 1 h. The reaction mixture was concentrated in vacuo and the residue purified by HPLC (reverse phase C-18 column, 0-55% acetonitrile/water containing 0.1% trifluoroacetic acid) to afford the trifluoroacetic acid salt of **5** (61.3 mg, 20%) as a light yellow solid. MS 390 (M+H).



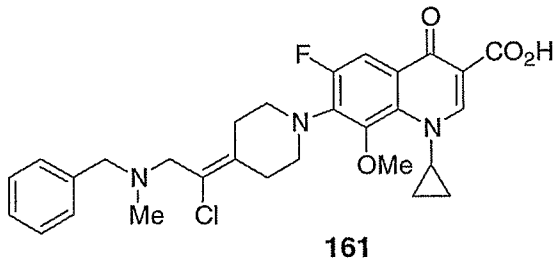
80

7-[3-(2-Amino-1-fluoro-ethylidene)azetidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (**80**). 7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydronaphthyridine-3-carboxylic acid (57 mg, 0.2016 mmol), amine **128** (R_5 = F) (67 mg, 0.2389 mmol) and triethylamine (0.5 mL) in acetonitrile (10 mL) were heated at reflux temperature overnight. After cooling, the volatiles were evaporated and the residue suspended in water (25 mL). The resulting solid was collected by filtration and dried. Ethanol (5 mL) was added to the solid followed by hydrazine (0.01 mL, 0.3138 mmol). The reaction mixture was heated at reflux temperature for 1 hour after which the volatiles were evaporated. Water (15 mL) was added to the residue and the resulting solid collected by filtration, washed with additional water and dried to afford **87** (49.1 mg, 69%) as an off-white powder. MS 363 (M + H).



160

7-[3-(2-Amino-1-fluoro-ethylidene)azetidin-1-yl]-1-cyclopropyl-8-difluoromethoxy-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**160**). A solution of amine **128** (R_5 = F) (83 mg, 0.2923 mmol), diacetyl quinolinyl borate **83** (111 mg, 0.2413 mmol) and triethylamine (0.5 mL) in acetonitrile (10 mL) were heated at reflux temperature overnight. The volatiles were evaporated and then THF (5 mL) and 10% aqueous HCl (4 mL) were added to the residue. This mixture was stirred for approximately 1 hour. The resulting solid was collected by filtration, washed with water and dried. Ethanol (4 mL) and hydrazine (0.01 mL) were added to the solid and the reaction heated at reflux temperature for 1.5 hours. The ethanol was evaporated in vacuo and water (20 mL) added to the remaining material. The solid was collected and dried to afford **160** as a yellow solid (20%). MS 428 (M + H).

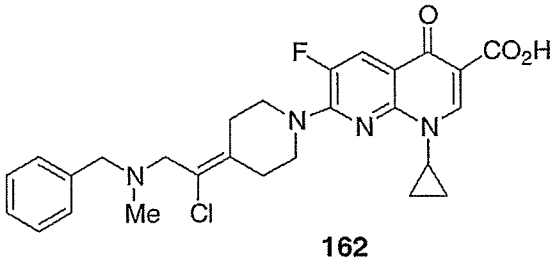


161

7-{4-[2-(N-Benzyl-N-methylamino)-1-chloroethylidene]piperidin-1-yl}-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid trifluoroacetic acid salt (**161**).

A solution of amine **135** (1.89 mmol) and triethylamine (1.2 mL, 8.59 mmol) in acetonitrile (15 mL) was treated with diacetyl quinolinyl borate **19** (727 mg, 1.72 mmol) under nitrogen. After 5 min, the reaction mixture was warmed to reflux temperature and the reaction mixture was allowed to stir for 24h. The resulting mixture was allowed to cool to room temperature, and then concentrated in

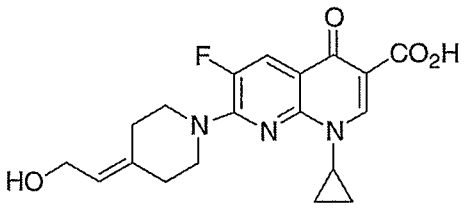
vacuo. The residue was dissolved in tetrahydrofuran (5 mL), treated with 10% aqueous hydrochloric acid (5 mL) at room temperature and stirred overnight. The resulting mixture was concentrated in vacuo and the residue purified by HPLC (reverse phase C-18 column, 30-90% acetonitrile/water containing 0.1% trifluoroacetic acid) to afford the trifluoroacetic acid salt of **161** (632 mg, 56%) as a yellow solid. MS 540 (M+H).



162

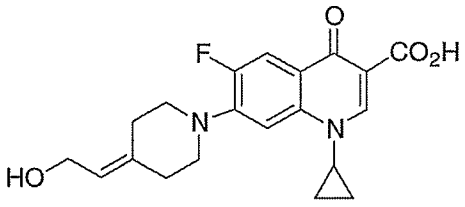
7-{4-[2-(N-Benzyl-N-methylamino)-1-chloroethylidene]piperidin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (**162**).

A solution of amine **135** (0.48 mmol) and triethylamine (0.28 mL, 2.0 mmol) in acetonitrile (7 mL) was treated with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (113 mg, 0.40 mmol) under nitrogen. After 5 min, the reaction mixture was warmed to reflux temperature and the reaction mixture was allowed to stir for 24h. The resulting mixture was allowed to cool to room temperature, concentrated in vacuo and the residue was diluted with water. The product was collected by filtration, and then washed with water and a small amount of methanol to afford the title compound (178 mg, 87%) as a white solid. MS 511 (M+H).



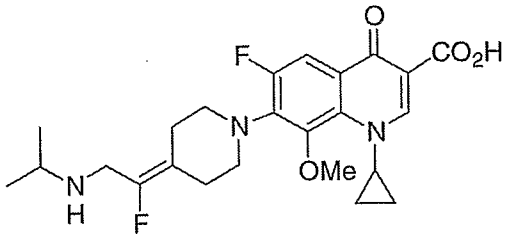
163

7-[4-(2-Hydroxyethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (**163**). A solution of amine **103** (256 mg, 1.06 mmol) and triethylamine (0.5 mL, 3.55 mmol) in acetonitrile (4 mL) was treated with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid (200 mg, 0.71 mmol) under nitrogen and the reaction mixture was allowed to stir for 16 h. The resulting mixture was concentrated in vacuo, and the residue was washed with water (3 x 10 mL) and allowed to dry overnight to afford the title compound **163** (105 mg, 40%). MS 374 (M+H).



164

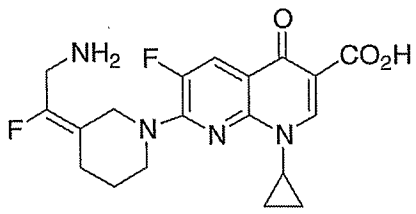
7-[4-(Hydroxyethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**164**). A solution of amine **103** (146 mg, 0.61 mmol) and triethylamine (0.55 mL, 4.0 mmol) in acetonitrile (4 mL) was treated with diacetyl quinolinyl borate **17** (125 mg, 0.60 mmol) under nitrogen. After 5 min, the reaction mixture was warmed to reflux temperature and the reaction mixture was allowed to stir for 12 h. The resulting mixture was allowed to cool to room temperature, concentrated in vacuo, and the residue was washed with water (3 x 10 mL). The residue was dissolved in tetrahydrofuran (3 mL) and treated with 10% aqueous hydrochloric acid (5 mL) at room temperature. After 30 min, the reaction mixture was concentrated in vacuo, diluted with water (10 min) and the solid collected by filtration. The solid residue was washed with water (3 x 5 mL) and allowed to dry for 15 min. The solid was collected to afford **157** (5.1 mg, 2.2%) as a light yellow solid. MS 373 (M+H).



252

1-Cyclopropyl-6-fluoro-7-[4-(1-fluoro-2-isopropylamino-ethylidene)-piperidin-1-yl]-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid trifluoroacetic acid salt (**252**).

Amine **246** (0.12 mmol), difluoroborate ester **223** (34 mg, 0.10 mmol), and triethylamine (0.07 mL) in anhydrous acetonitrile (2 mL) were heated at reflux temperature under a nitrogen atmosphere for 24 hours. After cooling, the volatiles were evaporated in vacuo. Ethanol (5 mL) and triethylamine (0.5 mL) were added to the residue. This was heated at reflux temperature for 19 hours. The volatiles were evaporated and the residue was purified by HPLC (reverse phase C-18 column, 36-50% acetonitrile/water containing 0.1% trifluoroacetic acid) to afford the trifluoroacetic acid salt of **252** (11.4 mg, 20%) as a light yellow solid. MS 462 (M+H).

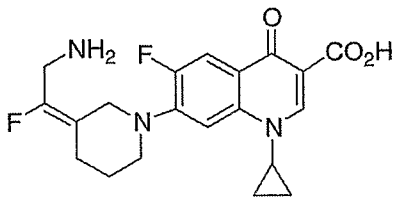


253

(E)-7-[3-(2-Amino-1-fluoro-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid trifluoroacetic acid salt (**253**).

A solution of amine ***E*-232** (0.276 mmol) and triethylamine (0.16 mL, 1.152 mmol) in acetonitrile (5 mL) was treated with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthpyridine-3-carboxylic acid (65 mg, 0.230 mmol) under nitrogen. After 5 min, the reaction mixture was heated to reflux temperature and the reaction mixture was allowed to stir for 24h. The resulting mixture was allowed to cool to room temperature and concentrated in vacuo.

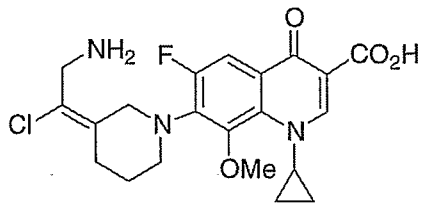
The residue was resuspended in methanol (5 mL) and the reaction mixture was treated with hydrazine (1 mL). The resulting mixture was stirred at room temperature overnight and concentrated in vacuo. The residue was purified by HPLC (reverse phase C-18 column, 25-40% acetonitrile/water containing 0.1% trifluoroacetic acid) to afford the trifluoroacetic acid salt of ***E*-232** (95.6 mg, 82%) as a white solid. MS 391 (M+H).



256

(E)-7-[3-(2-Amino-1-fluoro-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid trifluoroacetic acid salt (**256**).

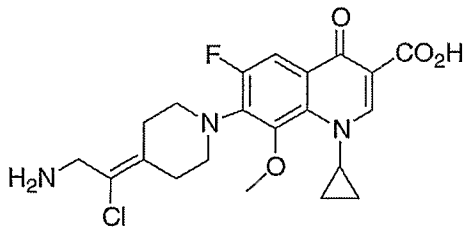
A solution of amine ***E*-232** (0.260 mmol) and triethylamine (0.15 mL, 1.085 mmol) in acetonitrile (5 mL) was treated with diacetyl quinolinyl borate **17** (85 mg, 0.217 mmol) under nitrogen. After 5 min, the reaction mixture was heated to reflux temperature and the reaction mixture was allowed to stir for 24h. The resulting mixture was allowed to cool to room temperature and concentrated in vacuo. The residue was dissolved in tetrahydrofuran (2 mL), treated with 10% aqueous hydrochloric acid (2 mL) at room temperature, and stirred overnight. The resulting mixture was concentrated in vacuo, the residue was resuspended in methanol (2 mL) and the reaction mixture was treated with hydrazine (0.5 mL). The resulting mixture was stirred at room temperature overnight and concentrated in vacuo. The residue was purified by HPLC (reverse phase C-18 column, 25-50% acetonitrile/water containing 0.1% trifluoroacetic acid) to afford the trifluoroacetic acid salt of **256** (27 mg, 25%) as a yellow solid. MS 390 (M+H).



261

(E)-7-[3-(2-Amino-1-chloro-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid trifluoroacetic acid salt (**261**).

Amine ***E*-233** (0.256 mmol), difluoroborate ester **223** (73 mg, 0.213 mmol), and triethylamine (0.15 mL) in anhydrous acetonitrile (5 mL) were heated at reflux temperature under a nitrogen atmosphere for 24 hours. After cooling, the volatiles were evaporated in vacuo. Ethanol (5 mL) and triethylamine (0.5 mL) were added to the residue. This was heated at reflux temperature for 19 hours. The volatiles were evaporated, the residue was resuspended in methanol (2 mL), and the reaction mixture was treated with hydrazine (0.5 mL). The resulting mixture was stirred at room temperature overnight and concentrated in vacuo. The residue was purified by HPLC (reverse phase C-18 column, 35-50% acetonitrile/water containing 0.1% trifluoroacetic acid) to afford the trifluoroacetic acid salt of **261** (26.6 mg, 23%) as a yellow solid. MS 436 (M+H).

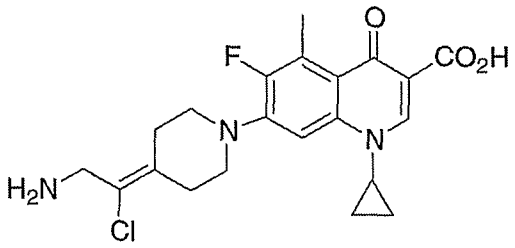


7

7-[-4-(2-Amino-1-chloroethylidene)piperidin-1-yl}-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**7**).

Amine **33** (34.95 mmol), difluoroborate ester **223** (7.29 g; 21.25 mmol) and triethylamine (35 mL) in anhydrous acetonitrile (250 mL) were heated at reflux temperature under a nitrogen atmosphere for 36 hours. After cooling, the

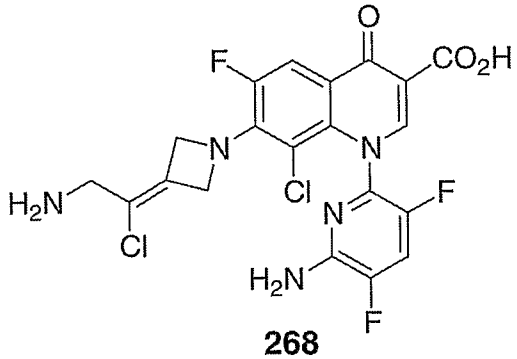
volatiles were evaporated in vacuo. Ethanol (350 mL) and triethylamine (30 mL) were added to the residue. This was heated at reflux temperature for 38 hours. The volatiles were evaporated and water (250 mL) was added to the residue. The resulting solid was collected by filtration, washed with additional water and dried. This solid was suspended in ethanol (100 mL) and hydrazine (2.5 mL; 80 mmol) was added. The reaction was heated to 60°C under a nitrogen atmosphere for 2 hours. The volatiles were evaporated. After the addition of water to the residue, the solid was collected, washed with water and dried to afford **7**. MS 436 (M + H).



263

7-[-4-(2-Amino-1-chloro-ethylidene)piperidin-1-yl}-1-cyclopropyl-6-fluoro-5-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**263**).

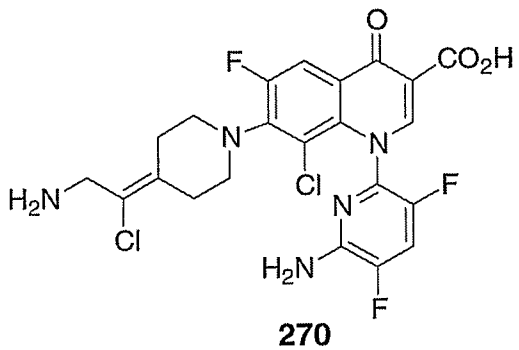
Amine **33** (1.15 mmol), difluoroborate ester **224** (145 mg; 0.4433 mmol) and triethylamine (2.5 mL) in anhydrous acetonitrile (10 mL) were heated at reflux temperature under a nitrogen atmosphere for 48 hours. The volatiles were evaporated. 1,2-dichloroethane (10 mL), ethanol (20 mL) and triethylamine (2 mL) were added and the suspension heated at reflux temperature for 36 hours. The volatiles were evaporated. Water (30 mL) was added to the residue. The resulting solid was collected by filtration, washed with water and dried to afford the phthalimide-protected amine (226 mg, 93%). This solid (220 mg; 0.40 mmol) and hydrazine (0.05 mL; 1.59 mmol) suspended in methanol (30 mL) were heated at 60°C for 5.5 hours. The volatiles were evaporated and water (25 mL) added to the gummy residue. After several minutes, a solid formed. This was filtered, washed with water and dried. **263** was isolated as a pale beige powder (146 mg; 87%). MS 420 (M + H).



268

7-[-3-(2-Amino-1-chloroethylidene)azetidin-1-yl}-1-(6-amino-3,5-difluoropyridi-2-yl)-8-chloro-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**268**).

1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6,7-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (0.412 mmol) (prepared by the methods described in WO09/11068 and US 4,885,386), amine **129** (0.455 mmol), and triethylamine (0.3 mL) in anhydrous acetonitrile (10 mL) were heated at 55°C under a nitrogen atmosphere for 1 hour. After cooling, the volatiles were evaporated in vacuo and water was added to the residue. The resulting solid was collected by filtration, washed with additional water and dried. This solid was suspended in methanol (10 mL) and treated with hydrazine (0.1 mL, 2.233 mmol). The reaction was stirred under a nitrogen atmosphere for 6 hours. The volatiles were evaporated. After the addition of water to the residue, the solid was collected, washed with methanol and dried to afford the title compound (37%). MS 501 (M + H).

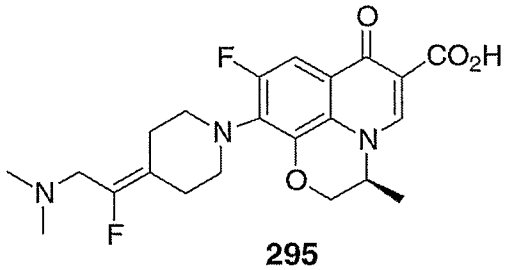


270

7-[-4-(2-Amino-1-chloroethylidene)piperidin-1-yl}-1-(6-amino-3,5-difluoropyridi-2-yl)-8-chloro-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**270**).

Amine **33** (1.0 mmol), 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6,7-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (0.5 mmol) (prepared by the methods described in WO09/11068 and US 4,885,386), and triethylamine (1.0

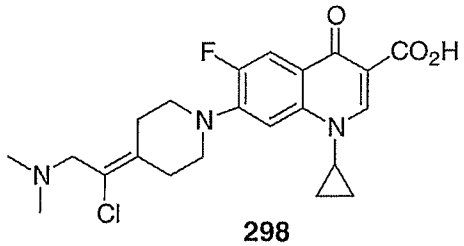
mmol) in anhydrous dimethylsulfoxide (1.5 mL) were heated at 70°C under a nitrogen atmosphere for 1 hour. Then, ethanol (25 mL) was added to the reaction and it was heated at 90°C for 10 minutes. After cooling, the resulting solid was collected by filtration, washed with additional ethanol and dried. This solid was suspended in ethanol (10 mL) and methylamine (33% in ethanol, 0.15 mL) was added. The reaction was stirred under a nitrogen atmosphere for 70 hours. The volatiles were evaporated. After the addition of water to the residue, the solid was collected, washed with water and dried to afford the title compound (57%). MS 529 (M + H).



295

(*S*)-9-[4-(2-Dimethylamino-1-fluoro-ethylidene)-piperidin-1-yl]-8-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (**295**).

To a solution **157** (0.553 mmol) in acetonitrile (7 mL) was added S-(-)-9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (0.0762 g, 0.271 mmol) and then triethylamine (0.79 mL). This mixture was refluxed for 5 days and then solvent was removed in vacuo. The resulting solid was dissolved in dimethylsulfoxide and purified by HPLC (reverse phase C-18 column, 10-90% acetonitrile/water containing 0.1% trifluoroacetic acid). The collected fractions were lyophilized to provide 0.0052 g of a yellow solid (3.5% yield for TFA salt). MS 434 (M+H).



298

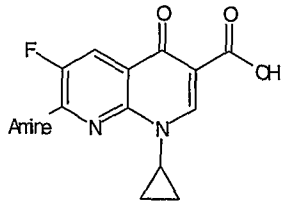
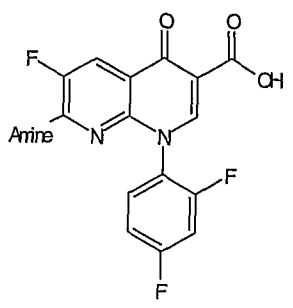
7-[4-(1-Chloro-2-dimethylamino-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid trifluoroacetic acid salt (**298**).

To **149** (0.506 mmol) in acetonitrile (7 mL) was added 1-cyclopropyl-1,4-dihydro-6,7-difluoro-4-oxo-quinoline-3-carboxylic acid (0.0699 g, 0.264mmol) and then triethylamine (0.76 mL). This mixture was refluxed for 5 days and then solvent was removed in vacuo. The resulting solid was dissolved in dimethylsulfoxide and purified by HPLC (reverse phase C-18 column, 10-90% acetonitrile/water containing 0.1% trifluoroacetic acid). The collected fractions were lyophilized to provide 0.1024 g of a tan solid (71% yield for TFA salt). MS 434 (M+H).

Table **4** lists the additional compounds of the instant invention prepared by the experimental procedures detailed above. In the case of the naphthyridines **2-4**, **59-63**, **69**, and **173-176** an analogous experimental procedure to that for compound **1** was used in their preparation. For the naphthyridines **171**, **172**, **185** and **271**, an analogous procedure to that for **163** was used. For the naphthyridines **81**, **183** and **184**, an analogous experimental procedure to that for **80** was used. For the naphthyridines **165-170**, **177-182**, **186**, and **247** a similar procedure to that for **162** was used in their preparation. In the case of naphthyridines **254** and **255**, an analogous experimental procedure to that for compound **253** was used in their preparation. Quinolones **262** and **273** were prepared in an analogous manner to the preparation of **7** above. For the quinolones **6**, **8-15**, **64-66**, **70**, **71**, **73**, **78**, **187**, **188**, **201-204**, **206-208**, **210**, **272**, and **274-277**, an analogous experimental procedure to that for compound **5** was used in their preparation. In addition to the method described above, quinolone **7** could also be prepared by an analogous method to that used for **5**. For the quinolones **76**, **77**, **189**, **205**, and **209**, an analogous procedure to that for **160** was used in their preparation. For the quinolones **190-200** and **248-251** an analogous procedure to that for **161** was used. For the quinolone **211** a similar procedure to that for **163** was used in its preparation. In the case of the quinolones **257-260**, an analogous experimental procedure to that for

compound **256** was used in their preparation. Quinolone **269** was prepared in an analogous manner to quinolone **268**. Quinolones **299** and **300** were prepared in an analogous manner to quinolone **298**. Quinolone **301** was prepared in an analogous manner to quinolone **256**. Quinolones **302** and **303** were prepared in an analogous fashion to quinolone **261**.

Table 4

Structure	Amine	Compound Number
	**27**	**59** (M + H) = 373
	32	**2** (M + H) = 387
	33	**3** (M + H) = 407
	39	**60** (M + H) = 389
	41	**61** (M + H) = 416
	43	**62** (M + H) = 403
	48	**63** (M + H) = 391
	129	**81** (M+H) = 379, 381
	148	**165** (M + H) = 525
	154	**166** (M + H) = 449
	134	**167** (M + H) = 495
	156	**168** (M + H) = 509
	158	**169** (M + H) = 447
	159	**170** (M + H) = 550
	105	**171** (M + H) = 388
	104	**172** (M + H) = 392
	85	**69** (M + H) = 401
	118	**173** (M + H) = 413
	119	**174** (M + H) = 427
	117	**175** (M + H) = 419
	120	**176** (M + H) = 452
	155	**177** (M + H) = 478
	110	**178** (M + H) = 404
	107	**179** (M + H) = 464
	149	**180** (M + H) = 435
	152	**181** (M + H) = 475
	157	**182** (M + H) = 419
	246	**247** (M + H) = 433
	***E*-233**	**254** (M + H) = 407
	***Z*-233**	**255** (M + H) = 407
	**31**	**4** (M + H) = 463
	128	**183** (M + H) = 435

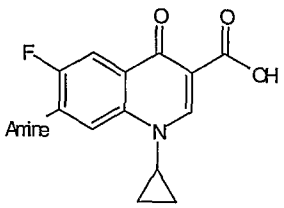
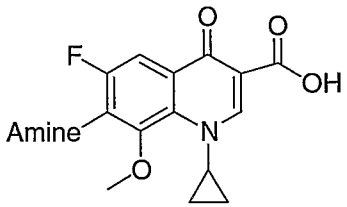
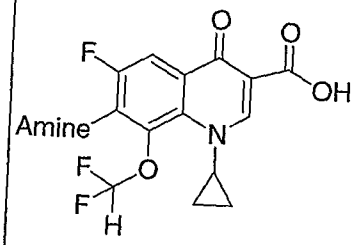
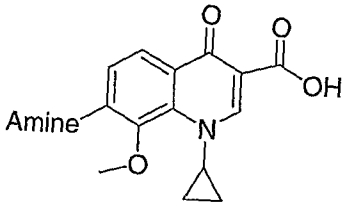
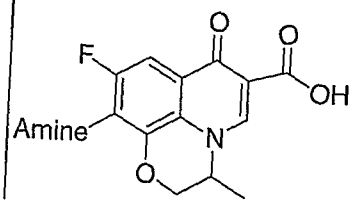
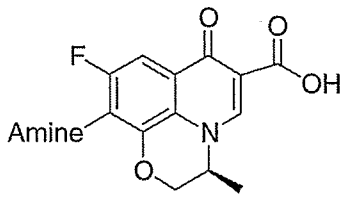
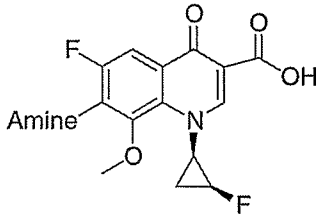
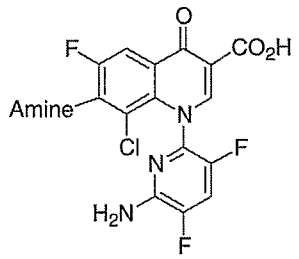
	129	**184** (M + H) = 451, 453
	103	**185** (M + H) = 446
	157	**186** (M + H) = 491
	33	**271** (M + H) = 479
	**32**	**64** (M + H) = 386
	33	**65** (M + H) = 406
	129	**76** (M + H) = 378, 380
	135	**187** (M + H) = 510
	134	**188** (M + H) = 494
	154	**248** (M + H) = 448
	246	**249** (M + H) = 432
	***E*-233**	**257** (M + H) = 406
	***Z*-233**	**258** (M + H) = 406
	128	**272** (M + H) = 362
	157	**299** (M + H) = 418
	152	**300** (M + H) = 474
	***Z*-238**	**301** (M + H) = 386

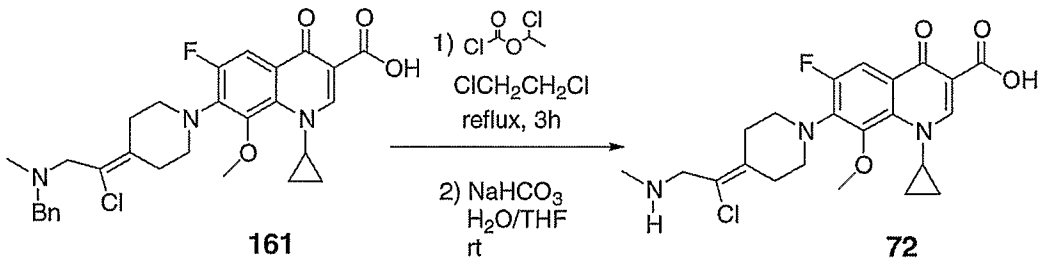
Table 4 continued

Structure	Amine	Compound Number
	31	6 (M + H) = 420
	Z-53	11 (M + H) = 434
	E-53	12 (M + H) = 434
	Z-37	13 (M + H) = 422
	E-37	14 (M + H) = 422
	58	15 (M + H) = 450
	129	189 (M + H) = 408, 410
	148	190 (M + H) = 554
	149	191 (M + H) = 464
	150	192 (M + H) = 492
	151	193 (M + H) = 490
	152	194 (M + H) = 504
	153	195 (M + H) = 506
	154	196 (M + H) = 478
	134	197 (M + H) = 524
	156	198 (M + H) = 538
	157	199 (M + H) = 448
	158	200 (M + H) = 476
	32	70 (M + H) = 402
	85	71 (M + H) = 430
	116	201 (M + H) = 446
	119	202 (M + H) = 456
	118	203 (M + H) = 442
	117	78 (M + H) = 448

	120	**204** (M + H) = 481
	27	**212** (M + H) = 402
	128	**273** (M + H) = 392
	Z-238	**302** (M + H) = 416
	E-232	**303** (M + H) = 420
	129	**205** (M + H) = 444, 446
	135	**106** (M + H) = 576
	134	**207** (M + H) = 560
	31	**208** (M + H) = 456
	33	**73** (M + H) = 472
	154	**250** (M + H) = 514
	246	**251** (M + H) = 498
	E-232	**259** (M + H) = 456
	E-233	**260** (M + H) = 472
	31	**10** (M + H) = 402
	129	**209** (M + H) = 390, 392
	128	**274** (M + H) = 374
	33	**275** (M + H) = 418
	31	**8** (M + H) = 406
	32	**9** (M + H) = 402
	43	**66** (M + H) = 418
	39	**210** (M + H) = 404

	105	**211** (M + H) = 427
	**33**	**277** (M + H) = 422
	128	**276** (M + H) = 378
	129	**77** (M + H) = 394, 396
	**33**	**262** (M + H) = 454
	**128**	**269** (M + H) = 484

Scheme XXXIII



161 **72**

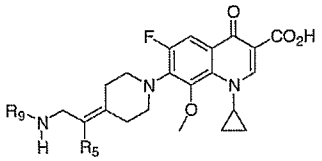
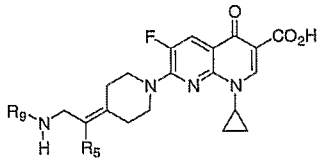
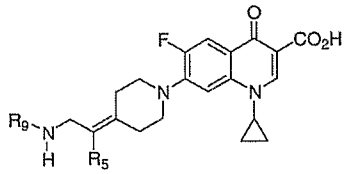
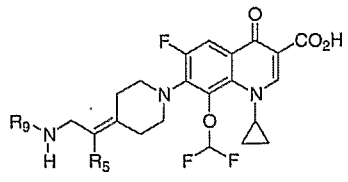
7-[4-(1-Chloro-2-methylaminoethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid trifluoroacetic acid salt (**72**).

A solution of **161** (160 mg, 0.24 mmol) was dissolved in 1,2-dichloroethane (4 mL) and was treated with 1-chloroethyl chloroformate (0.8 mL, 7.3 mmol) under

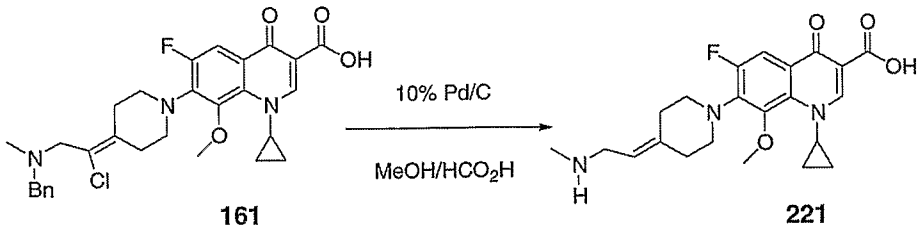
nitrogen. After 5 min, the reaction mixture was warmed to reflux temperature and the reaction mixture was allowed to stir for 3h. The resulting mixture was allowed to cool to room temperature, and then it was concentrated in vacuo. The residue was dissolved in tetrahydrofuran (5 mL), adjusted to pH>7 by the addition of $NaHCO_3$ and water at room temperature and stirred overnight. The resulting mixture was concentrated in vacuo and the residue purified by HPLC (reverse phase C-18 column, 35-90% acetonitrile/water containing 0.1% trifluoroacetic acid) to afford the trifluoroacetic acid salt of **72** (37 mg, 27%) as a yellow solid. MS 450 (M+H).

Table 10 lists the final products (**74**, **75**, **79**, **213-220**) prepared by an analogous procedure to that above.

Table 10

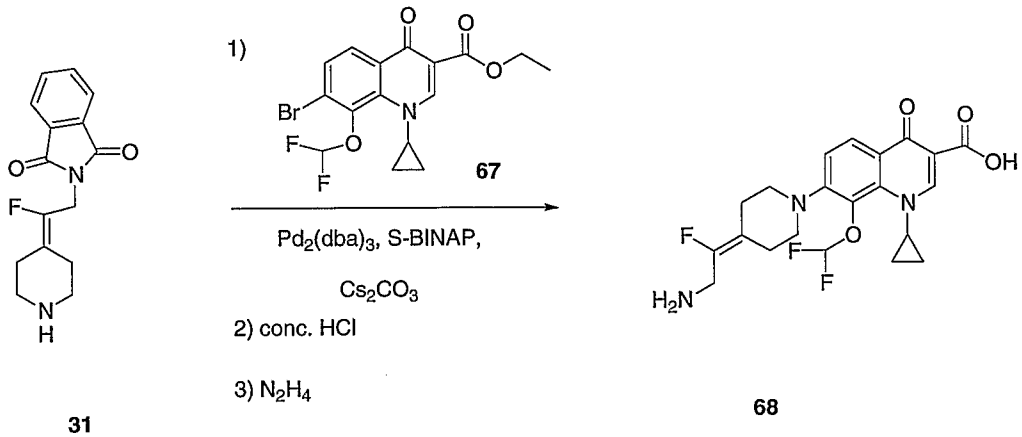
Structure	R_5	R_9	Compound Number	(M+H)
	Cl	Et	**75**	464
	F	Me	**213**	434
		Et	**214**	448
	Cl	Me	**215**	421
		Et	**216**	435
	F	Me	**79**	405
		Et	**217**	419
	Cl	Me	**218**	420
	F	Me	**219**	404
	Cl	Me	**74**	486
	F	Me	**220**	470

Scheme XXXIV



1-Cyclopropyl-6-fluoro-8-methoxy-7-[4-(2-methylaminoethylidene)piperidin-1-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid trifluoroacetic acid salt (**221**). A solution of **161** (70 mg, 0.11 mmol) in methanol/formic acid (v/v=20/1) (14 mL) was treated with 10% Pd/C (35 mg, 7.3 mmol) under nitrogen at rt and stirred for 3h. The resulting mixture was filtered and concentrated in vacuo. The residue was purified by HPLC (reverse phase C-18 column, 35-90% acetonitrile/water containing 0.1% trifluoroacetic acid) to afford the trifluoroacetic acid salt of **221** (8.3 mg, 15%) as a yellow solid. MS 416 (M+H).

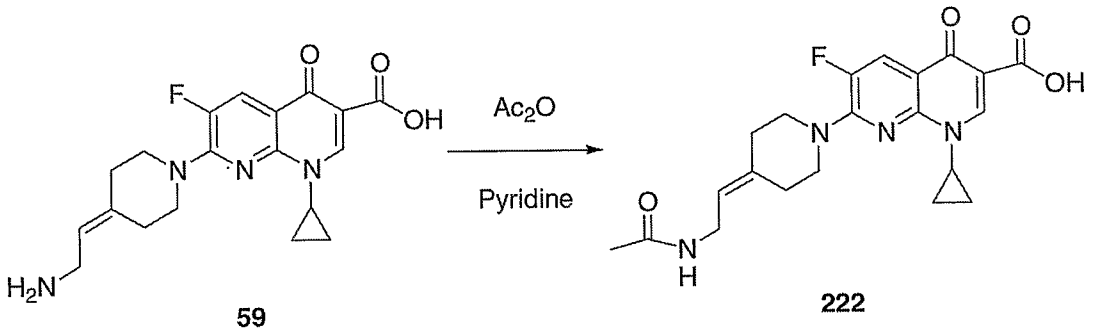
Scheme XXI



7-[4-(2-Amino-1-fluoroethylidene)-piperidin-1-yl]-1-cyclopropyl-8-difluoromethoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**68**). A solution of amine **31** (534 mg, 1.94 mmol) quinolone **67** (587 mg, 1.46 mmol) (prepared as described in EP1031569), cesium carbonate (717 mg, 2.2 mmol), (1S)-[1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine] (137 mg, 0.22 mmol) in toluene (75 mL) was treated with $Pd_2(dba)_3$ (66 mg, 0.072 mmol) and the reaction

mixture was warmed to reflux. After 12 h, the resulting mixture was allowed to cool to room temperature, concentrated in vacuo, and the residue was washed with water (3 x 10 mL). Purification by MPLC (0-100% ethyl acetate/hexanes) afforded a yellow residue. The residue was dissolved in concentrated hydrochloric acid (5 mL) and warmed to reflux. After 3 h, the reaction mixture was concentrated in vacuo, diluted with water (10 min) and the solid collected by filtration. The solid residue was washed with water (3 x 5 mL) and allowed to dry for 15 min. The solid was collected and resuspended in methanol (5 mL) and the reaction mixture was treated with hydrazine (1 mL). After 5 min, the reaction mixture was warmed to reflux and the resulting mixture was allowed to stir for 1 h. The reaction mixture was concentrated in vacuo and purified by HPLC (reverse phase C-18 column, 0-55% acetonitrile/water containing 0.1% trifluoroacetic acid) to afford the trifluoroacetic acid salt of the title compound **68** (75 mg, 12%) as a light yellow solid. MS 438 (M+H).

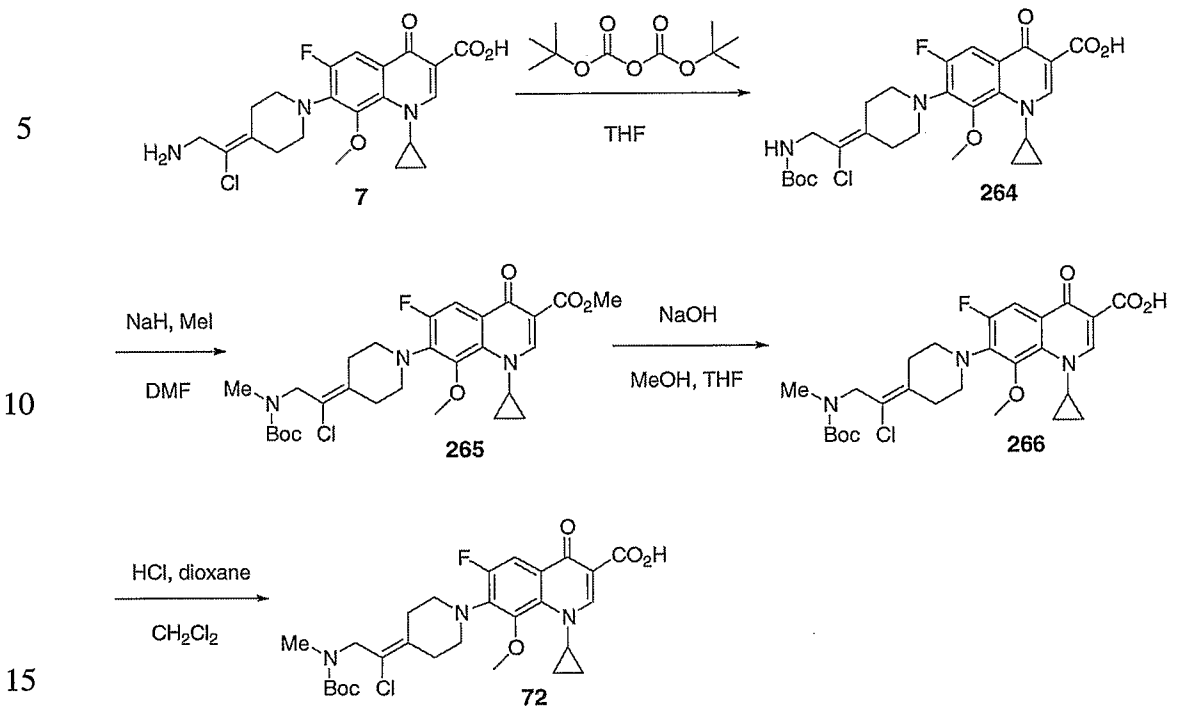
Scheme XXXV



59 222

7-[4-(2-Acetylamino-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (**222**). A mixture of **59** (25 mg, 0.067 mmol) and acetic anhydride (94 µL, 0.100 mmol) in pyridine (1 mL) was allowed to stir for 12 h at 25°C. The resulting mixture was concentrated in vacuo, and the residue was washed with water (3 x 10 mL) and allowed to dry overnight to afford the title compound **222** (15 mg, 54%). MS 415 (M+H).

Scheme XLII



7-[4-(2-N-methylamino-1-chloroethylidene)piperdin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride salt (**72**).

Step 1:

To 7-[4-(2-amino-1-chloroethylidene)piperdin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**7**) (1.96 g; 4.496 mmol) in anhydrous THF (100 mL) at 0°C, was added di-t-butyldicarbonate (1.09 g; 4/994 mmol). The ice bath was removed and the reaction stirred at room temperature for 3 hours. The volatiles were evaporated to afford 7-[4-(2-N-t-butoxycarbonylamino-1-chloroethylidene)piperdin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**264**) as a yellow foam (2.33 g; 97%). MS 536 (M + H).

Step 2:

To NaH (60% in oil, 191 mg; 4.98 mmol) in anhydrous DMF (4 mL) at 0°C, was added dropwise **264** from Step 1 (920 mg: 1.719 mmol) in anhydrous DMF (5 mL). The reaction was stirred for 15 minutes, then methyl iodide (0.23 mL; 3.69 mmol) was added. The reaction was warmed to room temperature and stirred for 24 hours. The reaction was carefully added dropwise to water (150

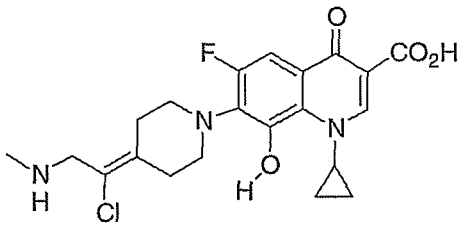
mL) with stirring. The solid was collected by filtration and dried to give methyl 7-[4-(2-N-t-butoxy-N-methylamino-1-chloroethylidene)piperdin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (**265**) as a cream-colored powder (886 mg; 92%). MS 564 (M + H).

Step 3:

Ester **265** from Step 2 (255 mg; 0.4529 mmol) and 1N NaOH (1.5 mL) in 1:1 methanol:THF (10 mL total) were heated at 50°C for 30 minutes under a nitrogen atmosphere. After cooling, the pH was adjusted to pH=4 with 1N HCl. The reaction mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with water (2 x 25 mL), dried ($MgSO_4$), filtered and evaporated. The resulting waxy semi-solid was triturated with cold ether to afford 7-[4-(2-N-t-butoxycarbonyl-N-methylamino-1-chloroethylidene)piperdin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**266**) as a pale yellow solid (212 mg; 86%). MS 550 (M + H).

Step 4:

7-[4-(2-N-t-butoxycarbonyl-N-methylamino-1-chloroethylidene)piperdin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**266**) from Step 3 (207 mg; 0.3770 mmol) and hydrochloric acid (4M in dioxane; 1.5 mL) in methylene chloride were stirred at room temperature overnight. Ether (5 mL) was added and the solid was collected by filtration, washed with additional ether, and dried to afford the title compound (**72**) as a yellow solid (183 mg; 93%). MS 450 (M + H).



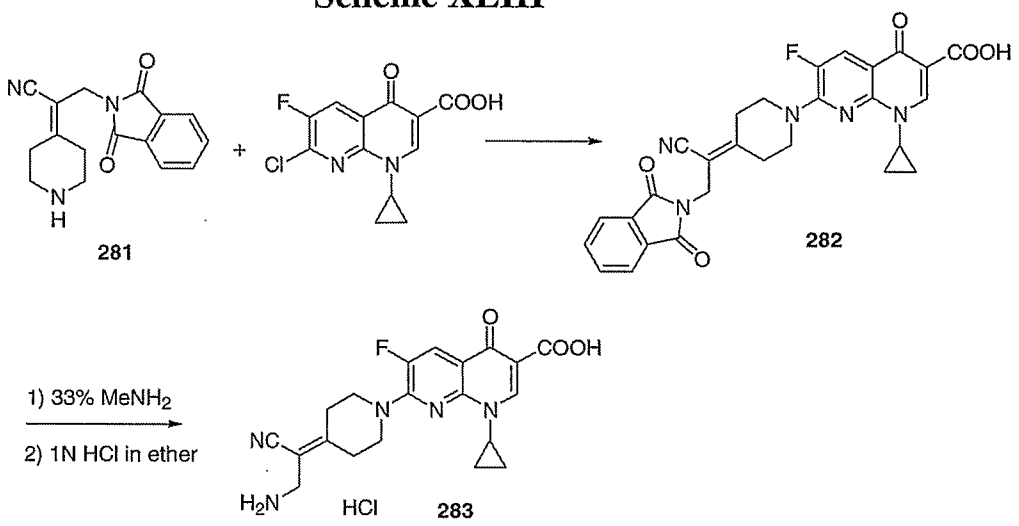
267

7-[4-(2-N-methylamino-1-chloroethylidene)piperidin-1-yl-1-cyclopropyl-6-fluoro-8-hydroxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid hydrochloride salt (**267**).

Methyl 7-[4-(2-N-t-butoxycarbonyl-N-methylamino-1-chloroethylidene)piperdin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-

carboxylate (**264**) (242 mg; 0.4298 mmol) in concentrated HCl (2 mL) was heated at 100°c for 1 hour. The reaction was evaporated to dryness. Methanol (5 mL) was added to the residue followed by the dropwise addition of ether until the solution became cloudy. This was stirred for 30 minutes and the solid was collected, washed with ether and dried to afford title compound **266** as a pale yellow solid (125 mg; 62%). MS 436 (M + H).

Scheme XLIII



7-[4-(2-Amino-1-cyano-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (**283**).

Step 1:

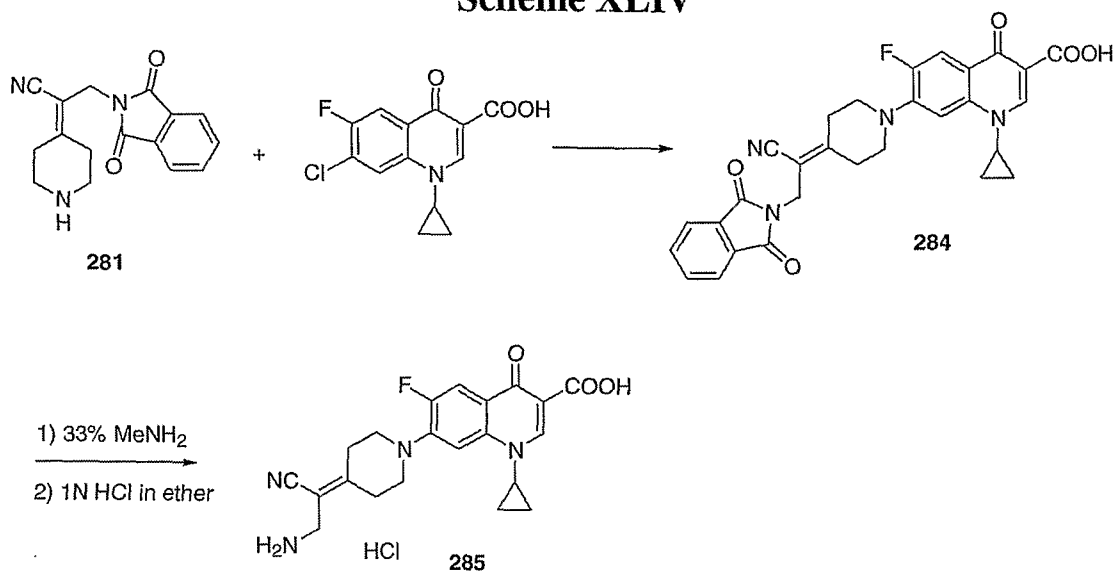
A solution of 3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-piperidin-4-ylidene-propionitrile (**281**; 180 mg, 0.64 mmol) and triethylamine (0.6 mL) in acetonitrile (4 mL) was treated with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-naphthpyridine-3-carboxylic acid (150 mg, 0.53 mmol) under nitrogen and the reaction mixture was allowed to stir at 60 deg. for 12 h. The resulting mixture was cooled down and the precipitate was filtered, washed with acetonitrile and dried to give the α,β-unsaturated nitrile (**282**) as a yellow solid (170 mg, 61%). MS 528 (M+H).

Step 2:

The α,β-unsaturated nitrile **282** (60 mg, 0.11 mmol) was dissolved in 3 mL methanol. To this solution was added 6 mL 33% methylamine in ethanol and the mixture was stirred at room temperature for 12 h. The solvent was

concentrated and the residue was dissolved in CH_2Cl_2 (5 mL). To this solution was added 1 N HCl in ethyl ether (0.15 mL) and the resulting precipitate was collected, washed with ether and dried to give 7-[4-(2-amino-1-cyano-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (**283**) (40 mg, 80%). MS 398 (M+H).

Scheme XLIV



7-[4-(2-Amino-1-cyano-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**285**).

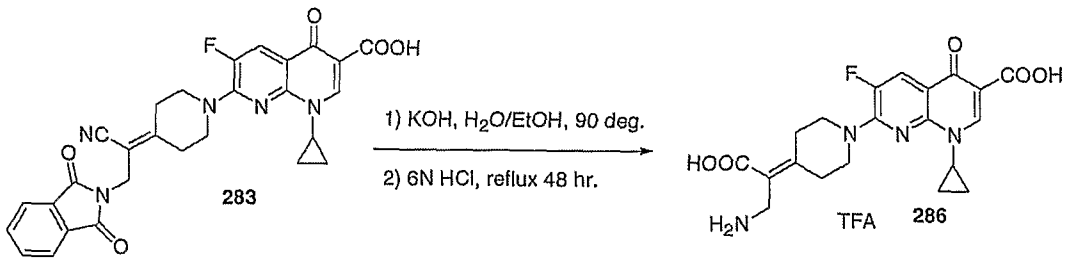
Step 1:

The α,β-unsaturated nitrile (**284**) was prepared in a similar manner as for the synthesis of **282**. MS 527 (M+H).

Step 2:

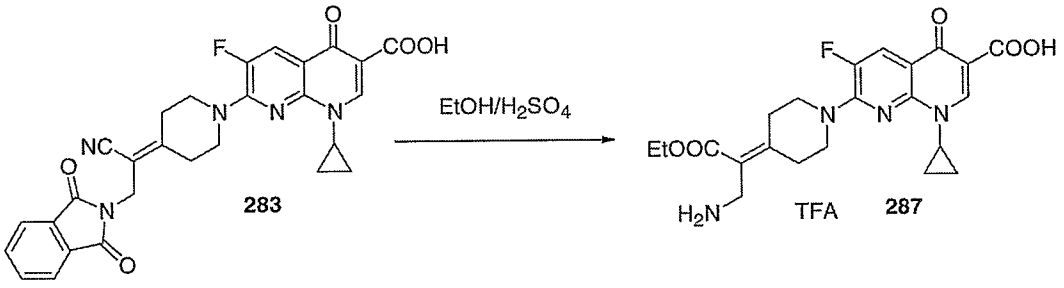
The title compound (**285**) compound was prepared in a similar manner as for the synthesis of **283**. MS 397 (M+H).

Scheme XLV



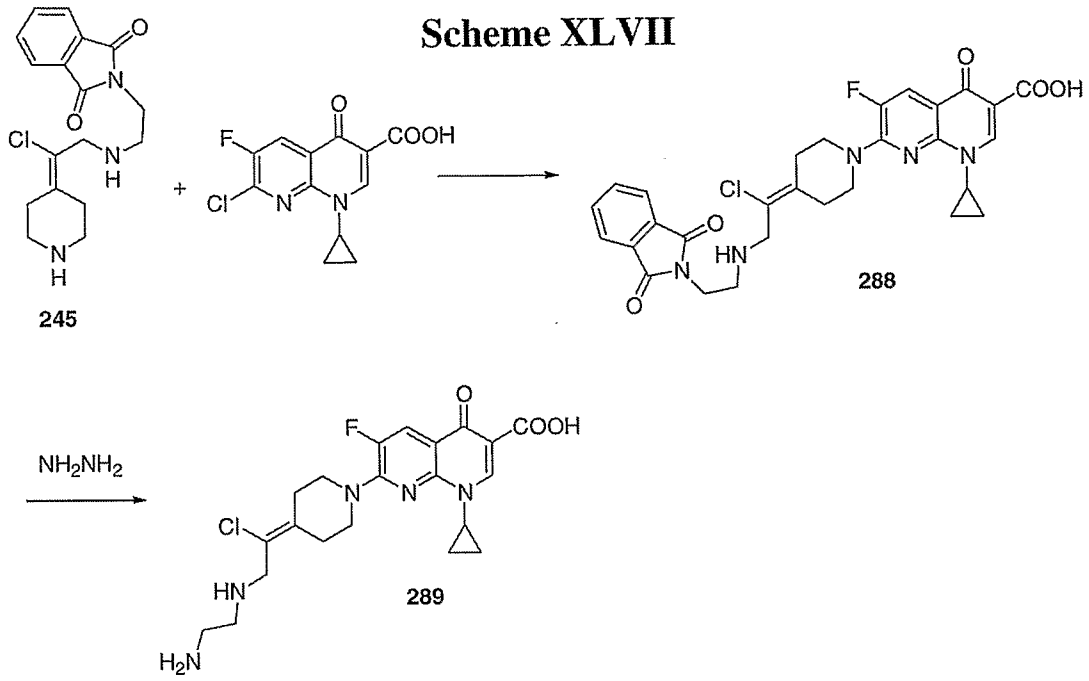
7-[4-(2-Amino-1-carboxy-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (**286**). Nitrile **283** (26 mg, 0.05 mmol) and potassium hydroxide (17 mg) were dissolved in ethanol (1 mL) and water (1 mL). The mixture was heated at 90 deg. for 1 h. The solution was cooled down and concentrated. The residue was acidified with 1N HCl and extracted with methylene chloride. The organic layer was concentrated to give a light yellow solid (30 mg). The above solid was dissolved in 10 mL 6N HCl and heated at reflux temperature for 48 h. The mixture was cooled down and purified by HPLC (reverse phase C-18 column, 10-50% acetonitrile/water containing 0.1% trifluoroacetic acid) to afford the trifluoroacetic acid salt of the title compound (4.0 mg, 15%). MS 417 (M+H).

Scheme XLVI



7-[4-(2-Amino-1-ethoxycarbonyl-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (**287**). The nitrile **283** (40 mg, 0.08 mmol) was dissolved in 10 mL ethanol and to this mixture was added 0.5 mL concentrated sulfuric acid. The reaction was heated at 160°C for 1 h. under microwave irradiation. The mixture was cooled down and purified by HPLC (reverse phase C-18 column, 10-90% acetonitrile/water containing 0.1% trifluoroacetic acid) to afford the trifluoroacetic acid salt of the title compound (3.0 mg, 7%). MS 445 (M+H).

Scheme XLVII



7-{4-[2-(2-(1,2-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-ethylamino)-1-chloro-1-ethylidene]-piperidin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid trifluoroacetic acid salt (**288**).

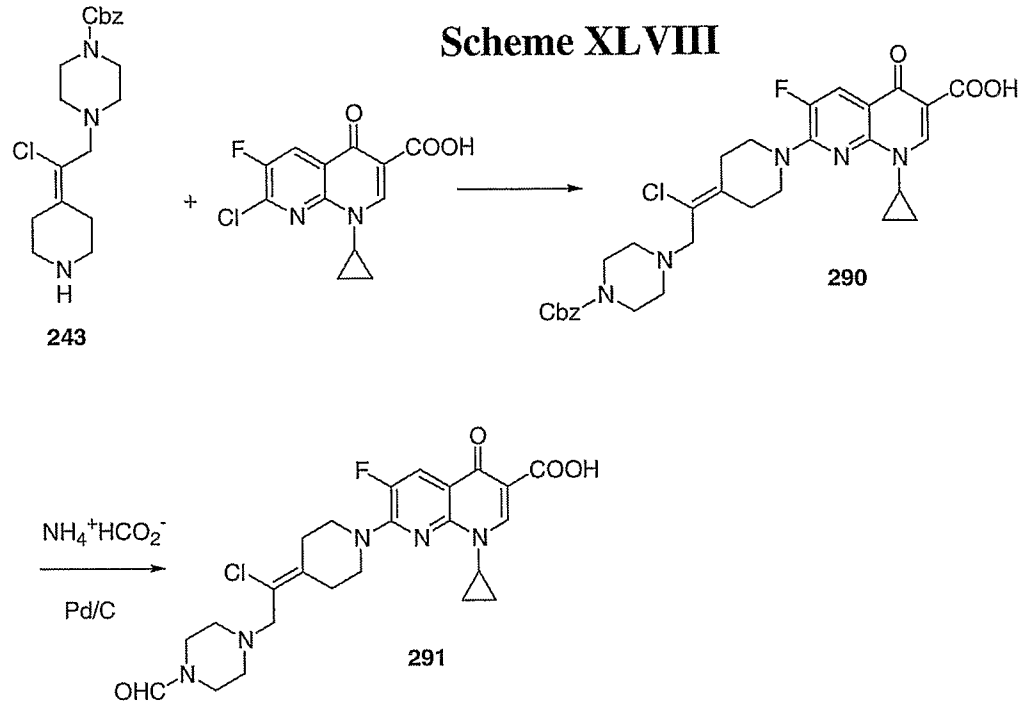
Step 1:

Coupling of amine **245** with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid was performed in a similar manner as for the preparation of **162**. MS 581 (M+H).

Step 2:

Hydrazinolysis of phthalimide **288** to provide the title compound **289** was performed in a similar manner as for the preparation of **68**. MS 450 (M+H).

Scheme XLVIII



7-{4-[1-Chloro-2-(4-formyl)-piperazin-1-yl-ethylidene]-piperidin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid trifluoroacetic acid salt (**291**).

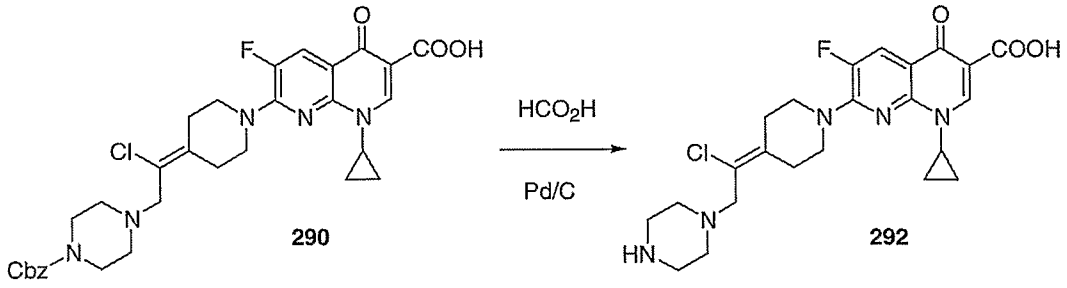
Step 1:

Coupling of amine **243** with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid was performed in a similar manner as for the preparation of **162**. MS 611 (M+H).

Step 2:

Cbz-protected piperazine derivative **290** (0.0505 g, 0.070 mmol) in tetrahydrofuran (3 mL), methanol (6 mL), and dimethylformamide (4 mL) was treated with ammonium formate (0.16 g, 2.6 mmol) and 10% palladium on carbon (0.0195 g, 0.018 mmol) added in three portions over 11 days. The mixture was filtered through celite and eluted with methanol. The mixture was concentrated, taken up in dimethylsulfoxide and purified by HPLC (reverse phase C-18 column, 10-90% acetonitrile/water containing 0.1% trifluoroacetic acid). The collected fractions were lyophilized to provide 0.0081 g of the title compound (**291**) as a white solid (19% yield). MS 504 (M+H).

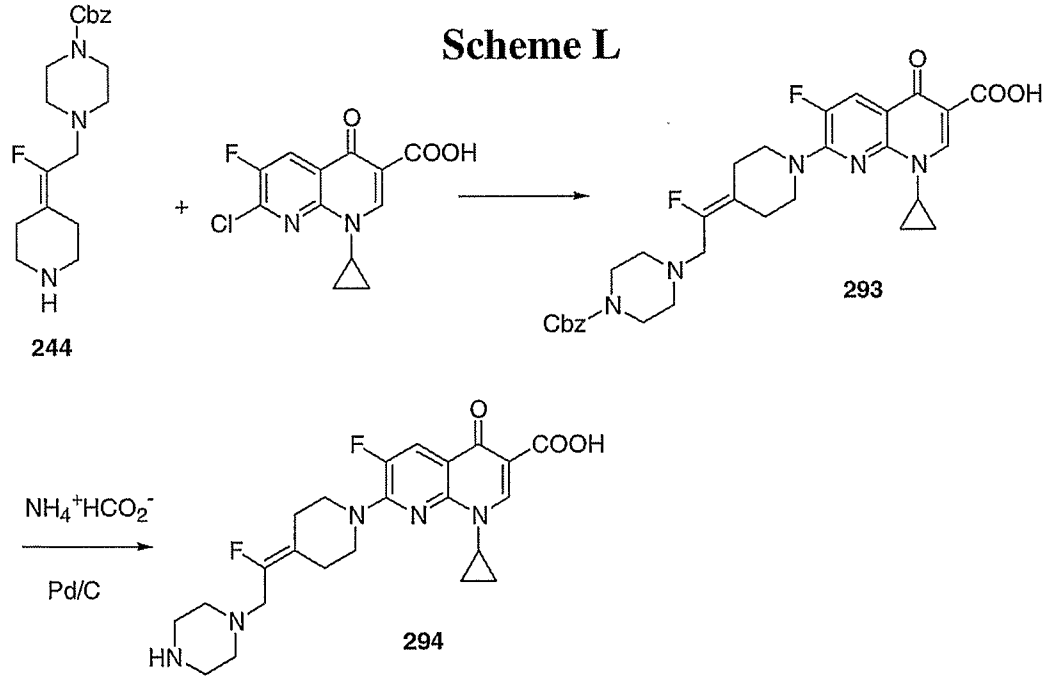
Scheme XLIX



7-[4-(1-chloro-2-piperazin-1-yl-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid trifluoroacetic acid salt (**292**).

To a solution of compound **290** (0.0475 g, 0.066 mmol) in methanol (9 mL) was added formic acid (0.5 mL, 13.2 mmol) and 10% palladium on carbon (0.0149 g, 0.014 mmol), and the mixture was stirred overnight. The mixture was filtered through celite and eluted with methanol. The mixture was concentrated, taken up in dimethylsulfoxide and purified by HPLC (reverse phase C-18 column, 10-90% acetonitrile/water containing 0.1% trifluoroacetic acid). The collected fractions were lyophilized to provide 0.0173 g of the title compound (**292**) as an orange solid (45%). MS 476 (M+H).

Scheme L



7-[4-(1-fluoro-2-piperazin-1-yl-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid trifluoroacetic acid salt (**294**).

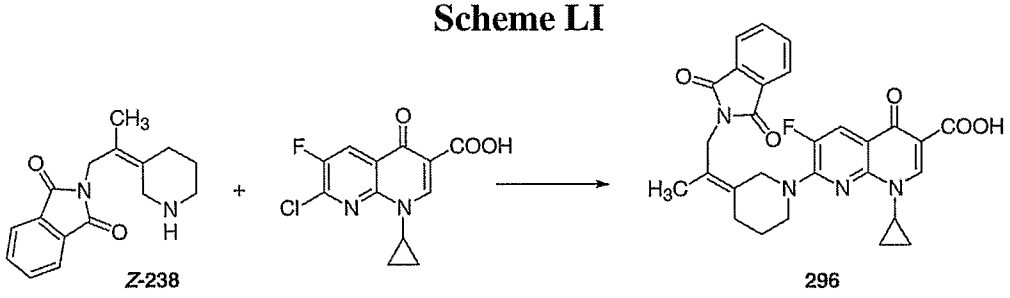
Step 1:

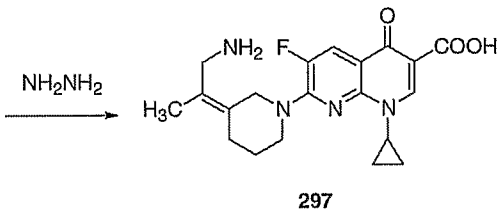
Coupling of amine **244** with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-naphthpyridine-3-carboxylic acid was performed in a similar manner as for the preparation of **162**. MS 594 (M+H).

Step 2:

Cbz-protected piperazine derivative **293** (0.0733 g, 0.104 mmol) in tetrahydrofuran (1 mL) and methanol (3 mL) was treated with ammonium formate (0.0377 g, 0.60 mmol) and 10% palladium on carbon (0.005 g, 0.005 mmol) and stirred overnight. The mixture was filtered through celite and eluted with methanol. The mixture was concentrated, taken up in dimethylsulfoxide and purified by HPLC (reverse phase C-18 column, 10-90% acetonitrile/water containing 0.1% trifluoroacetic acid). The collected fractions were lyophilized to provide 0.0321 g of the title compound (**294**) as a white solid (54%). MS 460 (M+H).

Scheme LI





(Z)-7-[3-(1-Amino-2-propylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid trifluoroacetic acid salt (**297**).

Step 1:

Coupling of amine ***Z*-238** with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-naphthpyridine-3-carboxylic acid was performed in a similar manner as for the preparation of **162**. MS 517 (M+H).

Step 2:

Hydrazinolysis of phthalimide **296** to provide the title compound (**297**) was performed in a similar manner as for the preparation of **68**. MS 387 (M+H).

Biological Activity

The compounds described in the present invention possess antibacterial activity due to their novel structure, and are useful as antibacterial agents for the treatment of bacterial infections in humans and animals.

Minimal inhibitory concentration (MIC) has been an indicator of in vitro antibacterial activity widely used in the art. The in vitro antimicrobial activity of the compounds was determined by the microdilution broth method following the test method from the National Committee for Clinical Laboratory Standards (NCCLS). This method is described in the NCCLS Document M7-A4, Vol.17, No.2, "Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically--Fourth Edition", which is incorporated herein by reference.

In this method two-fold serial dilutions of drug in cation adjusted Mueller-Hinton broth are added to wells in microdilution trays. The test organisms are prepared by adjusting the turbidity of actively growing broth cultures so that the final concentration of test organism after it is added to the wells is approximately 5×10^4 CFU/well.

Following inoculation of the microdilution trays, the trays are incubated at 35 °C for 16-20 hours and then read. The MIC is the lowest concentration of test compound that completely inhibits growth of the test organism. The amount of growth in the wells containing the test compound is compared with the amount of growth in the growth-control wells (no test compound) used in each tray. As set forth in Table 5, compounds of the present invention were tested against a variety of pathogenic bacteria resulting in a range of activities depending on the organism tested.

Table 5. MIC Values (μg/mL) of Some Compounds of the Present Invention

(**A**: *Staphylococcus aureus* OC4172; strains **B**, **C**, and **D** are fluoroquinolone-resistant clinical isolates of *Streptococcus pneumoniae* that contain different constellations of amino acid substitutions in the QRDR region; **E**: *Streptococcus pneumoniae* ATCC 49619)

	MIC (μg/mL)				
Compound/Organism	**A**	**B**	**C**	**D**	**E**
1	0.03	2	0.5	1	0.12
2	0.06	0.25	1	1	0.12
3	0.06	1	0.25	1	0.12
4	0.06	ND*	1	2	0.25
5	0.03	ND	1	ND	0.06
6	0.03	ND	0.5	ND	0.06
7	0.015	0.06	0.12	0.12	0.06
8	0.25	2	8	8	0.5
9	0.5	4	>16	>16	1
10	0.03	ND	0.5	1	0.12
11	0.03	ND	0.5	1	0.12
12	0.12	2	4	4	0.5
189	<0.12	4	2	4	2
76	0.03	2	1	2	0.25
77	0.12	8	16	16	1
80	0.06	0.5	2	1	0.12
205	0.25	2	8	4	0.5
81	0.06	1	2	2	0.25
160	0.06	2	2	1	0.12
183	0.12	ND	2	2	0.25
182	0.06	ND	1	2	0.25
209	0.12	ND	8	16	2
166	0.5	ND	4	4	1
191	0.25	8	8	2	0.5
193	0.12	8	8	2	0.5
194	0.12	2	4	1	0.5
195	0.12	8	8	2	1
196	0.12	ND	4	2	0.5
199	0.06	1	2	1	0.25
206	1	ND	4	4	4
207	1	8	8	2	4
72	0.03	0.25	0.5	0.25	0.12
75	0.12	1	1	1	0.25
213	0.12	ND	2	2	0.5

214	0.06	ND	1	1	0.25
215	0.25	2	2	2	0.25
216	0.06	0.12	2	1	0.25
79	0.06	ND	2	1	0.25
217	0.25	ND	2	2	0.25
218	0.12	ND	2	2	0.25
219	0.5	8	8	4	0.5
74	0.06	ND	1	0.25	0.12
220	0.12	2	4	0.5	0.5
221	0.12	2	4	4	0.5
201	0.12	ND	2	8	0.5
208	0.06	0.25	2	0.25	0.25
73	0.06	0.5	1	0.25	0.12
202	0.5	16	16	8	2
173	0.5	8	16	8	1
70	0.03	ND	0.25	0.25	0.12
69	0.06	ND	1	2	0.25
71	0.03	ND	0.25	0.5	0.12
65	0.03	ND	0.5	1	0.12
14	0.03	2	1	1	0.25
64	0.12	8	2	8	1
163	0.12	4	4	ND	1
185	0.12	16	16	ND	1
59	0.06	8	8	ND	0.5
164	0.12	32	>32	ND	2
172	0.06	32	16	ND	1
211	0.03	4	4	ND	0.5
60	2	ND	16	ND	16
61	0.12	ND	16	ND	1
210	8	16	16	ND	>16
62	2	>16	>16	ND	8
204	0.25	0.5	0.5	0.5	0.12
176	0.25	0.5	1	1	0.12
175	0.5	2	2	1	0.25
78	1	2	1	ND	0.25
173	0.06	1	2	2	0.25
203	0.06	0.06	1	0.5	0.12
212	0.06	1	2	2	0.12
177	1	8	>16	>16	4
178	0.5	1	8	4	4
179	0.5	>16	>16	>16	2
180	0.5	ND	8	2	0.5
181	1	ND	>16	8	2
247	0.5	ND	8	2	0.5
248	0.5	ND	16	4	2
249	1	ND	16	4	2

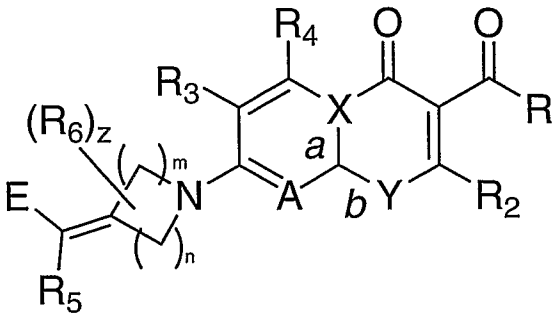
252	0.5	ND	8	4	1
250	0.25	ND	8	0.5	0.5
251	0.5	ND	16	>2	1
253	0.06	4	>16	4	0.5
254	0.06	ND	4	4	0.25
255	0.5	2	4	16	4
256	0.03	1	1	1	0.06
257	0.03	0.5	0.5	0.5	0.06
258	≤4	8	>16	>16	8
261	≤0.015	0.06	0.06	0.06	≤0.015
259	0.03	0.5	1	0.12	0.06
260	0.03	ND	0.5	0.06	0.06
262	≤0.015	ND	1	1	0.25
263	0.03	0.5	1	0.5	0.12
267	0.12	2	2	2	0.5
268	≤0.015	0.06	0.12	0.12	0.03
269	≤0.015	0.25	0.06	ND	0.03
270	0.06	ND	4	2	0.5
271	≤0.015	1	1	1	0.12
272	≤0.015	4	0.5	ND	0.5
273	0.03	4	0.5	ND	4
274	0.06	4	1	ND	1
275	0.03	1	1	1	0.12
276	≤0.015	0.5	2	4	0.25
277	≤0.015	0.25	0.25	0.5	0.03
283	0.25	2	4	8	0.5
285	0.25	ND	8	>16	1
286	4	ND	>16	>16	16
289	0.5	ND	1	2	0.25
291	2	ND	>16	8	8
292	1	ND	>16	16	4
294	2	>16	>16	>16	8
295	0.5	16	16	8	2
297	0.25	16	16	16	1
298	0.25	16	16	8	1
299	0.5	16	>16	2	1
300	0.5	>16	>16	2	2
301	0.12	8	8	8	0.25
302	≤0.03	1	≤0.5	1	≤0.12
303	≤0.015	0.25	0.12	0.25	0.03

*ND = not determined

What is Claimed is:

1. A compound having a structure according to Formula I:

(I)



wherein:

n is an integer from 1 to 3;

m is an integer from 1 to 3;

z is an integer from 0 to 3;

R is selected from hydrogen, hydroxy, and alkoxy;

$\mathbf{R_2}$ is hydrogen;

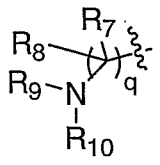
$\mathbf{R_3}$ and $\mathbf{R_4}$ are independently selected from hydrogen, halogen, amino, hydroxy, alkoxy, alkylthio, alkyl, alkenyl and alkynyl;

$\mathbf{R_5}$ is selected from hydrogen, hydroxy, halogen, alkyl, aryl, alkoxy, cyano, CO_2R_{13}, and alkylthio;

$\mathbf{R_6}$ is independently selected from alkyl, hydroxy, alkoxy, alkylthio, alkenyl, alkynyl, aryl, alkoxyimino, and halogen; or $\mathbf{R_5}$ and $\mathbf{R_6}$ join to form a 4- to 7-membered carbocyclic ring wherein each carbon atom of the ring can be optionally substituted with $\mathbf{R_{12}}$, wherein $\mathbf{R_{12}}$ is selected from the group consisting of halogen, amino, hydroxy, alkoxy, alkylthio, alkyl, alkenyl, alkynyl, oxo, alkoxyimino and hydroxyimino;

R_{13} is hydrogen, alkyl, aryl, or a carboxylic acid protecting group;

E is selected from the group consisting of:

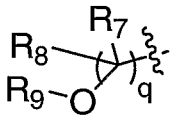
1) 

wherein,

q is an integer from 1 to 3;

R_7 and R_8 are each independently selected from hydrogen and alkyl, or R_7 and R_8 join to form a 3 to 6 membered carbocyclic ring, or either of R_7 or R_8 can be joined independently to either of R_9 or R_{10} to form a heterocyclic ring containing the nitrogen atom to which R_9 or R_{10} are bonded, wherein

R_9 and R_{10} are each independently selected from hydrogen, alkyl, aryl, arylalkyl, acyl, alkoxycarbonyl, or sulfonyl, or alternatively R_9 and R_{10} join to form a heterocyclic ring containing the nitrogen atom to which they are bonded;

2) 

wherein,

q is as defined above;

R_7 and R_8 are each independently selected from hydrogen and alkyl, or R_7 and R_8 join to form a 3- to 6-membered carbocyclic ring, and R_9 is selected from hydrogen, alkyl, acyl, alkoxycarbonyl, or sulfonyl; and

3) alkenyl;

A is selected from N and C(R_{11}), wherein R_{11} is selected from hydrogen, alkyl, halogen, hydroxy, alkoxy, alkylthio, and cyano;

X is selected from C and N, where if **X** is C, ***a*** is a double bond and ***b*** is a single bond, and if **X** is N, ***a*** is a single bond and ***b*** is a double bond; and

Y is selected from N(R_1) and C(R_1), with the proviso that when **Y** is N(R_1), **X** is C and when **Y** is C(R_1), **X** is N, wherein R_1 is selected from C3 to C6 cycloalkyl, C4 to C6 heterocycloalkyl, alkyl, alkene, a 6-membered aryl and a 6-membered heteroaryl; provided that

if **A** is C(R_{11}), **X** is C and **Y** is N(R_1), then R_{11} and R_1 can join to form a 6-membered heterocyclic ring optionally substituted by one or more alkyl groups for a corresponding hydrogen atom;

if **A** is C(R_{11}), **X** is C and **Y** is N(R_1), then R_2 and R_1 can join to form a monocyclic or bicyclic heterocyclic ring optionally substituted by one or more alkyl groups for a corresponding hydrogen atom; or

if **A** is C(R_{11}), **X** is C and **Y** is N(R_1), then R_2 and **R** can join to form a 5-membered heterocyclic ring optionally substituted by one or more alkyl groups for a corresponding hydrogen atom;

or an optical isomer, diastereomer or enantiomer thereof; a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

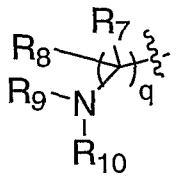
2. The compound of claim 1, wherein A is C(OCH_3), C($OCHF_2$), CH, CCl, or N.

3. The compound of claim 1, wherein **A** is C(R_{11}), **X** is C, **Y** is N(R_1) and R_{11} and R_1 can join to form a 6-membered heterocyclic ring optionally

substituted by one or more alkyl groups for a corresponding hydrogen atom.

4. The compound of claim 1, wherein Y is $N(R_1)$ and R_1 is selected from C3 to C6 cycloalkyl or 6-membered heterocyclic ring.

5. The compound of claim 1, wherein E is



6. The compound of claim 1, wherein m is 1 and n is 1, m is 2 and n is 2, or m is 1 and n is 3.

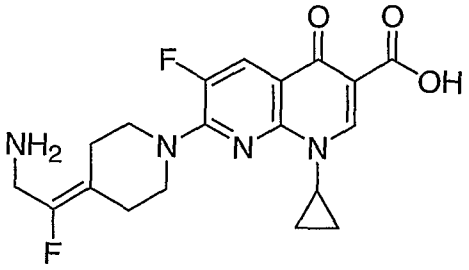
7. The compound of claim 1, wherein z is 0 or R_6 is methyl and z is 1.

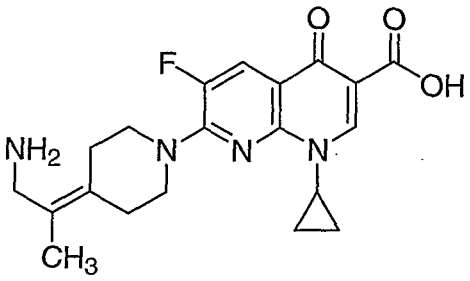
8. The compound of claim 4, wherein R_7 and R_8 are hydrogen.

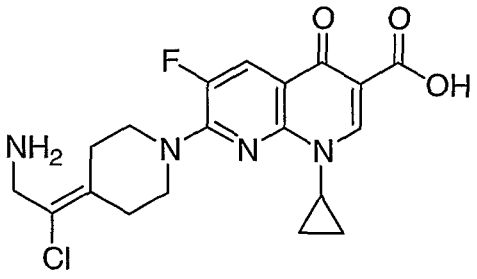
9. The compound of claim 7, wherein q is 1.

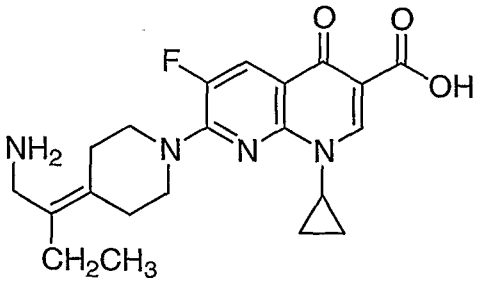
10. The compound of claim 8, wherein R_9 is hydrogen, methyl, or ethyl and R_{10} is hydrogen.

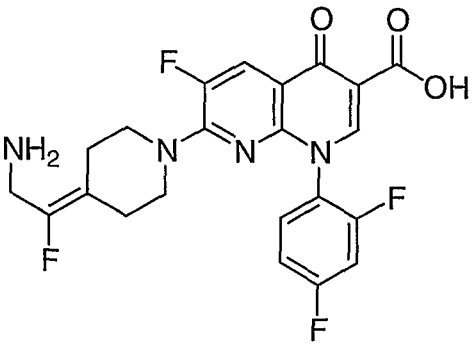
11. A compound of claim 1 selected from the group consisting of:

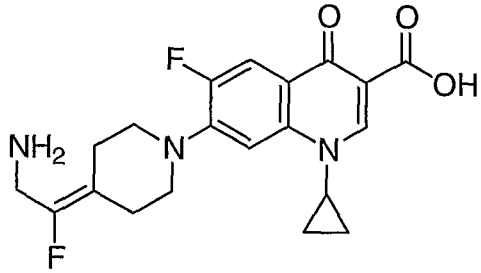


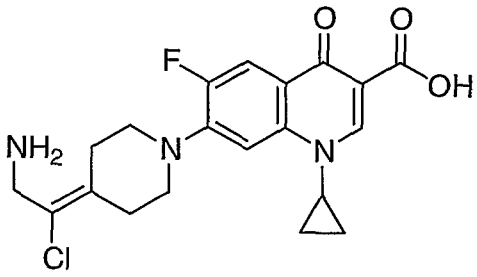


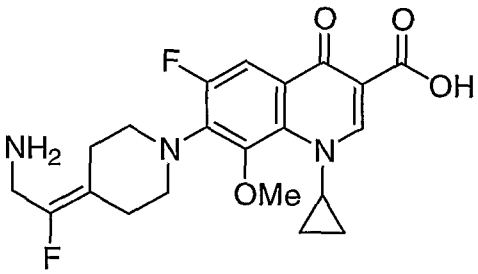


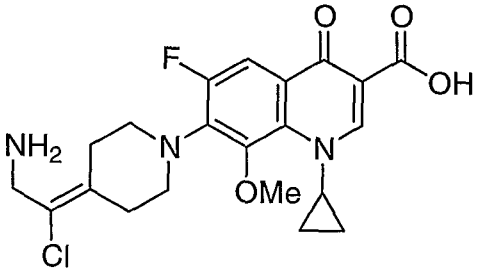


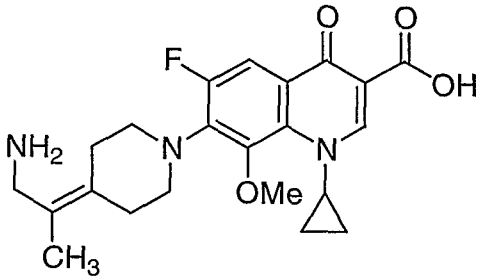




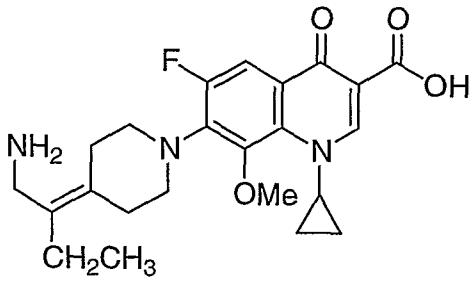


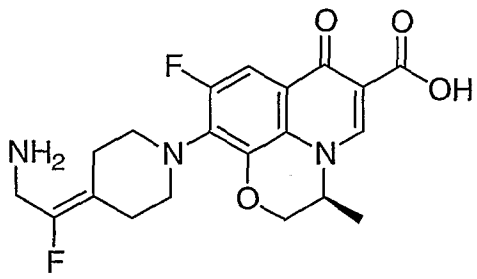


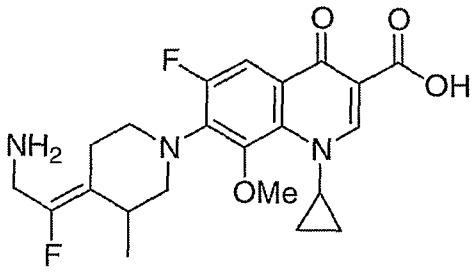


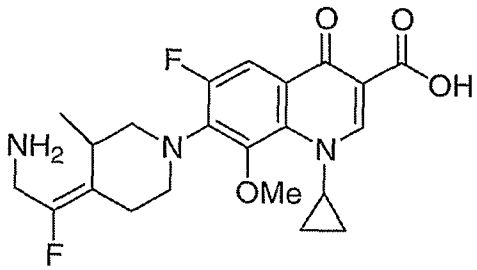


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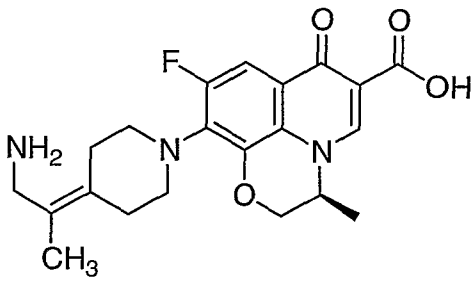


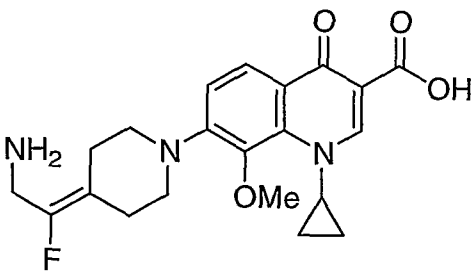


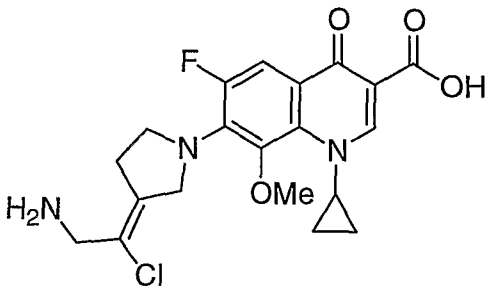


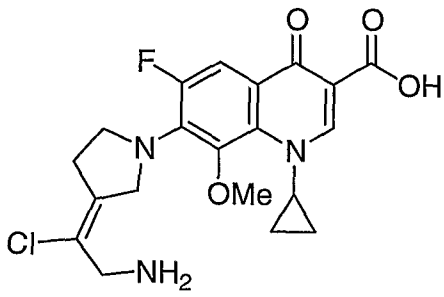


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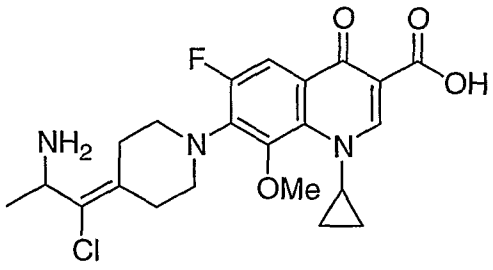


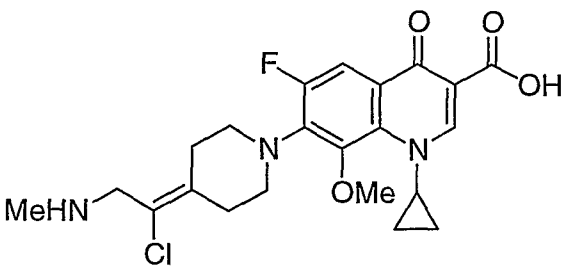


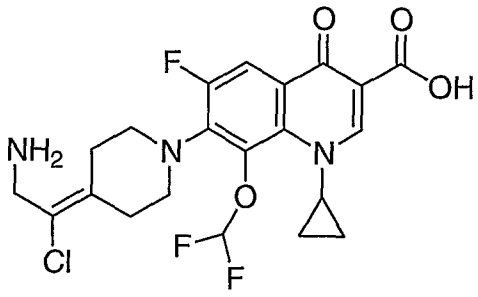


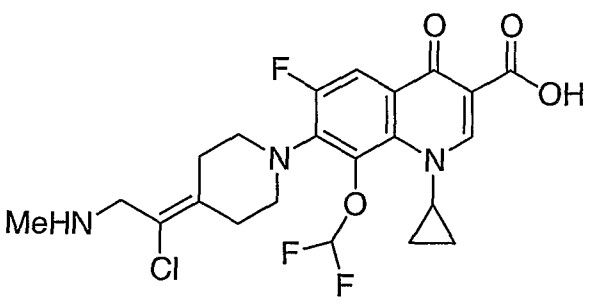


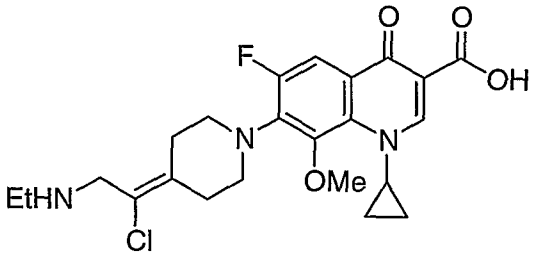
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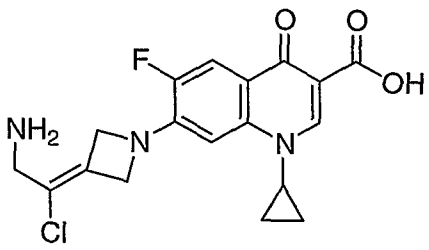


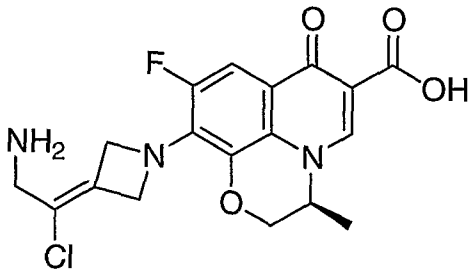


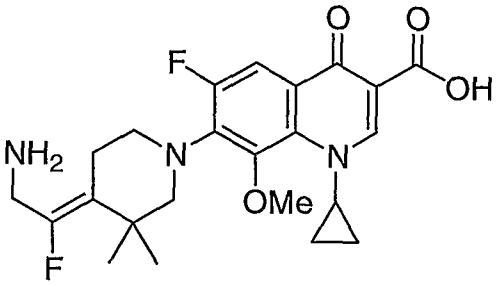


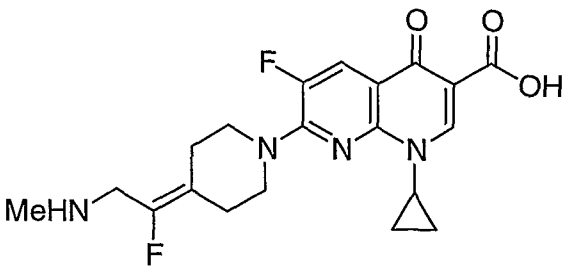


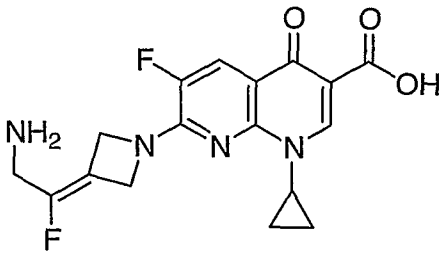




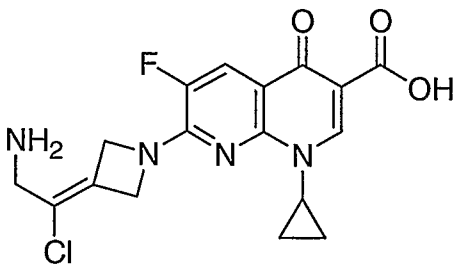


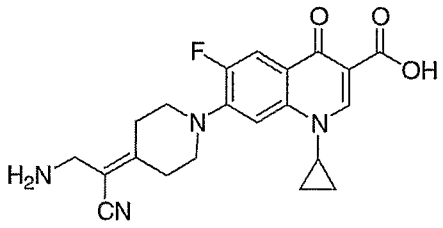


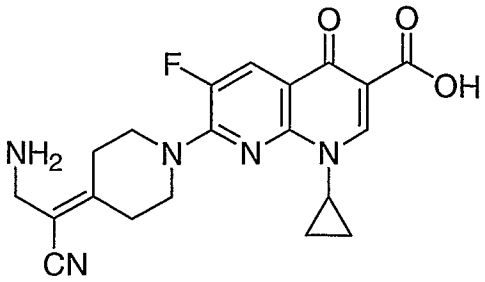


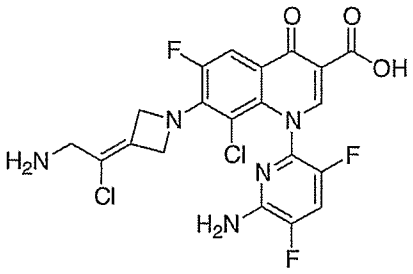


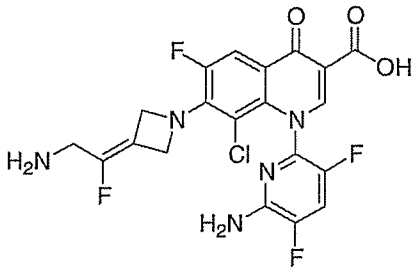
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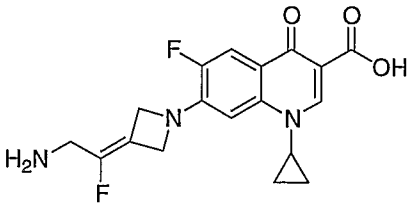


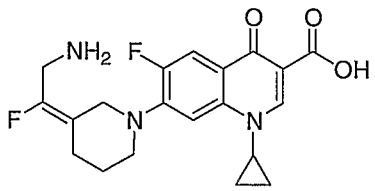


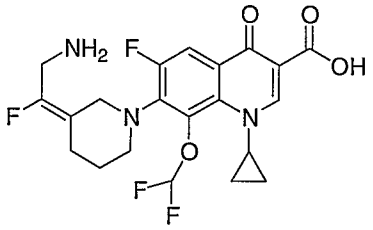


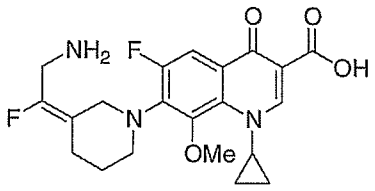


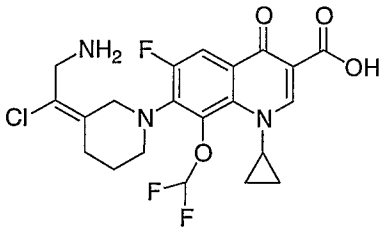


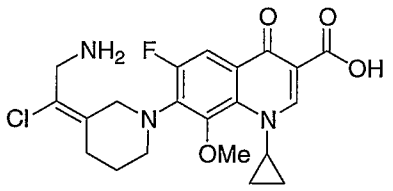


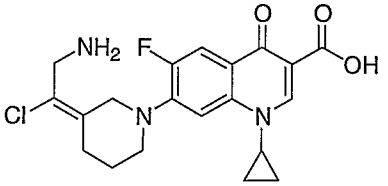


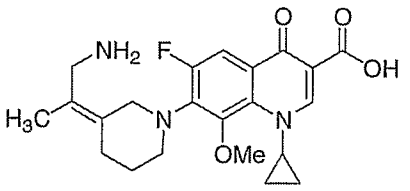




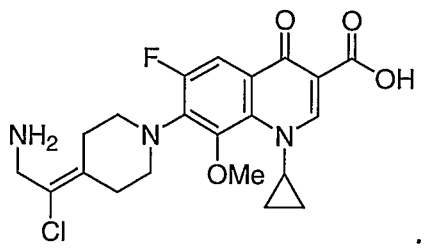






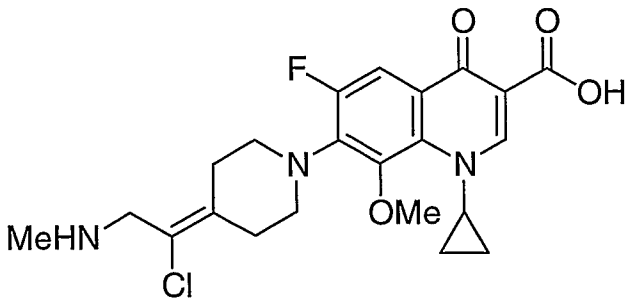


11. The compound of claim 1 having the formula:

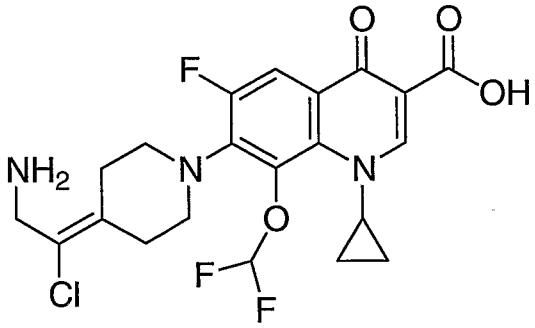


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12. The compound of claim 1 having the formula:



13. The compound of claim 1 having the formula:



14. A method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said mammal a therapeutically effective amount of the compound according to Claim 1.

15. A method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a prophylactically effective dose of a compound according to Claim 1.