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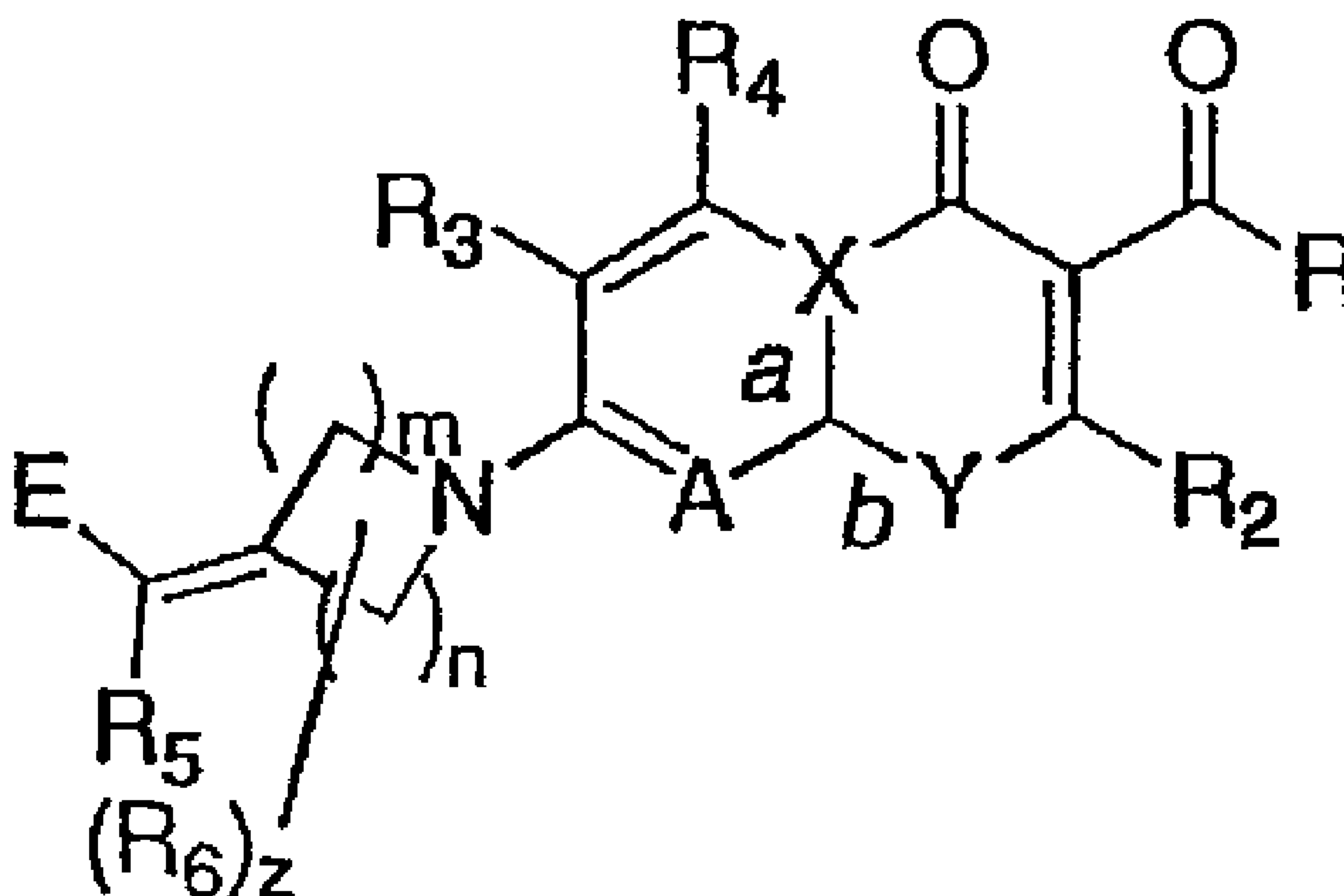
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(54) Title: 7-AMINO ALKYLIDENYL-HETEROCYCLIC QUINOLONES AND NAPHTHYRIDONES



Formula I

(57) Abrégé/Abstract:

The present invention relates to compounds having a structure according to Formula I wherein n, m, z, R, R2, R3, R4, R5, R6, A, E, X, Y a and b are as defined above; or an optical isomer, diastereomer or enantiomer thereof; a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

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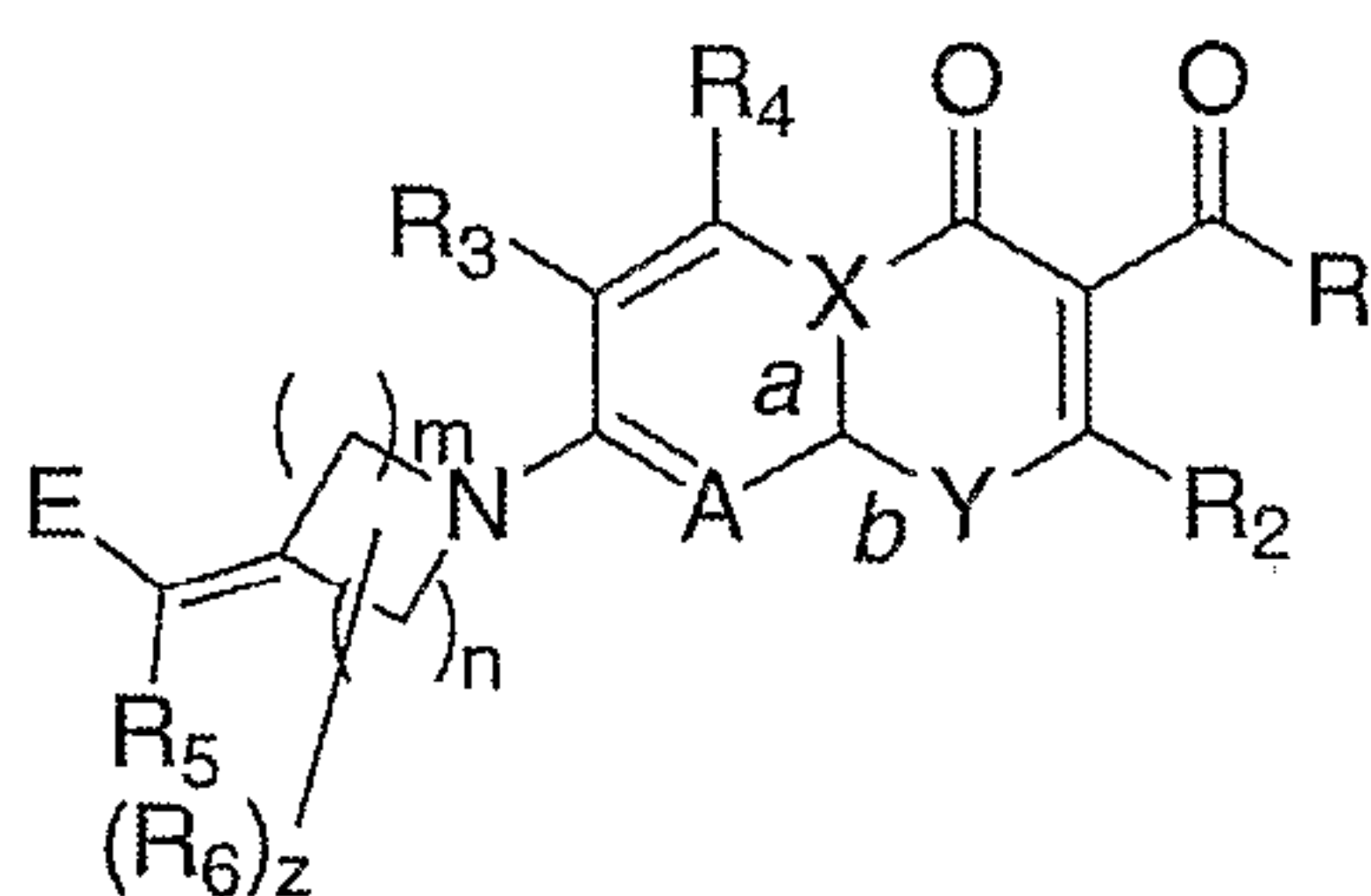
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(54) Title: 7-AMINO ALKYLIDENYL-HETEROCYCLIC QUINOLONES AND NAPHTHYRIDONES



(I)

(57) Abstract: The present invention relates to compounds having a structure according to Formula I wherein n, m, z, R, R₂, R₃, R₄, R₅, R₆, A, E, X, Y a and b are as defined above; or an optical isomer, diastereomer or enantiomer thereof; a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

WO 2005/033108 A1

7-Amino Alkylidenyl-Heterocyclic Quinolones and Naphthyridones

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Field of Invention

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

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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
20 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.,
25 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
30 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.

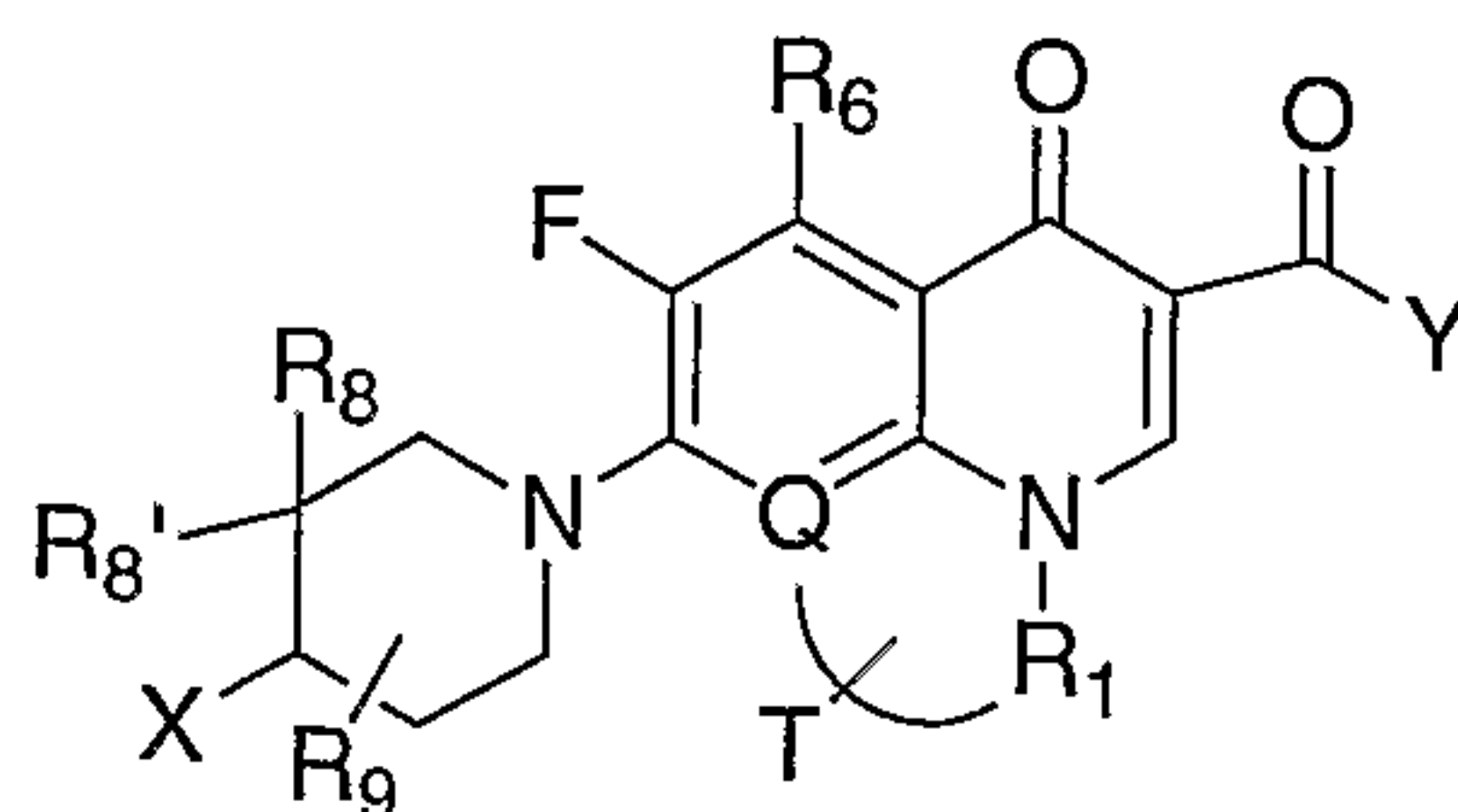
The pharmacological characteristics of antimicrobial agents, and their suitability for any given clinical use, vary. For example, the classes of antimicrobial agents (and members within a class) may vary in 1) their relative efficacy against different types of microorganisms, 2) their susceptibility 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.

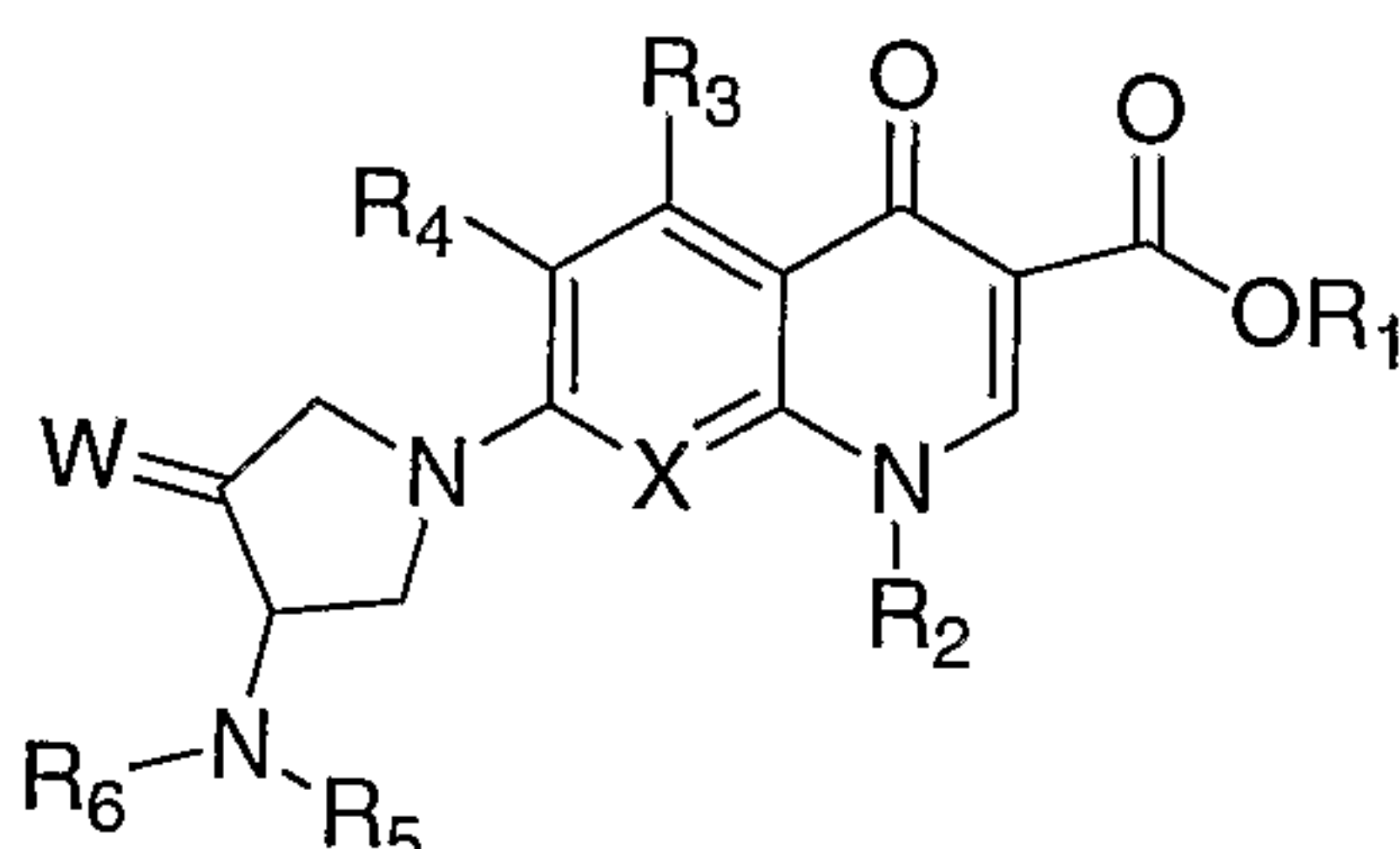
WO03050107 describes a series of dihydroquinolone, naphthyridine and related heterocyclic antibacterial agents. Of particular interest is the disclosure of compounds of the formula,



wherein R_8 and R_8' are hydrogen, alkyl, substituted alkyl, alkylamino, or aralkyl, R_9 is hydrogen, alkyl, alkylamino, dialkylamino, aryl, aralkyl, or trihaloalkyl, and X is hydroxy, alkoxy, acyloxy, amino or substituted amino.

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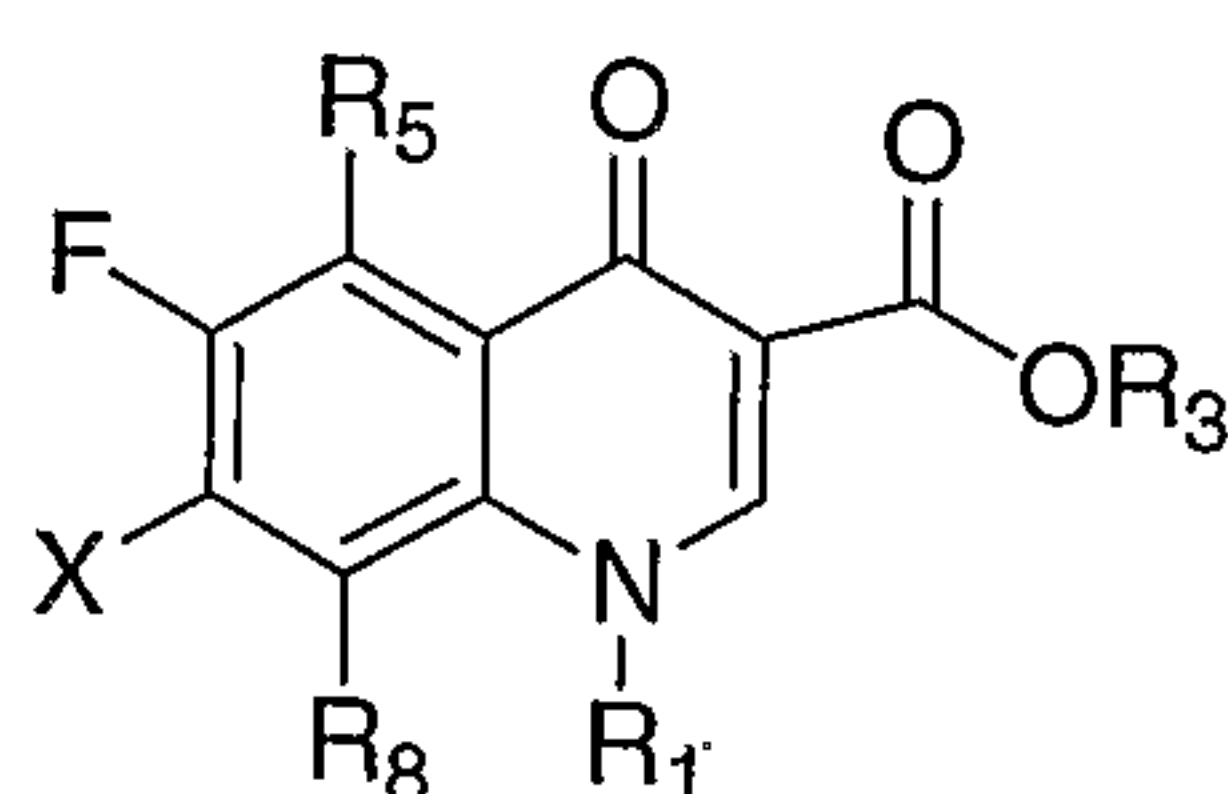
European Patent Publication 362759 discloses 1,4-dihydroquinolone and naphthyridine antibacterial agents of the formula,



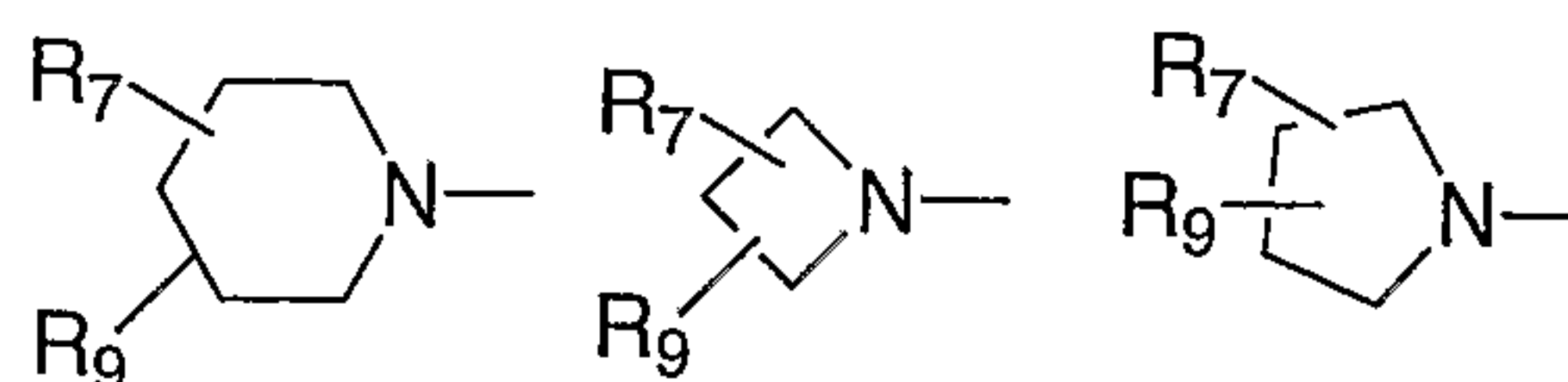
wherein W is C1-3 alkylidene and R_5 and R_6 are hydrogen or alkyl.

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International Patent Publication WO 99/14214 and US Patent 6329391 disclose quinolone antibacterial agents with C₇-piperdiny, C₇-azetidiny, or C₇-pyrrolidiny substituents of the formula,



X =

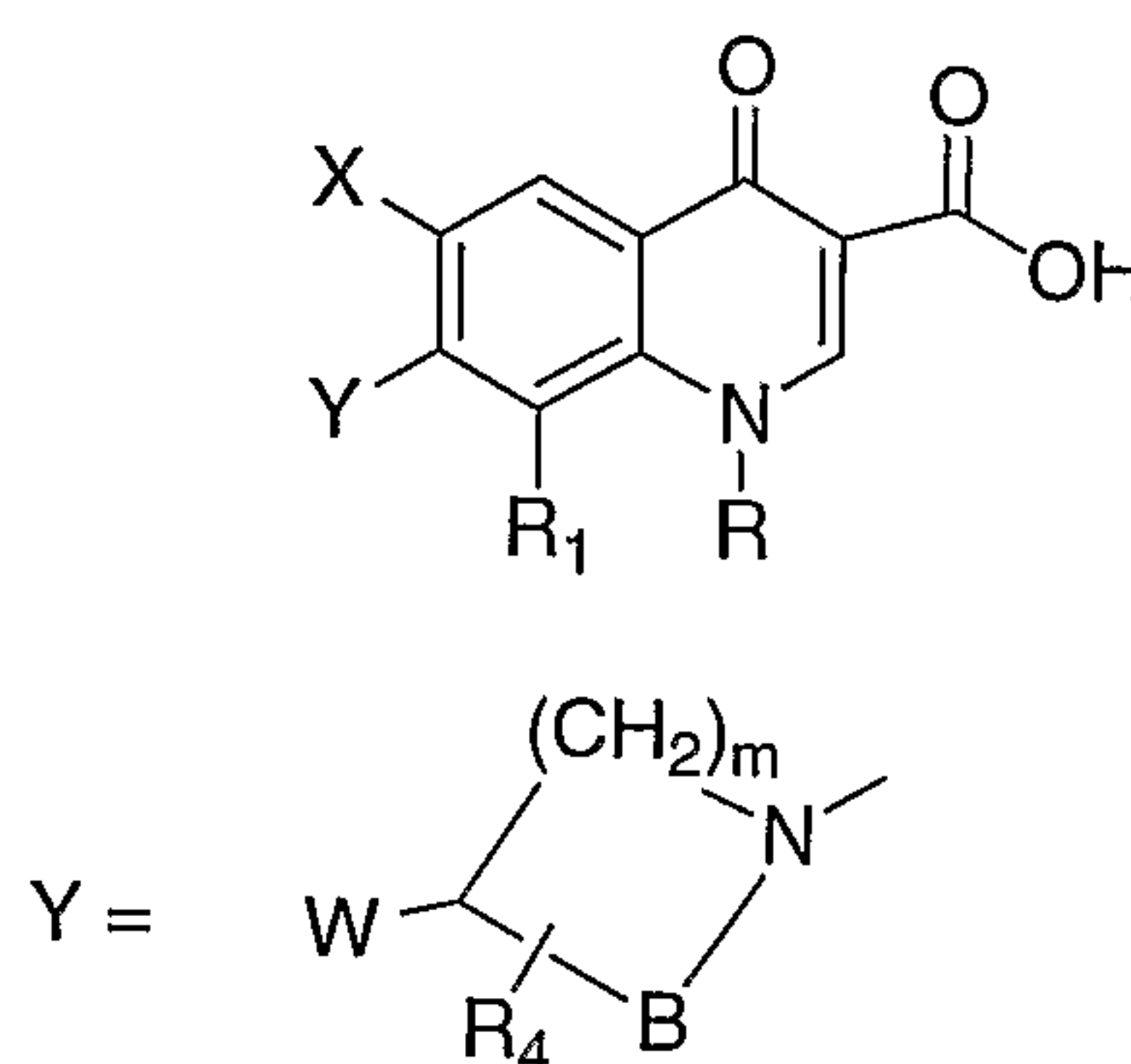


Of particular interest are those compounds wherein R_7 is amino, aminoalkyl, or substituted aminoalkyl and R_9 is selected from hydrogen, C₁-C₄ alkanyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or a C₃-C₆ fused or spirocyclic alkyl ring. For compounds with a substituted piperidine at the 7-position of the

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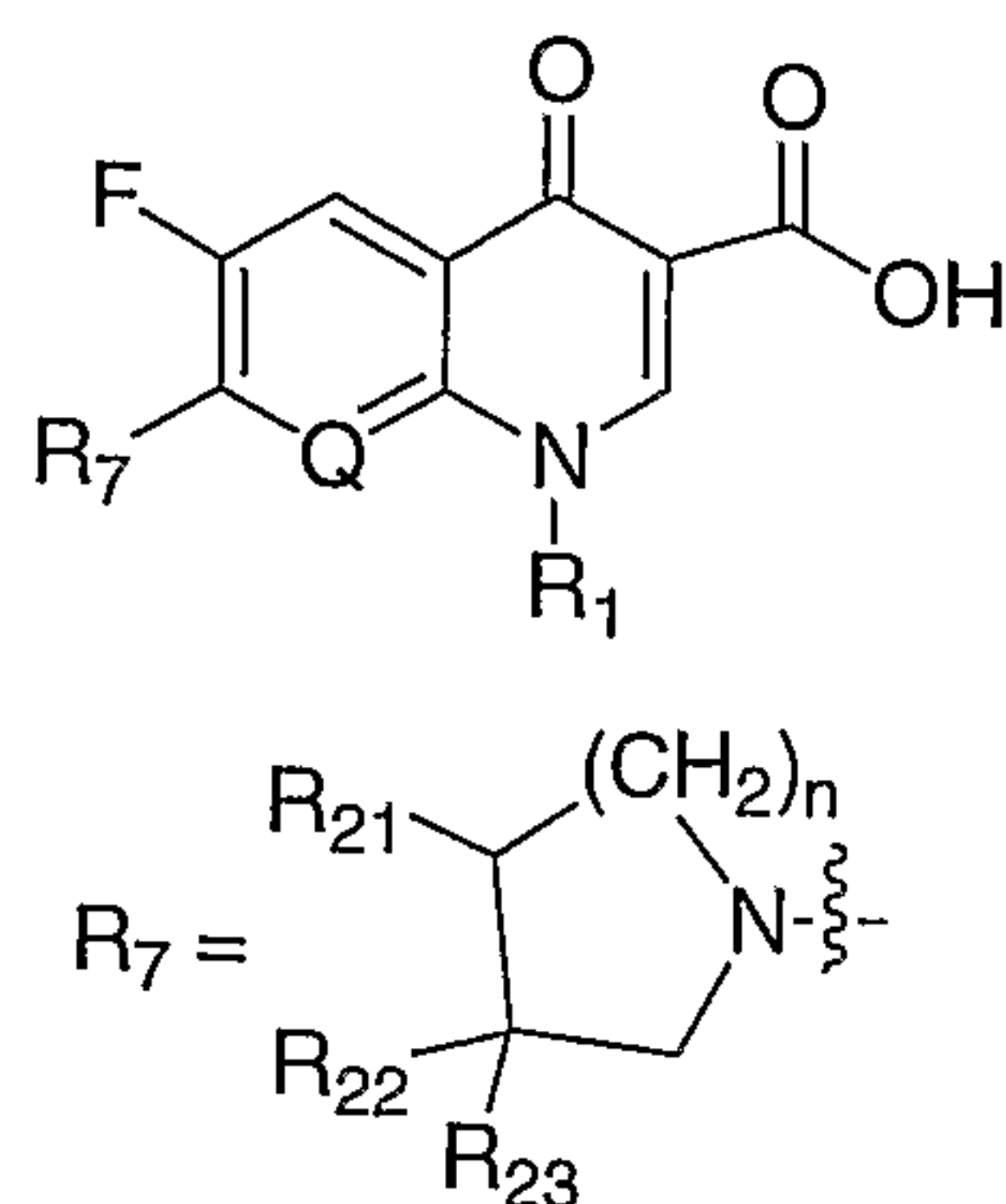
quinolonecarboxylic acid, among the preferred substituents are 3-amino-4-methyl, 3-amino-4,4-dimethyl, 3-amino-4-spirocyclopropyl, 3-amino-6-cyclopropyl, 3-aminomethyl, 4-aminomethyl and 3-methylamino. For compounds with a substituted pyrrolidine at the 7-position of the quinolonecarboxylic acid nucleus, 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,



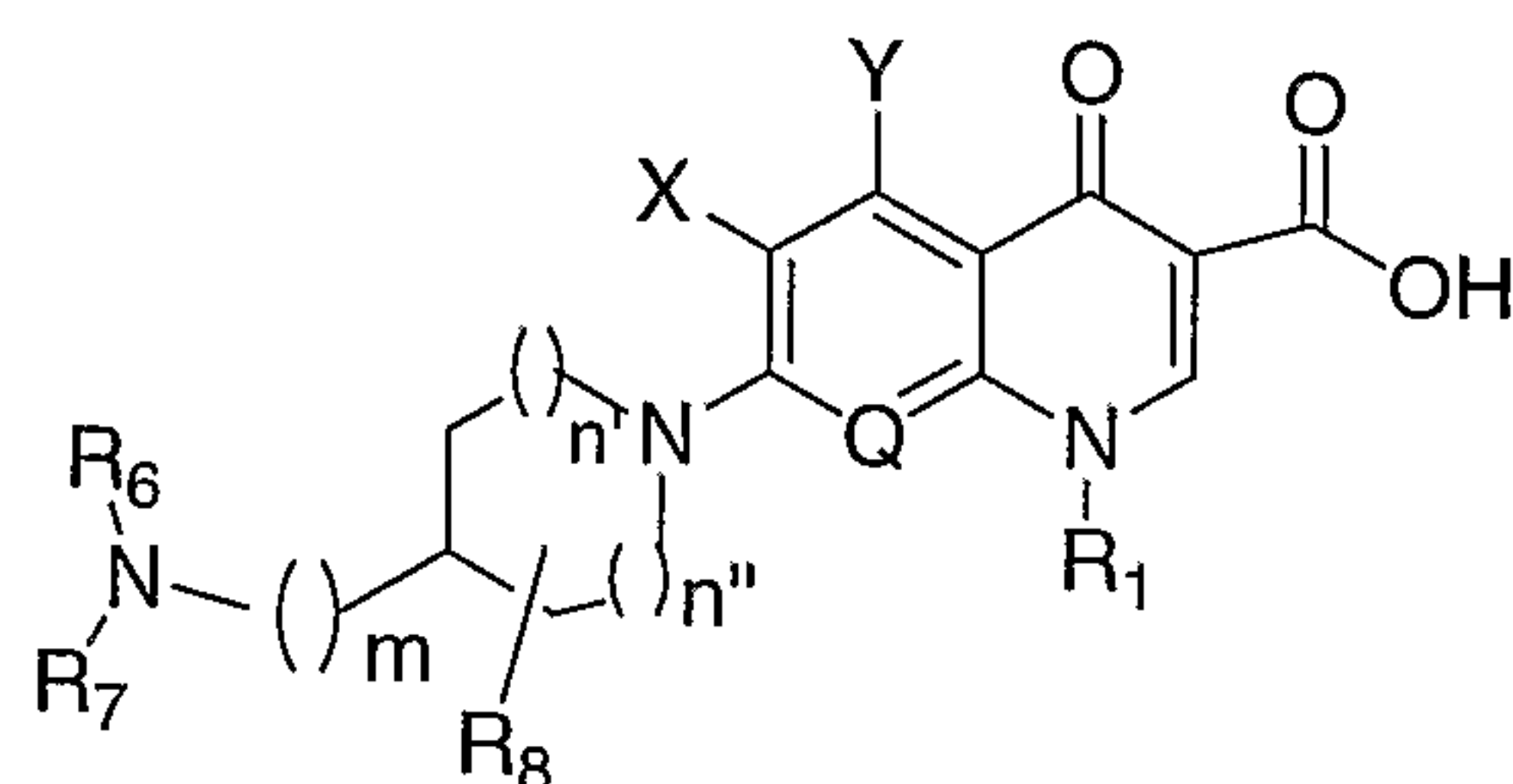
wherein B is $-\text{CH}_2-$, $-(\text{CH}_2)_2-$, or $-(\text{CH}_2)_3-$, R_4 is hydrogen, C_1 - C_3 alkyl, hydroxy, or C_1 - C_3 alkoxy, W is hydroxy, C_1 - C_3 alkoxy, or a group of the formula $\text{R}_5\text{R}_6\text{N}-(\text{CH}_2)_n-$ in which n is 0 or 1 and R_5 and R_6 are the same or different and each represents a hydrogen atom, a C_1 - C_3 alkyl group or an aralkyl 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,



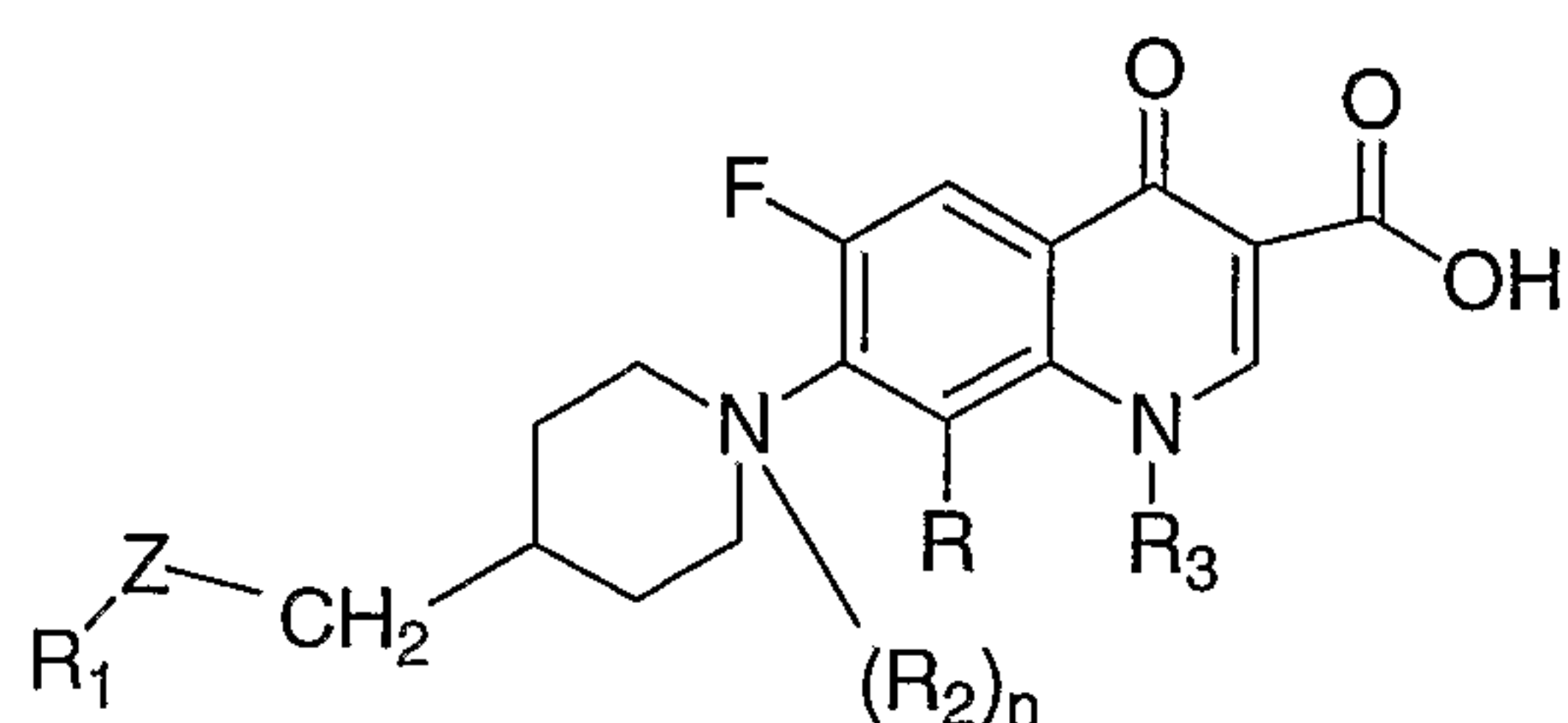
wherein R_{21} , R_{22} and R_{23} are each independently is a hydrogen atom, a halogen atom, amino, C_1 - C_6 alkyl, C_1 - C_8 alkoxy, or amino C_1 - C_8 alkyl and two of them may be combined with each other to form a spiro ring, and n is 1 or 2.

5 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 R_8 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, R₁ 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, R₂ 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).

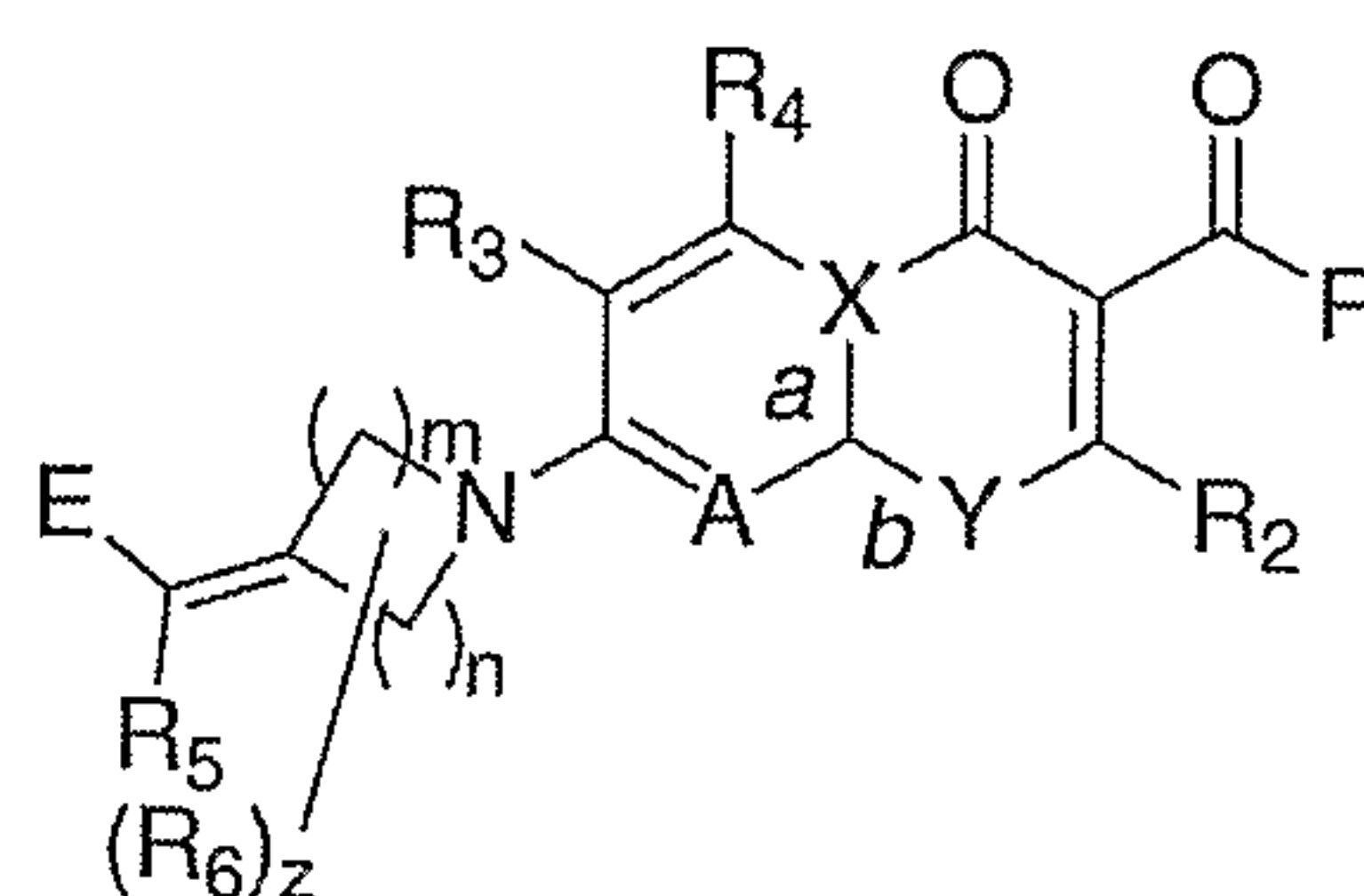
Pathogenic bacteria are known to acquire resistance via several distinct mechanisms including inactivation of the antibiotic by bacterial enzymes (e.g., β -lactamases hydrolyzing penicillin and cephalosporins); removal of the antibiotic using efflux pumps; modification of the target of the antibiotic via mutation and genetic recombination (e.g., penicillin-resistance in *Neisseria 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.

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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)



15

Formula I

wherein:

n is an integer from 1 to 3;

20 **m** is an integer from 1 to 3;

z is an integer from 0 to 3;

R is selected from hydrogen, hydroxy, and alkoxy;

R₂ is hydrogen;

25 **R₃** and **R₄** are independently selected from hydrogen, halogen, amino, hydroxy, alkoxy, alkylthio, alkyl, alkenyl and alkynyl;

R₅ is selected from hydrogen, halogen, alkyl, aryl, alkoxy, and alkylthio;

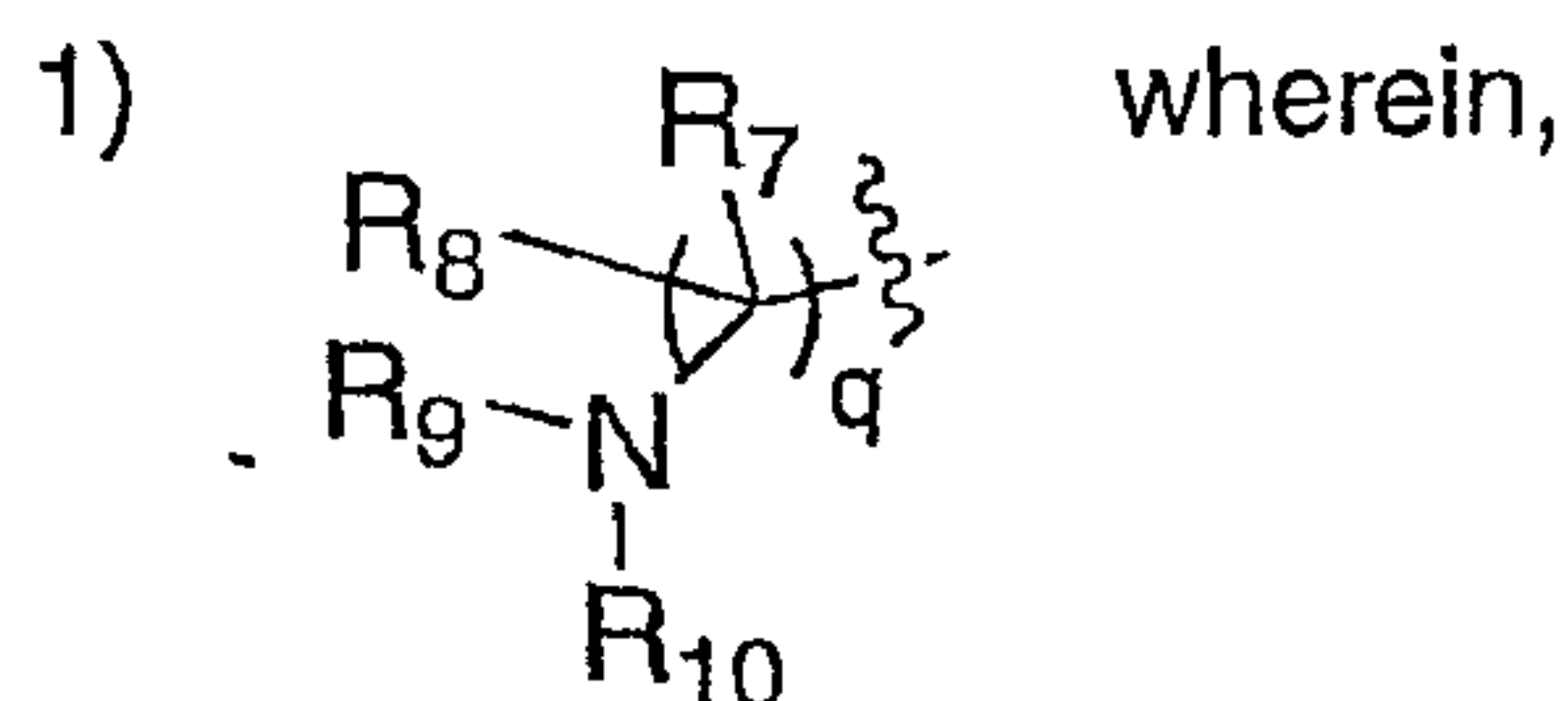
R₆ is independently selected from alkyl, hydroxy, alkoxy, alkylthio, alkenyl, alkynyl, aryl, alkoxyimino, and halogen; or **R₅** and **R₆** join to form a 4- to 7-

WO 2005/033108

PCT/US2004/029523

membered carbocyclic ring wherein each carbon atom of the ring is 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;

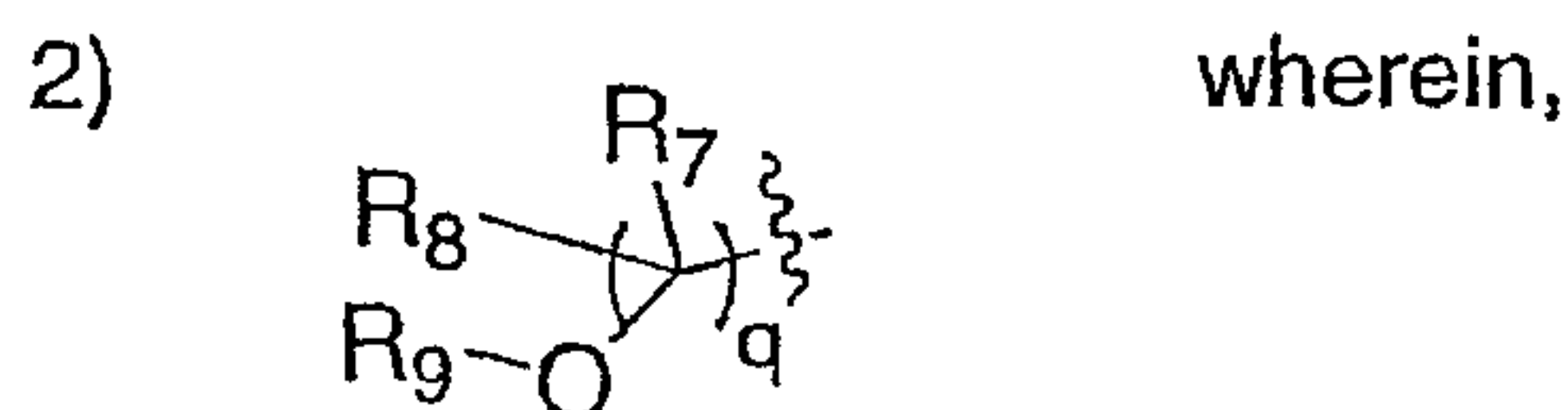
5 **E** is selected from the group consisting of:



10 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 are 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

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



20

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, alkoxy carbonyl, or sulfonyl;

25 and

3) alkenyl;

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

30 **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(R₁₁), X is C and Y is N(R₁), then R₁₁ and R₁ join to form a 6-membered heterocyclic ring, or

5 if A is C(R₁₁), X is C and Y is N(R₁), then R₂ and R₁ join to form a monocyclic or bicyclic heterocyclic ring, or

if A is C(R₁₁), X is C and Y is N(R₁), then R₂ and R join to form a 5-membered heterocyclic ring;

or an optical isomer, diastereomer or enantiomer thereof; a pharmaceutically

10 acceptable salt, hydrate 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

15 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

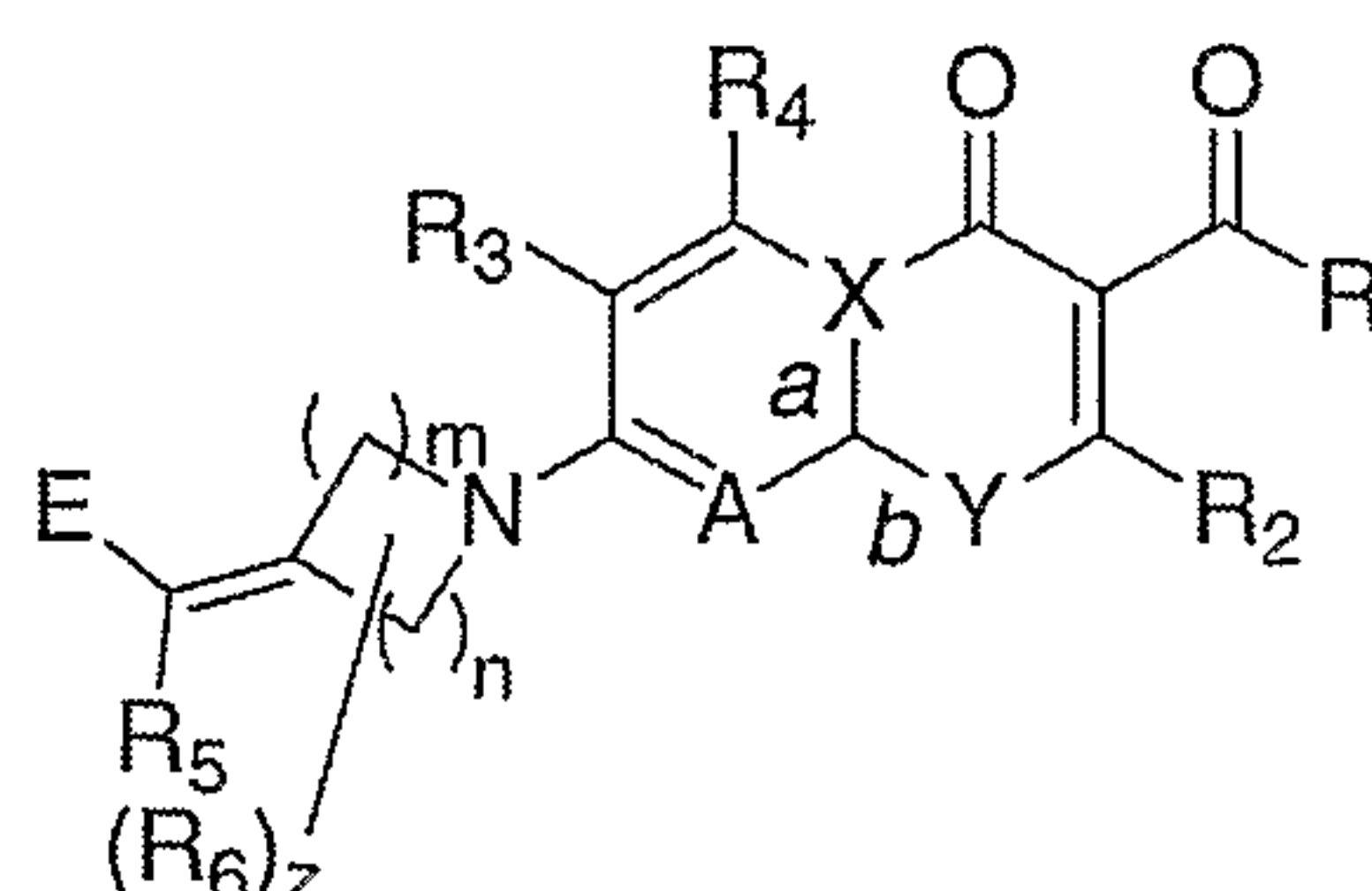
20 effective amount of the compound of Formula 1.

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.

25

Detailed Description

The subject invention provides compounds of Formula (I)



Formula I

5 wherein:

a, b, n, m, z, R, R₂, R₃, R₄, R₅, R₆, 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.

10 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.

15 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 bond. 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

25 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, -OCOR₁₃, -OR₁₃, -SR₁₃, -SOR₁₃, -SO₂R₁₃, -COOR₁₃, -NR₁₃R₁₄, -CONR₁₃R₁₄, -OCONR₁₃R₁₄, -NHCOR₁₃, -NHCOOR₁₃, and -NHCONR₁₃R₁₄, wherein R₁₃ and

R₁₄ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclo, aralkyl, heteroaralkyl, and heterocycloalkyl, or alternatively R₁₄ and R₁₅ may join to form a heterocyclic ring containing the nitrogen atom to which they are attached.

5 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.

10 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-
 15 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, C₁-C₈-alkyl, C₂-C₈-alkenyl, C₁-C₈-alkoxyl, C₁-C₈-alkylthio, C₁-C₈-alkyl-amino, di (C₁-C₈-alkyl)amino, (mono-, di-, tri-, and per-)halo-alkyl, formyl, carboxy, alkoxycarbonyl, C₁-C₈-
 20 alkyl-CO-O-, C₁-C₈-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, dimethylcarbamyphenyl and
 25 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
 30 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, quinoliny, isoquinoliny, indolyl, isothiazolyl, N-oxo-pyridyl, 1,1-dioxothienyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinoliny-N-oxide, benzimidazolyl, benzopyranyl, benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, indazolyl, indoliziny, benzofuryl, cinnoliny, quinoxaliny, pyrrolopyridiny, furopyridiny (such as furo[2,3-c]pyridiny, furo[3,2-b]pyridiny, or furo[2,3-b]pyridiny), imidazopyridiny (such as imidazo[4,5-b]pyridiny or imidazo[4,5-c]pyridiny), naphthyridiny, phthalazinyl, puriny, 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, C₁-C₈-alkyl, C₁-C₈-alkoxyl, C₁-C₈-alkylthio, C₁-C₈-alkyl-amino, di(C₁-C₈-alkyl)amino, (mono-, di-, tri-, and per-)halo-alkyl, formyl, carboxy, alkoxycarbonyl, C₁-C₈-alkyl-CO-O-, C₁-C₈-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, C₁-C₈-alkyl, C₁-C₈-alkoxyl, C₁-C₈-alkylthio, C₁-C₈-alkyl-amino, di(C₁-C₈-alkyl)amino, (mono-, di-, tri-, and per-)halo-alkyl, formyl, carboxy, alkoxycarbonyl, C₁-C₈-alkyl-CO-O-, C₁-C₈-alkyl-CO-NH-, or carboxamide.

Exemplary monocyclic heterocyclic groups include pyrrolidiny; oxetanyl; pyrazolinyl; imidazolinyl; imidazolidiny; oxazolinyl; oxazolidiny; isoxazolinyl; thiazolidiny; isothiazolidiny; tetrahydrofuryl; piperidiny; 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.

5 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;
10 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
15 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., C₁-C₈ or C₁₋₈) 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
20 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
25 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
30 example, in T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991).

Illustrative hydroxyl protecting groups include but are not limited to tetrahydropyranyl; benzyl; methylthiomethyl;

ethythiomethyl; 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, 5 salicylic acid and the like. Suitable salts are furthermore those of inorganic or organic bases, such as KOH, NaOH, $\text{Ca}(\text{OH})_2$, $\text{Al}(\text{OH})_3$, piperidine, morpholine, ethylamine, triethylamine and the like.

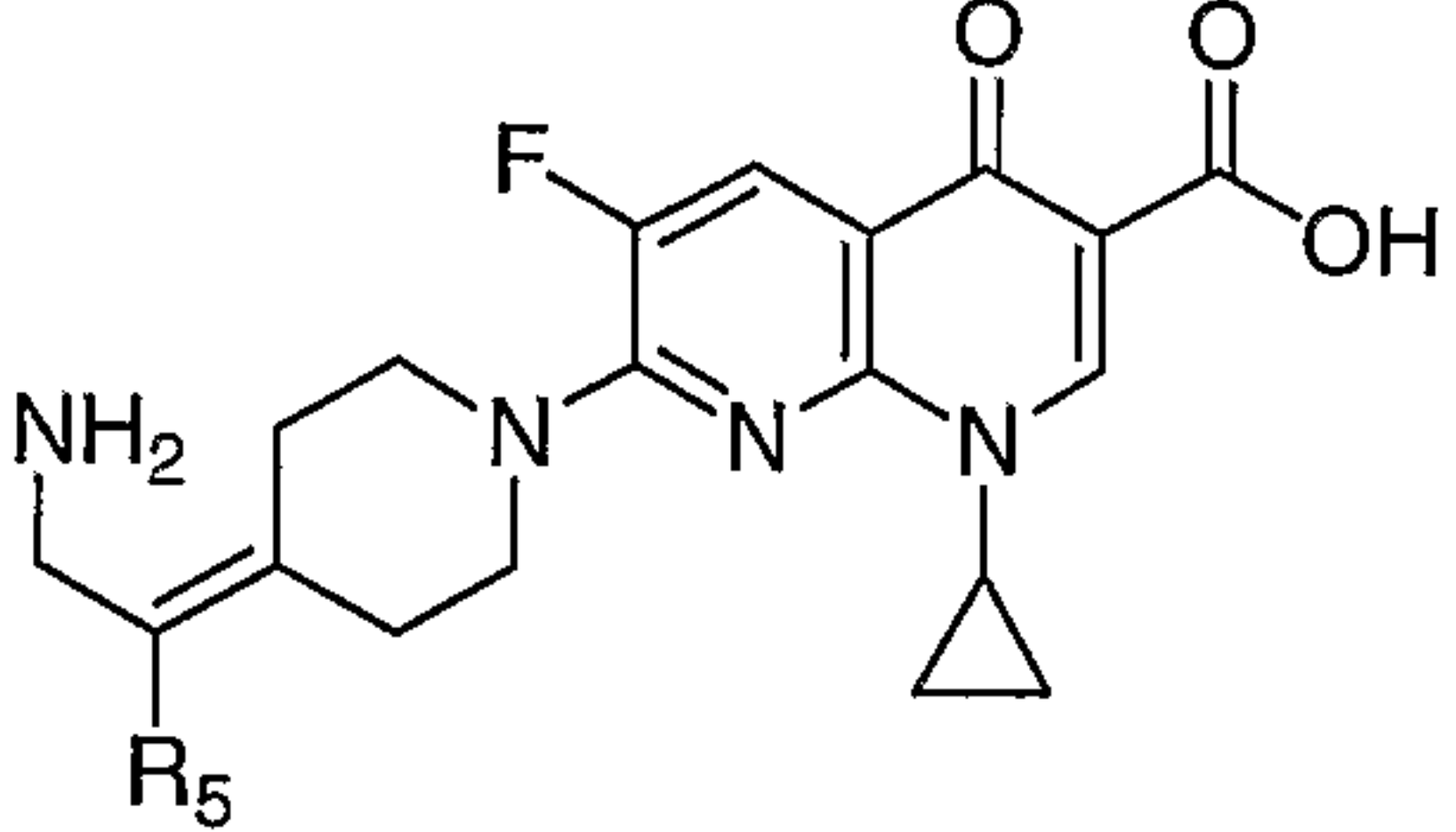
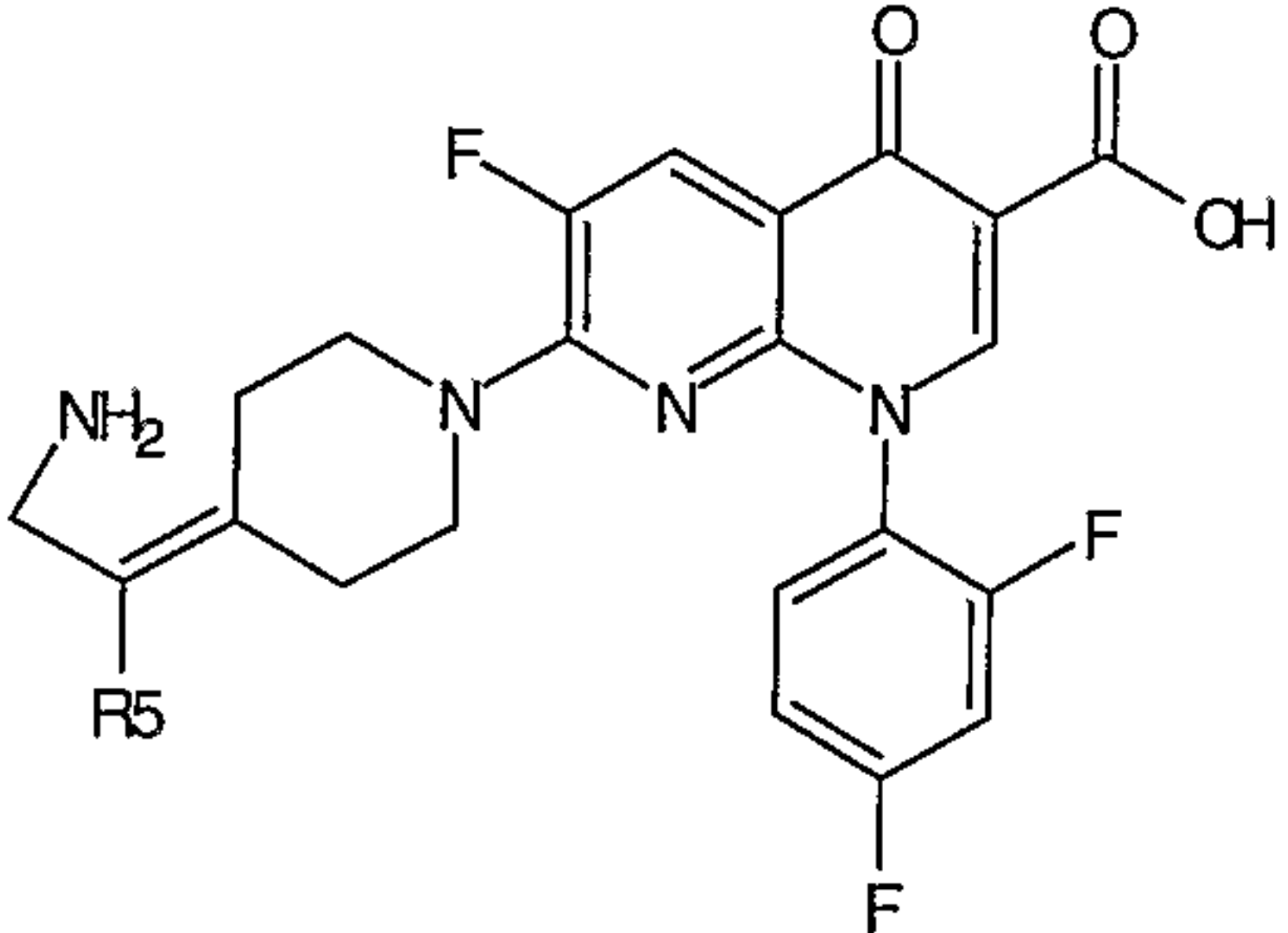
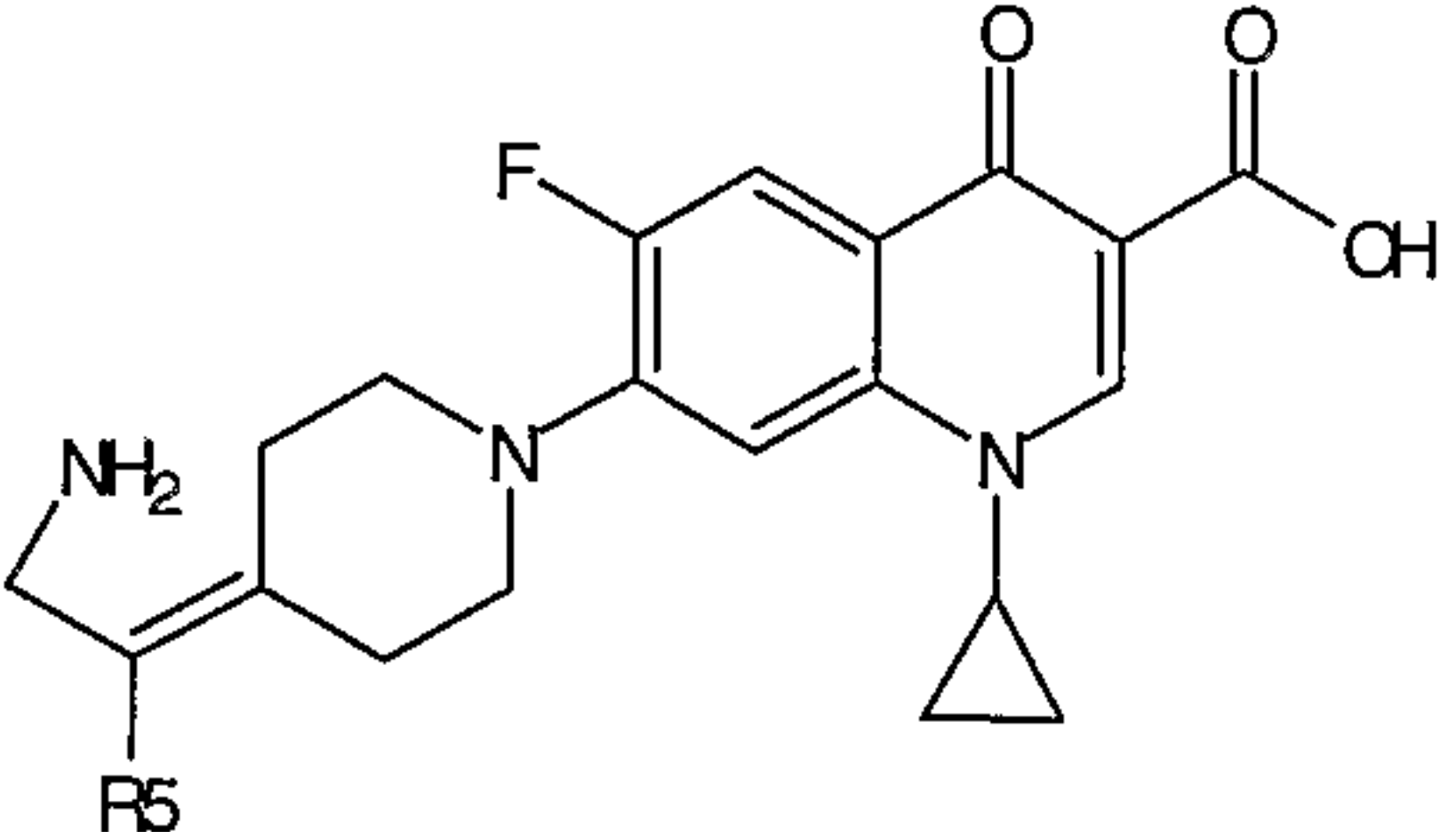
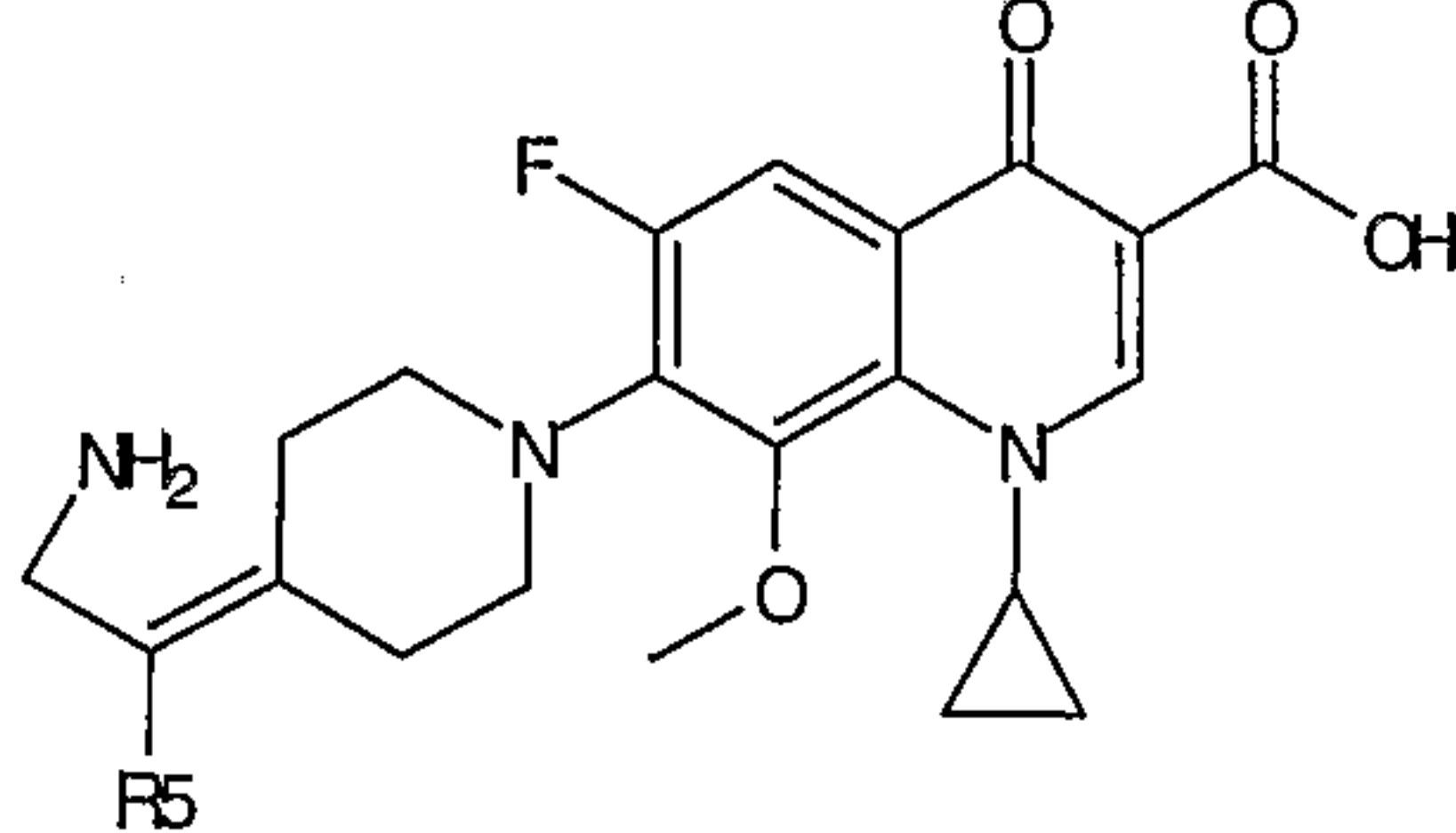
Included within the scope of the invention are the hydrated forms of the compounds that contain various amounts of water, for instance, the hydrate, 10 hemihydrate, and sesquihydrate forms. The present invention also includes within its scope prodrugs of the compounds of this invention. In general, such 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 15 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. 20 Bundgaard, Elsevier, 1985.

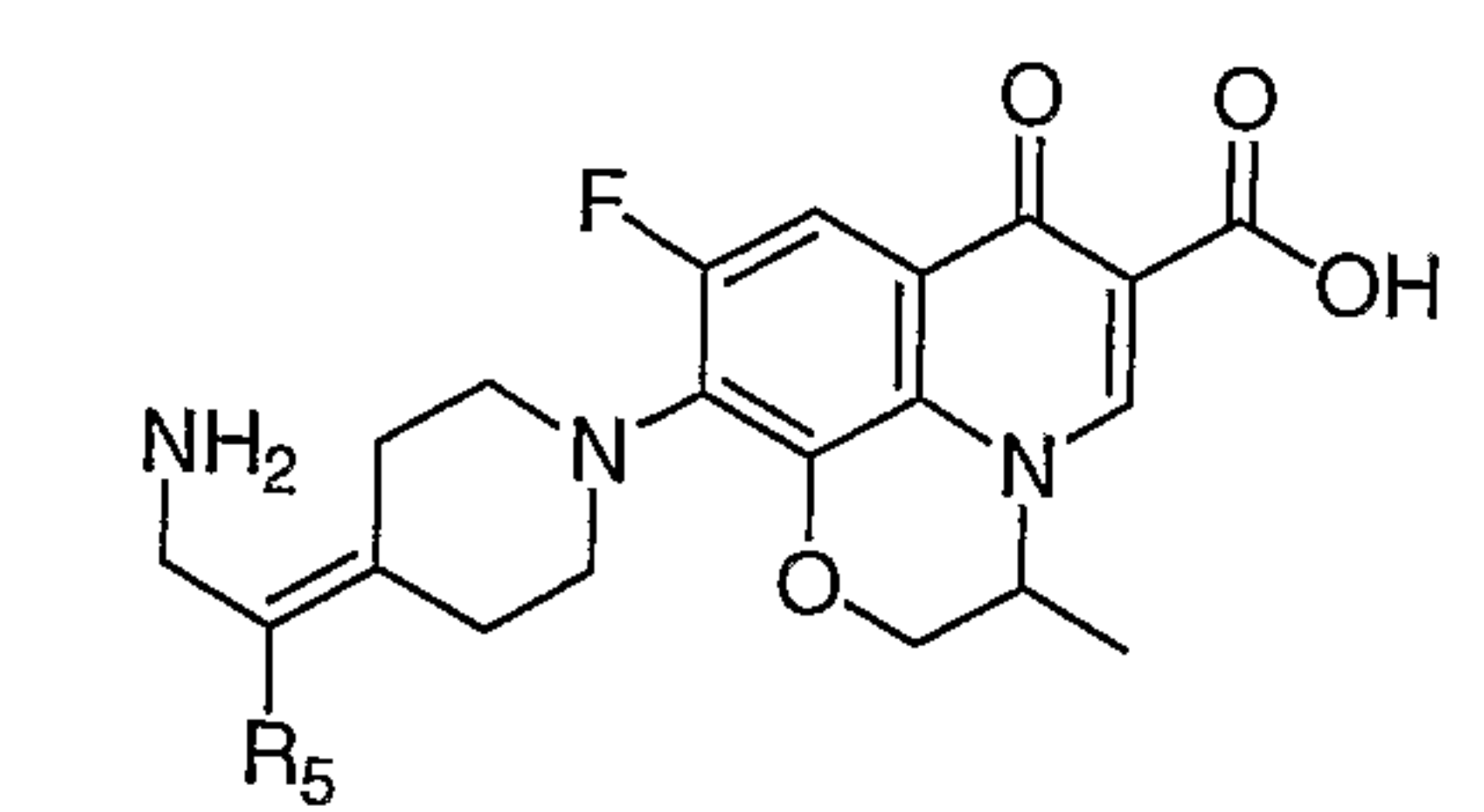
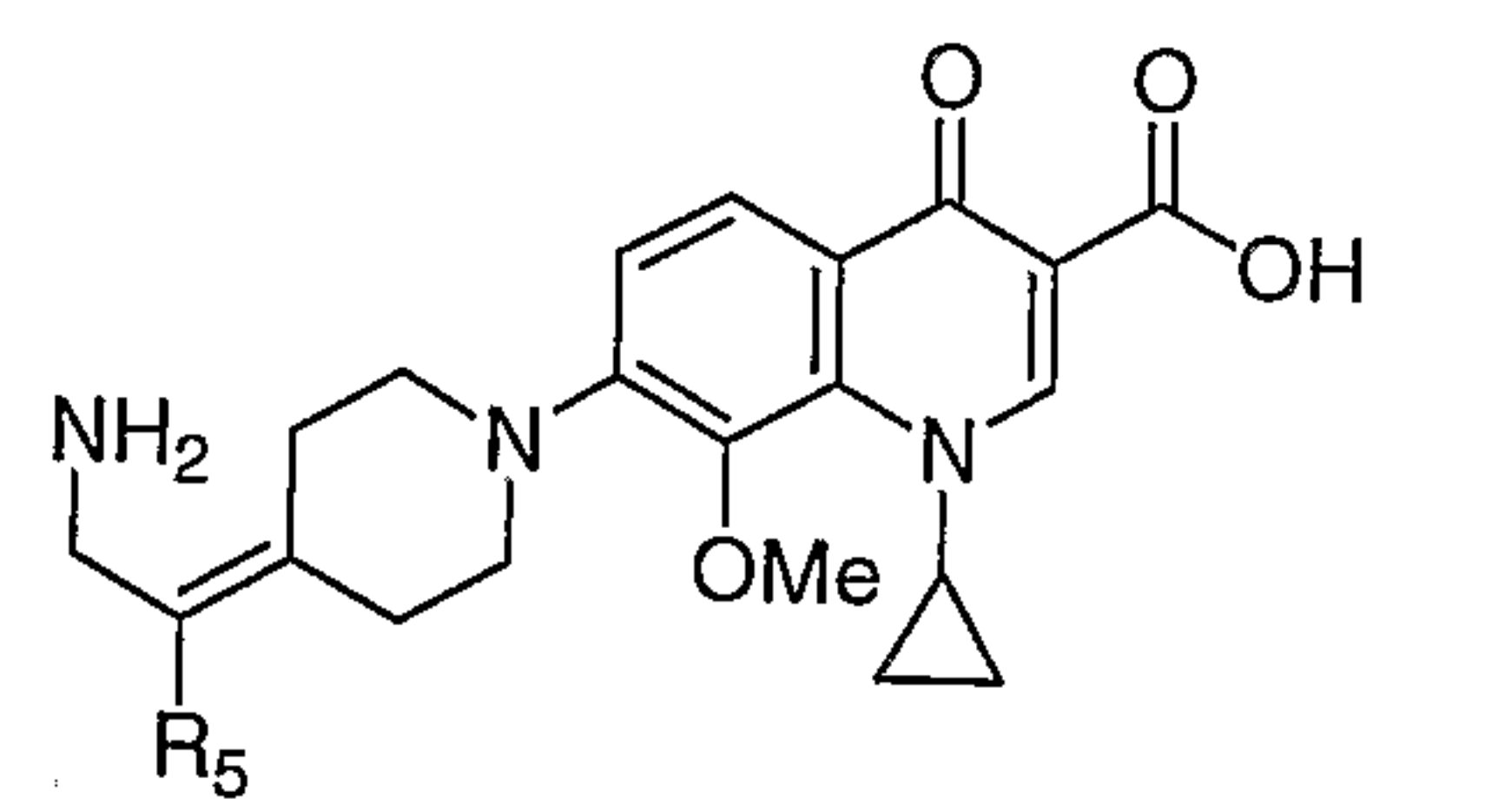
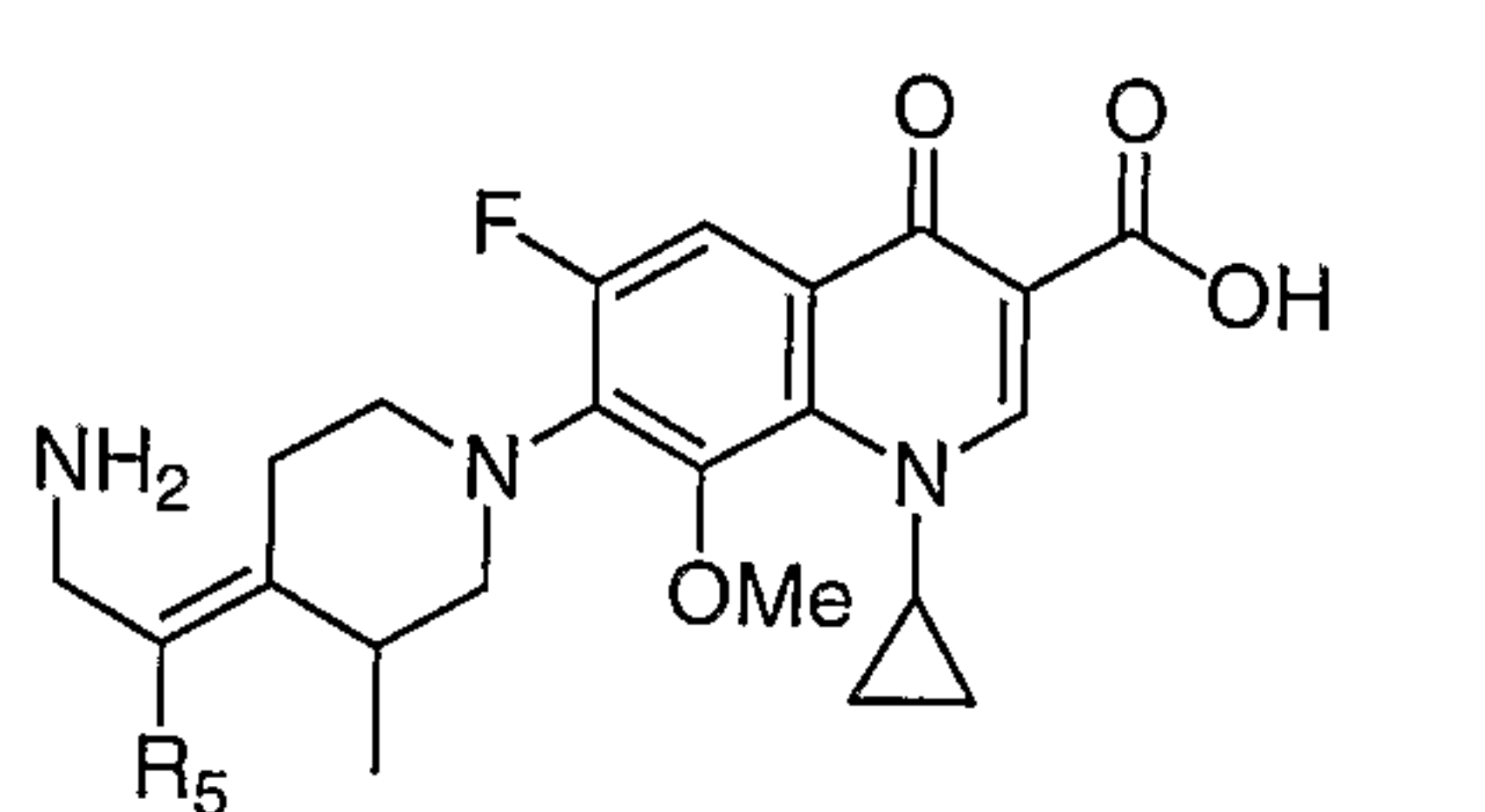
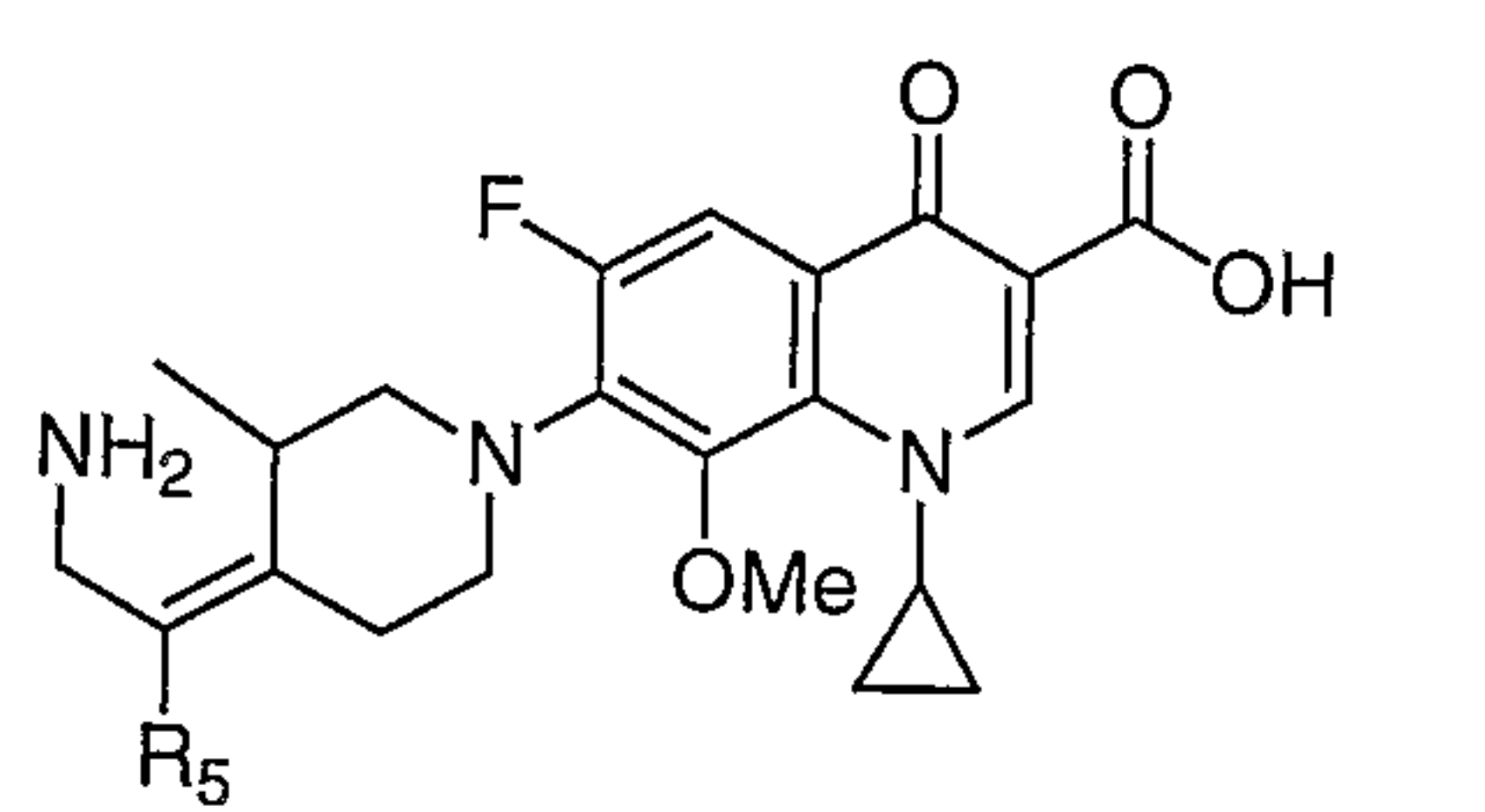
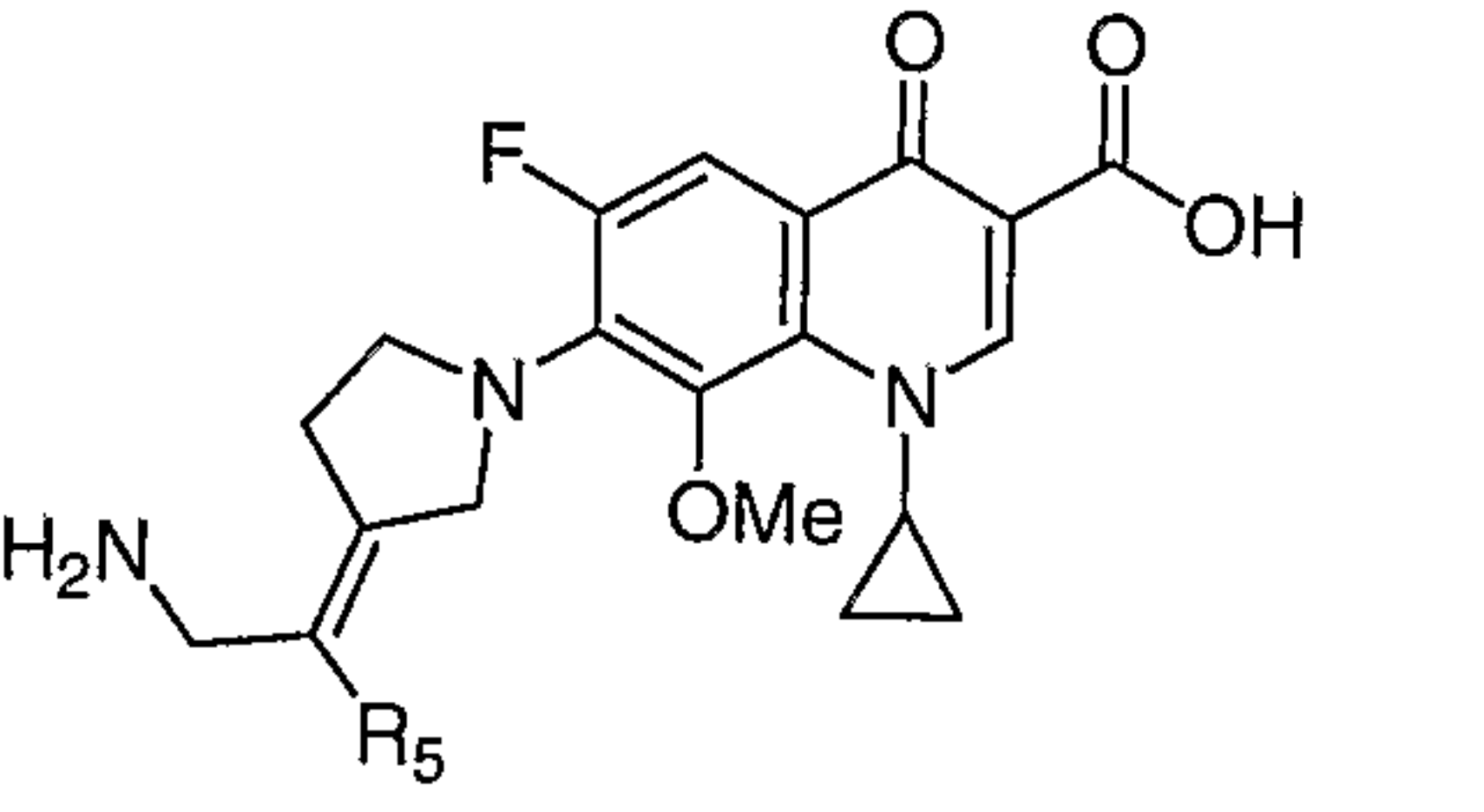
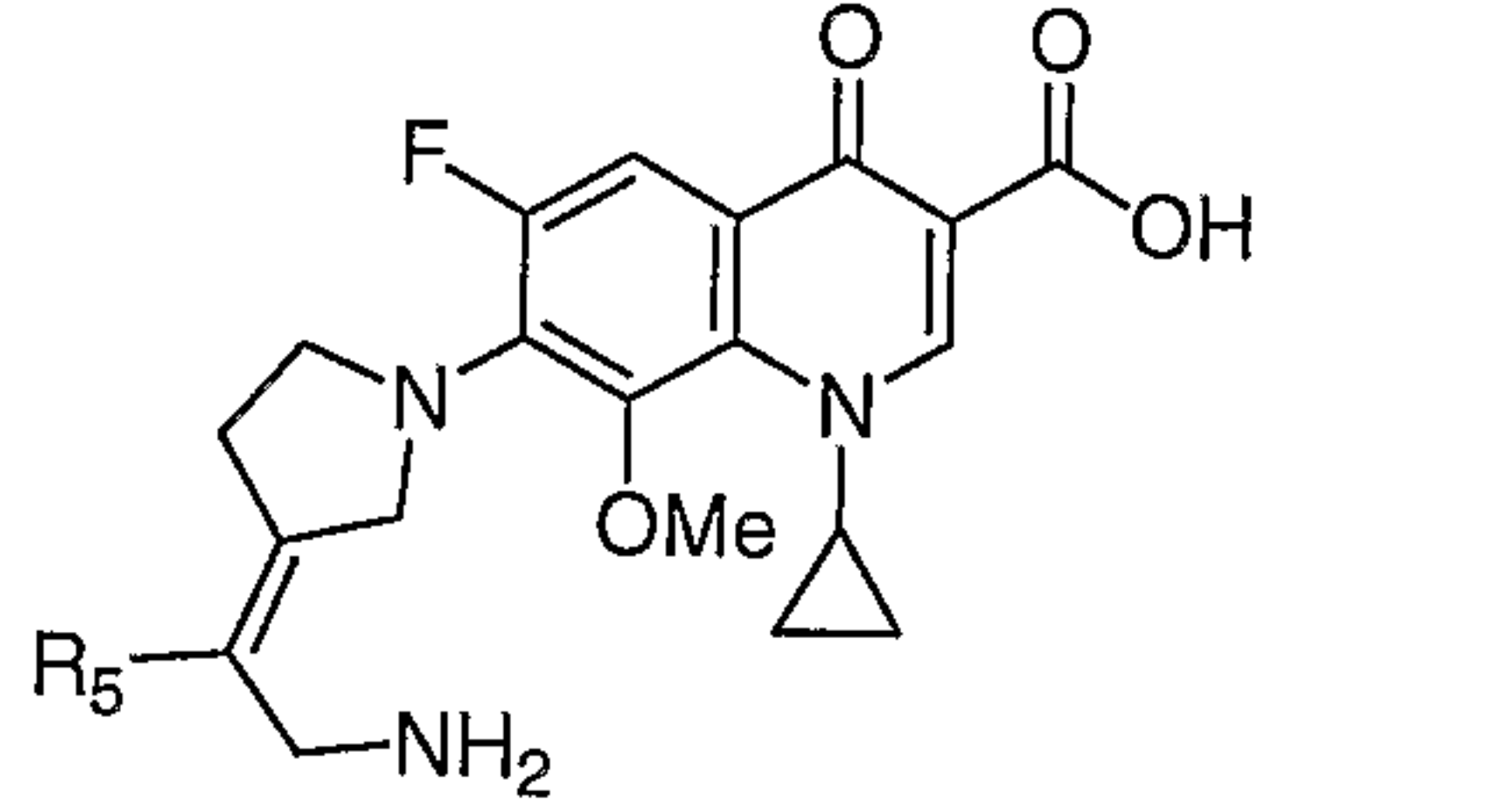
The term "subject" includes, without limitation, any animal or artificially modified animal. As a particular embodiment, the subject is a human.

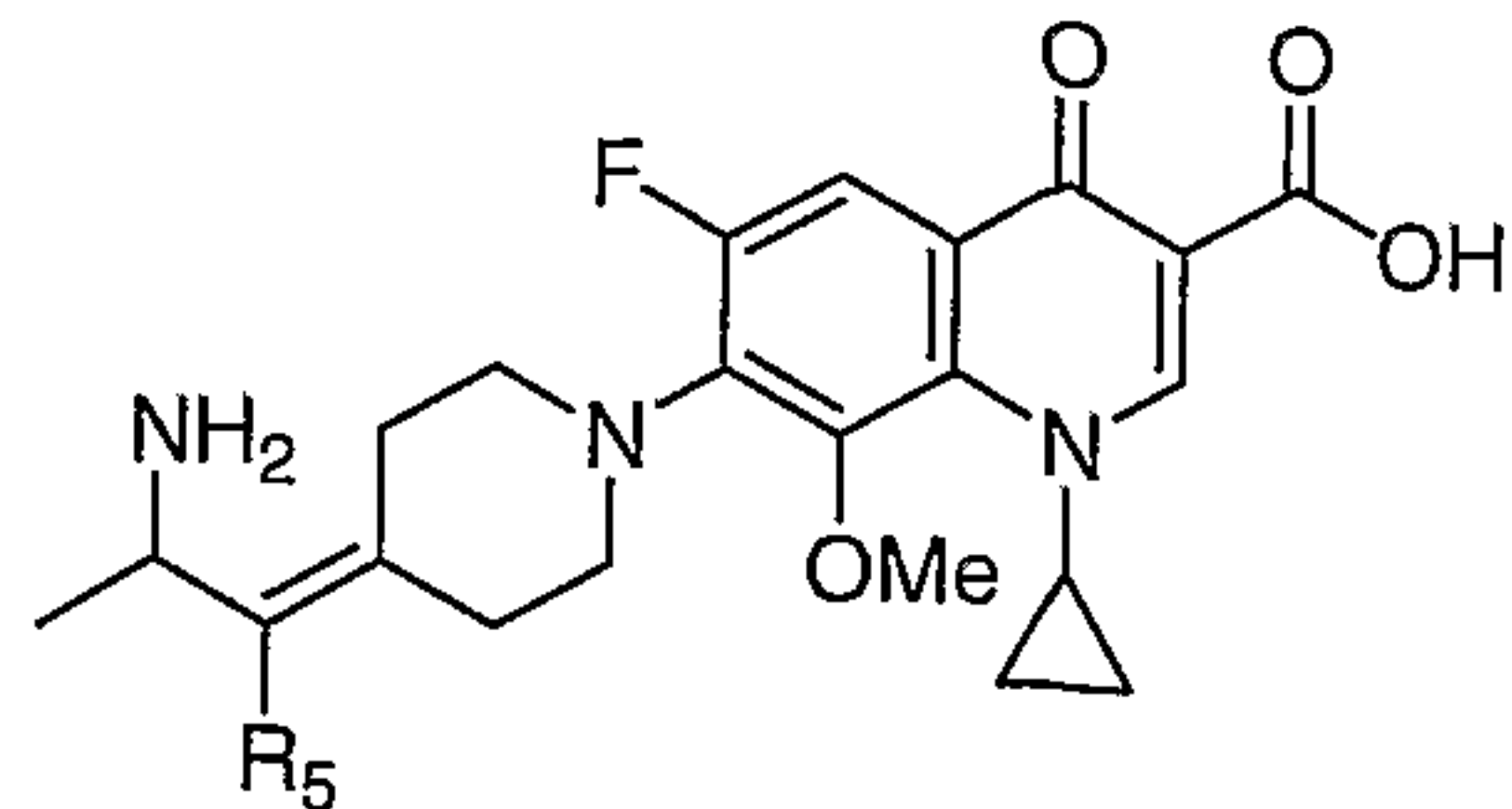
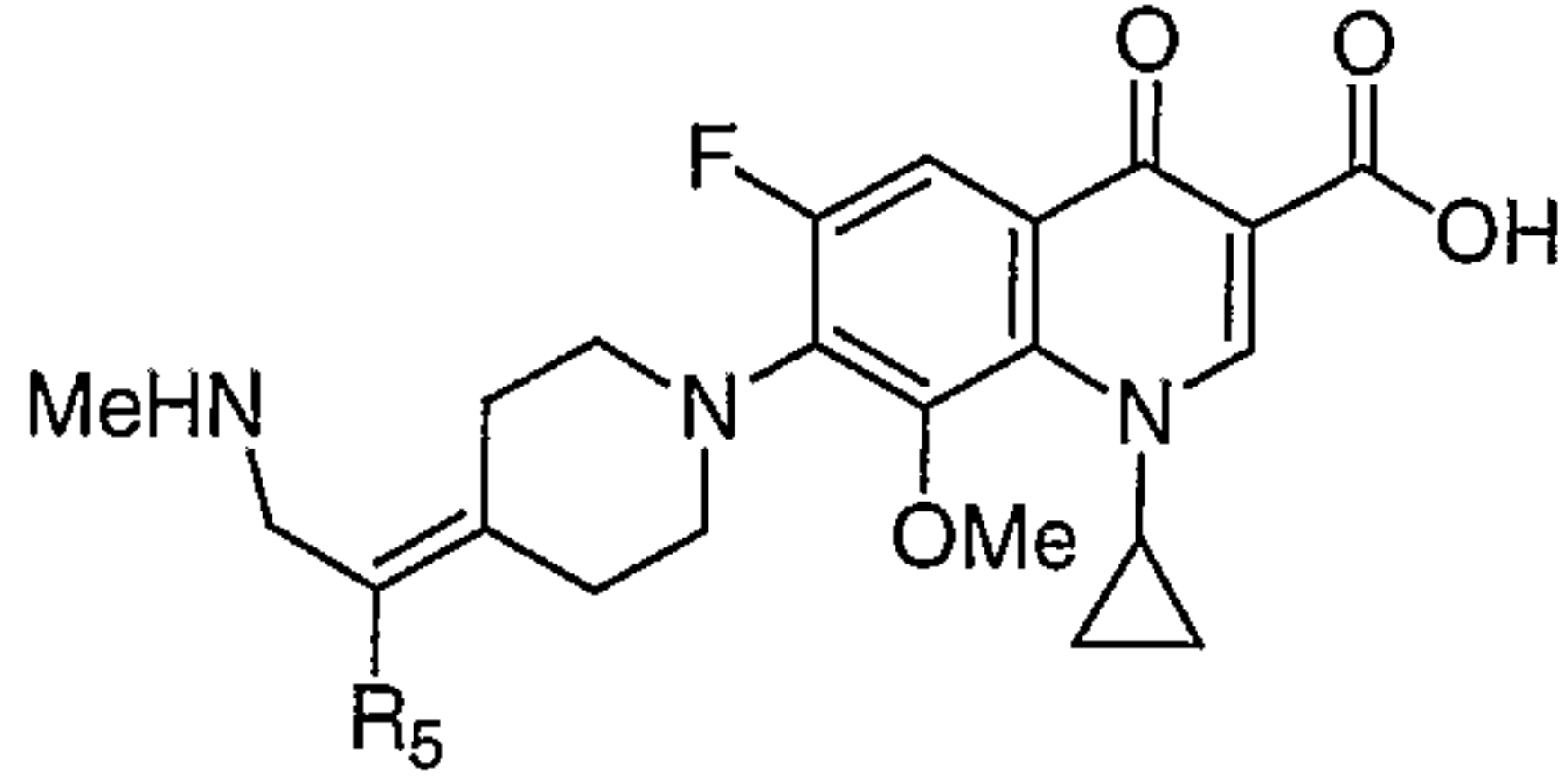
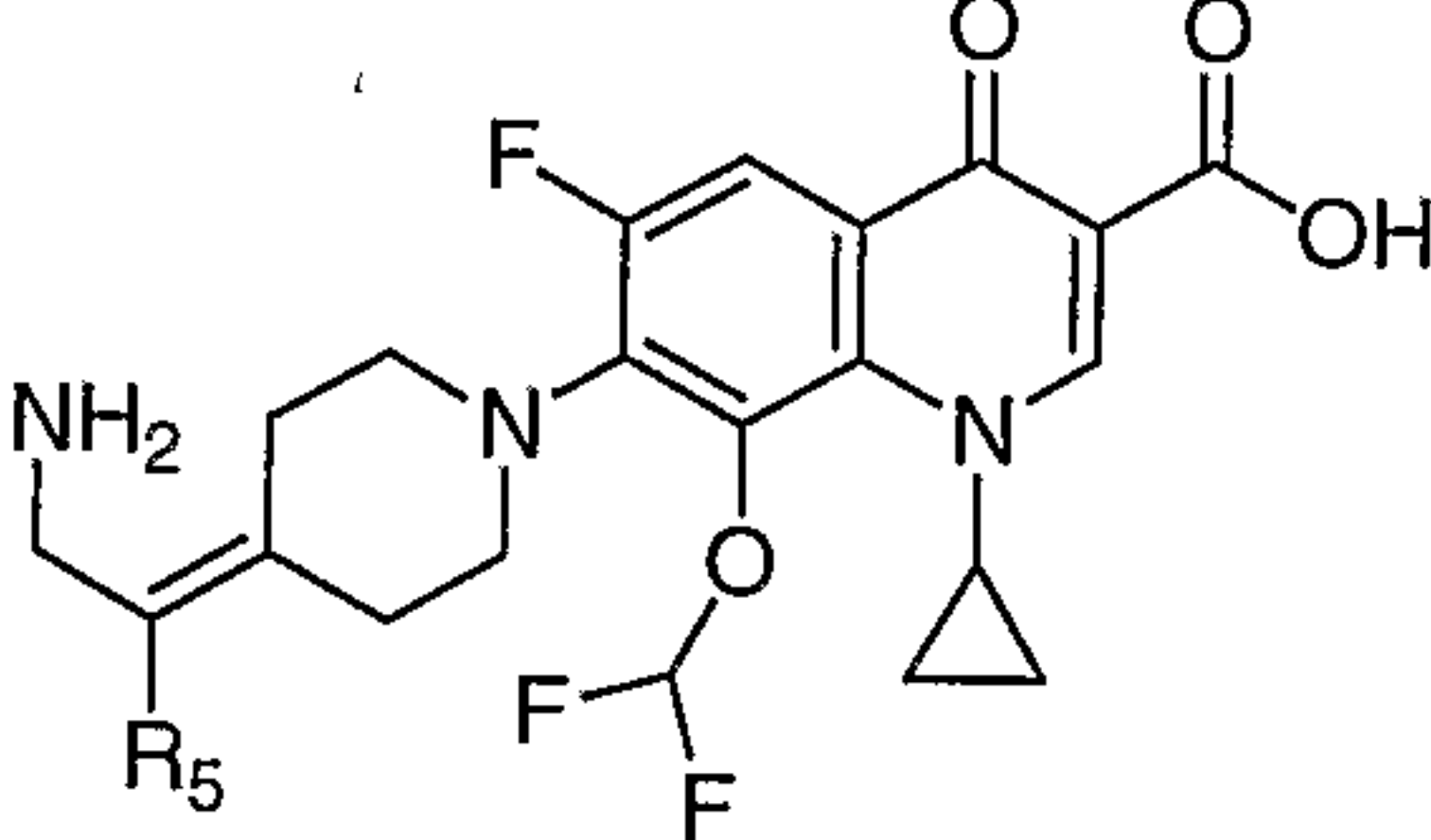
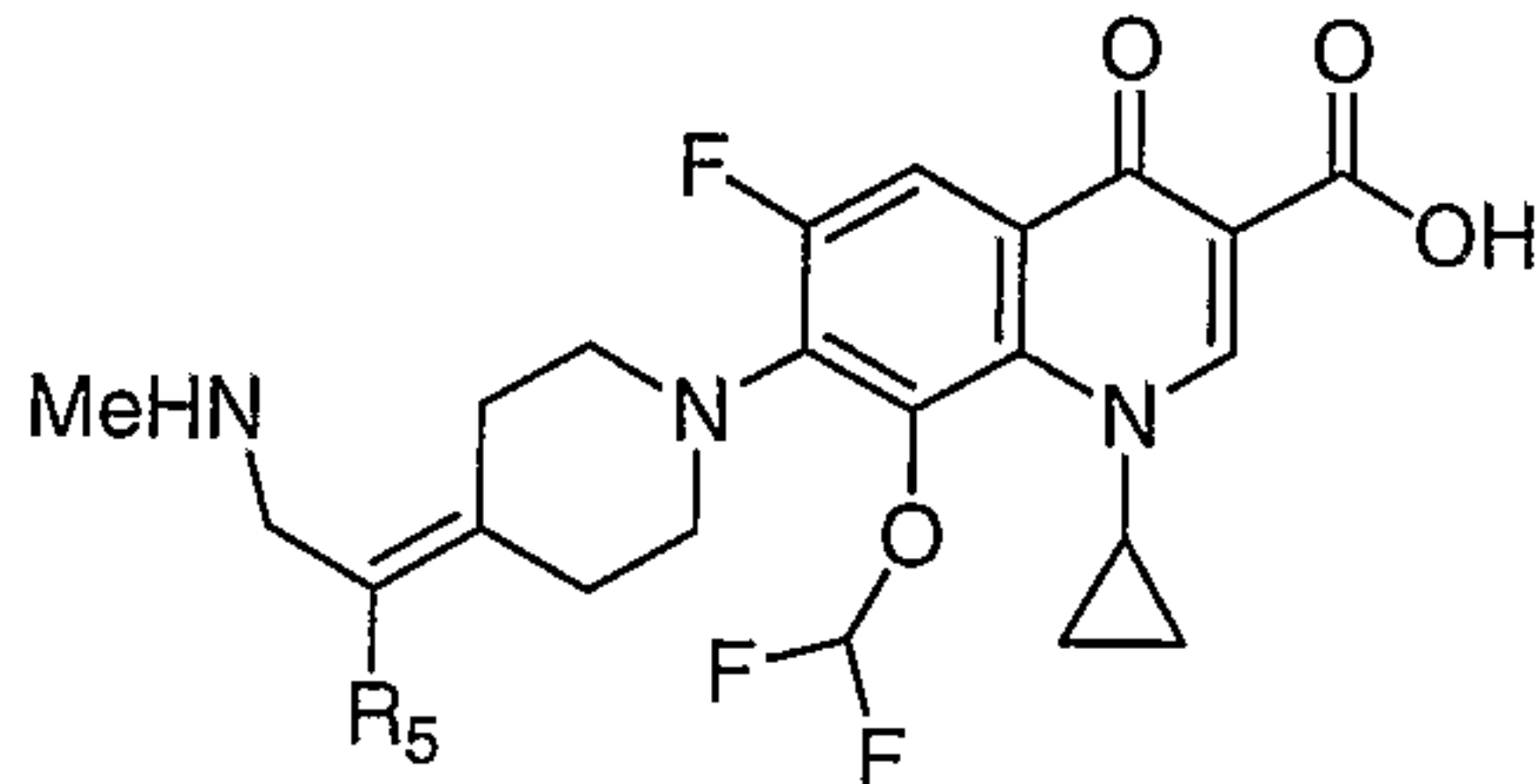
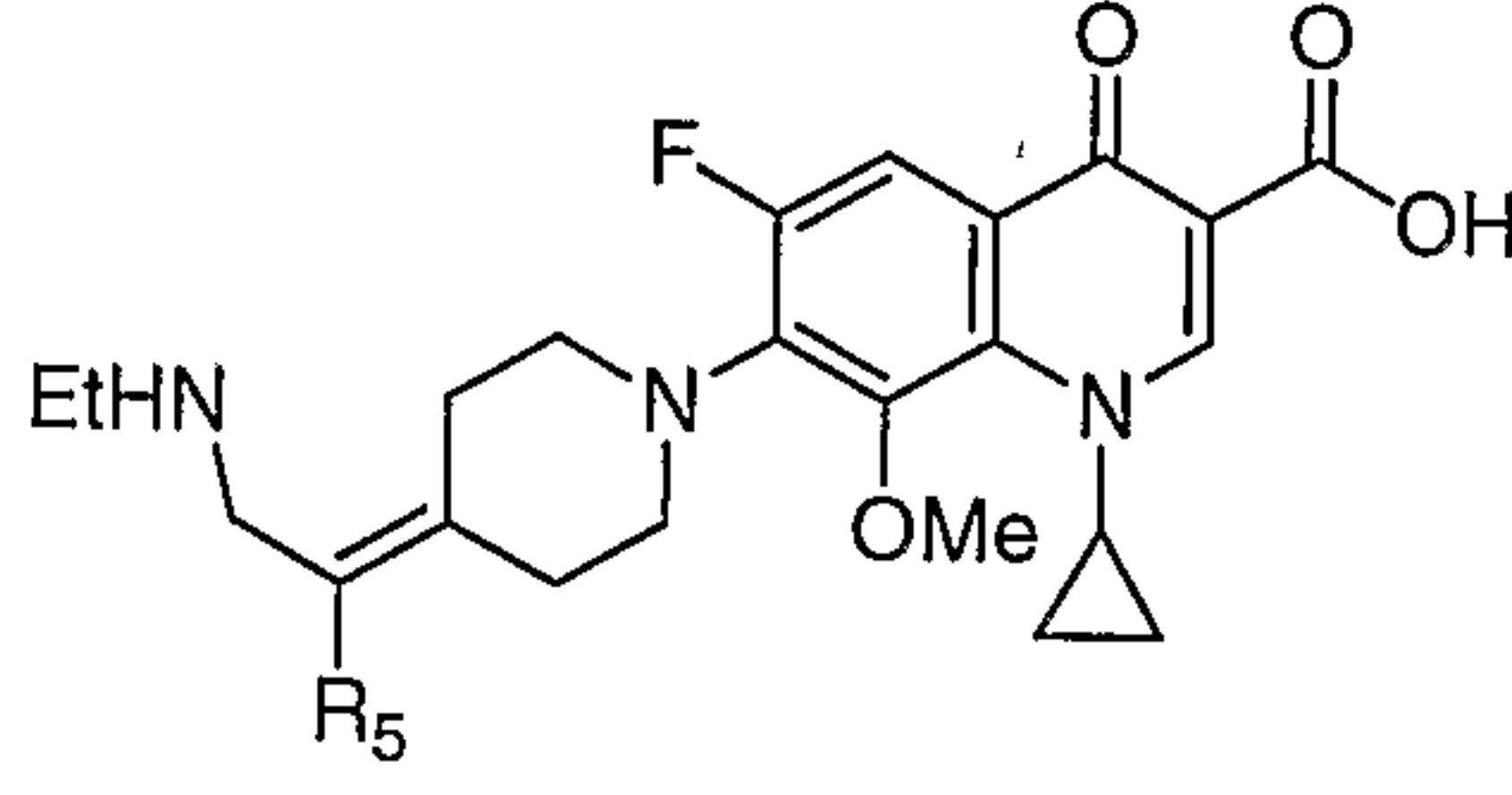
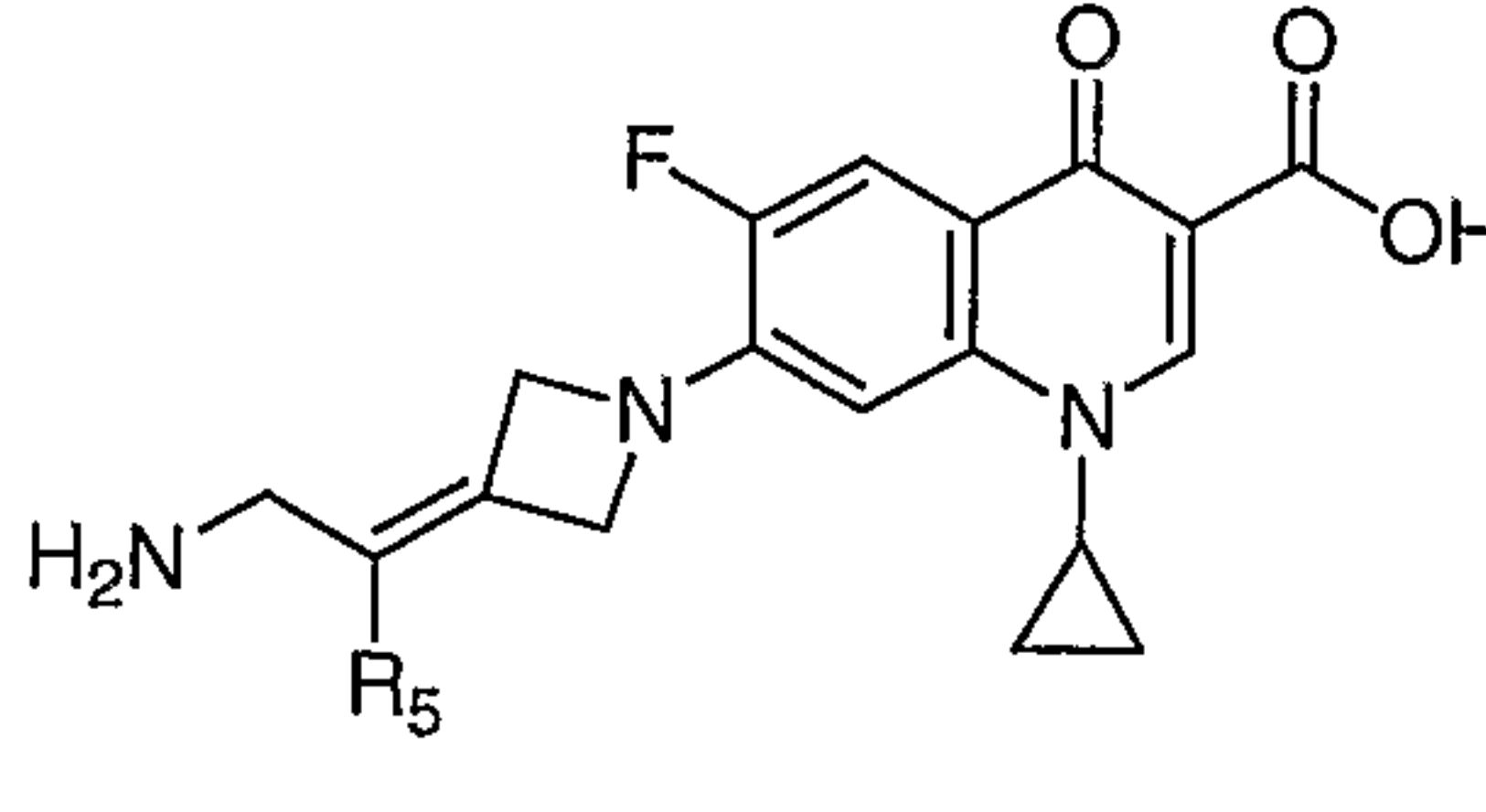
The term "drug-resistant" or "drug-resistance" refers to the characteristics of a microbe to survive in the presence of a currently available 25 antimicrobial agent such as an antibiotic at its routine, effective concentration.

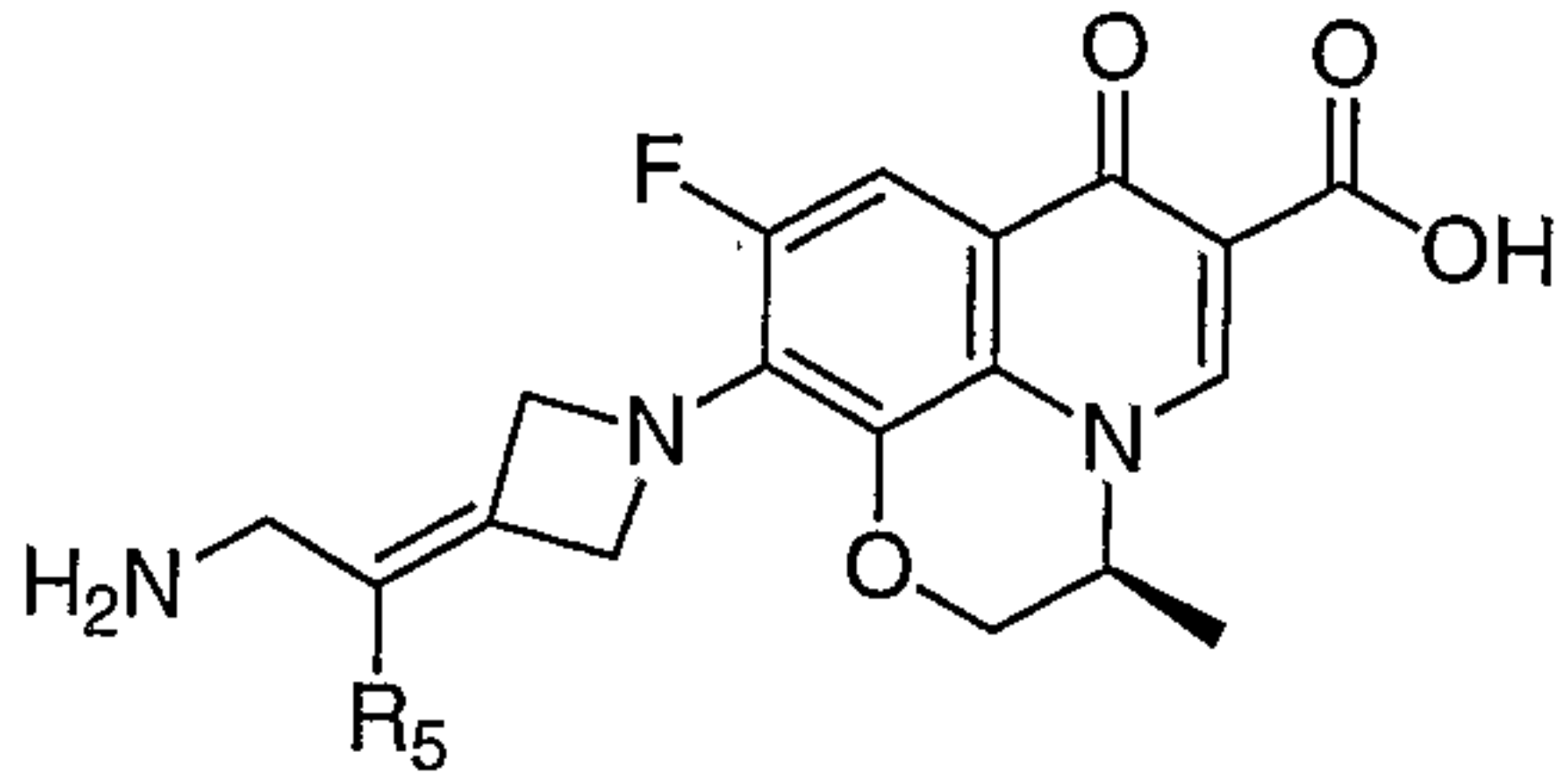
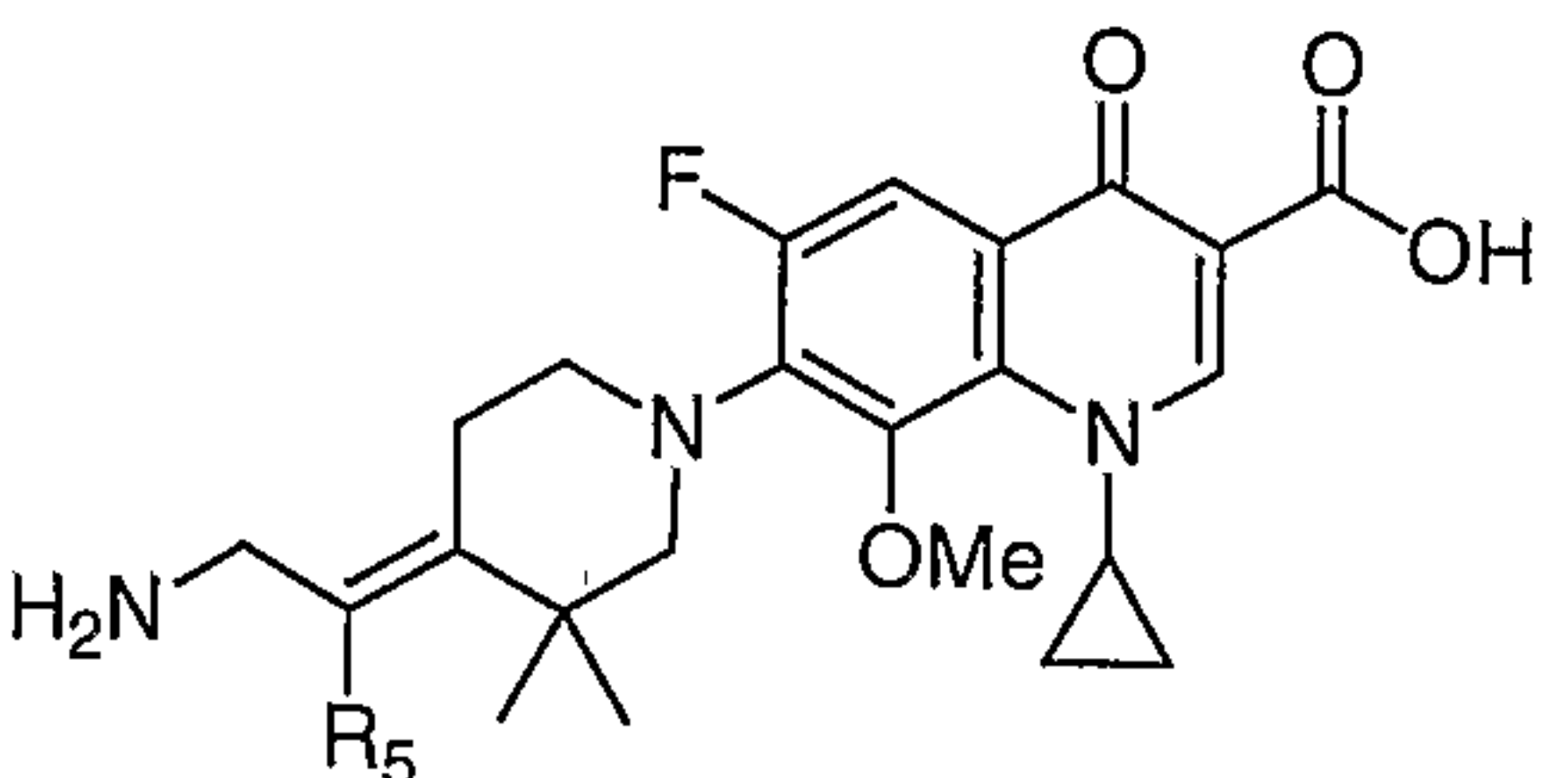
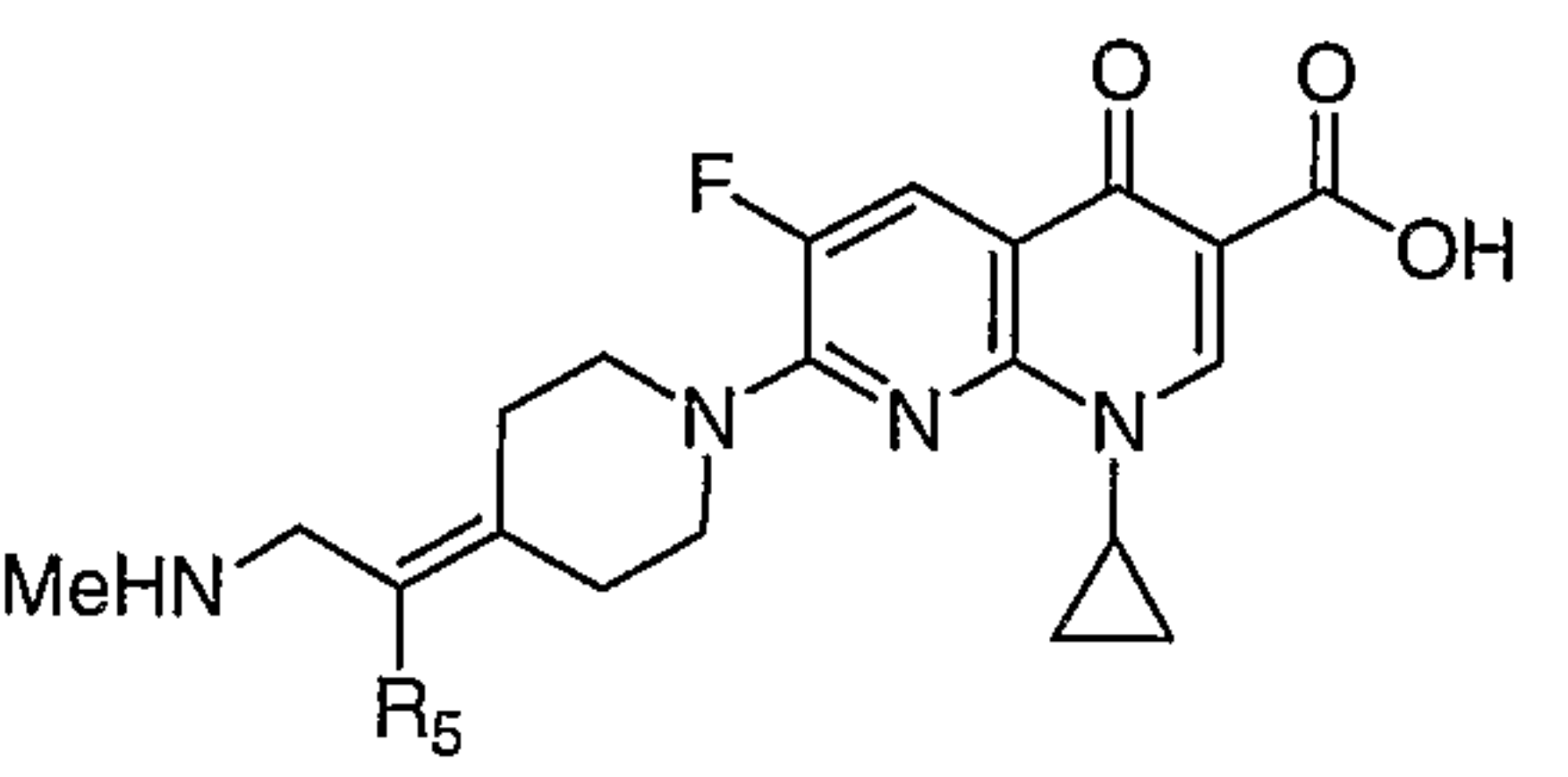
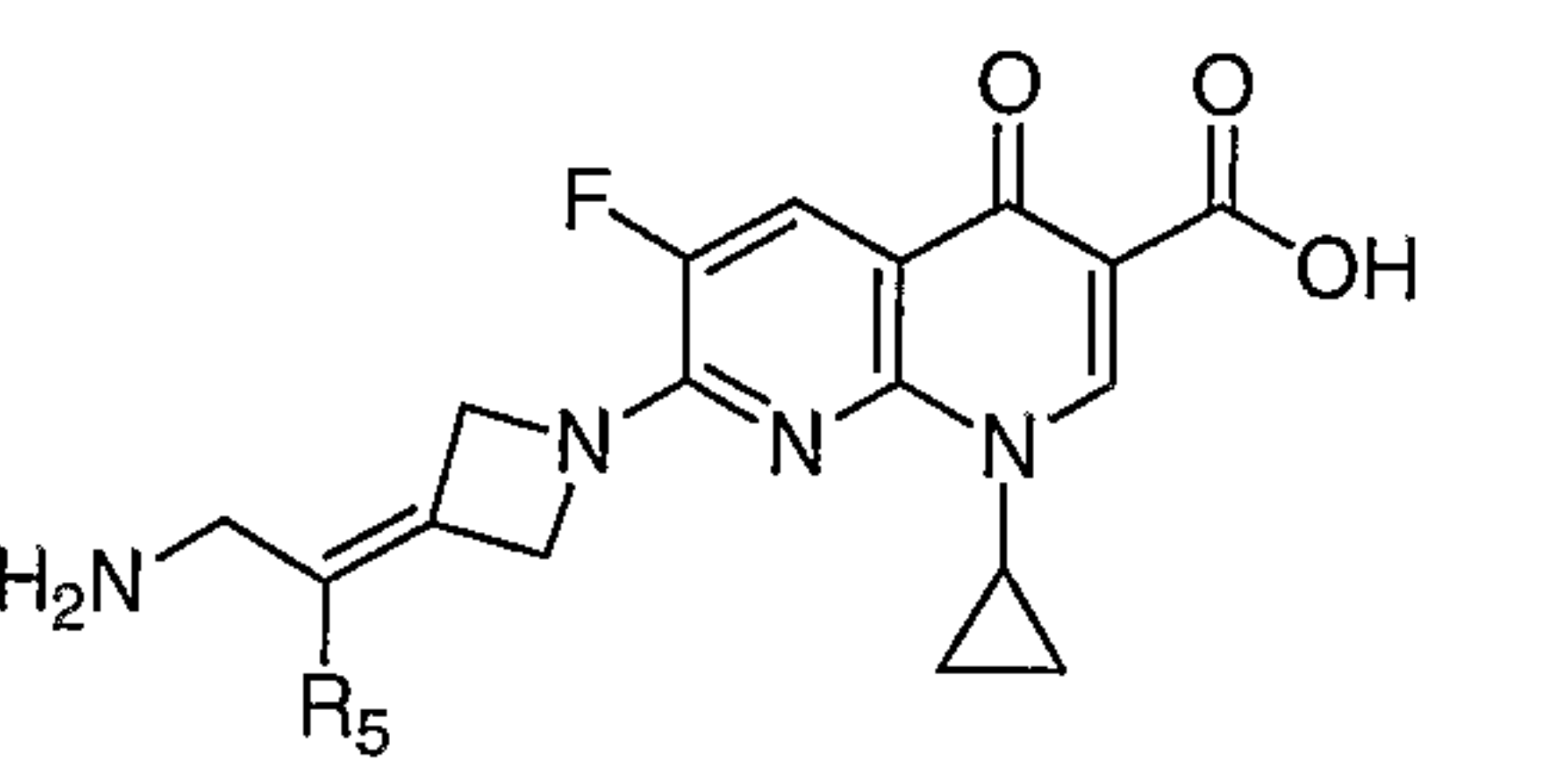
Table 1 contains a non-limiting list of preferred compounds of Formula I.

Table 1

Structure	R5 Substituent	Compound Number
	F	1
	CH ₃	2
	Cl	3
	CH ₃ CH ₂	69
	F	4
	F	5
	Cl	65
	F	6
	Cl	7
	CH ₃	70
	CH ₃ CH 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

5

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:

25

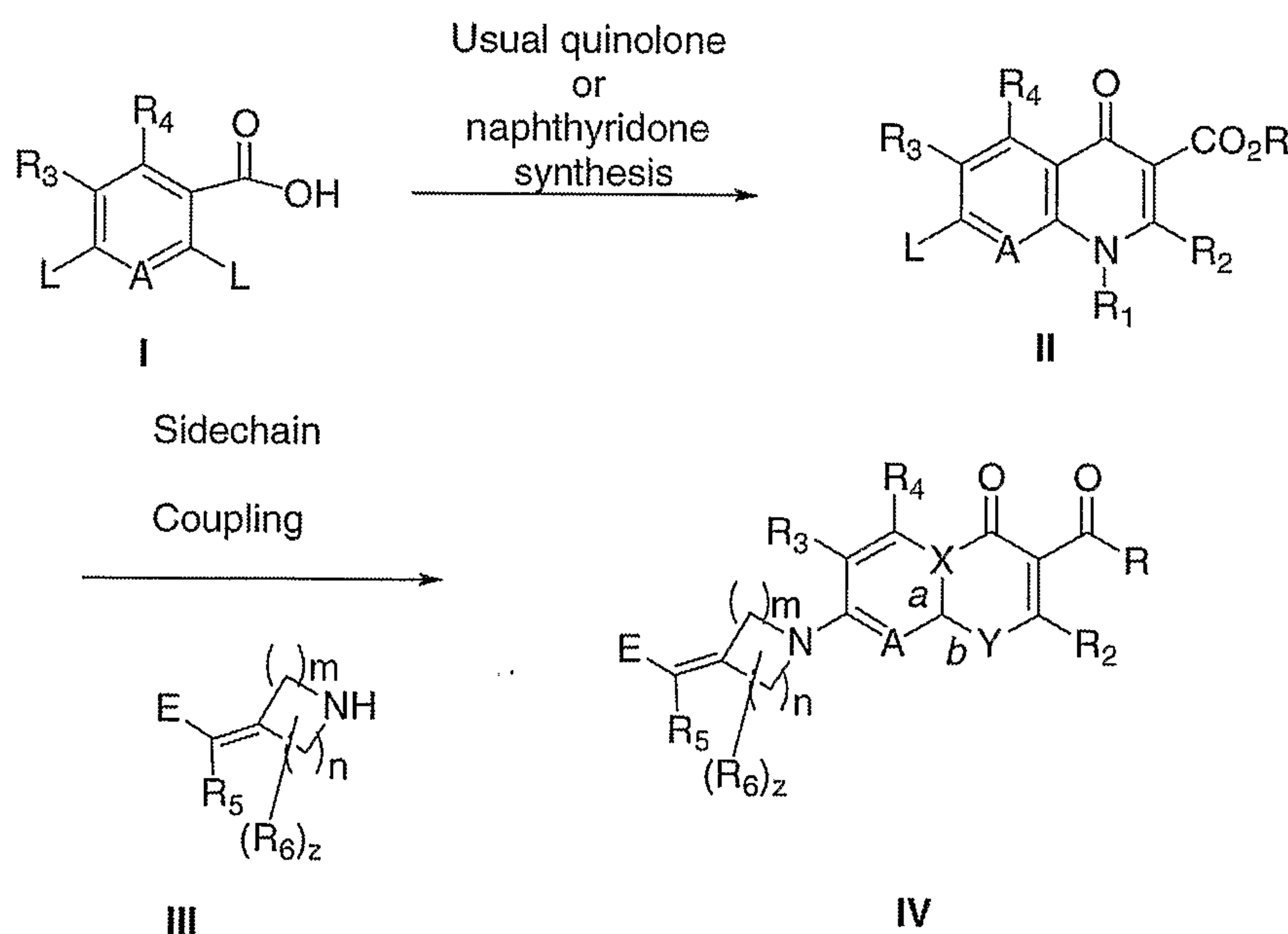
U.S. Patent 6329391, European Patent Publication 342849, International Patent Publication WO9711068, European Patent Publication 195316, European Patent Publication 1031569, U.S. Patent 6025370, European Patent Publication 153828, European Patent Publication 191451, European Patent Publication 153163, 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

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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.

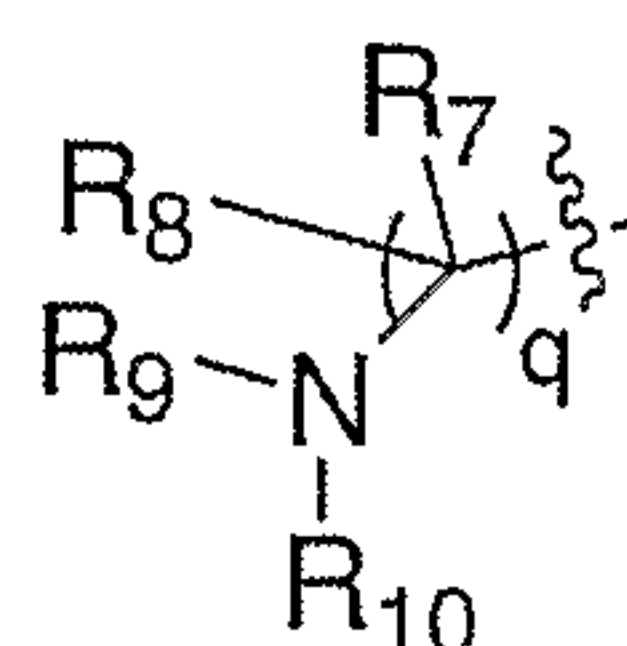
The compounds of the subject invention may be prepared in several ways. Versatile methodologies for preparation of the compounds of the invention are shown in Scheme I below, where L is a leaving group such as fluoro or chloro:

Scheme I



15

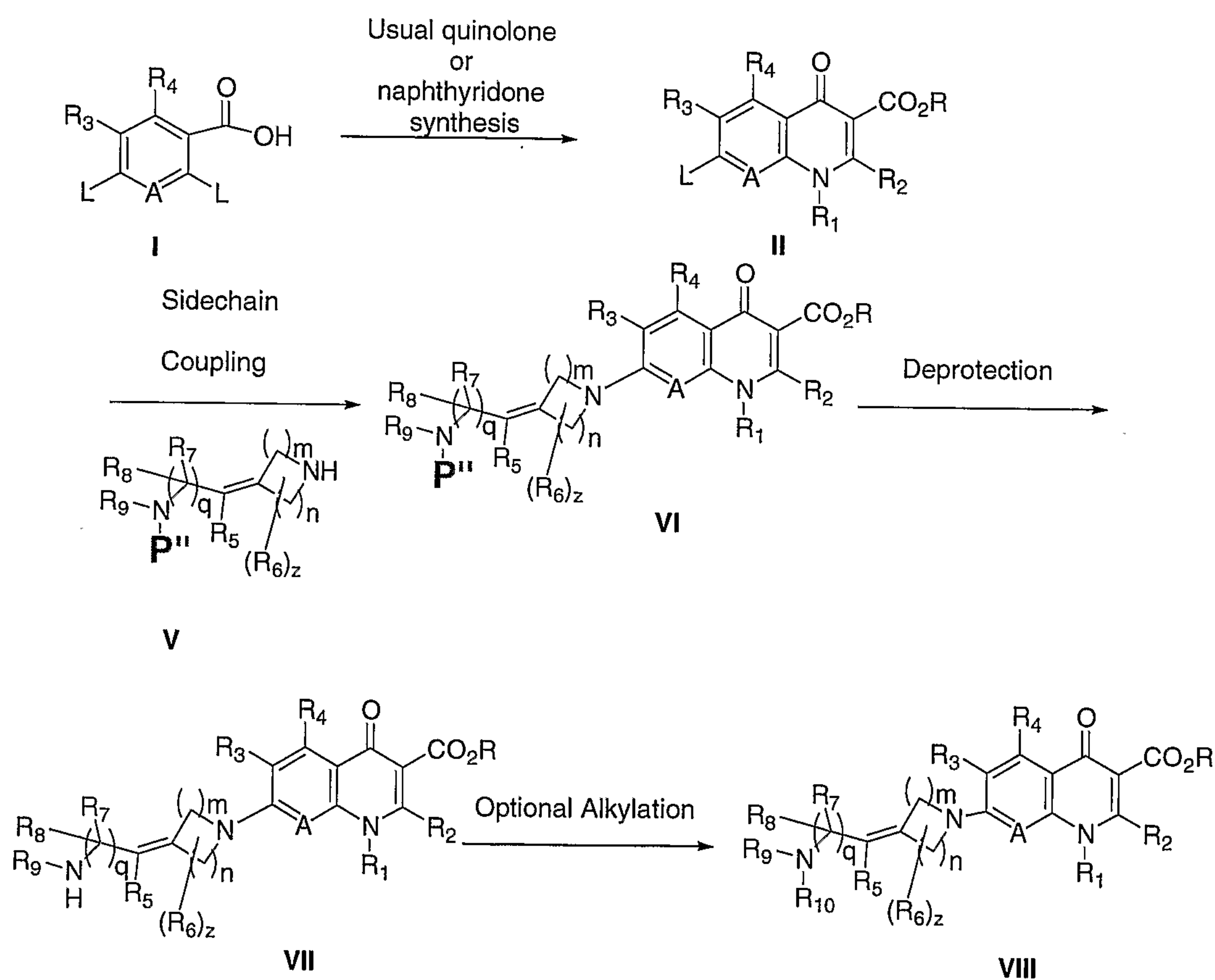
In the case where E is



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

11). In such case, standard amine protecting groups known to those skilled in the art, such as t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), benzyl (Bn), 9-fluorenylmethoxycarbonyl (Fmoc), allyloxycarbonyl (Alloc), 2-trimethylsilylethoxycarbonyl (Teoc), N-formyl, N-acetyl, N-benzoyl, or
 5 phthalimide, may be used to mask the terminal amine, as in compound **V**. Following sidechain 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**.

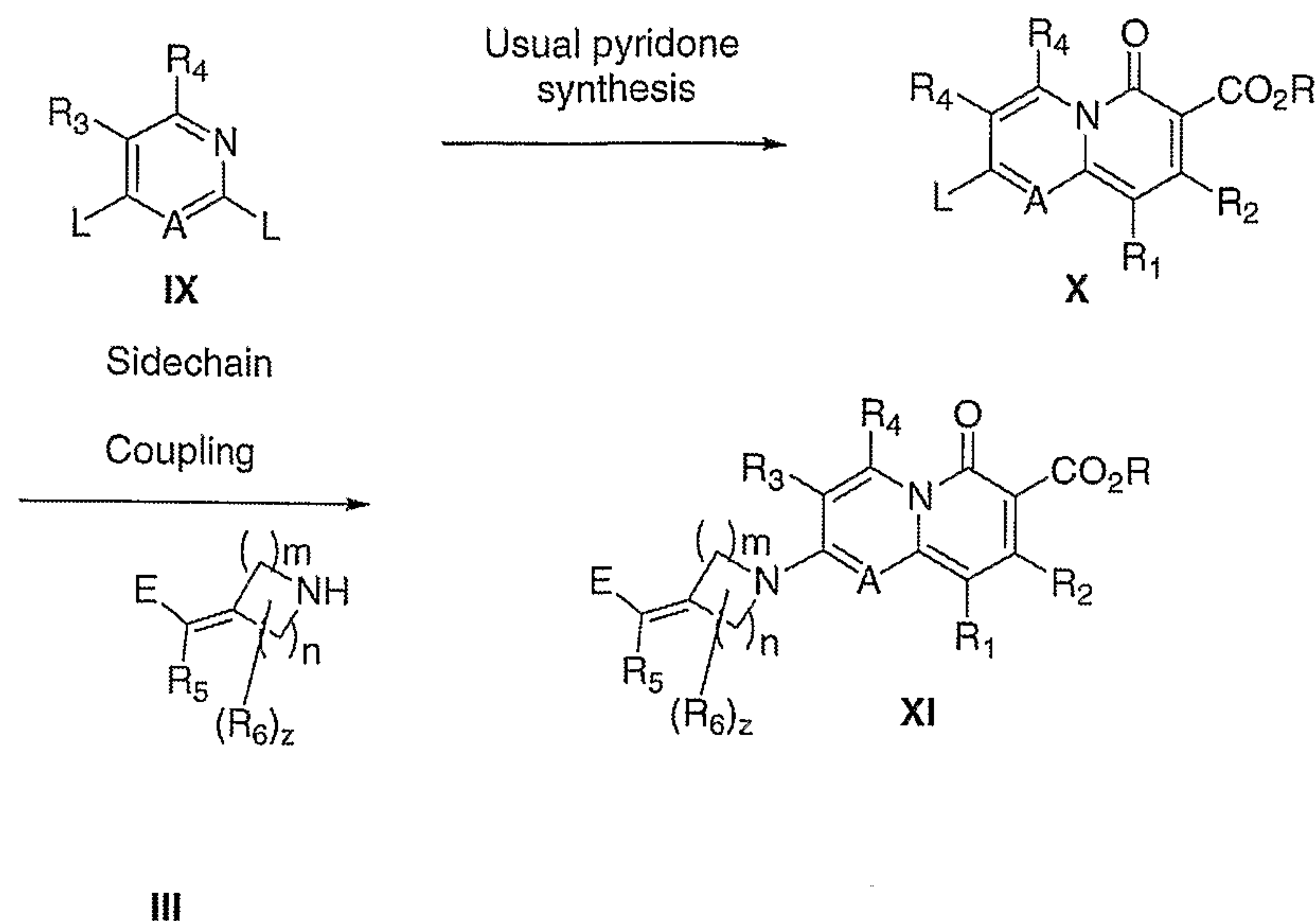
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Scheme II

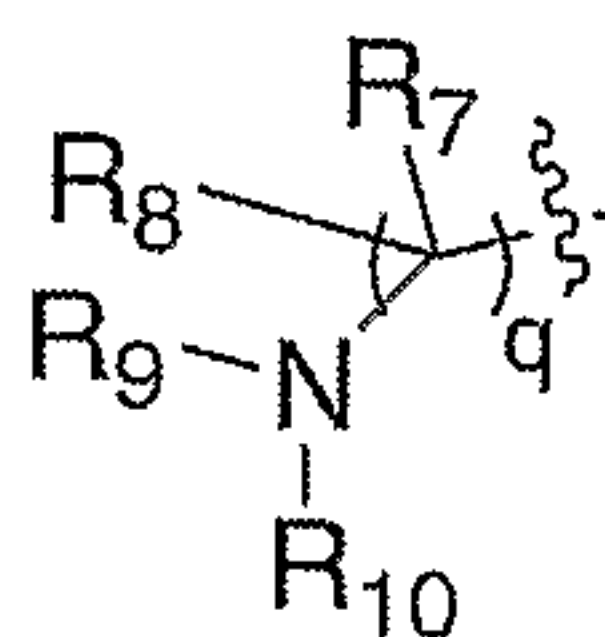
P'' = protecting group

Methodologies for providing the compounds of the invention where X is N and Y is C(R₁) are shown in Scheme III below:

Scheme III



5 As before, where E is

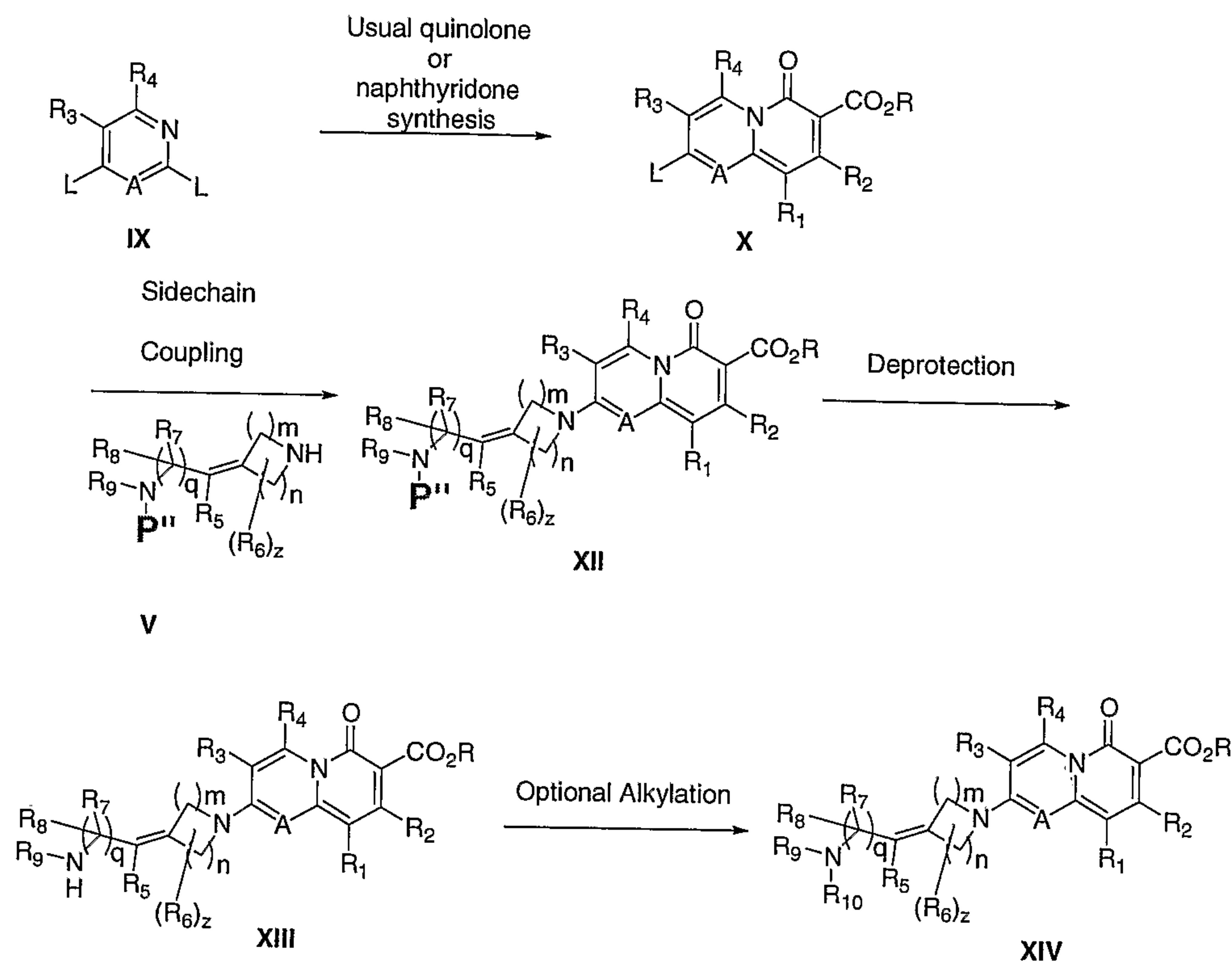


and at least one of R₉ and R₁₀ is hydrogen, it may be necessary to protect the terminal nitrogen to effect selective conversion to the desired product (Scheme IV). In such case, standard amine protecting groups known to those skilled in the art, such as *t*-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), 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



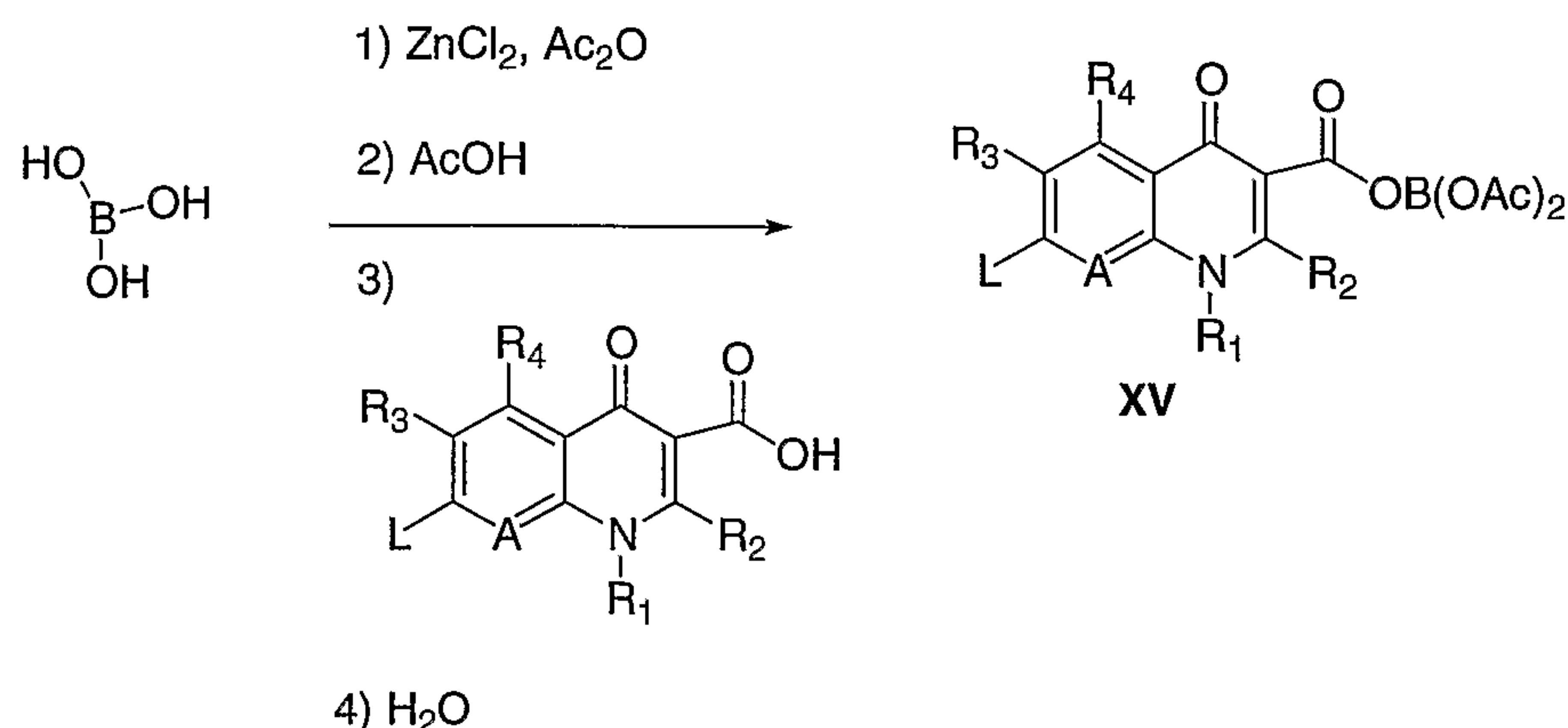
P'' = protecting group

5

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(R₁₁), wherein R₁₁ 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

quinolinyllborate (**XV**) is isolated by filtration after removal of the solvent. Scheme V illustrates this preferred method of activation.

Scheme V



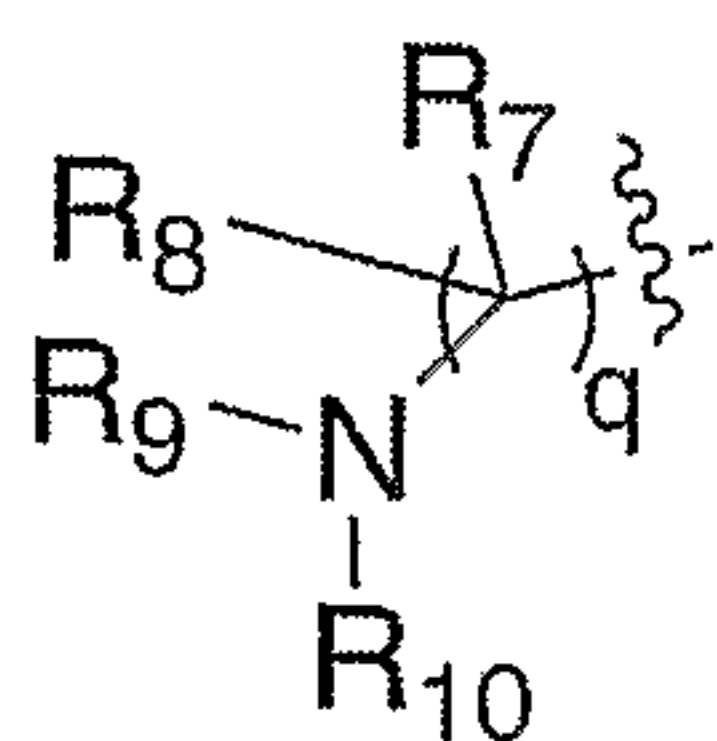
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Precursor Preparation – Side chain amine III

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

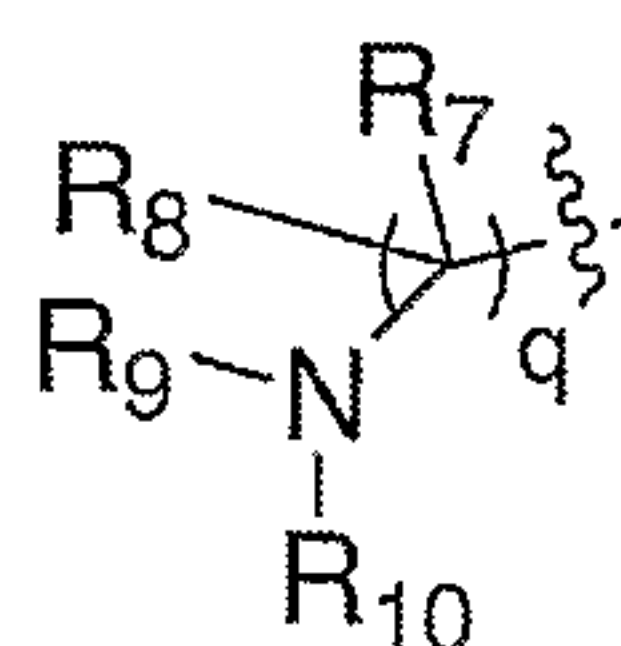
is

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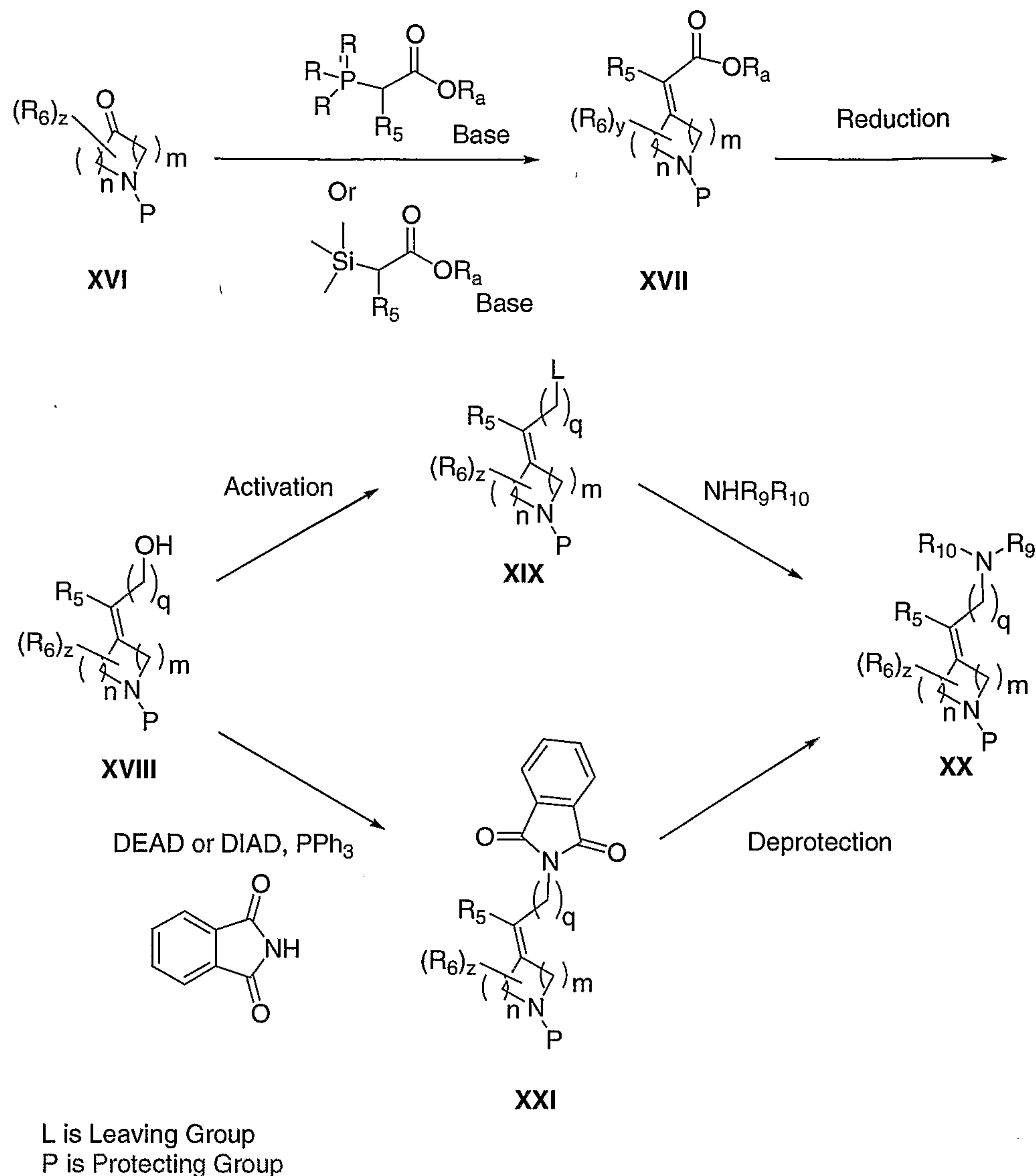
R_7 and R_8 are hydrogen, and q is 1. The trisubstituted or tetrasubstituted alkylidenes **XX** can be prepared by a Peterson, Wittig or Wadsworth-Horner-Emmons olefination of an appropriately substituted ketone (**XVI**) in a solvent such as, but not limited to, tetrahydrofuran, dimethylsulfoxide, or 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
 5 protecting group, P, under standard conditions known to those skilled in the art affords amine **III**, wherein E is

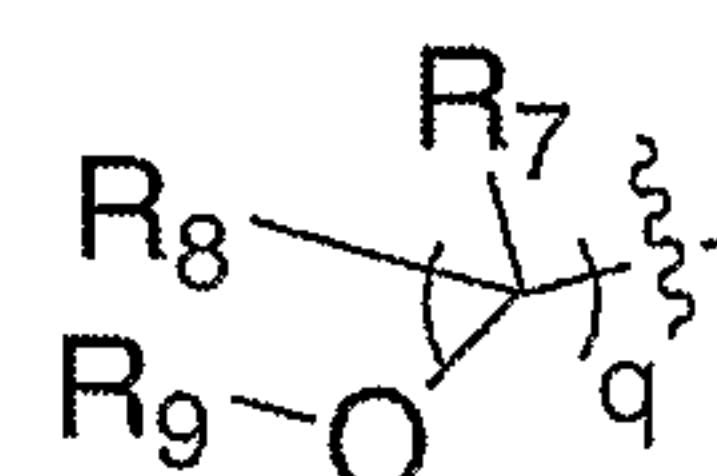


10 R₇ and R₈ are hydrogen, and q is 1. Alternatively, direct replacement of the alcohol **XVIII** can be accomplished via a Mitsunobu reaction with phthalimide and dialkyl azodicarboxylate to afford **XXI**. Deprotection of the phthalimide (**XXI**) with hydrazine in a solvent such as methanol or ethanol affords the
 15 amine (**XX**), wherein R₉ and R₁₀ are hydrogen. 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 R₇ and R₈ are hydrogen and R₉ and P" together with the nitrogen to which they are attached form a phthalimide group.

Scheme VI

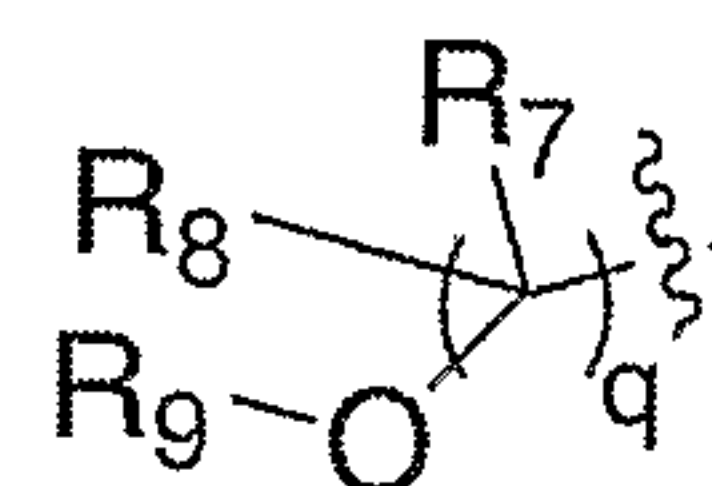


Scheme XXII illustrates the conversion of alcohols of formula XVIII to compounds of formula III, wherein E is alkenyl (LVIII). In addition, the Scheme outlines the synthesis of compounds of formula III, wherein E is

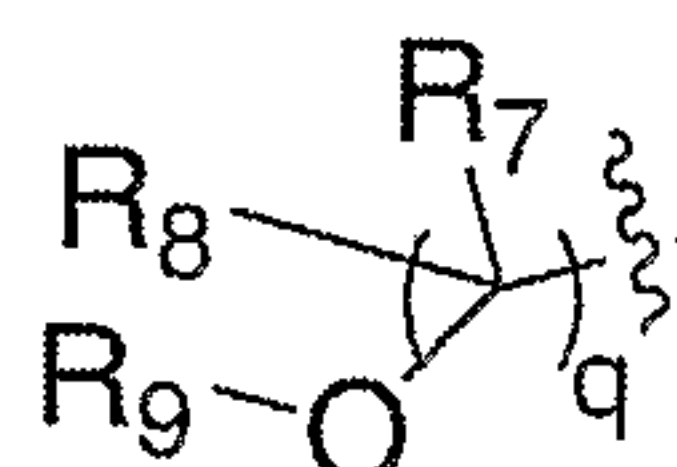


R_7 and R_8 are hydrogen and R_9 is acyl, alkoxycarbonyl, or sulfonyl (LX). Oxidation of alcohol XVIII with any of a number of suitable oxidizing agents, such as Dess-Martin periodinane, the Corey-Kim reagent, or the Swern reagent, affords the corresponding aldehyde (LVI). The aldehyde may be

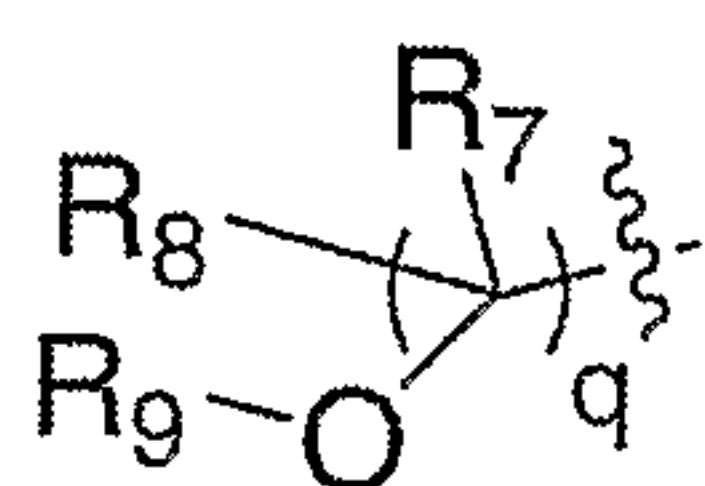
subjected to a base promoted olefination reaction, such as, but not limited to, the Wittig reaction to give **LVII**, wherein R_c is hydrogen or alkyl. Removal of the protecting group, P, from **LVII** under standard conditions known to those skilled in the art affords amine **III**, wherein E is alkenyl (**LVIII**). Scheme XX also illustrates the conversion of alcohols of formula **XVIII** to compounds of formula **III**, wherein E is



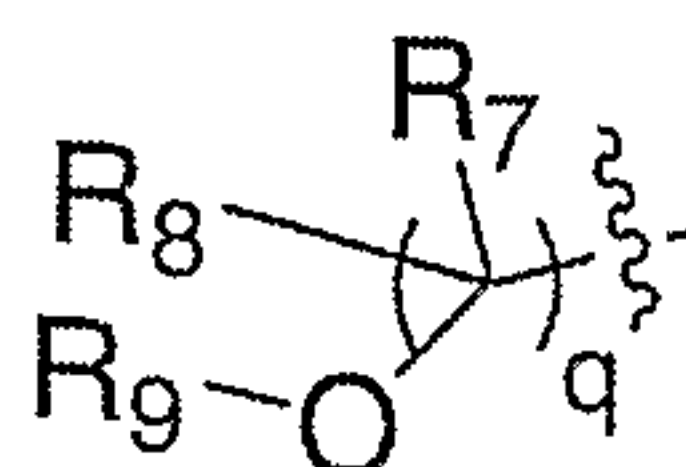
R_7 and R_8 are hydrogen, and R_9 is acyl, alkoxycarbonyl, or sulfonyl (**LX**). Reaction of alcohol **XVIII** with an acylating agent in the presence of an amine base, such as pyridine, in an inert solvent such as dichloromethane, tetrahydrofuran or toluene at temperatures ranging from -20°C to 60°C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

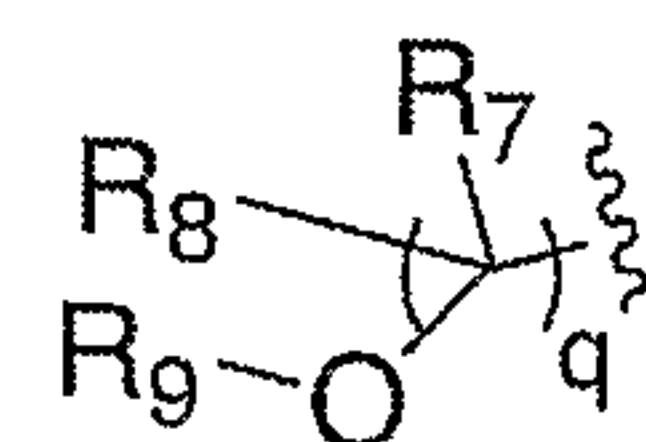


R_7 and R_8 are hydrogen and R_9 is alkoxycarbonyl (**LIX**) by reaction with a carbonylating agent in the presence of an amine base, such as pyridine, in an inert solvent such as dichloromethane, tetrahydrofuran or toluene at temperatures ranging from -20°C to 60°C for from 1-48 hours. Carbonylating 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.

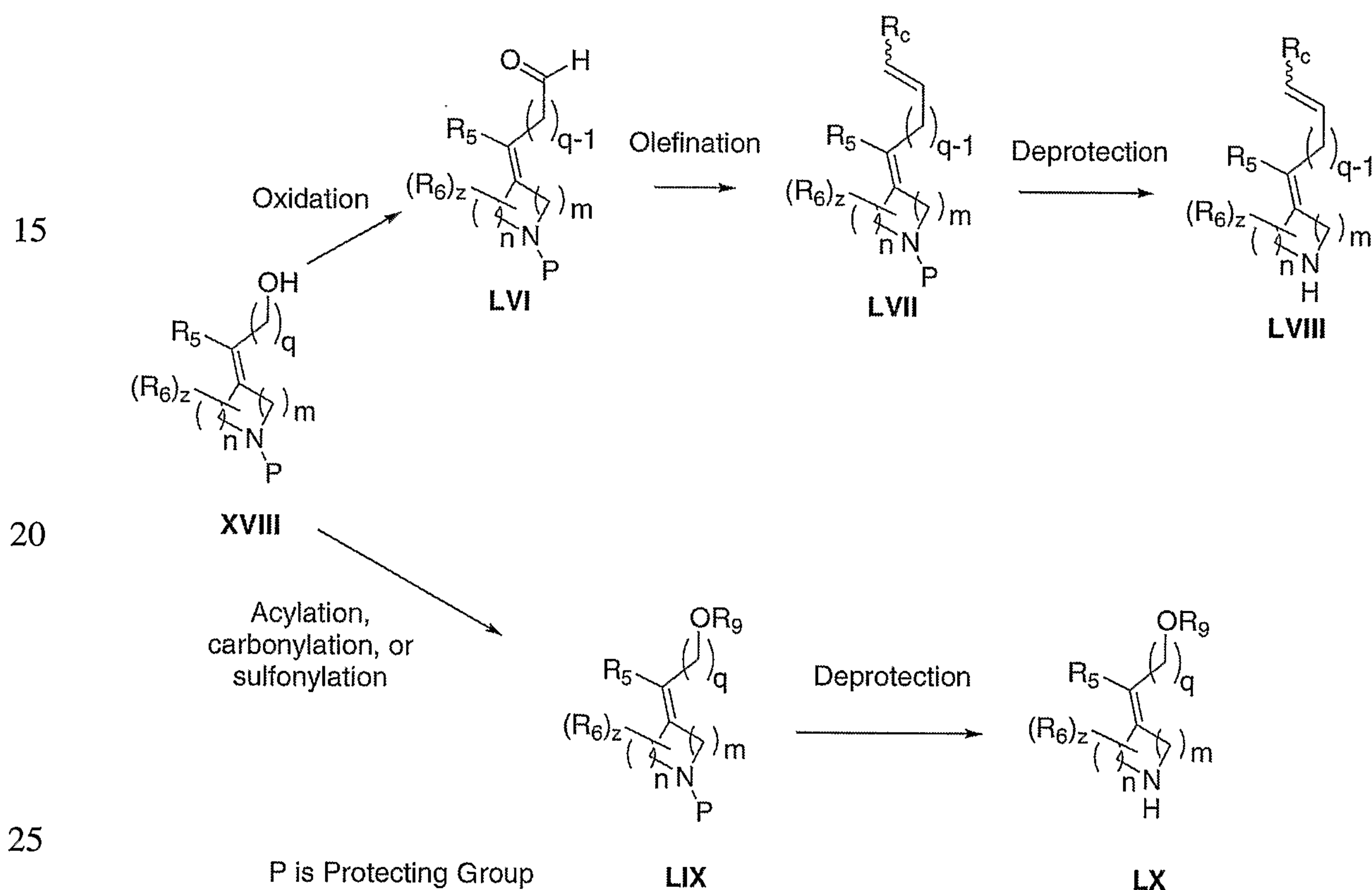
- 5 Removal of the protecting group, P, from **LIX** under standard conditions known to those skilled in the art affords amine **III**, wherein E is



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

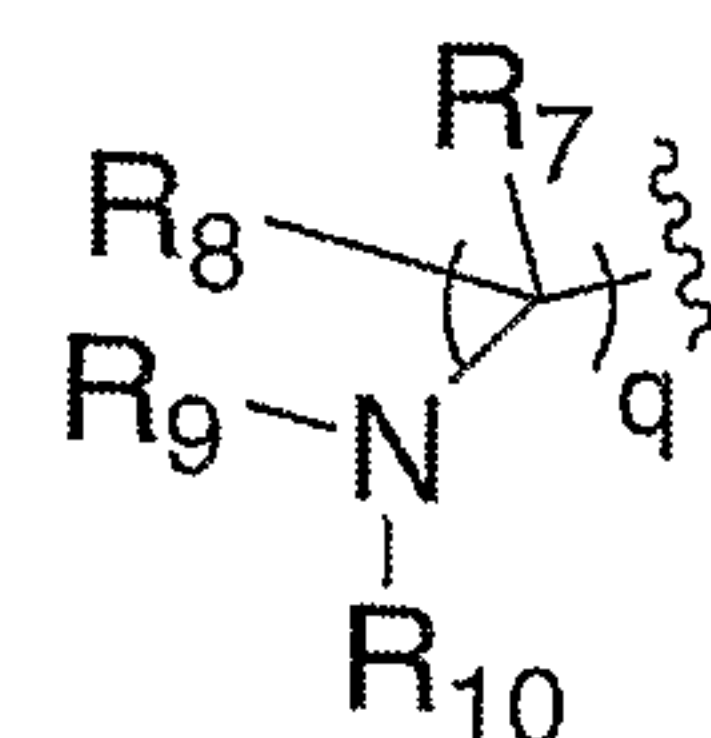
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Scheme XXII



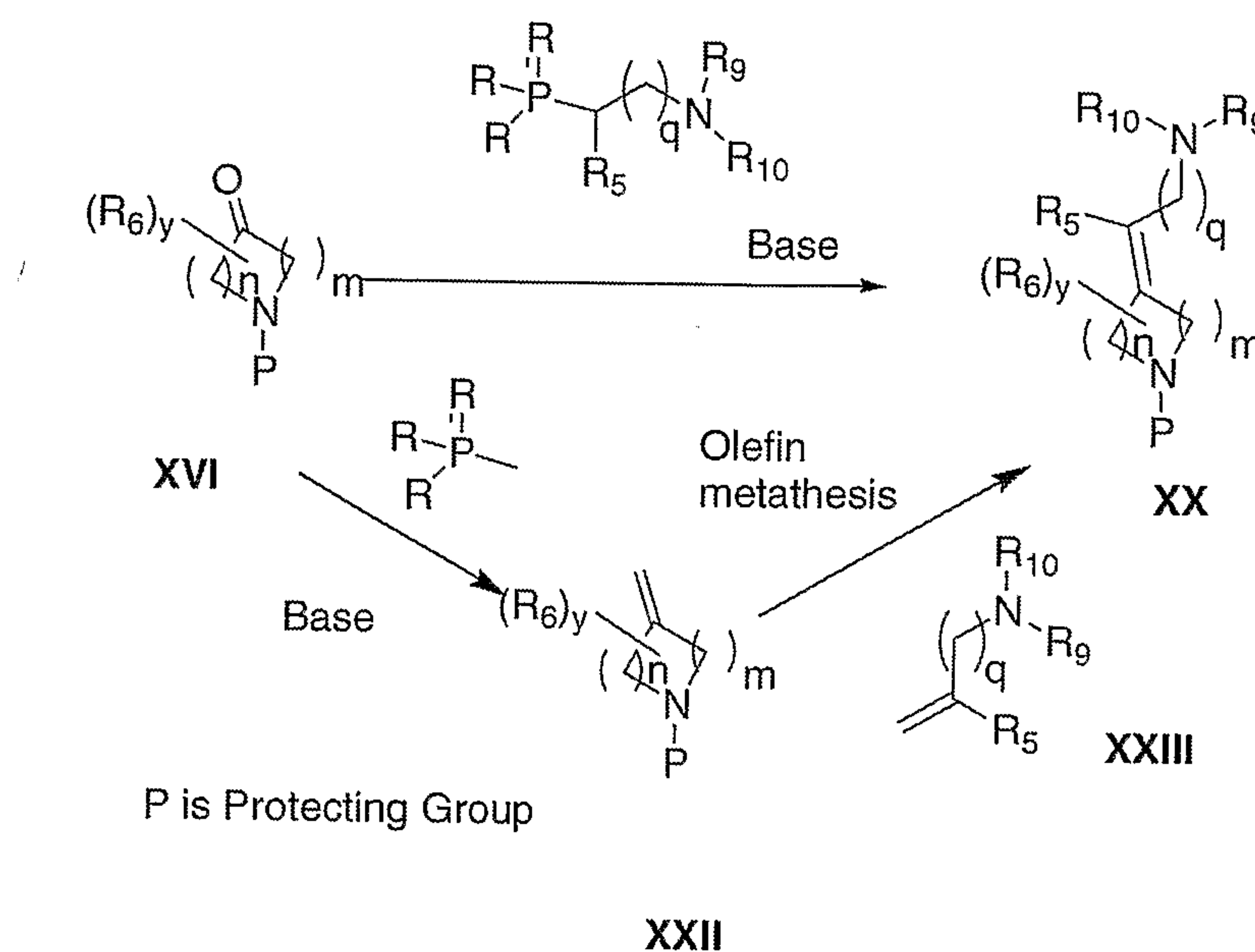
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- Scheme VII illustrates a direct conversion of ketone **XVI** to olefin **XX** using a base promoted olefination reaction such as, but not limited to, the Wittig, Wadsworth-Horner-Emmons, or Peterson olefination procedures.
- 30 Alternatively, amine **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



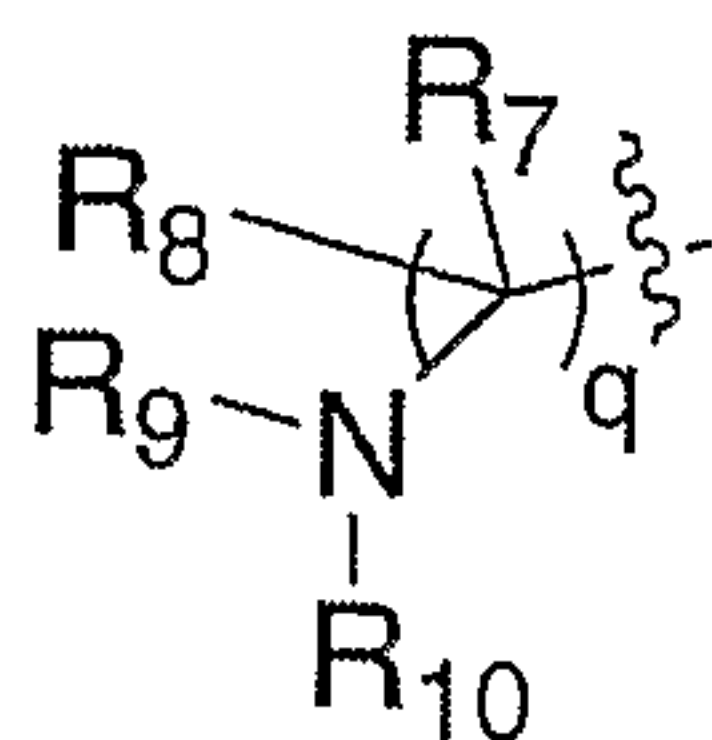
5 and R_7 and R_8 are hydrogen.

Scheme VII



10 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

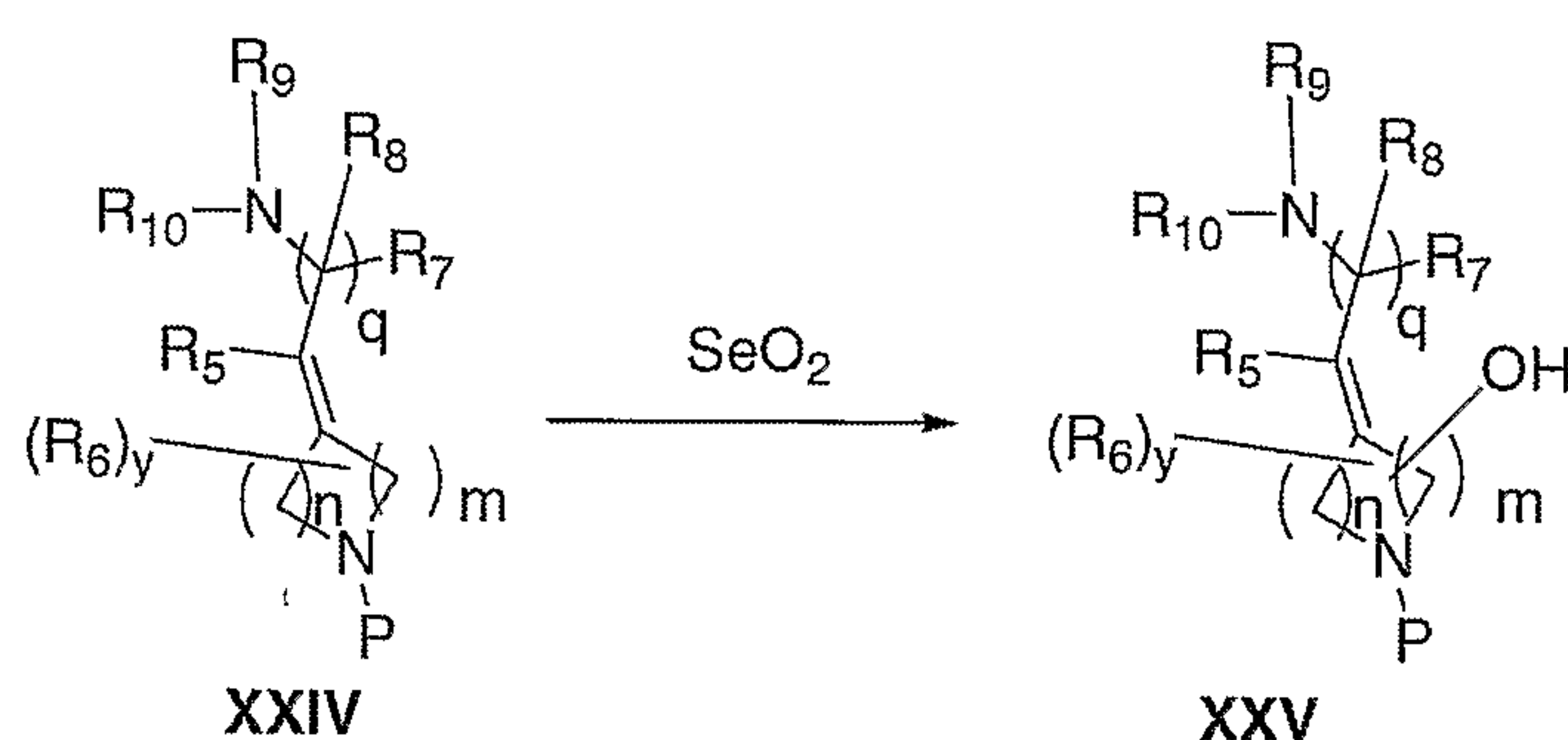
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and one of R_6 is hydroxy.

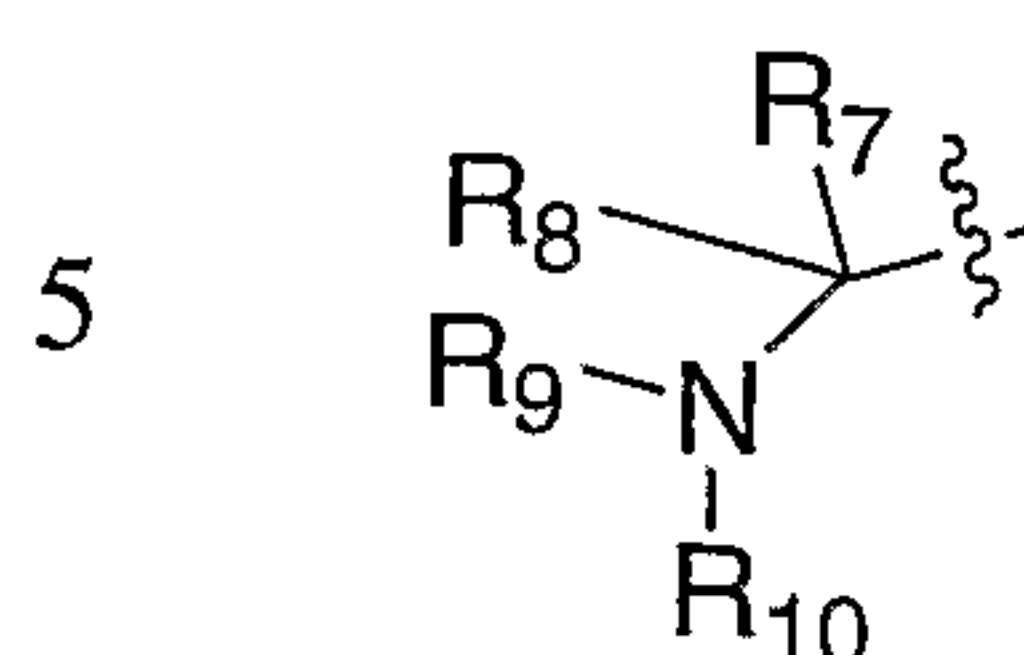
Scheme VIII



P is Protecting Group

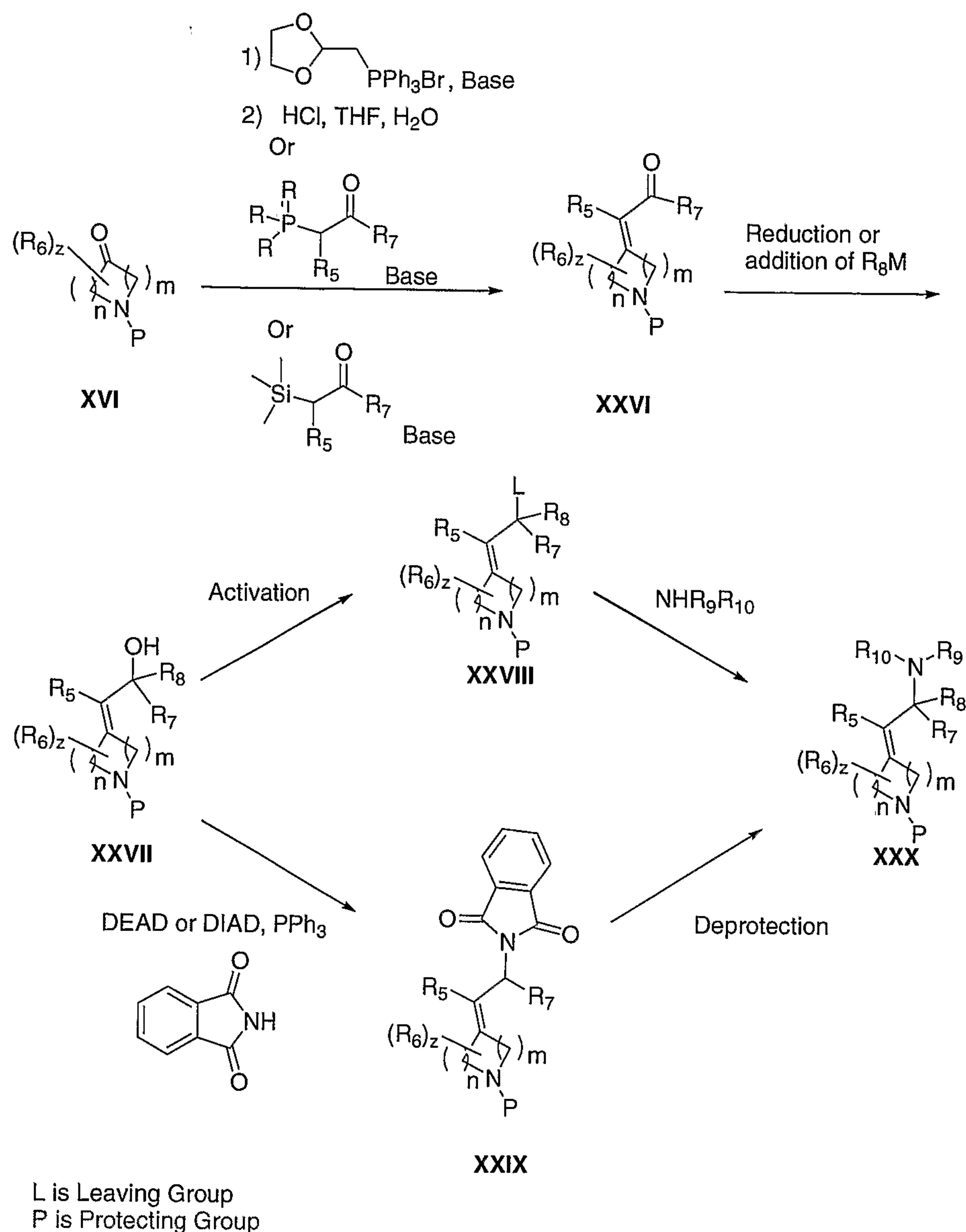
Scheme IX illustrates the preparation of α,β -unsaturated carbonyl compound **XXVI**, where R_7 is as defined previously, using a Peterson, Wittig or Wadsworth-Horner-Emmons olefination procedure of an appropriately substituted ketone (**XVI**) in a solvent such as, but not limited to, tetrahydrofuran, 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



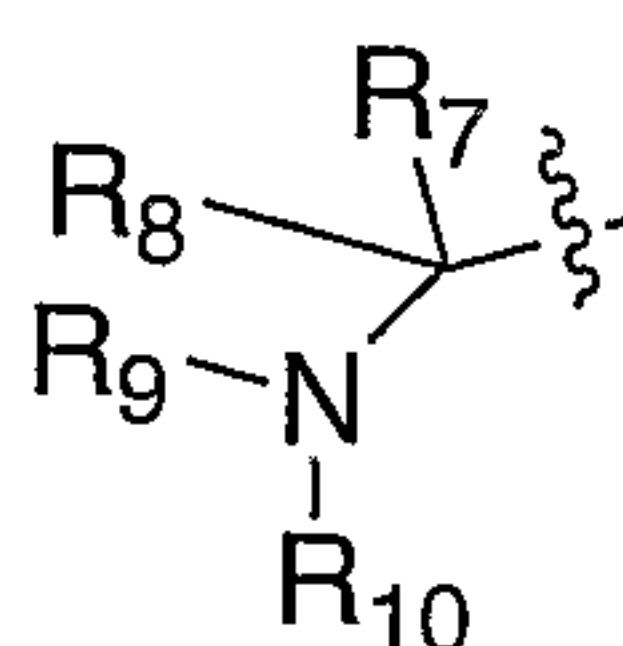
and one of R₇ and R₈ is hydrogen. Alternatively, where one of R₇ or R₈ is hydrogen, direct replacement of the alcohol **XXVII** can be accomplished via a Mitsunobu reaction with phthalimide and a dialkyl azodicarboxylate followed by deprotection of the phthalimide with hydrazine in a solvent such as 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 R₈ is hydrogen and R₉ and P" together with the nitrogen to which they are attached form a phthalimide group.

Scheme IX



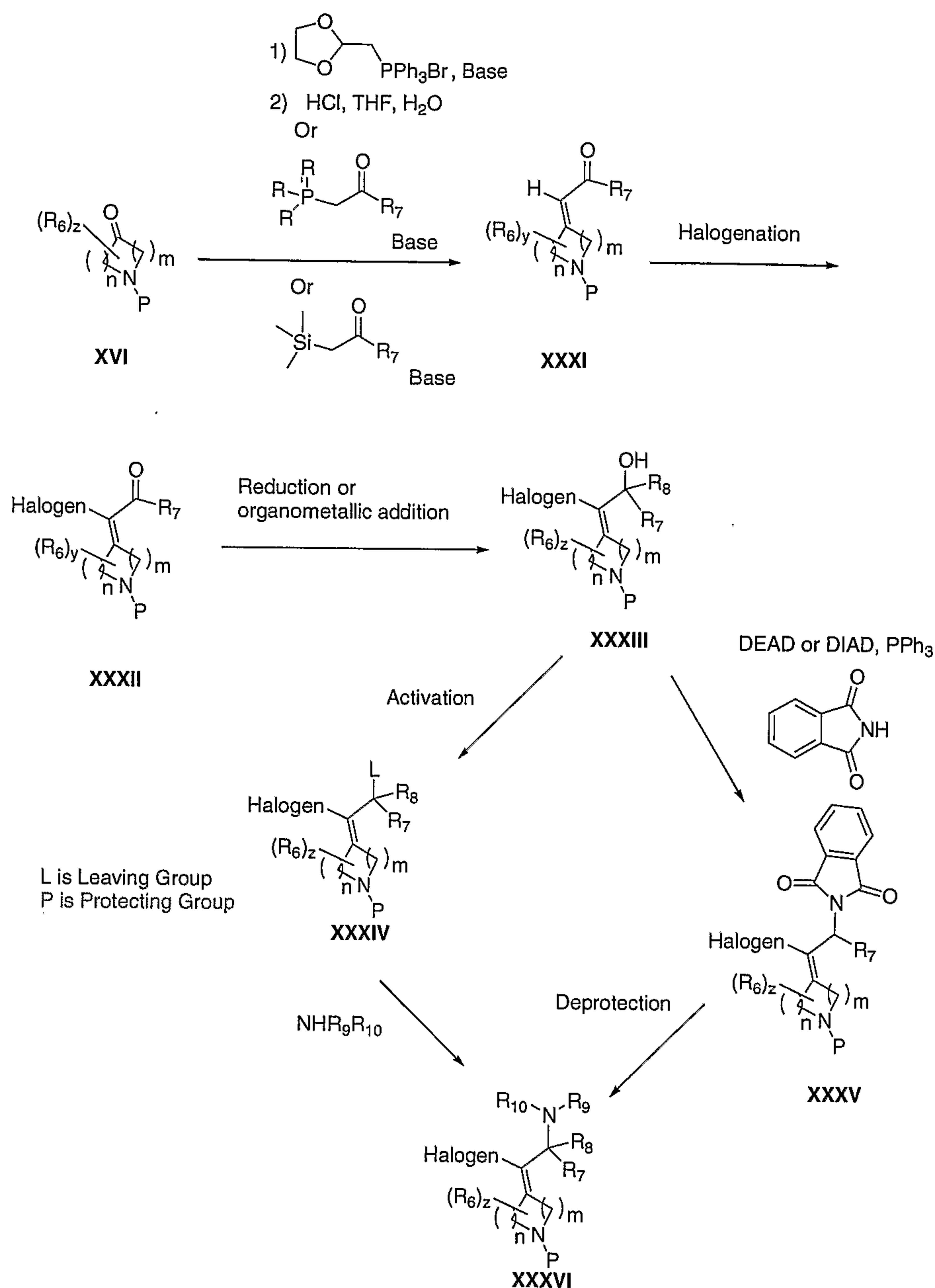
- Scheme X depicts the preparation of **XXXVI**, wherein R_5 is halogen.
- 5 Alkylidenes **XXXI**, wherein R_5 is hydrogen, can be halogenated with an appropriate halogenating agent such as, but not limited to, 1-bromo-2,5-pyrrolidinedione, 1,1,1-tris(acetyloxy)-1,1-dihydro-2-benziodoxol-3(1H)-one and a tetraalkylammonium bromide, or thionyl chloride to provide **XXXII**. Alkylidene **XXXII** can be reduced with a reducing agent such as, but not limited to,
- 10 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 R₈ 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 R₇ or R₈ 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



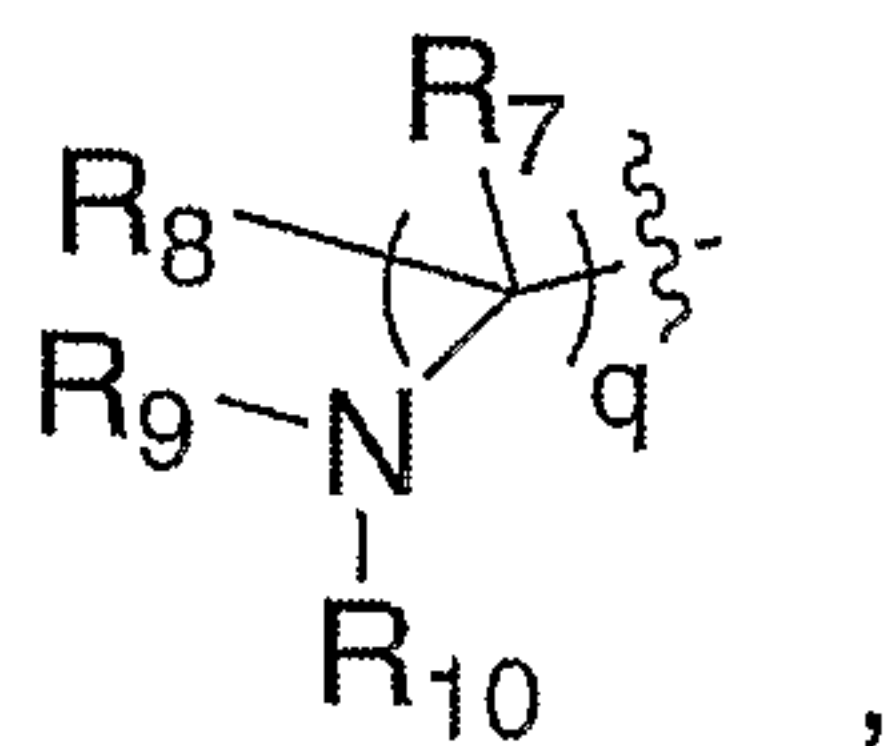
and one of R₇ and R₈ is hydrogen. Alternatively, where one of R₇ or R₈ is hydrogen, direct replacement of the alcohol **XXXIII** can be accomplished via a Mitsunobu reaction with phthalimide and a dialkyl azodicarboxylate followed by deprotection of the phthalimide with hydrazine in a solvent such as 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 R₈ is hydrogen and R₉ 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

5 is

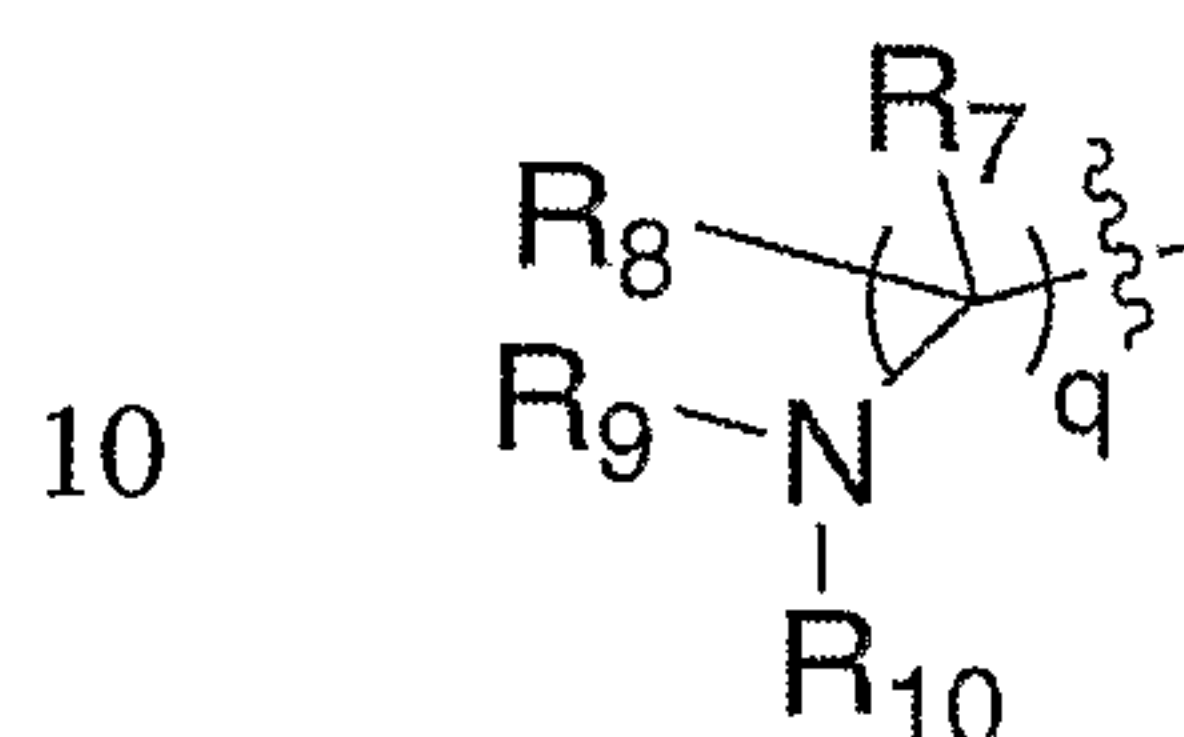


R_7 and R_8 are hydrogen and R_5 is substituted or branched-chain alkyl.

10 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 R_a 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

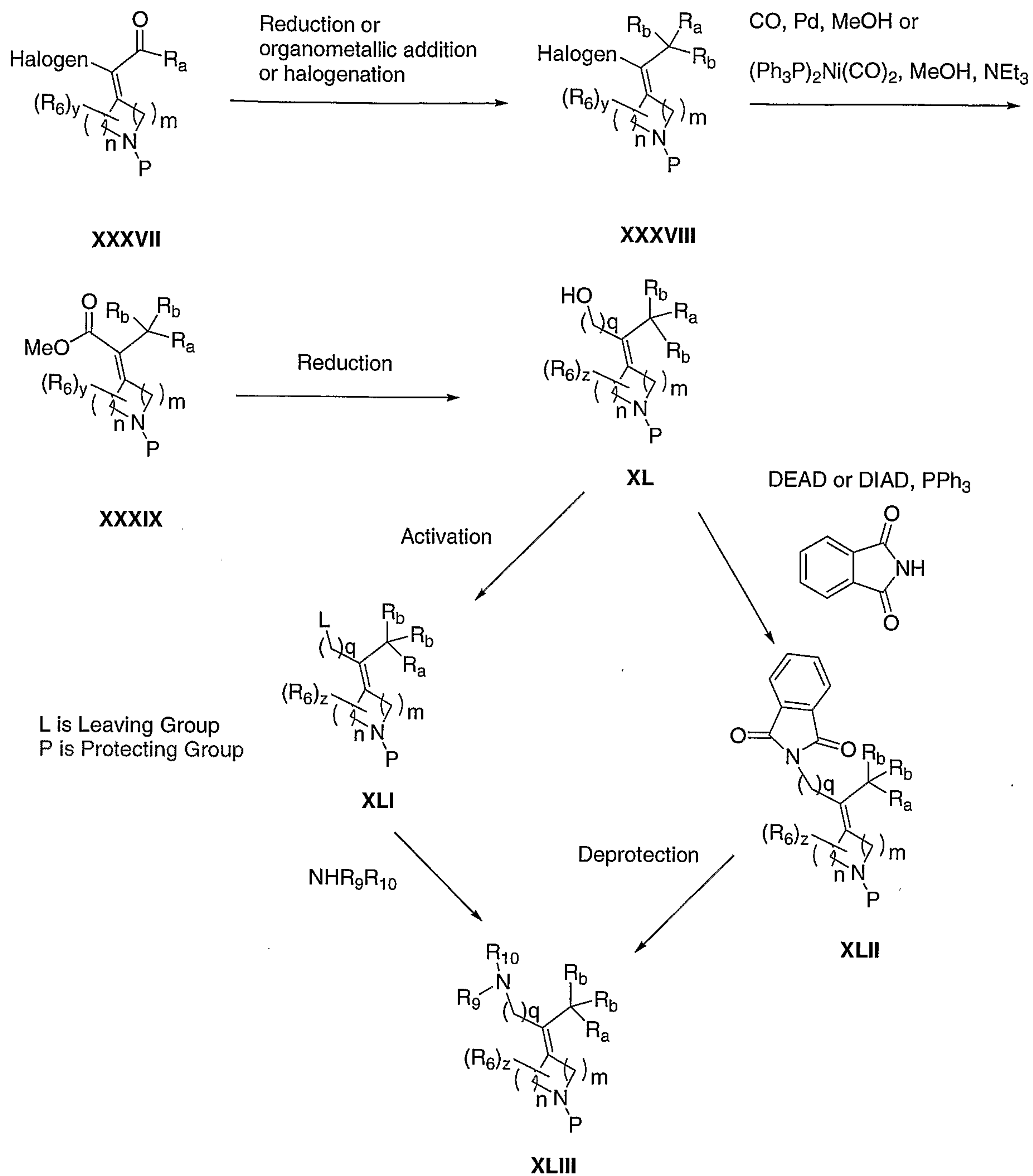
leaving group **XLI**, such as, but not limited to, bromide, mesylate or tosylate, under standard conditions and displacing the leaving group with an appropriately substituted amine in a solvent such as, but not limited to, dimethylformamide, dimethylsulfoxide, or tetrahydrofuran for from 1 to 24 h at 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



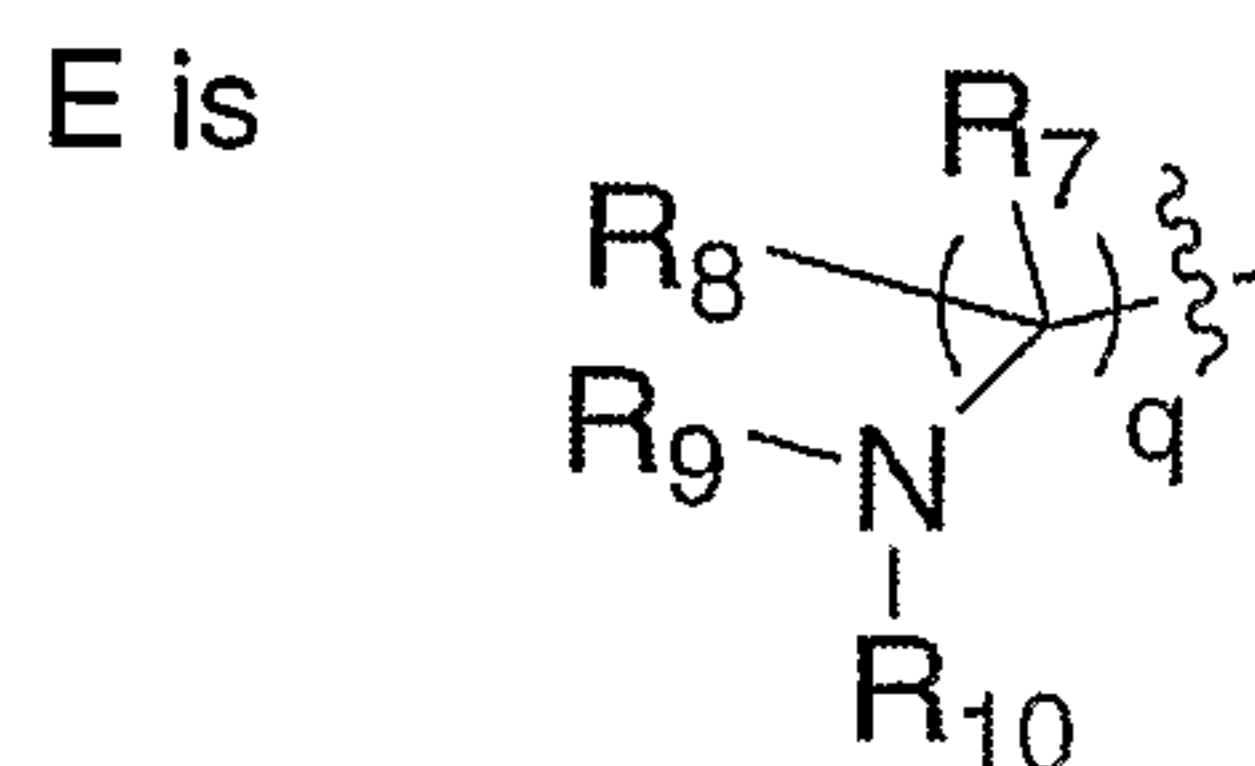
R₇ and R₈ are hydrogen and R₅ is CR_aR_aR_b. Alternatively, direct replacement of the alcohol **XL** may be accomplished via a Mitsunobu reaction with phthalimide and dialkyl azodicarboxylate to afford **XLII**. Deprotection of the phthalimide **XLII** with hydrazine in a solvent such as methanol or 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 R₇ and R₈ are hydrogen, R₉ and P" together with the nitrogen to which they are attached form a phthalimide group, and R₅ is CR_aR_aR_b.

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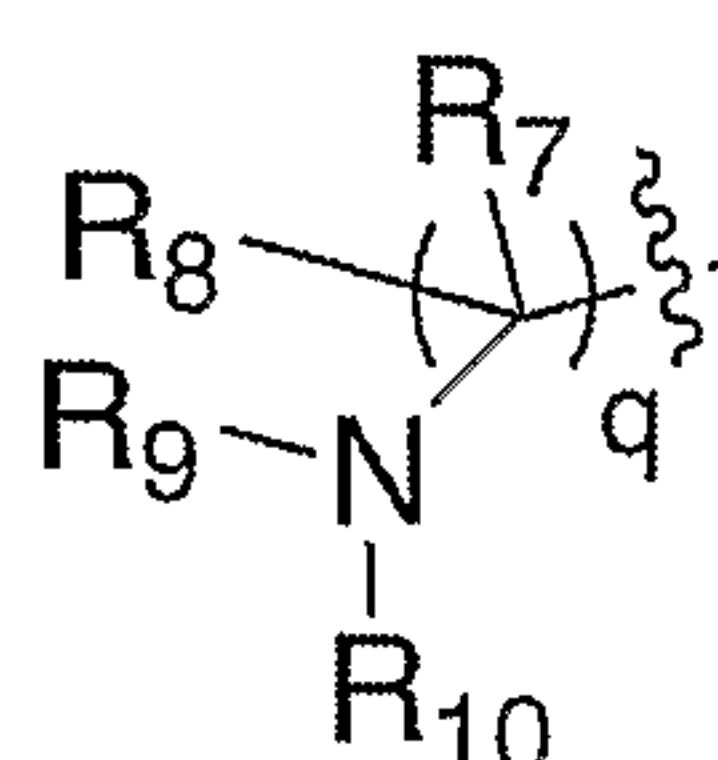
Scheme XI



Scheme XII illustrates the synthesis of the side chain amine III wherein

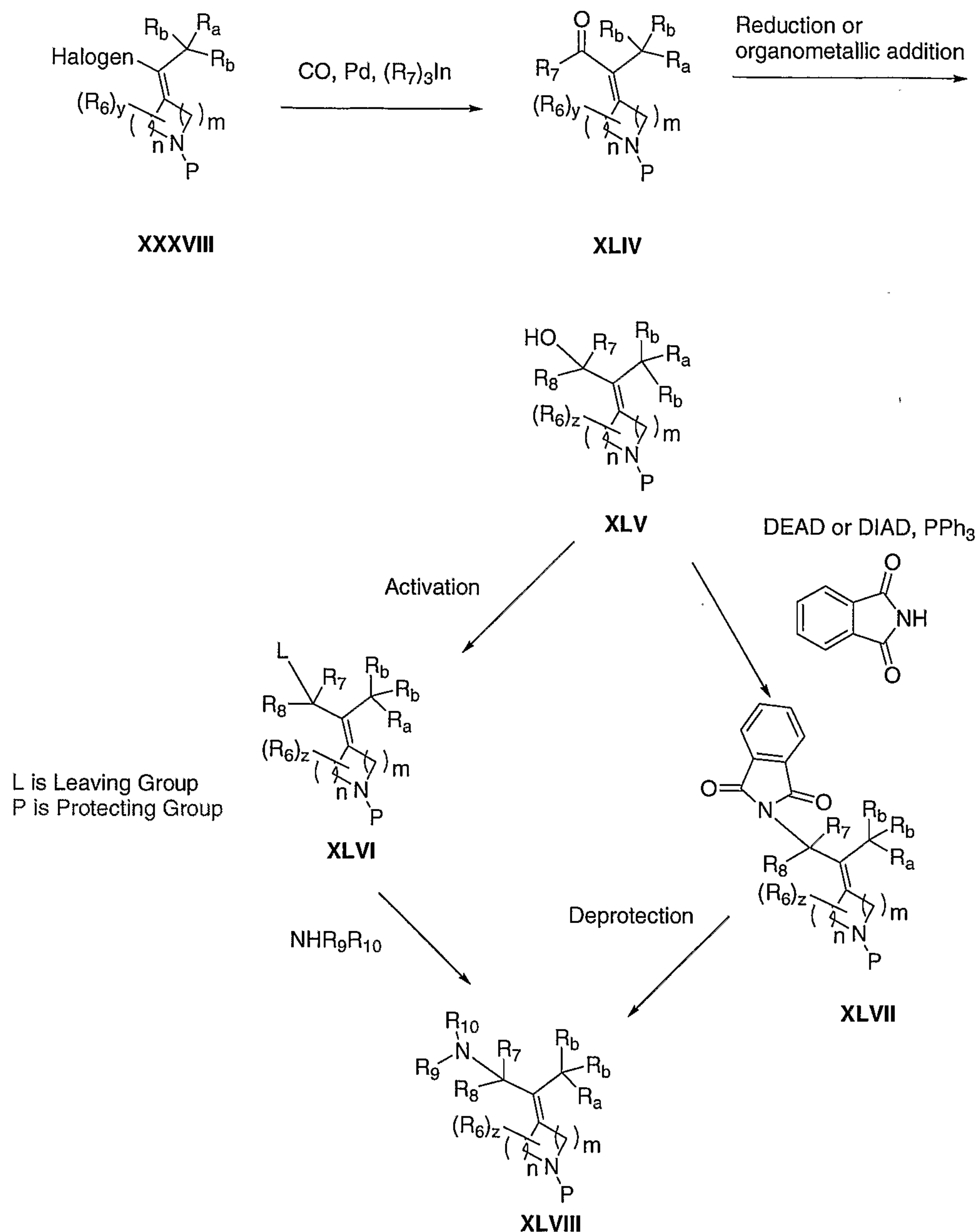


one of R_7 or R_8 is hydrogen and the other is alkyl, R_5 is substituted or branched-chain alkyl, and q is 1. Compound **XXXVIII**, prepared as described above, may be carbonylated in the presence of a transition metal catalyst, such as but not limited to palladium acetate, dicarbonylbis(triphenylphosphine)nickel, 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 R₇ and R₈ is hydrogen and the other is alkyl, R₅ is substituted or branched-chain alkyl, and q is 1. Alternatively, where one of R₇ or R₈ is hydrogen, direct replacement of the alcohol **XLV** can be accomplished via a Mitsunobu reaction with phthalimide and a dialkyl azodicarboxylate followed by
5 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 R₇ and R₈ is hydrogen and the other is alkyl, R₉ and P" together with the nitrogen to which they are attached form a phthalimide
10 group, R₅ is substituted or branched-chain alkyl, and q is 1.

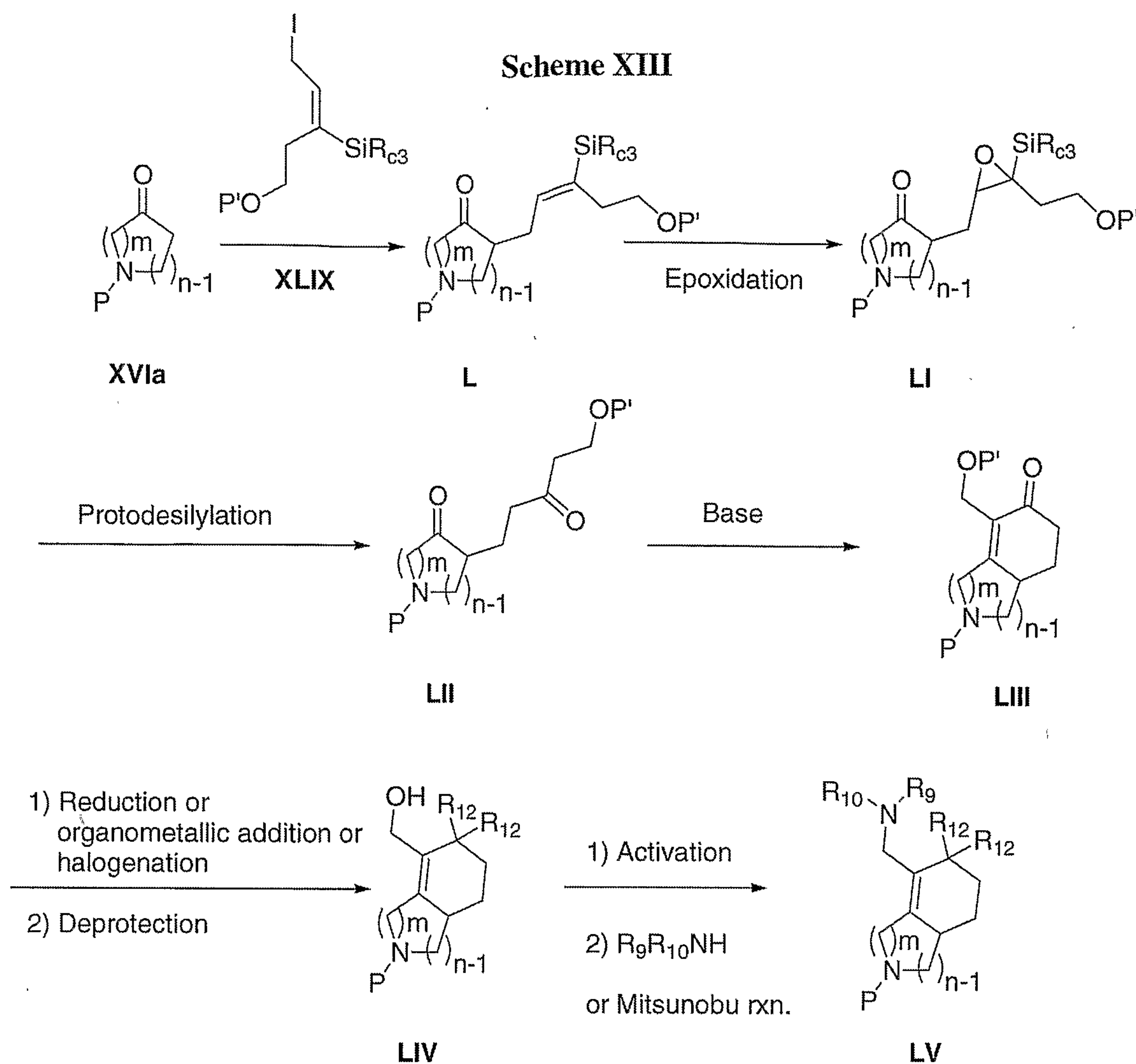
Scheme XII



Scheme XIII illustrates the conversion of ketone **XVla** to olefin **LIII** using a base promoted Stork-Jung vinylsilane Robinson annulation protocol (Tetrahedron Letters, **2001**, 42, 9123). Condensation of ketone **XVla** 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

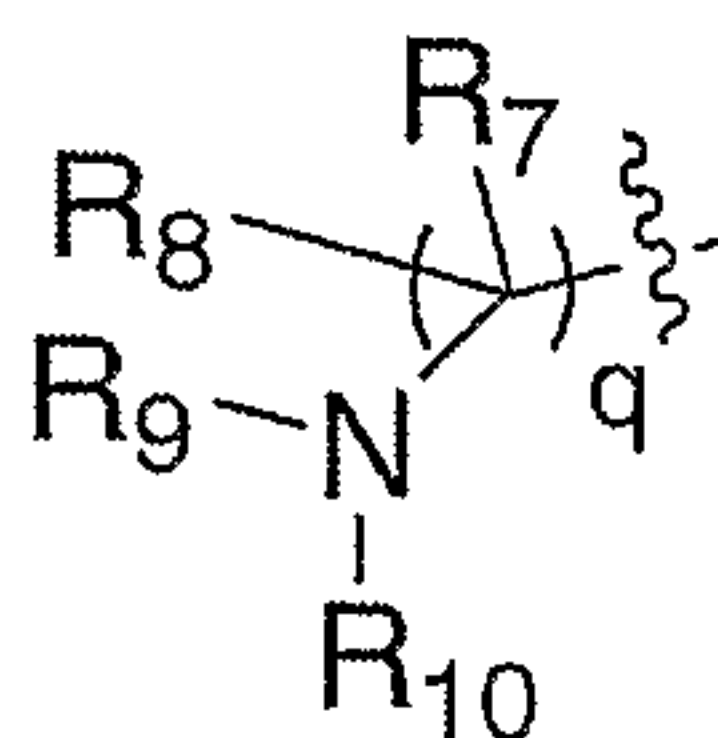
LI with agents such as, but not limited to, tetra-n-butylammonium fluoride or pyridinium poly(hydrogen fluoride) and aqueous acid, with concomitant epoxide ring opening affords ketone **LII**. Ring annulation of **LII** may be accomplished by treatment of **LII** with a base, such as but not limited 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



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



R₇ and R₈ are hydrogen, and R₅ and R₆ 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 R₉ and R₁₀ are hydrogen.

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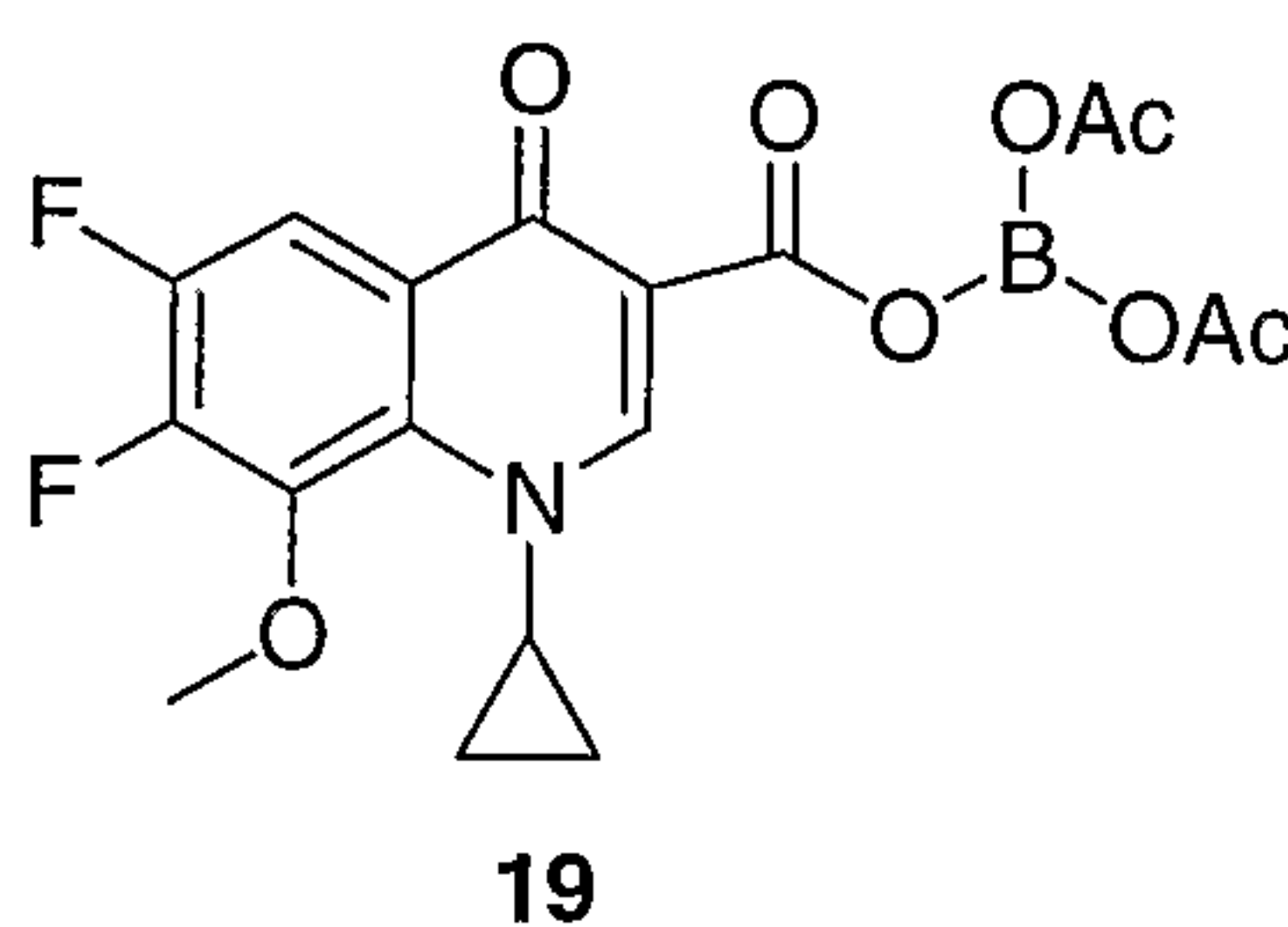
Experimental Section

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 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.

25

Precursor Preparation A - Preparation of Diacyl Quinoliny Borates



Compound 19 (Formula XV: L = F, A = C-OMe, R₁ = Cyclopropyl, R₂ = H, R₃ = F, R₄ = H)

5 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 10 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 15 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**).

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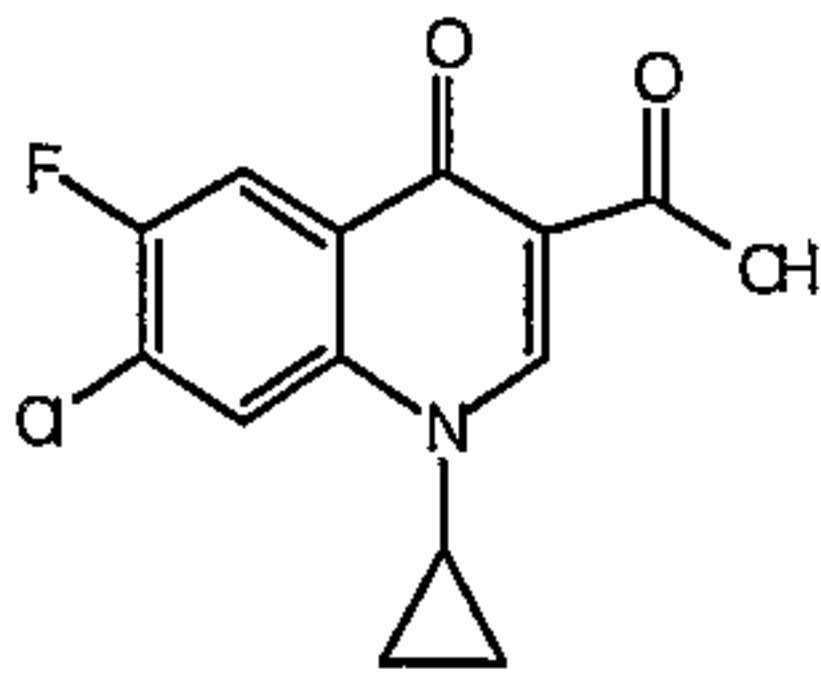
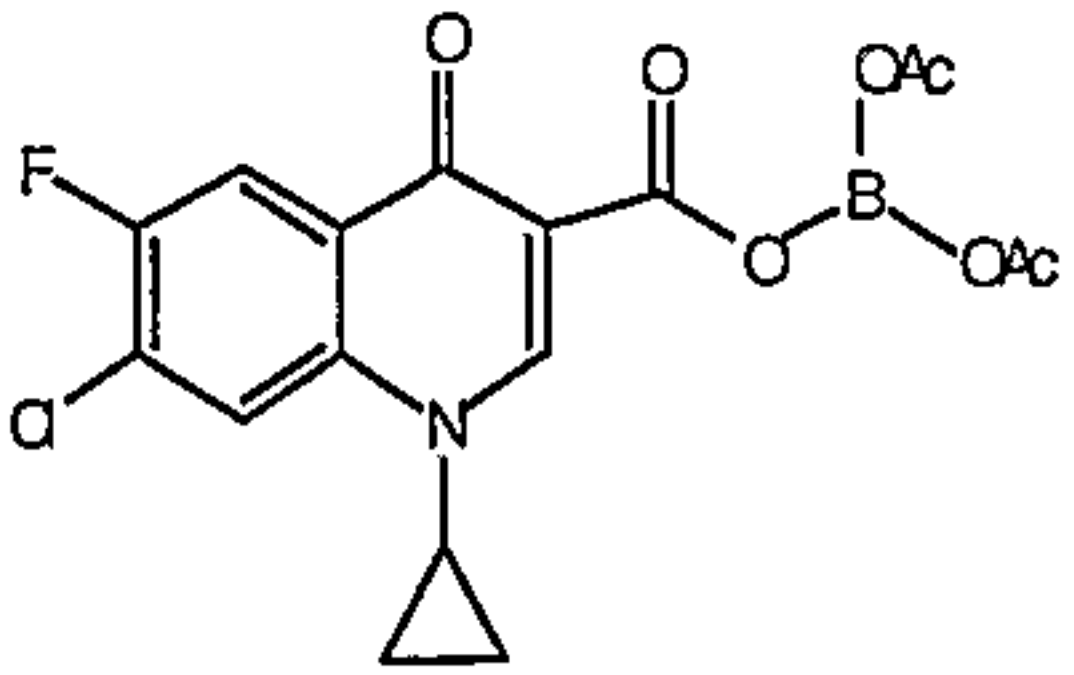
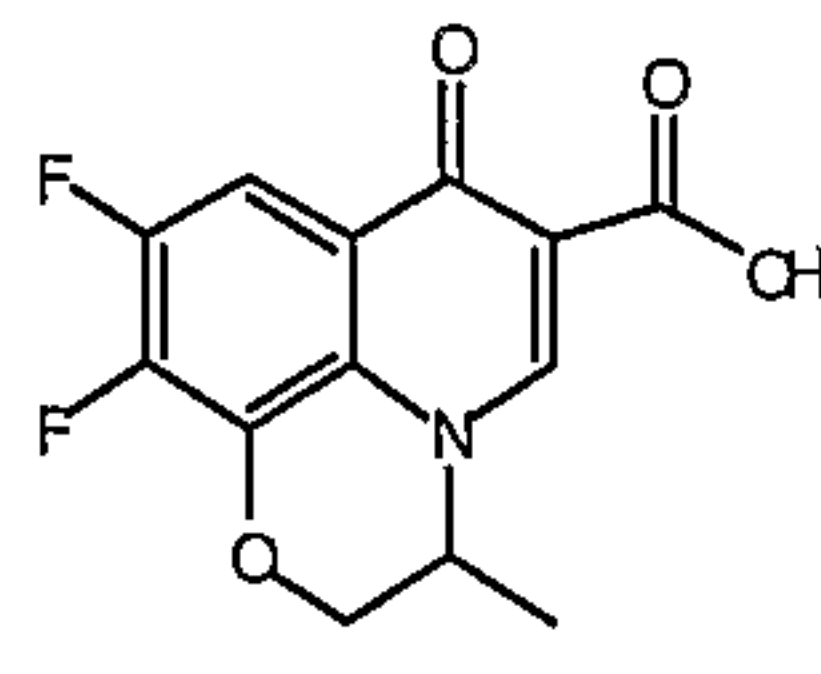
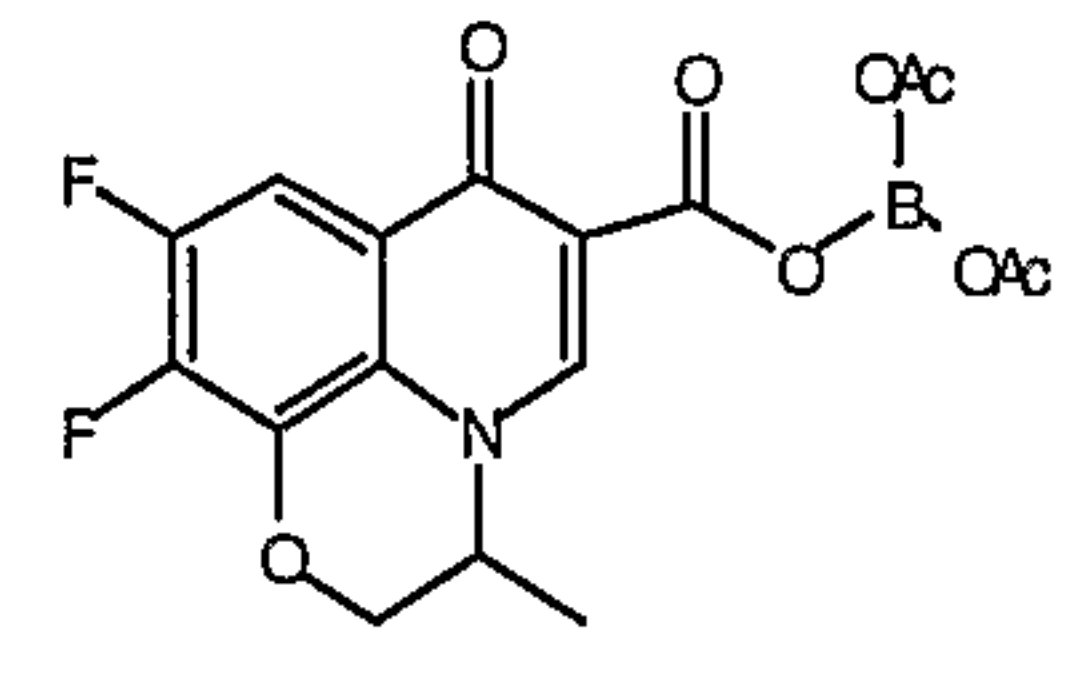
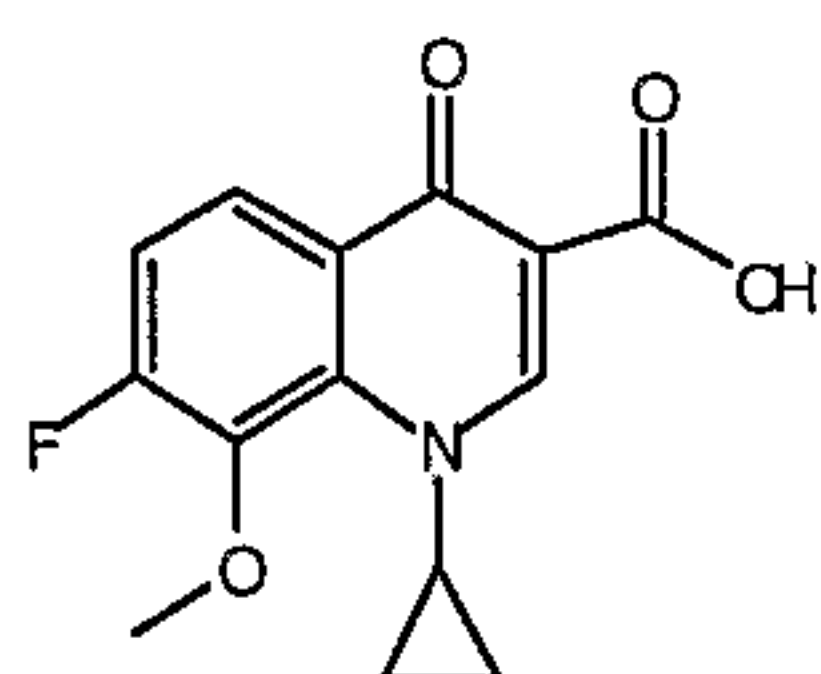
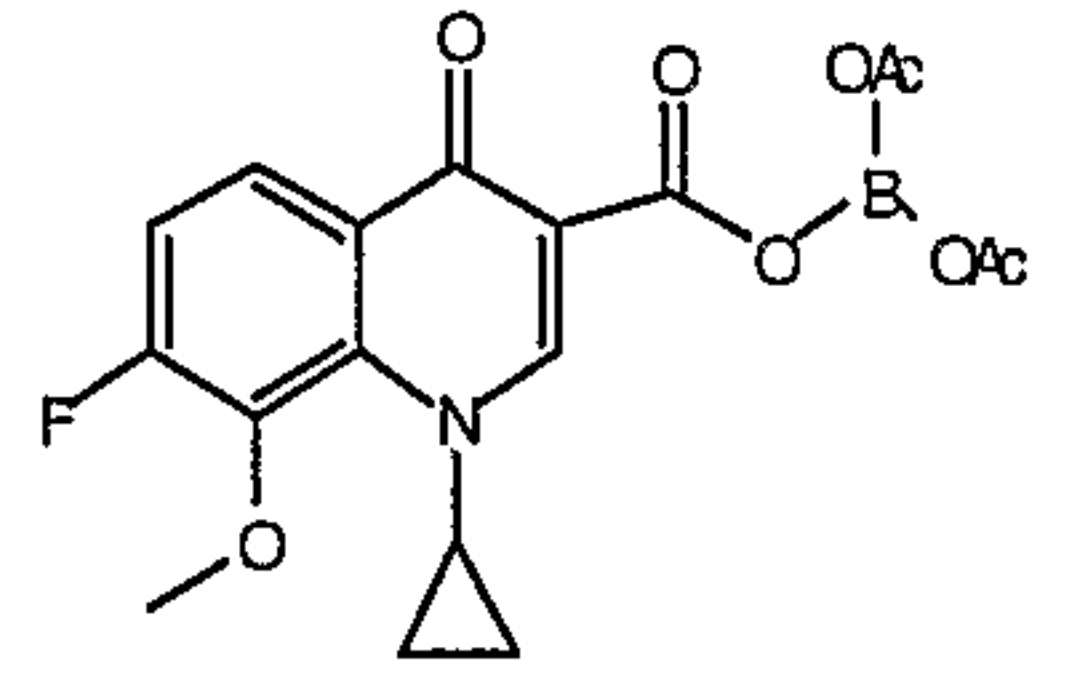
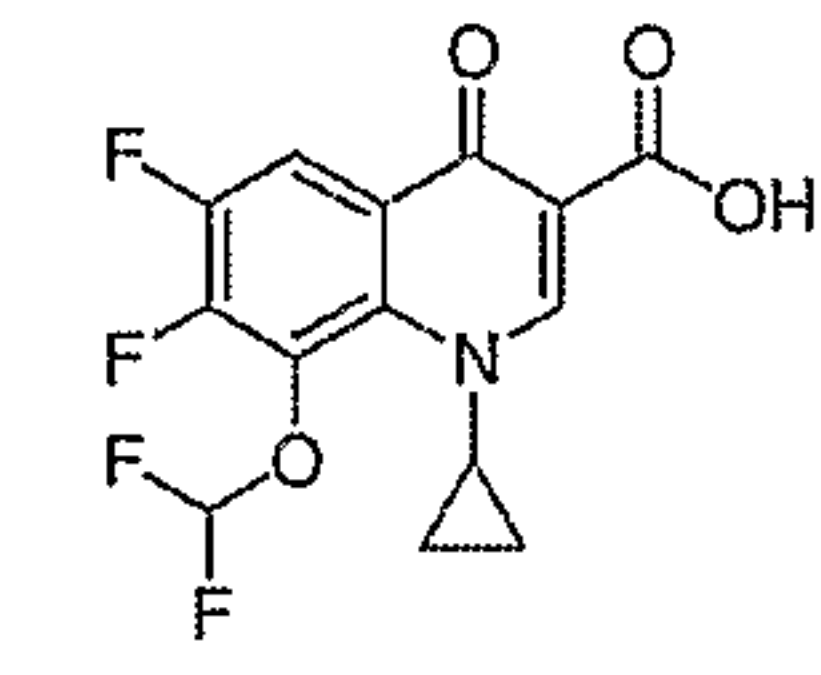
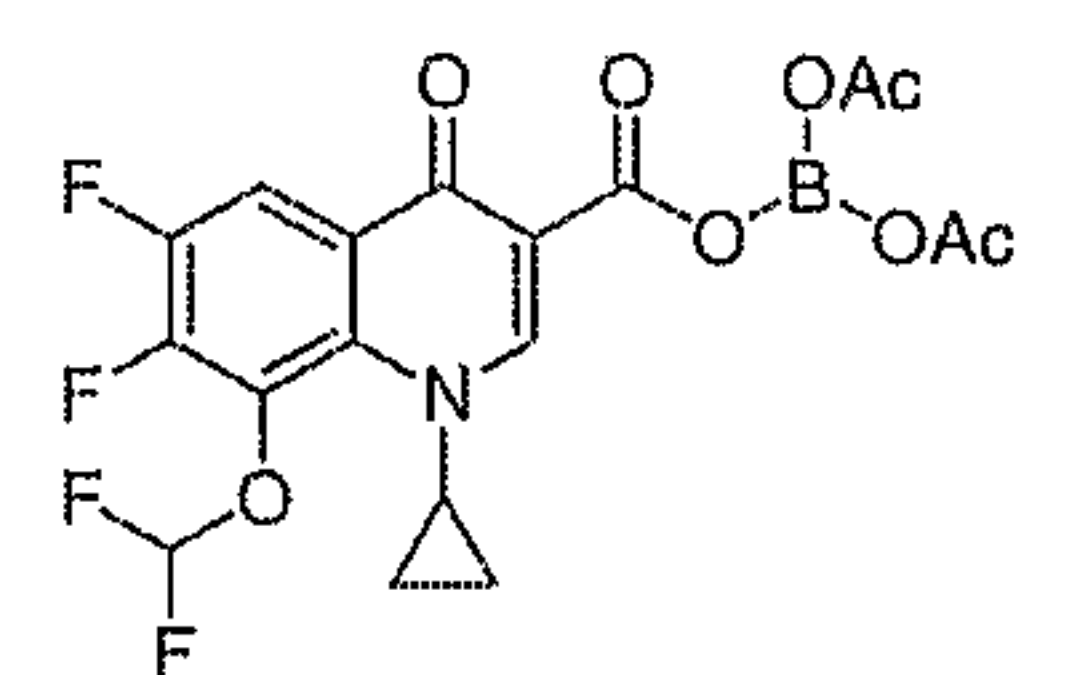
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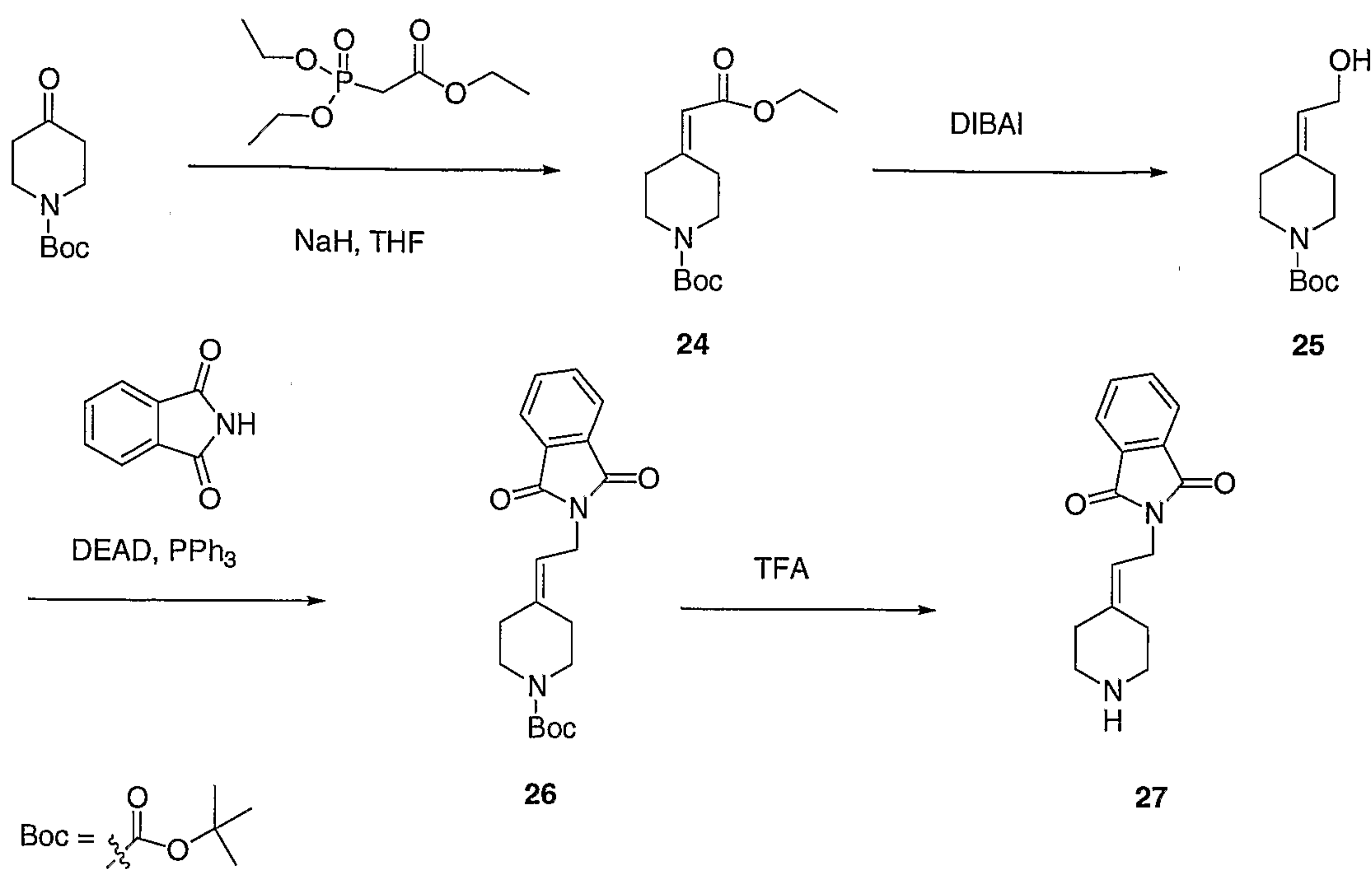
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Table 2

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

Precursor Preparation B – Side Chain III**Scheme XIV**

5

Compound 27 of Scheme XIV:

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

10

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

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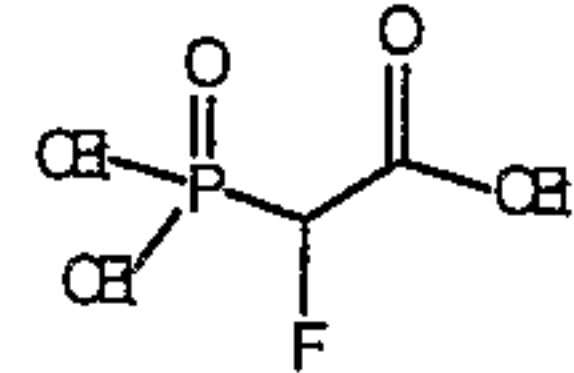
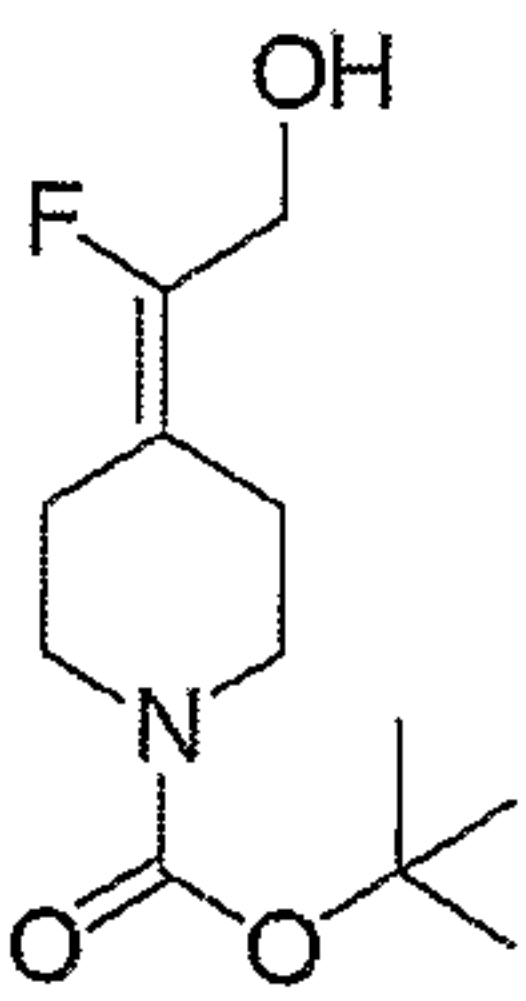
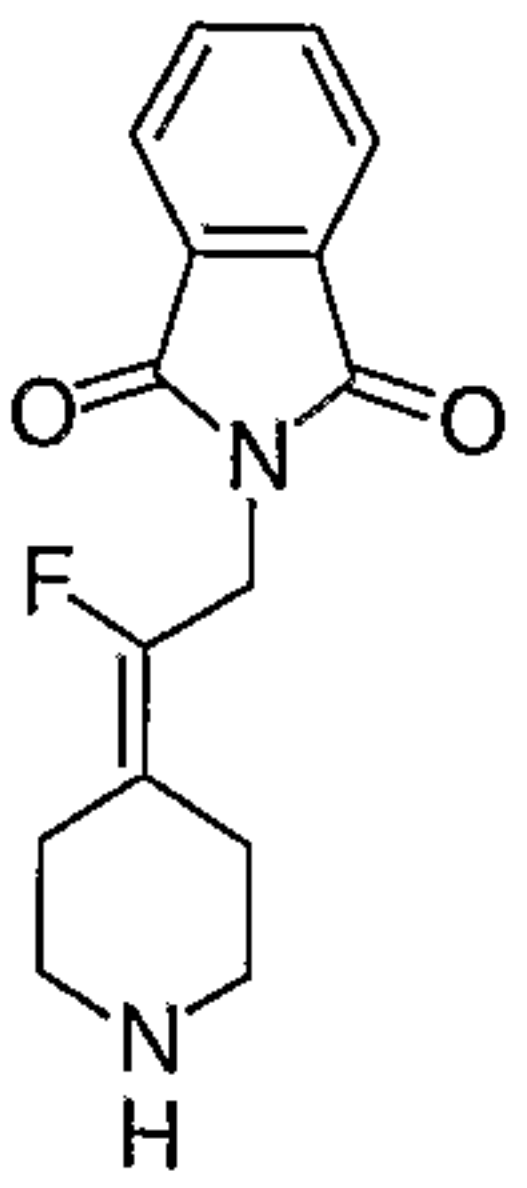
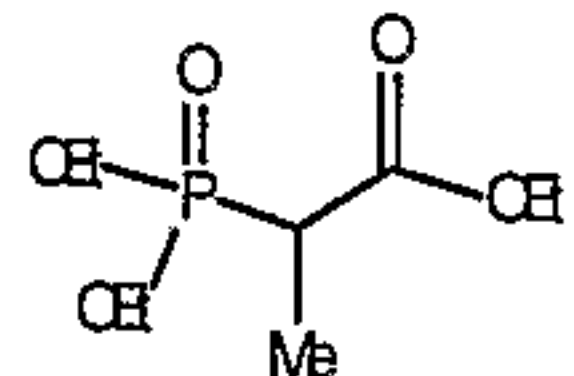
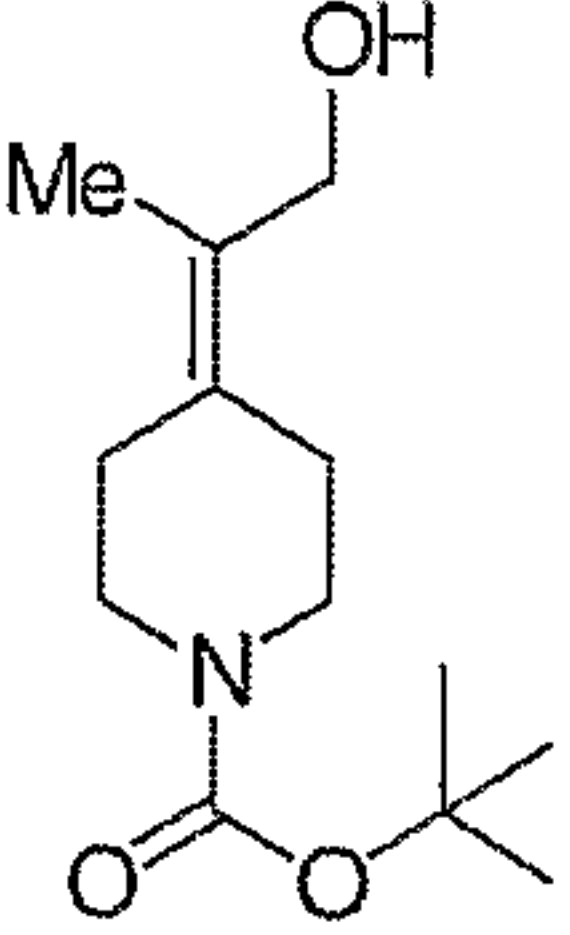
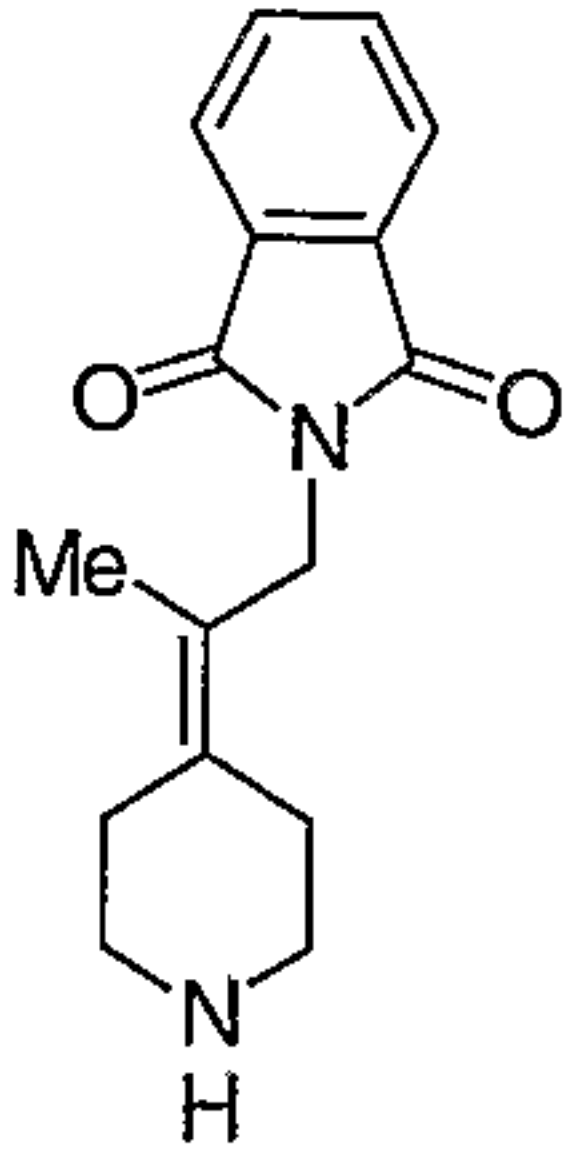
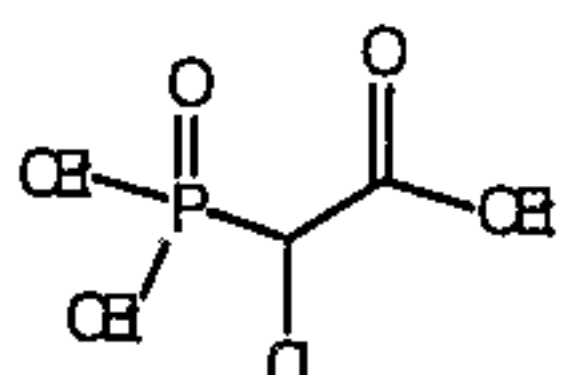
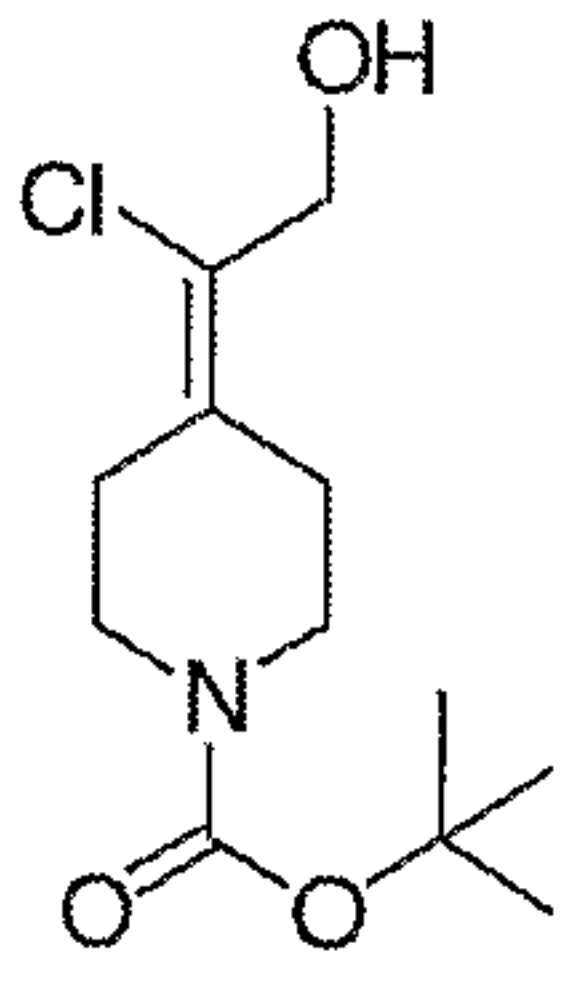
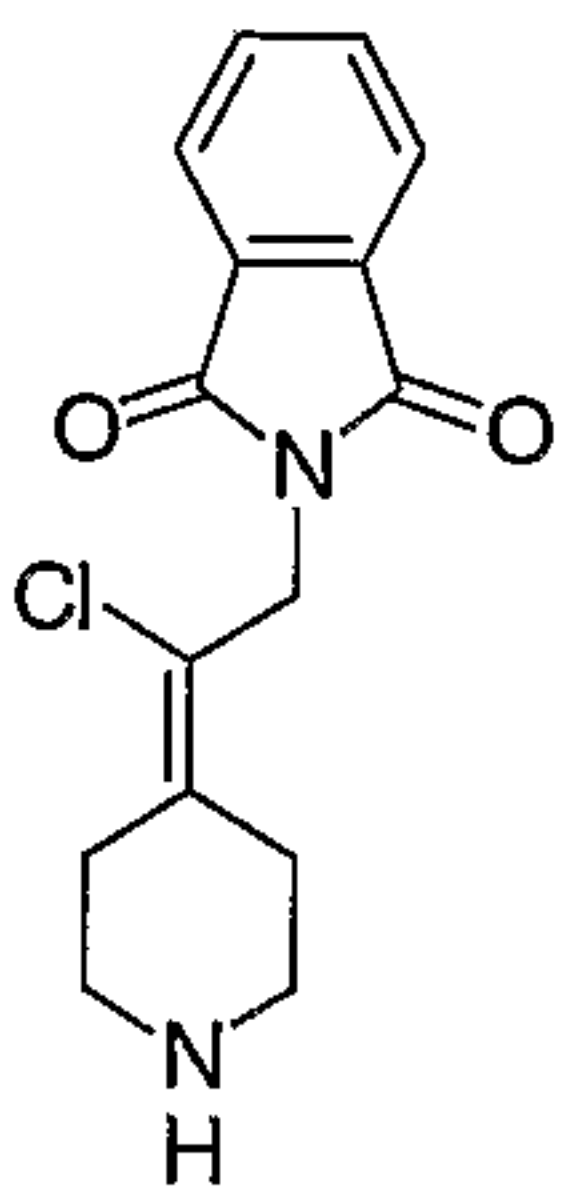
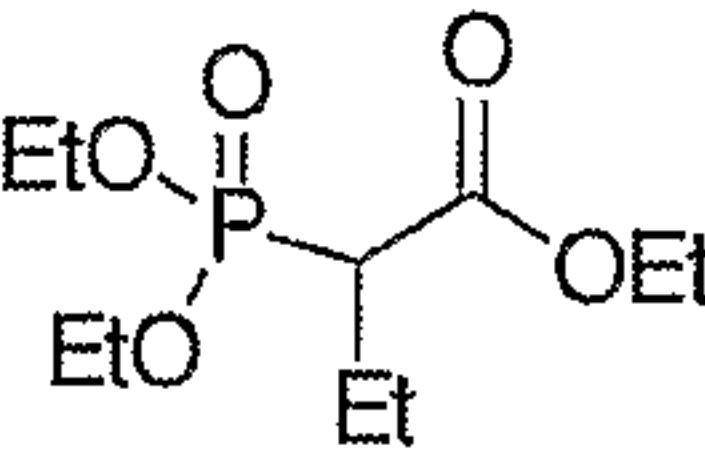
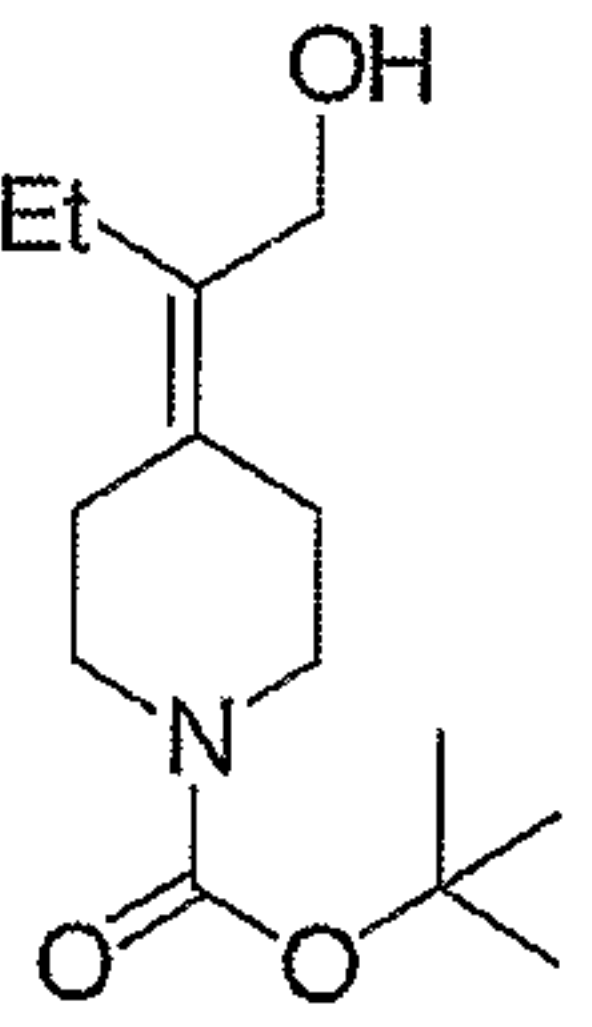
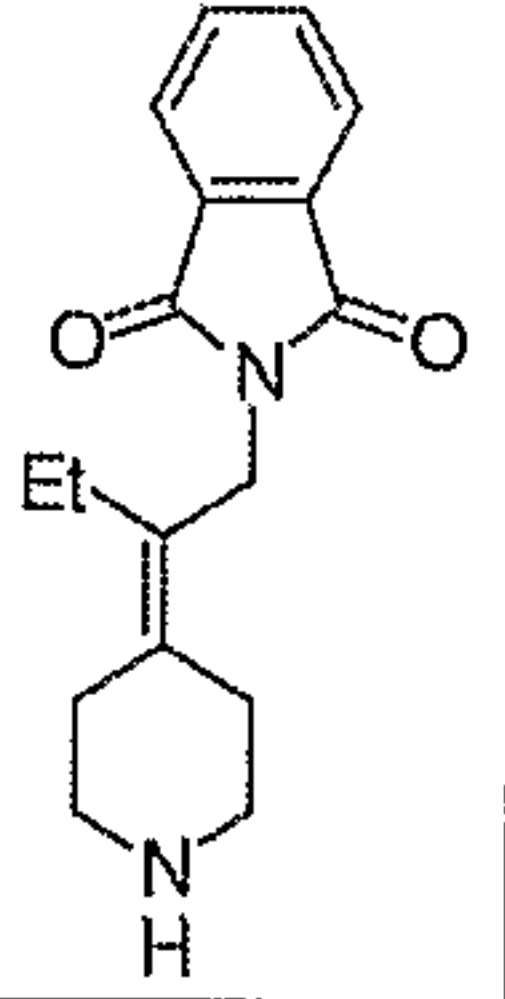
t-Butyl 4-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethylidene]-piperidiny-1-carboxylate (26) was prepared by a procedure adapted from *Synthesis* **1995**, 756. A solution of **25** (250 mg, 1.10 mmol), phthalimide (208 mg, 1.40 mmol), and triphenylphosphine (366 mg, 1.40 mmol) in dry THF (10 mL) was 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

20

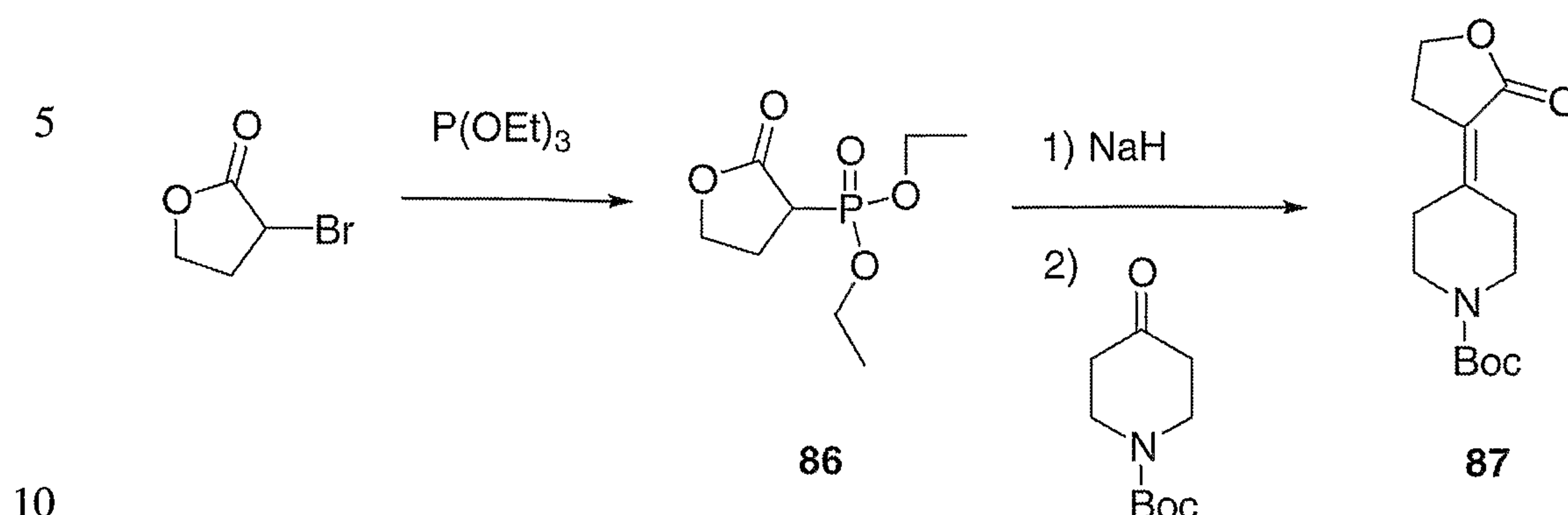
bicarbonate (2 x 25 mL), and dried (MgSO₄). Purification by flash chromatography (0-30% ethyl acetate/hexanes) afforded the title compound (389 mg, 78%) as a white foam. MS 357 (M+H).

- 5 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 CH₂Cl₂ (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).
- 10 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

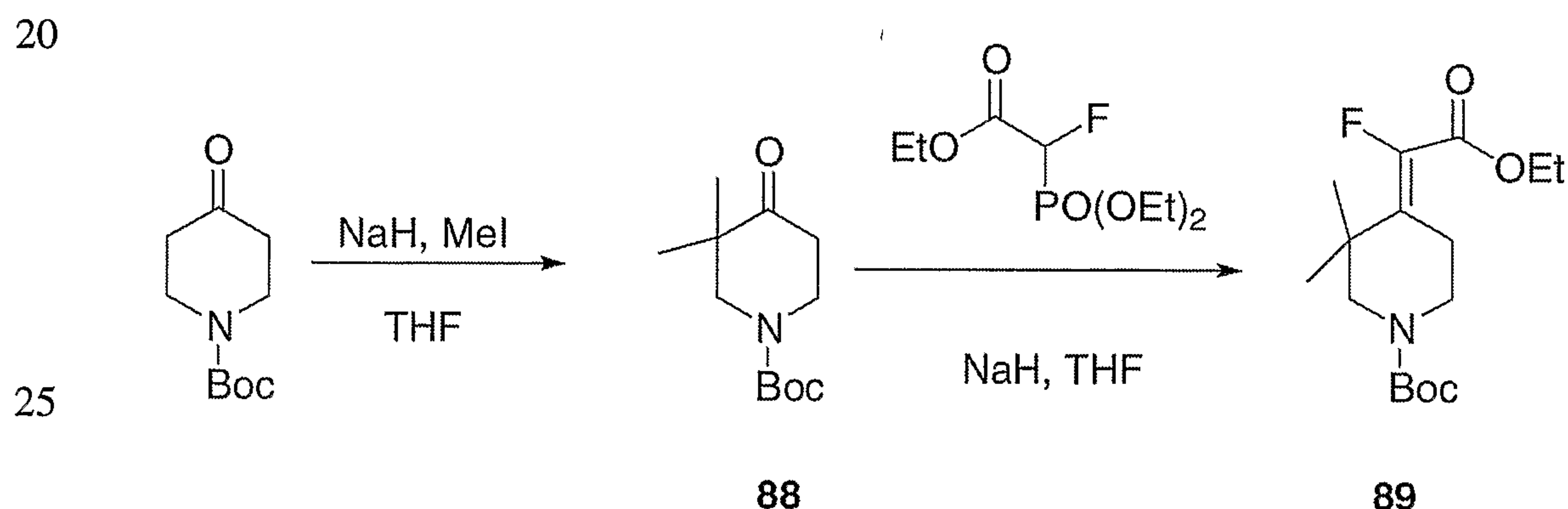
Scheme XXIII



(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.

15 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).

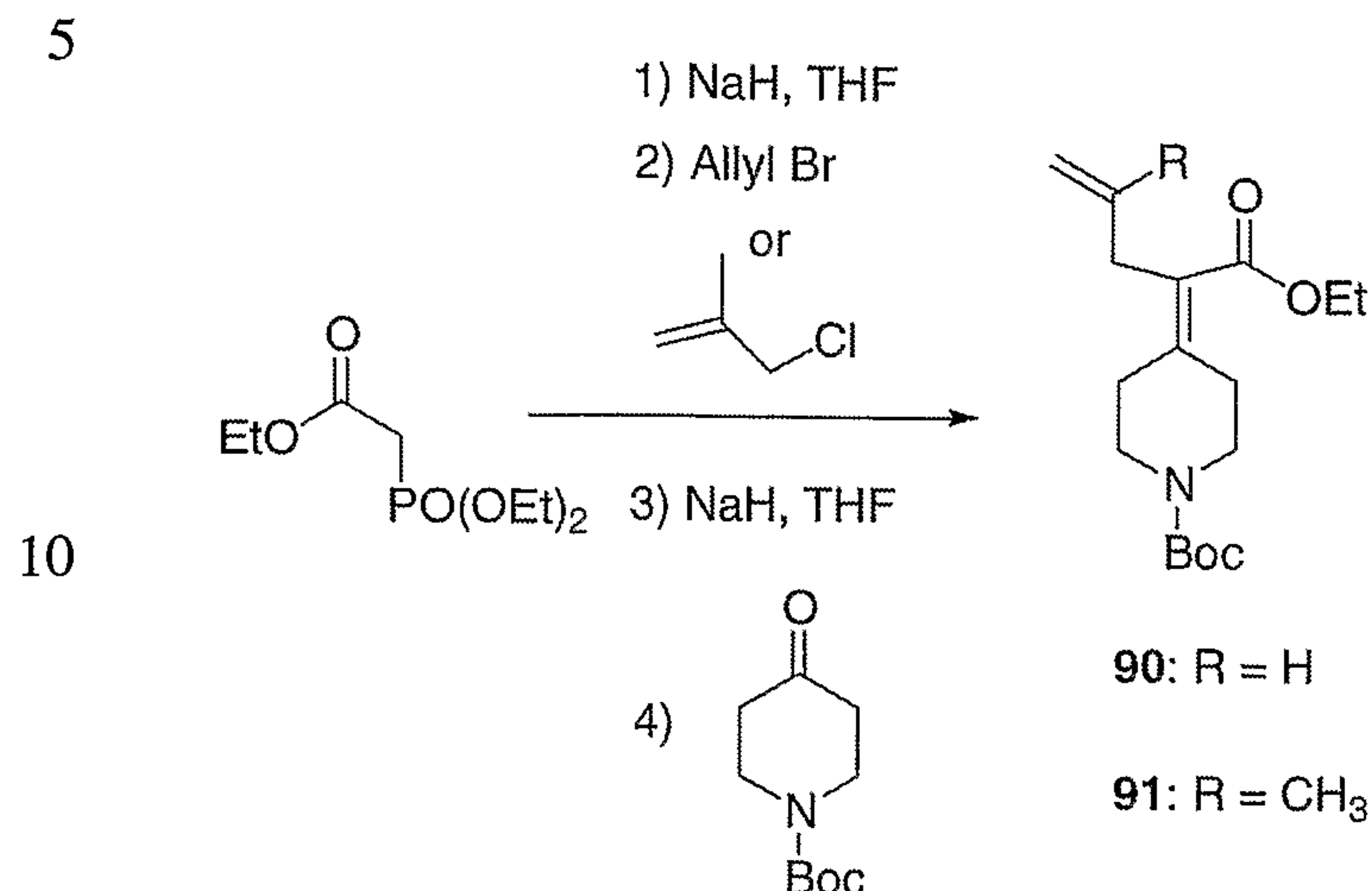
Scheme XXIV



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.

30 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



15 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

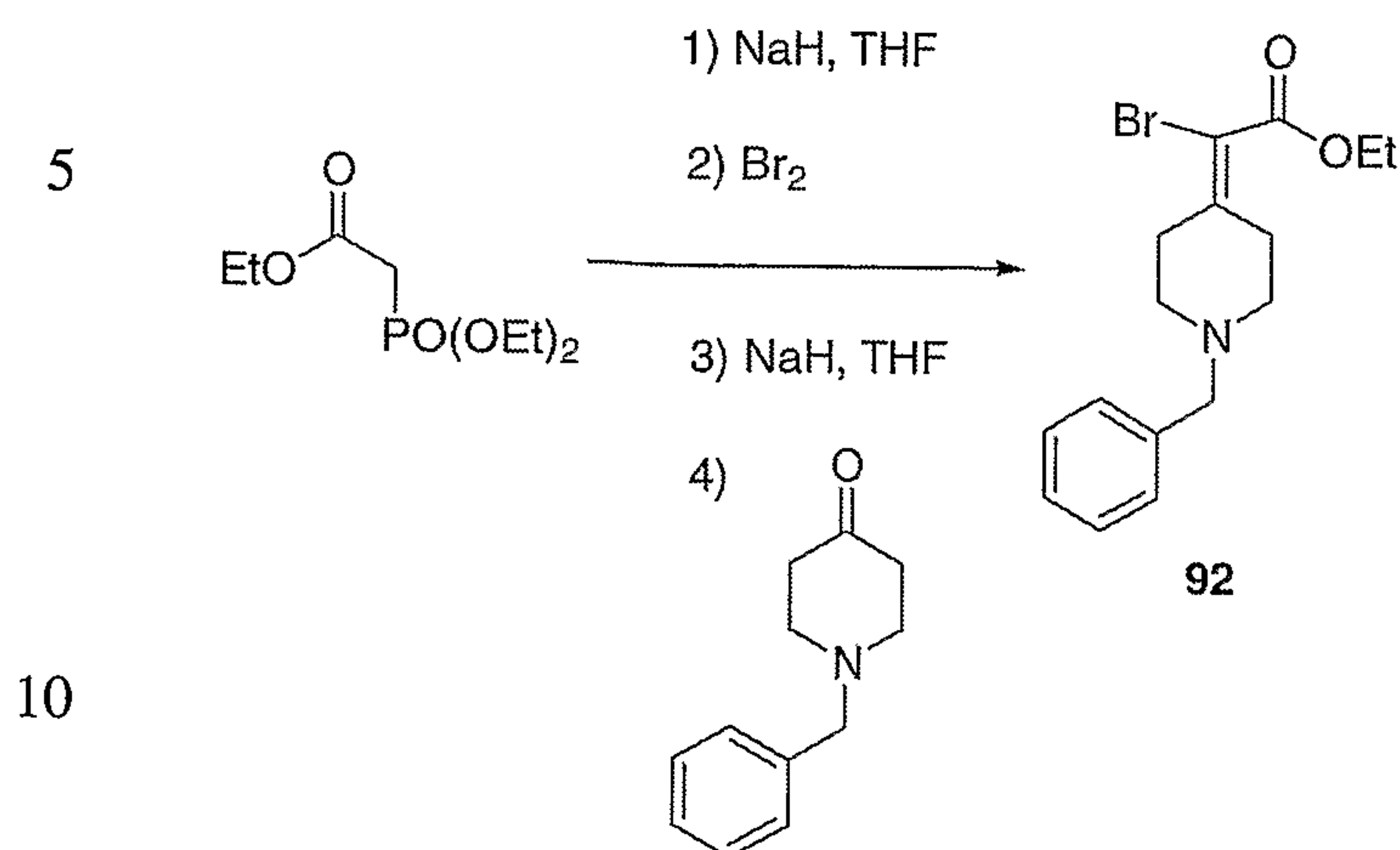
20 was recooled to 0°C, treated with sodium hydride (1.50 g, 37.6 mmol), and the resulting slurry was allowed to stir for 30 min at 0°C. A solution of 1-(tert-butoxycarbonyl)-4-piperidinone (5.0 g, 25 mmol) in THF (50 mL) was added via a cannula over 10 min and the resulting solution was allowed to warm to 25°C over 12 h. The reaction was quenched by the addition of 15% aqueous

25 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.

30

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

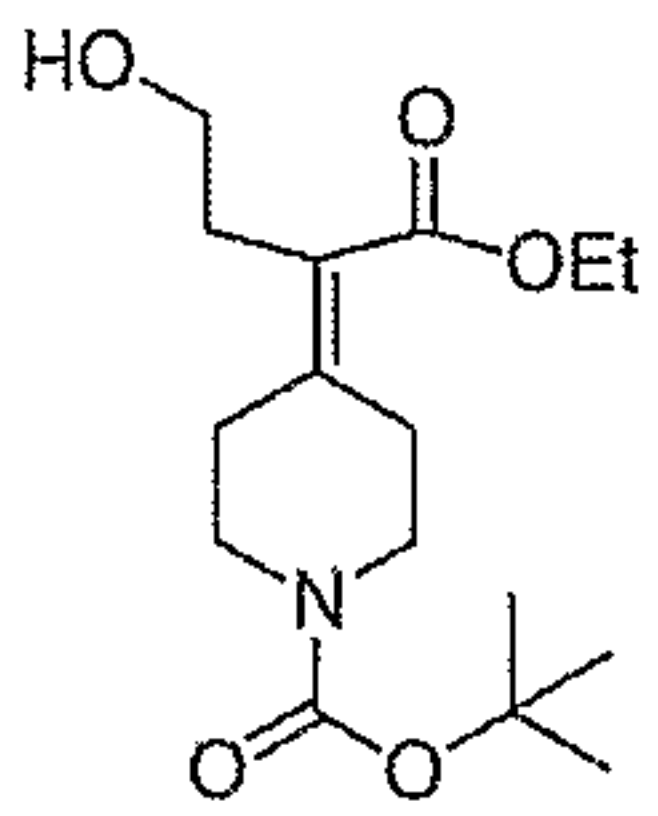
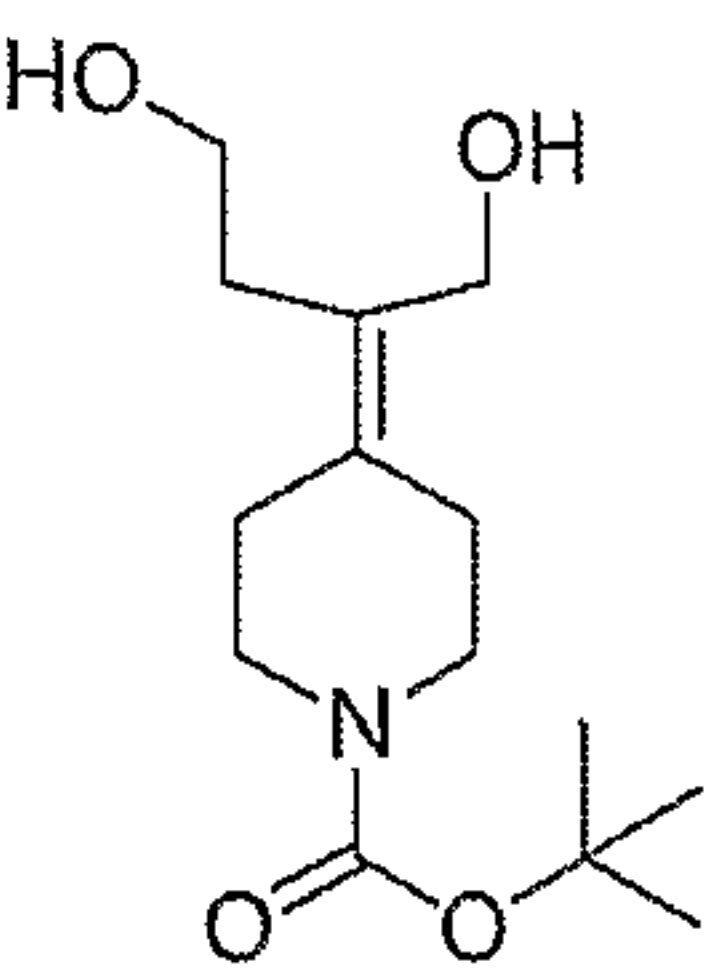
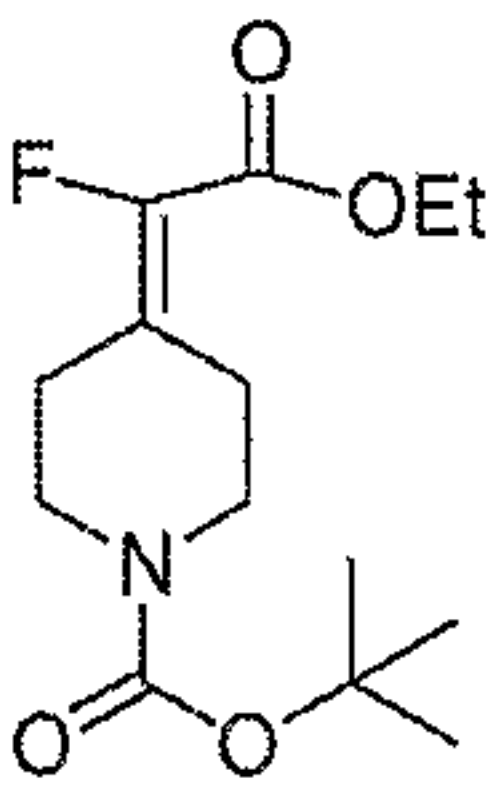
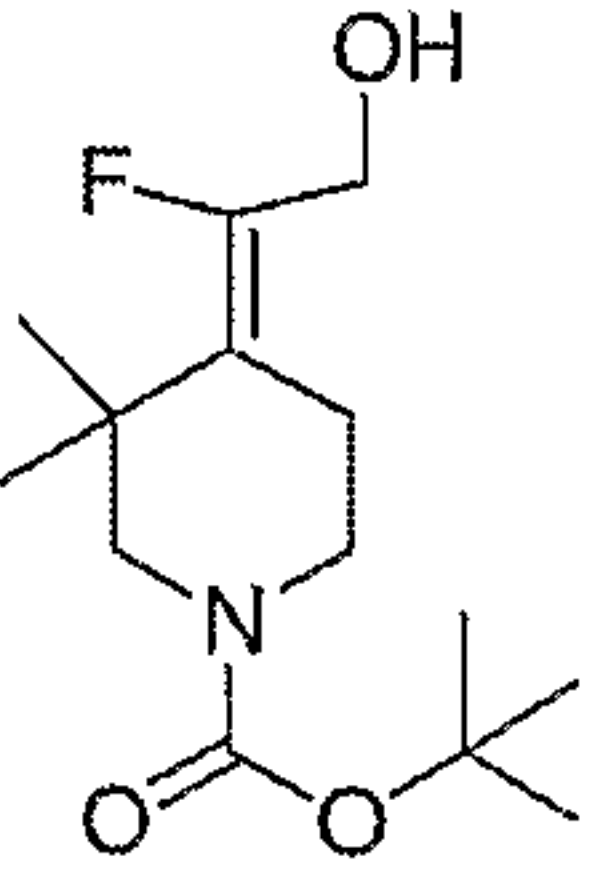
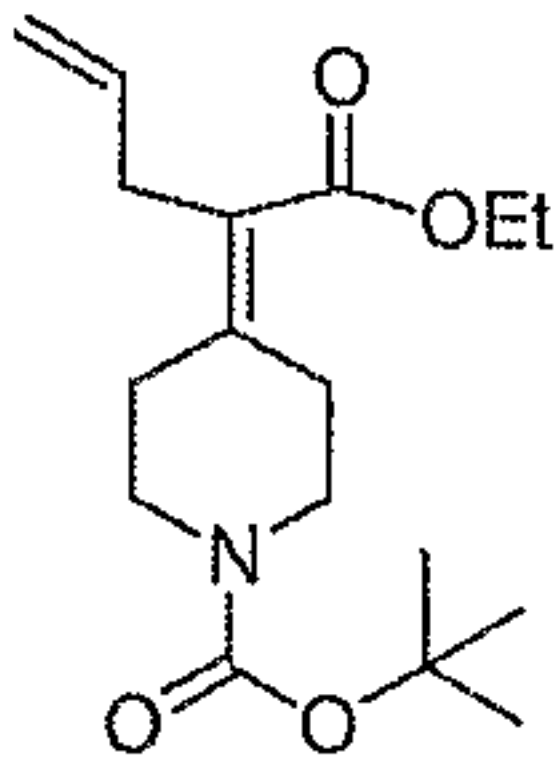
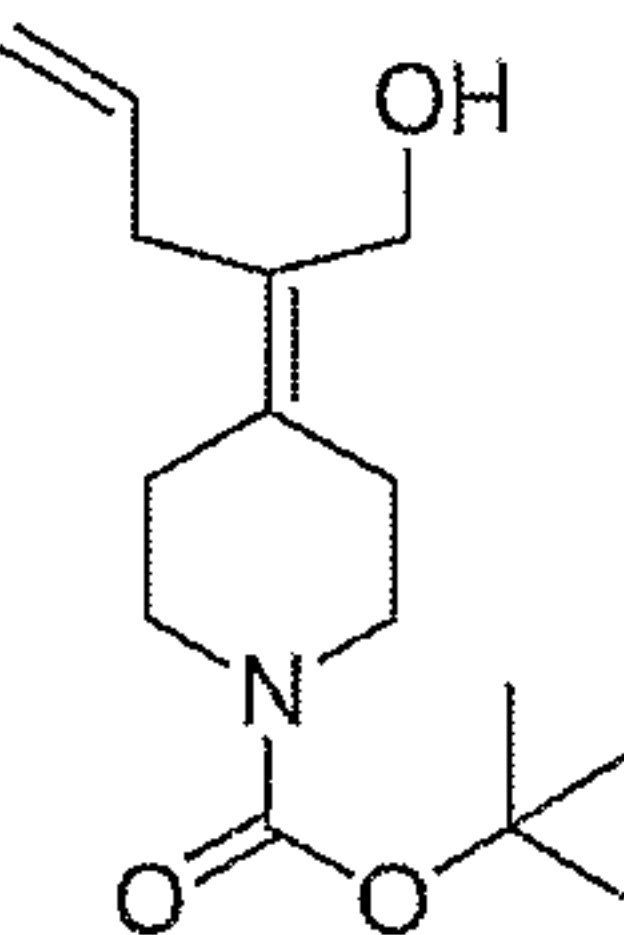
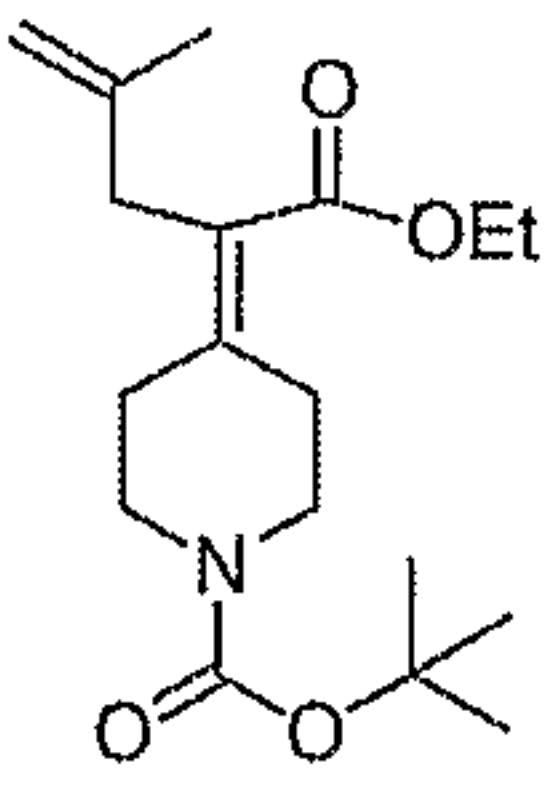
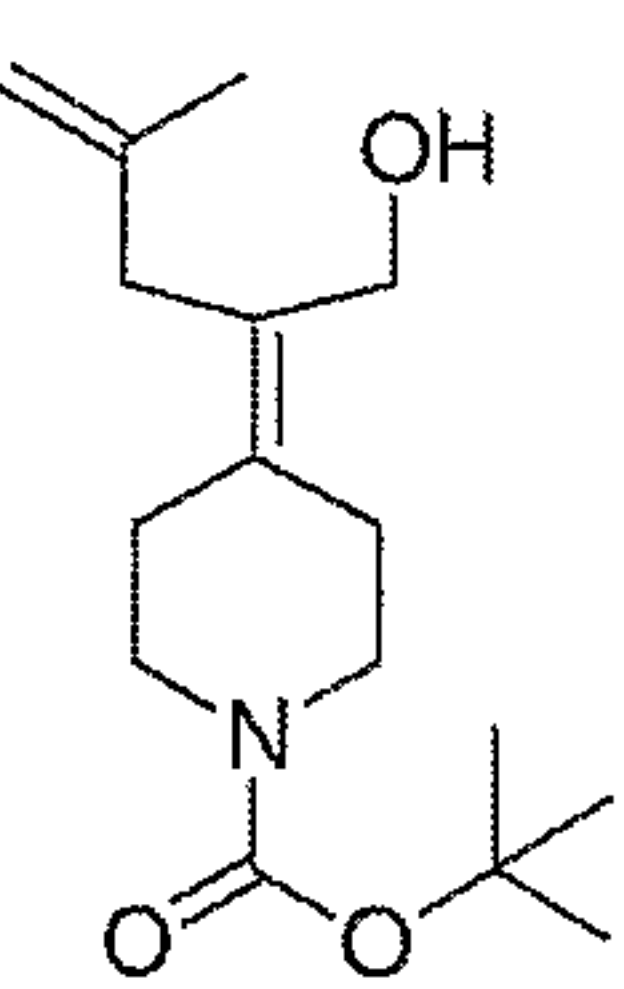
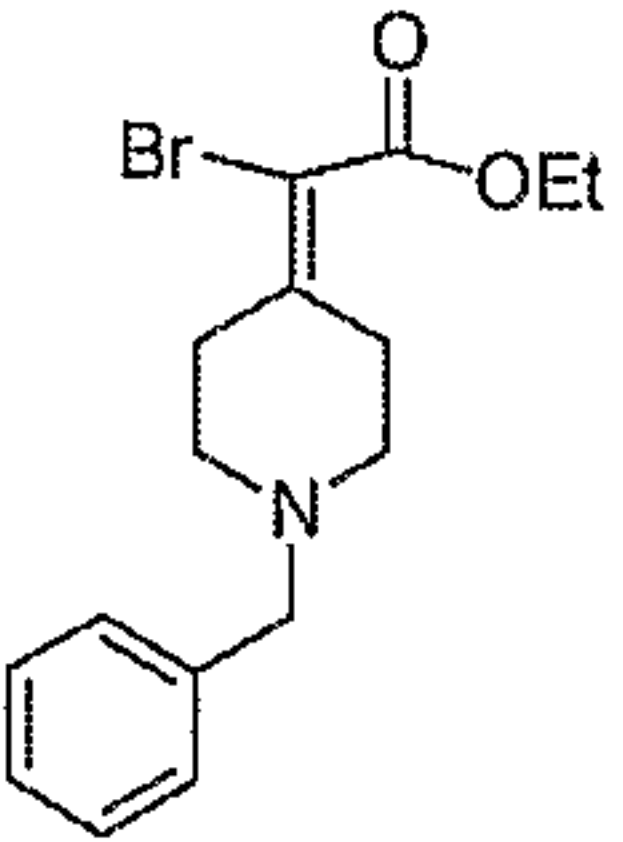
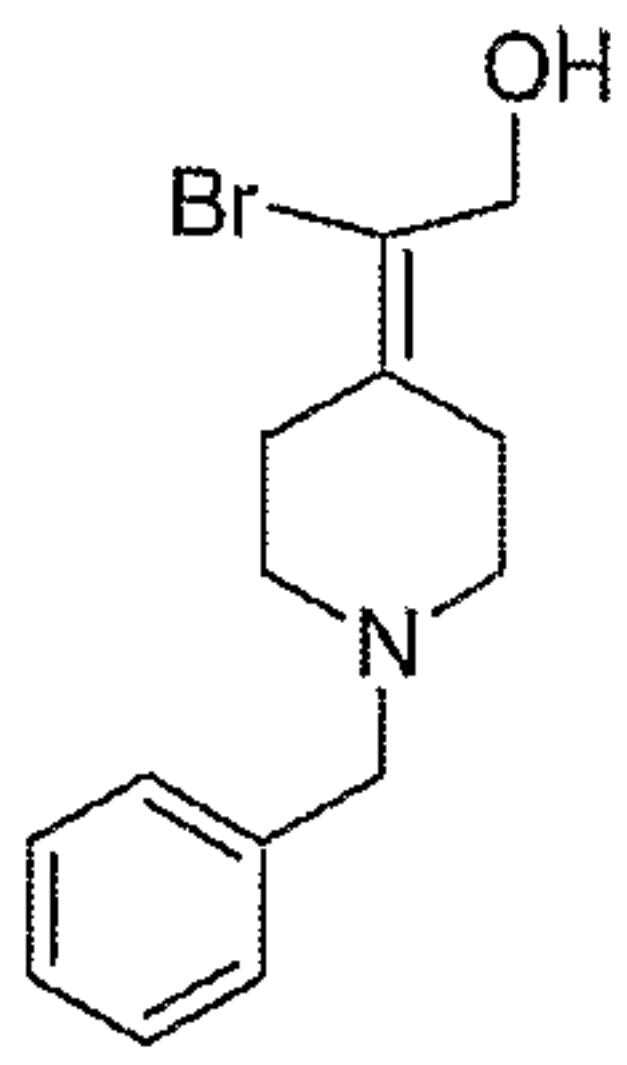


(1-Benzyl-piperidin-4-ylidene)bromoacetic acid ethyl ester (92; Scheme XXVI).

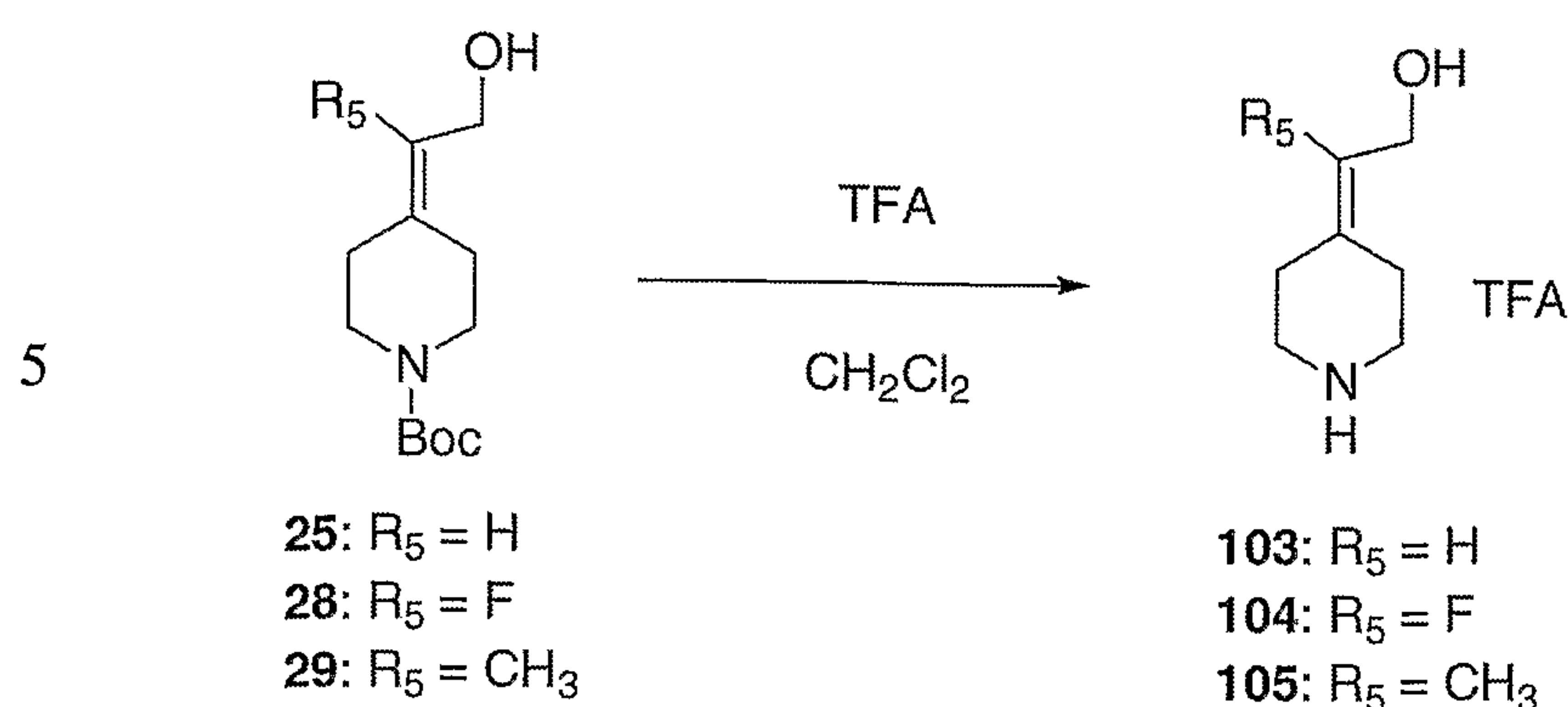
A slurry of sodium hydride (1.50 g, 37.6 mmol) in THF (100 mL) at 0°C under nitrogen was carefully treated with triethyl phosphonoacetate (8.12 mL, 37.6 mmol) via a syringe. After 30 min, the reaction mixture was treated with bromine (1.95 mL, 37.6 mmol) via a dropping funnel over 10 min and the resulting 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

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

Scheme XXVII



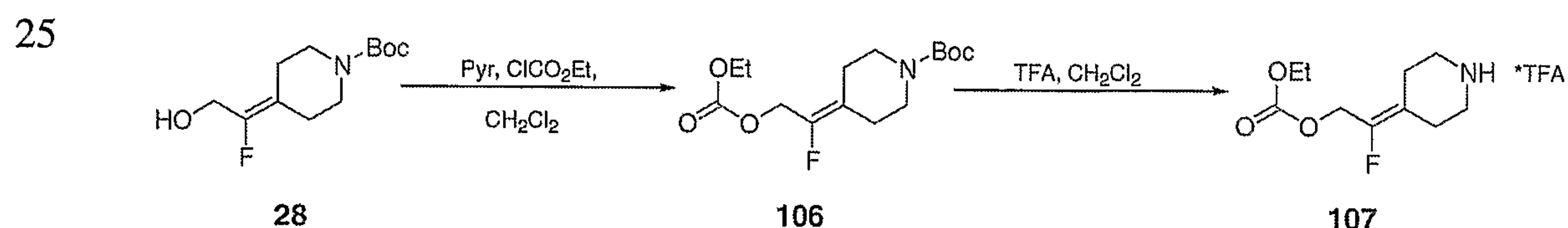
10 2-Piperidin-4-ylidene-ethanol trifluoroacetate (103; Scheme XXVII). A solution of **25** (191 mg, 0.5 mmol) was dissolved in CH₂Cl₂ (10 mL) and was treated with trifluoroacetic acid (0.5 mL) at room temperature. After 1h, the reaction mixture was concentrated in vacuo to afford the title compound (64 mg, 100%) as an oil. MS 129 (M+H).

15

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).

20 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



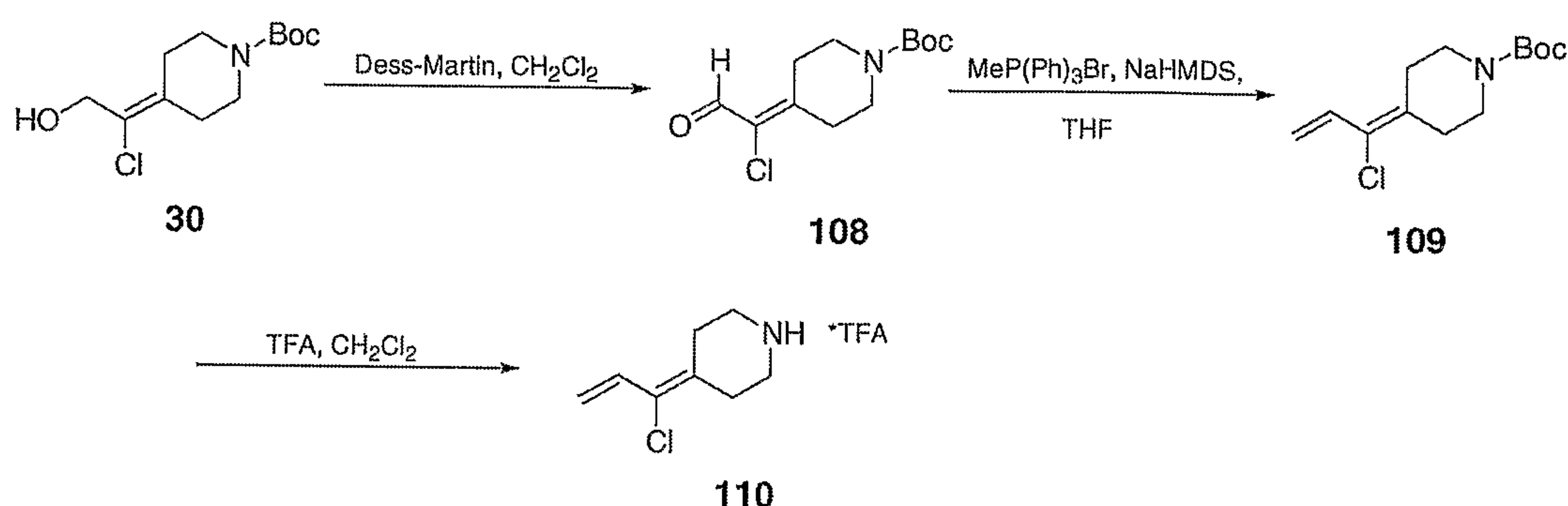
30 *t*-Butyl 4-(2-ethoxycarbonyloxy-1-fluoroethylidene)piperidine-1-carboxylate (106; Scheme XXVIII). To alcohol **28** (0.5064 g, 2.064 mmols) in CH₂Cl₂ (10 mL) at RT was added pyridine (0.23 mL, 2.8 mmols) and then ethyl chloroformate (0.22 mL, 2.2 mmols). After stirring overnight, sat. aq. NH₄Cl (10 mL) was added and the mixture extracted with CH₂Cl₂ (5 X 10 mL), dried over

Na₂SO₄, 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).

- 5 4-(2-Ethoxycarbonyloxy-1-fluoro-ethylidene)-piperidine (**107**; Scheme XXVIII). To compound **106** (0.1787 g, 0.5631 mmol) in CH₂Cl₂ (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).

10

Scheme XXIX



- 20 *t*-Butyl 4-(1-chloro-2-oxoethylidene)-piperidine-1-carboxylate (**108**; Scheme XXIX) To alcohol **30** (6.01 g, 23.0 mmols) in CH₂Cl₂ 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. Na₂S₂O₃ (60 mL) and sat. aq. NaHCO₃ (3 X 30 mL). The organic layer was dried over Na₂SO₄, 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).

- 25 *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°C 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. NH₄Cl (20 mL) and the

aqueous layer was extracted with EtOAc (6 X 20 mL). The combined organic layers were dried over Na₂SO₄, concentrated and chromatographed on silica (gradient elution with 0-10% MeOH/ CH₂Cl₂) to provide the title compound **109** (1.94 g, 96%) as a white crystalline solid. MS 258 (M + H).

5

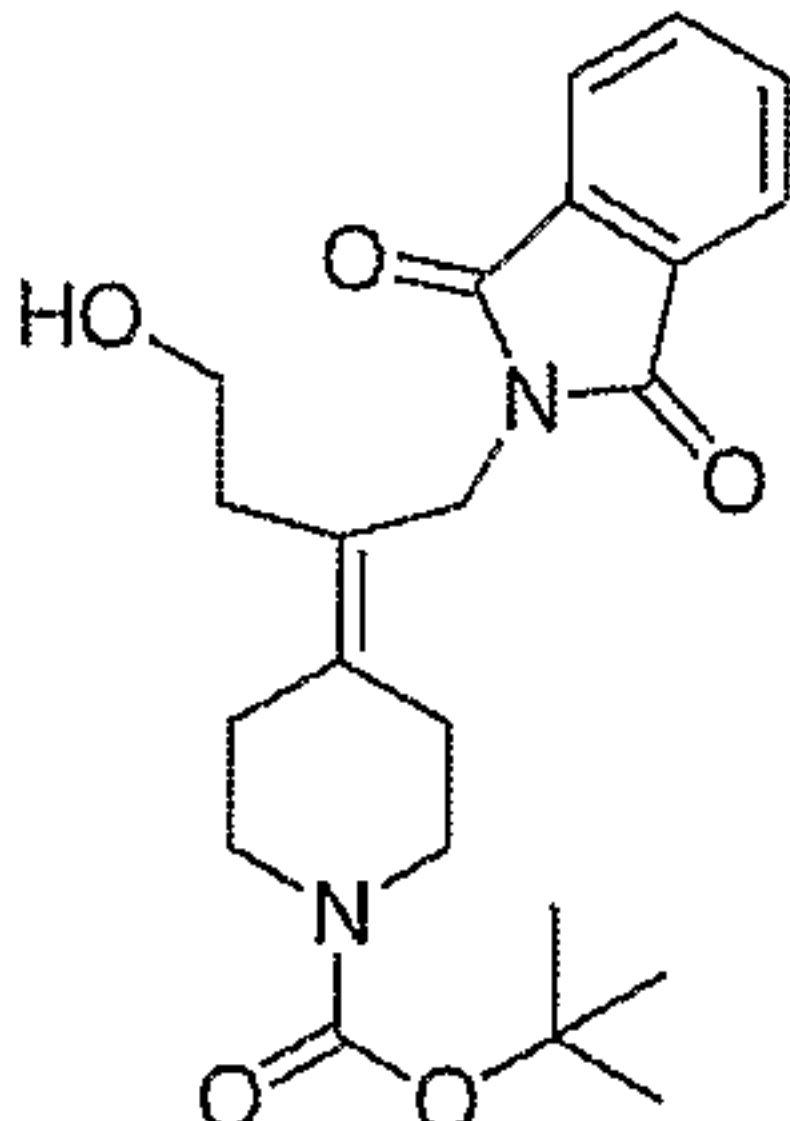
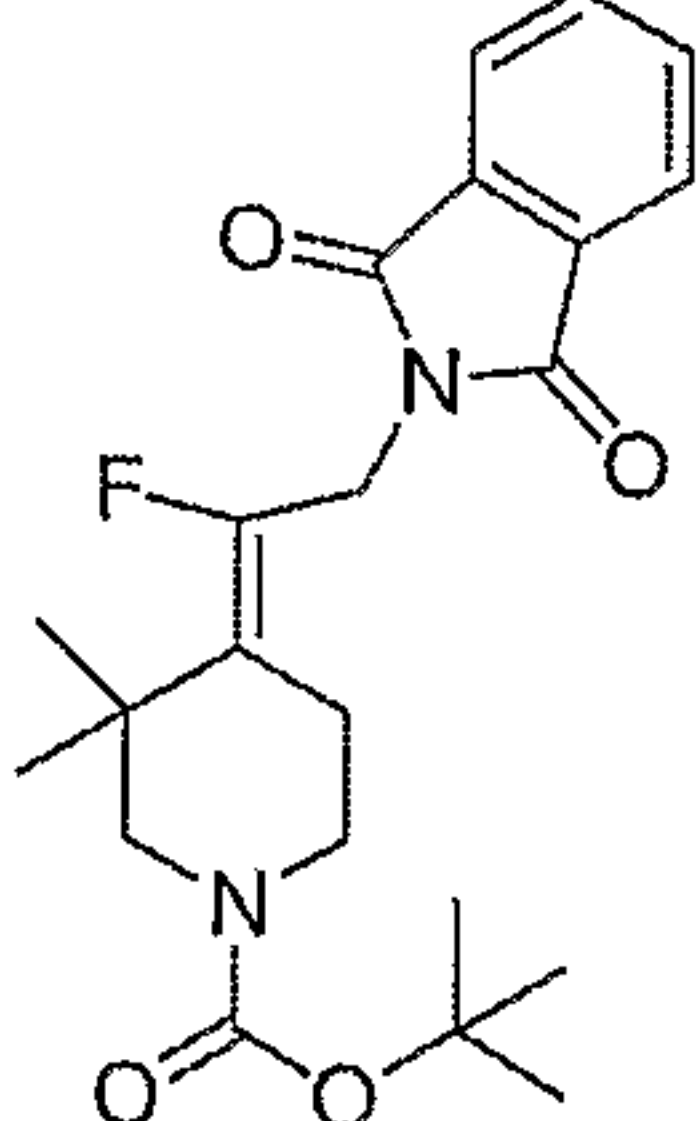
4-(1-Chloro-2-propenylidene)piperidine TFA salt (**110**; Scheme XXIX) To compound **109** (0.1415 g, 0.5489 mmol) in CH₂Cl₂ (5 mL) was added TFA (0.55 mL, 7.1 mmols) and the mixture stirred for 3hrs whereupon all volatile materials were removed in vacuo. The crude title compound so obtained was used without further purification. MS 158 (M + H).

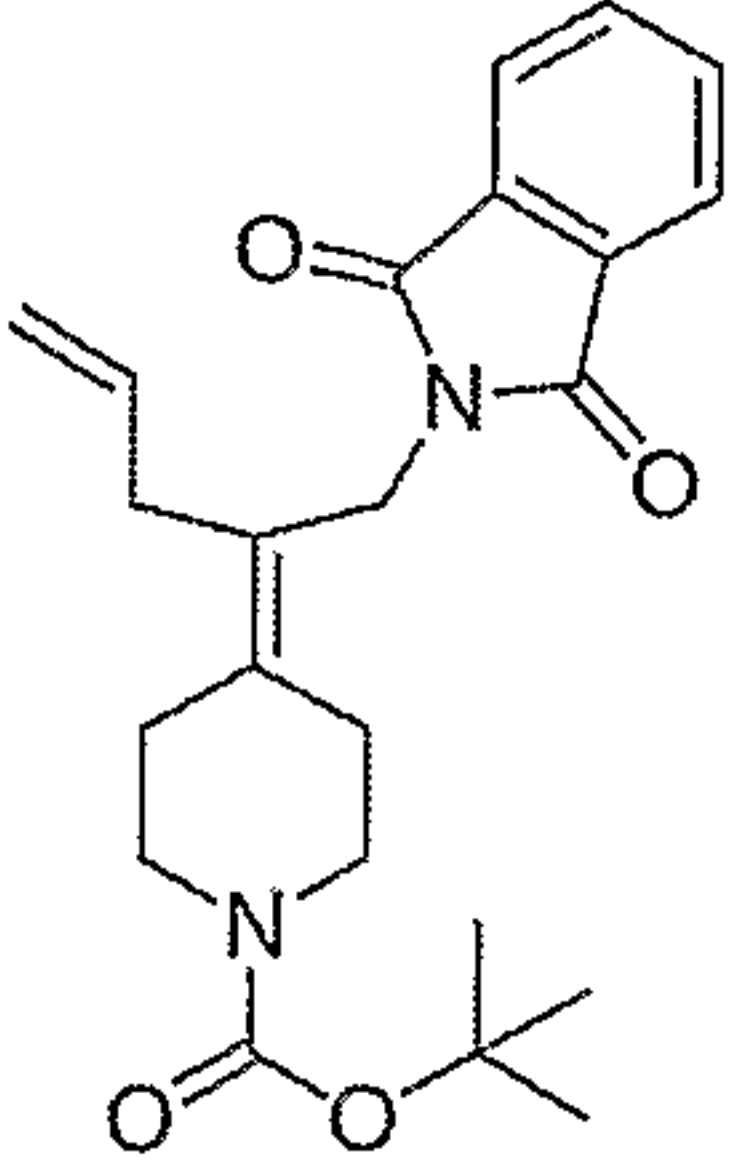
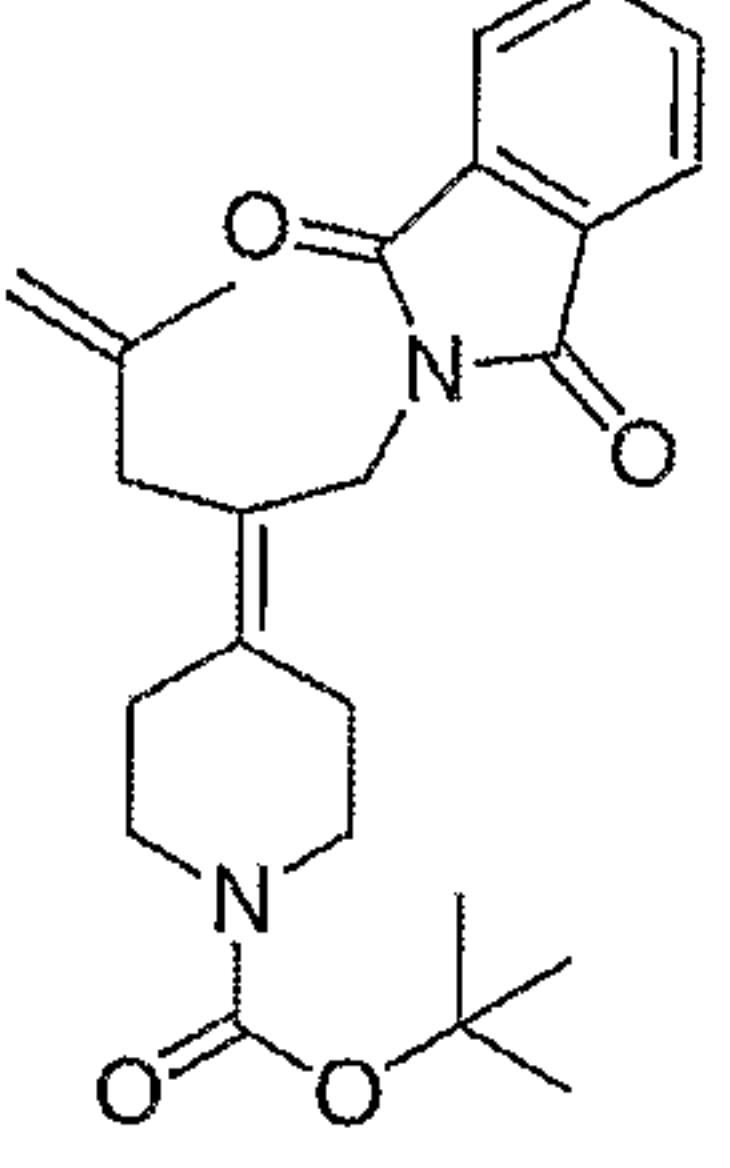
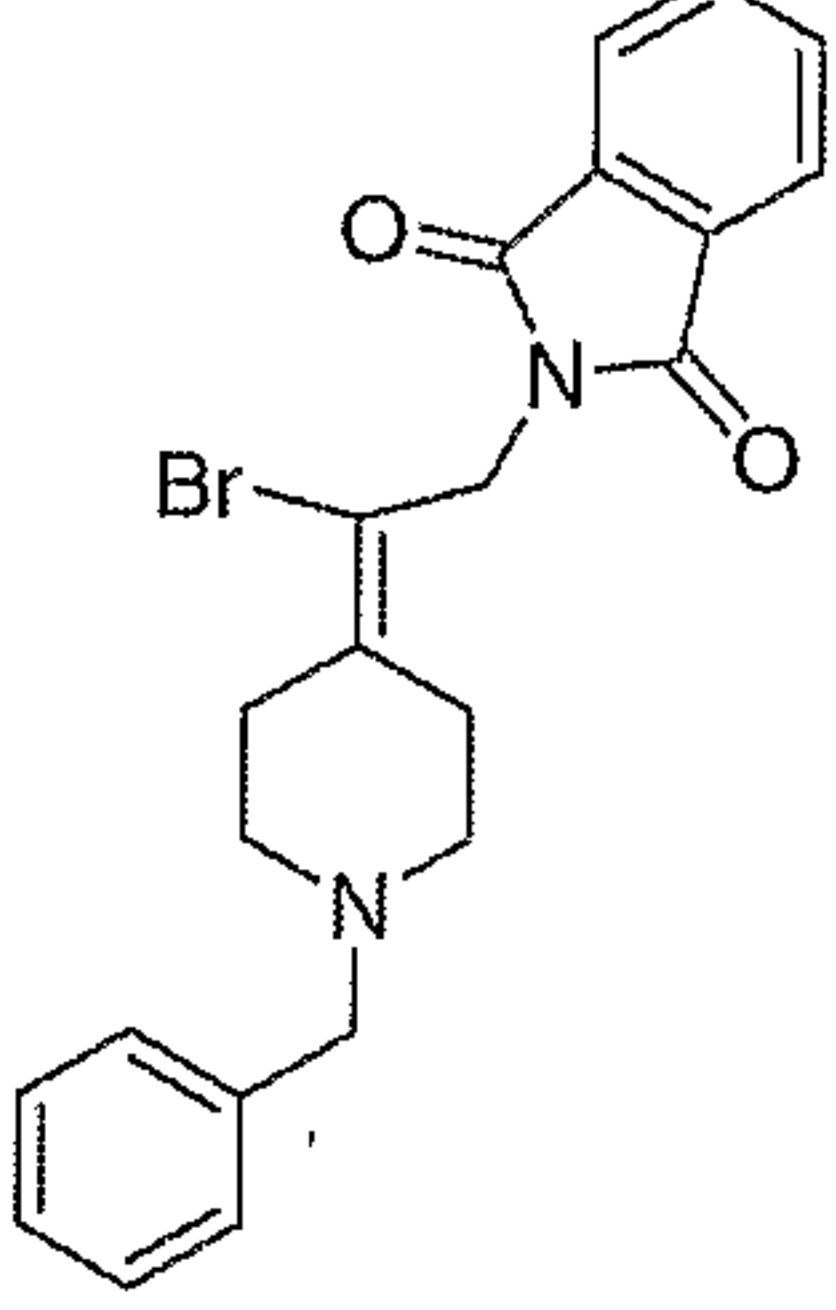
10

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**).

15

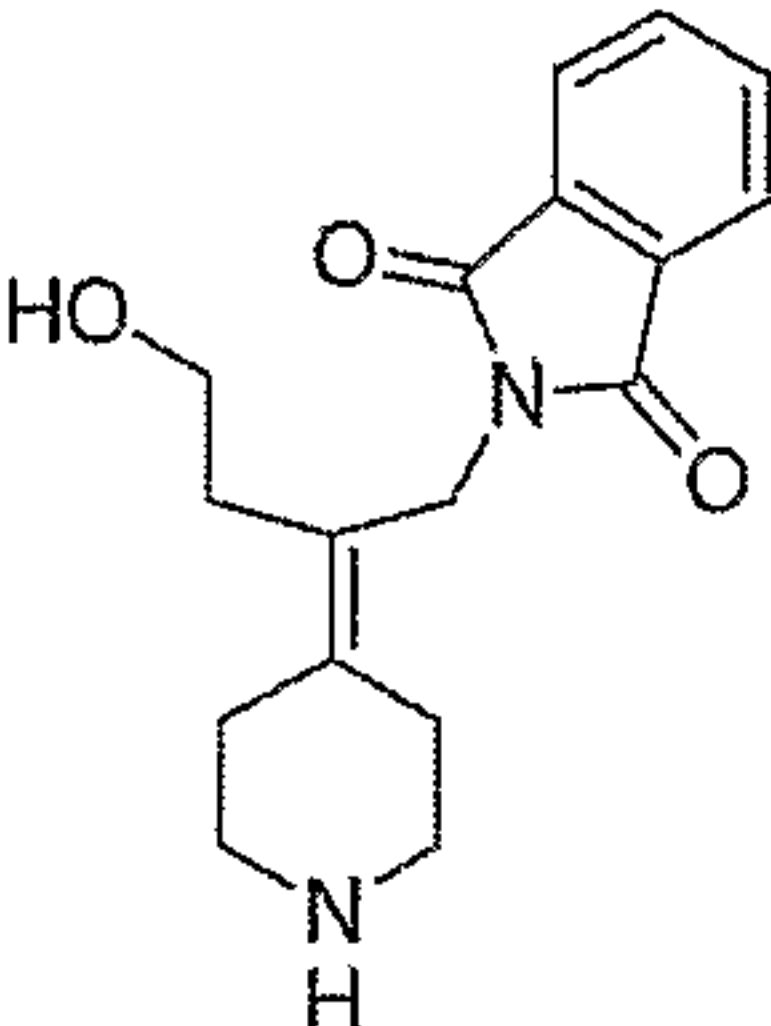
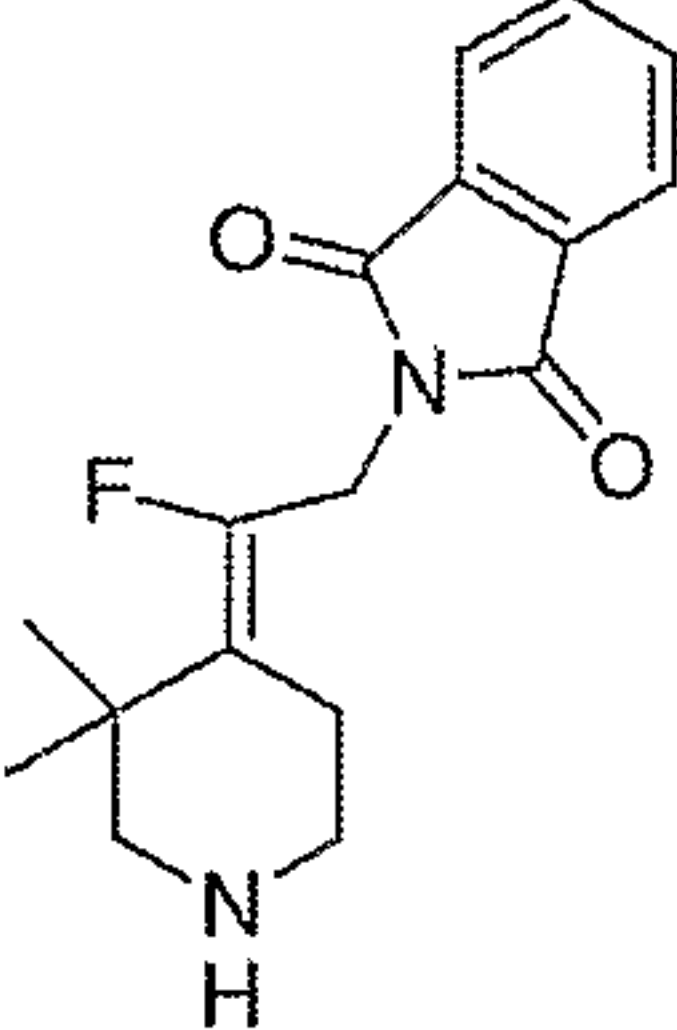
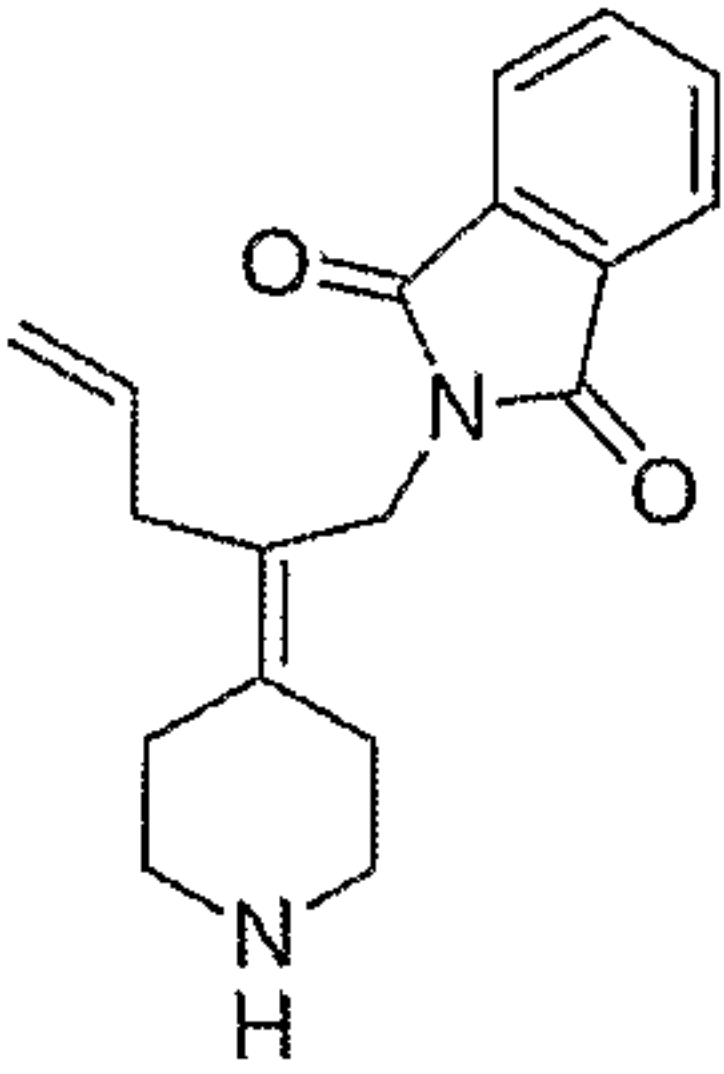
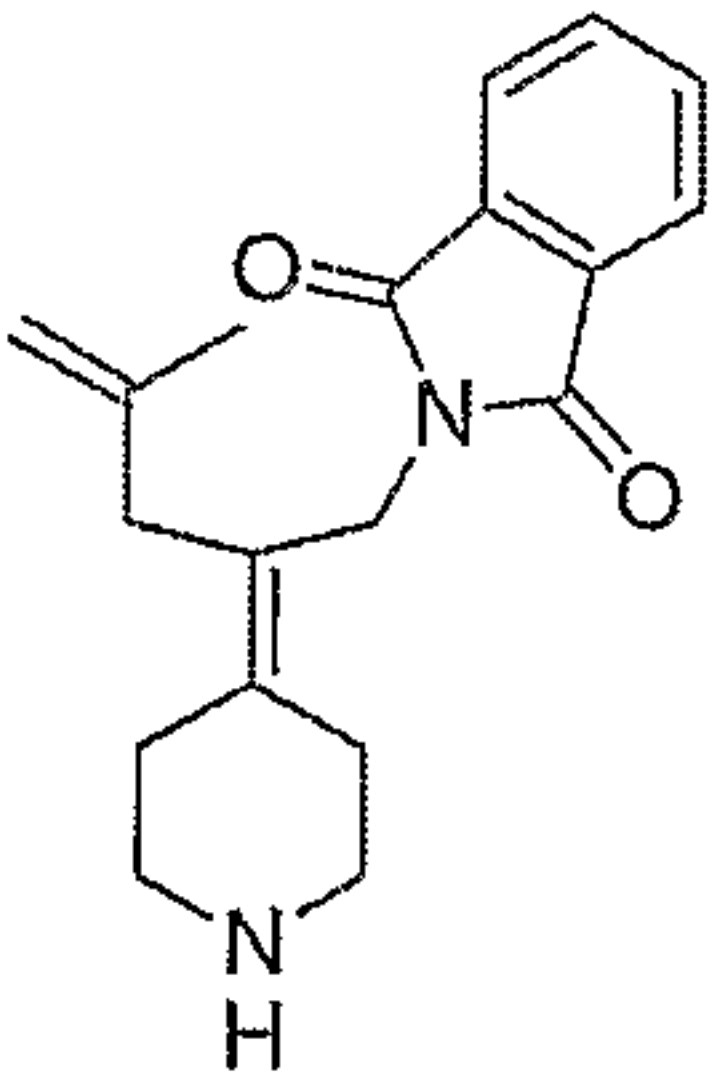
Table 7

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

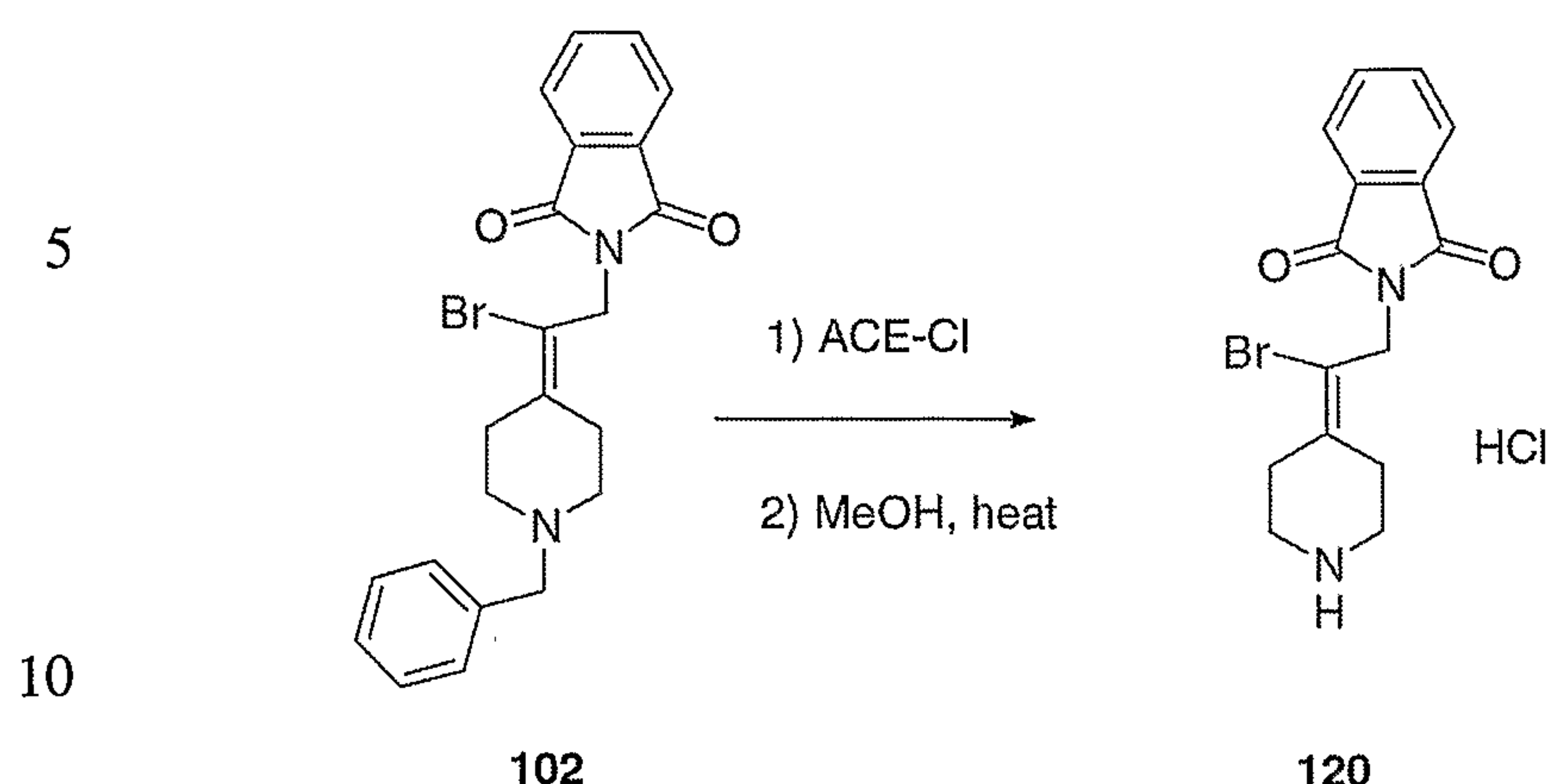
98		113	397
100		114	411
102		115	426

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
 5 instead of t-butyl 4-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)ethylidene]-piperidiny-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



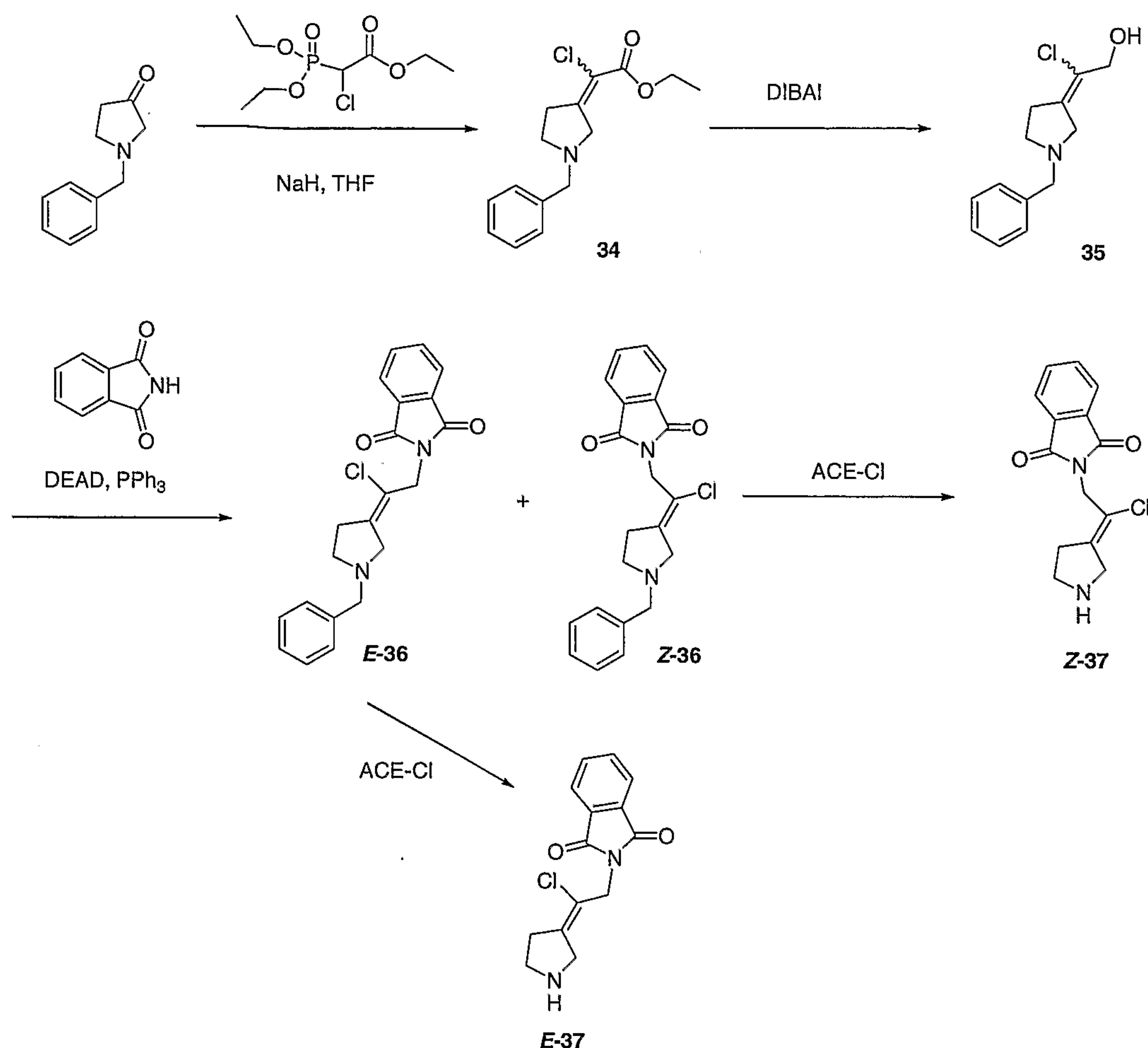
2-(2-Bromo-2-piperidin-4-ylidenylethyl)isoindole-1,3-dione hydrochloride (120: Scheme XXX). A mixture of **102** (0.50 g, 1.17 mmol) and 1-chloroethyl chloroformate (0.7 mL, 6.2 mmol) in dichloroethane (10 mL) was warmed to reflux temperature for 2h. The resulting solution was allowed to cool to room 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



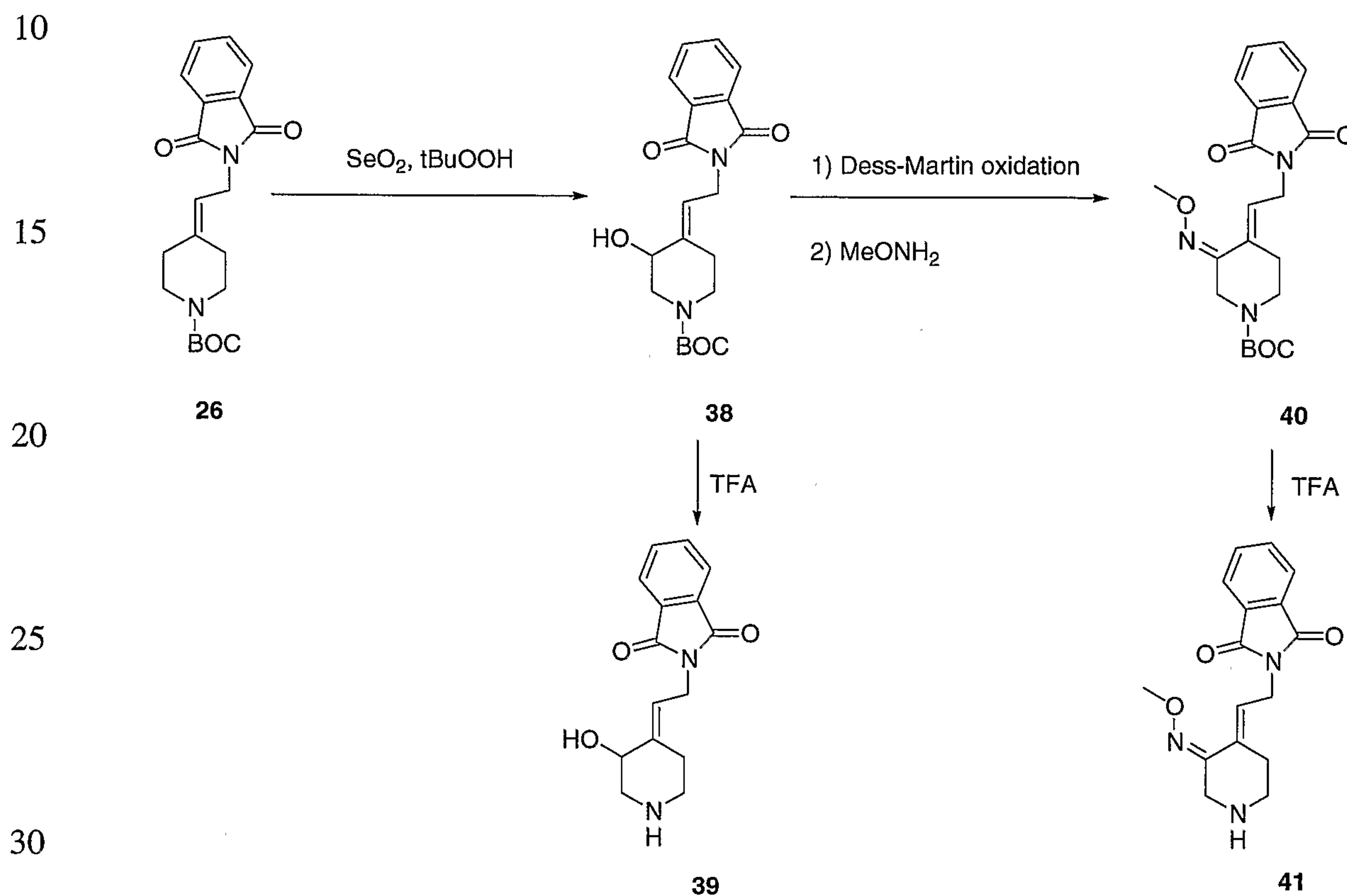
- (E/Z)-2-[2-(1-Benzyl-3-pyrrolidinylidene)-2-chloroethyl]-1H-isoindole-1,3(2H)-dione (**E-36** and **Z-36**). Prepared by the same procedure as in the synthesis of **26** except that **35** (1.58g) was used in place of **25**. The *E/Z* isomers were separated by MPLC (0-45% ethyl acetate/hexanes) to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

5 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



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

t-Butyl (E)-4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethylidene]-3-hydroxypiperidin-1-carboxylate (**38**). A slurry of SeO₂ (0.5g, 6.06 mmol) in CH₂Cl₂ (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
40 treated with a solution of ethylidene **26** (1.44g, 4.04 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (25 mL). The layers are separated, and the organic layer was washed with 15% aqueous sodium thiosulfate (15 mL), dried (MgSO₄), 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.
5 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**
10 was used in place of **26**. MS 273 (M + H).

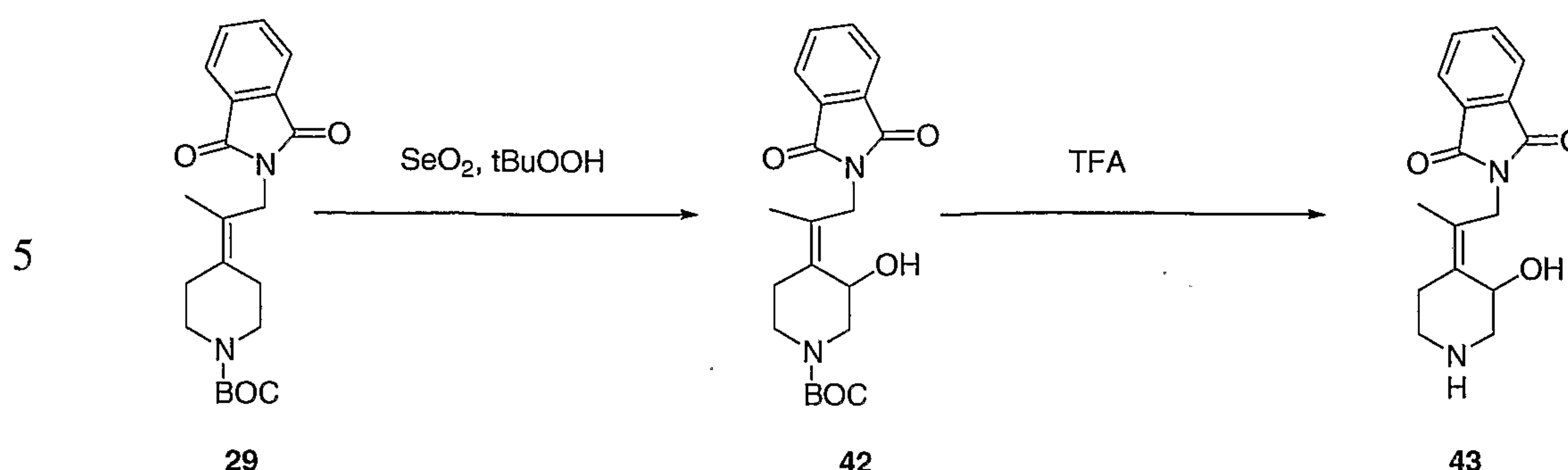
(E)-*t*-Butyl 4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethylidene]-3-methoxyimino-piperidinyl-1-carboxylate (40). A solution of **38** (0.51 g, 1.37 mmol) in CH₂Cl₂ (15 mL) at 25°C was treated with Dess-Martin periodinane
15 (0.254 g, 0.60 mmol). After 1 h, the reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with 10% aqueous NaHCO₃ (3 x 25 mL), dried (MgSO₄), 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
20 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 NaHCO₃ (3 x 25 mL), dried (MgSO₄), 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).

25

(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).

30

Scheme XVII

Compound **43** of Scheme XVII:

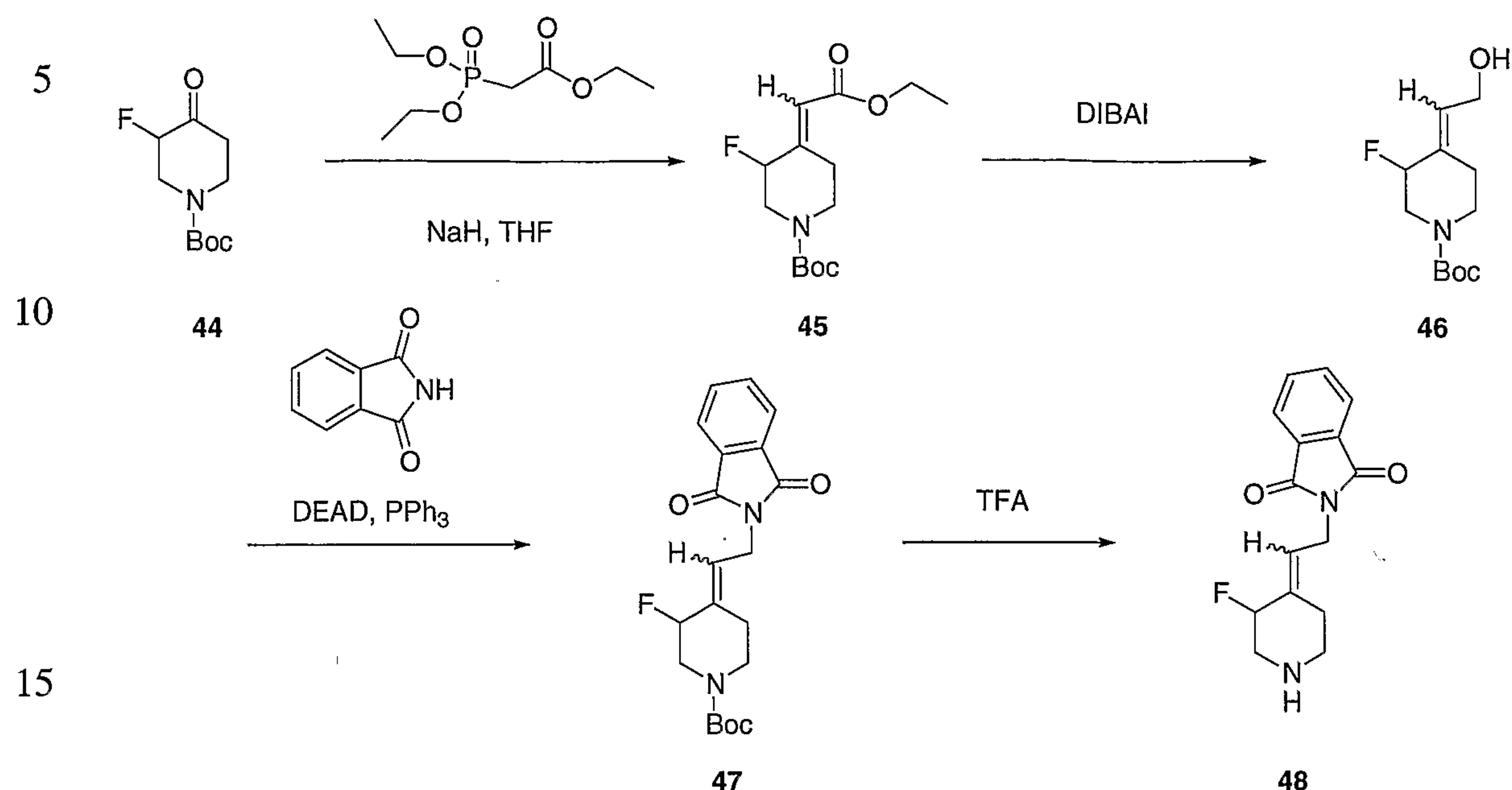
10 (Z)-*t*-Butyl 4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-methylethylidene]-3-hydroxy-piperidiny-1-carboxylate (**42**). A slurry of SeO₂ (1.3 g, 11.4 mmol) in CH₂Cl₂ (15 mL) at 0°C was treated with *tert*-butyl hydroperoxide (4 mL, 22 mmol, 5-6 M, 10% in undecane) via a syringe. After 20 min, the reaction mixture was treated with a solution of ethylidene **29** (3.4 g, 9.1 mmol) in CH₂Cl₂

15 (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 CH₂Cl₂ (25 mL). The layers were separated, and the organic layer was washed with 15% aqueous sodium thiosulfate (15 mL), dried (MgSO₄), filtered and

20 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).

25 (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).

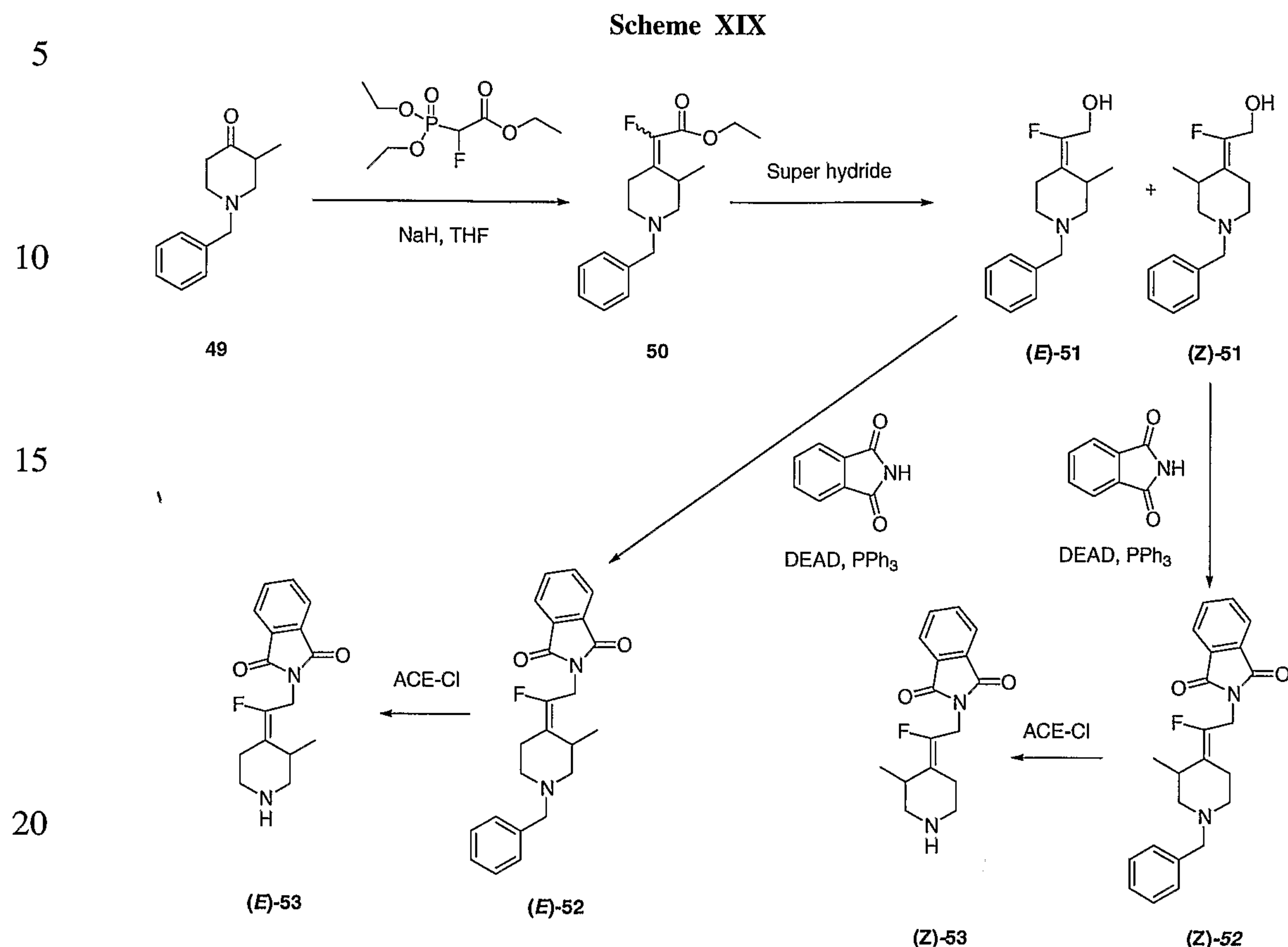
(E/Z)-t-Butyl 4-(2-hydroxyethylidene)-3-fluoropiperidinyl-1-carboxylate (46)

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-fluoropiperidinyl-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).



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

Ethyl 1-[3-methyl-1-(phenylmethyl)-4-piperidinyldienyl]-1-fluoroacetate (50).

25 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).

30 2-[3-methyl-1-(phenylmethyl)-4-piperidinyldienyl]-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 NaHCO₃ (3 x 50 mL), dried (MgSO₄) 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).

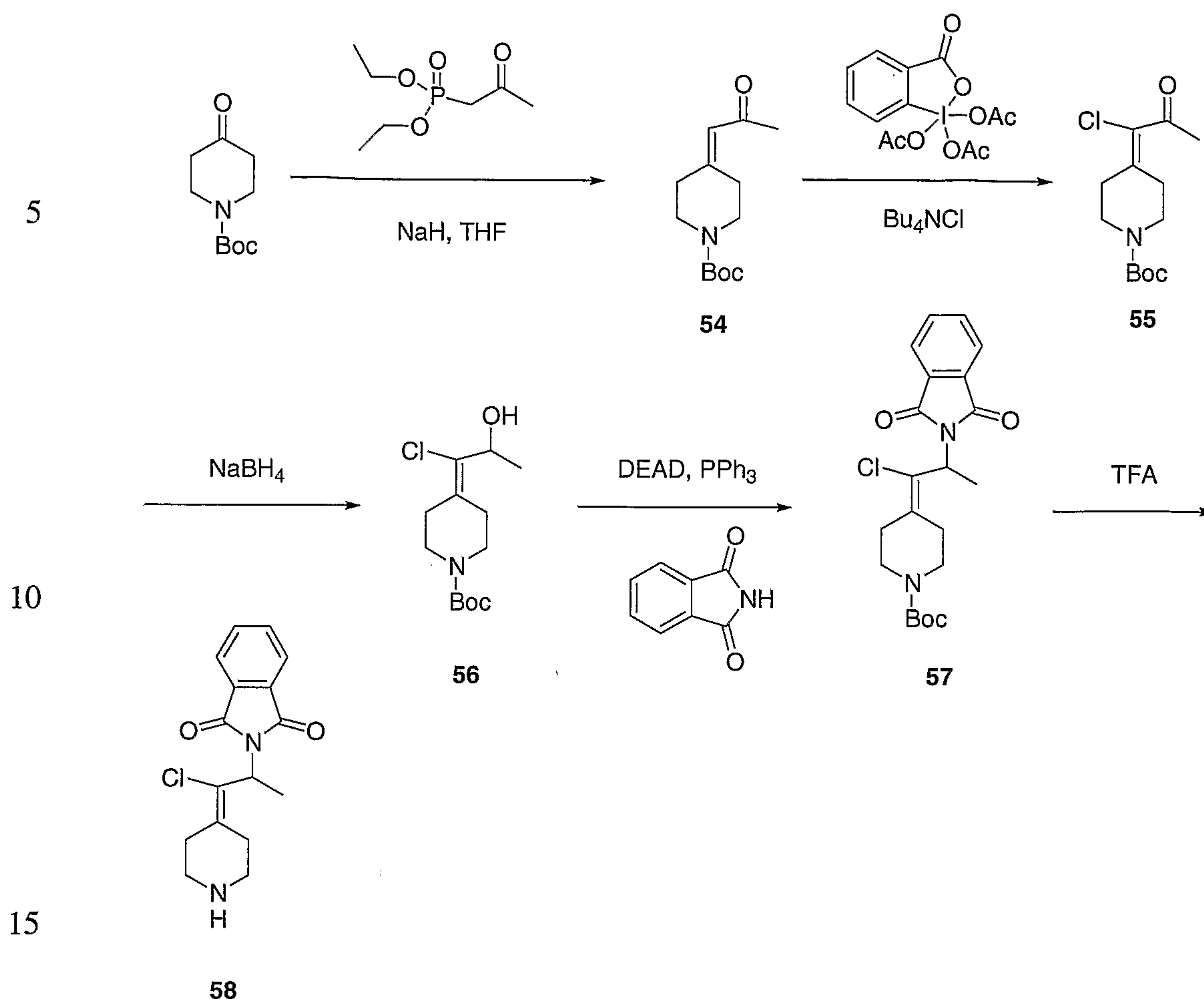
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(E)-2-[2-(3-methyl-1-(phenylmethyl)-4-piperidinylidenyl)-2-fluoroethyl]-1H-isoindole-1,3(2H)-dione (E-52). Prepared by the same procedure as in the synthesis of **26** except that E-**51** was used in place of **25**. MS 379 (M + H).

(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
20 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
25 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
30 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 x 100 mL), dried (MgSO₄), 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).

5

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 (MgSO₄). 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).

15

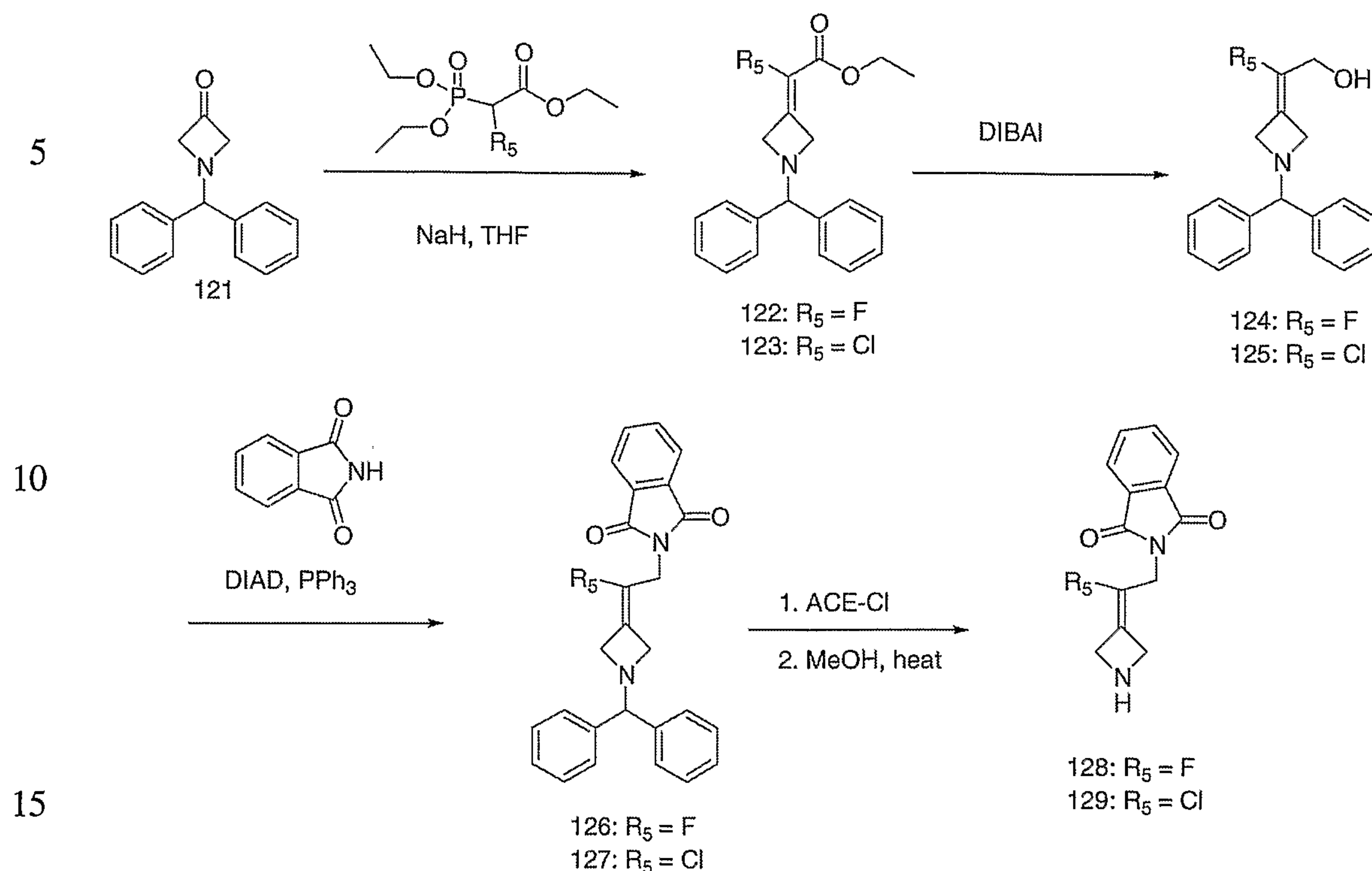
4-[1-Chloro-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propylidene]piperidine-1-carboxylic acid tert-butyl ester (57). Prepared by the same procedure as in the synthesis of **26** except that **56** was used in place of **25**. MS 427 (M + Na).

20 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).

25

30

Scheme XXXI

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**; $R_5 = Cl$).

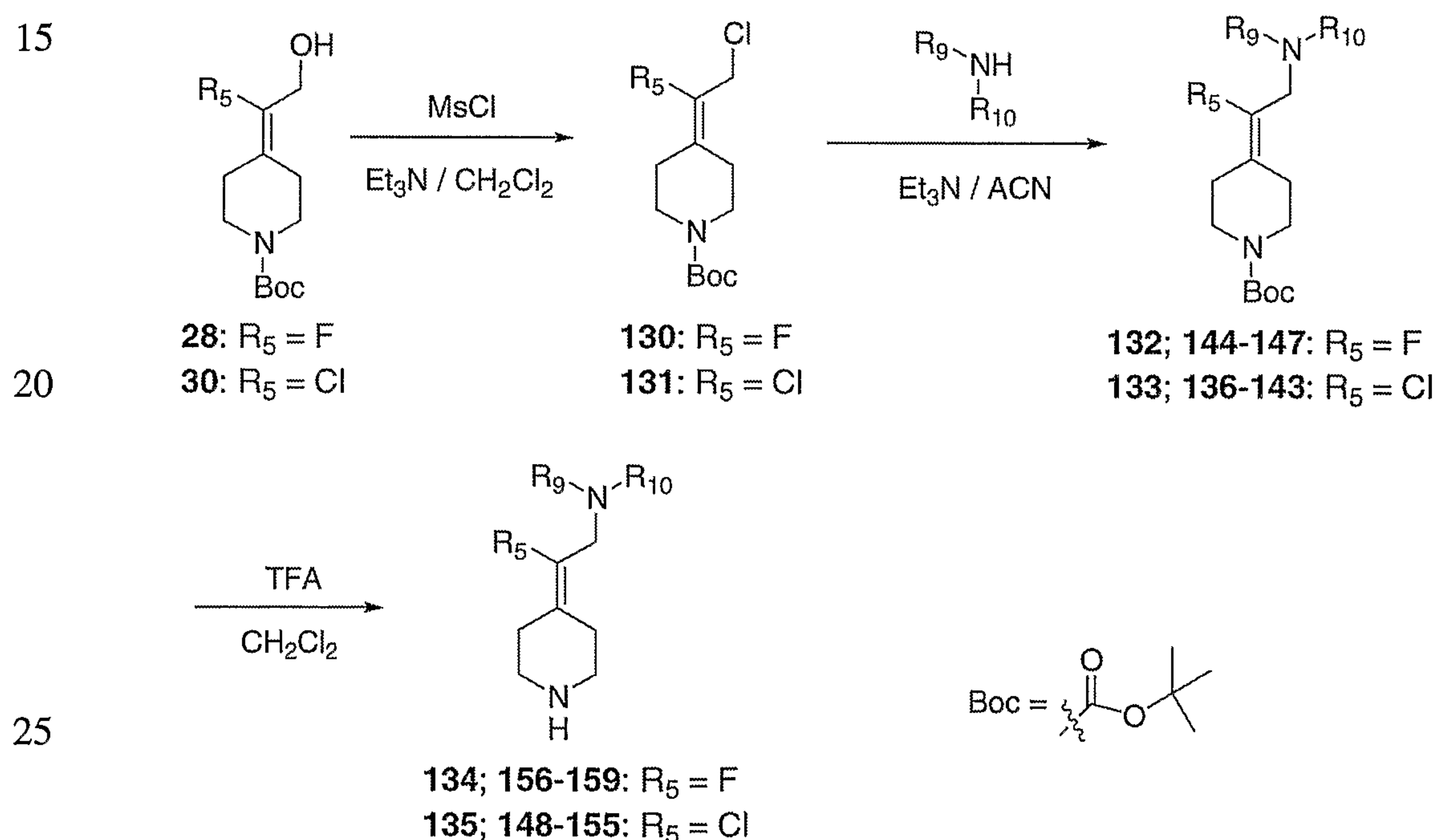
This was prepared in a similar manner to the procedure described above except that triethyl 2-chloro-2-phosphonoacetate was utilized in place of triethyl 2-fluoro-2-phosphonoacetate in the reaction. Ester **123** ($R_5 = Cl$) was isolated as a white solid (77%). MS 342, 344 ($M + H$).

- 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**; $R_5 = \text{Cl}$). This was prepared in a similar manner to the procedure described above except that ester **123** ($R_5 = \text{Cl}$) was used in place of ester **122** ($R_5 = F$). Alcohol **125** ($R_5 = \text{Cl}$) 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**; $R_5 = \text{Cl}$). This was prepared in a similar manner to the procedure described above except that alcohol **125** ($R_5 = \text{Cl}$) was used in place of alcohol **124** ($R_5 = F$) in the Mitsunobu reaction. Phthalimide **127** ($R_5 = \text{Cl}$) 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



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**; R₅ = F).

- 5 This was prepared in a similar manner to the procedure described above except that alcohol **28** (R₅ = F) was used in place of alcohol **30** (R₅ = Cl).

t-Butyl 4-[2-(N-benzyl-N-methylamino)-1-chloroethylidene]piperidinyl-1-carboxylate (**133**; R₅ = Cl; R₉ = methyl; R₁₀ = benzyl).

- 10 A solution of **131** (R₅ = 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 (MgSO₄). Purification by flash
15 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**; R₅ = F; R₉ = methyl; R₁₀ = benzyl).

- 20 This was prepared in a similar manner to the procedure described above except that chloride **130** (R₅ = F) was used in place of chloride **131** (R₅ = Cl). MS 349 (M+H).

N-Benzyl-N-methyl-(2-chloro-2-piperidin-4-ylidene)ethylamine (**135**; R₅ = Cl).

- 25 A solution of **133** (R₅ = Cl) (690 mg, 1.89 mmol) was dissolved in CH₂Cl₂ (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).

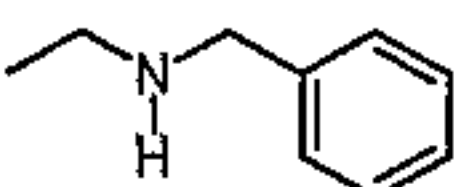
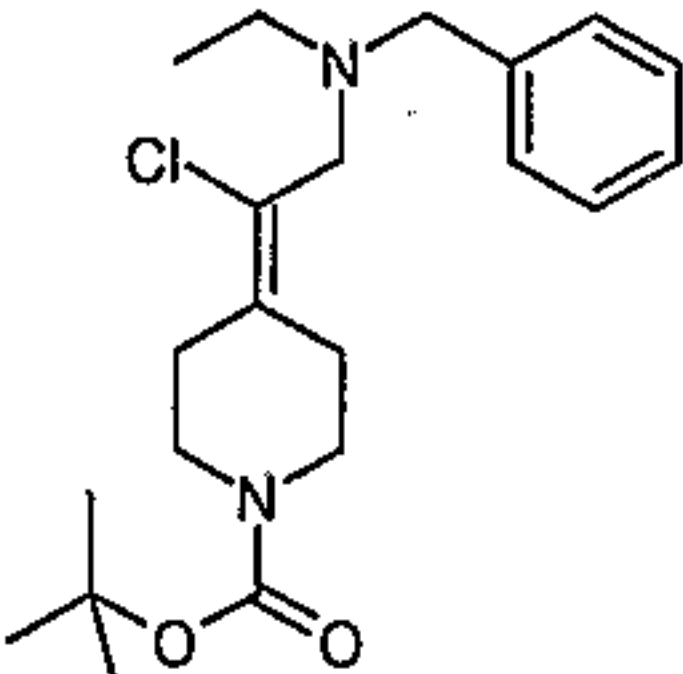
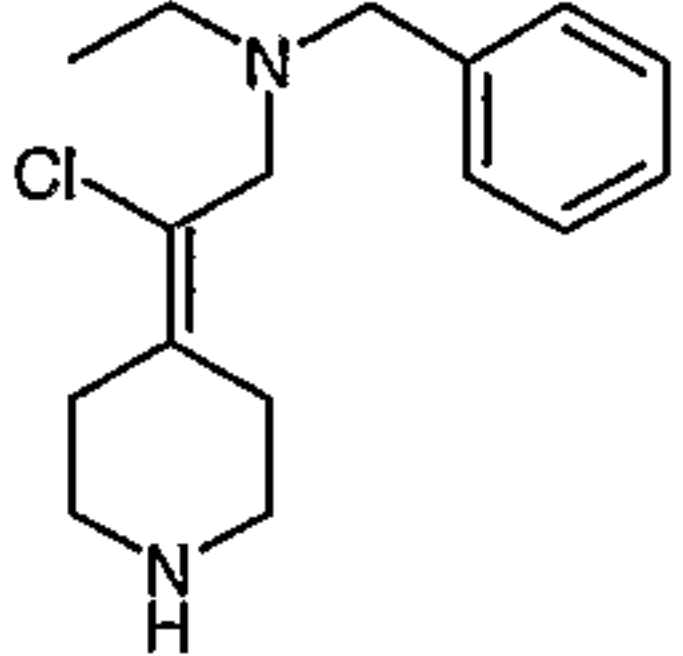
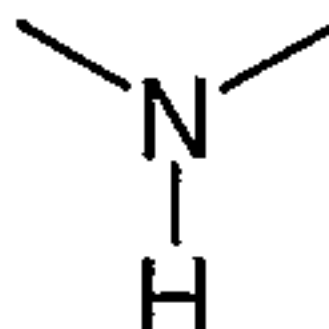
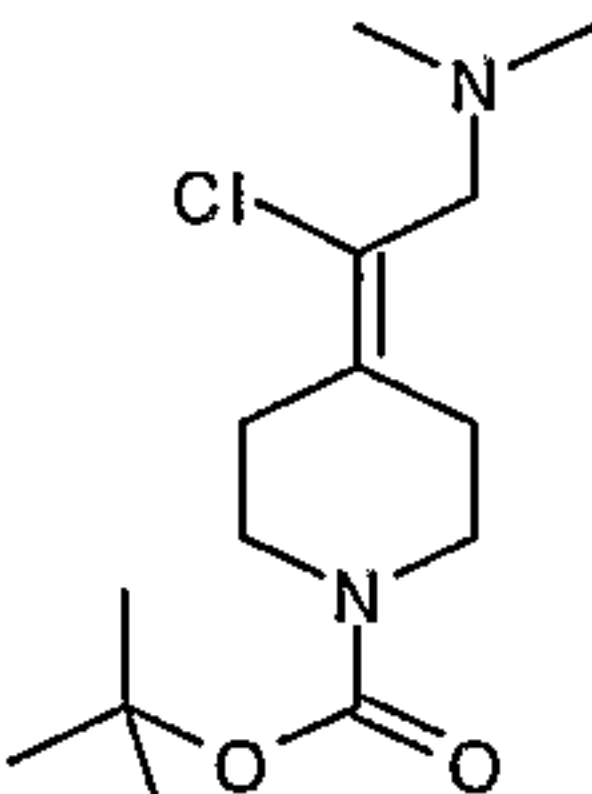
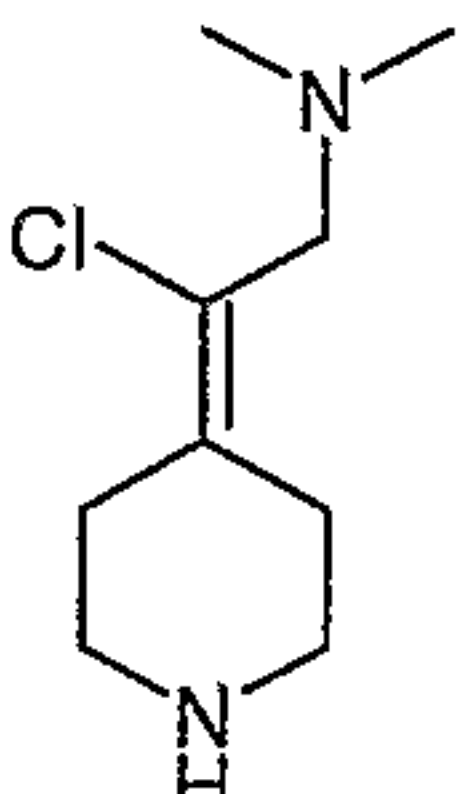
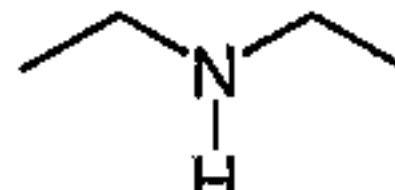
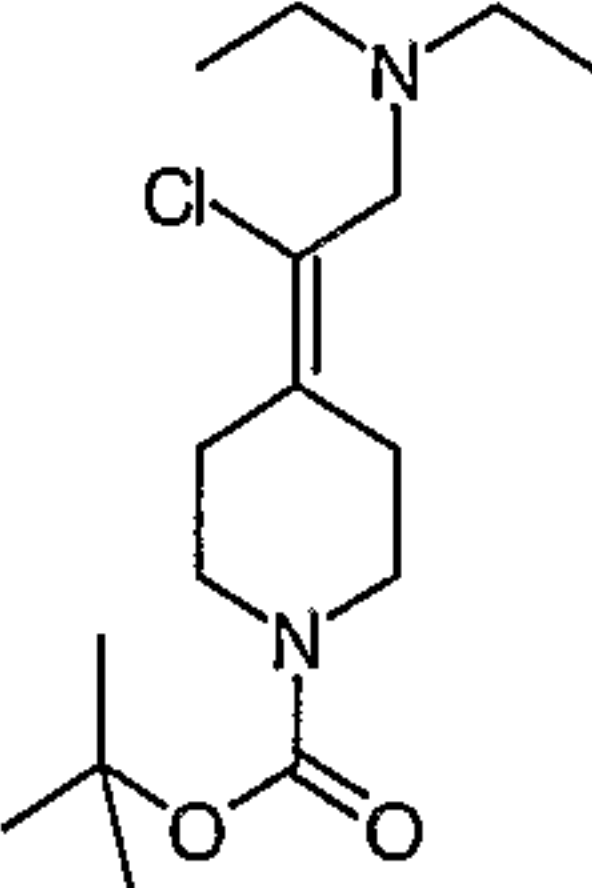
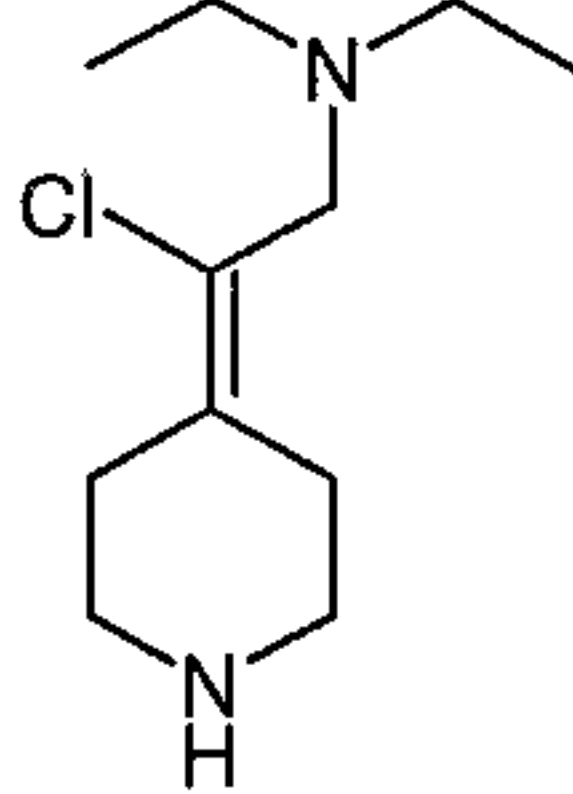
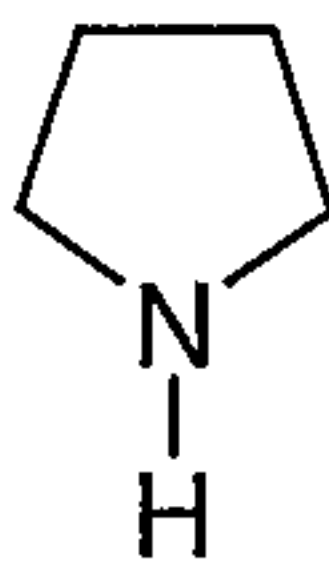
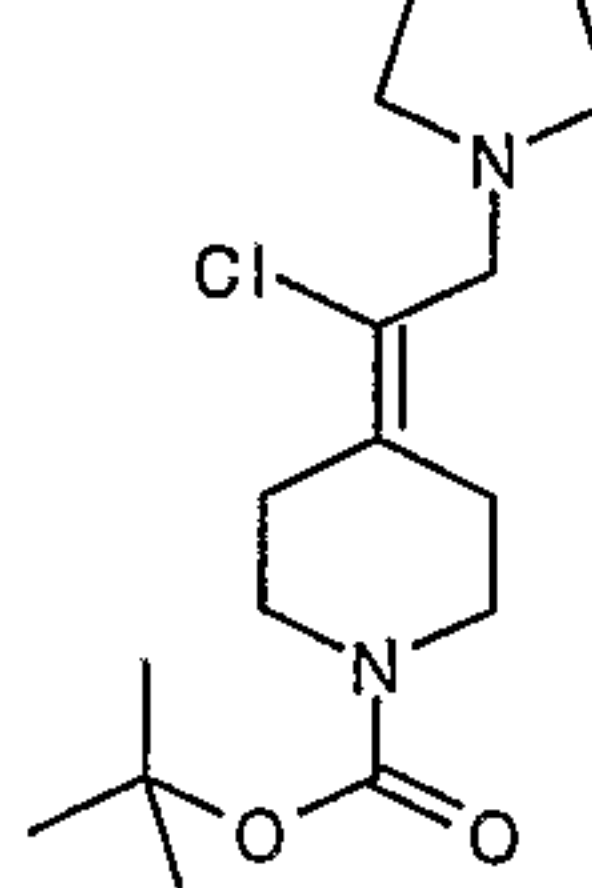
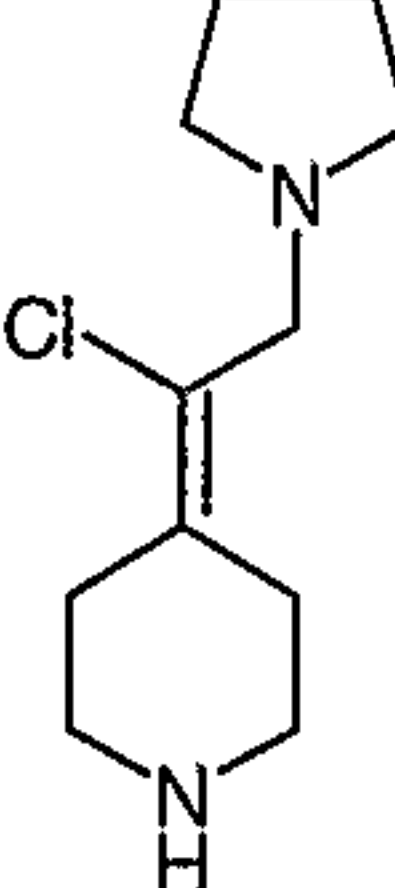
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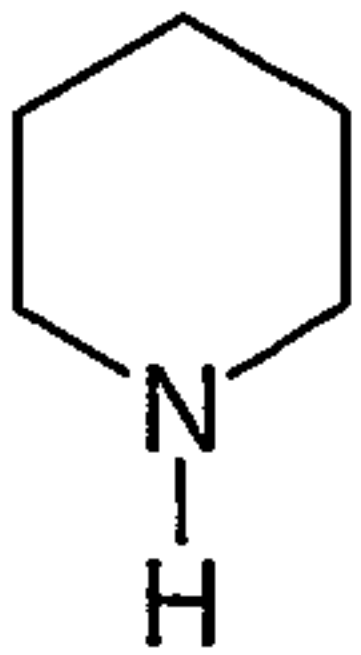
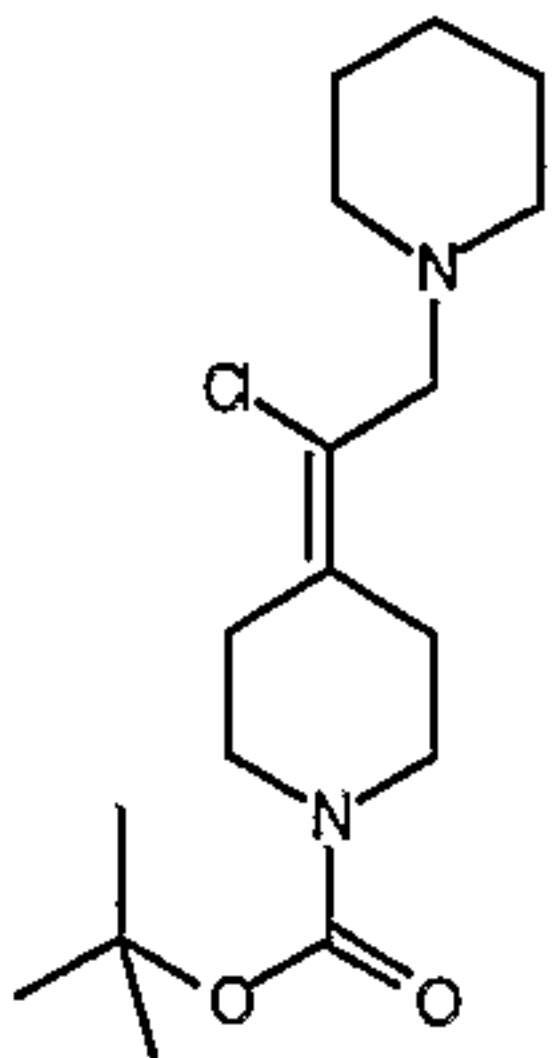
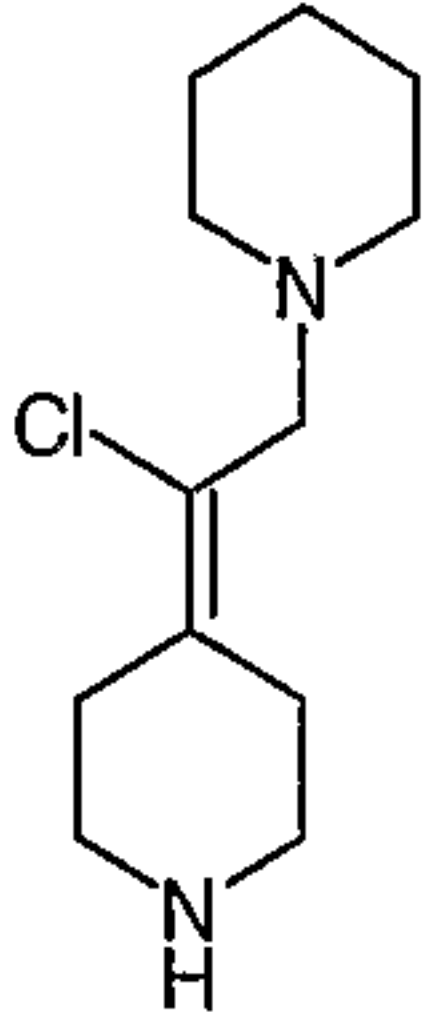
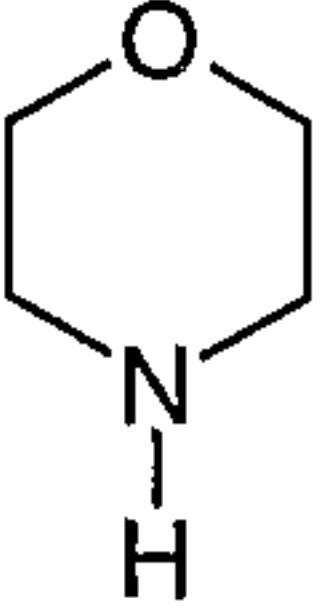
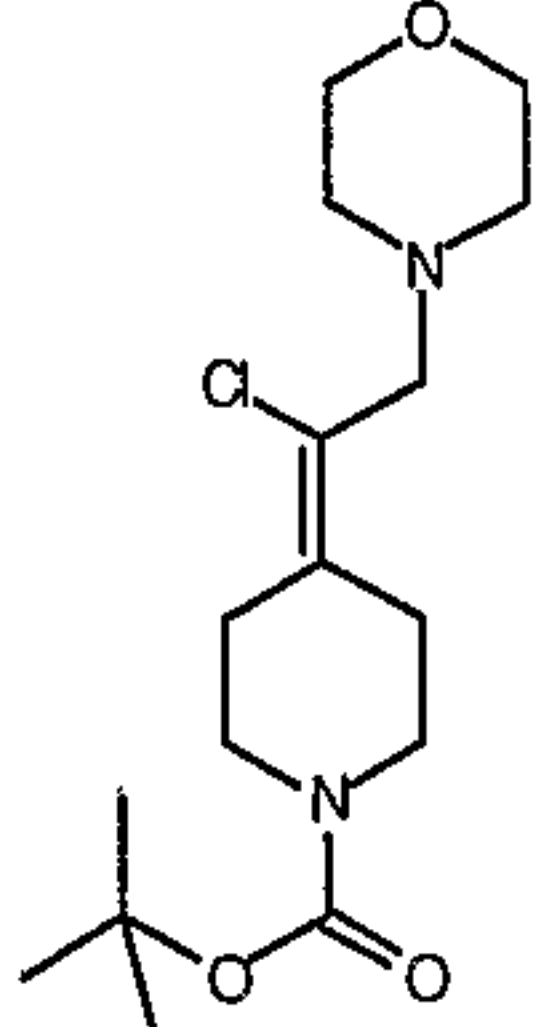
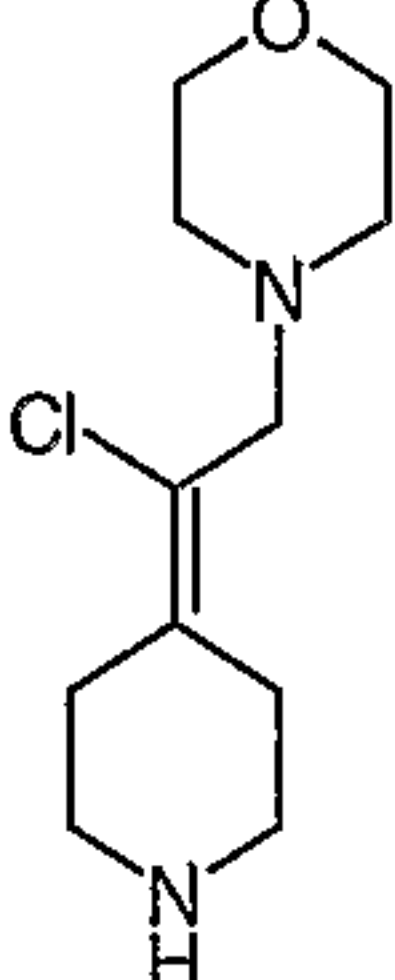
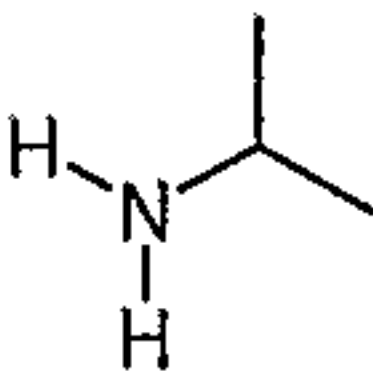
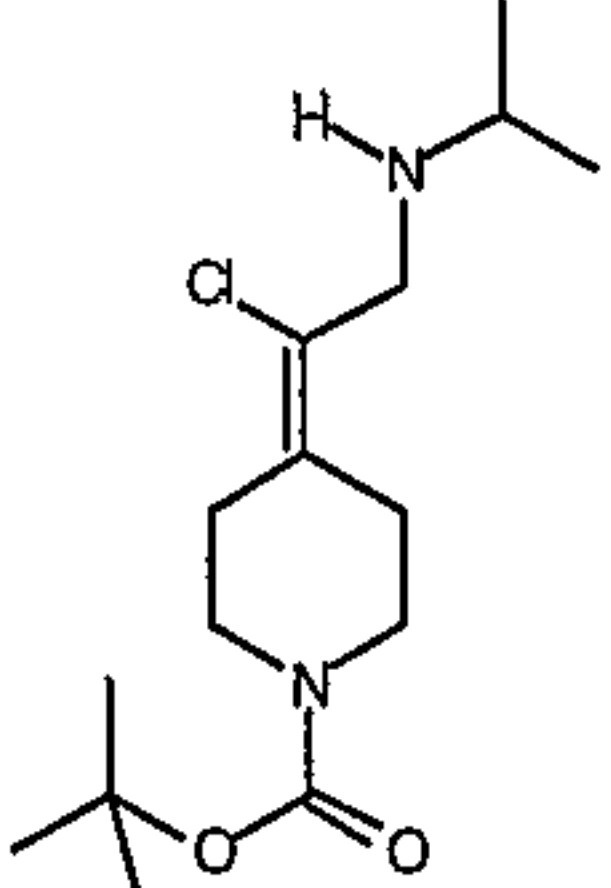
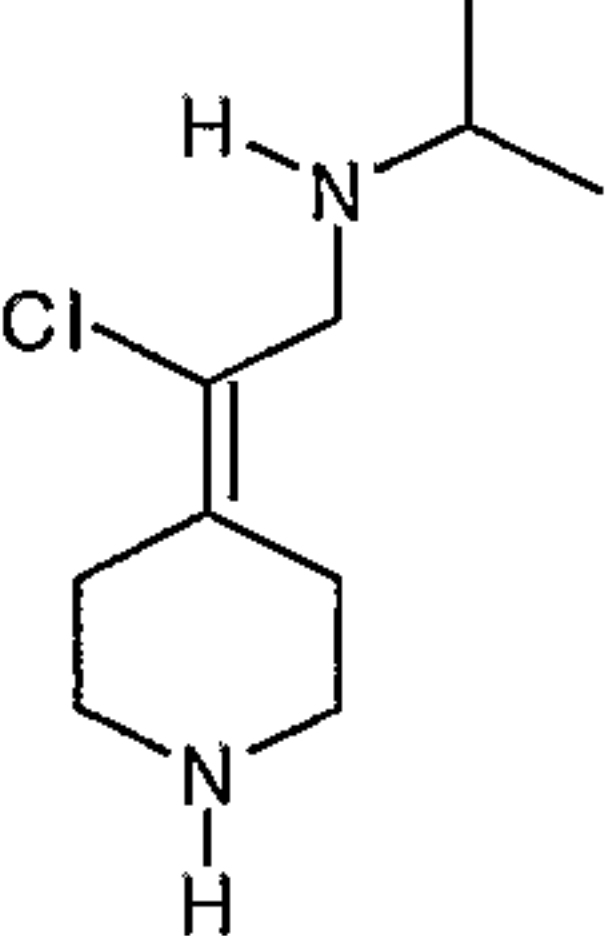
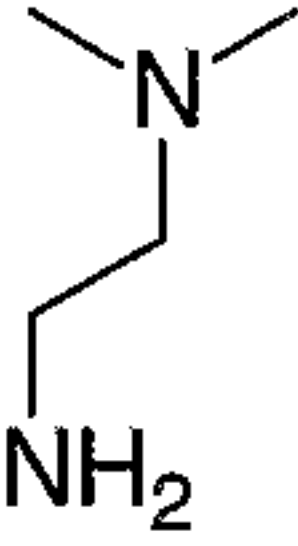
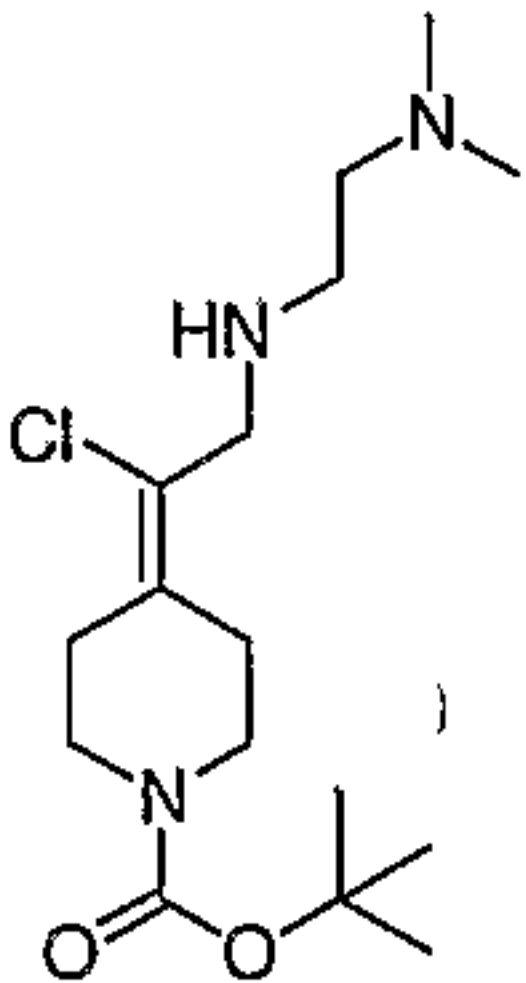
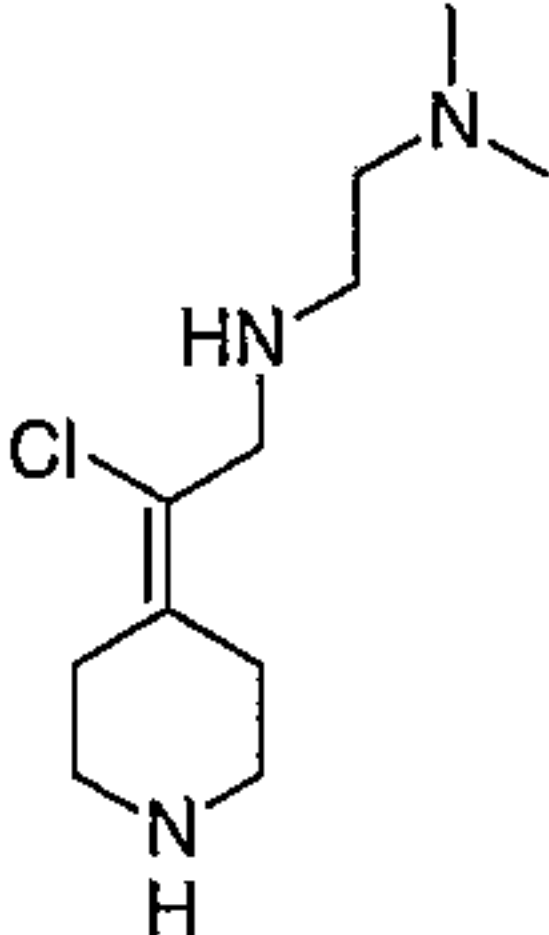
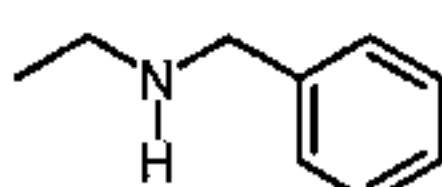
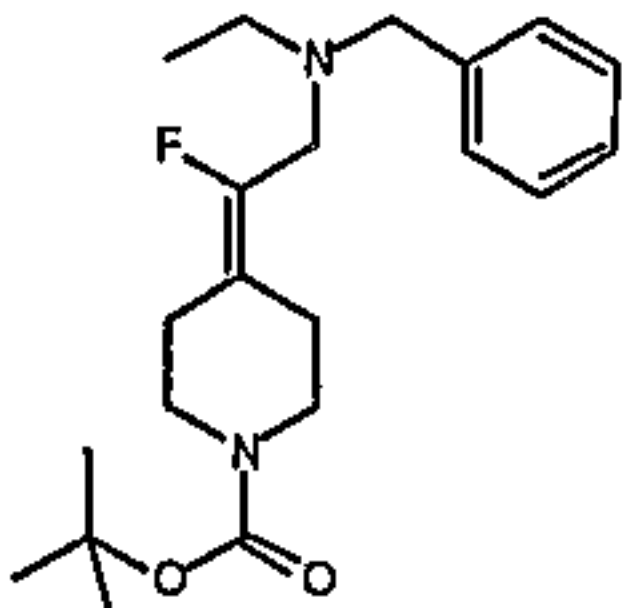
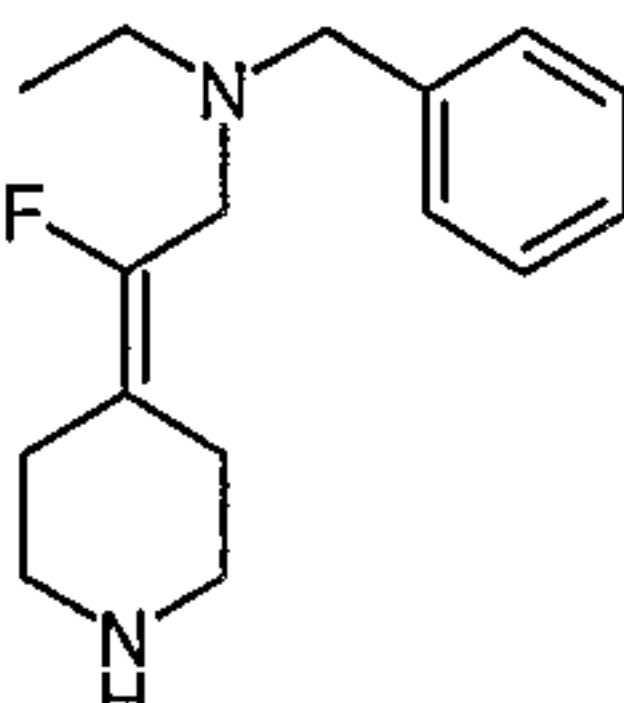
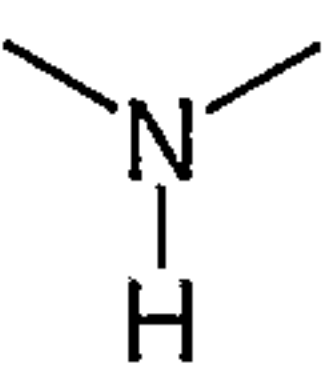
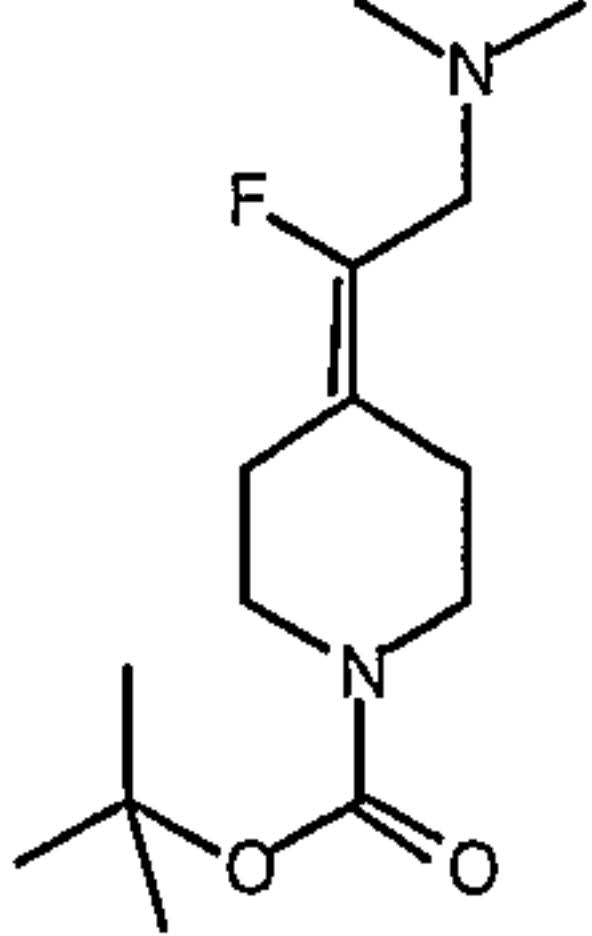
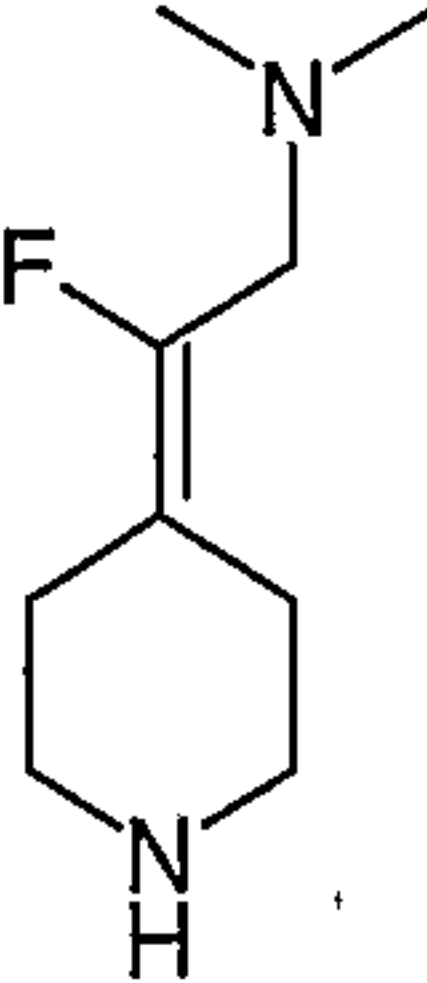
N-Benzyl-N-methyl-(2-fluoro-2-piperidin-4-ylidene)ethylamine (**134**; R₅ = F).

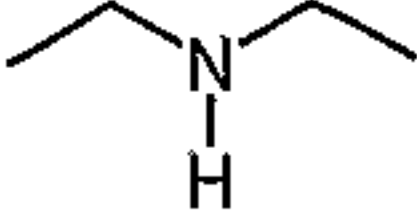
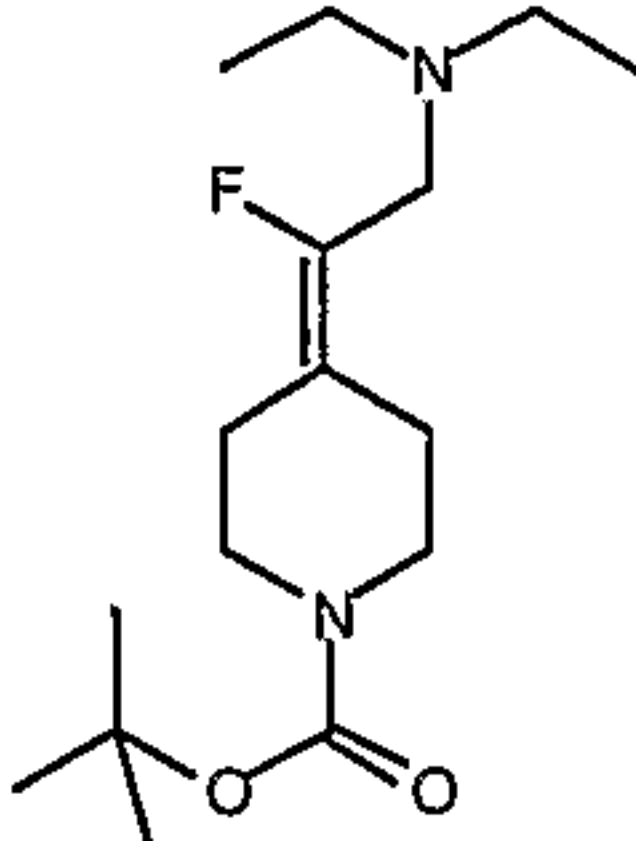
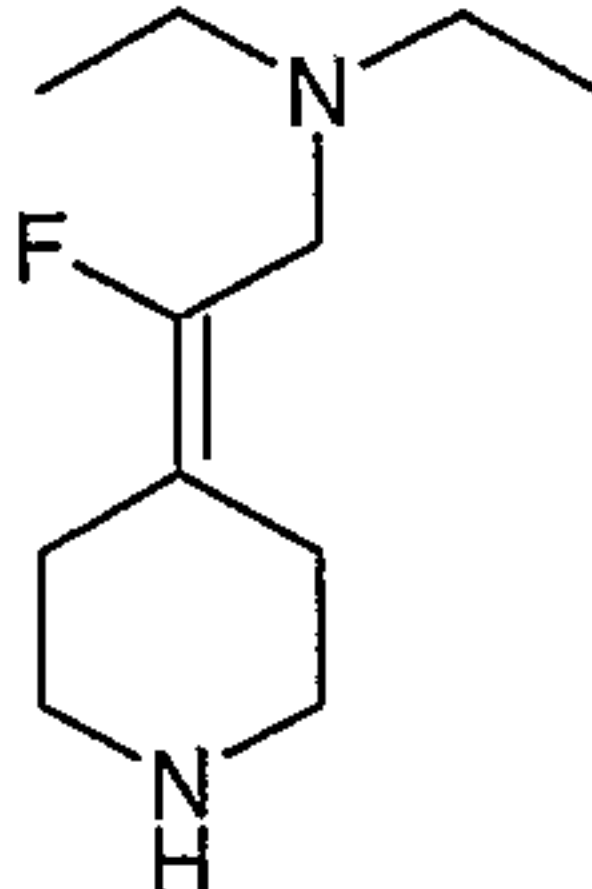
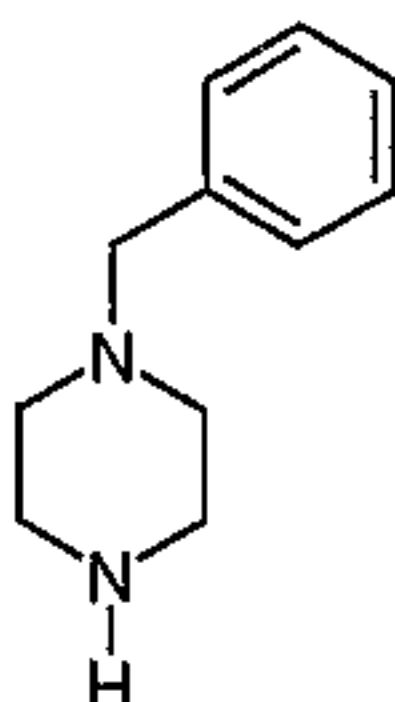
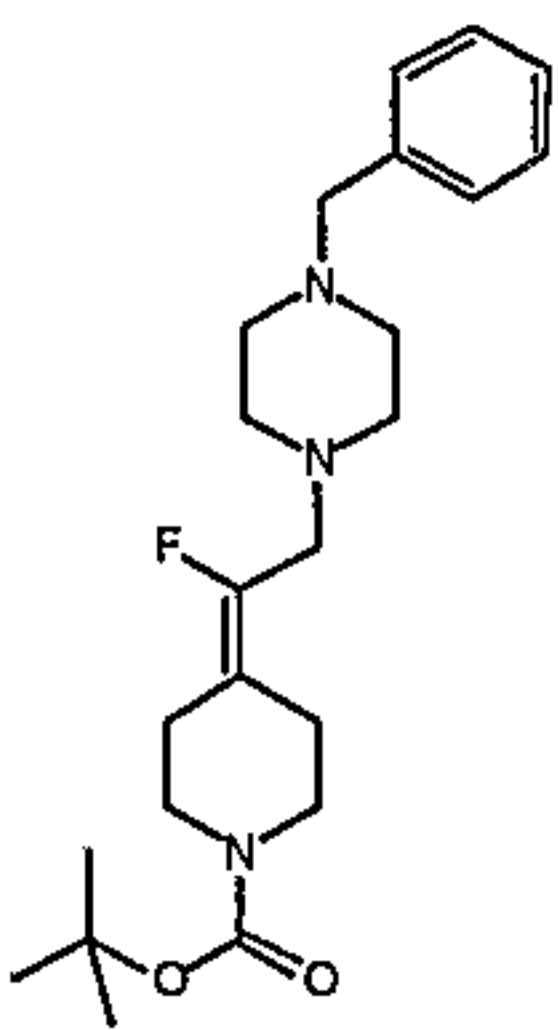
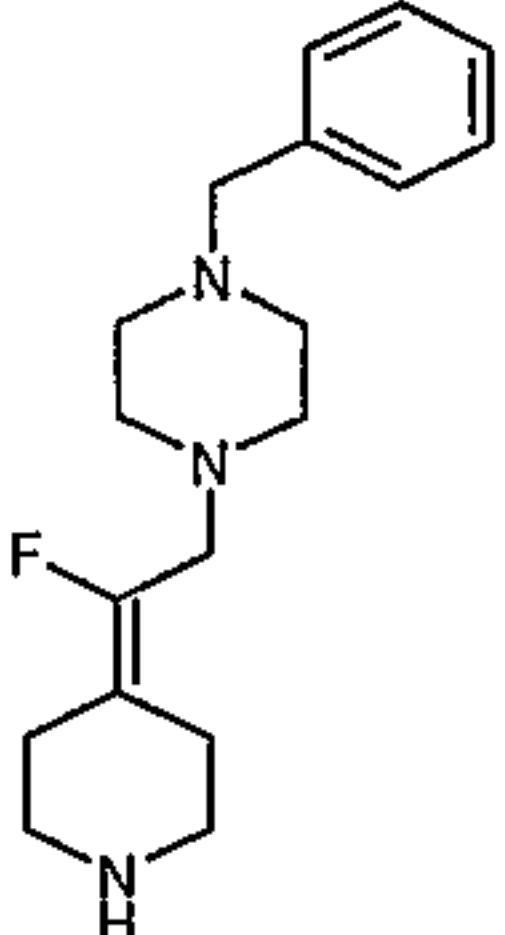
This was prepared in a similar manner to the procedure described above except that amine **132** ($R_5 = F$) was used in place of amine **133** ($R_5 = Cl$). MS 249 ($M+H$).

- 5 Table 9 lists the Boc-protected amines (**136-147**) and the derived amines (**148-159**) prepared by analogous procedures to those detailed above.

Table XX

NHR ₉ R 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

Final Product Preparation

7-[4-(2-Amino-1-fluoro-ethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-
 5 1,4-dihydronaphthyridine-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).

7-[4-(2-Amino-1-fluoro-ethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-
 20 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).

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).

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).

10 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).

25 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).

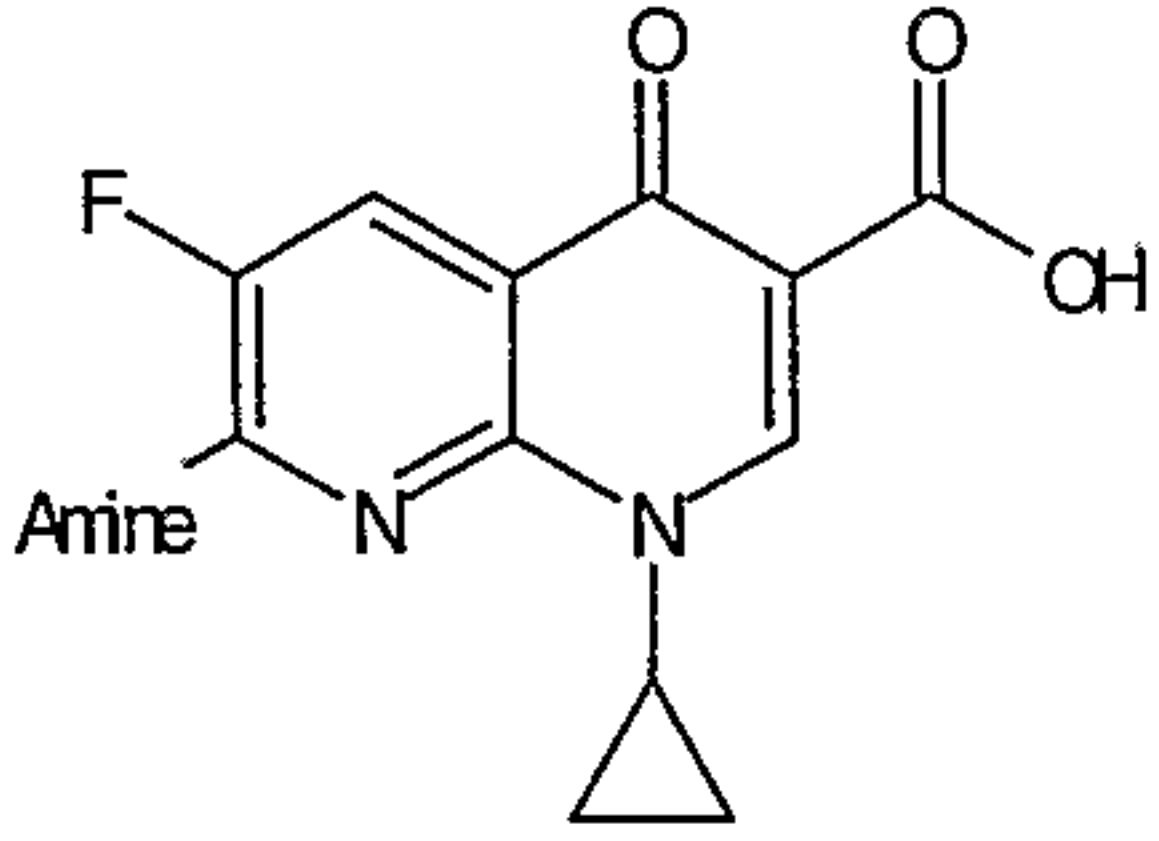
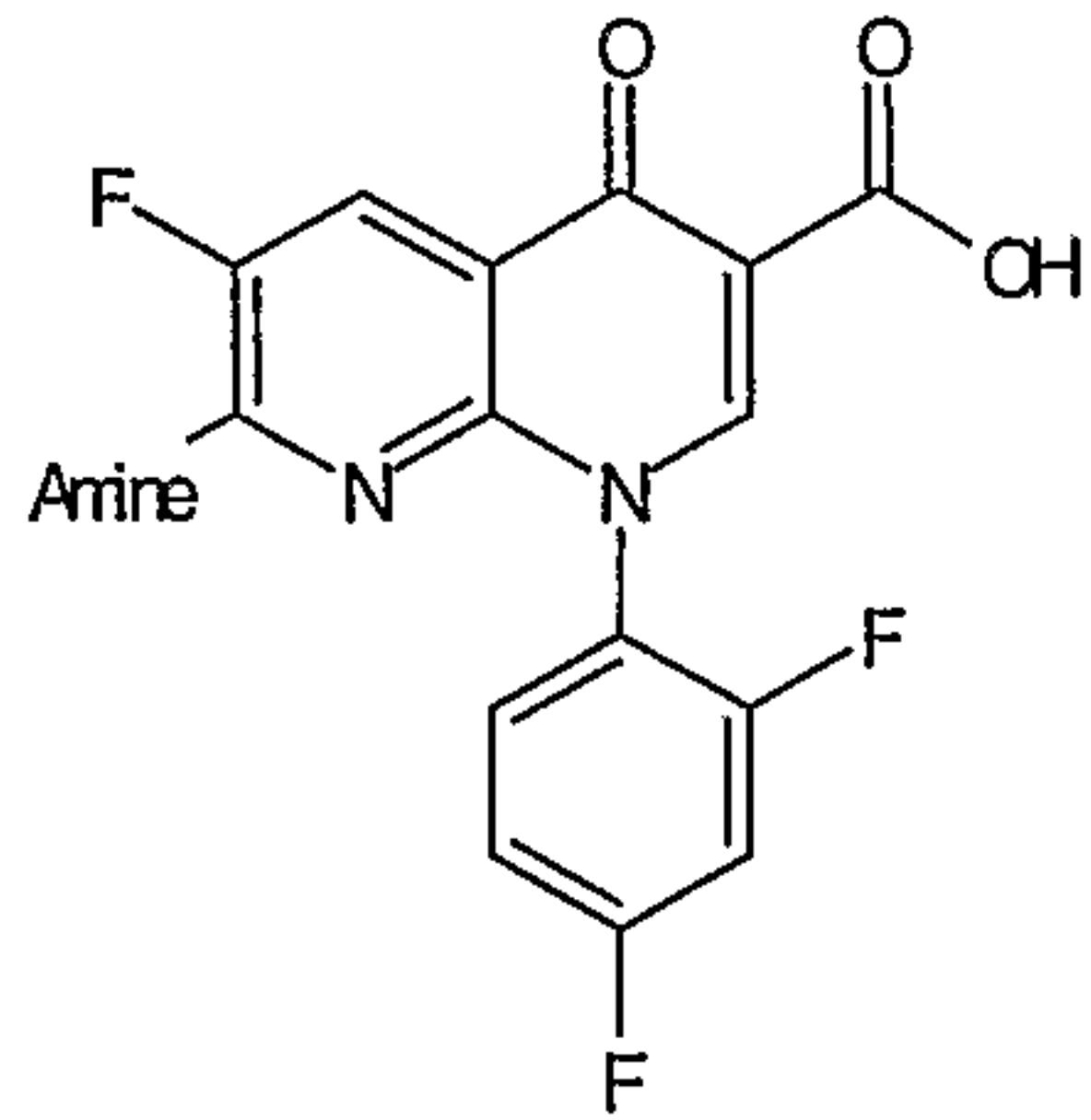
5 7-[4-(2-Hydroxyethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydronaphthyridine-3-carboxylic acid (163) A solution of amine **103** (256 mg, 1.06 mmol) and triethylamine (0.5 mL, 3.55 mmol) in acetonitrile (4 mL) was treated with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid (200 mg, 0.71 mmol) under nitrogen and the reaction mixture
10 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).

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 quinolinyI 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
20 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
25 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).

Table 4 lists the additional compounds of the instant invention prepared by the
30 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**, and **185**, 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**, and **186** a similar procedure to that for **162** was used in their preparation. For the quinolones **6-15**, **64-66**, **70**, **71**, **73**, **78**, **187**, **188**, **201-204**, **206-208**, and **210**, an analogous experimental procedure to that for compound **5** was used in their preparation. 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** 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.

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
	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

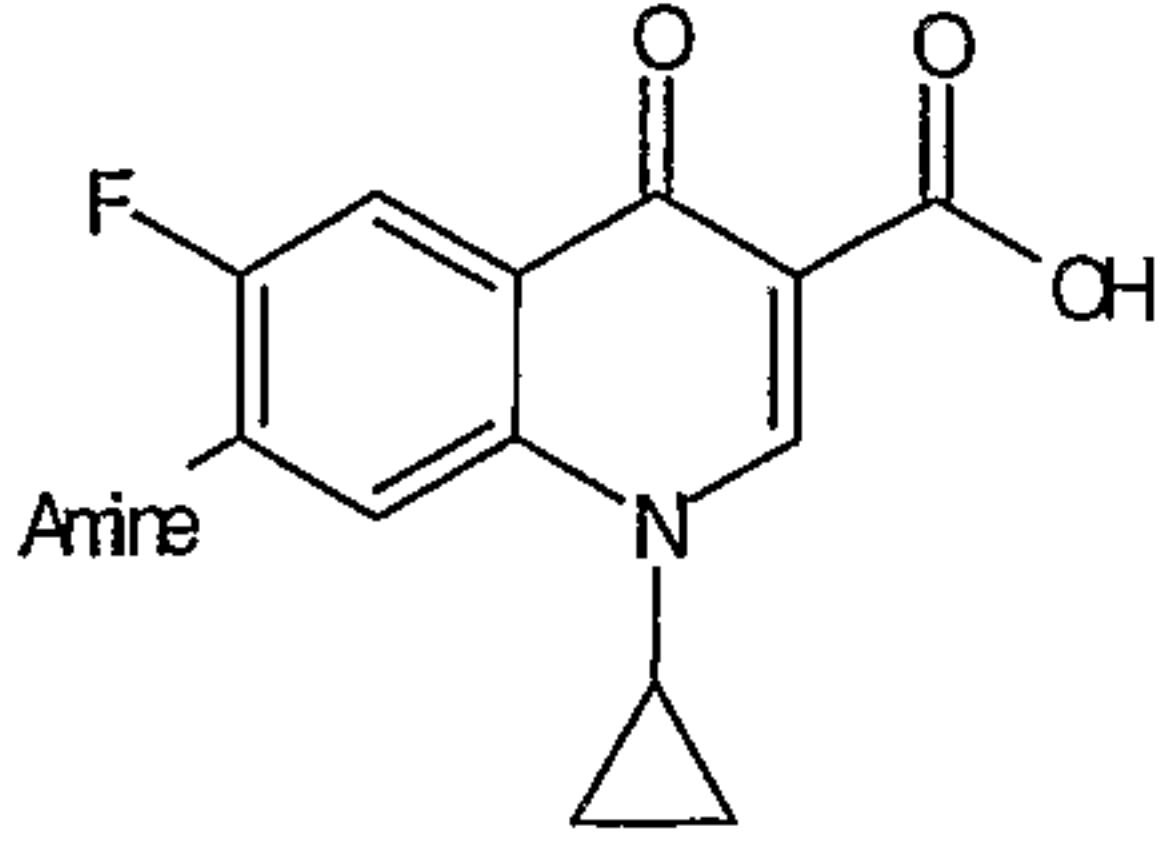
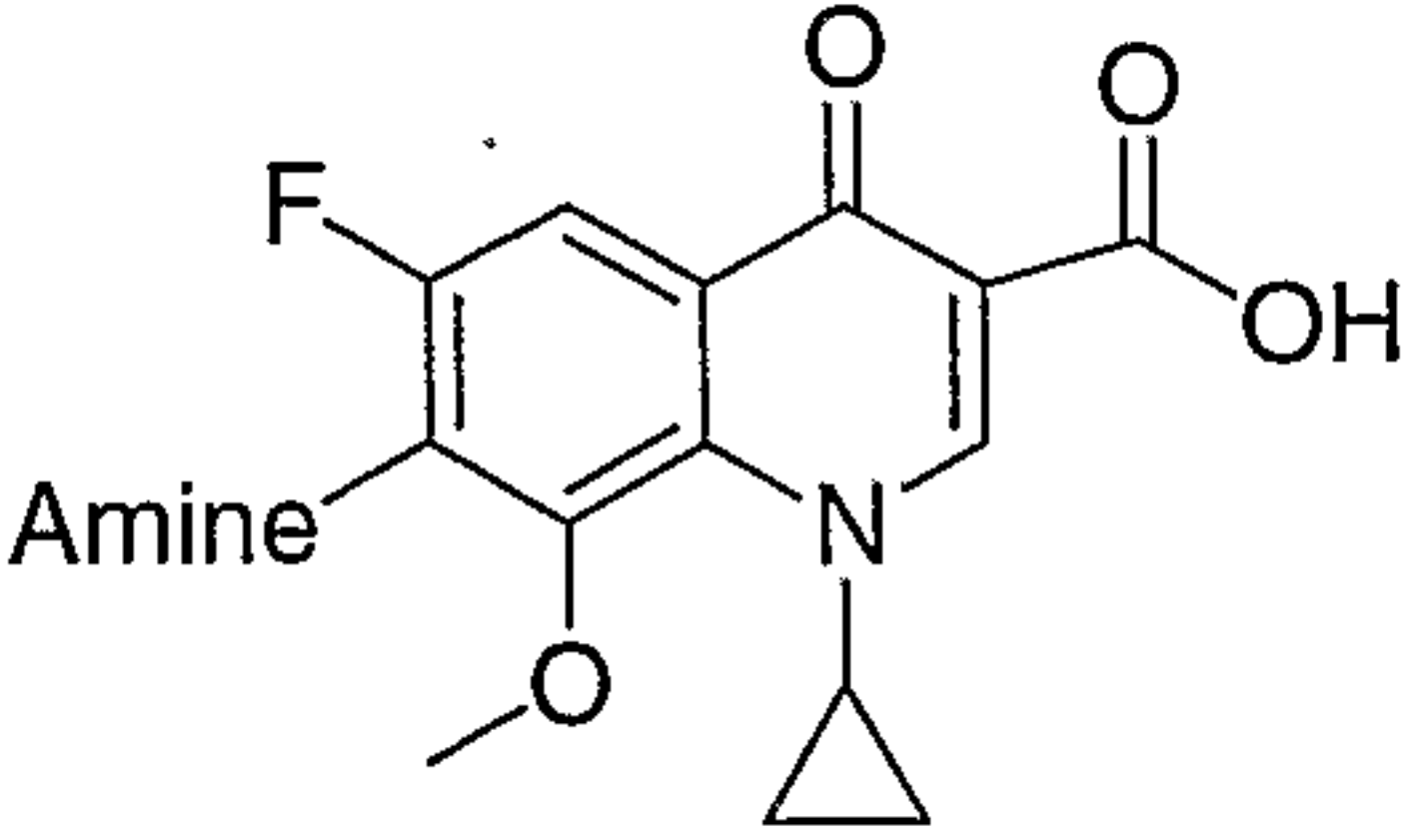
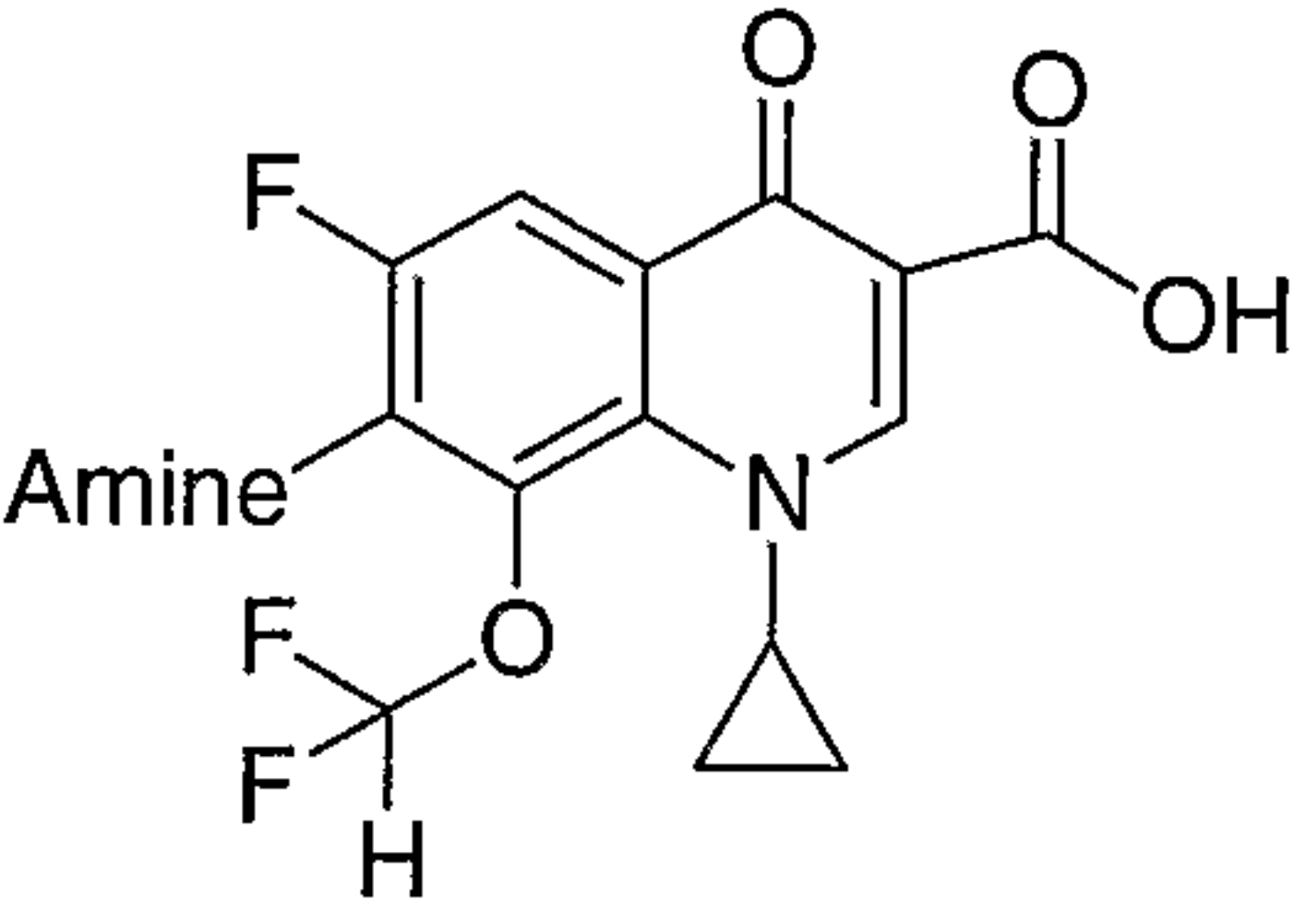
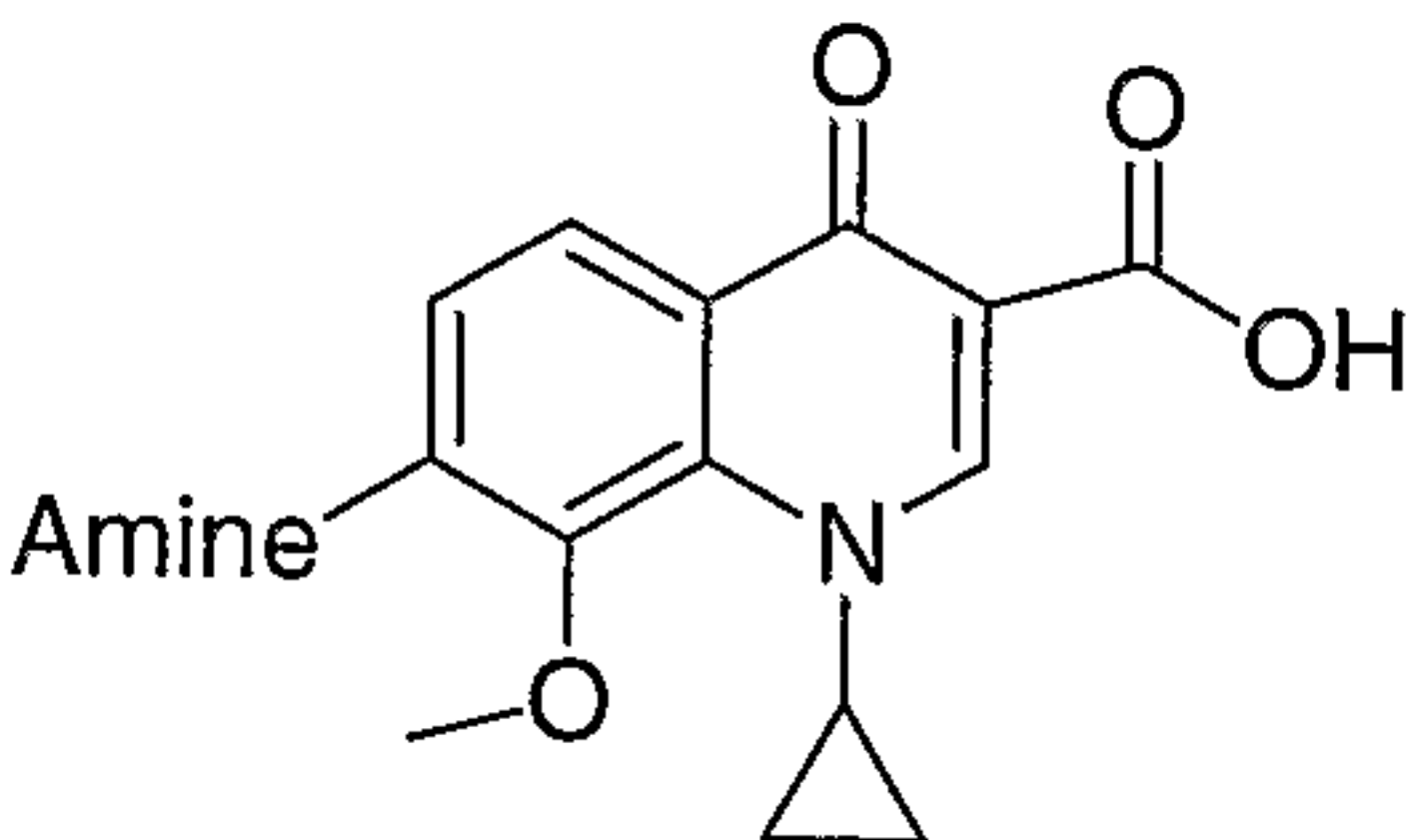
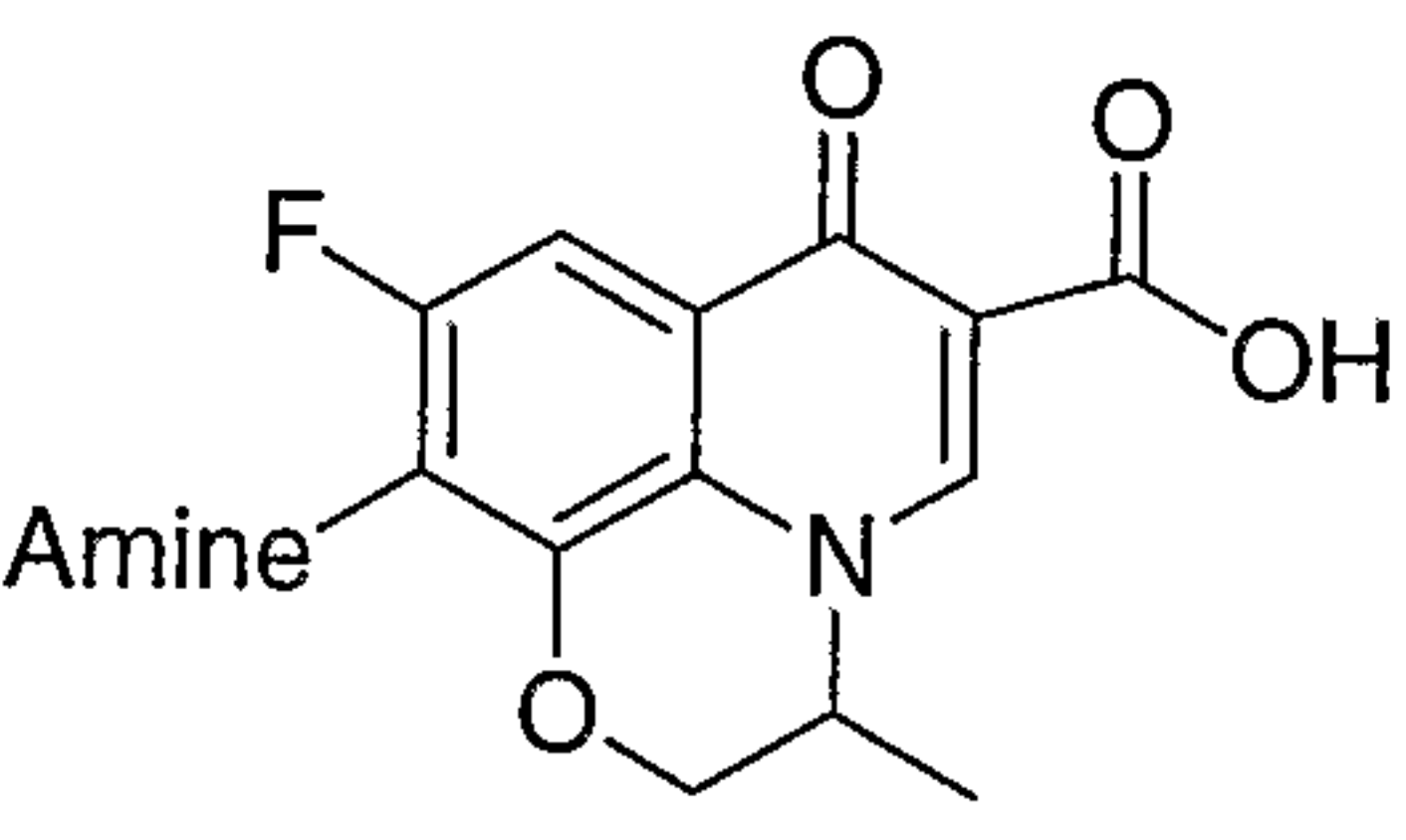
	32	64 (M + H) = 386
	33	65 (M + H) = 406
	129	76 (M + H) = 378, 380
	135	187 (M + H) = 510
	134	188 (M + H) = 494

Table 4 continued

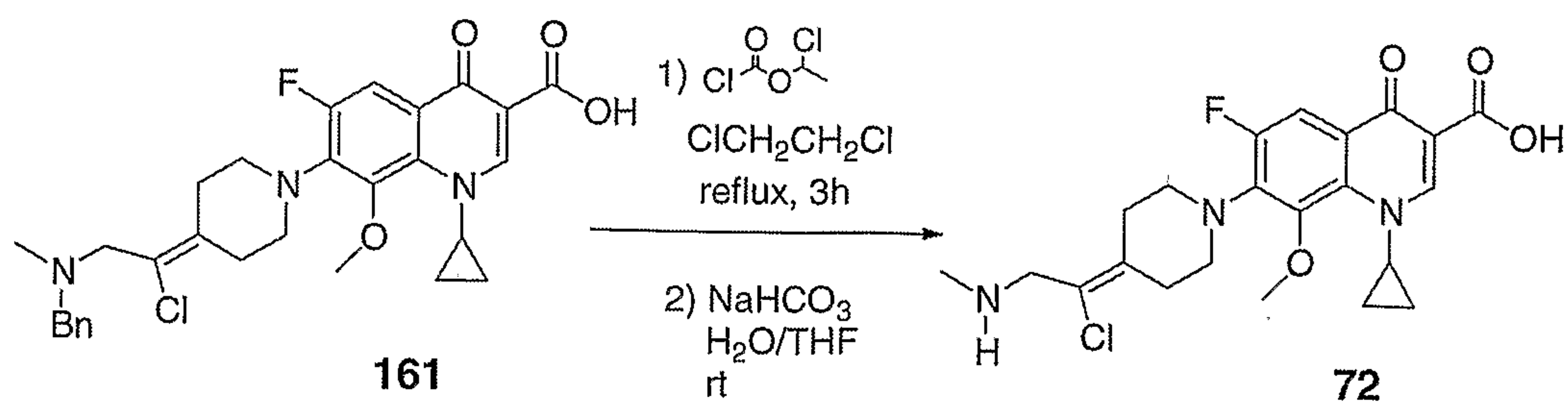
Structure	Amine	Compound Number
	31	6 (M + H) = 420
	33	7 (M + H) = 436
	Z-53	11 (M + H) = 434
	E-53	12 (M + H) = 434
	Z-37	13 (M + H) = 422
	E-37	14 (M + H) = 422
	58	15 (M + H) = 450
	129	189 (M + H) = 408, 410
	148	190 (M + H) = 554
	149	191 (M + H) = 464
	150	192 (M + H) = 492
	151	193 (M + H) = 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
	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
	31	10 (M + H) = 402
	129	209 (M + H) = 390, 392
	31	8 (M + H) = 406
	32	9 (M + H) = 402
	43	66 (M + H) = 416
	129	77 (M + H) = 394, 396
	39	210 (M + H) = 404
	105	211 (M + H) = 427

Scheme XXXIII

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10



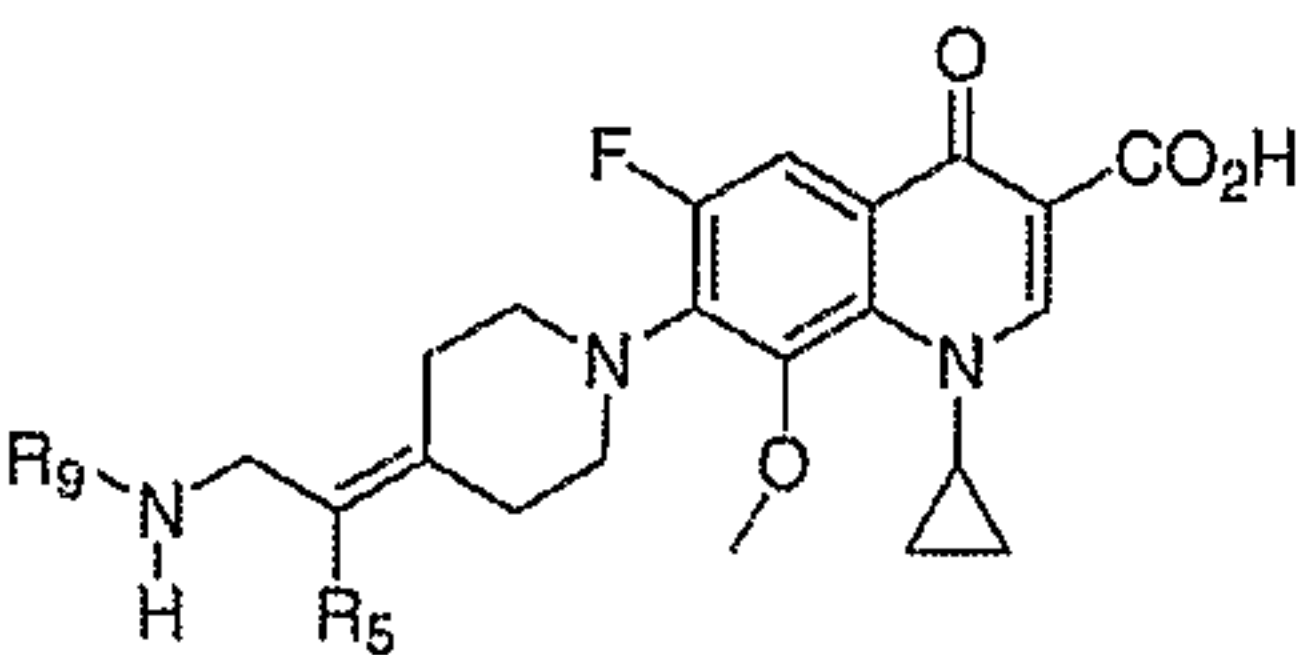
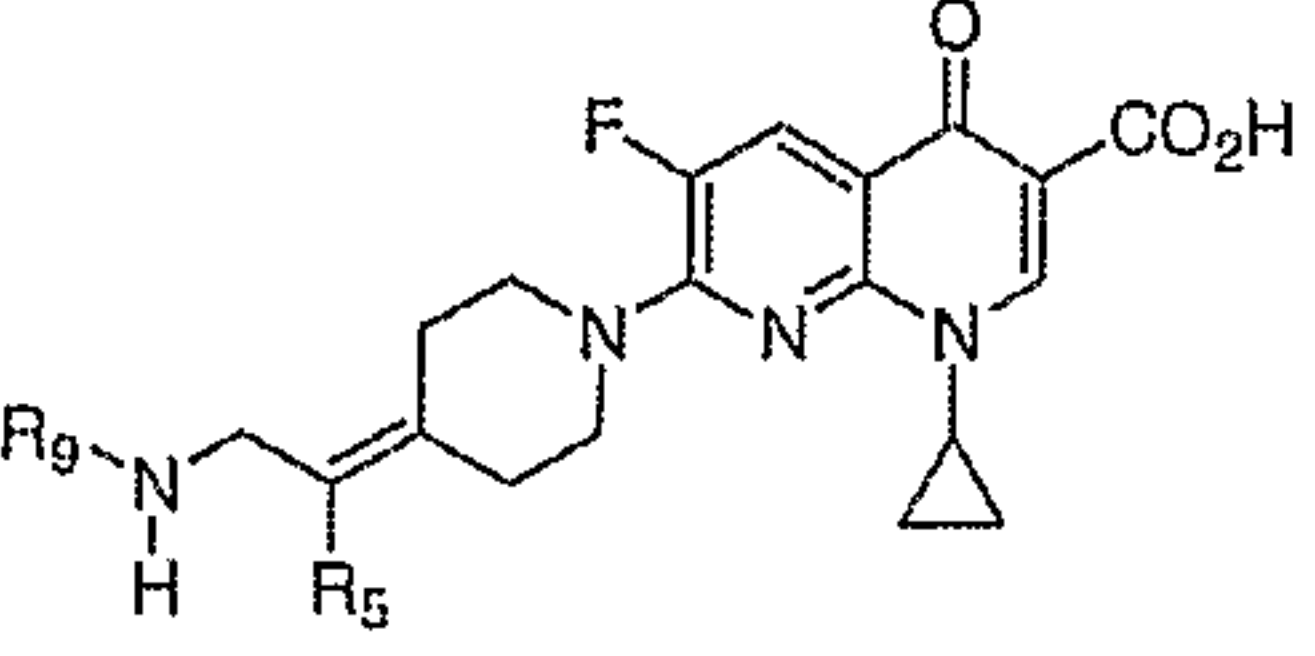
7-[4-(1-Chloro-2-methylaminoethylidene)piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid trifluoroacetic acid salt (**72**).

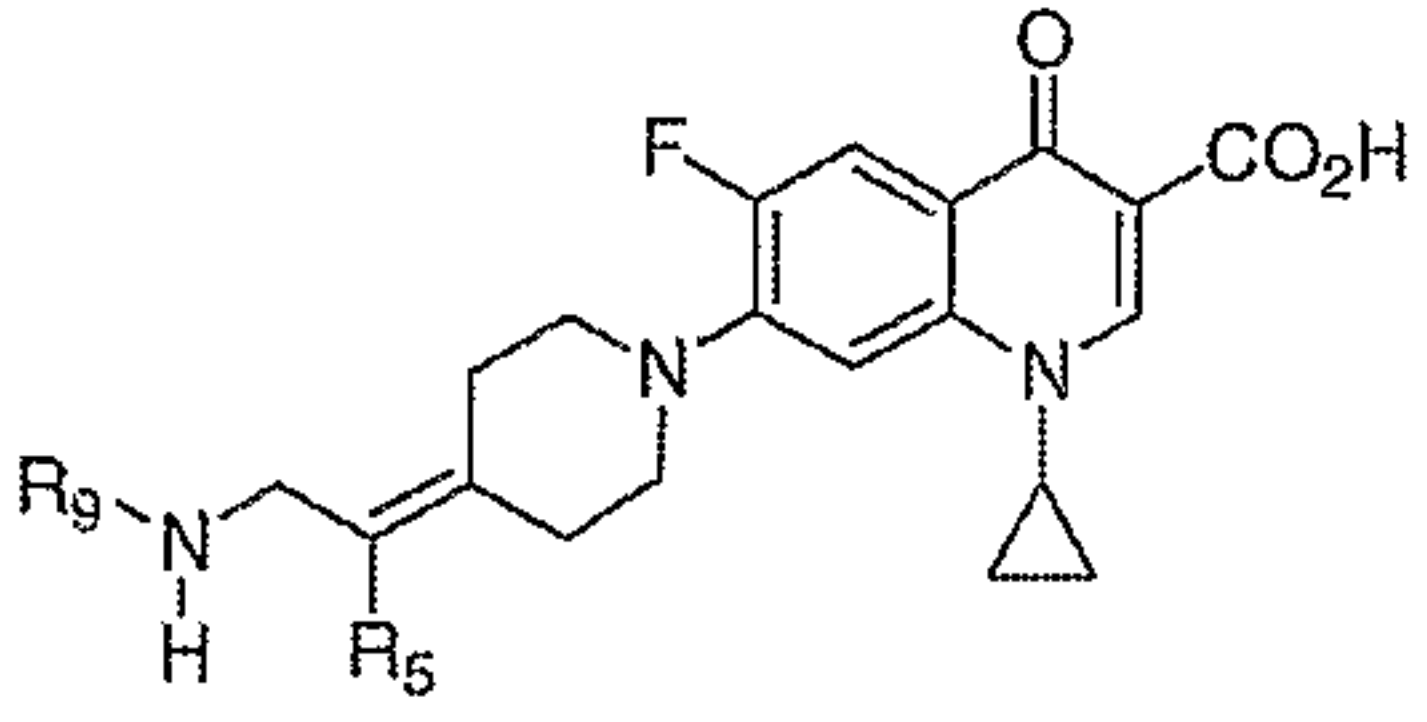
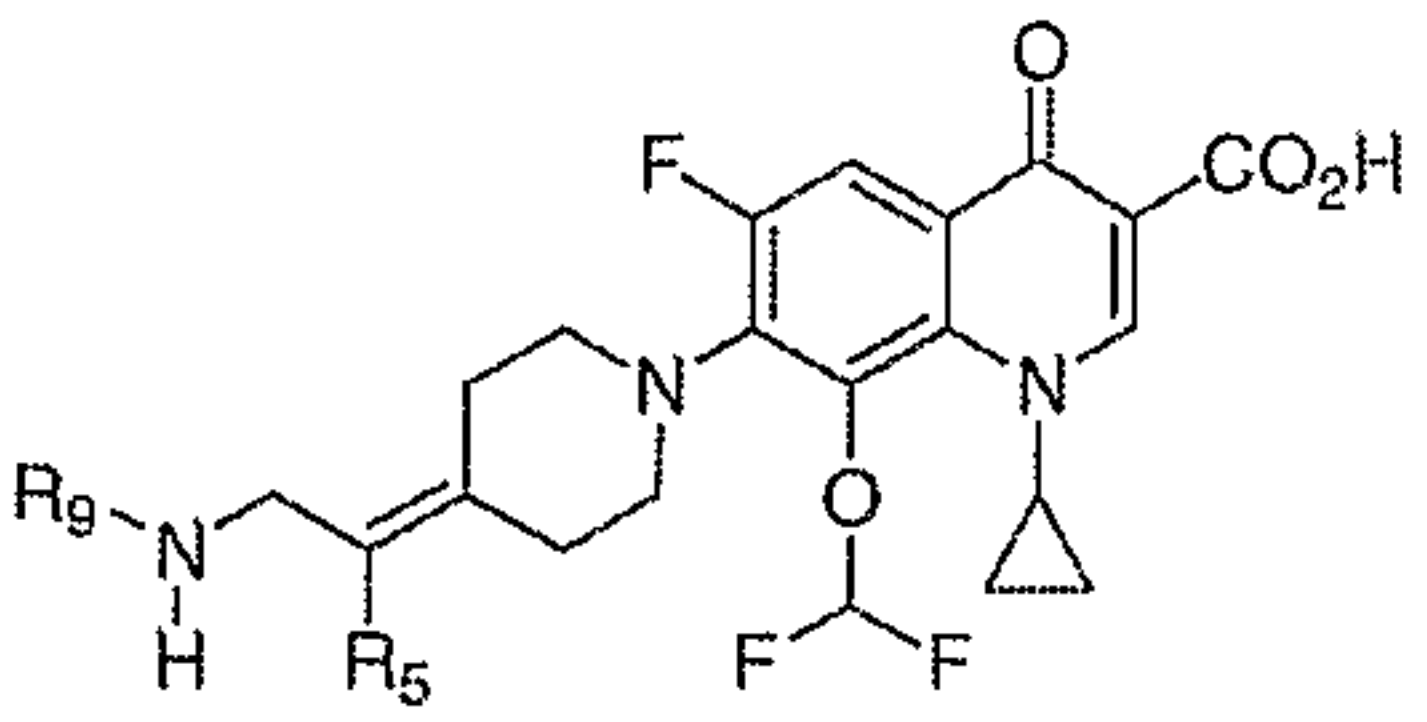
- 5 A solution of **154** (160 mg, 0.24 mmol) was dissolved in 1,2-dichloroethane (4 mL) and was treated with 1-chloroethyl chloroformate (0.8 mL, 7.3 mmol) under nitrogen. After 5 min, the reaction mixture was warmed to reflux temperature and the reaction mixture was allowed to stir for 3h. The resulting mixture was allowed to cool to room temperature, and then it was concentrated in vacuo.
- 10 The residue was dissolved in tetrahydrofuran (5 mL), adjusted to pH>7 by the addition of NaHCO₃ 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
- 15 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.

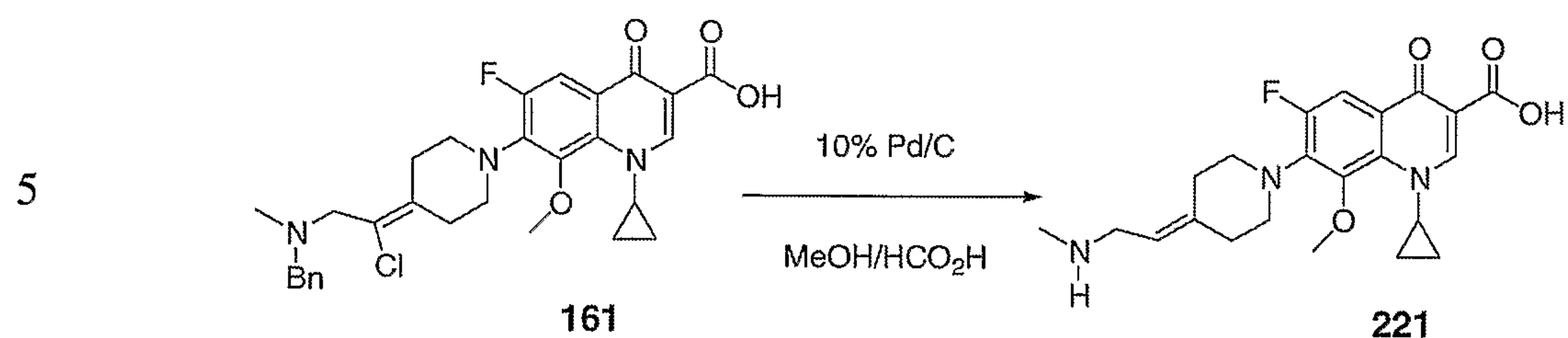
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Table 10

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

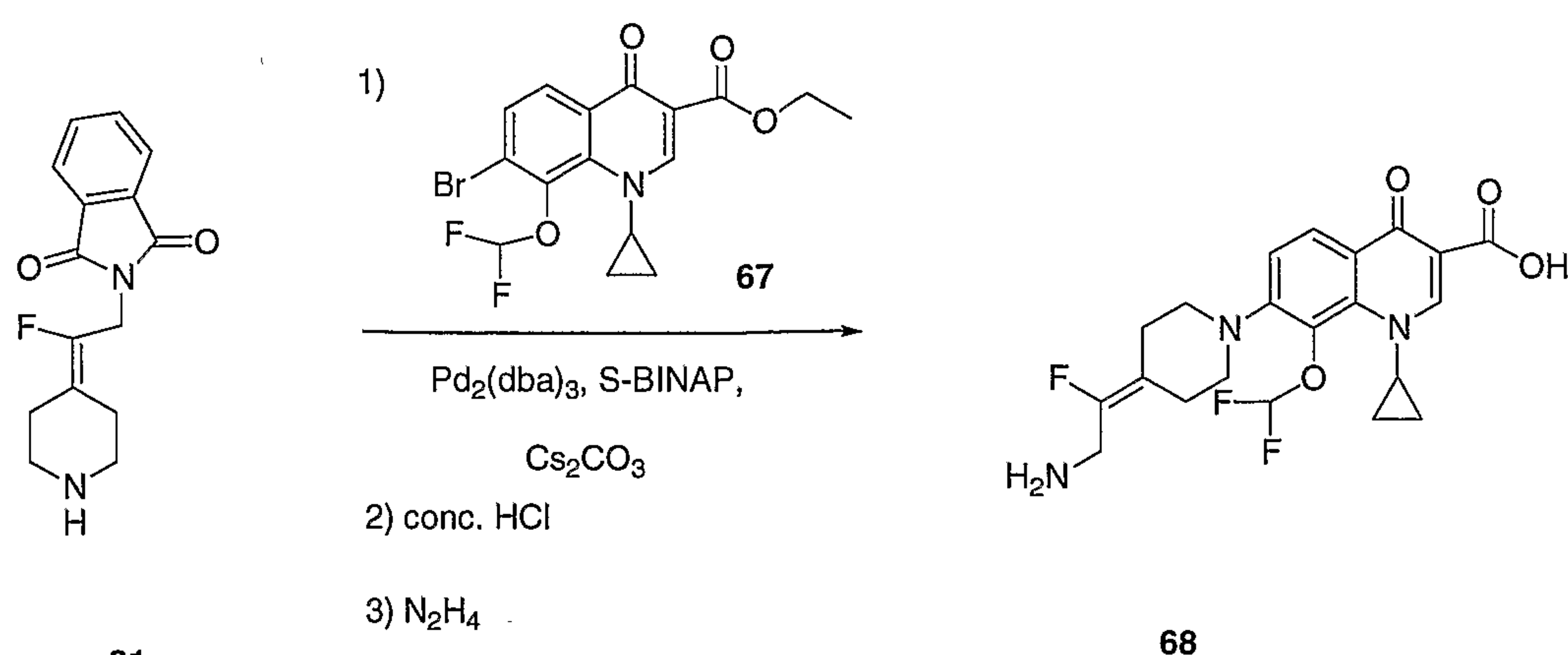
Scheme XXXIV



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**).

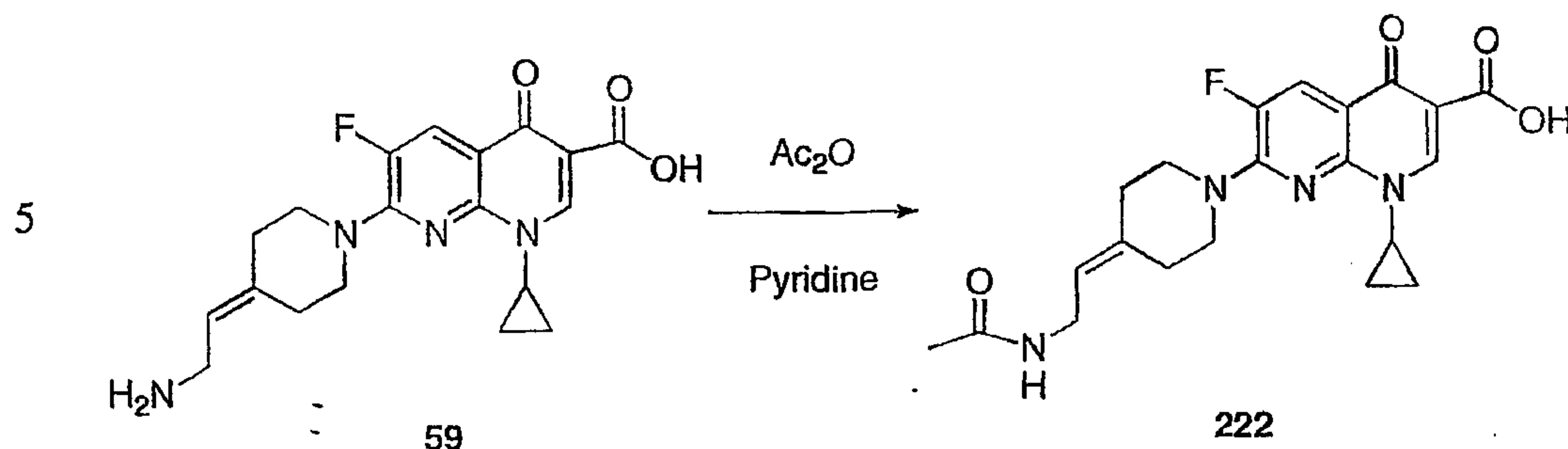
- 10 A solution of **161** (70 mg, 0.11 mmol) in methanol/formic acid (v/v=20/1) (14 mL) was treated with 10% Pd/C (35 mg, 7.3 mmol) under nitrogen at rt and stirred for 3h. The resulting mixture was filtered and concentrated in vacuo. The residue was purified by HPLC (reverse phase C-18 column, 35-90%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

Scheme XXI



31
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
 5 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 $\text{Pd}_2(\text{dba})_3$ (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
 10 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
 15 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%
 20 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



10 7-[4-(2-Acetyl-amino-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 μ L, 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
 15 overnight to afford the title compound 222 (15 mg, 54%). MS 415 (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
 20 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
 25 (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".

In this method two-fold serial dilutions of drug in cation adjusted Mueller-
 30 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

WO 2005/033108

PCT/US2004/029523

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

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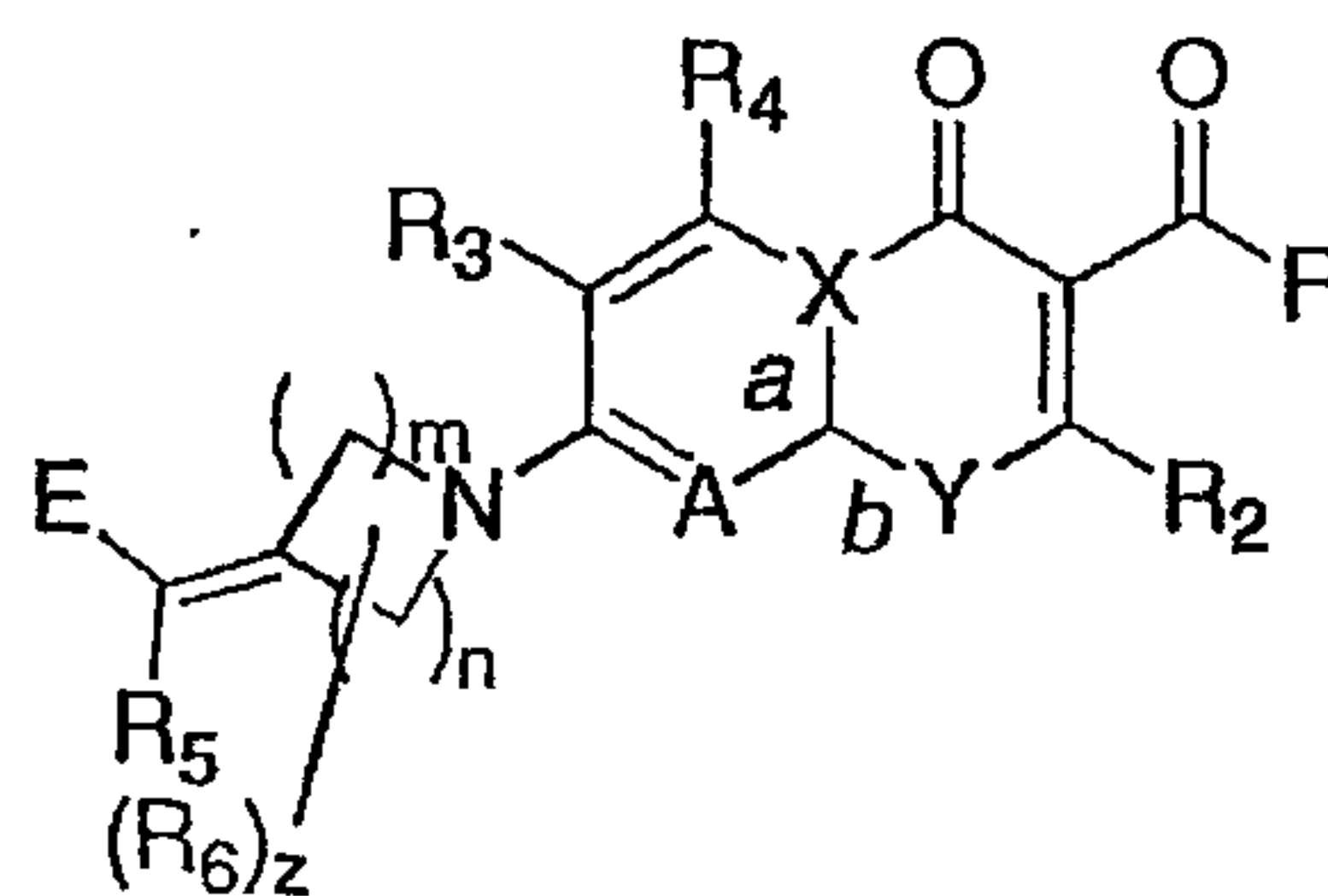
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203	0.06	0.06	1	0.5	0.12
212	0.06	1	2	2	0.12
177	1	8	>16	>16	4
178	0.5	1	8	4	4
179	0.5	>16	>16	>16	2
180	0.5	ND	8	2	0.5
181	1	ND	>16	8	2

*ND = not determined

What is Claimed is:

1. A compound having a structure according to Formula I



5

Formula I

wherein:

10 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;

15 R_2 is hydrogen;

R_3 and R_4 are independently selected from hydrogen, halogen, amino, hydroxy, alkoxy, alkylthio, alkyl, alkenyl and alkynyl;

R_5 is selected from hydrogen, hydroxy, halogen, alkyl, aryl, alkoxy, and alkylthio;

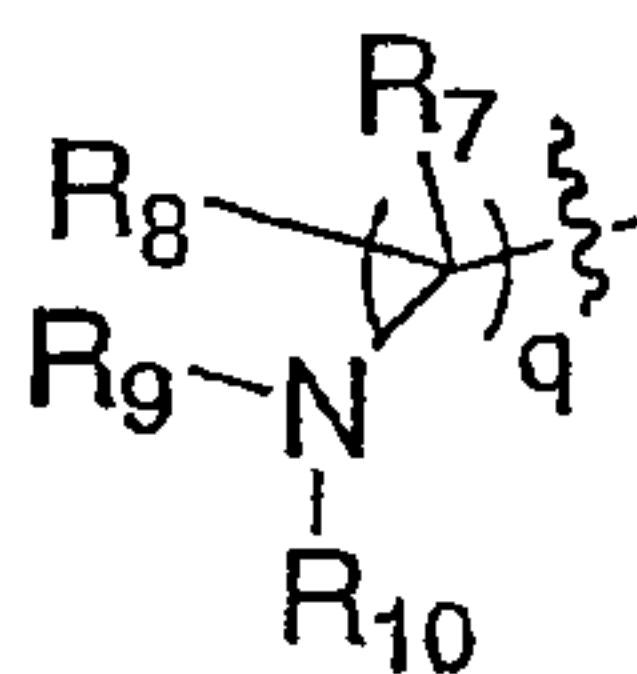
20 R_6 is independently selected from alkyl, hydroxy, alkoxy, alkylthio, alkenyl, alkynyl, aryl, alkoxyimino, and halogen; or R_5 and R_6 join to form a 4- to 7-membered carbocyclic ring wherein each carbon atom of the ring is optionally substituted with R_{12} , wherein R_{12} is selected from the group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

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E is selected from the group consisting of:

1)

wherein,



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q is an integer from 1 to 3;

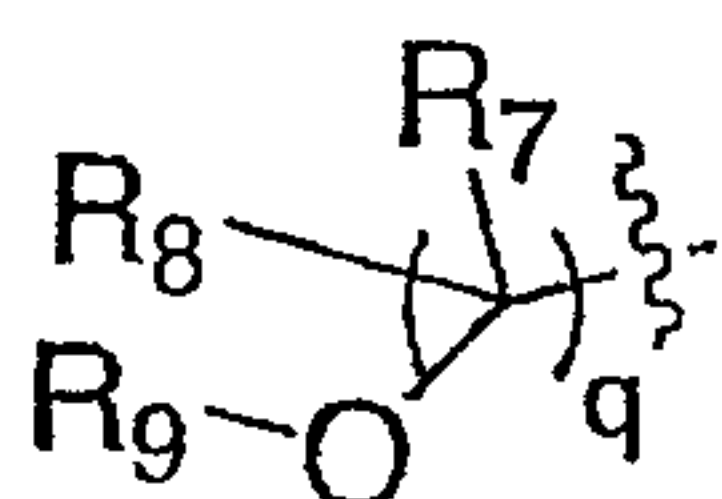
R_7 and R_8 are each independently selected from hydrogen and alkyl, or R_7 and R_8 join to form a 3 to 6 membered carbocyclic ring, or either of R_7 or R_8

are 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,

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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, alkoxyfluoro, 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 join to form a 6-membered heterocyclic ring, or

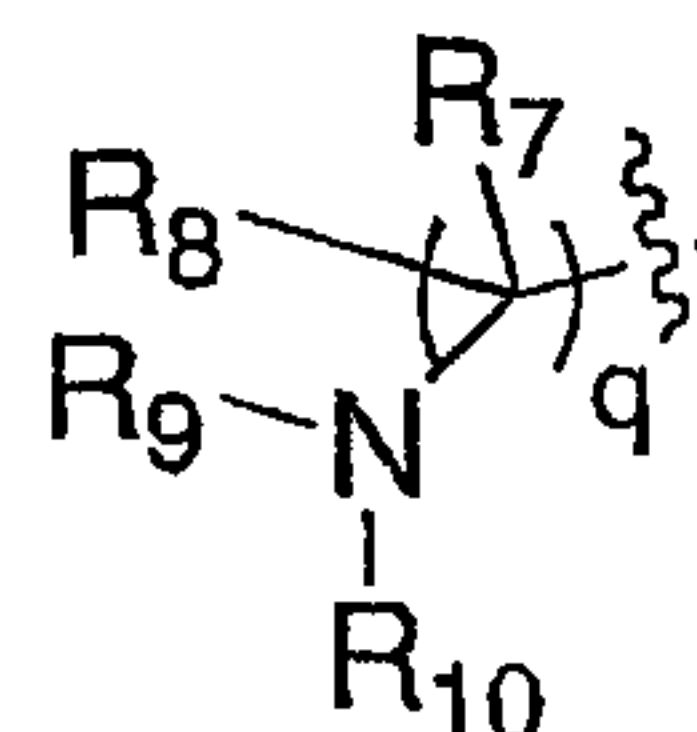
if A is $C(R_{11})$, X is C and Y is $N(R_1)$, then R_2 and R_1 join to form a monocyclic or bicyclic heterocyclic ring, or

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

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

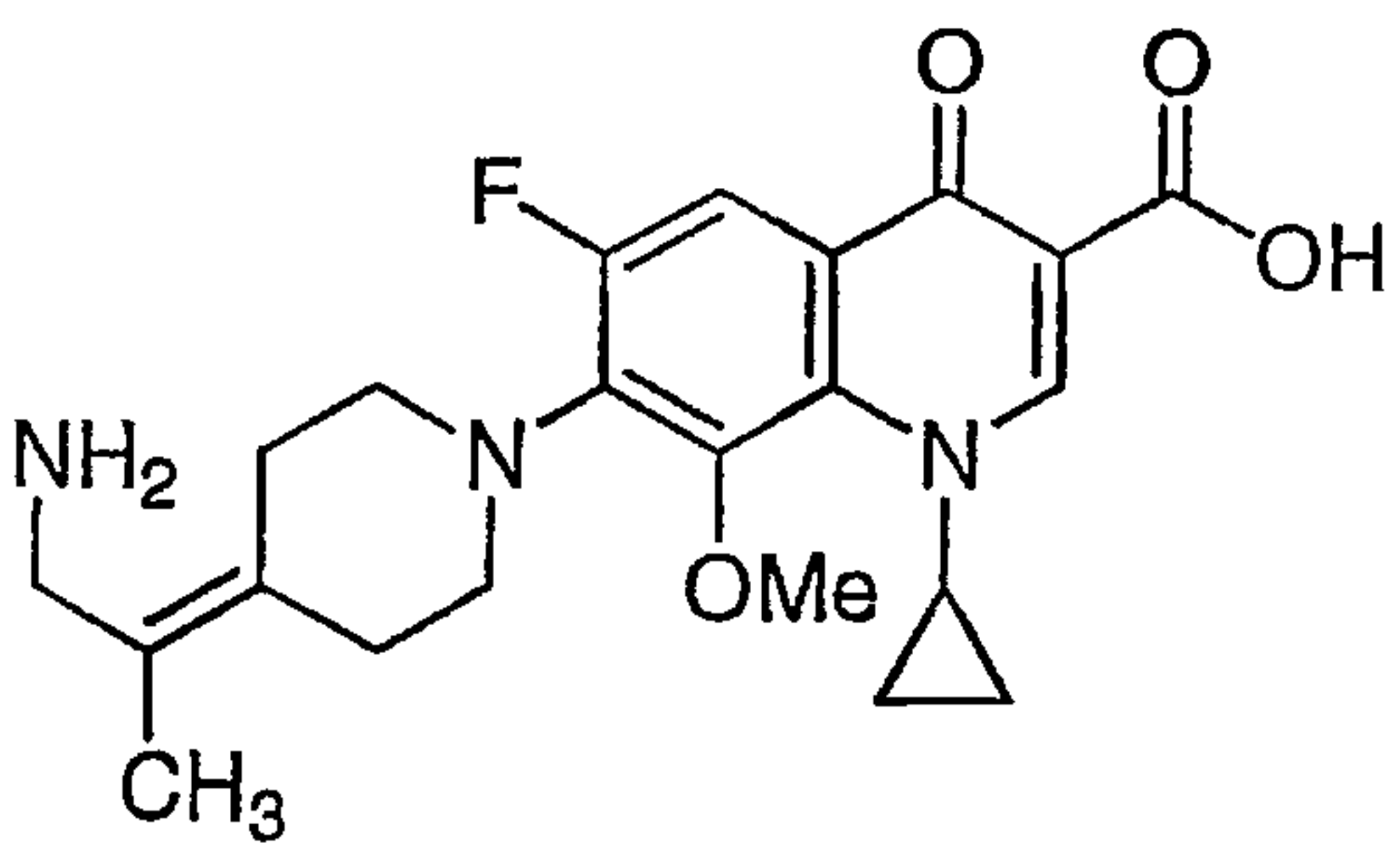
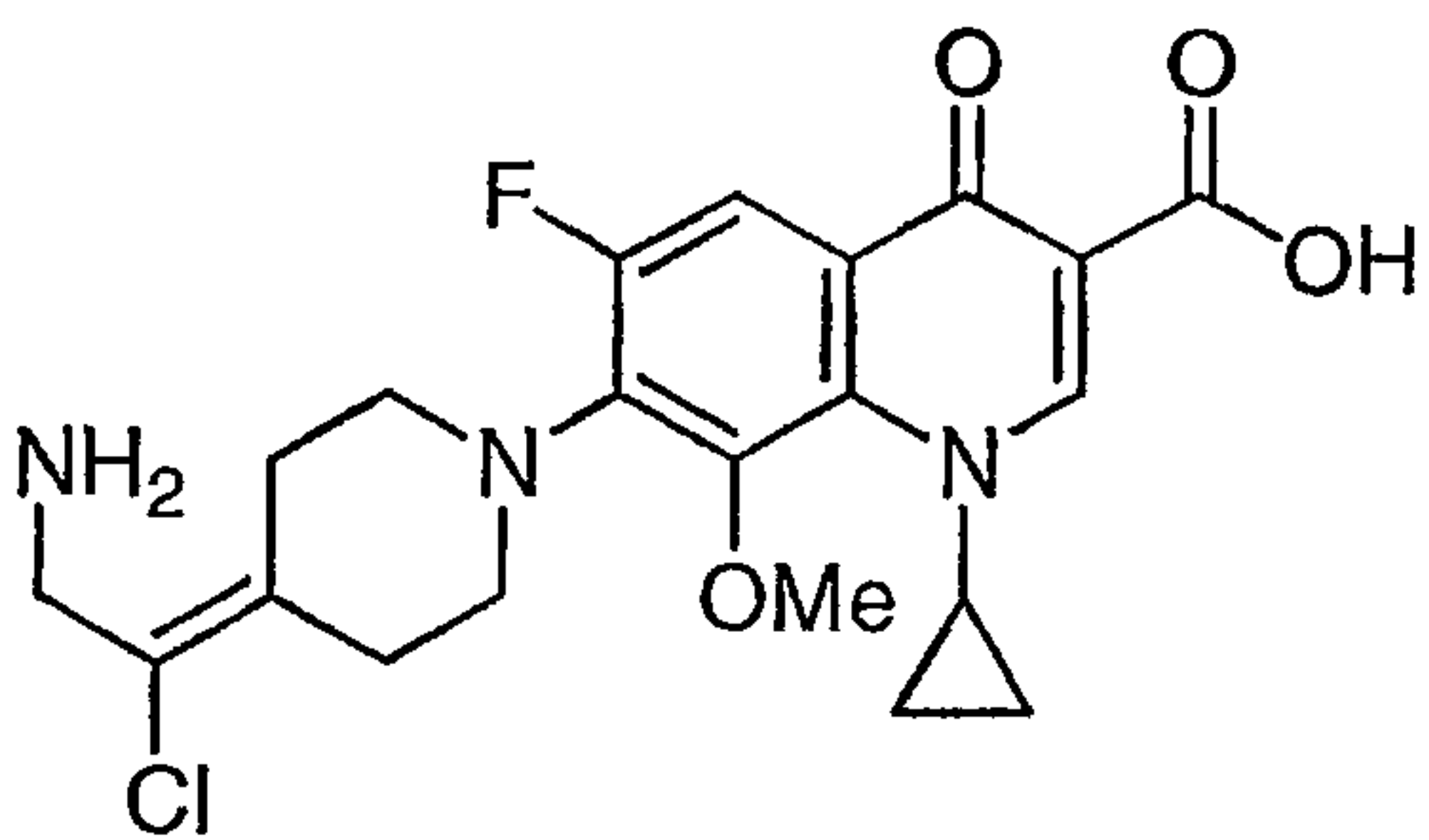
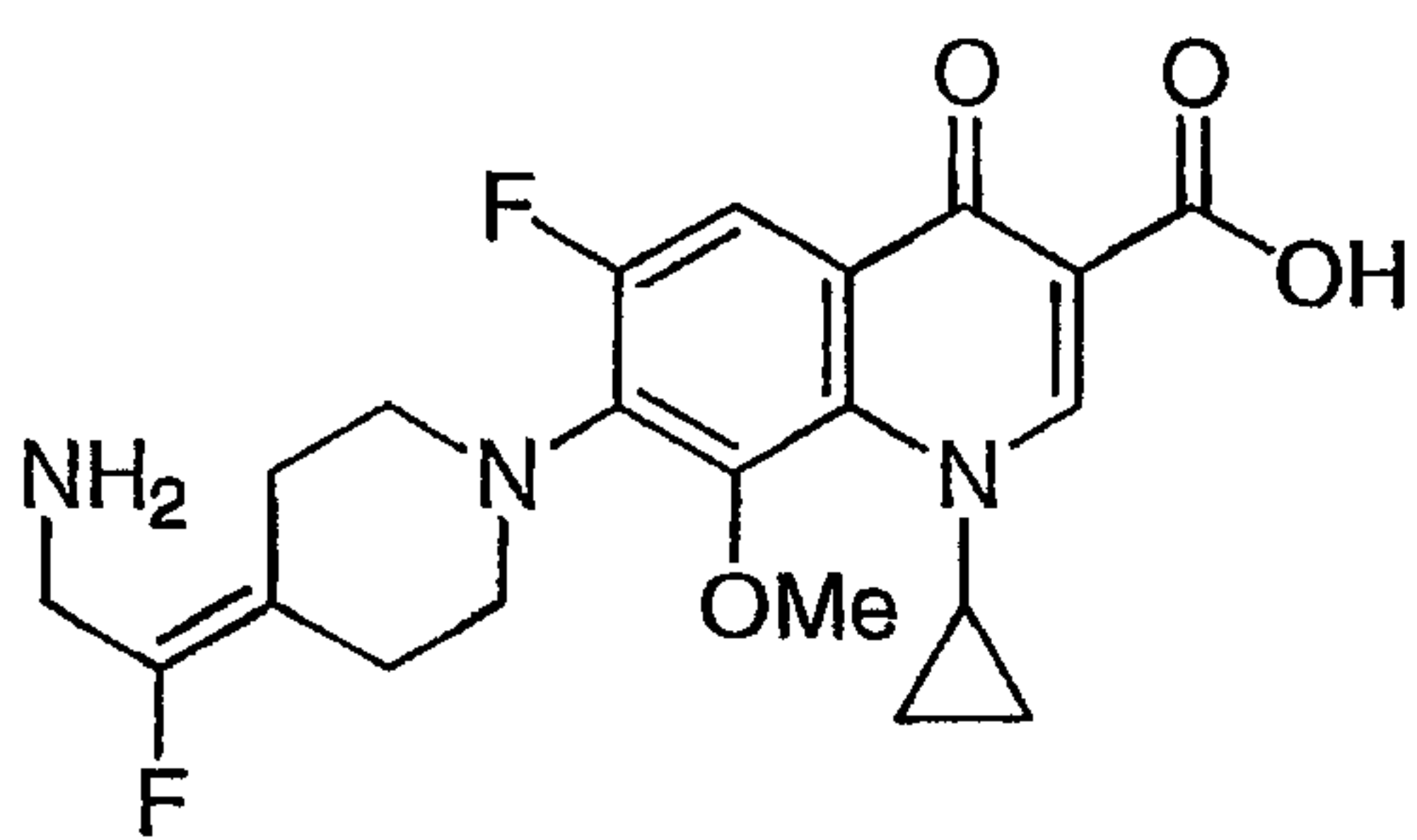
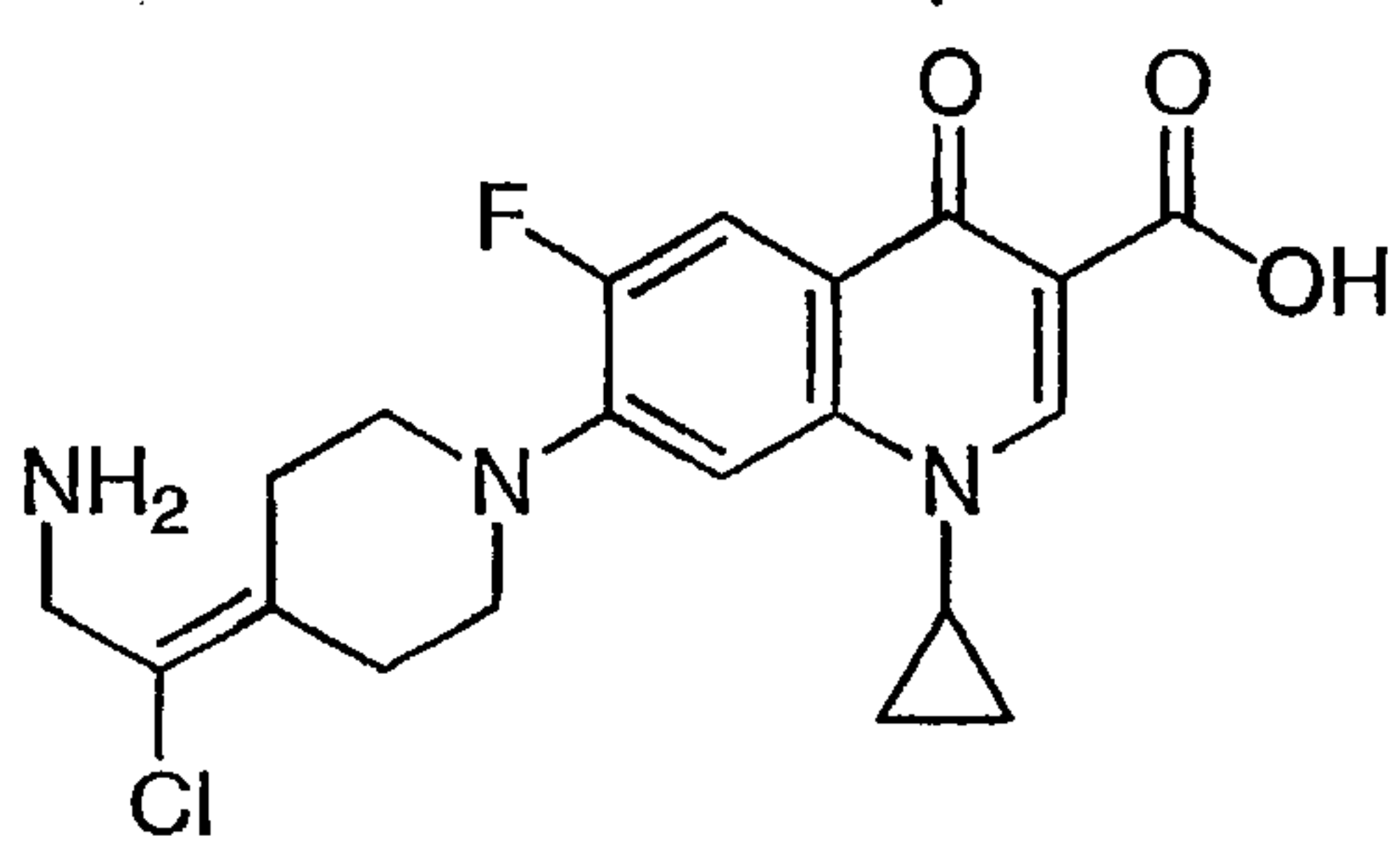
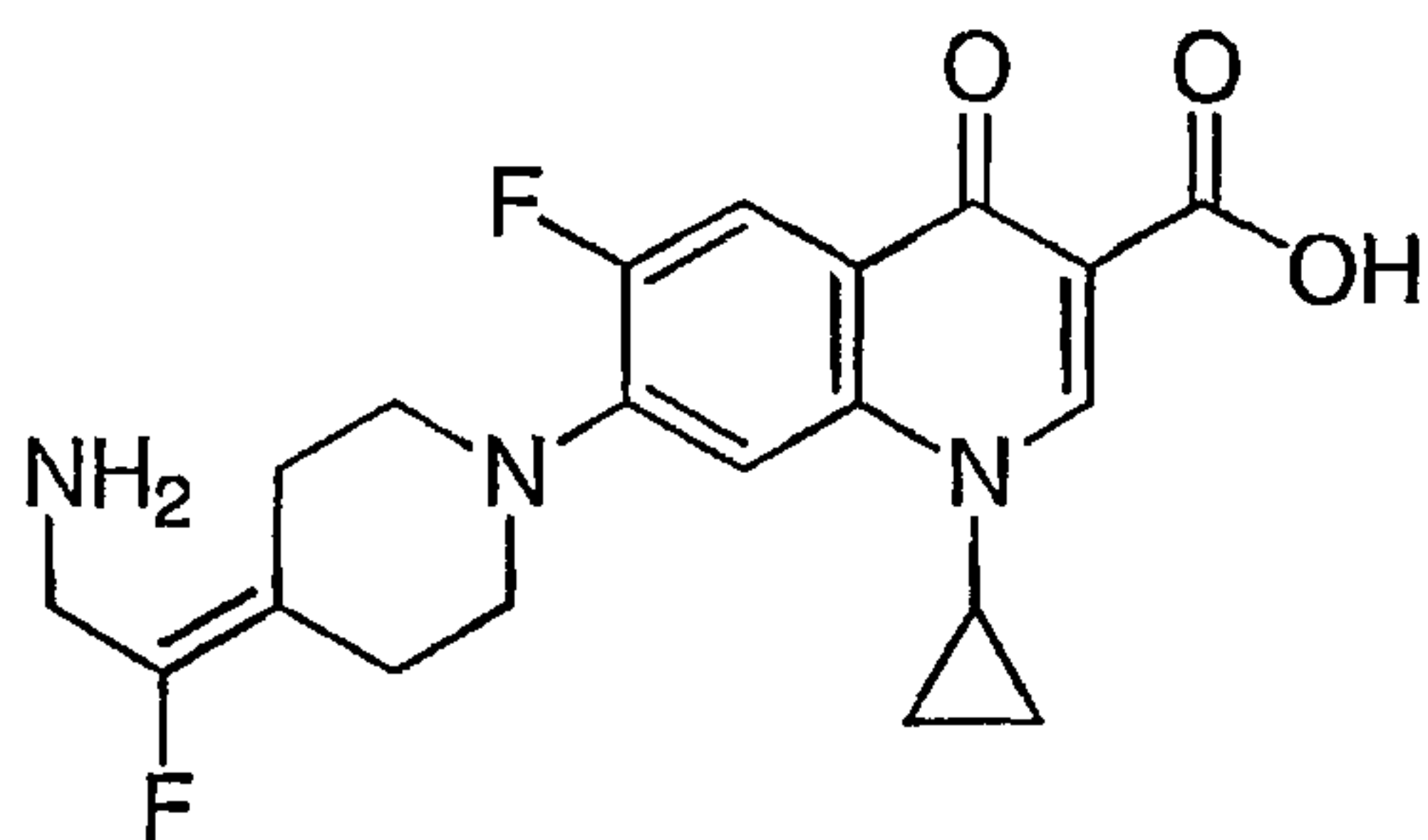
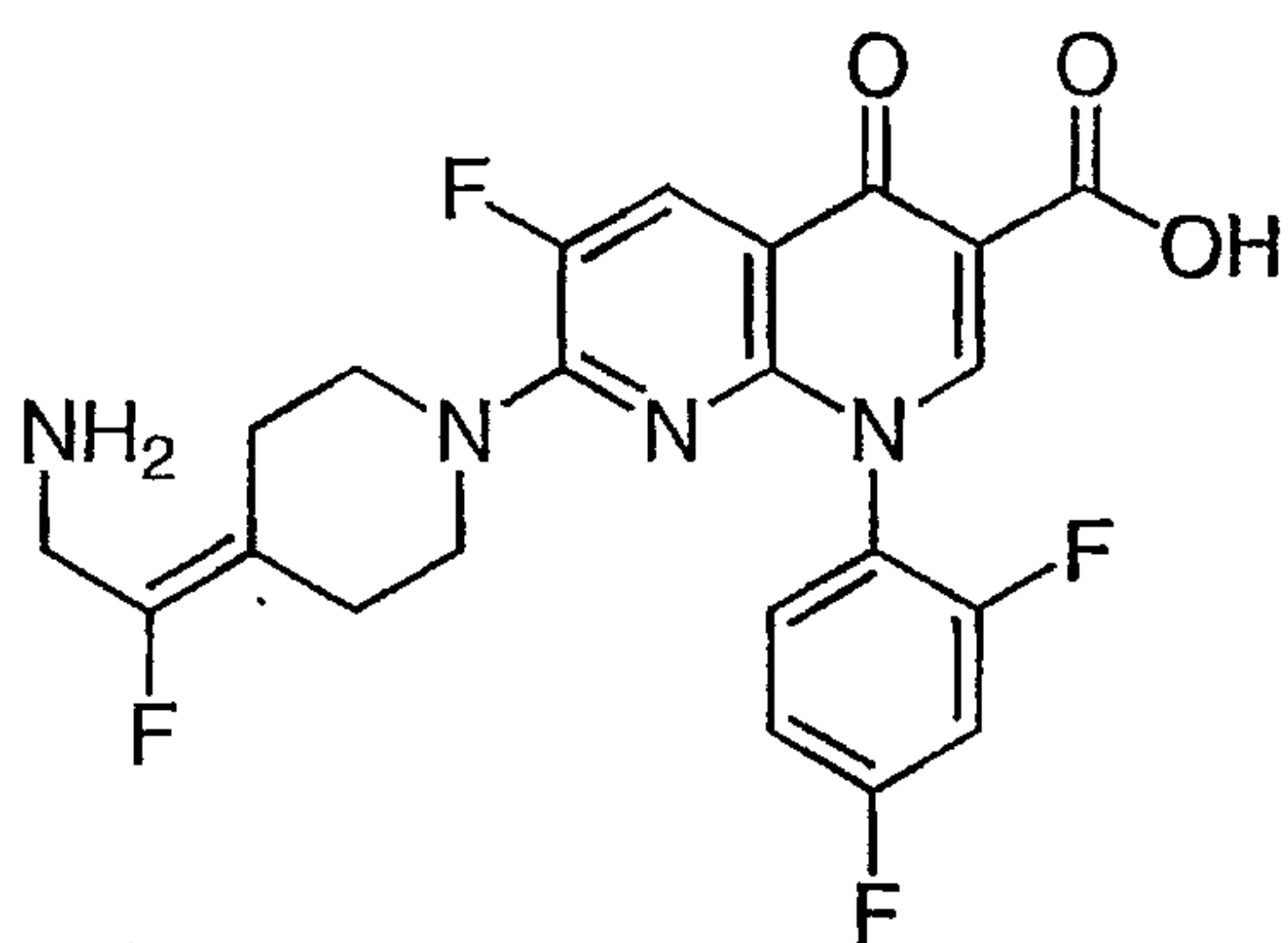
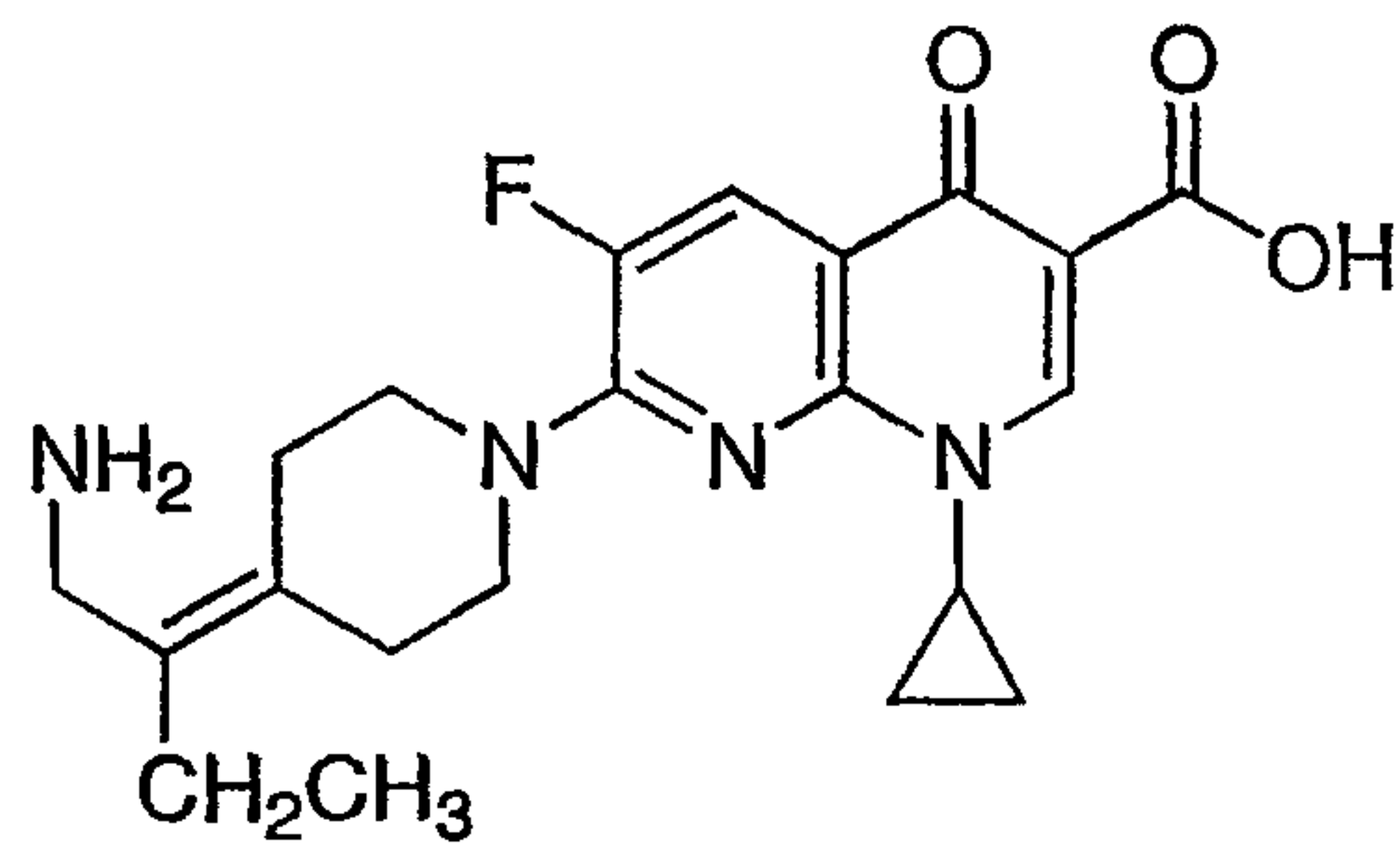
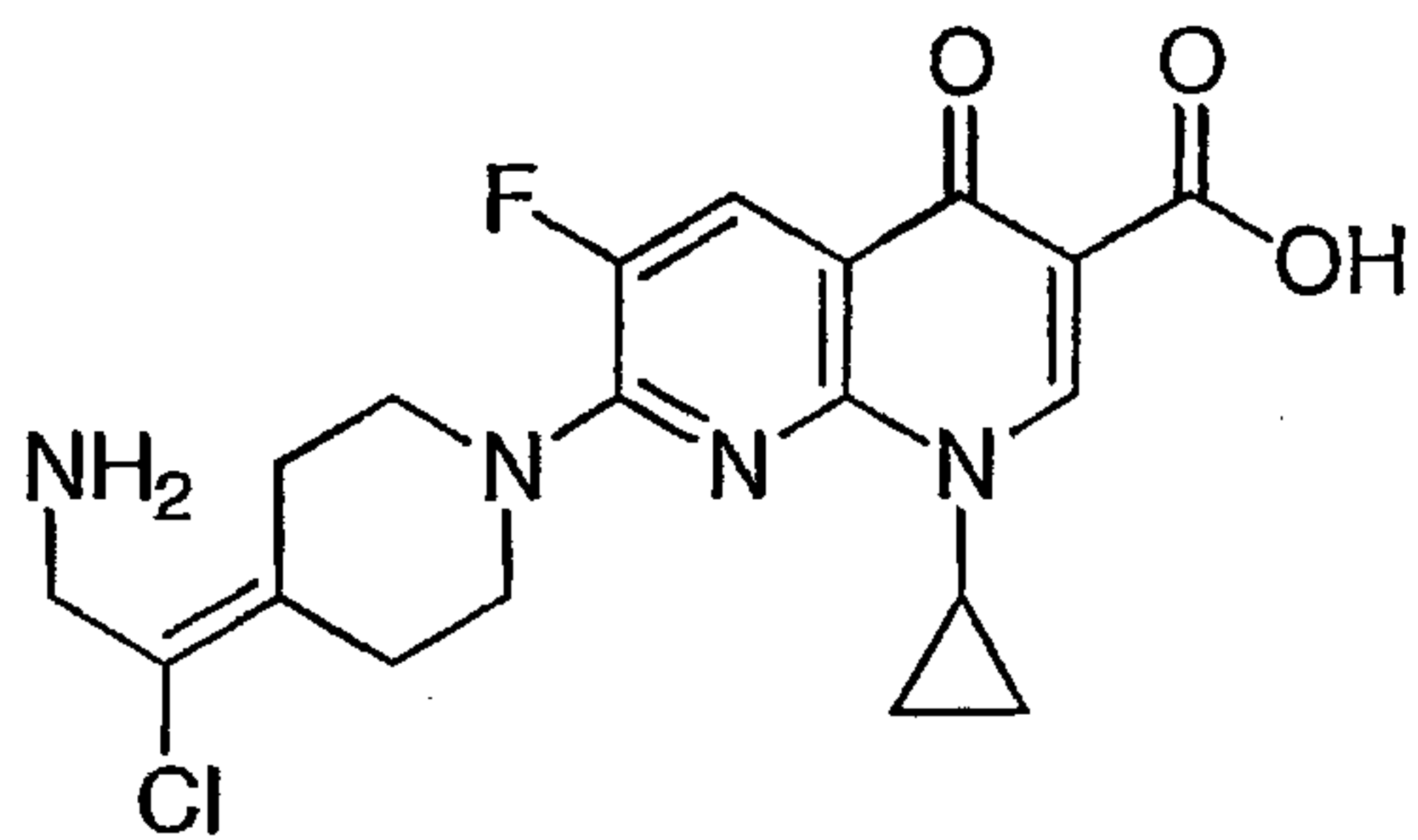
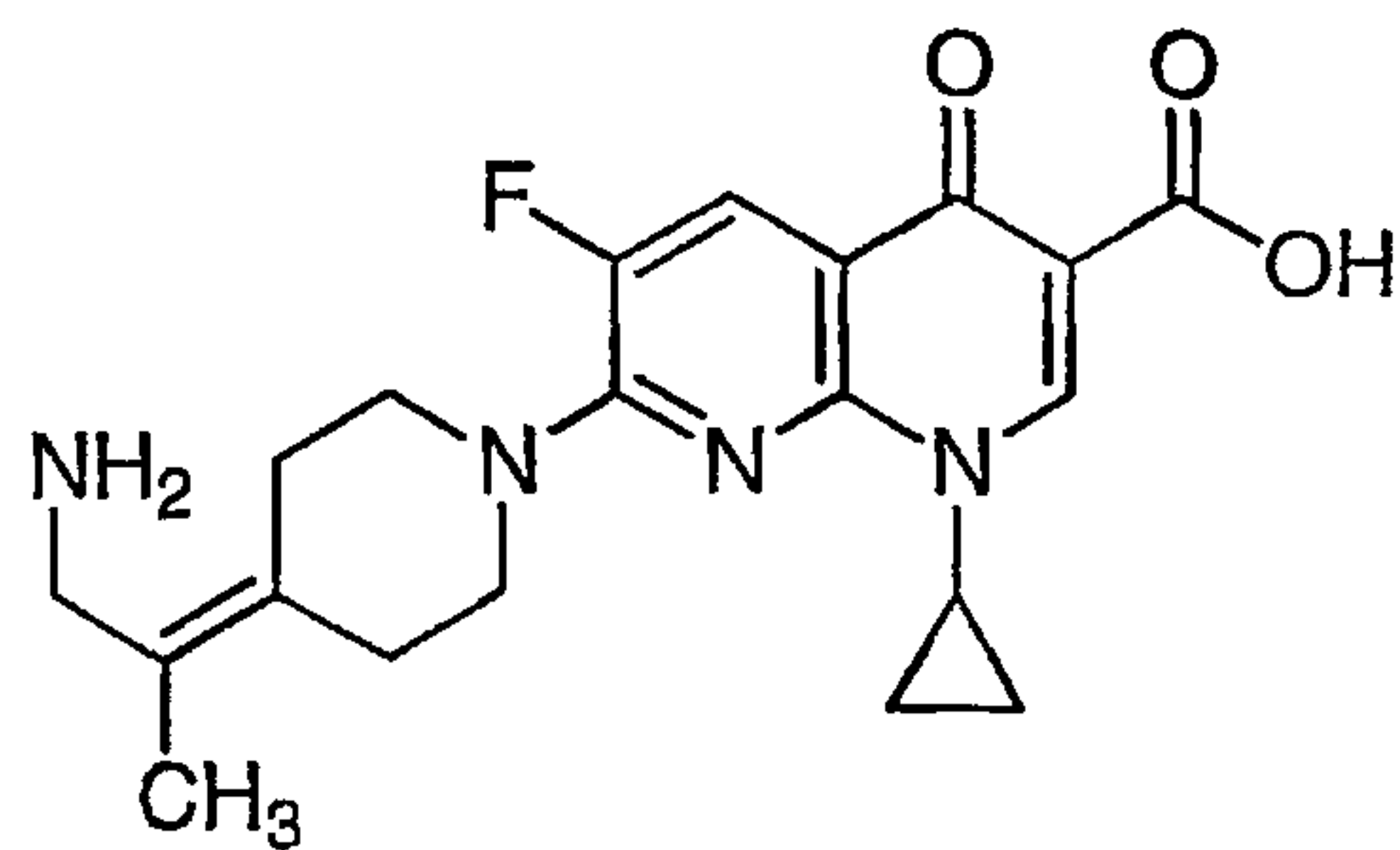
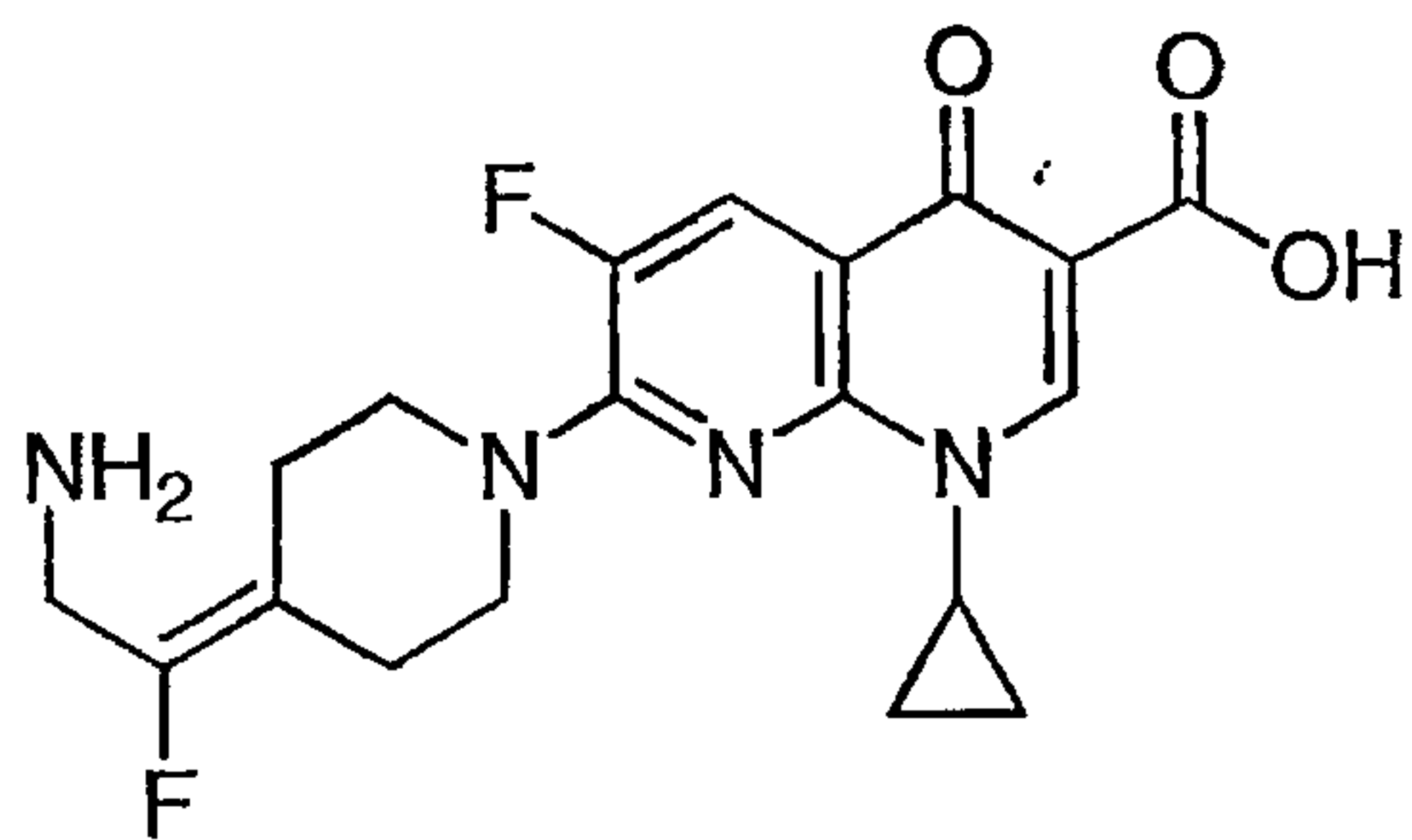
2. The compound of claim 1, wherein A is C(OCH₃), C(OCHF₂), or N.
3. The compound of claim 1, wherein Y is N(R₁) and R₁ is selected from
5 C3 to C6 cycloalkyl.

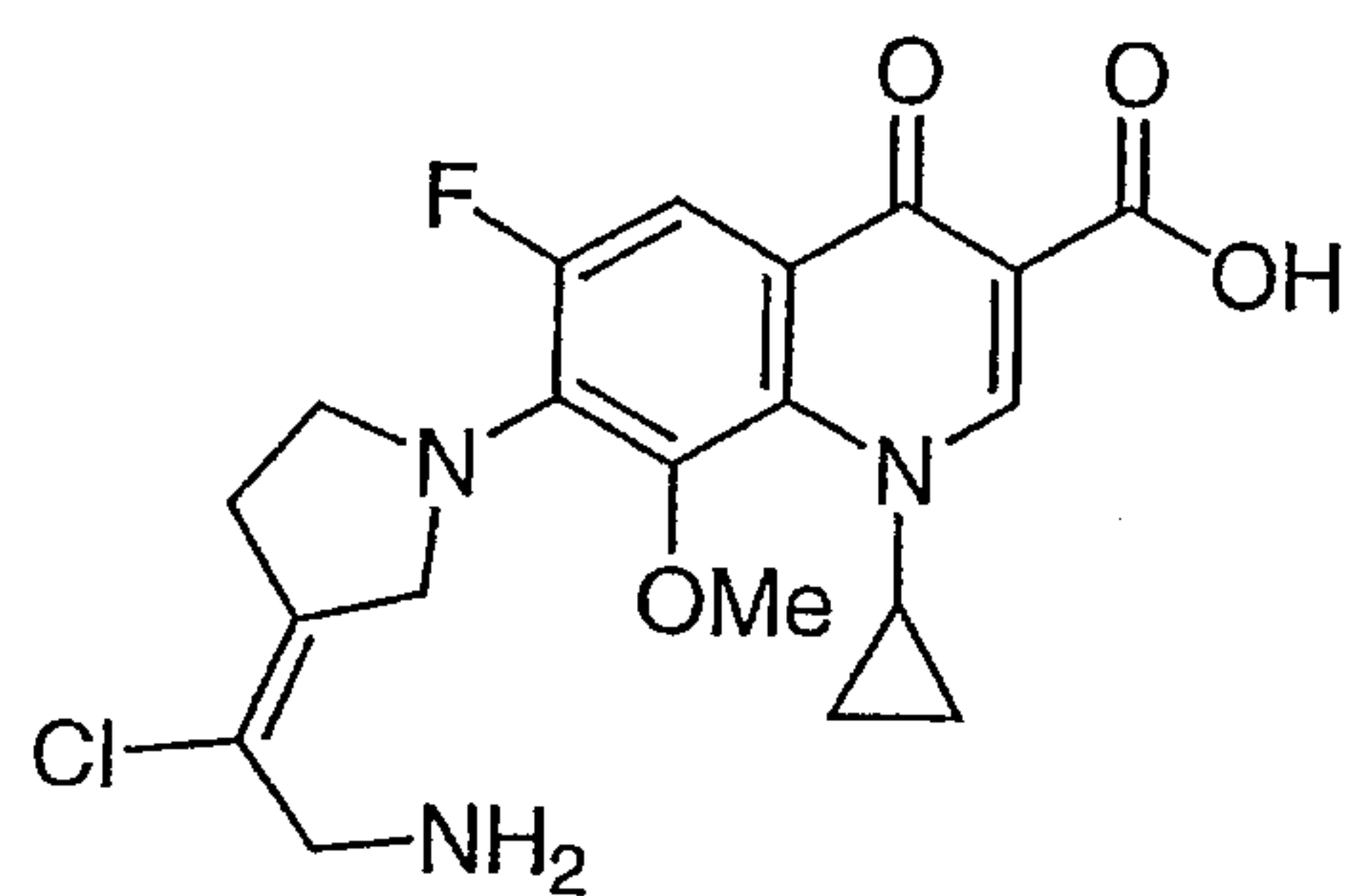
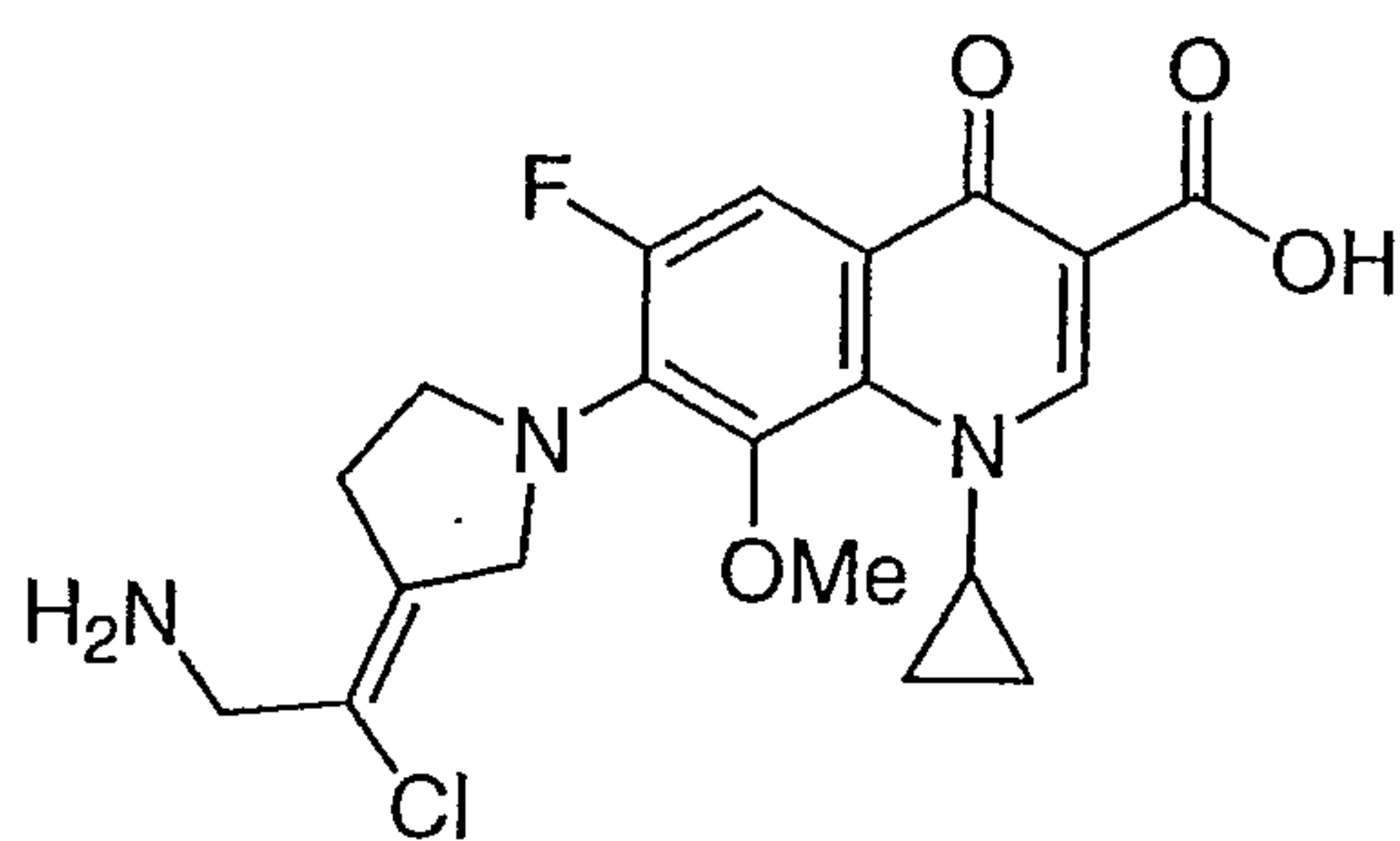
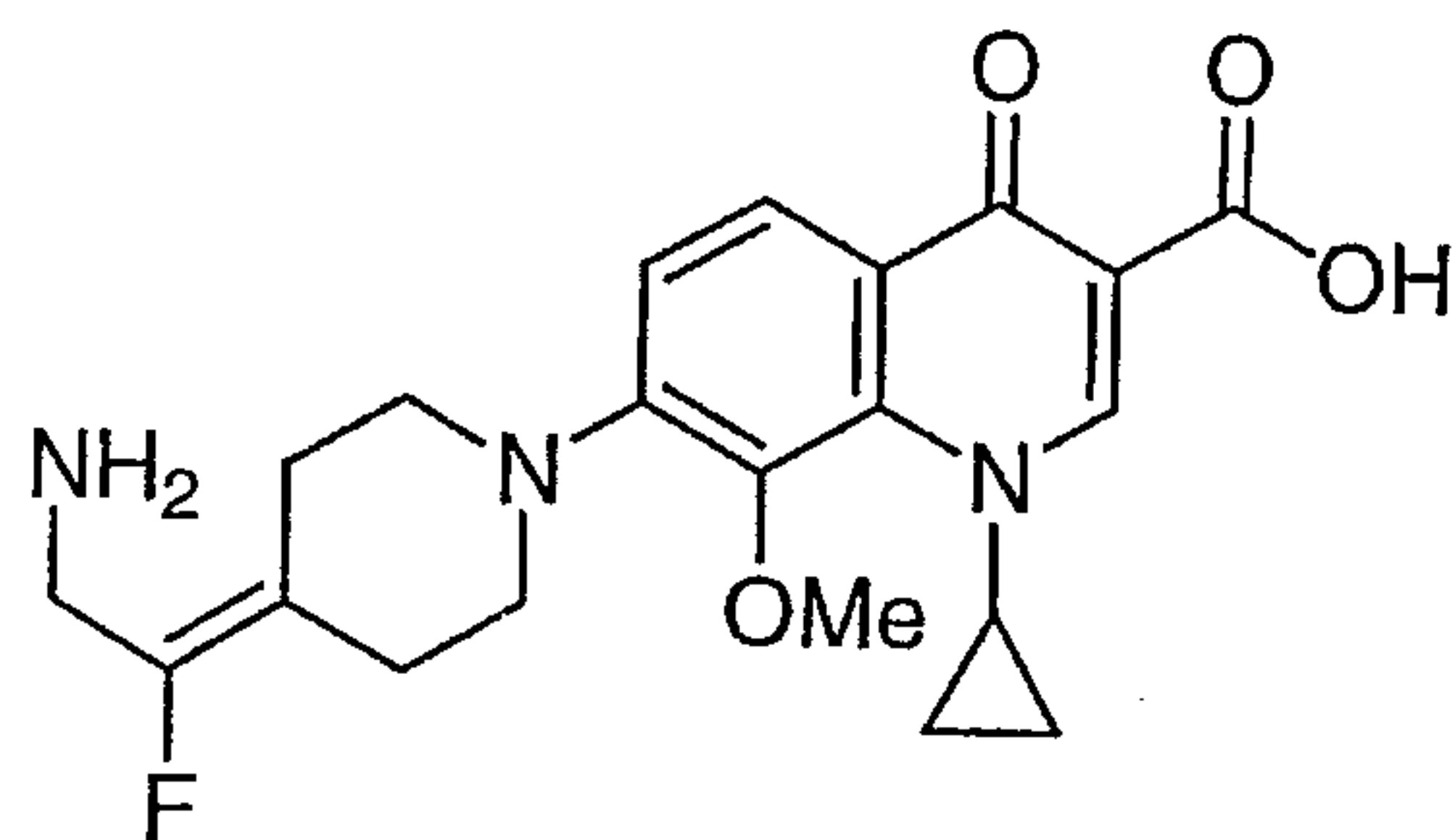
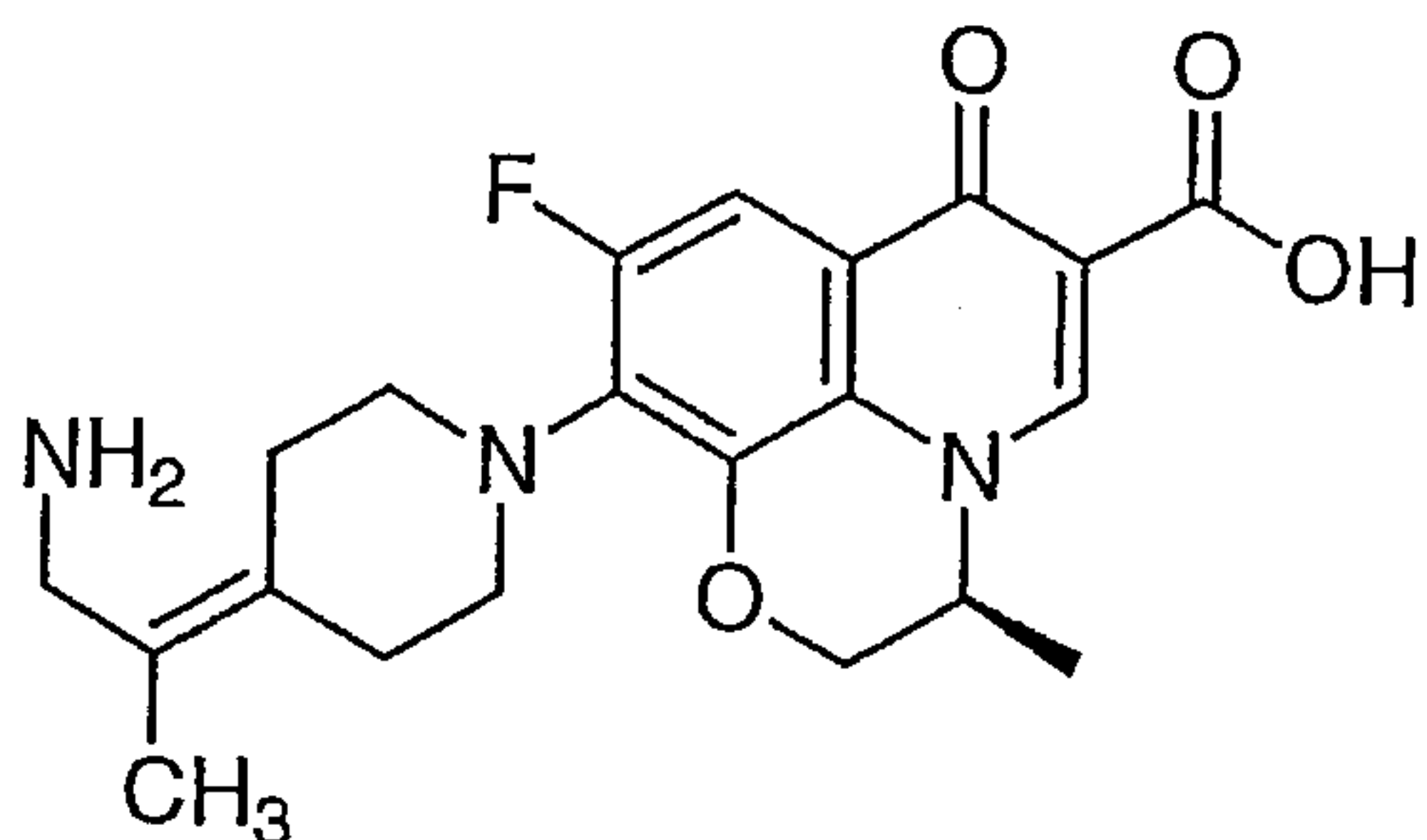
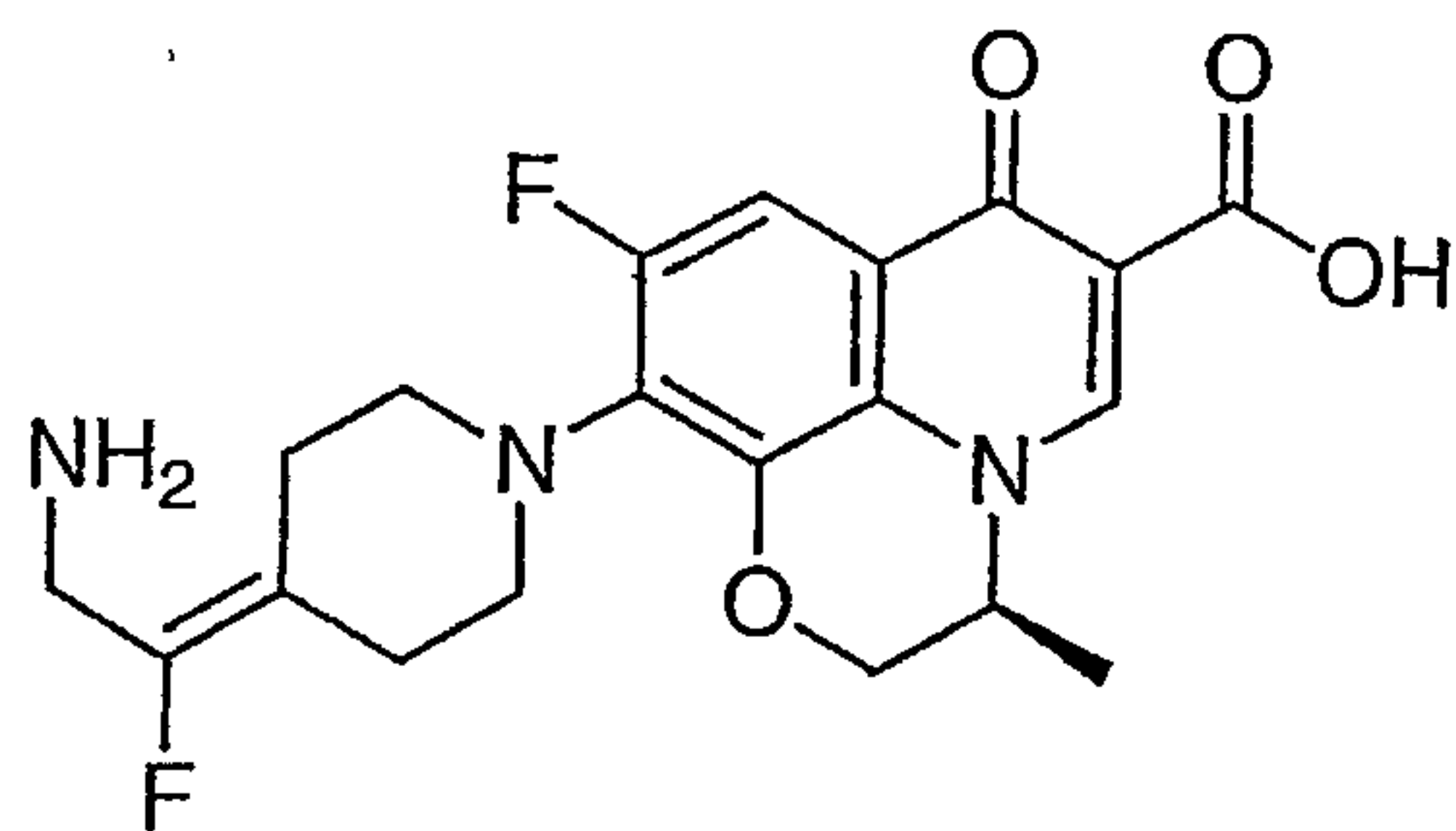
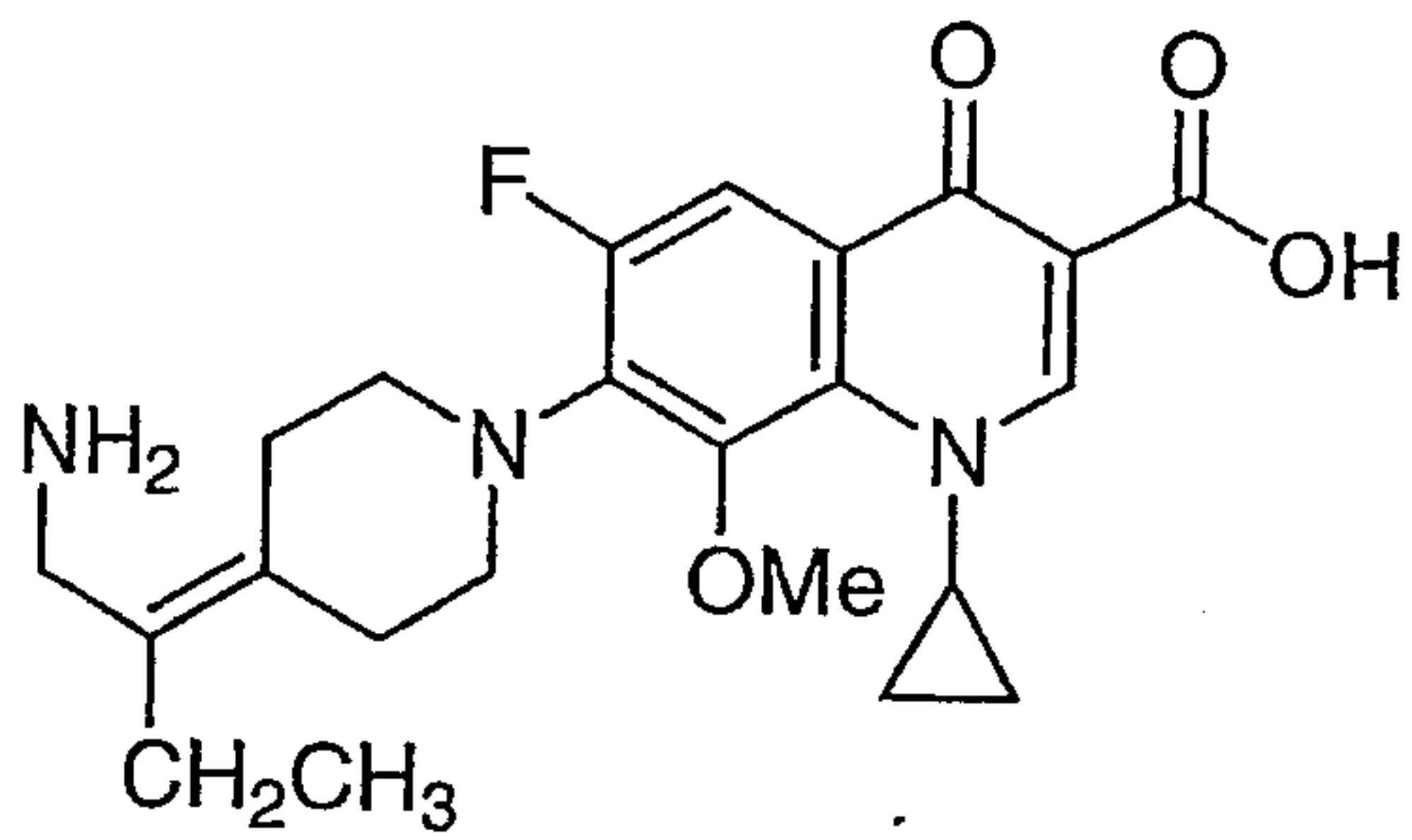
4. The compound of claim 1, wherein E is



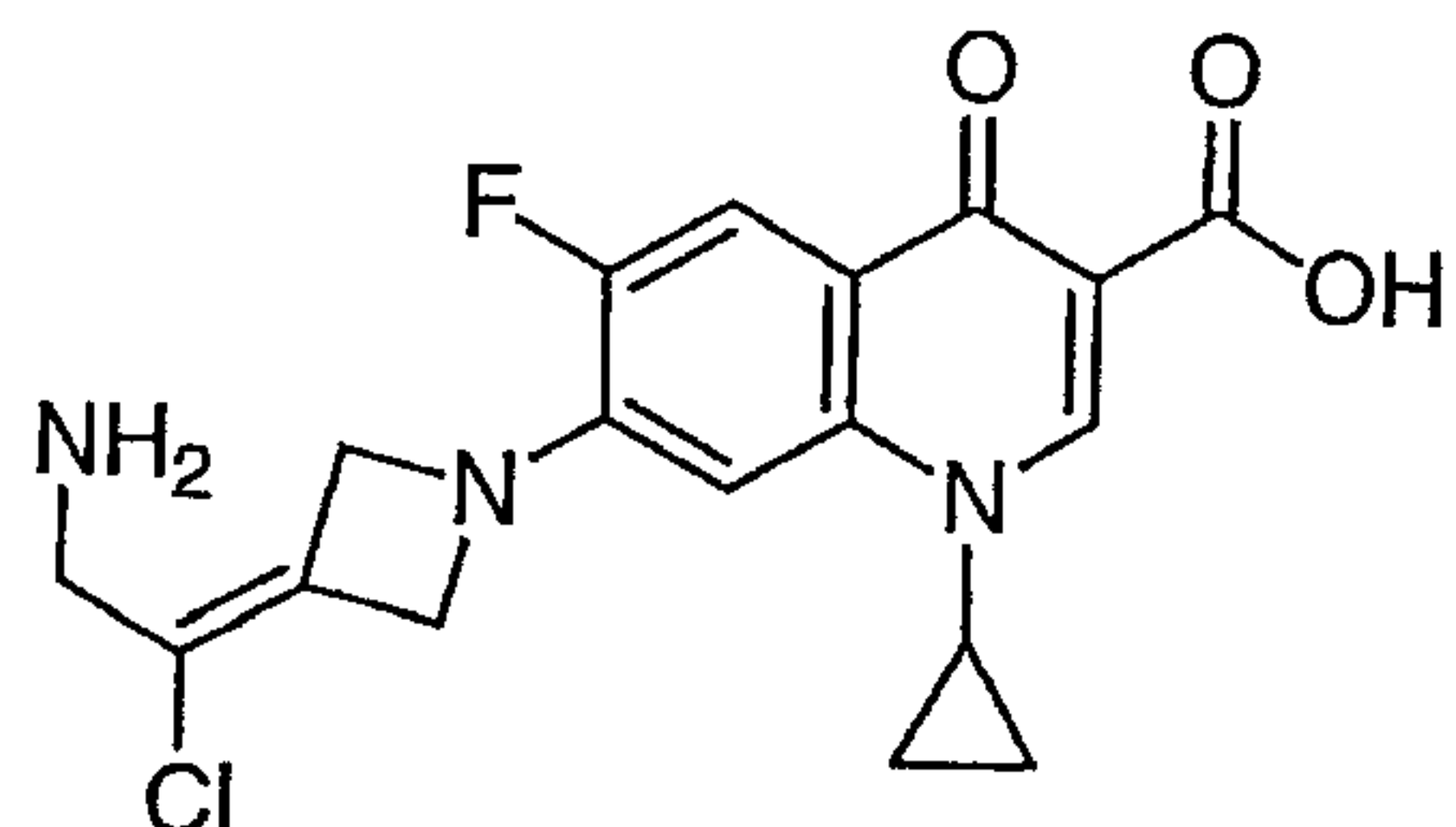
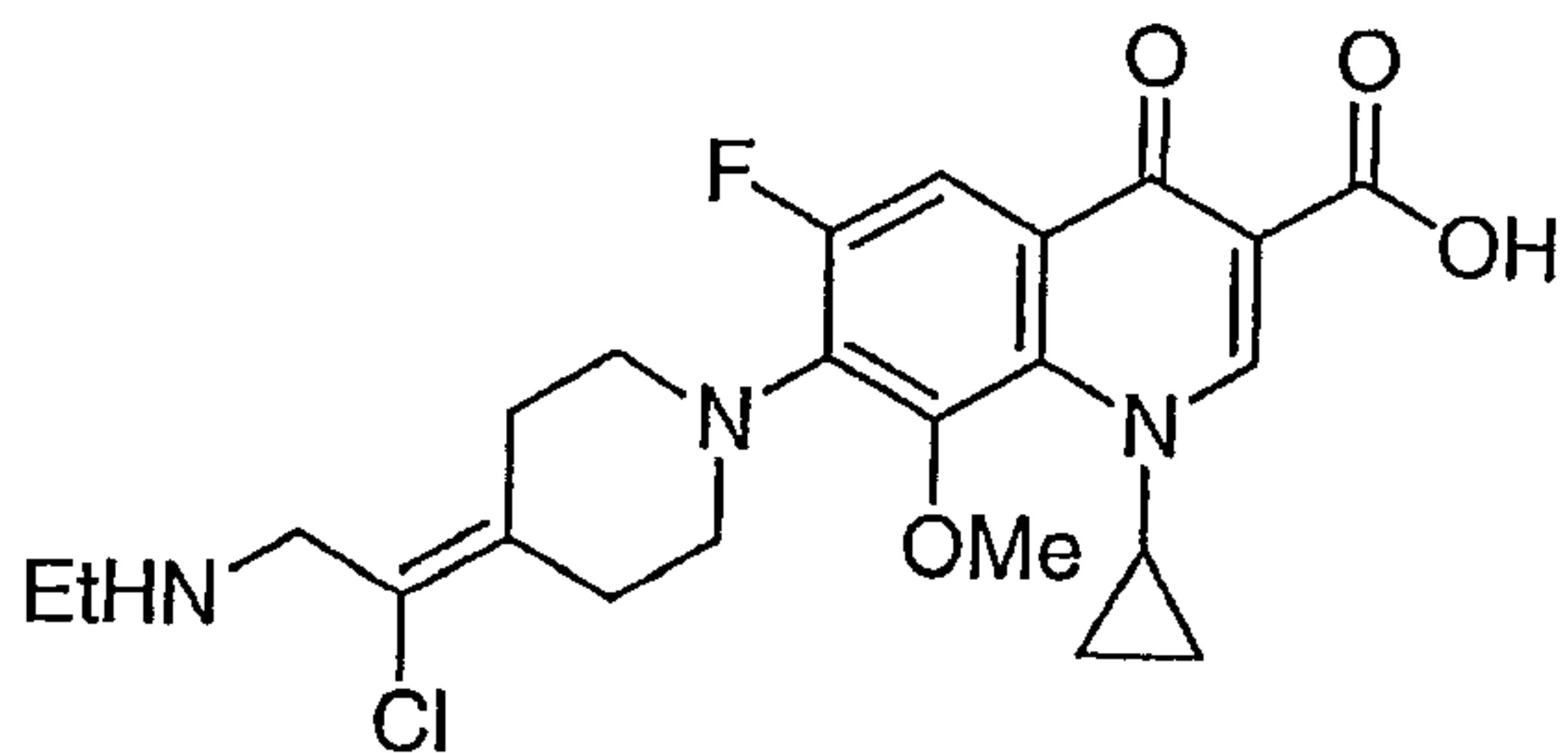
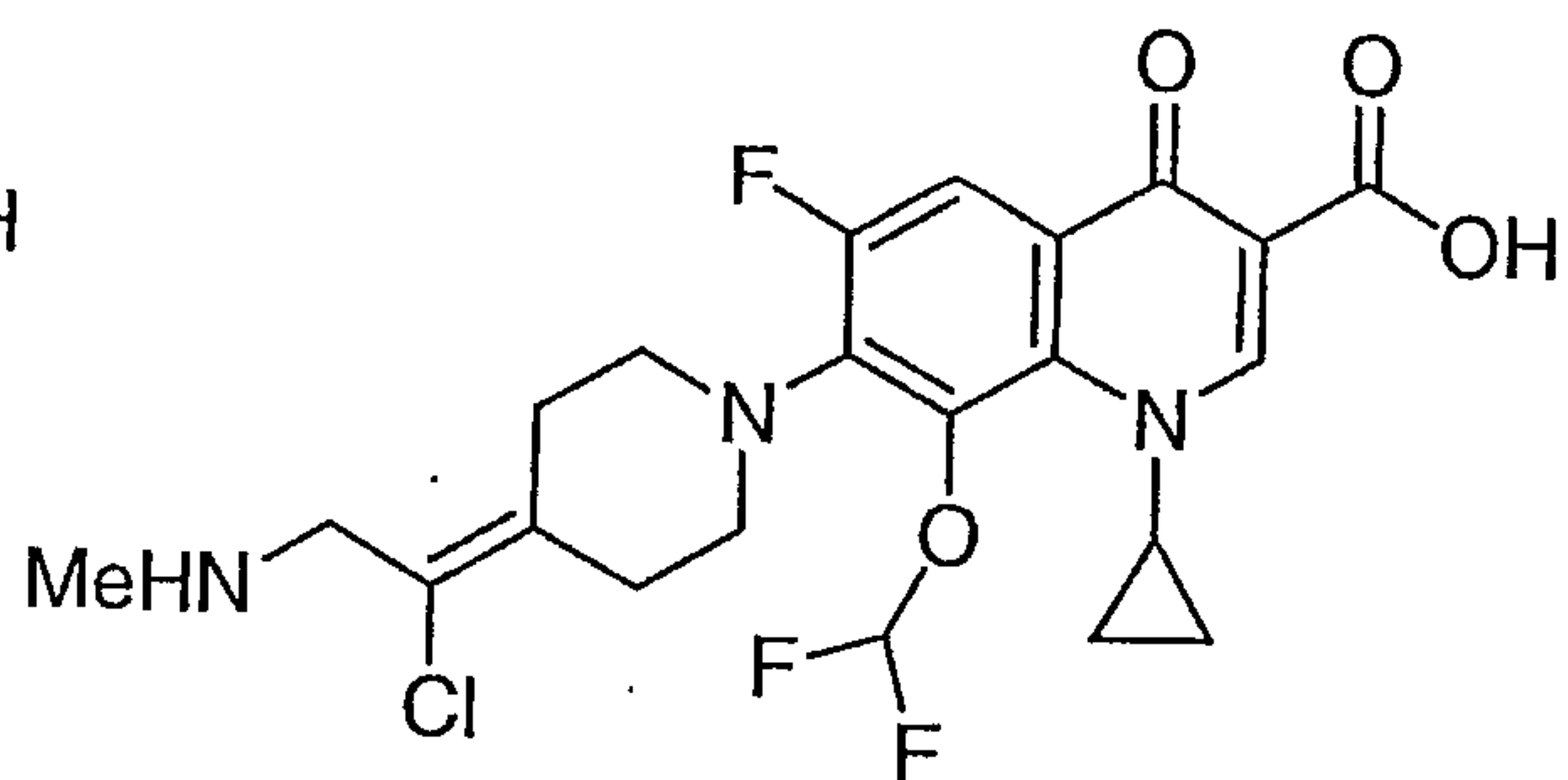
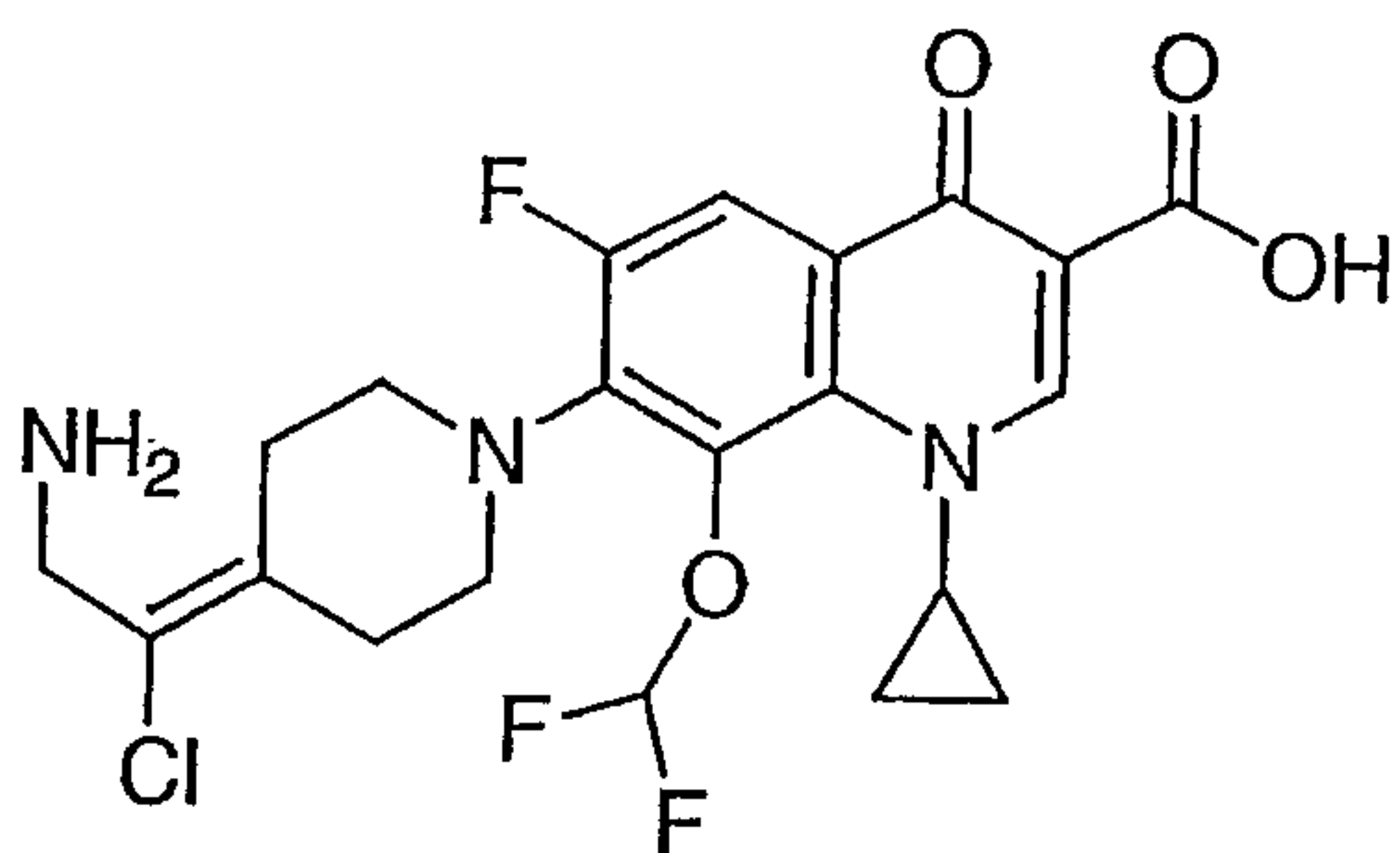
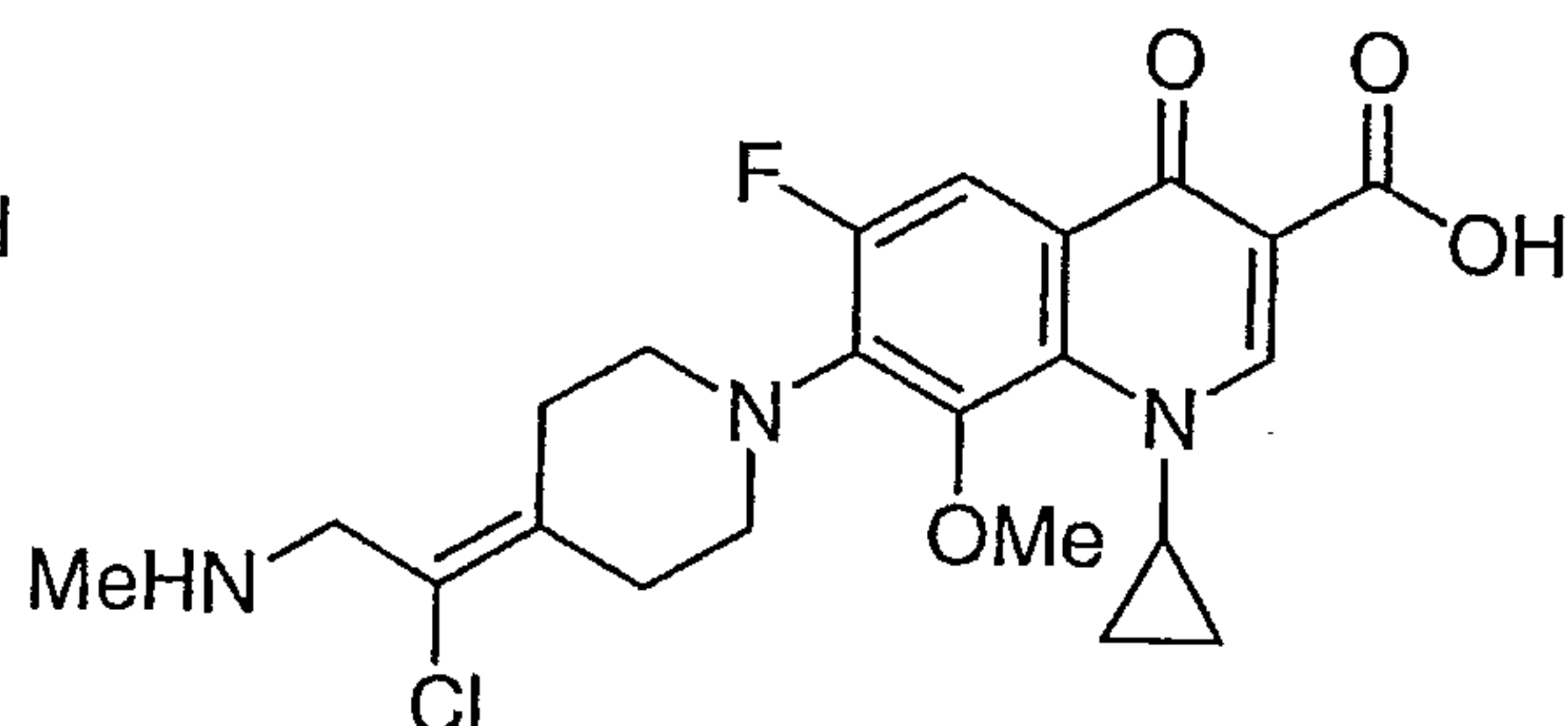
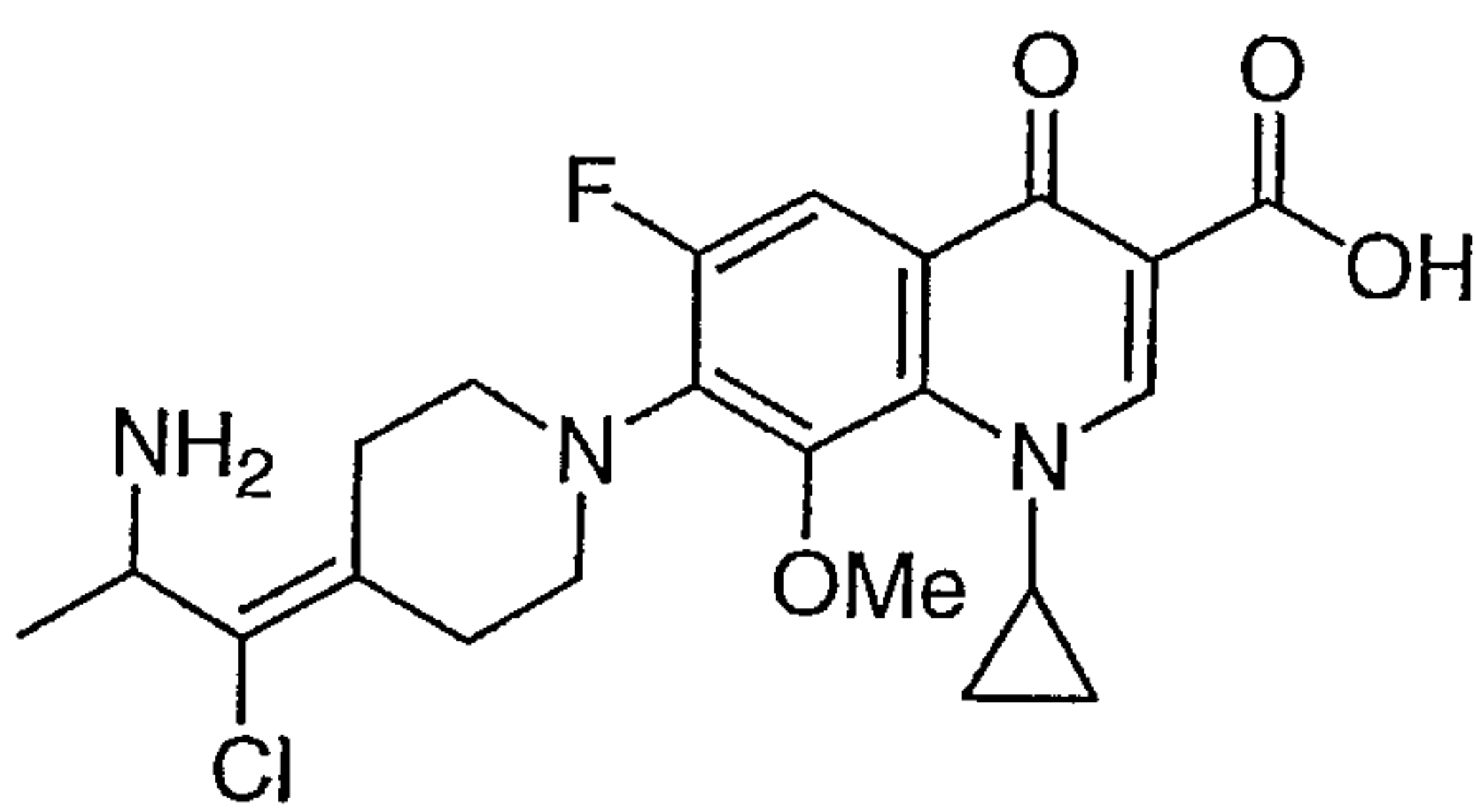
5. The compound of claim 1, wherein m is 1 and n is 1 or m is 2 and n is 2.
6. The compound of claim 1, wherein z is 0 or R₆ is methyl and z is 1.
7. The compound of claim 4, wherein R₇ and R₈ are hydrogen.
8. The compound of claim 7, wherein q is 1.
9. The compound of claim 8, wherein R₉ is hydrogen, methyl, or ethyl and
20 R₁₀ is hydrogen.

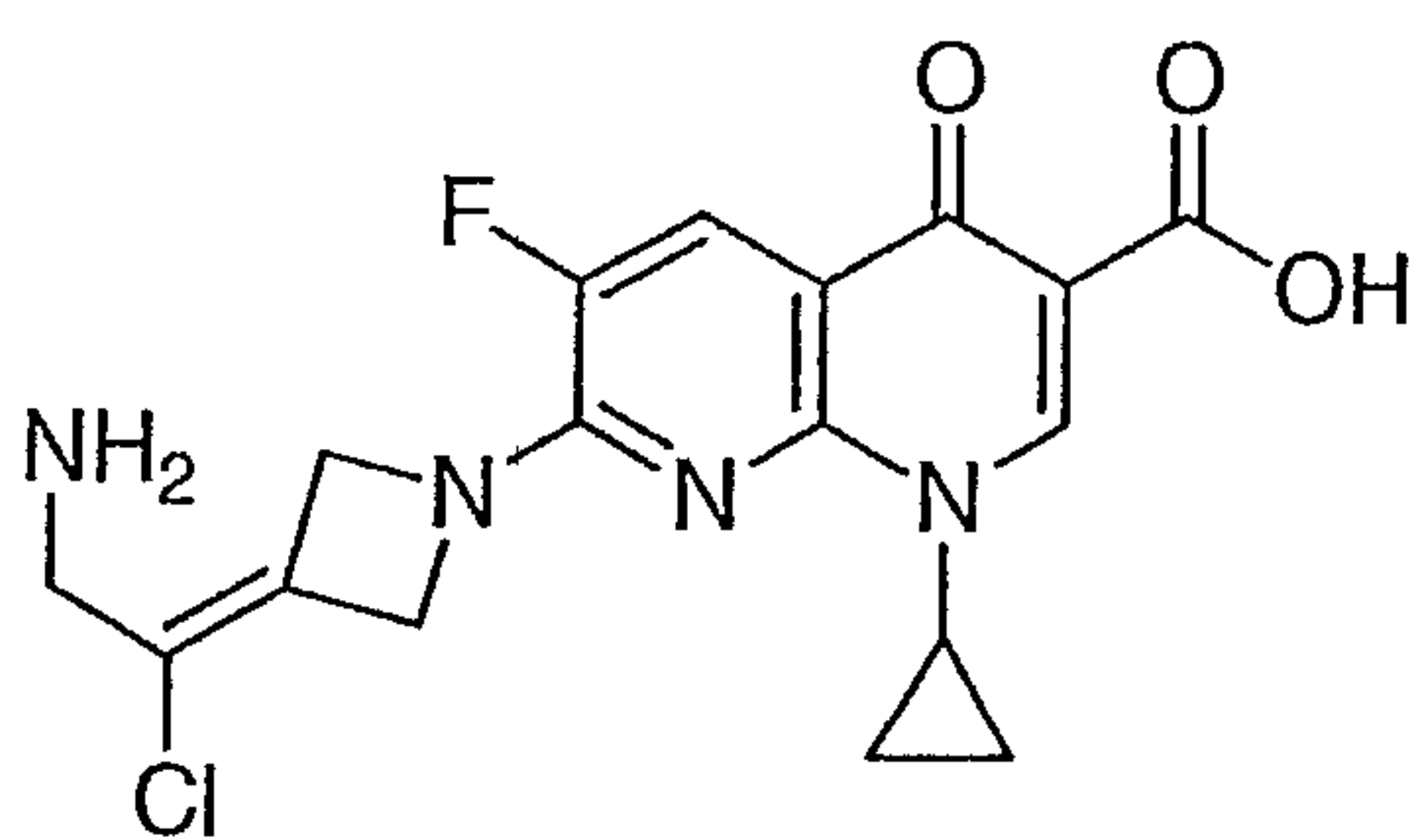
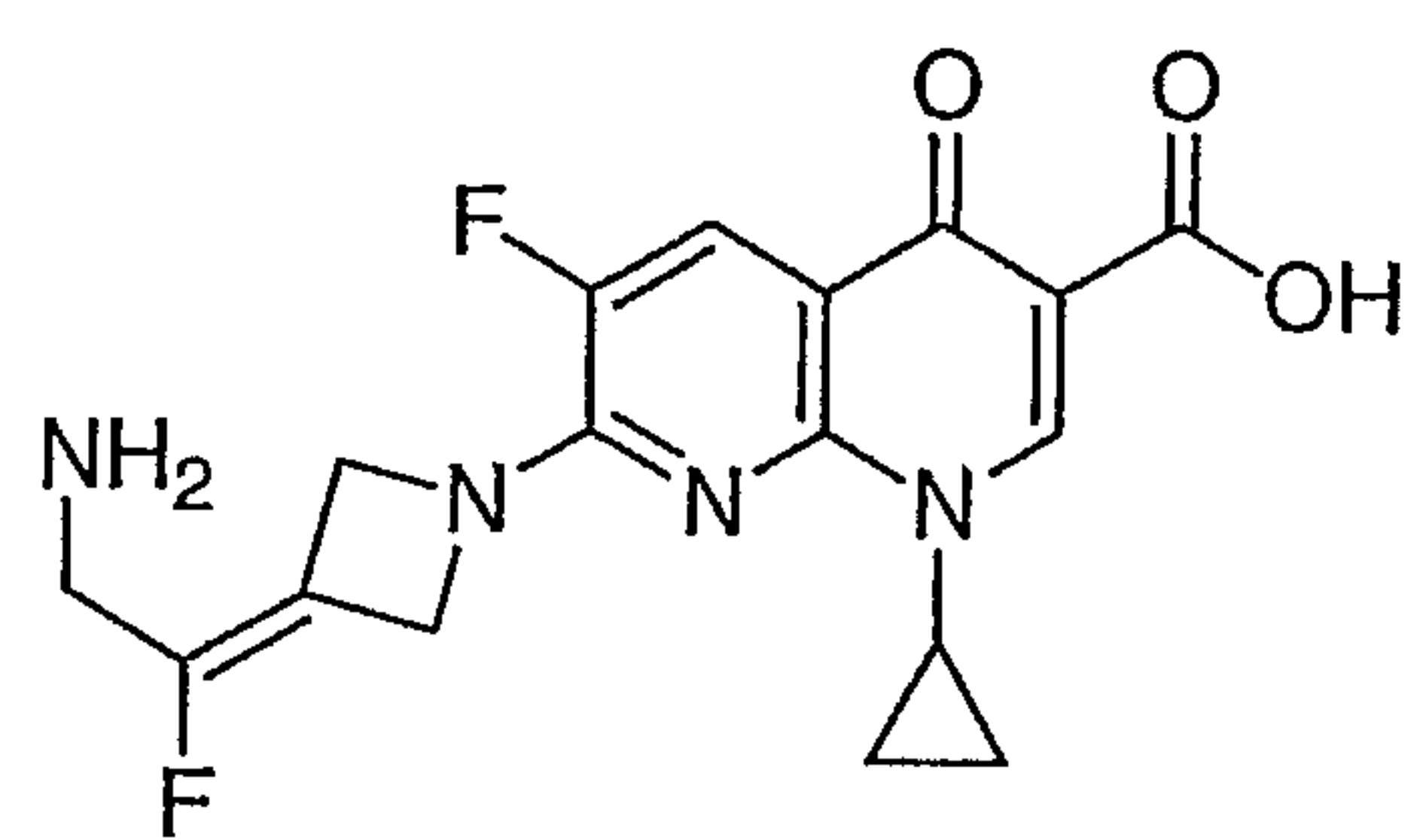
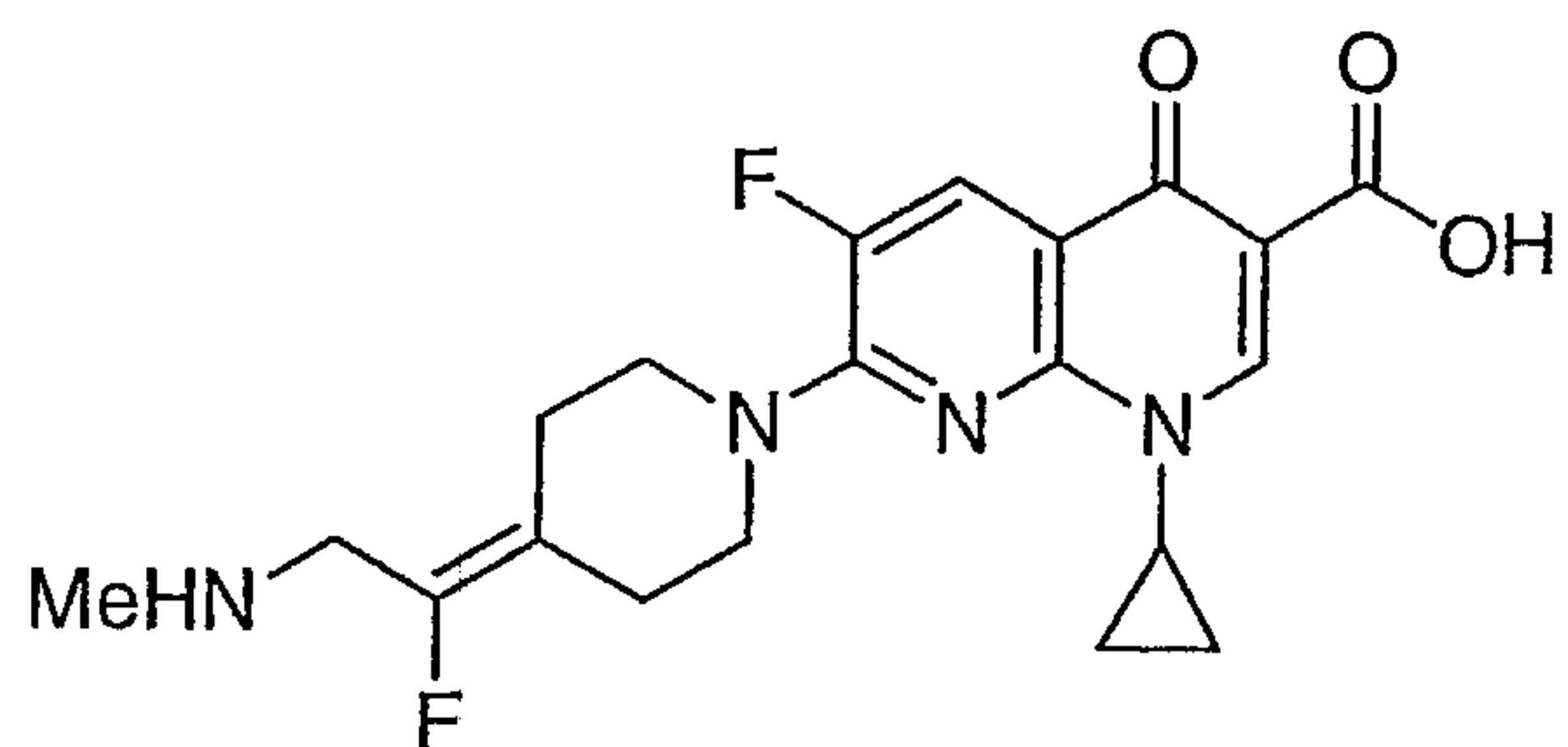
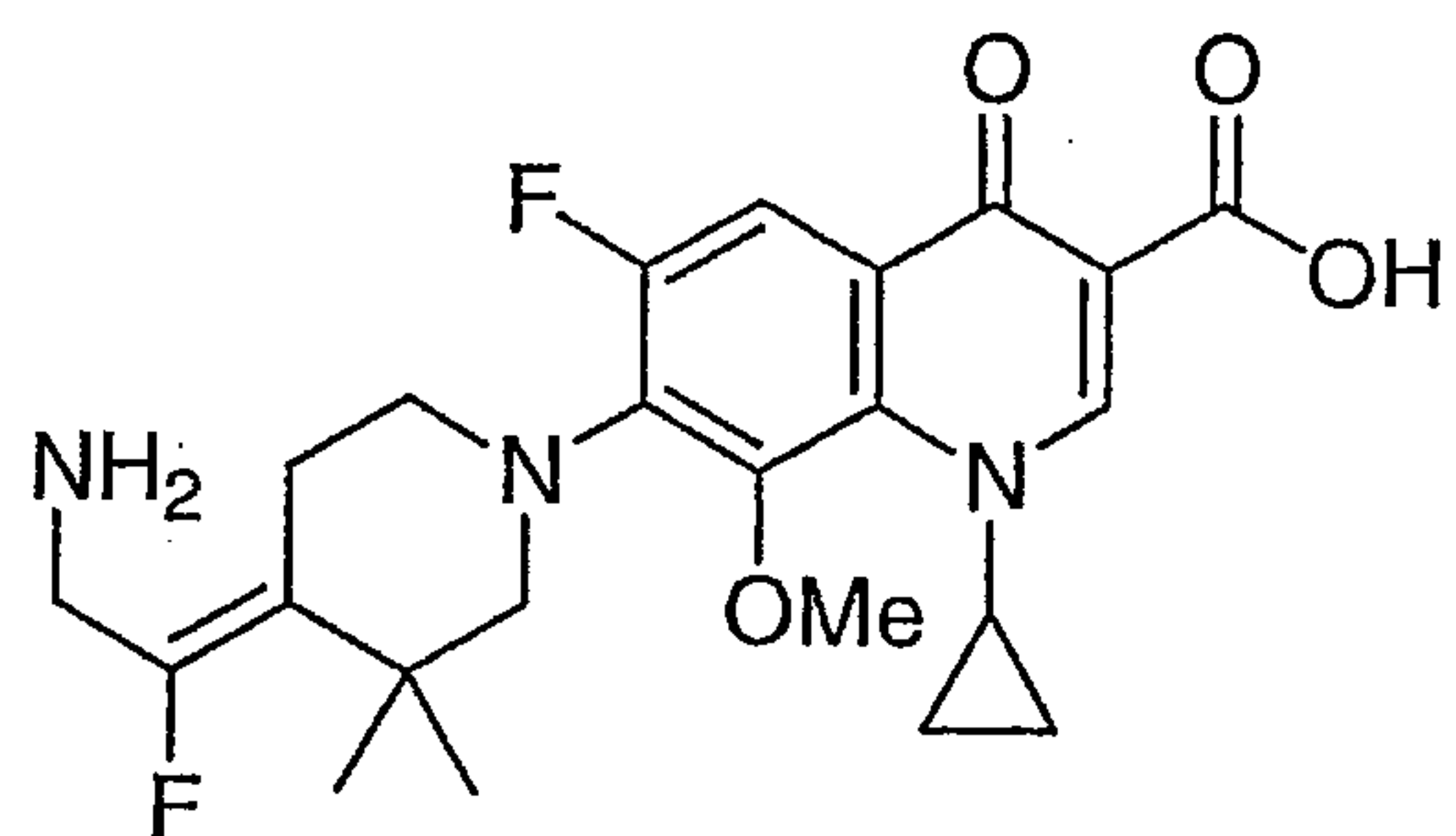
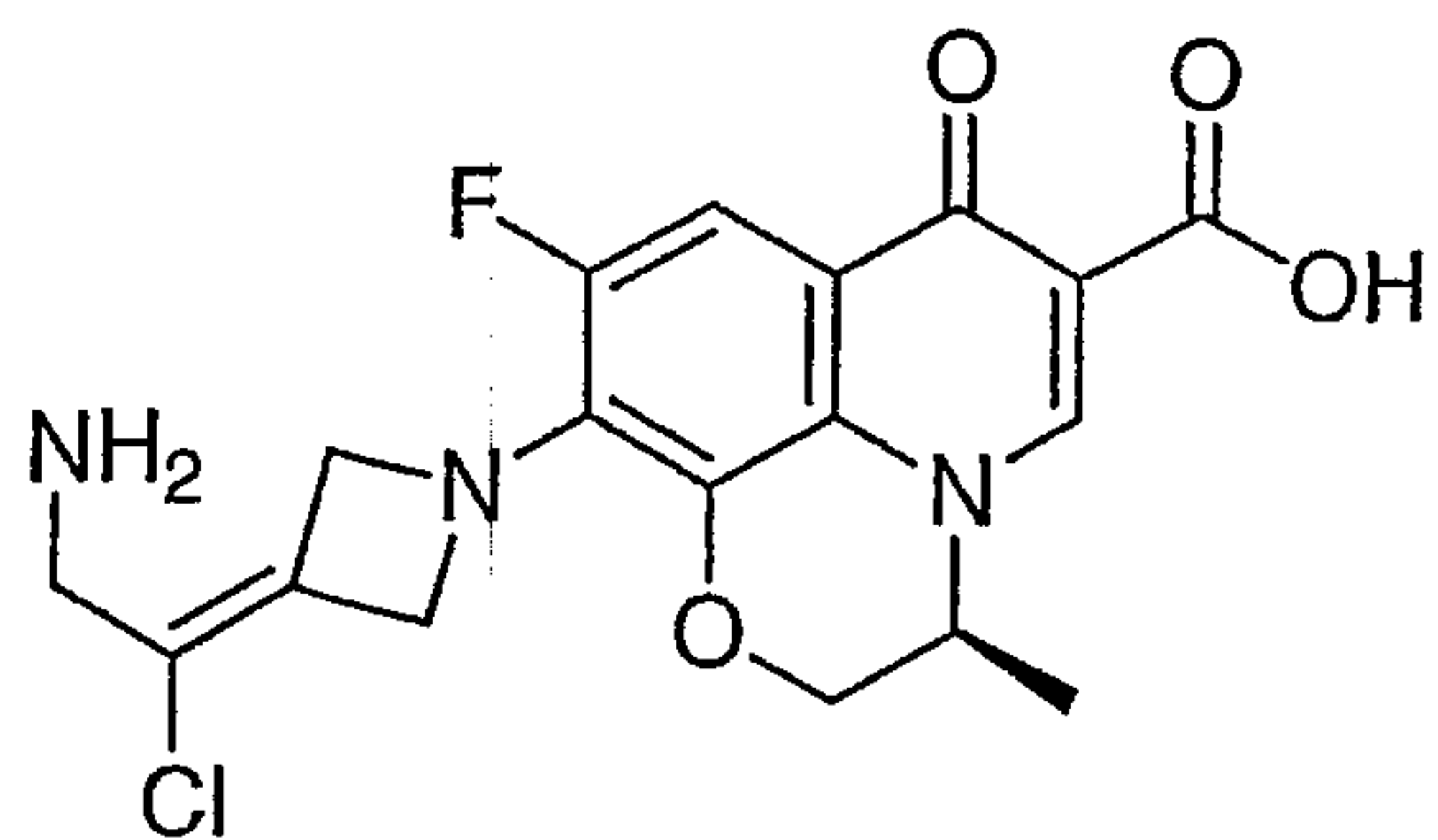
10.A compound of claim 1 selected from the group consisting of:





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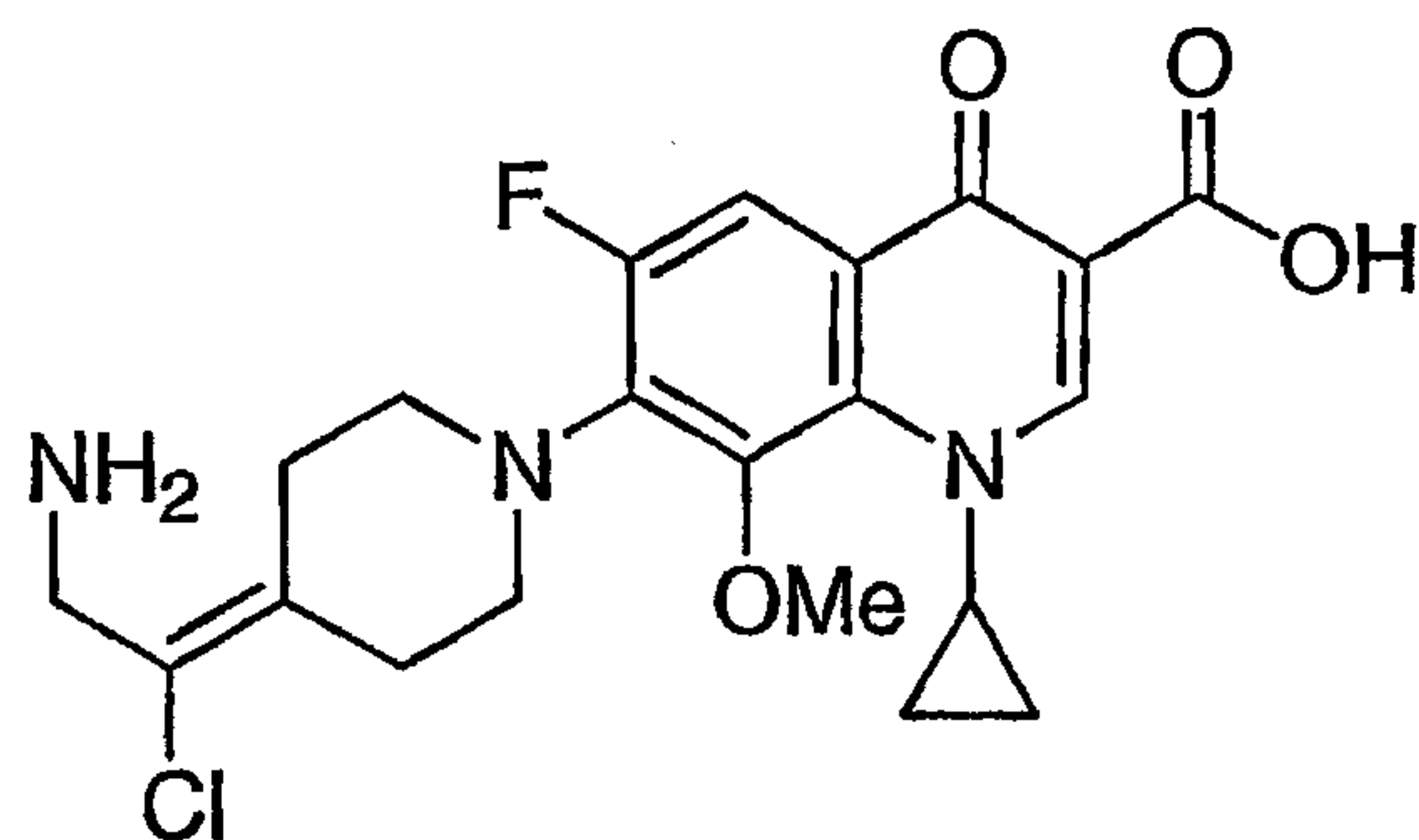
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11. The compound of claim 1 having the formula:

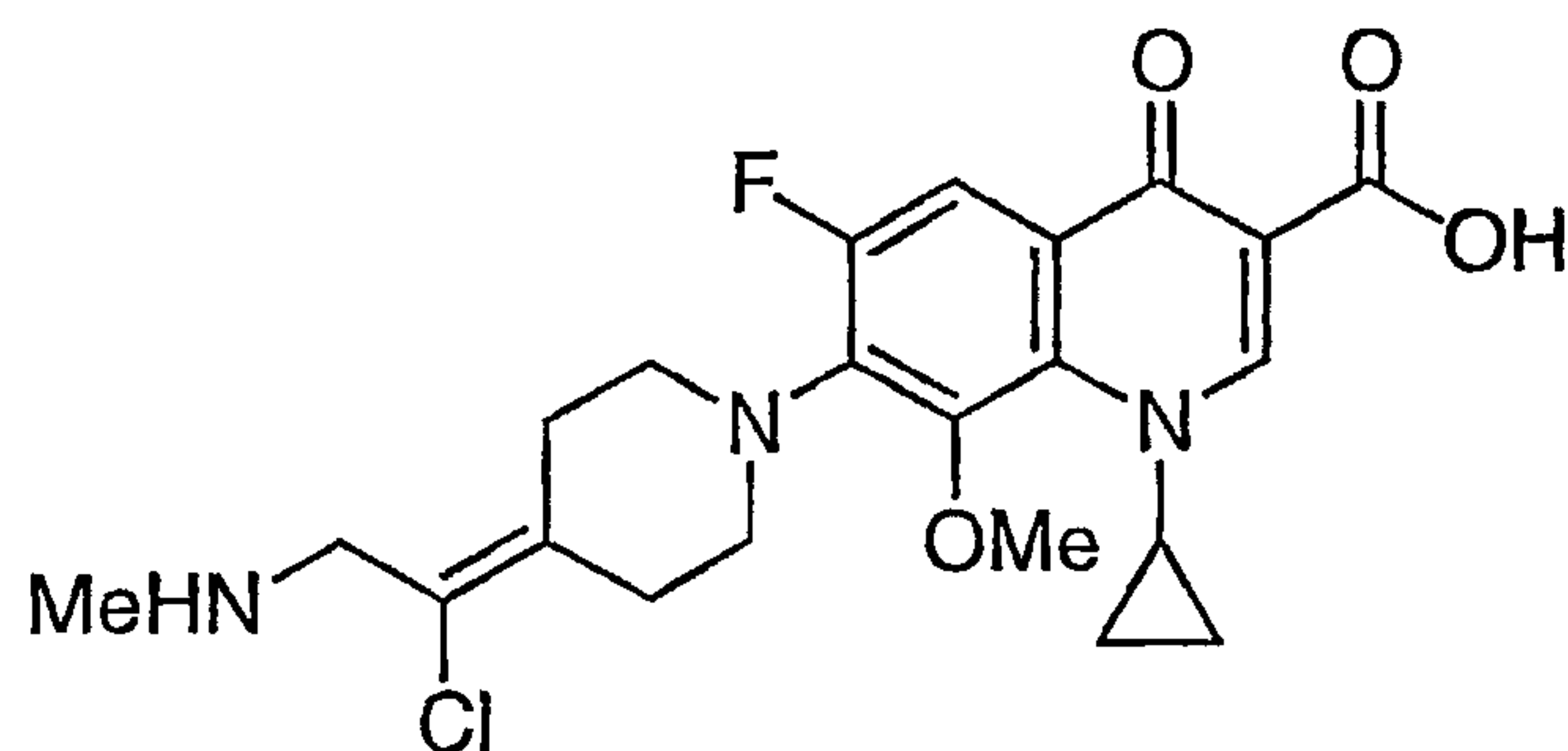
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12. The compound of claim 1 having the formula:

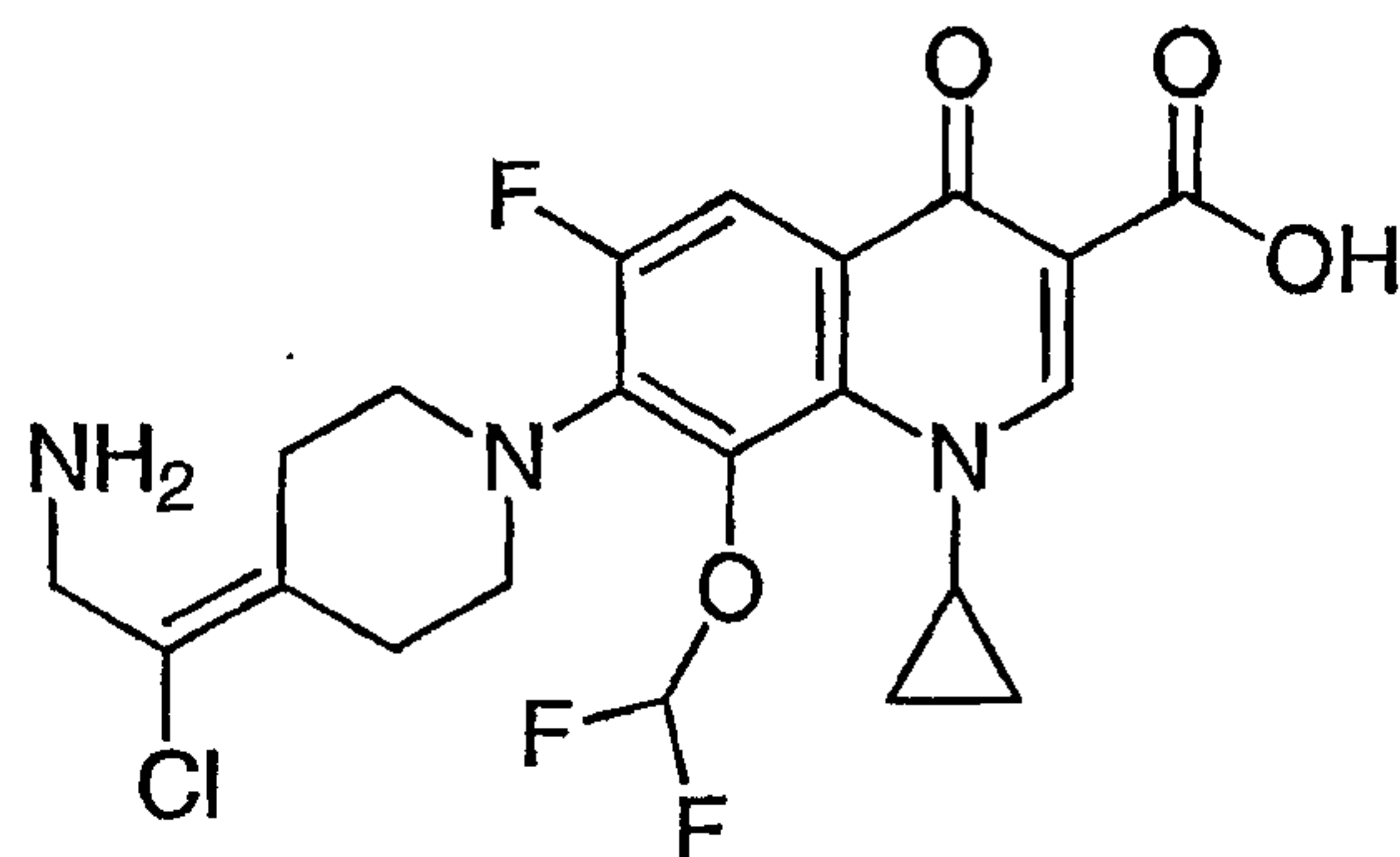
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13. The compound of claim 1 having the formula:

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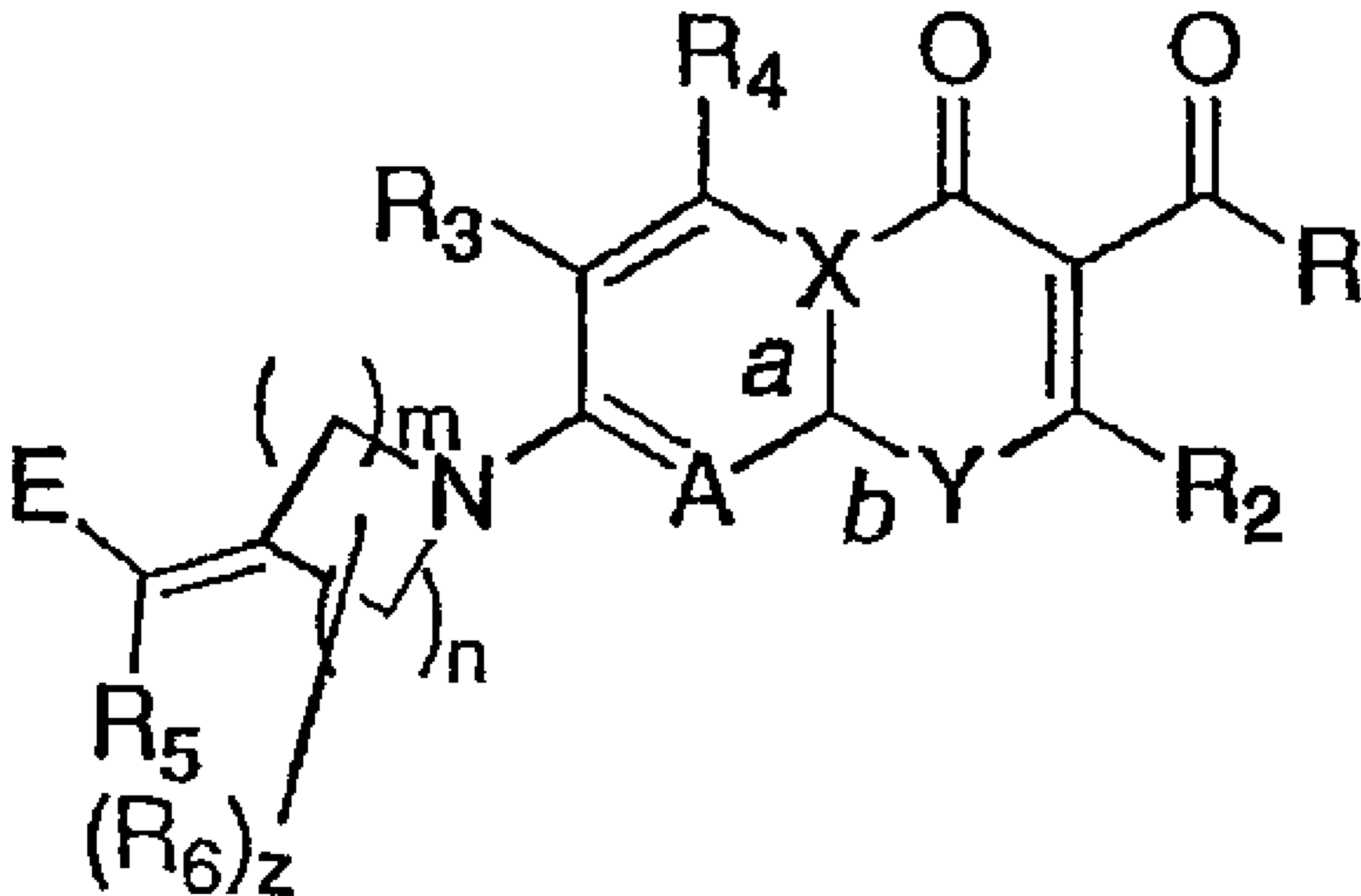
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14. A use of a therapeutically effective amount of a compound according to claim 1 for treating a subject having a condition caused by or contributed to by bacterial infection.

5 15. A use of a prophylactically effective dose of a compound according to claim 1 for preventing a subject from suffering a condition caused by or contributed to by bacterial infection.

16. A use of a therapeutically effective amount of a compound according to claim
10 1 in the preparation of a medicament for treating a subject having a condition caused by or contributed to by bacterial infection.

17. A use of a therapeutically effective amount of a compound according to claim
15 1 in the preparation of a medicament for preventing a subject from suffering a condition caused by or contributed to by bacterial infection.



Formula I