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(54) Title: AZETIDINYL QUINOLONES AS ANTIBACTERIAL AGENTS

(57) Abstract: Compounds of formula (I) and methods for their preparation are disclosed. Further disclosed are methods of making biologically active compounds of formula (I) as well as pharmaceutically acceptable compositions comprising compounds of formula (I). Compounds of formula (I) as disclosed herein can be used in a variety of applications including use as antibacterial agents.

AZETIDINYL QUINOLONES AS ANTIBACTERIAL AGENTS

This application claims benefits of U.S. Provisional Application No. 60/502,771, filed on September 12, 2003.

FIELD OF THE INVENTION

The invention relates to compounds bearing a quinolone core structure which exhibit antibacterial activity, methods for their preparation, as well as pharmaceutically acceptable compositions comprising such compounds.

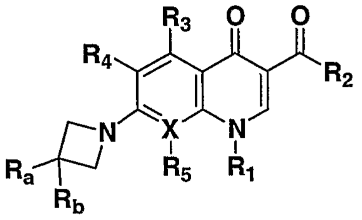
BACKGROUND OF THE INVENTION

Antibacterial resistance is a global clinical and public health problem that has emerged with alarming rapidity in recent years and undoubtedly will increase in the near future. Resistance is a problem in the community as well as in health care settings, where transmission of bacteria is greatly amplified. Because multiple drug resistance is a growing problem, physicians are now confronted with infections for which there is no effective therapy. The morbidity, mortality, and financial costs of such infections pose an increasing burden for health care systems worldwide. Strategies to address these issues emphasize enhanced surveillance of drug resistance, increased monitoring and improved usage of antimicrobial drugs, professional and public education, development of new drugs, and assessment of alternative therapeutic modalities.

As a result, alternative and improved agents are needed for the treatment of bacterial infections, particularly for the treatment of infections caused by resistant strains of bacteria, e.g. penicillin-resistant, methicillin-resistant, ciprofloxacin-resistant, and/or vancomycin-resistant strains.

SUMMARY OF THE INVENTION

These and other needs are met by the present invention, which is directed to a compound of formula I

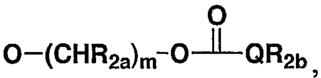


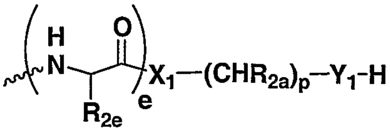
I

or a pharmaceutically acceptable salt thereof, wherein:

X is N or C, provided that when X is N, R_5 is absent at that position;

R_1 is $(C_1\text{-}C_6)$alkyl,
    halo$(C_1\text{-}C_6)$alkyl,
    $(C_3\text{-}C_6)$cycloalkyl,
    halo$(C_3\text{-}C_6)$cycloalkyl
    aryl, and
    heteroaryl;

R_2 is OH,
    OBF_2,
    $O(C_1\text{-}C_6)$alkyl,
    $O(C_3\text{-}C_6)$cycloalkyl,
    
    $O{-}(CHR_{2a})_m{-}O{-}\overset{O}{\overset{\|}{C}}{-}QR_{2b}$, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or $(C_1\text{-}C_6)$alkyl and R_{2b} is $(C_1\text{-}C_6)$alkyl, aryl, or heteroaryl,
    $O{-}(CHR_{2a})_n{-}Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl, or
    NR_{2d}, wherein R_{2d} is as defined above,



, wherein " ~ " indicates the point of attachment, 2a is as defined above, R_{2e} is H or $(C_1$-$C_6)$alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

R_3, R_4, and R_5 are each independently H,

halo,

NH_2,

$(C_1$-$C_6)$alkyl,

halo$(C_1$-$C_6)$alkyl,

$(C_1$-$C_6)$alkoxy, or

halo$(C_1$-$C_6)$alkoxy; or

R_1 and R_5 together with the carbons to which they are attached form an optionally substituted 5 or 6 membered ring containing 1 or 2 heteroatoms selected from NH, N-$(C_1$-$C_6)$alkyl, S, or O;

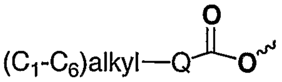
R_a is H,

aryl,

$(C_1$-$C_6)$alkyl,

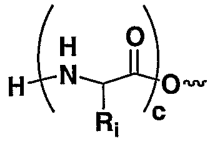
halo$(C_1$-$C_6)$alkyl,

$(C_3$-$C_6)$cycloalkyl,



$(C_1\text{-}C_6)\text{alkyl}{-}Q{-}C(=O){-}O{\sim}$

, wherein " ~ " indicates the point of attachment and Q is O or is absent,



, wherein "〰" indicates the point of attachment, R_i is H or $(C_1\text{-}C_6)$alkyl, and c is an integer having a value of from 1 to 10,

$R_{ii}O(C_1\text{-}C_6)$alkyl,

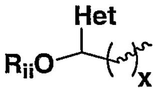
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,

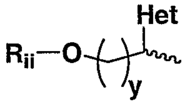
$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,



, wherein "〰" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;



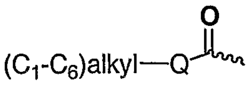
, wherein "〰" indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R_{ii} is H,

$(C_1\text{-}C_6)$alkyl,

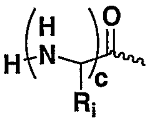
$PO(OH)_2$,

$PO(OC_1\text{-}C_6alkyl)_2$,



$(C_1\text{-}C_6)\text{alkyl}-Q-C(=O)-$

, as defined above, or



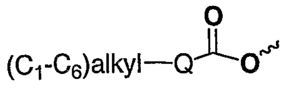
, as defined above;

provided that 3 or fewer of R_c R_d, R_e, and R_f are H; or

R_b is OH,

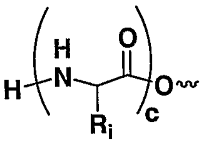
$PO(OH)_2$,

PO(OC$_1$-C$_6$alkyl)$_2$,



$(C_1\text{-}C_6)\text{alkyl}\text{—}Q\text{—}C(=O)\text{—}O\sim$

, wherein "〰" indicates the point of attachment and Q is O or is absent,



, wherein "〰" indicates the point of attachment, R$_i$ is H or (C$_1$-C$_6$)alkyl, and c is an integer having a value of from 1 to 10,

R$_{ii}$O(C$_1$-C$_6$)alkyl,

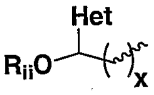
R$_{ii}$O(C$_1$-C$_6$)haloalkyl,

R$_{ii}$O(C$_3$-C$_6$)cycloalkyl,

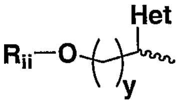
R$_{ii}$O(C$_1$-C$_6$)alkyl-O-,

R$_{ii}$O(C$_1$-C$_6$)haloalkyl-O-,

R$_{ii}$O(C$_3$-C$_6$)cycloalkyl-O-,



, wherein "〰" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;



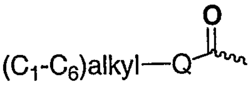
, wherein "〰" indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R$_{ii}$ is H,

(C$_1$-C$_6$)alkyl,

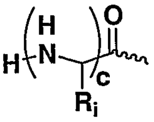
PO(OH)$_2$,

PO(O(C$_1$-C$_6$)alkyl)$_2$,



$(C_1\text{-}C_6)\text{alkyl}\text{—}Q\text{—}C(=O)\sim$

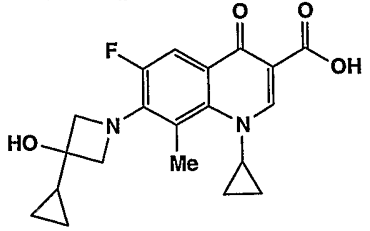
, as defined above, or



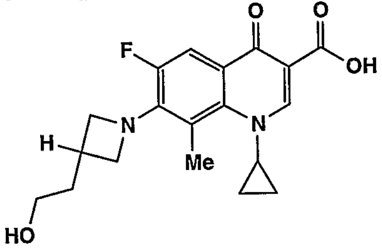
, as defined above.

What is also provided is a compound which is:

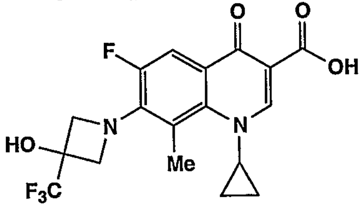
1-Cyclopropyl-7-(3-cyclopropyl-3-hydroxy-azetidin-1-yl)-6-fluoro-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid;



1-Cyclopropyl-6-fluoro-7-[3-(2-hydroxy-ethyl)-azetidin-1-yl]-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid; or



1-Cyclopropyl-6-fluoro-7-(3-hydroxy-3-trifluoromethyl-azetidin-1-yl)-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.



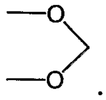
What is also provided is a pharmaceutical formulation comprising a compound of one of formula I admixed with a pharmaceutically acceptable diluent, carrier, or excipient.

What is also provided is a method of treating a bacterial infection in a mammal, comprising administering to a mammal in need thereof an effective amount of a compound of one of formula I.

DETAILED DESCRIPTION OF THE INVENTION

Reference will now be made in detail to presently preferred compositions or embodiments and methods of the invention, which constitute the best modes of practicing the invention presently known to the inventors.

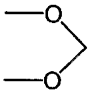
The term “alkyl” as used herein refers to a straight or branched hydrocarbon of from 1 to 6 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, *tert*-butyl, n-pentyl, n-hexyl, and the like. The alkyl group can also be substituted with one or more of the substituents selected from lower (C_1-C_6)alkoxy, (C_1-C_6)thioalkoxy, halogen, oxo, thio, -OH, -SH, -F, -CF_3,- OCF_3, -NO_2, -CO_2H, -CO_2(C_1-C_6)alkyl, or



.

The term “(C_3-C_6)cycloalkyl” means a hydrocarbon ring containing from 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. Where possible, the cycloalkyl group may contain double bonds, for example, 3-cyclohexen-1-yl. The cycloalkyl ring may be unsubstituted or substituted by one or more substituents selected from alkyl, alkoxy, thioalkoxy, hydroxy, thiol, halogen, formyl, carboxyl, -CO_2(C_1-C_6)alkyl, -CO(C_1-C_6)alkyl, aryl, heteroaryl, wherein alkyl, aryl, and heteroaryl are as defined herein, or as indicated above for alkyl. Examples of substituted cycloalkyl groups include fluorocyclopropyl.

The term “halo” includes chlorine, fluorine, bromine, and iodine.

The term “aryl” means a cyclic or polycyclic aromatic ring having from 5 to 12 carbon atoms, and being unsubstituted or substituted with one or more of the substituent groups recited above for alkyl groups including, halogen, nitro, cyano -OH, -SH, -F, -CF_3, -OCF_3,  -CO_2H, -CO_2(C_1-C_6)alkyl, or - SO_2alkyl. Examples include, but are not limited to phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-chloro-3-methylphenyl, 2-chloro-4-methylphenyl, 2-chloro-5-methylphenyl, 3-chloro-2-methylphenyl, 3-

chloro-4-methylphenyl, 4-chloro-2-methylphenyl, 4-chloro-3-methylphenyl, 5-chloro-2-methylphenyl, 2,3-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2,3-dimethylphenyl, 3,4-dimethylphenyl, thienyl, naphthyl, 4-thionaphthyl, tetralinyl, anthracinyl, phenanthrenyl, benzonaphthenyl, fluorenyl, 2-acetamidofluoren-9-yl, and 4′-bromobiphenyl.

The term "heteroaryl" means an aromatic cyclic or polycyclic ring system having from 1 to 4 heteroatoms selected from N, O, and S. Typical heteroaryl groups include 2- or 3-thienyl, 2- or 3-furanyl, 2- or 3-pyrrolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5-pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 3- or 5-1,2,4-triazolyl, 4- or 5-1,2,3-triazolyl, tetrazolyl, 2-, 3-, or 4-pyridinyl, 3-, 4-, or 5-pyridazinyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[*b*]thienyl, 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 5-, 6-, or 7-benzothiazolyl. The heteroaryl groups may be unsubstituted or substituted by 1 to 3 substituents selected from those described above for alkyl, alkenyl, and alkynyl, for example, cyanothienyl and formylpyrrolyl. Preferred aromatic fused heterocyclic rings of from 8 to 10 atoms include but are not limited to 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl-, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[*b*]thienyl, 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 5-, 6-, or 7-benzothiazolyl. Heteroaryl also includes 2- and 3- aminomethylfuran, 2- and 3- aminomethylthiophene and the like..

The term "heterocyclic" means a monocyclic, fused, bridged, or spiro bicyclic heterocyclic ring systems. Monocyclic heterocyclic rings contain from about 3 to 12 ring atoms, with from 1 to 5 heteroatoms selected from N, O, and S, and preferably from 3 to 7 member atoms, in the ring. Bicyclic heterocyclics contain from about 5 to about 17 ring atoms, preferably from 5 to 12 ring atoms. Bicyclic heterocyclic rings may be fused, spiro, or bridged ring systems. Examples of heterocyclic groups include cyclic ethers (oxiranes) such as ethyleneoxide, tetrahydrofuran, dioxane, and substituted cyclic ethers, wherein the substituents are those described above for the alkyl and cycloalkyl groups. Typical substituted cyclic ethers include propyleneoxide, phenyloxirane (styrene oxide), cis-2-butene-oxide (2,3-dimethyloxirane), 3-chlorotetrahydrofuran, 2,6-dimethyl-1,4-dioxane, and the like. Heterocycles containing nitrogen are groups such as pyrrolidine, piperidine, piperazine, tetrahydrotriazine, tetrahydropyrazole, and substituted groups such as 3-aminopyrrolidine, 4-methylpiperazin-1-yl, and the like. Typical sulfur containing heterocycles include tetrahydrothiophene, dihydro-1,3-dithiol-2-yl, and hexahydrothiophen-4-yl and substituted groups such as aminomethyl thiophene. Other commonly employed heterocycles include dihydro-oxathiol-4-yl, dihydro-1*H*-isoindole, tetrahydro-oxazolyl, tetrahydro-oxadiazolyl, tetrahydrodioxazolyl, tetrahydrooxathiazolyl, hexahydrotriazinyl, tetrahydro-oxazinyl, morpholinyl, thiomorpholinyl, tetrahydropyrimidinyl, dioxolinyl, octahydrobenzofuranyl, octahydrobenzimidazolyl, and octahydrobenzothiazolyl. For heterocycles containing sulfur, the oxidized sulfur heterocycles containing SO or SO_2 groups are also included. Examples include the sulfoxide and sulfone forms of tetrahydrothiophene.

When a bond is represented by a symbol such as "------" this is meant to represent that the bond may be absent or present provided that the resultant compound is stable and of satisfactory valency.

When a bond is represented by a line such as "∿∿∿" this is meant to represent that the bond is the point of attachment between two molecular subunits.

The term "patient" means all mammals, including humans. Other examples of patients include cows, dogs, cats, goats, sheep, pigs, and rabbits.

A "therapeutically effective amount" is an amount of a compound of the present invention that, when administered to a patient, provides the desired effect; i.e., lessening in the severity of the symptoms associated with a bacterial infection.

It will be appreciated by those skilled in the art that compounds of the invention having one or more chiral centers may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, geometric, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine activity or cytotoxicity using the standard tests described herein, or using other similar tests which are well known in the art.

Certain compounds of Formula I are also useful as intermediates for preparing other compounds of Formula I. Thus, a compound wherein R_2 is NR_2, can be metabolized to form another compound of the invention wherein R_2 is H. This conversion can occur under physiological conditions. To that end, both the non-metabolized compound of the invention and the metabolized compound of the invention--that is, the compound wherein R_2 is NR_2 and the compound wherein R_2 is H--can have antibacterial activity.

Some of the compounds of Formula I are capable of further forming pharmaceutically acceptable acid-addition and/or base salts. All of these forms are within the scope of the present invention. Thus, pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinates suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzensoulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 1977;66:1-19).

The acid addition salt of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner.

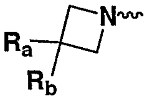
Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N′-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S.M., supra., 1977).

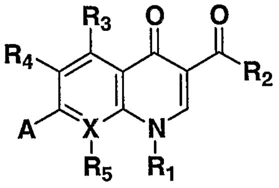
The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

A "prodrug" is an inactive derivative of a drug molecule that requires a chemical or an enzymatic biotransformation in order to release the active parent drug in the body.

Specific and preferred values for the compounds of the present invention are listed below for radicals, substituents, and ranges are for illustration purposes only, and they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

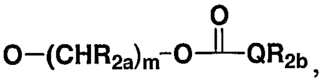
Thus, we turn now to a compound of formula I, which has the following structure wherein A is  :



I

In one embodiment of a compound of formula I,

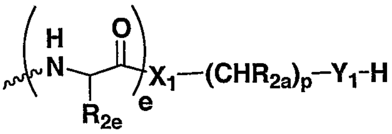
R_1 is $(C_1\text{-}C_6)$alkyl,
  halo$(C_1\text{-}C_6)$alkyl,
  $(C_3\text{-}C_6)$cycloalkyl,
  halo$(C_3\text{-}C_6)$cycloalkyl
  aryl, and
  heteroaryl;

R_2 is OH,
  OBF_2,
  $O(C_1\text{-}C_6)$alkyl,
  $O(C_3\text{-}C_6)$cycloalkyl,
  
  $O{-}(CHR_{2a})_m{-}O{-}\overset{O}{\overset{\|}{C}}{-}QR_{2b}$, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or $(C_1\text{-}C_6)$alkyl and R_{2b} is $(C_1\text{-}C_6)$alkyl, aryl, or heteroaryl,
  $O{-}(CHR_{2a})_n{-}Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are

each independently H, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl,

or

NR_{2d}, wherein R_{2d} is as defined above,



, wherein "~~~" indicates the point of attachment, 2a is as defined above, R_{2e} is H or $(C_1\text{-}C_6)$alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

R_3, R_4, and R_5 are each independently H,

halo,

NH_2,

$(C_1\text{-}C_6)$alkyl,

halo$(C_1\text{-}C_6)$alkyl,

$(C_1\text{-}C_6)$alkoxy, or

halo$(C_1\text{-}C_6)$alkoxy;

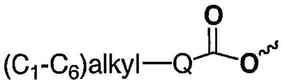
R_a is H,

aryl,

$(C_1\text{-}C_6)$alkyl,

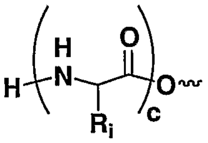
halo$(C_1\text{-}C_6)$alkyl,

$(C_3\text{-}C_6)$cycloalkyl,



$(C_1\text{-}C_6)\text{alkyl}—Q—C(=O)—O—$

, wherein "~~~" indicates the point of attachment and Q is O or is absent,



, wherein "~~~" indicates the point of attachment, R_i is H or $(C_1\text{-}C_6)$alkyl, and c is an integer having a value of from 1 to 10,

$R_{ii}O(C_1\text{-}C_6)$alkyl,

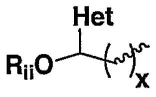
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,

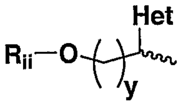
$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,



, wherein "∿" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;



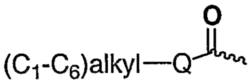
, wherein "∿" indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R_{ii} is H,

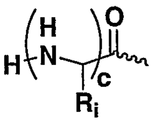
$(C_1\text{-}C_6)$alkyl,

$PO(OH)_2$,

$PO(OC_1\text{-}C_6alkyl)_2$,

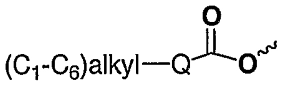


$(C_1\text{-}C_6)\text{alkyl}-Q-C(=O)-$, as defined above, or

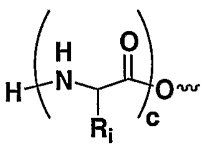


, as defined above;

R_b is OH,



$(C_1\text{-}C_6)\text{alkyl}-Q-C(=O)-O-$, wherein "∿" indicates the point of attachment and Q is O or is absent,



, wherein "∿" indicates the point of attachment, R_i is H or $(C_1\text{-}C_6)$alkyl, and c is an integer having a value of from 1 to 10,

$R_{ii}O(C_1\text{-}C_6)$alkyl,

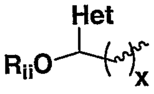
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,

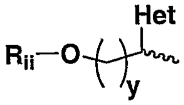
$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,



, wherein " ~~~ " indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;



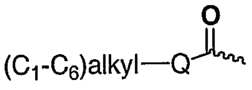
, wherein " ~~~ " indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R_{ii} is H,

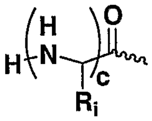
$(C_1\text{-}C_6)$alkyl,

$PO(OH)_2$,

$PO(O(C_1\text{-}C_6)alkyl)_2$,



$(C_1\text{-}C_6)\text{alkyl}—Q—C(=O)—$, as defined above, or



, as defined above.

In another embodiment of a compound of formula I,

R_1 is $(C_1\text{-}C_6)$alkyl,

halo$(C_1\text{-}C_6)$alkyl,

$(C_3\text{-}C_6)$cycloalkyl,

halo$(C_3\text{-}C_6)$cycloalkyl

aryl, and

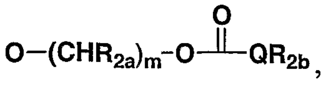
heteroaryl;

R_2 is OH,

OBF_2,

$O(C_1\text{-}C_6)$alkyl,

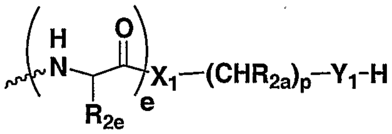
$O(C_3\text{-}C_6)$cycloalkyl,



$O-(CHR_{2a})_m-O-C(=O)-QR_{2b}$, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or $(C_1\text{-}C_6)$alkyl and R_{2b} is $(C_1\text{-}C_6)$alkyl, aryl, or heteroaryl,

$O-(CHR_{2a})_n-Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl, or

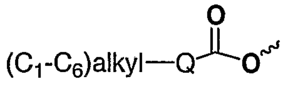
NR_{2d}, wherein R_{2d} is as defined above,



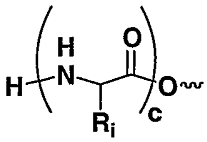
, wherein “ ∿ ” indicates the point of attachment, 2a is as defined above, R_{2e} is H or $(C_1\text{-}C_6)$alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

R_3, R_4, and R_5 are each independently H,
halo,
NH_2,
$(C_1\text{-}C_6)$alkyl,
halo$(C_1\text{-}C_6)$alkyl,
$(C_1\text{-}C_6)$alkoxy, or
halo$(C_1\text{-}C_6)$alkoxy;

R_a is H,
aryl,
$(C_1\text{-}C_6)$alkyl,
halo$(C_1\text{-}C_6)$alkyl,
$(C_3\text{-}C_6)$cycloalkyl,



$(C_1\text{-}C_6)alkyl-Q-C(=O)-O\sim$, wherein “ ∿ ” indicates the point of attachment and Q is O or is absent,



, wherein "∿" indicates the point of attachment, R_i is H or $(C_1\text{-}C_6)$alkyl, and c is an integer having a value of from 1 to 10,

$R_{ii}O(C_1\text{-}C_6)$alkyl,

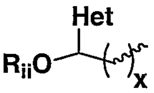
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,

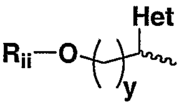
$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,



, wherein "∿" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;

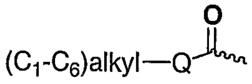


, wherein "∿" indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R_{ii} is H,

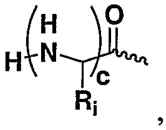
$(C_1\text{-}C_6)$alkyl,

$PO(OH)_2$,



$(C_1\text{-}C_6)\text{alkyl}-Q-C(=O)\sim$

, as defined above, or



, as defined above;

R_b is OH,

$R_{ii}O(C_1\text{-}C_6)$alkyl,

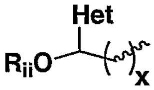
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,

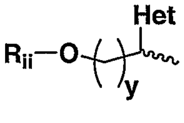
$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,

$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,


, wherein "〰" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;

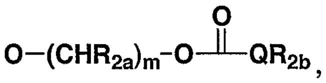

, wherein "〰" indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R_{ii} is H or $(C_1\text{-}C_6)$alkyl.

In yet another embodiment of a compound of formula I,

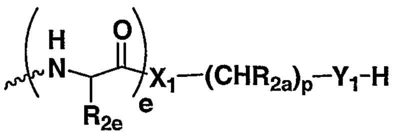
R_1 is $(C_1\text{-}C_6)$alkyl,
halo$(C_1\text{-}C_6)$alkyl,
$(C_3\text{-}C_6)$cycloalkyl,
halo$(C_3\text{-}C_6)$cycloalkyl
aryl, and
heteroaryl;

R_2 is OH,
OBF_2,
$O(C_1\text{-}C_6)$alkyl,
$O(C_3\text{-}C_6)$cycloalkyl,


$O{-}(CHR_{2a})_m{-}O{-}\overset{O}{\overset{\|}{C}}{-}QR_{2b}$, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or $(C_1\text{-}C_6)$alkyl and R_{2b} is $(C_1\text{-}C_6)$alkyl, aryl, or heteroaryl,

$O{-}(CHR_{2a})_n{-}Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl, or

NR_{2d}, wherein R_{2d} is as defined above,



, wherein "∿∿" indicates the point of attachment, 2a is as defined above, R_{2e} is H or (C_1-C_6)alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

R_3, R_4, and R_5 are each independently H,

halo,

NH_2,

(C_1-C_6)alkyl,

halo(C_1-C_6)alkyl,

(C_1-C_6)alkoxy, or

halo(C_1-C_6)alkoxy;

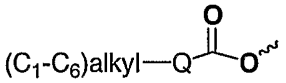
R_a is H,

aryl,

(C_1-C_6)alkyl,

halo(C_1-C_6)alkyl,

(C_3-C_6)cycloalkyl,



, wherein "∿∿" indicates the point of attachment and Q is O or is absent,

$R_{ii}O$(C_1-C_6)alkyl,

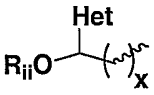
$R_{ii}O$(C_1-C_6)haloalkyl,

$R_{ii}O$(C_3-C_6)cycloalkyl,

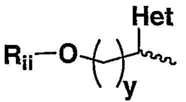
$R_{ii}O$(C_1-C_6)alkyl-O-,

$R_{ii}O$(C_1-C_6)haloalkyl-O-,

$R_{ii}O$(C_3-C_6)cycloalkyl-O-,



, wherein "∿∿" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;

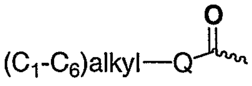


, wherein “ ∿∿ ” indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

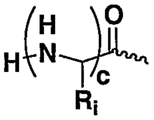
wherein R_{ii} is H,

$(C_1\text{-}C_6)$alkyl,

$PO(OH)_2$,



$(C_1\text{-}C_6)\text{alkyl}\text{—}Q\text{—}C(=O)\text{—}$, as defined above, or



, as defined above;

R_b is OH,

$R_{ii}O(C_1\text{-}C_6)$alkyl,

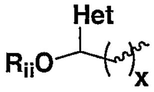
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,

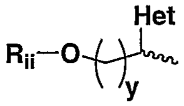
$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,



, wherein “ ∿∿ ” indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;



, wherein “ ∿∿ ” indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R_{ii} is H or $(C_1\text{-}C_6)$alkyl.

In another embodiment of a compound of formula I,

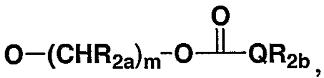
R_1 is $(C_1\text{-}C_6)$alkyl,

halo$(C_1\text{-}C_6)$alkyl,

$(C_3\text{-}C_6)$cycloalkyl,

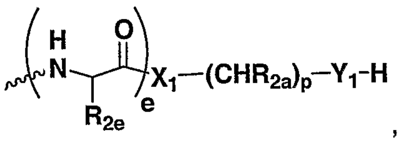
halo(C_3-C_6)cycloalkyl
aryl, and
heteroaryl;

R_2 is OH,
OBF_2,
O(C_1-C_6)alkyl,
O(C_3-C_6)cycloalkyl,


$O-(CHR_{2a})_m-O-\overset{O}{\overset{\|}{C}}-QR_{2b}$, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or (C_1-C_6)alkyl and R_{2b} is (C_1-C_6)alkyl, aryl, or heteroaryl,

$O-(CHR_{2a})_n-Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, (C_1-C_6)alkyl, or (C_3-C_6)cycloalkyl, or

NR_{2d}, wherein R_{2d} is as defined above,


, wherein " ∿∿ " indicates the point of attachment, 2a is as defined above, R_{2e} is H or (C_1-C_6)alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

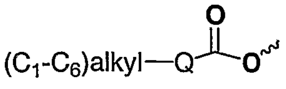
R_3, R_4, and R_5 are each independently H,
halo,
NH_2,
(C_1-C_6)alkyl,
halo(C_1-C_6)alkyl,
(C_1-C_6)alkoxy, or
halo(C_1-C_6)alkoxy;

R_a is H,
aryl,

$(C_1\text{-}C_6)$alkyl,

halo$(C_1\text{-}C_6)$alkyl,

$(C_3\text{-}C_6)$cycloalkyl,



$(C_1\text{-}C_6)\text{alkyl}{-}Q{-}C(=O){-}O{-}$

, wherein "∿∿∿" indicates the point of attachment and Q is O or is absent,

$R_{ii}O(C_1\text{-}C_6)$alkyl,

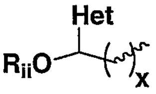
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,

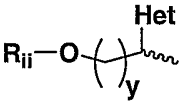
$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,



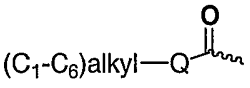
, wherein "∿∿∿" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;



, wherein "∿∿∿" indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

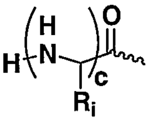
wherein R_{ii} is H,

$(C_1\text{-}C_6)$alkyl,



$(C_1\text{-}C_6)\text{alkyl}{-}Q{-}C(=O){-}$

, as defined above, or



, as defined above;

R_b is OH,

$R_{ii}O(C_1\text{-}C_6)$alkyl,

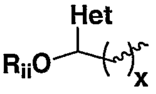
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,

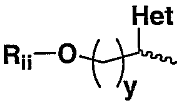
$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,



, wherein " ∿∿ " indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;



, wherein " ∿∿ " indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10; wherein R_{ii} is H or $(C_1\text{-}C_6)$alkyl.

In another embodiment of a compound of formula I,

R_1 is $(C_1\text{-}C_6)$alkyl,

halo$(C_1\text{-}C_6)$alkyl,

$(C_3\text{-}C_6)$cycloalkyl,

halo$(C_3\text{-}C_6)$cycloalkyl

aryl, and

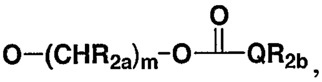
heteroaryl;

R_2 is OH,

OBF_2,

$O(C_1\text{-}C_6)$alkyl,

$O(C_3\text{-}C_6)$cycloalkyl,

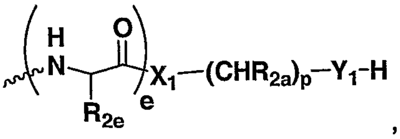


$O\text{—}(CHR_{2a})_m\text{-}O\text{—}\overset{O}{\overset{\|}{C}}\text{—}QR_{2b}$

, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or $(C_1\text{-}C_6)$alkyl and R_{2b} is $(C_1\text{-}C_6)$alkyl, aryl, or heteroaryl,

$O\text{—}(CHR_{2a})_n\text{—}Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl, or

NR_{2d}, wherein R_{2d} is as defined above,



, wherein "∿" indicates the point of attachment, 2a is as defined above, R_{2e} is H or (C_1-C_6)alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

R_3, R_4, and R_5 are each independently H,
halo,
NH_2,
(C_1-C_6)alkyl,
halo(C_1-C_6)alkyl,
(C_1-C_6)alkoxy, or
halo(C_1-C_6)alkoxy;

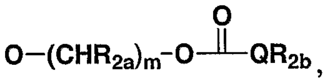
R_a is H,
aryl,
(C_1-C_6)alkyl,
halo(C_1-C_6)alkyl,
(C_3-C_6)cycloalkyl,
$R_{ii}O$(C_1-C_6)alkyl,
$R_{ii}O$(C_1-C_6)haloalkyl,
$R_{ii}O$(C_3-C_6)cycloalkyl,
$R_{ii}O$(C_1-C_6)alkyl-O-,
$R_{ii}O$(C_1-C_6)haloalkyl-O-, or
$R_{ii}O$(C_3-C_6)cycloalkyl-O-, wherein R_{ii} is H or (C_1-C_6)alkyl; and

R_b is OH,
$R_{ii}O$(C_1-C_6)alkyl,
$R_{ii}O$(C_1-C_6)haloalkyl,
$R_{ii}O$(C_3-C_6)cycloalkyl,
$R_{ii}O$(C_1-C_6)alkyl-O-, or
$R_{ii}O$(C_1-C_6)haloalkyl-O-, wherein R_{ii} is H or (C_1-C_6)alkyl.

In another embodiment of a compound of formula I,

R_1 is $(C_1\text{-}C_6)$alkyl,
 halo$(C_1\text{-}C_6)$alkyl,
 $(C_3\text{-}C_6)$cycloalkyl,
 halo$(C_3\text{-}C_6)$cycloalkyl
 aryl, and
 heteroaryl;

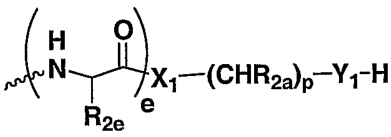
R_2 is OH,
 OBF_2,
 $O(C_1\text{-}C_6)$alkyl,
 $O(C_3\text{-}C_6)$cycloalkyl,



$O\text{—}(CHR_{2a})_m\text{-}O\text{—}C(=O)\text{—}QR_{2b}$, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or $(C_1\text{-}C_6)$alkyl and R_{2b} is $(C_1\text{-}C_6)$alkyl, aryl, or heteroaryl,

$O\text{—}(CHR_{2a})_n\text{—}Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl, or

NR_{2d}, wherein R_{2d} is as defined above,



, wherein "~~~" indicates the point of attachment, 2a is as defined above, R_{2e} is H or $(C_1\text{-}C_6)$alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

R_3, R_4, and R_5 are each independently H,
 halo,
 NH_2,
 $(C_1\text{-}C_6)$alkyl,
 halo$(C_1\text{-}C_6)$alkyl,

$(C_1$-$C_6)$alkoxy, or
halo$(C_1$-$C_6)$alkoxy;

R_a is H,
aryl,
$(C_1$-$C_6)$alkyl,
halo$(C_1$-$C_6)$alkyl,
$(C_3$-$C_6)$cycloalkyl,
$R_{ii}O(C_1$-$C_6)$alkyl,
$R_{ii}O(C_1$-$C_6)$haloalkyl,
$R_{ii}O(C_3$-$C_6)$cycloalkyl, or
$R_{ii}O(C_3$-$C_6)$cycloalkyl-O-, wherein R_{ii} is H or $(C_1$-$C_6)$alkyl; and

R_b is OH,
$R_{ii}O(C_1$-$C_6)$alkyl,
$R_{ii}O(C_1$-$C_6)$haloalkyl,
$R_{ii}O(C_3$-$C_6)$cycloalkyl,
$R_{ii}O(C_1$-$C_6)$alkyl-O-, or
$R_{ii}O(C_1$-$C_6)$haloalkyl-O-, wherein R_{ii} is H or $(C_1$-$C_6)$alkyl.

In another embodiment of a compound of formula I,

R_1 is $(C_1$-$C_6)$cycloalkyl,
halo$(C_1$-$C_6)$cycloalkyl,
aryl, or
heteroaryl;

R_2 is OH, $O(C_1$-$C_6)$alkyl or OBF_2;

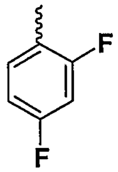
R_3 is H or NH_2;

R_4 is H or halo; and

R_5 is halo,
methyl,
trifluoromethyl,
methoxy,
fluoromethoxy,
difluoromethoxy, or

trifluoromethoxy.

In another embodiment of a compound of formula I,
R_1 is cyclopropyl,
fluorocyclopropyl,



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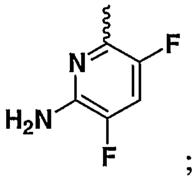
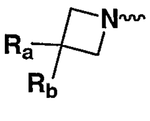


;

R_2 is OH;
R_3 is H or NH_2;
R_4 is H or F; and
R_5 is halo,
methyl,
trifluoromethyl, or
methoxy.

In another embodiment, compounds of formula I have the following core structures, wherein R_2 is OH, O(C_1-C_6)alkyl or OBF_2, R_4 is H or F and A' is



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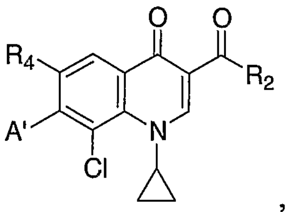

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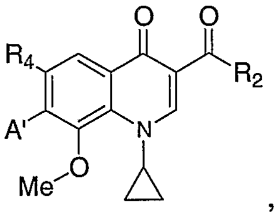

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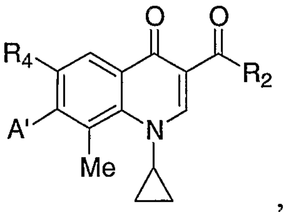

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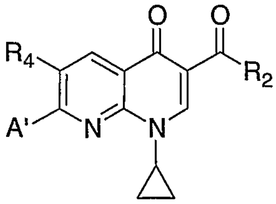
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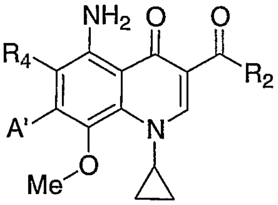
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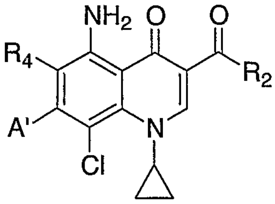
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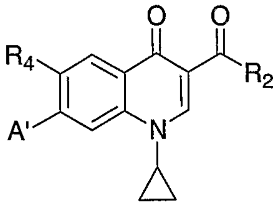
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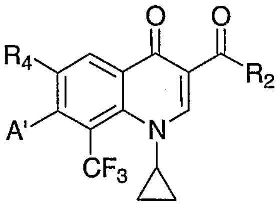
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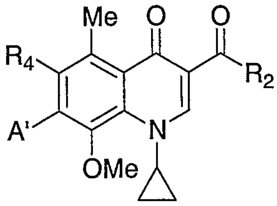
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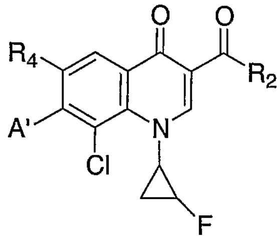
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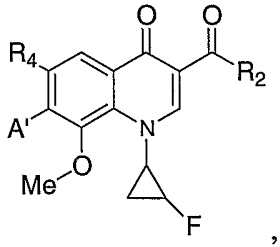
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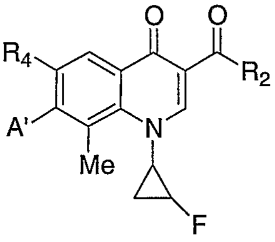
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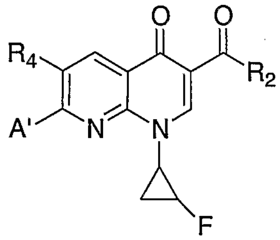
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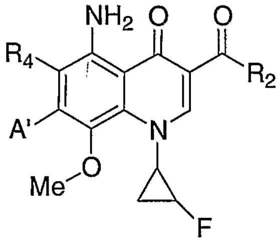
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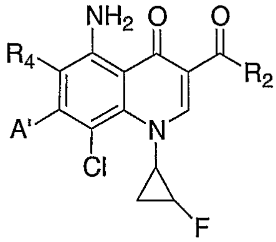
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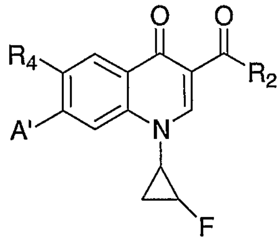
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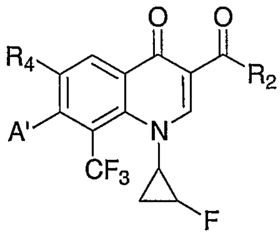
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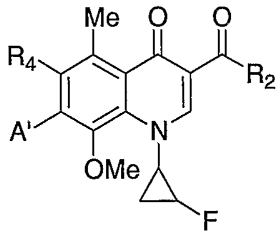
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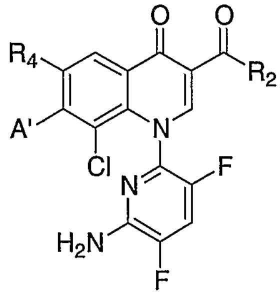
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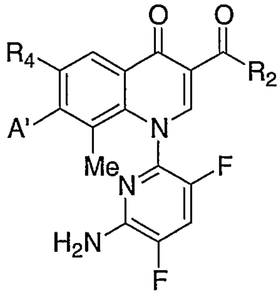
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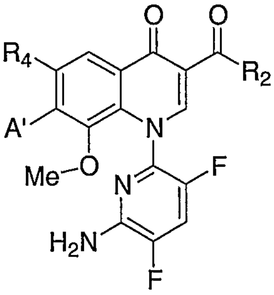
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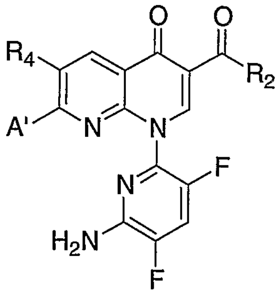
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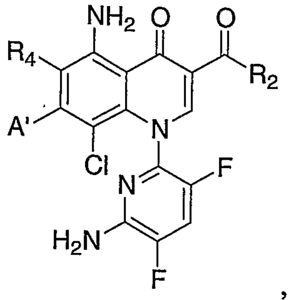
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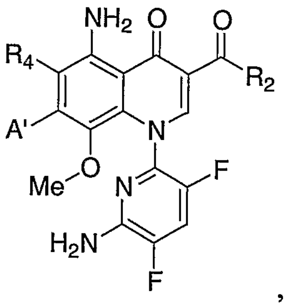
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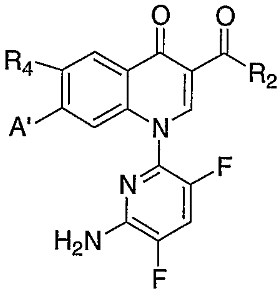
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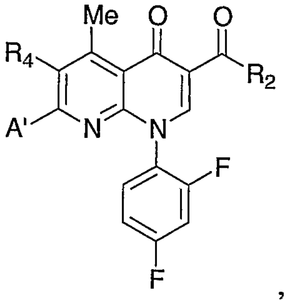
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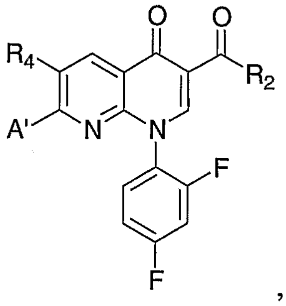
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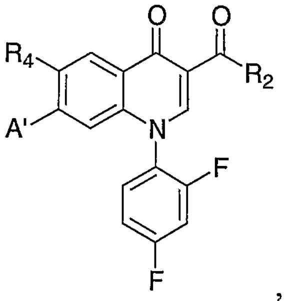
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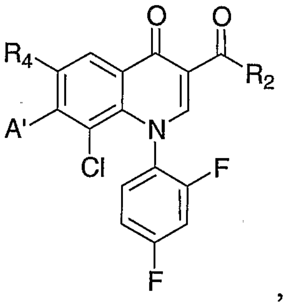
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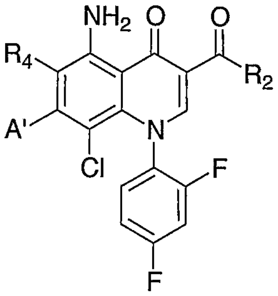
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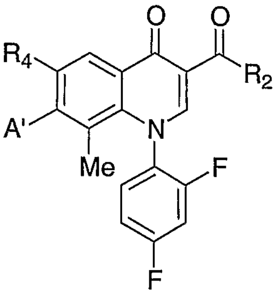
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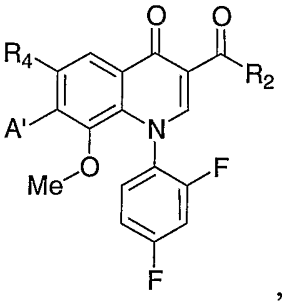
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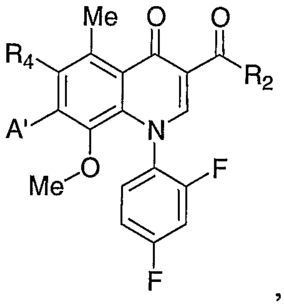
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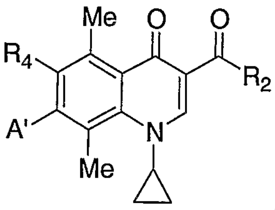
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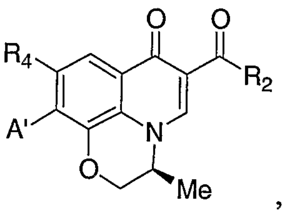
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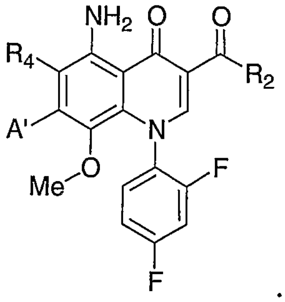
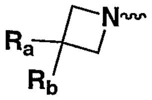
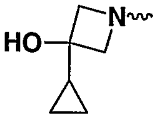
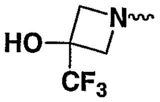
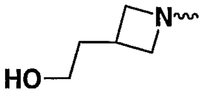
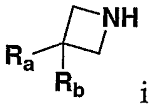

.

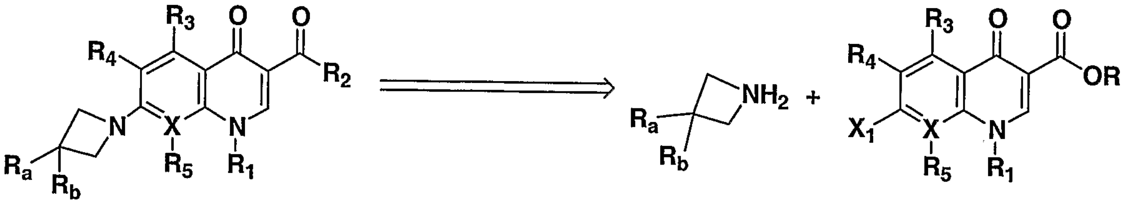
In another embodiment, compounds of the invention are as disclosed above, wherein R_2 is OH and  is , , , .

Preparation of Invention Compounds

Strategies for the preparation of invention compounds are in Scheme I, and more specifically in the subsequent schemes.

As is readily apparent from this disclosure, compounds of the present invention are characterized by a quinolone core, covalently bound to an hydroxylated azetidinyl C-7 sidechain. As retrosynthetically depicted in Scheme I, the invention compounds can be prepared via coupling of a suitably C-7 substituted quinolone core precursor, wherein X is halo, triflate, or a similar reactive group known to the skilled artisan, and  is an appropriately substituted azetidine.

Scheme I



C-7 Hydroxylated Sidechain

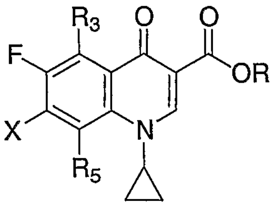
Quinolone Core
X_1= halo, OSO_2CF_3,
R= H, $(C_1\text{-}C_6)$alkyl, BF_2

Reflecting the synthetic strategy summarized in Scheme I, the following section describing the preparation of the invention compounds has several parts. The first part describes the synthesis of the requisite quinolone core precursors. The second part describes the synthesis of the requisite C-7 sidechain precursors.

The final part describes the coupling of the C-7 sidechain and quinolone core precursors to provide the invention compounds, and details any further chemical elaboration of invention compounds to produce other invention compounds.

A. Synthesis of Aminoquinazolinedione Core Precurors

The quinolone core precursors that are used to prepare the invention compounds are generally known to the skilled artisan and can be commercially obtained, or alternatively, can be prepared using routine synthetic methods. The following sections provide relevant citations that describe the preparation of the quinolone core precursors used to practice the invention disclosed herein.



1. Preparation of Quinolone Core Precursors

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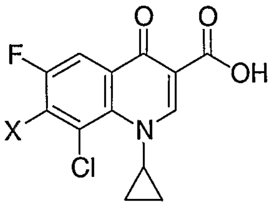
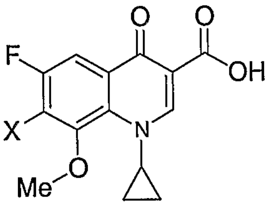


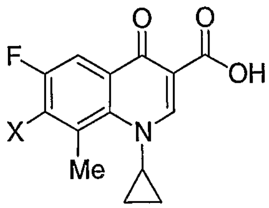
EP 0357047;
EP 0167763;
EP 0195841

b.

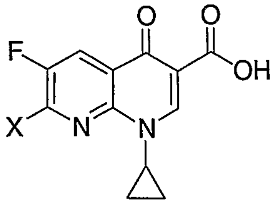


JP8-9958
US 5,869,991

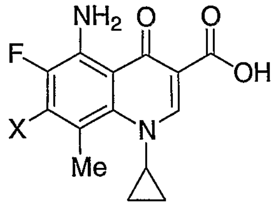
c.



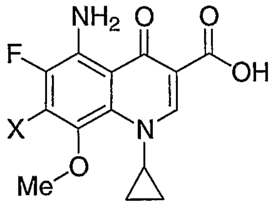
EP 0357047



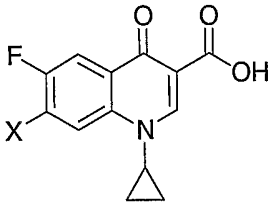
d. EP 0172651



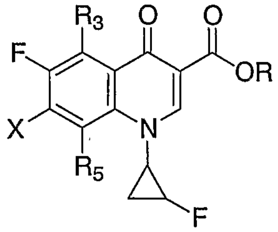
e. US 5,859,026



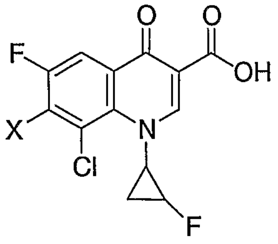
f. EP 0610958



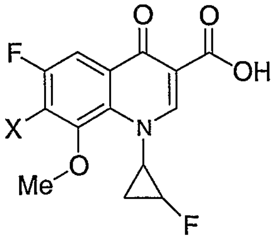
g. US 5,639,886



2. Preparation of Quinolone Core Precursors

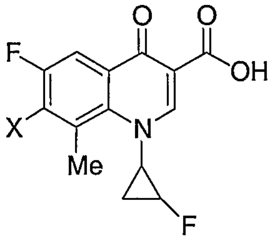


a. As provided for 1A, above, except fluorocyclopropyl amine is used instead of cyclopropyl amine b.



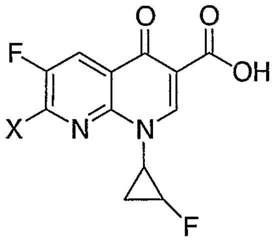
As provided for 1A, above, except fluorocyclopropyl amine is used instead of cyclopropyl amine

c.



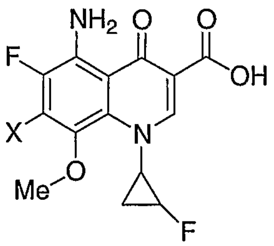
As provided for 1C, above, except fluorocyclopropyl amine is used instead of cyclopropyl amine

d.

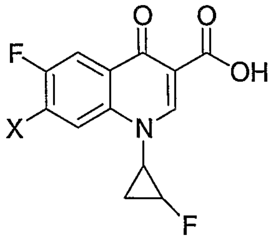


As provided for 1D, above, except fluorocyclopropyl amine is used instead of cyclopropyl amine

e.

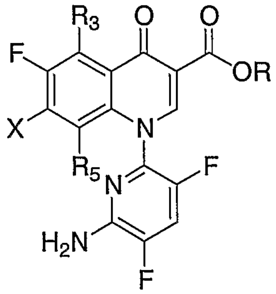


As provided for 1F, above, except fluorocyclopropyl amine is used instead of cyclopropyl amine f.



As provided for 1H, above, except fluorocyclopropyl amine is used instead of cyclopropyl amine

3. Preparation of



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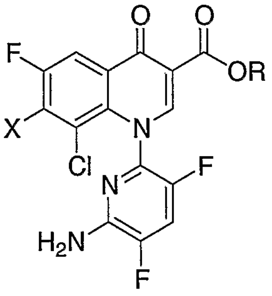
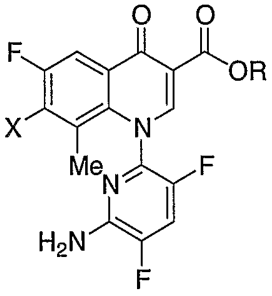


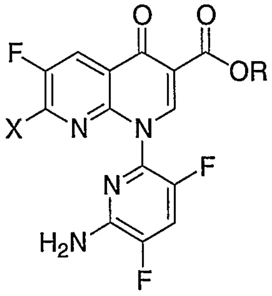
US 5,998436

b.

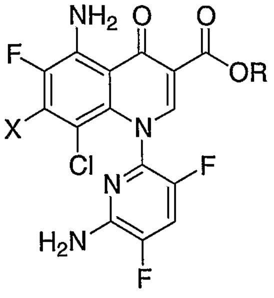


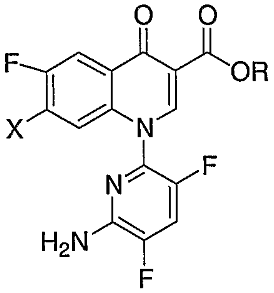
US 5,998436

c.



US 5,998436

d.  US 5,998436

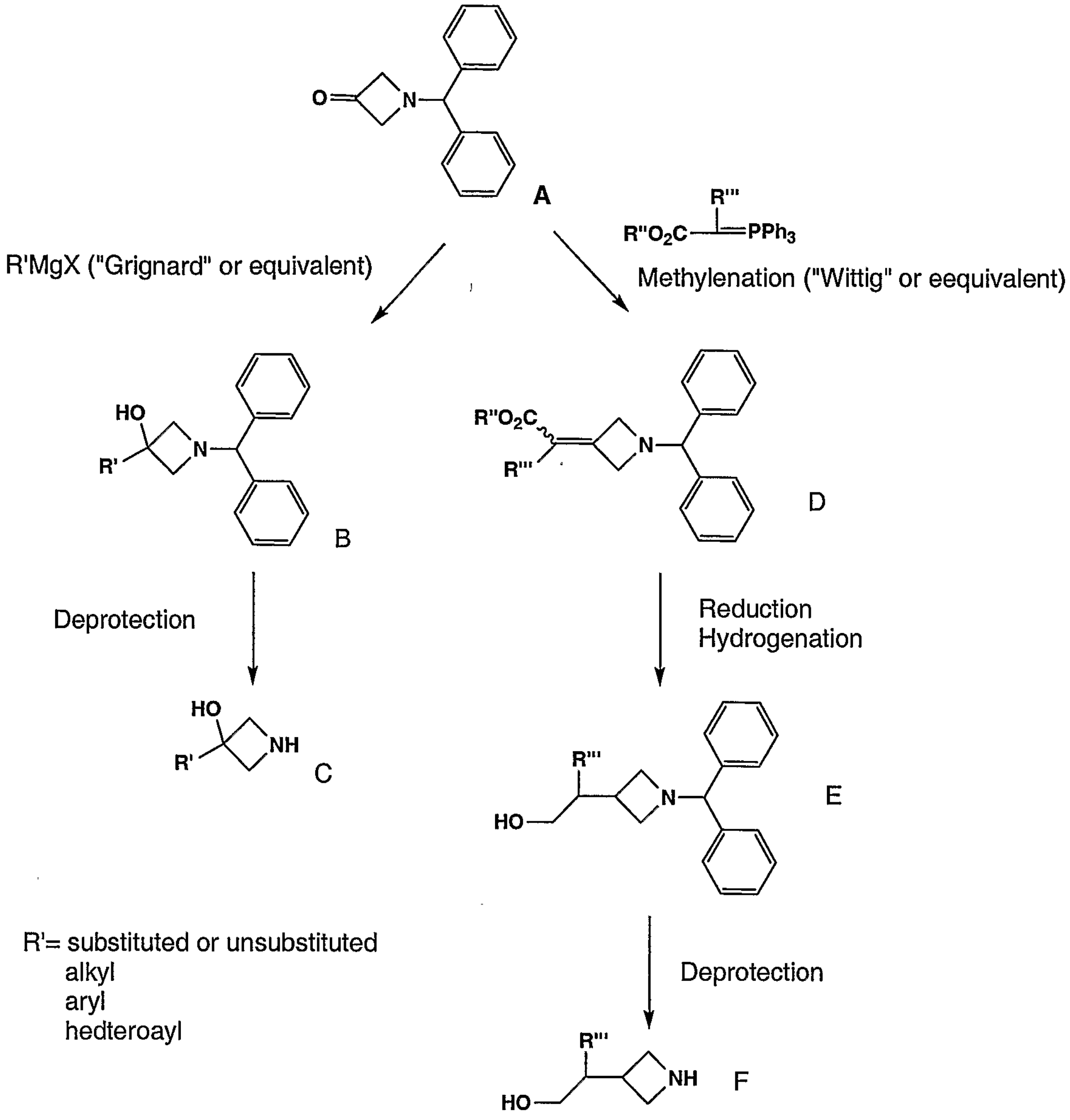
e.  US 5,998436

B. Synthesis of Hydroxylated C-7 Sidechain Precurors

The requisite hydroxylated azetidinol sidechains used to prepare the invention compounds are readily prepared as indicated below in Scheme B1. Thus, azetidinol sidechains can be prepared via Grignard addtion of a substituted or unsubstituted alkyl, aryl, or heteroaryl Grignard reagents to the corresponding ketone A to provide B. Deprotection of B provides the requisite azetidinol C. See, e.g., Rosenberg, S.H.; Spina, K.P.; Condon, S.L.; Polakowski, J.; Yao, Z.; Kovar, P.; Stein, H.H.; Cohen, J.; Barlow, J.L.; Klinghofer, V.; Egan, D.A.; Tricarico, K.A.; Perun, T.J.; Baker, W.R.; Kleinert, H.D. J. Med. Chem. 1993, 36, 460-467.

Sidechains bearing an hydroxylated alkyl substituent can be prepared via methylenation of the ketone moiety in A, for instance, using Wittig methodology to provide compound D. Reduction of sidechain functional groups such as esters as depicted in Scheme B-1 is readily effected using LAH or the like, followed by hydrogenation, provides compound E. Deprotection of E provides the requisite azetidinol F.

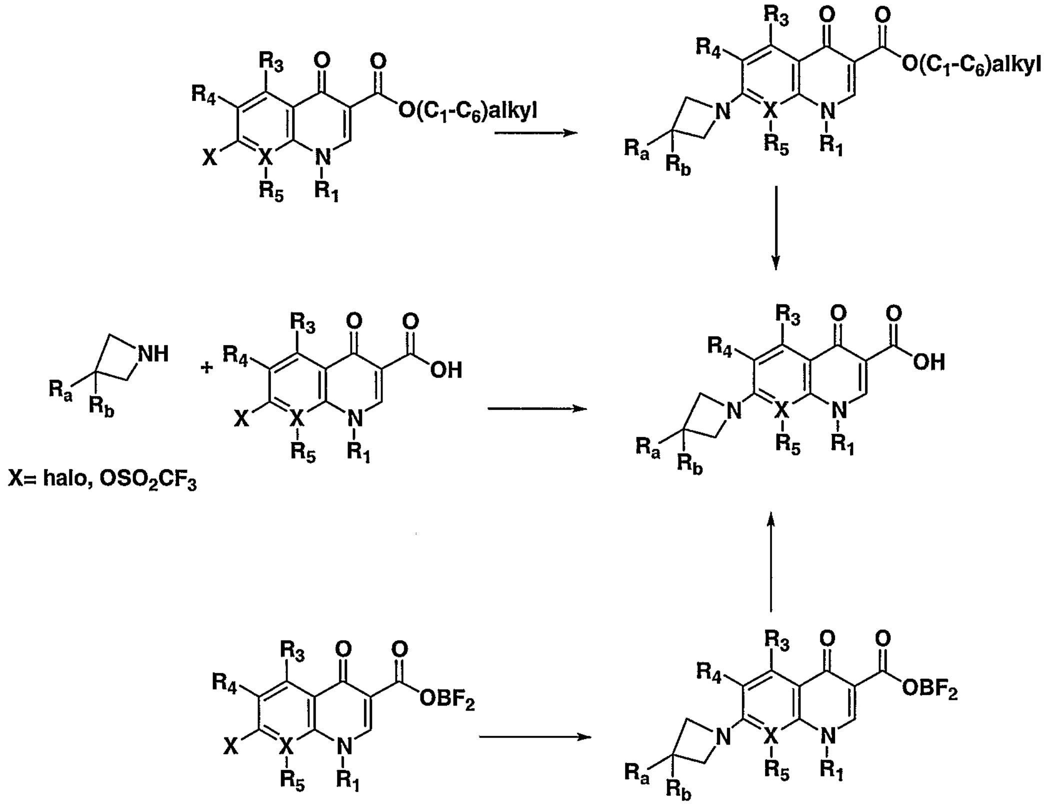
Scheme B-1



C. Coupling of Hydroxylated C-7 Sidechain and Quinolone Core Precurors to Provide Invention Compounds

Coupling of the sidechain precursor to the quinolone core precursor to provide the compounds of the present invention can occur from either the core precursor as the free acid, alkyl ester, or borate ester, as depictedin Scheme C-1.

Scheme C-1



Typically, when a free acid is used in the coupling reaction, a molar excess of the side chain precursor is combined with the quinolone core in a polar solvent such as acetonitrile. A molar excess of an amine base such as triethylamine is added, and the reaction mixture is heated to about 80 °C. Typically, the reaction mixtures becomes homogenous. The mixture is heated for sufficient time to drive the reaction to completion, typically from about 3 to about 12 hours. The mixture is then worked up according to procedures widely uused by the skilled artisan to provide a compound of the invention.

When an alkyl ester is used in the coupling reaction, the quinolone core, sidechain, and triethylamine are combined in a solvent such as acetonitrile. The resulting reaction mixture is heated to 80 °C and stirred for 12 hours. is heated to about 80 °C. Typically, the reaction mixtures becomes homogenous. The mixture is heated for sufficient time to drive the raction to completion, typically from about 3 to about 12 hours. The mixture is then worked up according to procedures widely used by the skilled artisan to provide a compound of the invention.

When a borate ester is used in the coupling reaction, the requisite borate ester is typically prepared from the free acid upon reaction with BF_3 according to conditions available to the skilled artisan. The borate ester is typically combined with the side chain in a solvent such as acetonitrile and treated with an amine base such as triethylamine. The resulting reaction mixture is typically stirred at room temperature for sufficient time to drive the reaction to completion, typically from about 24 to about 96 hours. The mixture is then worked up according to procedures widely used by the skilled artisan to provide a compound of the invention.

Pharmaceutical Formulations

The present invention also provides pharmaceutical compositions which comprise a bioactive invention compound or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier. The compositions include those in a form adapted for oral, topical or parenteral use and can be used for the treatment of bacterial infection in mammals including humans.

Compounds of the invention can be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other bioactive agents such as antibiotics. Such methods are known in the art and are not described in detail herein.

The composition can be formulated for administration by any route known in the art, such as subdermal, by-inhalation, oral, topical or parenteral. The compositions may be in any form known in the art, including but not limited to tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention can be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present, for example, from about 1% up to about 98% of the formulation. For example, they may form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods will known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavoring or coloring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle or other suitable solvent. In preparing solutions, the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, agents such as a local anesthetic preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain, for example, from about 0.1% by weight, e.g., from about 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will contain, for example, from about 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will range, for example, from about 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to about 1.5 to 50 mg/kg per day. Suitably the dosage is, for example, from about 5 to 20 mg/kg per day.

Biological Activity

The invention compounds can be screened to identify bioactive molecules with different biological activities using methods available in the art. The bioactive molecules, for example, can possess activity against a cellular target, including but not limited to enzymes and receptors, or a microorganism. A target cellular ligand or microorganism is one that is known or believed to be of importance in the etiology or progression of a disease. Examples of disease states for which compounds can be screened for biological activity include, but are not limited to, inflammation, infection, hypertension, central nervous system disorders, and cardiovascular disorders.

In one embodiment, the invention provides methods of treating or preventing a bacterial infection in a subject, such as a human or other animal subject, comprising administering an effective amount of an invention compound as disclosed herein to the subject. In one embodiment, the compound is administered in a pharmaceutically acceptable form optionally in a pharmaceutically acceptable carrier. As used herein, an “infectious disorder” is any disorder characterized by the presence of a microbial infection, such as bacterial infections. Such infectious disorders include, for example central nervous system infections, external ear infections, infections of the middle ear, such as acute otitis media, infections of the cranial sinuses, eye infections, infections of the oral cavity, such as infections of the teeth, gums and mucosa, upper respiratory tract infections, lower respiratory tract infections, genitourinary infections, gastrointestinal infections, gynecological infections, septicemia, bone and joint infections, skin and skin structure infections, bacterial endocarditis, burns, antibacterial prophylaxis of surgery, and antibacterial prophylaxis in immunosuppressed patients, such as patients receiving cancer chemotherapy, or organ transplant patients. The compounds and compositions comprising the compounds can be administered by routes such as topically, locally or systemically. Systemic application includes any method of introducing the compound into the tissues of the body, e.g., intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, sublingual, rectal, and oral administration. The specific dosage of antimicrobial to be administered, as well as the duration of treatment, may be adjusted as needed.

The compounds of the invention may be used for the treatment or prevention of infectious disorders caused by a variety of bacterial organisms. Examples include Gram positive and Gram negative aerobic and anaerobic bacteria, including Staphylococci, for example S. aureus; Enterococci, for example E. faecalis; Streptococci, for example S. pneumoniae; Haemophilus, for example H. influenza; Moraxella, for example M. catarrhalis; and Escherichia, for example E. coli. Other examples include Mycobacteria, for example M. tuberculosis; intercellular microbes, for example Chlamydia and Rickettsiae; and Mycoplasma, for example M. pneumoniae.

The ability of a compound of the invention to inhibit bacterial growth, demonstrate in vivo activity, and enhanced pharmacokinetics are demonstrated using pharmacological models that are well known to the art, for example, using models such as the tests described below.

Test A--Antibacterial Assays

The compounds of the present invention were tested against an assortment of Gram-negative and Gram-positive organisms using standard microtitration techniques (Cohen et. al., *Antimicrob.*, 1985;28:766; Heifetz, et. al., *Antimicrob.*, 1974;6:124). The results of the evaluation are shown in Tables 1A and B.

Table 1A

Minimum Inhibitory Concentrations µg/mL

Gram Negative Bacteria

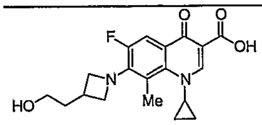
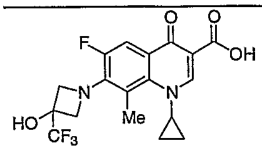
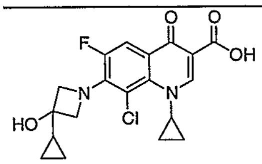
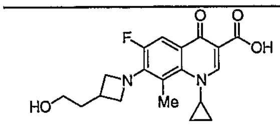
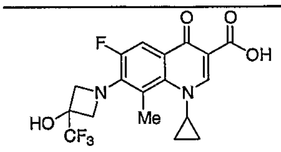
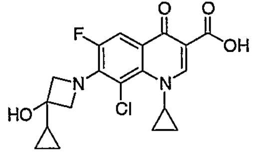
Compound	H. influenzae HI-3542	M. catarrhalis BC-3531	E. coli EC-2549
	0.008	0.015	0.002
	0.03	0.06	0.0004
	0.03	0.03	0.002

Table 1B

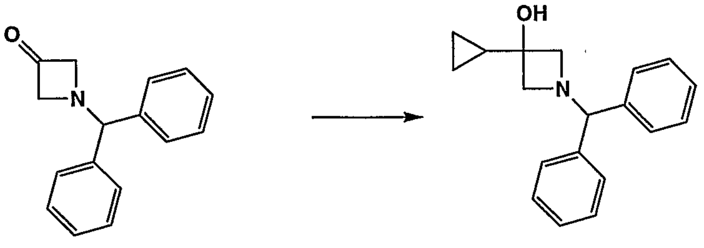
Compound	E. faecalis MGH-2	S. aureus UC-76	S pyogenes C203
	Minimum Inhibitory Concentrations μg/mL **Gram Positive Bacteria**		
	0.25	0.03	0.25
	0.5	0.03	0.5
	0.5	0.03	0.5

Examples

The following examples are provided to illustrate but not limit the claimed invention.

A. Sidechain Preparation

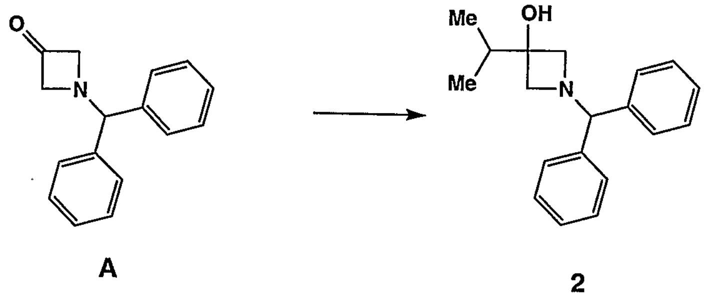
Example A-1: 1-Benzhydryl-3-cyclopropyl-azetidin-3-ol (1)



A 1

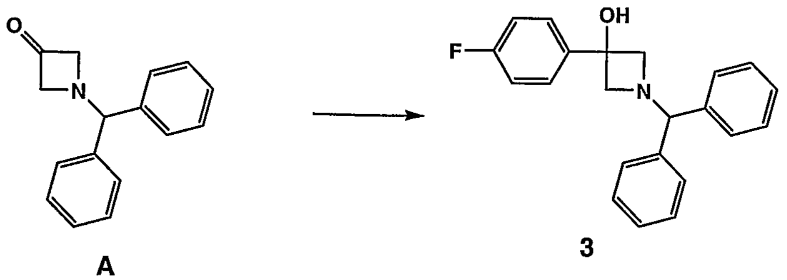
To 0.5 M cyclopropylmagnesium bromide in tetrahydrofuran (THF) (40 mL, 20.0 mmol) at -78 °C was added 1-benzhydryl-azetidin-3-one (A) (1.70g, 7.16 mmol), dropwise as a solution in 10 mL tetrahydrofuran. After 30 minutes the reaction was poured onto saturated aqueous sodium bicarbonate and extracted with diethylether (3 times). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give an oil that was purified by silica gel chromatography (gradient 2%-15% isopropanol/hexanes) to give 1.649g (82%) of the title compound. MS(APCI+): 280.2 (m+1/z)

Example A-2: 1-Benzhydryl-3-isopropyl-azetidin-3-ol (2)



To 2.0 M isopropylmagnesium bromide in tetrahydrofuran (13.0 mL, 26.0 mmol) cooled in an acetone/water-ice bath was added 1-benzhydryl-azetidin-3-one (2.00g, 8.43 mmol), dropwise, as a 7 mL solution in tetrahydrofuran. After 1 hour the reaction was poured onto 10% aqueous sodium bicarbonate and extracted with diethylether (3 times). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give a yellow oil. Purification by silica gel chromatography (gradient 2% to 10% isopropanol/dichloromethane) gave 1.60g (67%) of the title compound as a yellow oil. MS(APCI+): 282.2 (m+1/z)

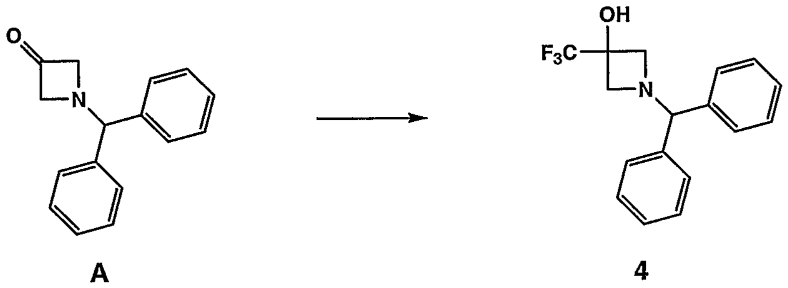
Example A-3: 1-Benzhydryl-3-(4-fluoro-phenyl)-azetidin-3-ol (3)



To 1.0 M 4-fluorophenylmagnesium bromide in tetrahydrofuran (30.0 mL, 30.0 mmol) cooled in an acetone/water-ice bath was dropwise added 1-benzhydryl-azetidin-3-one (A) (2.00g, 8.43 mmol) as a 7 mL solution in tetrahydrofuran. After 1 hour the reaction was poured onto 10% aqueous sodium

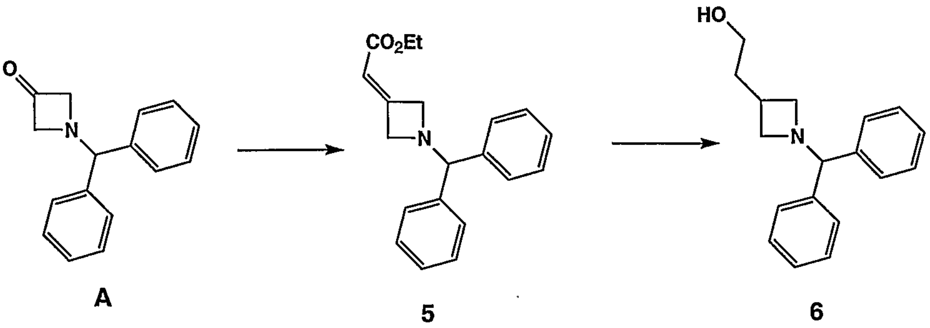
bicarbonate and extracted with diethylether (3 times). The combined organic layers were dried over sodium sulfate and evaporated *in vacuo* to give a pale yellow oil. Purification by silica gel chromatography (2% to 10% isopropanol in dichloromethane) gave 2.119g (75%) of the title compound. MS(APCI+): 334.10 (m+1/z)

Example A-4: 1-Benzhydryl-3-trifluoromethyl-azetidin-3-ol (4)



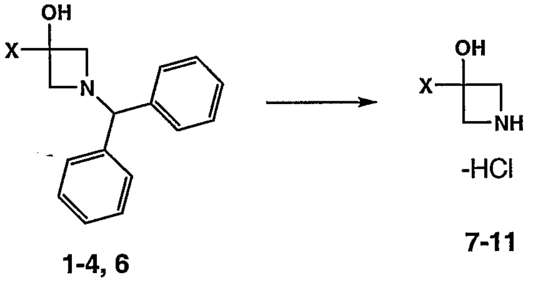
To a solution of 1-benzhydryl-azetidin-3-one (A) (2.00g, 8.43 mmol) in 7 mL tetrahydrofuran at 23 °C was added trifluoromethyltrimethylsilane (1.80g, 12.6 mmol) followed by cesium fluoride (1.95g, 12.8 mmol). After 15 minutes, the reaction was quenched by the addition of 7 mL of saturated aqueous ammonium chloride and 1.00 g of tetrabutylammonium fluoride hydrate. The resulting biphasic mixture was stirred vigorously for 1 day then extracted with diethyl ether (3 times). The combined organic layers were dried over sodium sulfate and evaporation *in vacuo* gave an orange oil that was purified by silica gel chromatography (gradient 2% to 10% isopropanol in dichloromethane) to give 1.98g (76%) of the title compound. MS(APCI+): 308.1 (m+1/z); 349.1 (m+41/z) (acetonitrile)

Example A-5: 2-(1-Benzhydryl-azetidin-3-yl)-ethanol (6)



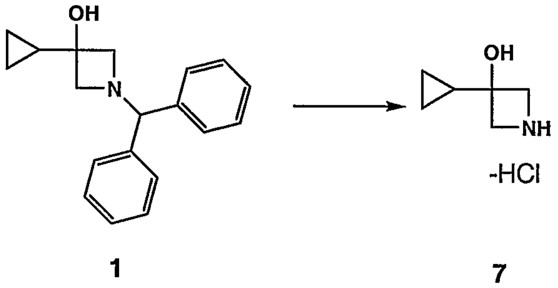
To a solution of 1-benzhydryl-azetidin-3-one (A) (6.00g, 25.3 mmol) in 46 mL tetrahydrofuran at 23 °C was added (carbethoxymethylene)triphenyl phosphorane (9.45g, 27.1 mmol) as a single portion. After 3 days the reaction was evaporated *in vacuo* to a viscous oil. Trituration with 20% ethyl acetate in hexanes resulted in a liquid/solid biphase from which the organic liquid was decanted and evaporated *in vacuo* to give a yellow oil. Further purification by silica gel chromatography (gradient 1% to 15% ethyl acetate in hexanes) gave 5.75g (74%) of (1-benzhydryl-azetidin-3-ylidene)-acetic acid ethyl ester (5) as a slightly yellow oil. MS(APCI+): 308.1 (m+1/z). To a solution of **5** (3.18g, 10.3 mmol) in 20 mL tetrahydrofuran at -78 °C was added dropwise 1.0 M lithium aluminum hydride (LAH) in diethylether (20 mL, 80 mmol hydride). The reaction was stirred for 20 minutes at -78 °C then allowed to warm to 23 °C. After 4 hours, the reaction was treated sequentially with 0.75 mL water, 0.75 mL 1.0 N sodium hydroxide 2.25 mL of water, then filtered. Evaporation of the filtrate gave 2.75g (99%) of the title compound. MS(APCI+): 268.1 (m+1/z)

Example A-6: General Procedure for N-deprotection



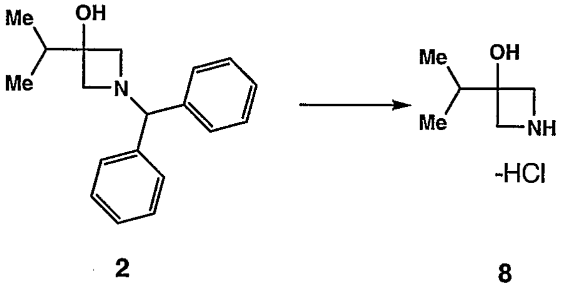
General Procedure for N-deprotection: To a solution of the benzhydrylazetidine (10 mmol) in 50 mL methanol was added concentrated hydrochloric acid (10 mmol) followed by an equivalent weight of 20% palladium(II) hydroxide on carbon. The mixture was shaken in a Parr shaker charged with hydrogen gas (approximately 50 psi) until complete consumption of the benzhydrylazetidine was indicated by mass spectrometry. The reaction was then filtered. The filtrate was evaporated *in vacuo* to give a colorless biphasic mixture that was washed with hexane (5 times) to remove the diphenylmethane by-product. The remaining azetidine hydrochloride salt was typically used without further purification or could be purified by precipitation from ethyl acetate to obtain a powder form.

Example A-7: 3-Cyclopropyl-azetidin-3-ol hydrochloride (7)



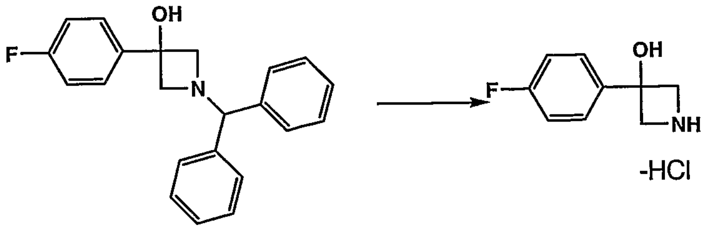
The title compound was obtained in 76% yield as a colorless solid. MS(APCI+): 114.0 (m+1/z).

Example A-8: 3-Isopropyl-azetidin-3-ol hydrochloride (8)



The title compound was obtained using General Procedure 7 in 95% yield as a colorless oil. MS(APCI+): 116.0 (m+1/z).

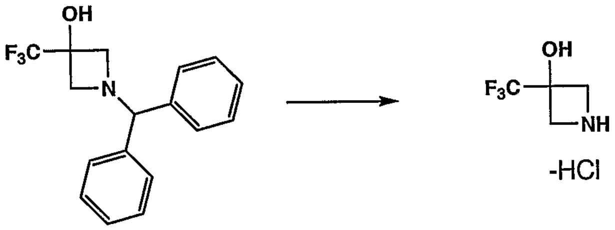
Example A-9: 3-(4-Fluoro-phenyl)-azetidin-3-ol hydrochloride (9)



3 9

The title compound was obtained using General Procedure 7 in 69% yield as a colorless solid. MS(APCI+): 168.2 (m+1/z).

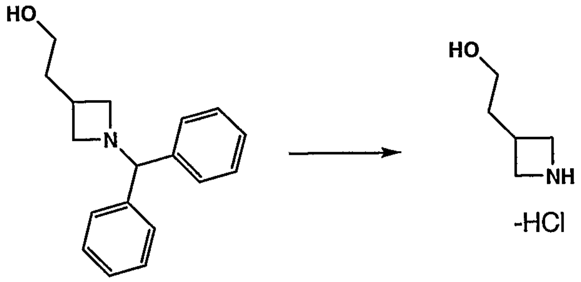
Example A-10: 3-Trifluoromethyl-azetidin-3-ol hydrochloride (10)



4 10

The title compound was obtained using General Procedure 7 in 36% yield as a colorless powder. MS(APCI+): 142.0 (m+1/z); 183.0 (m+41/z) (acetonitrile)

Example A-11: 2-Azetidin-3-yl-ethanol hydrochloride (11)

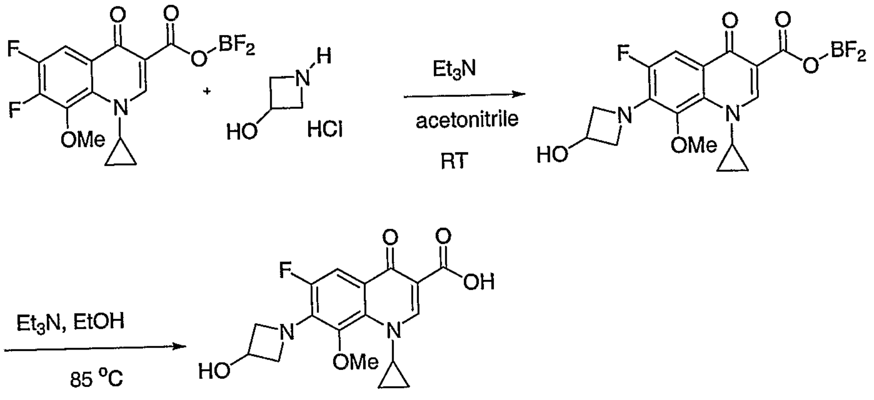


6 11

The title compound was obtained using General Procedure 7 in 89% yield as a colorless oil. MS(APCI+): 102.0 (m+1/z).

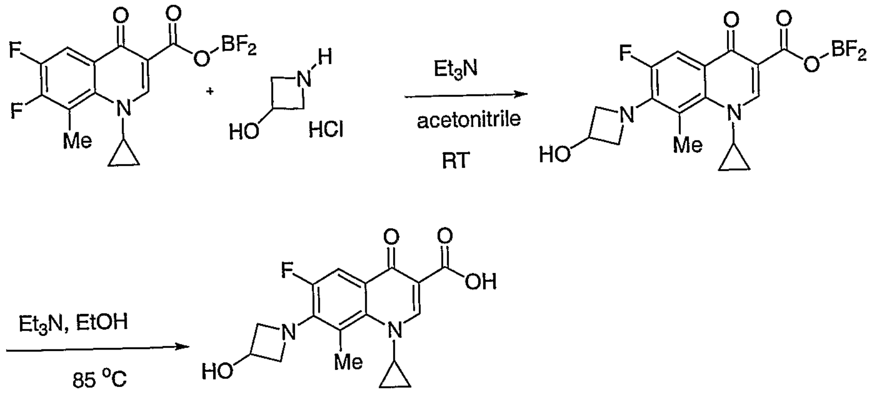
B. Coupling Reactions

Example B-1: 1-Cyclopropyl-6-fluoro-7-(3-hydroxy-azetidin-1-yl)-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



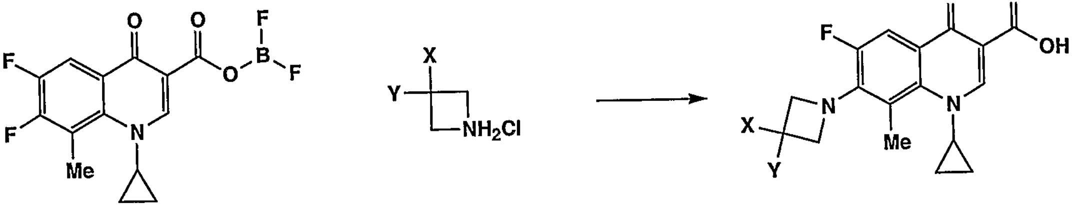
To a solution of 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid difluoroborate ester (0.16 g, 0.46 mmol) and 3-hydroxyazetidine hydrochloride (0.068 g, 0.93 mmol) in acetonitrile (4 mL) was added triethylamine (0.32 mL, 2.3 mmol). The reaction mixture was stirred at room temperature for 24 hours and concentrated *in vacuo*. The resulting residue was dissolved in ethanol (6 mL), treated with triethylamine (0.32 mL, 2.3 mmol), and heated at 85 °C. After 3 hours, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between chloroform and 1.0 N hydrochloric acid. The aqueous phase was extracted three times with chloroform, and the combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford the title compound (0.17 g, 100%) as a yellow solid; mp 246-250 °C.

Example B-2: 1-Cyclopropyl-6-fluoro-7-(3-hydroxy-azetidin-1-yl)-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



To a solution of 1-cyclopropyl-6,7-difluoro-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid difluoroborate ester (0.50 g, 1.5 mmol) and 3-hydroxyazetidine (0.17 g, 2.3 mmol) in acetonitrile (8 mL) was added triethylamine (1.1 mL, 7.9 mmol). The reaction mixture was heated at 65 °C for 50 hours and concentrated *in vacuo*. The resulting residue was dissolved in ethanol (20 mL), treated with triethylamine (1.1 mL, 7.9 mmol), and heated at 85 °C. After 3 hours, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was triturated with chloroform (100 mL), and the resulting yellow solid was absorbed onto diatomaceous earth (Celite®) and purified on a 35 g Isco column (5% methanol/dichloromethane at 30 minutes, then 10% methanol/dichloromethane at 50 minutes) to afford the title compound (0.27 g, 53%) as a yellow solid; mp 260-262 °C.

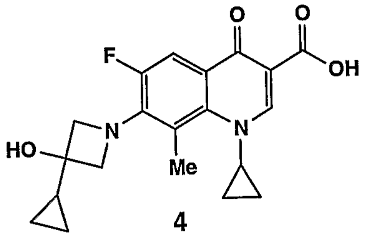
Example B-3: General Procedure



1 2 3

A neat mixture of 1-cyclopropyl-6,7-difluoro-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid difluoroborate ester (**1**) (0.60 mmol, 1 equivalent) and the azetidine hydrochloride salt (**2**) (0.90 mmol) was suspended in 5 mL acetonitrile at 23 °C then 0.5 mL triethylamine was added and the reaction was heated to 60 °C. After 24 hours the reaction was evaporated *in vacuo* and redissolved in 10 mL 4:1 ethanol-triethylamine and heated at 55 °C for 16 hours. The mixture was cooled to 23 °C and the precipitate was collected by vacuum filtration. Purification by silica gel chromatography (gradient 0% to 15% isopropanol in dichloromethane) gave the title compounds.

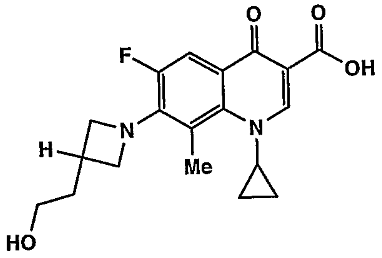
Example B-4: 1-Cyclopropyl-7-(3-cyclopropyl-3-hydroxy-azetidin-1-yl)-6-fluoro-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



4

The title compound was prepared as provided in Example B-3 and isolated as a yellow powder in 30% yield. MS(APCI+): 373.0 (m+1/z)

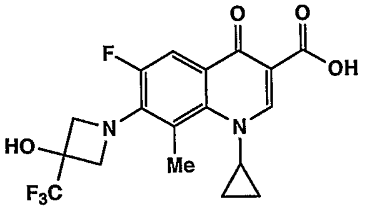
Example B-5: 1-Cyclopropyl-6-fluoro-7-[3-(2-hydroxy-ethyl)-azetidin-1-yl]-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid; compound with methane (5)



5

The title compound was prepared as provided in Example B-3 and isolated as an orange powder in 86% yield. MS(APCI+): 361.0 (m+1/z)

Example B-5: 1-Cyclopropyl-6-fluoro-7-(3-hydroxy-3-trifluoromethyl-azetidin-1-yl)-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid. (6)



6

The title compound was prepared as provided in Example B-3 and isolated as a yellow powder in 13% yield. MS(APCI+): 400.9 (m+1/z).

Example C

The following illustrates representative pharmaceutical dosage forms, containing a compound of Formula I ("Invention Compound"), for therapeutic or prophylactic use in humans.

(i) Tablet	mg/tablet
'Invention Compound'	25.0
Lactose	50.0
Corn Starch (for mix)	10.0
Corn Starch (paste)	10.0
Magnesium Stearate (1%)	3.0
	300.0

The invention compound, lactose, and corn starch (for mix) are blended to uniformity. The corn starch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for treatment of pathogenic bacterial infections.

(ii) Tablet	mg/capsule
'Invention Compound	10.0
Colloidal Silicon Dioxide	1.5
Lactose	465.5
Pregelatinized Starch	120.0
Magnesium Stearate (1%)	3.0
	600.0

(iii) Preparation for Oral Solution	Amount
'Invention Compound'	400 mg
Sorbitol Solution (70 % N.F.)	40 mL
Sodium Benzoate	20 mg
Saccharin	5 mg
Cherry Flavor	20 mg
Distilled Water q.s.	100 mL

The sorbitol solution is added to 40 mL of distilled water, and the invention compound is dissolved therein. The saccharin, sodium benzoate, flavor, and dye are added and dissolved. The volume is adjusted to 100 mL with distilled water. Each milliliter of syrup contains 4 mg of invention compound.

(iv) Parenteral Solution

In a solution of 700 mL of propylene glycol and 200 mL of water for injection is suspended 20 g of an invention compound. After suspension is complete, the pH is adjusted to 6.5 with 1 N hydrochloric acid, and the volume is made up to 1000 mL with water for injection. The Formulation is sterilized, filled into 5.0 mL ampoules each containing 2.0 mL, and sealed under nitrogen.

(v) Injection 1 (1 mg/mL)	Amount
'Invention Compound'	1.0
Dibasic Sodium Phosphate	12.0
Monobasic Sodium Phosphate	0.7
Sodium Chloride	4.5
N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(vi) Injection 2 (10 mg/mL)	Amount
'Invention Compound'	10.0
Dibasic Sodium Phosphate	1.1
Monobasic Sodium Phosphate	0.3
Polyethylene glyco 400	200.0
N hydrochloric acid solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

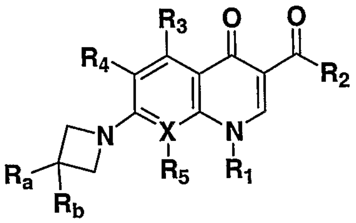
(vii) Injection 2 (10 mg/mL)	Amount
'Invention Compound'	20.0
Oleic Acid	10.0
Trichloromonofluoromethane	5,000.0
Dichlorodifluoromethane	10,000.0
Dichlorotetrafluoroethane	5,000.0.

All patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

Claims

What is claimed is:

1. A compound of formula I



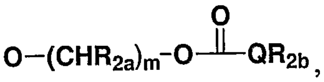
I

or a pharmaceutically acceptable salt thereof, wherein:

X is N or C, provided that when X is N, R_5 is absent at that position;

R_1 is $(C_1\text{-}C_6)$alkyl,
halo$(C_1\text{-}C_6)$alkyl,
$(C_3\text{-}C_6)$cycloalkyl,
halo$(C_3\text{-}C_6)$cycloalkyl
aryl, and
heteroaryl;

R_2 is OH,
OBF_2,
$O(C_1\text{-}C_6)$alkyl,
$O(C_3\text{-}C_6)$cycloalkyl,

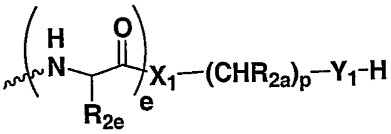


$O{-}(CHR_{2a})_m{-}O{-}\overset{O}{\overset{\|}{C}}{-}QR_{2b}$, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or $(C_1\text{-}C_6)$alkyl and R_{2b} is $(C_1\text{-}C_6)$alkyl, aryl, or heteroaryl,

$O{-}(CHR_{2a})_n{-}Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl,

or

NR_{2d}, wherein R_{2d} is as defined above,



, wherein "∿" indicates the point of attachment, 2a is as defined above, R_{2e} is H or $(C_1\text{-}C_6)$alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

R_3, R_4, and R_5 are each independently H,

halo,

NH_2,

$(C_1\text{-}C_6)$alkyl,

halo$(C_1\text{-}C_6)$alkyl,

$(C_1\text{-}C_6)$alkoxy, or

halo$(C_1\text{-}C_6)$alkoxy; or

R_1 and R_5 together with the carbons to which they are attached form an optionally substituted 5 or 6 membered ring containing 1 or 2 heteroatoms selected from NH, N-$(C_1\text{-}C_6)$alkyl, S, or O;

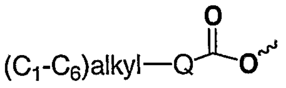
R_a is H,

aryl,

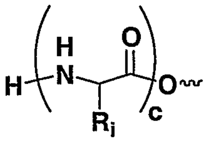
$(C_1\text{-}C_6)$alkyl,

halo$(C_1\text{-}C_6)$alkyl,

$(C_3\text{-}C_6)$cycloalkyl,



, wherein "∿" indicates the point of attachment and Q is O or is absent,


, wherein "~~~" indicates the point of attachment, R_i is H or $(C_1\text{-}C_6)$alkyl, and c is an integer having a value of from 1 to 10,

$R_{ii}O(C_1\text{-}C_6)$alkyl,

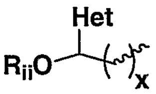
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,

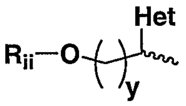
$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,

$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,


, wherein "~~~" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;

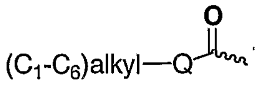

, wherein "~~~" indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

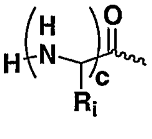
wherein R_{ii} is H,

$(C_1\text{-}C_6)$alkyl,

$PO(OH)_2$,

$PO(OC_1\text{-}C_6alkyl)_2$,


$(C_1\text{-}C_6)\text{alkyl}{-}Q{-}C(=O){-}$
, as defined above, or

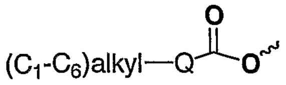

, as defined above;

provided that 3 or fewer of R_c R_d, R_e, and R_f are H; or

R_b is OH,

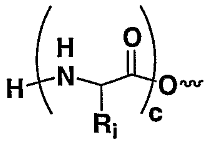
$PO(OH)_2$,

PO(OC$_1$-C$_6$alkyl)$_2$,



$(C_1\text{-}C_6)\text{alkyl}{-}Q{-}C(=O){-}O$

, wherein "~" indicates the point of attachment and Q is O or is absent,



, wherein "~" indicates the point of attachment, R$_i$ is H or (C$_1$-C$_6$)alkyl, and c is an integer having a value of from 1 to 10,

R$_{ii}$O(C$_1$-C$_6$)alkyl,

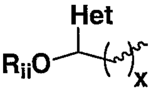
R$_{ii}$O(C$_1$-C$_6$)haloalkyl,

R$_{ii}$O(C$_3$-C$_6$)cycloalkyl,

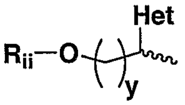
R$_{ii}$O(C$_1$-C$_6$)alkyl-O-,

R$_{ii}$O(C$_1$-C$_6$)haloalkyl-O-,

R$_{ii}$O(C$_3$-C$_6$)cycloalkyl-O-,



, wherein "~" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;



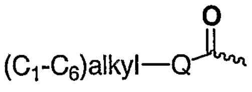
, wherein "~" indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R$_{ii}$ is H,

(C$_1$-C$_6$)alkyl,

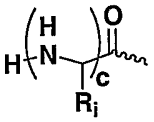
PO(OH)$_2$,

PO(O(C$_1$-C$_6$)alkyl)$_2$,



$(C_1\text{-}C_6)\text{alkyl}{-}Q{-}C(=O){-}$

, as defined above, or

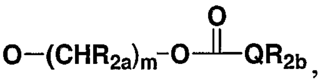


, as defined above.

2. The compound of claim 1, wherein:

R_1 is $(C_1\text{-}C_6)$alkyl,
halo$(C_1\text{-}C_6)$alkyl,
$(C_3\text{-}C_6)$cycloalkyl,
halo$(C_3\text{-}C_6)$cycloalkyl
aryl, and
heteroaryl;

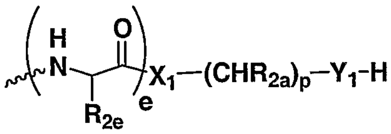
R_2 is OH,
OBF_2,
$O(C_1\text{-}C_6)$alkyl,
$O(C_3\text{-}C_6)$cycloalkyl,



$O{-}(CHR_{2a})_m{-}O{-}C(=O){-}QR_{2b}$, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or $(C_1\text{-}C_6)$alkyl and R_{2b} is $(C_1\text{-}C_6)$alkyl, aryl, or heteroaryl,

$O{-}(CHR_{2a})_n{-}Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl, or

NR_{2d}, wherein R_{2d} is as defined above,

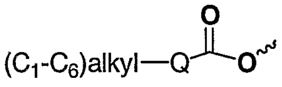


, wherein " ∿∿∿ " indicates the point of attachment, 2a is as defined above, R_{2e} is H or $(C_1\text{-}C_6)$alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

R_3, R_4, and R_5 are each independently H,
halo,
NH_2,

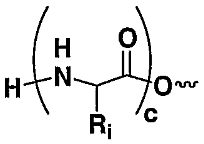
$(C_1\text{-}C_6)$alkyl,
halo$(C_1\text{-}C_6)$alkyl,
$(C_1\text{-}C_6)$alkoxy, or
halo$(C_1\text{-}C_6)$alkoxy;

R_a is H,
aryl,
$(C_1\text{-}C_6)$alkyl,
halo$(C_1\text{-}C_6)$alkyl,
$(C_3\text{-}C_6)$cycloalkyl,



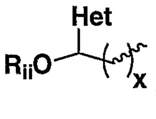
$(C_1\text{-}C_6)\text{alkyl}{-}Q{-}\overset{O}{\overset{\|}{C}}{-}O\text{〰}$

, wherein "〰" indicates the point of attachment and Q is O or is absent,

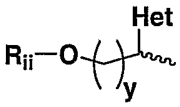


, wherein "〰" indicates the point of attachment, R_i is H or $(C_1\text{-}C_6)$alkyl, and c is an integer having a value of from 1 to 10,

$R_{ii}O(C_1\text{-}C_6)$alkyl,
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,
$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,
$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,
$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,
$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,



, wherein "〰" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;

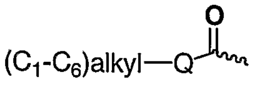


, wherein "〰" indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R_{ii} is H,

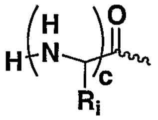
$(C_1$-$C_6)$alkyl,

$PO(OH)_2$,



$(C_1\text{-}C_6)\text{alkyl—Q—}\overset{O}{\overset{\|}{C}}\text{~}$

, as defined above, or



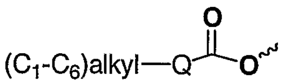
, as defined above;

provided that 3 or fewer of R_c R_d, R_e, and R_f are H; or

R_b is OH,

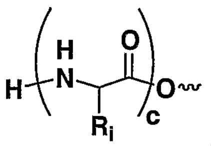
$OPO(OH)_2$,

$OPO(O(C_1$-$C_6)alkyl)_2$,



$(C_1\text{-}C_6)\text{alkyl—Q—}\overset{O}{\overset{\|}{C}}\text{—O~}$

, wherein "~" indicates the point of attachment and Q is O or is absent,



, wherein "~" indicates the point of attachment, R_i is H or $(C_1$-$C_6)$alkyl, and c is an integer having a value of from 1 to 10,

$R_{ii}O(C_1$-$C_6)$alkyl,

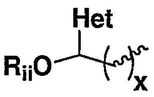
$R_{ii}O(C_1$-$C_6)$haloalkyl,

$R_{ii}O(C_3$-$C_6)$cycloalkyl,

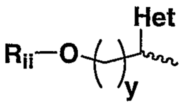
$R_{ii}O(C_1$-$C_6)$alkyl-O-,

$R_{ii}O(C_1$-$C_6)$haloalkyl-O-,

$R_{ii}O(C_3$-$C_6)$cycloalkyl-O-,



, wherein "~" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;



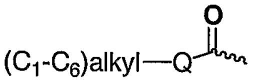
, wherein " ∿∿ " indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R_{ii} is H,

$(C_1\text{-}C_6)$alkyl,

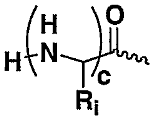
$PO(OH)_2$,

$PO(O(C_1\text{-}C_6)alkyl)_2$,



$(C_1\text{-}C_6)alkyl—Q—C(=O)—$

, as defined above, or



, as defined above.

3. The compound of claim 1, wherein:

R_1 is $(C_1\text{-}C_6)$alkyl,

halo$(C_1\text{-}C_6)$alkyl,

$(C_3\text{-}C_6)$cycloalkyl,

halo$(C_3\text{-}C_6)$cycloalkyl

aryl, and

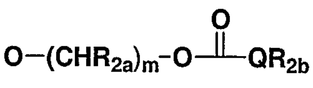
heteroaryl;

R_2 is OH,

OBF_2,

$O(C_1\text{-}C_6)$alkyl,

$O(C_3\text{-}C_6)$cycloalkyl,

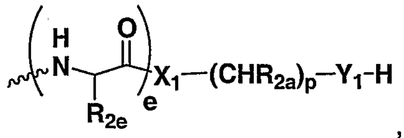


$O—(CHR_{2a})_m\text{-}O—C(=O)—QR_{2b}$

, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or $(C_1\text{-}C_6)$alkyl and R_{2b} is $(C_1\text{-}C_6)$alkyl, aryl, or heteroaryl,

$O—(CHR_{2a})_n—Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl, or

NR_{2d}, wherein R_{2d} is as defined above,



$$\sim\left(\overset{H}{N}-\underset{R_{2e}}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}\right)_e X_1-(CHR_{2a})_p-Y_1-H$$

, wherein "∿∿∿" indicates the point of attachment, 2a is as defined above, R_{2e} is H or $(C_1\text{-}C_6)$alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

R_3, R_4, and R_5 are each independently H,

halo,

NH_2,

$(C_1\text{-}C_6)$alkyl,

halo$(C_1\text{-}C_6)$alkyl,

$(C_1\text{-}C_6)$alkoxy, or

halo$(C_1\text{-}C_6)$alkoxy;

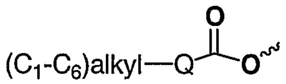
R_a is H,

aryl,

$(C_1\text{-}C_6)$alkyl,

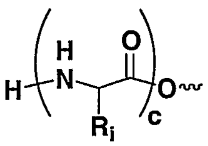
halo$(C_1\text{-}C_6)$alkyl,

$(C_3\text{-}C_6)$cycloalkyl,



$$(C_1\text{-}C_6)\text{alkyl}-Q-\overset{O}{\overset{\|}{C}}-O\sim$$

, wherein "∿∿∿" indicates the point of attachment and Q is O or is absent,



$$H\left(\overset{H}{N}-\underset{R_i}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}\right)_c O\sim$$

, wherein "∿∿∿" indicates the point of attachment, R_i is H or $(C_1\text{-}C_6)$alkyl, and c is an integer having a value of from 1 to 10,

$R_{ii}O(C_1\text{-}C_6)$alkyl,

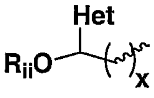
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,

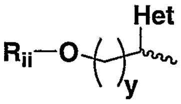
$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,



, wherein "∿" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;

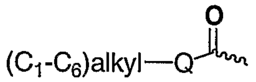


, wherein "∿" indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

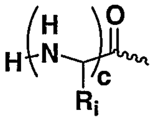
wherein R_{ii} is H,

$(C_1\text{-}C_6)$alkyl,

$PO(OH)_2$,



$(C_1\text{-}C_6)\text{alkyl—Q—}C(=O)\text{—}$, as defined above, or



, as defined above;

provided that 3 or fewer of R_c R_d, R_e, and R_f are H; or

R_b is OH,

$R_{ii}O(C_1\text{-}C_6)$alkyl,

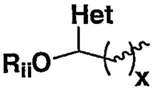
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,

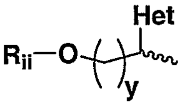
$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,

$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,


, wherein " ∿∿ " indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;

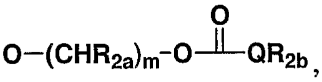

, wherein " ∿∿ " indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R_{ii} is H or $(C_1\text{-}C_6)$alkyl.

4. The compound of claim 1, wherein:

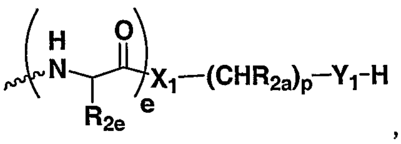
R_1 is $(C_1\text{-}C_6)$alkyl,
halo$(C_1\text{-}C_6)$alkyl,
$(C_3\text{-}C_6)$cycloalkyl,
halo$(C_3\text{-}C_6)$cycloalkyl
aryl, and
heteroaryl;

R_2 is OH,
OBF_2,
$O(C_1\text{-}C_6)$alkyl,
$O(C_3\text{-}C_6)$cycloalkyl,


$O{-}(CHR_{2a})_m{-}O{-}\overset{O}{\overset{\|}{C}}{-}QR_{2b}$, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or $(C_1\text{-}C_6)$alkyl and R_{2b} is $(C_1\text{-}C_6)$alkyl, aryl, or heteroaryl,

$O{-}(CHR_{2a})_n{-}Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl, or

NR_{2d}, wherein R_{2d} is as defined above,

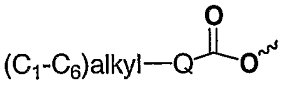


$\left(\text{NH}-\text{CH}(R_{2e})-\text{C}(=\text{O})\right)_e-X_1-(\text{CHR}_{2a})_p-Y_1-\text{H}$

, wherein " ~ " indicates the point of attachment, 2a is as defined above, R_{2e} is H or (C_1-C_6)alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

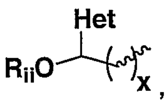
R_3, R_4, and R_5 are each independently H,
halo,
NH_2,
(C_1-C_6)alkyl,
halo(C_1-C_6)alkyl,
(C_1-C_6)alkoxy, or
halo(C_1-C_6)alkoxy;

R_a is H,
aryl,
(C_1-C_6)alkyl,
halo(C_1-C_6)alkyl,
(C_3-C_6)cycloalkyl,



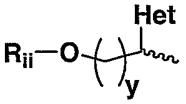
$(C_1\text{-}C_6)\text{alkyl}-Q-\text{C}(=\text{O})-\text{O}$

, wherein " ~ " indicates the point of attachment and Q is O or is absent,
$R_{ii}O$(C_1-C_6)alkyl,
$R_{ii}O$(C_1-C_6)haloalkyl,
$R_{ii}O$(C_3-C_6)cycloalkyl,
$R_{ii}O$(C_1-C_6)alkyl-O-,
$R_{ii}O$(C_1-C_6)haloalkyl-O-,
$R_{ii}O$(C_3-C_6)cycloalkyl-O-,



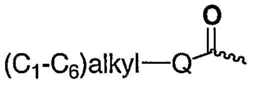
, wherein " ~ " indicates the point of

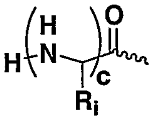
attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;


, wherein "∿" indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R_{ii} is H,

$(C_1\text{-}C_6)$alkyl,
$PO(OH)_2$,
$PO(O(C_1\text{-}C_6)alkyl)_2$,

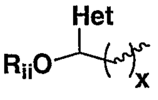

, as defined above, or

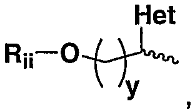

, as defined above;

provided that 3 or fewer of R_c R_d, R_e, and R_f are H; or

R_b is OH,

$R_{ii}O(C_1\text{-}C_6)$alkyl,
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,
$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,
$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,
$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,
$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,


, wherein "∿" indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;

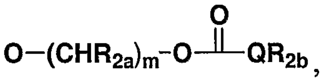

, wherein "∿" indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R_{ii} is H or $(C_1\text{-}C_6)$alkyl.

5. The compound of claim 1, wherein:

R_1 is $(C_1\text{-}C_6)$alkyl,
halo$(C_1\text{-}C_6)$alkyl,
$(C_3\text{-}C_6)$cycloalkyl,
halo$(C_3\text{-}C_6)$cycloalkyl
aryl, and
heteroaryl;

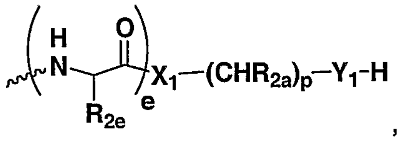
R_2 is OH,
OBF_2,
$O(C_1\text{-}C_6)$alkyl,
$O(C_3\text{-}C_6)$cycloalkyl,


$O{-}(CHR_{2a})_m{-}O{-}C(=O){-}QR_{2b}$

, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or $(C_1\text{-}C_6)$alkyl and R_{2b} is $(C_1\text{-}C_6)$alkyl, aryl, or heteroaryl,

$O{-}(CHR_{2a})_n{-}Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl, or

NR_{2d}, wherein R_{2d} is as defined above,

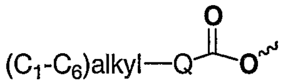


, wherein "〰" indicates the point of attachment, 2a is as defined above, R_{2e} is H or $(C_1\text{-}C_6)$alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

R_3, R_4, and R_5 are each independently H,
halo,

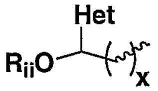
NH$_2$,
(C$_1$-C$_6$)alkyl,
halo(C$_1$-C$_6$)alkyl,
(C$_1$-C$_6$)alkoxy, or
halo(C$_1$-C$_6$)alkoxy;

R$_a$ is H,
aryl,
(C$_1$-C$_6$)alkyl,
halo(C$_1$-C$_6$)alkyl,
(C$_3$-C$_6$)cycloalkyl,

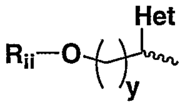

$(C_1\text{-}C_6)\text{alkyl}{-}Q{-}C(=O){-}O{\sim}$

, wherein " ∿∿ " indicates the point of attachment and Q is O or is absent,

R$_{ii}$O(C$_1$-C$_6$)alkyl,
R$_{ii}$O(C$_1$-C$_6$)haloalkyl,
R$_{ii}$O(C$_3$-C$_6$)cycloalkyl,
R$_{ii}$O(C$_1$-C$_6$)alkyl-O-,
R$_{ii}$O(C$_1$-C$_6$)haloalkyl-O-,
R$_{ii}$O(C$_3$-C$_6$)cycloalkyl-O-,

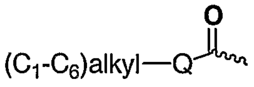


, wherein " ∿∿ " indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;

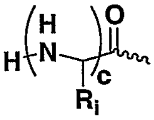


, wherein " ∿∿ " indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R$_{ii}$ is H,
(C$_1$-C$_6$)alkyl,


$(C_1\text{-}C_6)\text{alkyl}{-}Q{-}C(=O){\sim}$

, as defined above, or


, as defined above;

provided that 3 or fewer of R_c R_d, R_e, and R_f are H; or

R_b is OH,

$R_{ii}O(C_1\text{-}C_6)$alkyl,

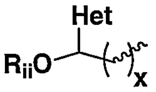
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,

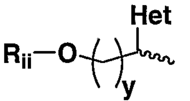
$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,

$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-,

$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-,


, wherein " ∿∿ " indicates the point of attachment, het is a 5- or 6-membered heterocyclo or heteroaryl group, and x is an integer of from 0 to 10;


, wherein " ∿∿ " indicates the point of attachment, het is as defined above, and y is an integer of from 1 to 10;

wherein R_{ii} is H or $(C_1\text{-}C_6)$alkyl.

6. The compound of claim 1, wherein:

R_1 is $(C_1\text{-}C_6)$alkyl,

halo$(C_1\text{-}C_6)$alkyl,

$(C_3\text{-}C_6)$cycloalkyl,

halo$(C_3\text{-}C_6)$cycloalkyl

aryl, and

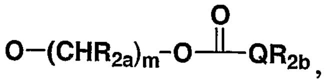
heteroaryl;

R_2 is OH,

OBF_2,

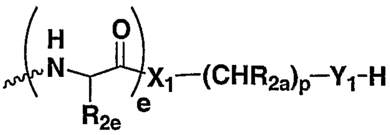
$O(C_1\text{-}C_6)$alkyl,

O(C_3-C_6)cycloalkyl,


$\mathrm{O{-}(CHR_{2a})_m{-}O{-}C(=O){-}QR_{2b}}$, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or (C_1-C_6)alkyl and R_{2b} is (C_1-C_6)alkyl, aryl, or heteroaryl,

$\mathrm{O{-}(CHR_{2a})_n{-}Y}$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, (C_1-C_6)alkyl, or (C_3-C_6)cycloalkyl, or

NR_{2d}, wherein R_{2d} is as defined above,



, wherein "~~~" indicates the point of attachment, 2a is as defined above, R_{2e} is H or (C_1-C_6)alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

R_3, R_4, and R_5 are each independently H,
halo,
NH_2,
(C_1-C_6)alkyl,
halo(C_1-C_6)alkyl,
(C_1-C_6)alkoxy, or
halo(C_1-C_6)alkoxy;

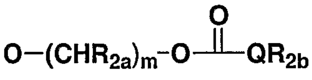
R_a is H,
aryl,
(C_1-C_6)alkyl,
halo(C_1-C_6)alkyl,
(C_3-C_6)cycloalkyl,
R_{ii}O(C_1-C_6)alkyl,

$R_{ii}O(C_1\text{-}C_6)$haloalkyl,
$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,
$R_{ii}O(C_1\text{-}C_6)$alkyl-O-,
$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-, or
$R_{ii}O(C_3\text{-}C_6)$cycloalkyl-O-, wherein R_{ii} is H or $(C_1\text{-}C_6)$alkyl; and

R_b is OH,
$R_{ii}O(C_1\text{-}C_6)$alkyl,
$R_{ii}O(C_1\text{-}C_6)$haloalkyl,
$R_{ii}O(C_3\text{-}C_6)$cycloalkyl,
$R_{ii}O(C_1\text{-}C_6)$alkyl-O-, or
$R_{ii}O(C_1\text{-}C_6)$haloalkyl-O-, wherein R_{ii} is H or $(C_1\text{-}C_6)$alkyl.

7. The compound of claim 1, wherein:
R_1 is $(C_1\text{-}C_6)$alkyl,
halo$(C_1\text{-}C_6)$alkyl,
$(C_3\text{-}C_6)$cycloalkyl,
halo$(C_3\text{-}C_6)$cycloalkyl
aryl, and
heteroaryl;

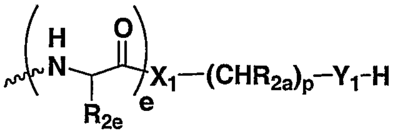
R_2 is OH,
OBF_2,
$O(C_1\text{-}C_6)$alkyl,
$O(C_3\text{-}C_6)$cycloalkyl,



$O-(CHR_{2a})_m-O-\overset{O}{\overset{\|}{C}}-QR_{2b}$, wherein m is an integer of from 1 to 10, Q is O or is absent, and R_{2a} is H or $(C_1\text{-}C_6)$alkyl and R_{2b} is $(C_1\text{-}C_6)$alkyl, aryl, or heteroaryl,

$O-(CHR_{2a})_n-Y$, wherein R_{2a} is as defined above, n is an integer of from 2 to 10, Y is OH or $NR_{2c}R_{2d}$, wherein R_{2c} and R_{2d} are each independently H, (C_1-C_6)alkyl, or (C_3-C_6)cycloalkyl, or

NR_{2d}, wherein R_{2d} is as defined above,



, wherein "∿∿" indicates the point of attachment, 2a is as defined above, R_{2e} is H or (C_1-C_6)alkyl, e is an integer of from 1 to 10, p is an integer of from 2 to 10, and X_1 and Y_1 are each independently NH or O;

R_3, R_4, and R_5 are each independently H,

halo,

NH_2,

(C_1-C_6)alkyl,

halo(C_1-C_6)alkyl,

(C_1-C_6)alkoxy, or

halo(C_1-C_6)alkoxy;

R_a is H,

aryl,

(C_1-C_6)alkyl,

halo(C_1-C_6)alkyl,

(C_3-C_6)cycloalkyl,

$R_{ii}O(C_1-C_6)$alkyl,

$R_{ii}O(C_1-C_6)$haloalkyl,

$R_{ii}O(C_3-C_6)$cycloalkyl, or

$R_{ii}O(C_3-C_6)$cycloalkyl-O-, wherein R_{ii} is H or (C_1-C_6)alkyl; and

R_b is OH,

$R_{ii}O(C_1-C_6)$alkyl,

$R_{ii}O(C_1-C_6)$haloalkyl,

$R_{ii}O(C_3-C_6)$cycloalkyl,
$R_{ii}O(C_1-C_6)$alkyl-O-, or
$R_{ii}O(C_1-C_6)$haloalkyl-O-, wherein R_{ii} is H or (C_1-C_6)alkyl.

8. The compound of claim 7, wherein
R_1 is (C_1-C_6)cycloalkyl,
halo(C_1-C_6)cycloalkyl,
aryl, or
heteroaryl;

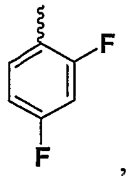
R_2 is OH,
OBF_2, or
$O(C_1-C_6)$alkyl;

R_3 is H or NH_2;

R_4 is H or halo; and

R_5 is halo,
methyl,
trifluoromethyl,
methoxy,
fluoromethoxy,
difluoromethoxy, or
trifluoromethoxy.

9. The compound of claim 8, wherein
R_1 is cyclopropyl,
fluorocyclopropyl,



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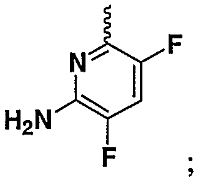


;

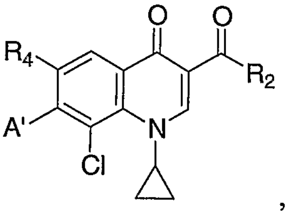
R_2 is OH;

R_3 is H or NH_2;

R_4 is H or F; and

R_5 is halo,
methyl,
trifluoromethyl, or
methoxy.

10. The compound of claim 2 which is:



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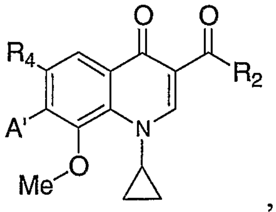

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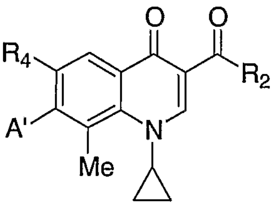

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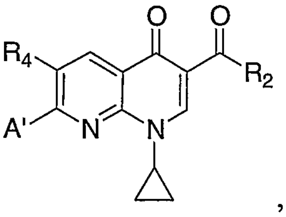

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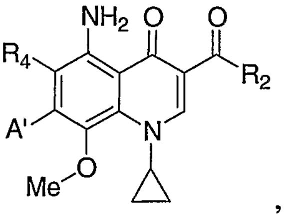

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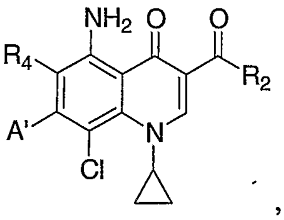

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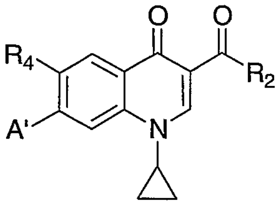
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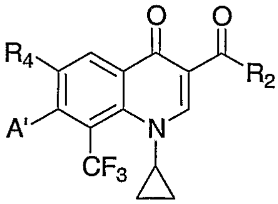
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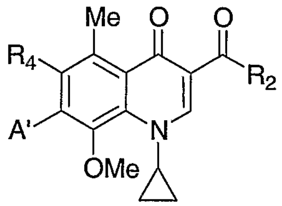
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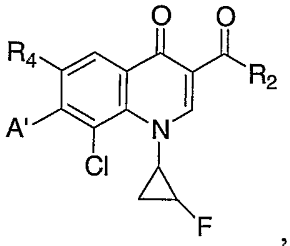
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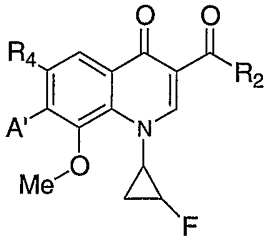
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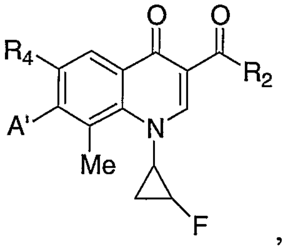
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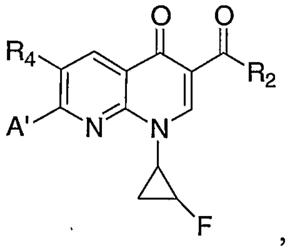
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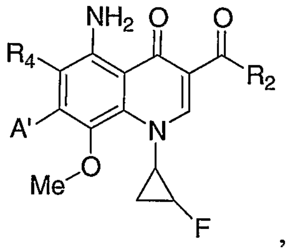
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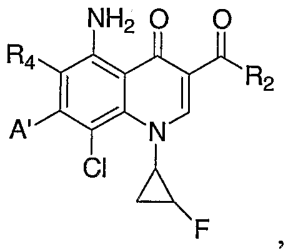
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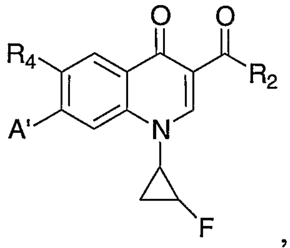
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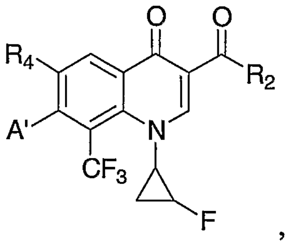
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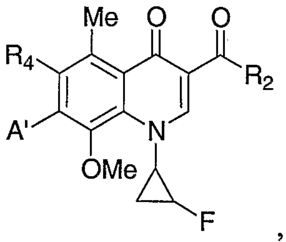
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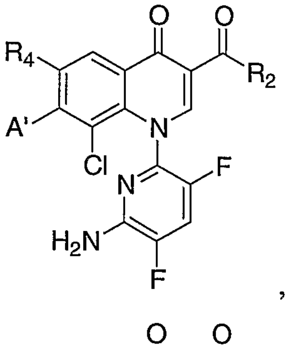
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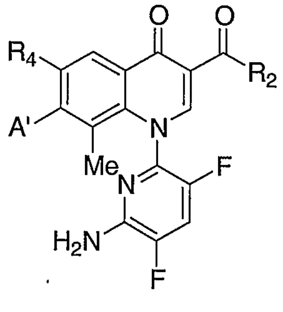
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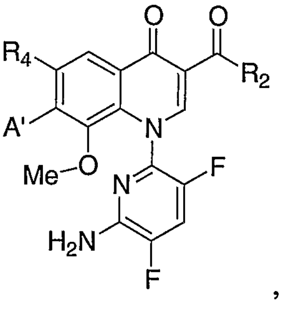
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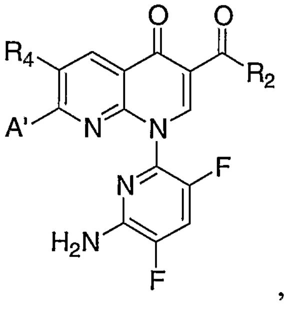
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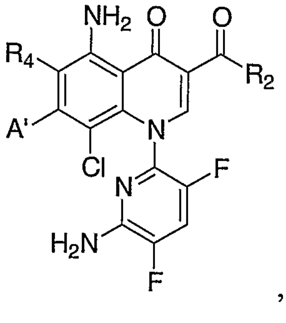
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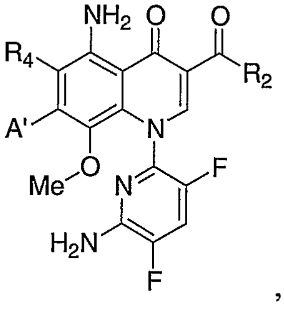
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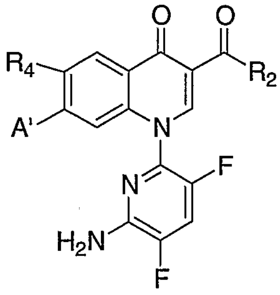
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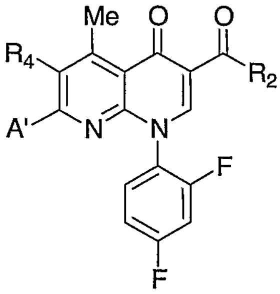
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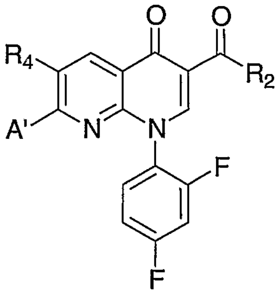
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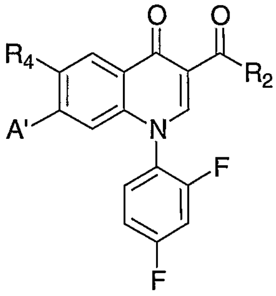
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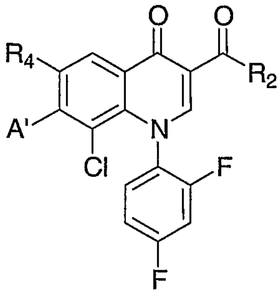
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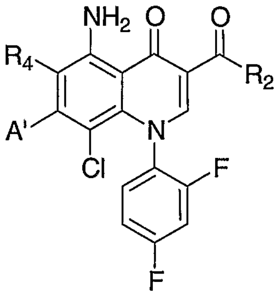
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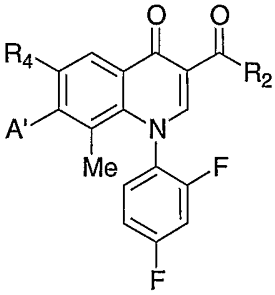
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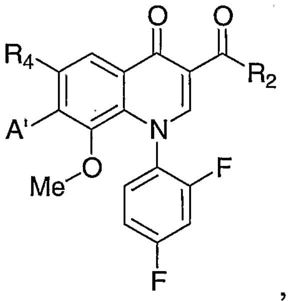
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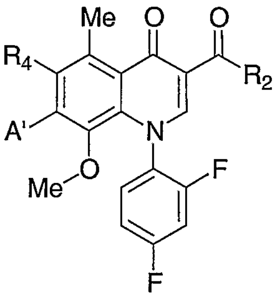
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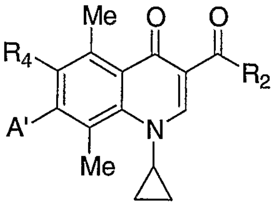
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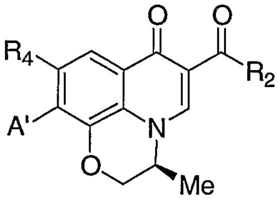
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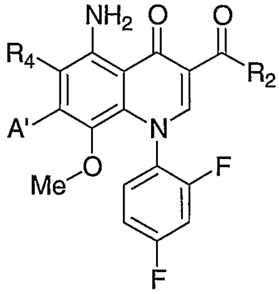
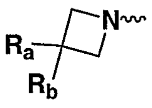
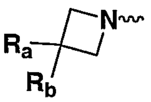
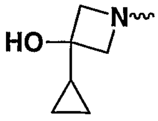
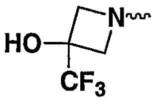
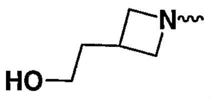

,

wherein R_4 is OH, O(C_1-C_6)alkyl or OBF_2, O R_4 is H or F and A' is  .

11. The compound of claim 10 wherein R_2 is OH.

12. The compound of claim 4, wherein  is , , , .

13. A compound which is

1-Cyclopropyl-6-fluoro-7-(3-hydroxy-azetidin-1-yl)-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid;

1-Cyclopropyl-6-fluoro-7-(3-hydroxy-azetidin-1-yl)-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid;

1-Cyclopropyl-7-(3-cyclopropyl-3-hydroxy-azetidin-1-yl)-6-fluoro-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid;

1-Cyclopropyl-6-fluoro-7-[3-(2-hydroxy-ethyl)-azetidin-1-yl]-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid; or

1-Cyclopropyl-6-fluoro-7-(3-hydroxy-3-trifluoromethyl-azetidin-1-yl)-8-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

14. A pharmaceutical formulation comprising a compound of claim 1 admixed with a pharmaceutically acceptable diluent, carrier, or excipient.

15. A method of treating a bacterial infection in a mammal, comprising administering to a mammal in need thereof an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

rnational Application No

;T/IB2004/002857

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/04 A61K31/4709 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OKADA T ET AL: "Quantitative Structure-Activity Relationships of Antibacterial Agents, 7-Heteroyclic Amine Substituted 1-Cyclopropyl-6,8-difluoro-4-oxoquinoline-3-carboxylic Acids" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 41, no. 1, 1993, pages 126-131, XP002115350 ISSN: 0009-2363 table III; compound 25	1-15
X	WO 01/66542 A (DAINIPPON PHARMACEUTICAL CO ; CHIBA KATSUMI (JP); MIZUNO KAZUHIRO (JP)) 13 September 2001 (2001-09-13) claim 1	1-15

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search 14 December 2004	Date of mailing of the international search report 22/12/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Wörth, C

INTERNATIONAL SEARCH REPORT

ternational Application No
T/IB2004/002857

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRIGOLA J ET AL: "7-Azetidinylquinolones as Antibacterial Agents. Synthesis and Structure-Activity Relationships" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 36, no. 7, 1993, pages 801-810, XP002115351 ISSN: 0022-2623 table III; compounds 31B-D,32B-D,32U, 32V,33B	1-15
X	FRIGOLA J ET AL: "7-Azetidinylquinolones as Antibacterial Agents. 2. Synthesis and Biological Activity of 7-(2,3-Disubstituted-1-azetidinyl)-4-oxoquino line- and -1,8-naphthyridine-3-carboxylic Acids. Properties and Structure-Activity Relationships of Quinolones with an Azetidine Moiety" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, no. 24, 1994, pages 4195-4210, XP002115349 ISSN: 0022-2623 table 2; compounds 21A-D,22A-D	1-15
X	EP 0 314 362 A (PFIZER) 3 May 1989 (1989-05-03) claims 1,7; examples 3,5	1-15
X	FR 2 625 200 A (ESTEVE LABOR DR) 30 June 1989 (1989-06-30) claim 1; examples 1,2,4	1-15
X	EP 0 324 298 A (ESTEVE LABOR DR) 19 July 1989 (1989-07-19) examples; claim 1	1-15

INTERNATIONAL SEARCH REPORT

nternational application No.
PCT/IB2004/002857

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
T/IB2004/002857

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Information on patent family members

International Application No

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