624810

FORM 1 SPRUSON & FERGUSON

Commonwealth of Australia

Patents Act 1990

APPLICATION FOR A STANDARD PATENT

F Hoffmann-La Roche & Co Aktiengesellschaft, of Grenzacherstrasse 124-184, 4002 Basle, Switzerland hereby apply for the grant of a standard patent for an invention entitled:

Acyl Derivatives

which is described in the accompanying complete specification.

Details of basic applications:

Basic Applic. No.	Country:	Application Date:
175,471	US	31 March 1988
197,943	US	24 May 1988
89102071.1	EP	7 February 1989

The address for service is:-

Spruson & Ferguson
Patent Attorneys
Level 33 St Martins Tower
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Sydney New South Wales Australia

DATED this TWENTY-NINTH day of MARCH 1989

F Hoffmann-La Roche & Co Aktiengesellschaft

By:

Registered Patent Attorney

IRN: 88100 INSTR CODE: 55541

TMS/8438T

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made for a patent for an invention entitled:

Acyl Derivatives

I, Fridolin Klausner, of 187 Baselmattweg, CH-4123 Allschwil, Switzerland do solemnly and sincerely declare as follows:-

1. I am are authorised by F. Hoffmann-La Roche & Co. Aktiengesellschaft, the applicant for the patent to make this declaration on its behalf.

2. The basic applications as defined by Section 141 of the Act were made in United States of America on 31 March, 1988 by Harry A. Albrecht, Dennis D. Keith, Chung-Chen Wei, Manfred Weigele and Roxana Yang, in the United States of America on 24 May, 1988 by Harry A. Albrecht, Dennis D. Keith, ederick M. Konzelmann, Pamela L. Rossman and Manfred Weigele and in the European Patent Office, Federal Republic of Germany on 7 February, 1989 by F. Hoffmann-La Roche & Co. Aktiengesellschaft

3. Harry Allen Albrecht, Dennis Dalton Keith, Frederick Martin Konzelmann, Pamela Loreen Rossman, Chung-Chen Wei, Manfred Weigele and Roxana Yang, of 139 Waughaw Road, Towaco, New Jersey 07082; 8 Mendel Terrace, Montclair, New Jersey 07042; Old Rifle Camp road, West Paterson, New Jersey 07424; 82 Oakley Terrace, Nutley, New Jersey 07110; 244 Malapardis Road, Cedar Knolls, New Jersey 07927; 4 Andover Drive, North Caldwell, New Jersey 07006 and 77 Elmwood Terrace, West Caldwell, New Jersey 07006, all in United States of America [respectively], are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows:

   The said Applicant is the assignee of the actual inventors.

4. The basic applications referred to in paragraph 2 of this Declaration were the first applications made in a Convention country in respect of the inventions the subject of the application.

DECLARED at Basle, this 17th day of May, 1989

Fridolin Klausner
Signature of Declarant

TO: THE COMMISSIONER OF PATENTS
AUSTRALIA

sbr/164M

(12) PATENT ABRIDGMENT (11) Document No. AU-B-32271/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 624810

(54) Title
ACYL DERIVATIVES

International Patent Classification(s)
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C07D 501/46 A61K 031/545
(51)[5] C07D 501/28 C07D 501/32 C07D 501/34
C07D 501/56 C07D 519/00

(21) Application No. : 32271/89 (22) Application Date : 30.03.89

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(43) Publication Date : 12.10.89

(44) Publication Date of Accepted Application : 25.06.92

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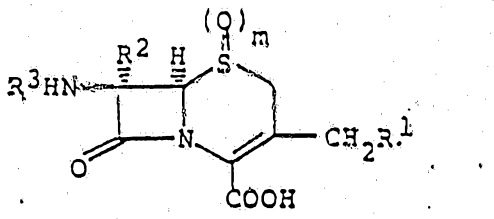
(56) Prior Art Documents
AU 43583/89 C07D 501/34
AU 80926/87 C07D 501/34
AU 39985/85 C07D 519/00

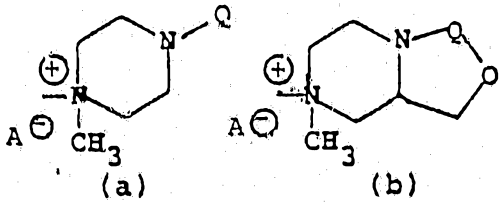
(57) Claim

1. Acyl derivatives of the general formula



I

wherein R^1 is a substituted N-heterocyclus of the formulas



(a) (b)

$-OCOR^{10}$

(c)

.../2

624810

S & F Ref: 38100

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

Name and Address of Applicant: F Hoffmann-La Roche & Co Aktiengesellschaft
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4002 Basle
SWITZERLAND

Address for Service: Spruson & Ferguson, Patent Attorneys
Level 33 St Martins Tower, 31 Market Street
Sydney, New South Wales, 2000, Australia

Complete Specification for the invention entitled:

Acyl Derivatives

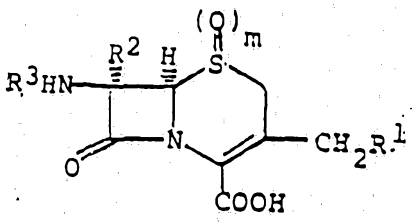
The following statement is a full description of this invention, including the best method of performing it known to me/us

5845/3

RAN 4410/216k

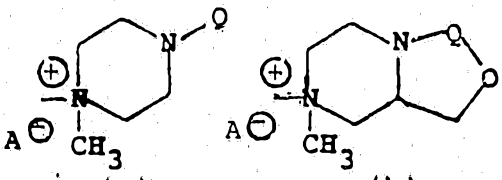
Abstract

Acyl derivatives of the general formula



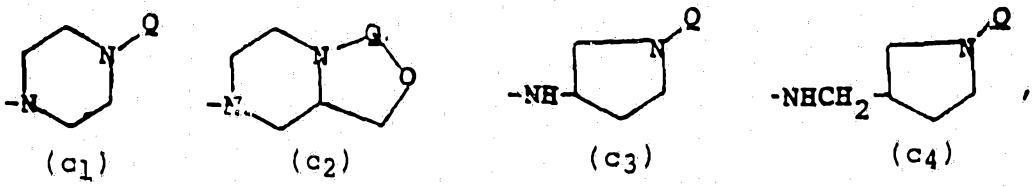
I

wherein R^1 is a substituted N-heterocyclus of the formulas



(a) (b) $-OCOR^{10}$ (c)

where R^{10} is one of the groups



(c_1) (c_2) (c_3) (c_4)

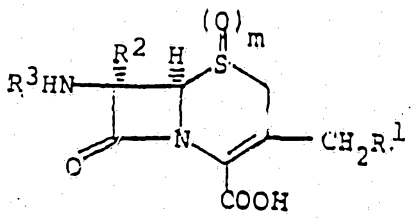
Q represents a substituted quinolinyl or naphthyridinyl group and the N-heterocyclic nucleus may optionally be substituted with one or more lower alkyl groups; R^2 is selected from the group consisting of hydrogen, lower alkoxy, lower alkylthio and lower alkanoylamino; R^3 is an acyl groups; m is zero, 1 or 2; and A is a pharmaceutically acceptable anion

and readily hydrolyzable esters and pharmaceutically acceptable salts of these compounds and hydrates of the compounds of formula I or of their esters or salts.

The products are antibacterially active.

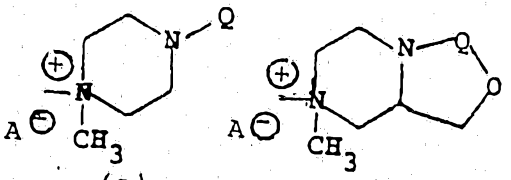
RAN 4410/216k

The present invention relates to acyl derivatives of the general formula



I

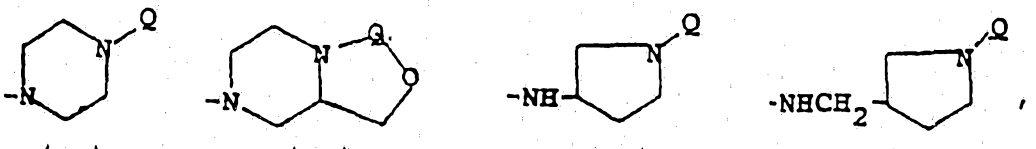
wherein R^1 is a substituted N-heterocyclus of the formulas



(a) (b)

$-OCOR^{10}$ (c)

where R^{10} is one of the groups



(c_1) (c_2) (c_3) (c_4)

Q represents a substituted quinolinyl or naphthyridinyl group and the N-heterocyclic nucleus may optionally be substituted with one or more lower alkyl groups; R^2 is selected from the group consisting of hydrogen, lower alkoxy, lower alkylthio and lower alkanoylamino; R^3 is an acyl groups; m is zero, 1 or 2; and A is a pharmaceutically acceptable anion,

and readily hydrolyzable esters and pharmaceutically acceptable salts of these compounds and hydrates of the compounds of formula I or of their esters or salts.

As used herein, the terms "lower alkyl" and "alkyl" refer to both straight and branched chain saturated hydrocarbon groups having 1 to 8, and preferably 1 to 4, carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, t-butyl, and the like.

As used herein, the term "lower alkoxy" or "alkoxy" refers to a straight or branched chain hydrocarbonoxy group wherein the "alkyl" portion is a lower alkyl group as defined above. Examples include methoxy, ethoxy, n-propoxy and the like.

The term "halogen", or "halo", used herein refers to all four forms, that is, chloro, bromo, iodo and fluoro, unless specified otherwise.

By the term "aryl" is meant a substituted or unsubstituted aromatic moiety, such as, phenyl, tolyl, xylyl, mesityl, cumenyl, naphthyl, and the like, wherein said aryl group may have 1 to 3 suitable substituents, such as halo (fluoro, chloro, bromo, etc.), hydroxy and the like.

By the term "lower alkanoyl" or "alkanoyl" as utilized herein is intended a moiety or the formula

$$R^{25}\text{-}CO\text{-}$$

wherein R^{25} is hydrogen or C_1 to C_6 lower alkyl. Examplary of such groups are formyl, acetyl, propionyl, n-butyryl and the like.

By the term "substituted phenyl" is meant phenyl mono- or di-substituted by e.g. halo (e.g. chloro, bromo, fluoro, etc.), lower alkyl, amino, nitro or trifluoromethyl.

By the term "substituted alkyl" is meant a "lower alkyl" moiety substituted by, for example, halo (e.g. chloro, fluoro, bromo, etc.), trifluoromethyl, amino, cyano, etc.

By the term "lower alkenyl" or "alkenyl" is meant straight or branched chain hydrocarbon groups which contain an olefinic double bond having 2 to 6 carbon atoms, i.e. the radical of compounds of the formula C_nH_{2n} wherein n is 2 to 6, e.g. vinyl, allyl, etc.

By the term "aralkyl" is meant a hydrocarbon group having both aromatic and aliphatic structures, that is, a hydrocarbon group in which a lower alkyl hydrogen atom is substituted by a monocyclic aryl group, e.g. by phenyl, tolyl, etc.

The expression "5-, 6- or 7-membered heterocyclic ring containing 1-4 nitrogen, oxygen and/or sulfur atoms" is intended to represent the following groups: a 6-membered nitrogen-containing hetero ring, e.g. pyridyl, piperidyl, piperidino, N-oxido-pyridyl, pyrimidyl, piperazinyl, pyridazinyl, N-oxido-pyridazinyl, etc.; a 5-membered nitrogen-containing hetero ring such as pyrazolyl, pyrrolidinyl, imidazolyl, thiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, etc., and others. Each of these hetero rings may be further substituted and, as the

substituents, there may be mentioned, for example, lower alkyls such as methyl, ethyl, n-propyl, etc., lower alkoxys such as methoxy, ethoxy, etc., halogens such as chlorine, bromine, etc., halogen substituted alkyls such as trifluoromethyl, trichloroethyl, etc., amino, mercapto, hydroxy, carbamoyl or carboxy, etc.

By the term "cyclo-lower-alkyl" or "cycloalkyl" is meant a 3-6 membered saturated carbocyclic moiety, e.g. cyclopropyl, cyclobutyl, cyclohexyl, etc.

The term "acyl" used in conjunction with R^3 herein refers to all organic radicals derived from an organic acid, such as a carboxylic acid, by removal of the hydroxyl group. Although the group R^3 may be any one of many acyl radicals, certain acyl groups are preferred, as described below.

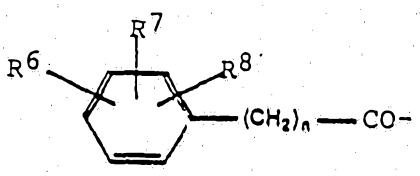
Exemplary acyl group R^3 are those groups which have been used in the past to acylate ß-lactam antibiotics, including 6-aminopenicillanic acid and derivatives and 7-aminocephalosporanic acid and derivatives; see, for example, Cephalosporins and Penicillins, edited by Flynn, Academic Press (1972), Belgian patent 866,038, published October 17, 1978, Belgian patent 867,994, published December 11, 1978, United States patent 4,152,432, issued May 1, 1979, United States patent 3,971,778, issued July 27, 1976, and United States patent 4,173,199, issued October 23, 1979. The portions of these references describing various acyl groups are incorporated herein by reference. The following list of acyl groups is presented to further exemplify the term "acyl", without intending to limit that term to only those groups set forth:

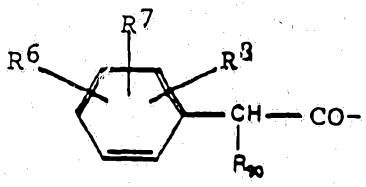
(a) Aliphatic acyl groups having the formula

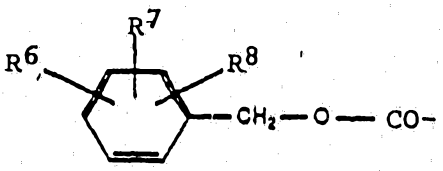
$$R^5CO-$$

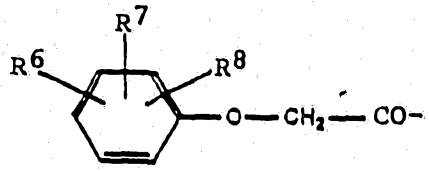
wherein R^5 is selected from the group consisting of hydrogen, lower alkyl, C_3-C_7 cycloalkyl, lower alkoxy, lower alkenyl, C_3-C_7 cycloalkenyl or cyclohexadienyl, or lower alkyl or lower alkenyl substituted with one or more halogen, cyano, nitro, amino, mercapto, lower alkylthio or cyanomethylthio groups.

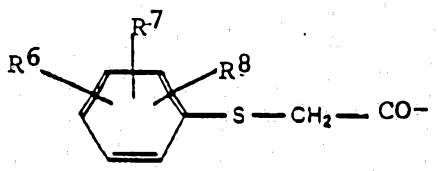
(b) Aromatic acyl groups selected from the group consisting of

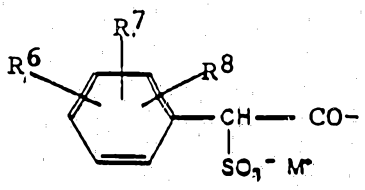


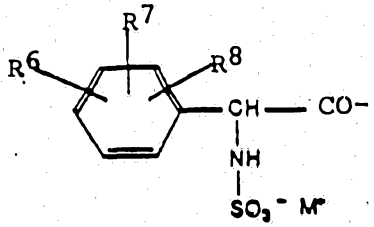






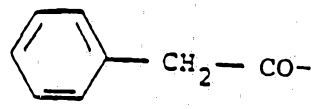


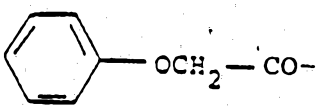


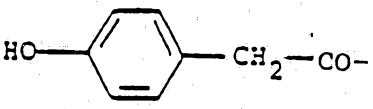


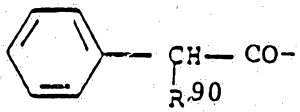
wherein n is 0, 1, 2 or 3; R^6, R^7, and R^8 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms and aminomethyl; and R^{90} is selected from the group consisting of amino, acylamino, hydroxy, a carboxy salt, protected carboxy, e.g. benzyloxycarbonyl, formyloxy, azido and a sulfo salt, and M is a cation.

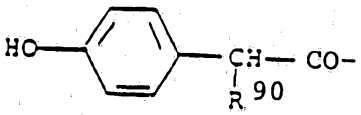
Preferred carbocyclic aromatic acyl groups include those having the formulas











Particularly preferred is the second group above (phenoxyacetyl).

R^{90} is preferably an amino group, a hydroxy group or a carboxy salt or sulfo salt.

Examples of other acyl groups suitable for the purposes of the present invention are sulfophenylacetyl, hydroxysulfonyloxyphenylacetyl, sulfamoylphenylacetyl, (phenoxycarbonyl)phenylacetyl, (p-tolyloxycarbonyl)phenylacetyl, formyloxyphenylacetyl, carboxyphenylacetyl, formylaminophenylacetyl, benzyloxycarbonylphenylacetyl, 2-(N,N-dimethylsulfamoyl)-2-phenylacetyl, etc.

(c) Heteroaromatic groups having the formula

$$R^{101}-(CH_2)_n-CO-$$

$$R^{101}-\underset{\displaystyle R^{90}}{\underset{|}{CH}}-CO-$$

$$R^{101}-O-CH_2-CO-$$

$$R^{101}-S-CH_2-CO- \qquad \text{or}$$

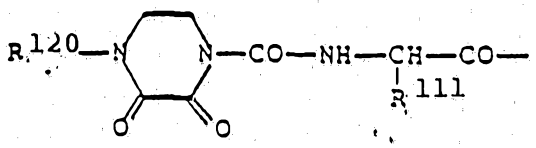
$$R^{101}-CO-CO-$$

wherein n is 0, 1, 2 or 3; R^{90} is as defined above; and R^{101} is a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 (preferably 1 or 2) nitrogen, oxygen and/or sulfur atoms.

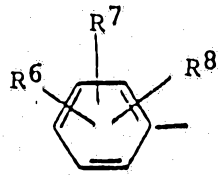
Exemplary heterocyclic rings are thienyl, furyl, pyrrolyl, pyridinyl, pyrazinyl, thiazolyl, pyrimidinyl and tetrazolyl. Exemplary substituents are halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms.

Preferred heteroaromatic acyl groups include those groups of the above formulas wherein R^{101} is 2-amino--4-thiazolyl, 2-amino-5-halo-4-thiazolyl, 4-aminopyridin--2-yl, 2-amino-1,3,4-thiadiazol-5-yl, 2-thienyl, 2-furanyl, 4-pyridinyl or 2,6-dichloro-4-pyridinyl.

(d) [[(4-Substituted-2,3-dioxo-1-piperazinyl)carbonyl]-amino]arylacetyl groups having the formula



wherein R^{111} is lower alkyl, hydroxy-lower alkyl or an aromatic group (including carbocyclic aromatics) such as those of the formula



wherein R^6, R^7 and R^8 are as previously defined and heteroaromatics as included within the definition of R^{101}; and R^{120} is lower alkyl, substituted alkyl (wherein the alkyl group is substituted with one or more halogen, cyano, nitro, amino or mercapto groups), e.g., 4-lower alkyl (preferably ethyl or methyl)-2,3-dioxo--1-piperazinecarbonyl-D-phenylglycyl.

(e) (Substituted oxyimino) arylacetyl groups having the formula

$$R^{130}\text{-O-N=C(}R^{101}\text{)-CO-}$$

wherein R^{101} is as defined above and R^{130} is hydrogen, lower alkyl, C_3-C_7 cycloalkyl, carboxy-C_3-C_7-cycloalkyl or substituted lower alkyl [wherein the lower alkyl group is substituted with one or more halogen, cyano, nitro, amino, mercapto, lower alkylthio, aromatic group (as defined by R^{111}), carboxy (including salts thereof), lower alkanoylamino, carbamoyl, lower alkoxycarbonyl, phenylmethoxycarbonyl, diphenylmethoxycarbonyl, hydroxy-lower-alkoxyphosphinyl, dihydroxyphosphinyl, hydroxy(phenylmethoxy)phosphinyl, di-lower-alkoxyphosphinyl substituents].

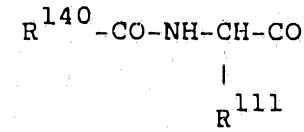
Examples of the

$$R^{130}\text{-O-N=C(}R^{101}\text{)-CO-}$$

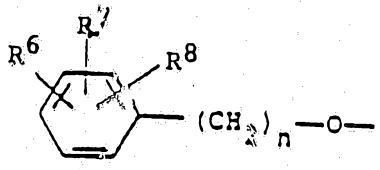
grouping are [2-[(chloroacetyl)amino]-4-thiazolyl](methoxyamino)acetyl, (2-amino-4-thiazolyl)(1-methylethoxyimino)acetyl, (2-amino-4-thiazolyl)(methoxyimino)acetyl, (2-furyl)(methoxyimino)acetyl, (4-hydroxyphenyl)(methoxyimino)acetyl, (methoxyimino)(phenyl)acetyl, (hydroxyimino)(phenyl)acetyl, (hydroxyimino)(2-thienyl)acetyl, [[(dichloroacetyl)oxy]imino](2-thienyl)acetyl, [5-chloro-2-[(chloroacetyl)amino]-4-thiazolyl](methoxyimino)acetyl, (2-amino-5-chloro-4-thiazolyl)(methoxyimino)acetyl, [[[1-(1,1-dimethylethoxy)carbonyl]-1-methylethoxy]imino]-2-sulfoamino-4-thiazolyl)acetyl, [[[1-(1,1-dimethylethoxycarbonyl]-1-methylethoxy]imino]-[[2-(triphenylmethyl)amino]-4-thiazolyl]acetyl, (methoxyimino)(2-sulfoamino-4-thiazolyl)acetyl, [(1-methylethoxy)imino]-[2-[(methylsulfonyl)amino]-4-thiazolyl]acetyl, [(3-methylsul-

fonyl)-2[3H]-thiazolimin-4-yl]-[1-(methylethoxy)imino]acetyl, [[2-(chloracetyl)amino]-4-thiazolyl][[[[(4-nitrophenyl)-methoxy]carbonyl]methoxy]imino]acetyl, (2-amino-4-thiazolyl)[(carboxymethoxy)imino]acetyl, (2-amino-4-thiazolyl)-[1-carboxy-(1-methylethoxy)imino]acetyl, (2-amino-4-thiazolyl)[[(aminocarbonyl)methoxy]imino]acetyl.

(f) (Acylamino)acetyl groups having the formula



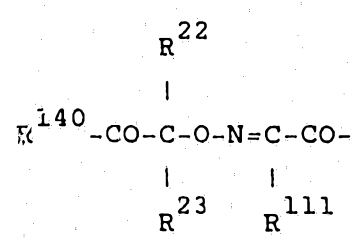
wherein R^{111} is as defined above and R^{140} is



(where R^6, R^7, R^8 and n are as previously defined), hydrogen, lower alkyl, substituted lower alkyl, amino, lower alkylamino, di-lower-alkylamino, (cyano-lower-alkyl)amino, hydrazino, lower alkyl-hydrazino, aryl-hydrazino or acyl-hydrazino.

Preferred (acylamino)acetyl groups of the above formula include those groups wherein R^{140} is amino or acylamino. Also preferred are those groups wherein R^{111} is phenyl or 2-thienyl.

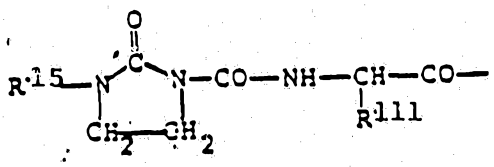
(g) Substituted oxyiminoacetyl groups having the tormula



wherein R^{111} and R^{140} are as defined above, and R^{22} and R^{23} are independently selected from the group consisting of hydrogen and lower alkyl, or R^{22} and R^{23} taken together with the carbon atom to which they are attached form a C_3-C_7 carbocyclic ring, for example, cyclopropyl, cyclobutyl or cyclopentyl.

Preferred substituted oxyimino acetyl groups of the above formula include those groups wherein R^{140} is amino. Also preferred are those groups wherein R^{111} is 2-amino-4-thiazolyl.

(h) [[[3-Substituted-2-oxo-1-imidazolidinyl]carbonyl]-amino]acetyl groups having the formula



wherein R^{111} is as defined above and R^{15} is hydrogen, lower alkylsulfonyl, arylmethyleneamino (i.e., $-N=CHR^{111}$ wherein R^{111} is as defined above), $R^{16}CO-$ (wherein R^{16} is hydrogen, lower alkyl or halogen substituted lower alkyl), aromatic group (as defined by R^{111} above), lower alkyl or substituted lower alkyl (wherein the lower alkyl group is

substituted with one or more halogen, cyano, nitro, amino or mercapto groups).

Preferred [[[3-substituted -2-oxo-1-imidazolidinyl]-carbonyl]amino]acetyl groups of the above formula include those wherein R^{111} is phenyl or 2-thienyl. Also preferred are those groups wherein R^{15} is hydrogen, methylsulfonyl, phenylmethyleneamino or 2-furylmethyleneamino.

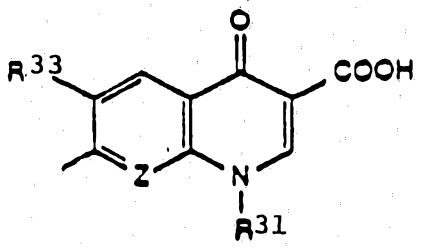
R^1 in formula I is any of the substituted N-heterocyclic groups (a), (b) and (c) above, preferably group (a) or group (c) in which R^{10} is group (c_1). R^1 can be any of the following groups:

(i) Groups (a) and (b) (quaternary piperazinium salts)

Hereunder A represents a pharmaceutically acceptable anion pertaining to a pharmaceutically acceptable organic or inorganic acid. Examples of such acids are hydrohalic acids (e.g. hydrochloric acid, hydrobromic acid and hydroiodic acid) as well as other mineral acids such as sulphuric acid, nitric acid, phosphoric acid and the like; lower alkane-sulphonic and arylsulfonic acids such as ethane-, toluene- and benzene-sulfonic acid, and also other organic acids such as acetic acid, trifluoroacetic acid, tartaric acid, maleic acid, malic acid, citric acid, benzoic acid, salicylic acid, ascorbic acid and others. Under A is also unterstood the anion formed from the 2-carboxy group of the cephalosporin nucleus after dissociating off a proton and thus forming a zwitterion which is neutralized by the accompanying positive charge on the quaternary nitrogen atom.

Preferred embodiments of the anion A are the iodide anion, the trifluoroacetate anion and the 2-carboxylate anion on the cephalosporin nucleus which forms an inner salt with the piperazinium moiety present in R^1.

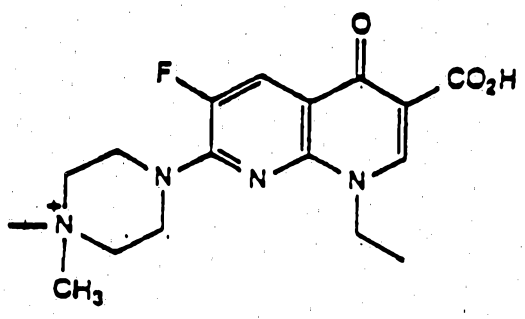
Q in groups (a) and (b) is a substituted quinolinyl or naphthyridinyl group, preferably of the formula

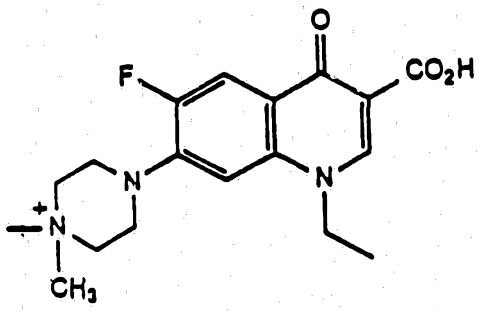


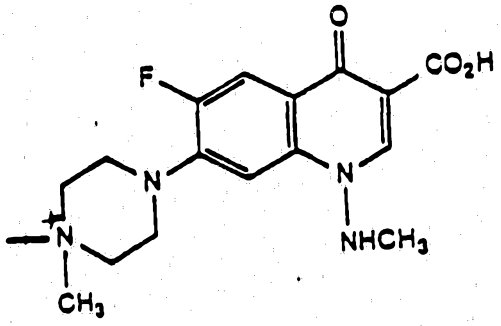
wherein Z represents R^{30}-C or nitrogen, R^{30} represents hydrogen, halogen or an oxymethylene ($-CH_2O-$) bridge to the piperazine nucleus to form a fused six-membered ring; R_{31} represents hydrogen, lower alkyl, lower alkenyl, C_3-C_7 cycloalkyl, halo-lower alkyl or mono-, di- or tri-halophenyl; R^{30} and R^{11} when taken together represent a C_3-C_5-alkylene group, a C_2-C_4-alkylene mono-oxy group, a C_1-C_2 alkylene dioxy group or a group of the formula $-OCH_2N(CH_3)-$; and R^{33} represents hydrogen or halogen.

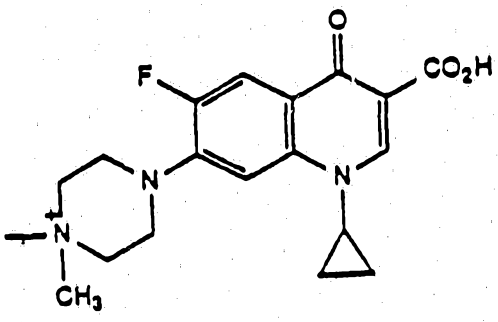
In a preferred embodiment thereof, Z is R^{30}-C wherein R^{30} is hydrogen, bromine, chlorine or fluorine, most preferably hydrogen or flourine; and R^{31} is lower alkyl, most preferably ethyl, or halogen substituted lower alkyl, most preferably fluoroethyl, or alternatively C_3-C_7-cycloalkyl, most preferably cyclopropyl; and R^{33} is hydrogen, chlorine or fluorine, most preferably hydrogen or fluorine.

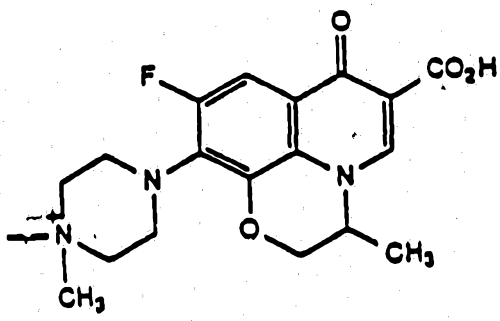
As used herein the substituted piperazinium substituent R^1 as groups (a) and (b) includes, among others, groups of the formulae

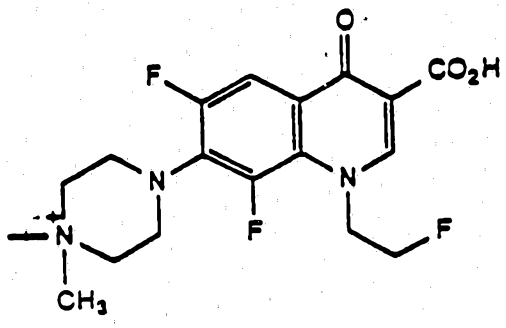


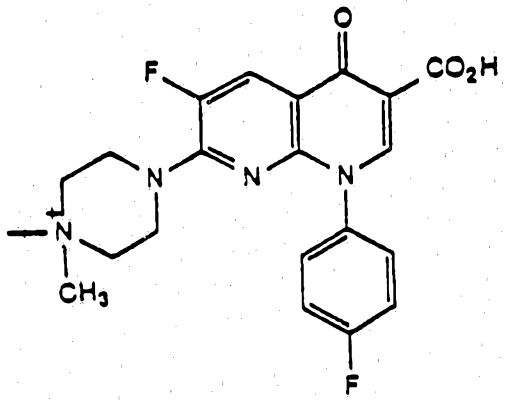


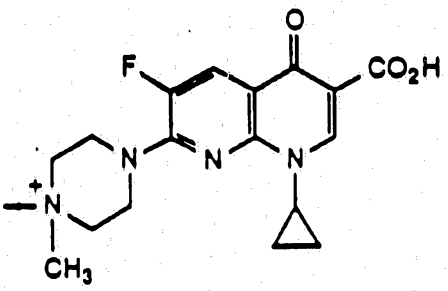


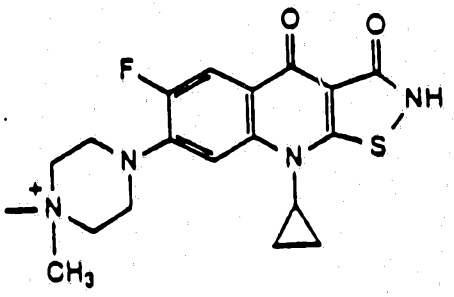


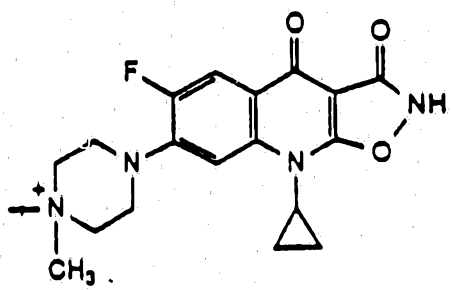


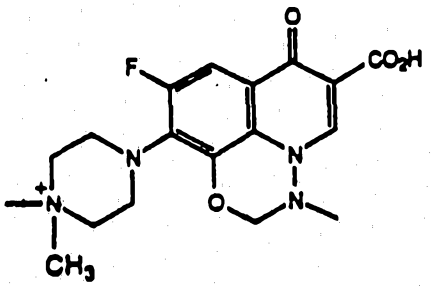


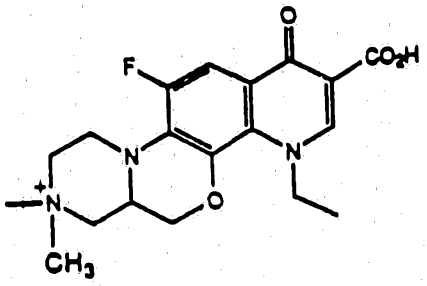






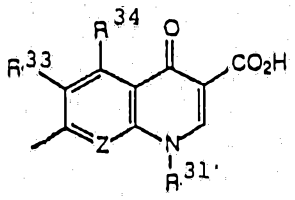






(ii) Group (c) (urethanes)

Q in group (c) is preferably of the formula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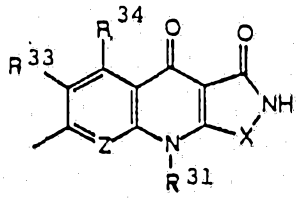
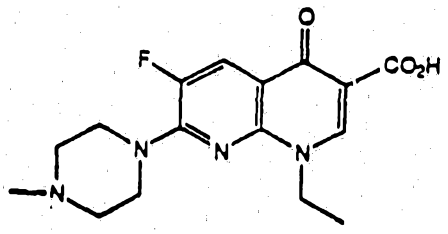


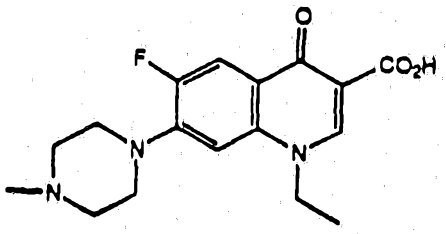
wherein Z represents R^{30}-C or nitrogen, X represents oxygen or sulfur, R^{30} represents hydrogen, halogen or an oxymethylene (-CH_2O-) bridge to the piperazine nucleus to form a fused six-membered ring; R^{31} represents hydrogen, lower alkyl, lower alkenyl, C_3-C_7 cycloalkyl, halo-lower alkyl or mono-, di- or tri-halophenyl; R^{30} and R^{31} when taken together represent a C_3-C_5 alkylene group, a C_2-C_4

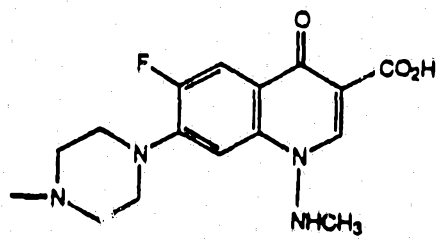
alkylene mono-oxy group, a C_1-C_2 alkylene dioxy group or a group of the formula $-OCH_2N(CH_3)-$; R^{33} is hydrogen or halogen; and R^{34} is hydrogen or amino.

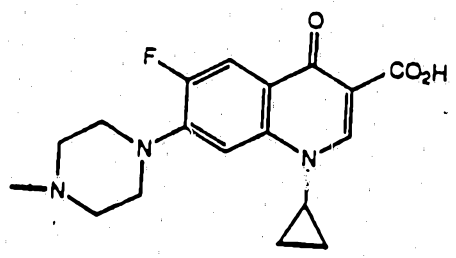
In a preferred embodiment thereof, Z is R^{30}-C wherein R^{30} is hydrogen, chlorine, bromine or fluorine, most preferably hydrogen or fluorine, R^{31} is lower alkyl, most preferably ethyl, or halo-lower alkyl, most preferably fluoroethyl, or C_3-C_7-cycloalkyl, most preferably cyclopropyl, and R^{33} is hydrogen, chlorine or fluorine, most preferably hydrogen or fluorine.

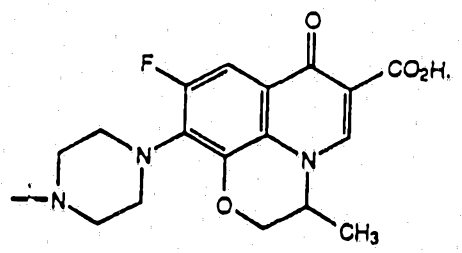
As used herein the urethane group (c) as a meaning of R^1 includes, among others, groups of the formulas

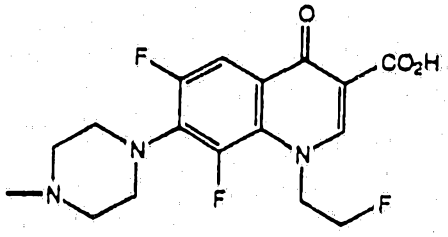


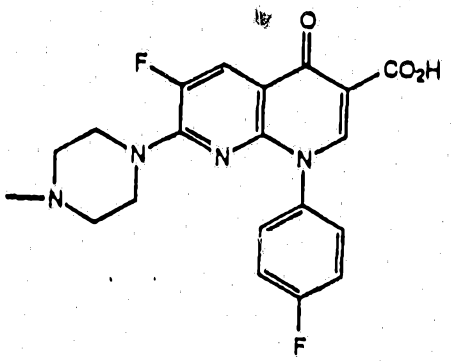


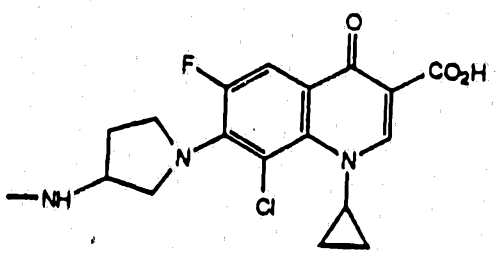


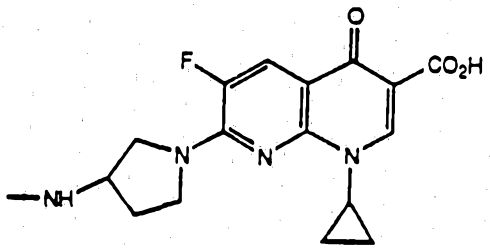


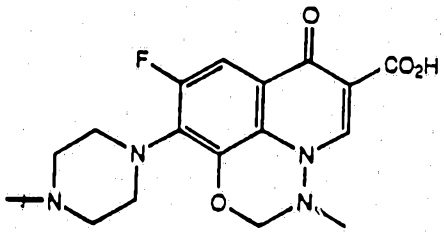


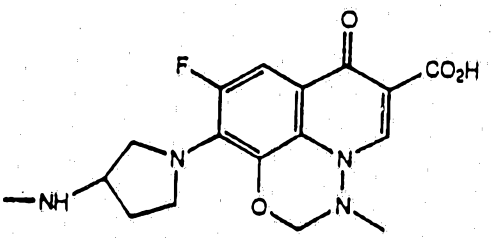


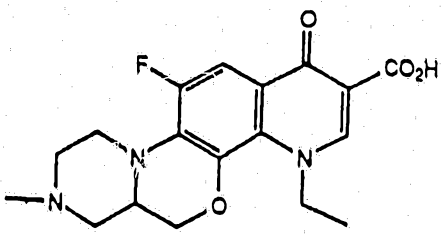


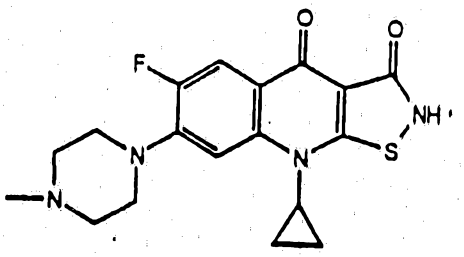


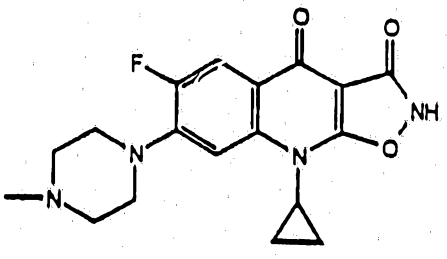


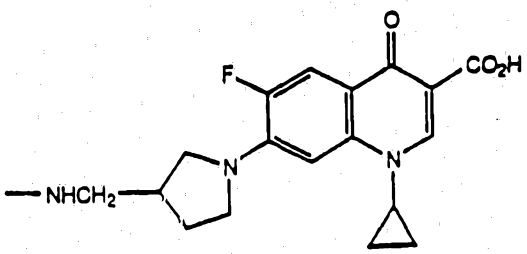


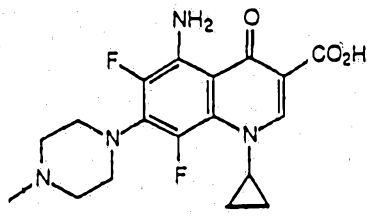




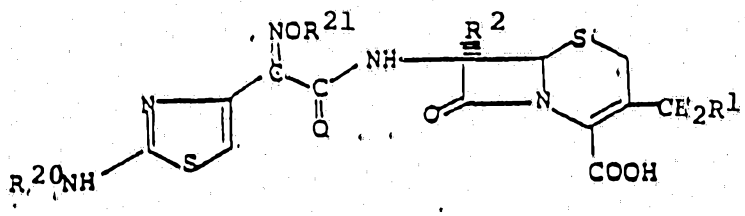






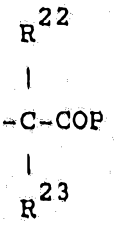


Preferred compounds within the purview of the present invention are those of formula I in which m is zero and R^2 is hydrogen. A still more preferred class of compounds are of the formula



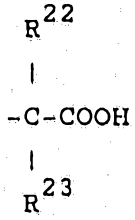
Ia

wherein R^1 and R^3 are as above, R^{20} is hydrogen or an amino protecting group, for example, trityl or chloroacetyl, or, preferably, hydrogen; and R^{21} is hydrogen, lower alkyl or a group of the formula



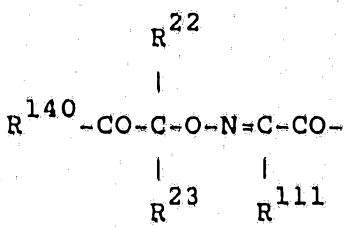
wherein R^{22} and R^{23} are as defined above and P is hydroxy or $-NHR^{19}$ where R^{19} is hydrogen, lower alkyl, amino, lower alkylamino, arylamino or acylamino.

Still more preferred are compounds of the formula Ia in which R^{20} is hydrogen, and R^{21} is methyl or a group of the formula

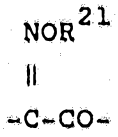


wherein R^{22} and R^{23} are selected from the group consisting of hydrogen and methyl.

Preferably, the

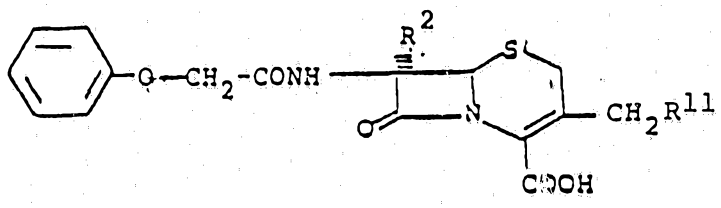


and



groupings are in the syn-form, i.e., the Z-form, or as mixtures in which the syn-form predominates.

Still another preferred class of compounds are those of the formula



Ib

wherein R^2 is as above and R^{11} is one of groups (a) and (b) above.

As readily hydrolyzable esters of the compounds of formula I there are to be understood compounds of formula I, the carboxy group(s) of which (e.g., the 2-carboxy group) is/are present in the form of readily hydrolyzable ester groups. Examples of such esters, which can be of the conventional type, are the lower alkanoyloxyalkyl esters (e.g., the acetoxymethyl, pivaloyloxymethyl, 1-acetoxyethyl and 1-pivaloyloxyethyl ester), the lower alkoxycarbonyloxyalkyl esters (e.g. the methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl and 1-isopropoxycarbonyloxyethyl ester), the lactonyl esters (e.g., the phthalidyl and thiophthalidyl ester), the lower alkoxymethyl esters (e.g., the methoxymethyl ester) and the lower alkanoylaminomethyl esters (e.g., the acetamidomethyl ester). Other esters (e.g., the benzyl and cyanomethyl esters) can also be used.

Examples of salts of the compounds of formula I are alkali metal salts such as the sodium and potassium salt, the ammonium salt, alkaline earth metal salts such as the calcium salt, salts with organic bases such as salts with amines (e.g., salts with N-ethyl-piperidine, procaine, dibenzylamine, N,N'-dibenzylethylenediamine, alkylamines or dialkylamines) as well as salts with amino acids such as, for example, salts with arginine or lysine.

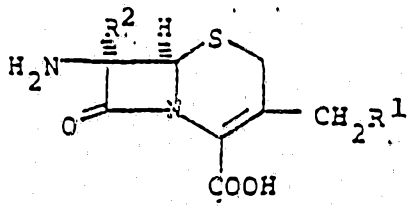
The compounds of formula I, when they contain a basic functional group such as an amine, also form addition salts with organic or inorganic acids. Examples of such salts are hydrohalides (e.g. hydrochlorides, hydrobromides and hydroiodides) as well as other mineral acid salts such as sulphates, nitrates, phosphates and the like, lower alkylsulphonates and monoarylsulphonates such as ethanesulfonates, toluenesulphonates, benzenesulphonates and the like and also other organic acid salts such as acetates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates and the like.

The compounds of formula I as well as their salts and readily hydrolyzable esters can be hydrated. The hydration can be effected in the course of the manufacturing process or can occur gradually as a result of hygroscopic properties of an initially anhydrous product.

The acyl derivatives aforesaid are manufactured in accordance with the present invention by a process which comprises

a) for the manufacture of a compound of formula I, in which

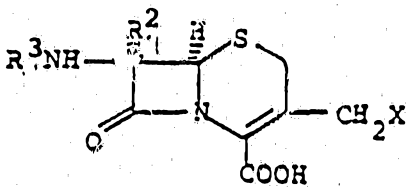
m is zero, reacting a compound of the general formula



II

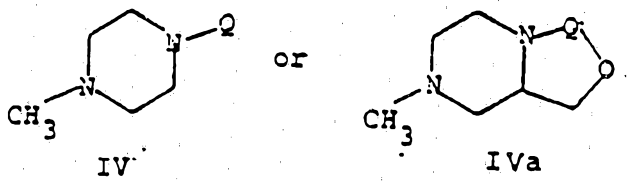
wherein R^1 and R^2 are as above,
or a readily hydrolyzable ester or salt thereof with a carboxylic acid of the general formula R^3OH or a reactive derivative thereof, or

b) for the manufacture of a compound of formula I, in which m is zero and R^1 is one of the groups (a) and (b), reacting a compound of the formula



III

wherein R^2 and R^3 are as above and X is a leaving group, and amino, hydroxy and carboxy groups present may be protected,
or a readily hydrolyzable ester or salt thereof with a compound of the formula

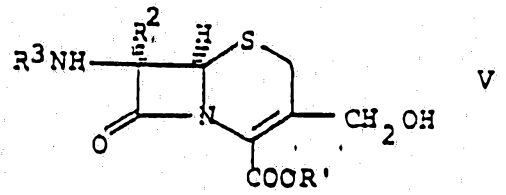


IV IVa

wherein Q is as above and the nitrogen atoms may be protected,

or

c) for the manufacture of a readily hydrolyzable ester of a carboxylic acid of formula I, in which m is zero and R^1 is group (c), reacting a compound of the formula

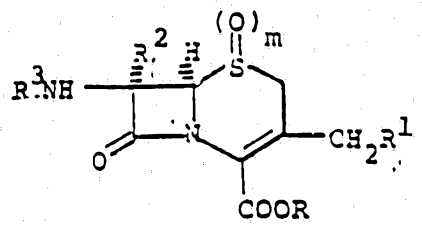


V

wherein R^2 and R^3 are as above and R' is the residue of a readily hydrolyzable ester,

in the presence of a base with phosgene and reacting the reaction product obtained with a compound of formula $R^{10}H$, in which R^{10} is as above, except that amino, hydroxy and/or carboxy functions thereof may be protected, followed by cleavage of any protecting group present, or

d) for the manufacture of a carboxylic acid of formula I converting an ester of the formula

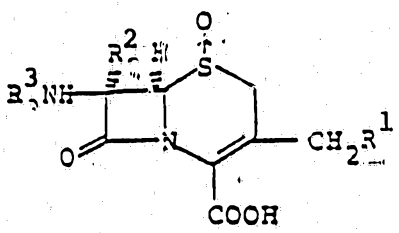


VI

wherein R^1, R^2, R^3 and m are as above, and R is a carboxylic acid protecting group,

to the carboxylic acid of formula I, or

e) for the manufacture of the compound of formula I, in which m is zero, or a readily hydrolyzable ester or salt thereof reducing a compound of the formula

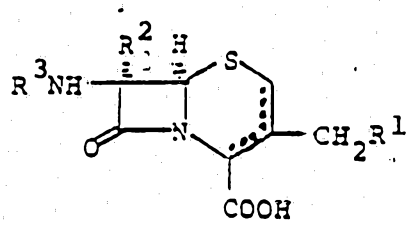


VII

wherein R^1, R^2 and R^3 are as above,

or a readily hydrolyzable ester or salt thereof, or

f) for the manufacture of a compound of formula I in which m is 1 or 2 or a readily hydrolyzable ester or salt thereof oxidizing a compound of the formula

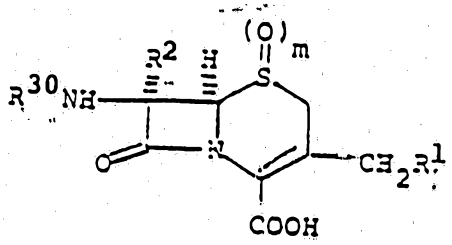


VIII

wherein R^1, R^2 and R^3 are as above and the dotted lines indicates the presence of a Δ2 or Δ3 double bond,

or a readily hydrolyzable ester of salt thereof, or

g) for the manufacture of a compound of formula I, in which R^3 contains an amino substituent, or a readily hydrolyzable ester or salt thereof cleaving off an amino protecting group in the substituent R^{30} of a compound of formula



IX

wherein R^1, R^2 and m are as above and R^{30} is an acyl group containing a protected amino substituent,

or of a readily hydrolyzable ester or salt thereof, or

h) for the manufacture of a readily hydrolyzable ester of a compound of formula I subjecting a carboxylic acid of formula I to a corresponding esterification, or

i) for the manufacture of salts or hydrates of a compound of formula I or hydrates of said salts converting a compound of formula I into a salt or hydrate or into a hydrate of said salt.

The reaction of compounds II with the acids R^3OH or their reactive derivatives according to embodiment (a) can be carried out in a manner known per se. The carboxy group in compounds II can be protected; for example, by esterification to form a readily cleavable ester such as a silyl ester (e.g. the trimethylsilyl ester). The carboxy group can also be protected in the form of one of the aforementioned readily hydrolyzable esters. Furthermore, the carboxy group can be protected by salt formation with an inorganic or tertiary organic base such as triethylamine. Amino groups present in groups R^3 can be protected. Possible protecting groups are, for example, protecting groups which are cleavable by acid hydrolysis (e.g. the tert.butoxycarbonyl or trityl groups) or by basic hydrolysis (e.g. the trifluoroacetyl group). Preferred protecting groups are the chloroacetyl, bromoacetyl and iodoacetyl groups, especially the chloroacetyl group. These last-mentioned protecting groups can be cleaved off by treatment with thiourea. The 7-amino group in compounds II can be protected, for example, by a silyl protecting group such as the trimethylsilyl group.

Examples of reactive functional derivatives of acids of formula R^3OH are halides (i.e. chlorides, bromides and fluorides), azides, anhydrides, especially mixed anhydrides with strong acids, reactive esters (e.g. N-hydroxy-succinimide esters) and amides (e.g. imidazolides).

In reacting a 7-amino compound of formula II with an acid of formula R^3OH or a reactive functional derivative thereof, for example, a free acid of formula R^3OH can be

reacted with an aforementioned ester of a compound of formula II in the presence of a carbodiimide such as dicyclohexylcarbodiimide in an inert solvent such as ethyl acaetate, acetonitrile, dioxan, chloroform, methylene chloride, benzene or dimethylformamide, and subsequently the ester group can be cleaved off. Oxazolium salts (e.g. N-ethyl-5-phenyl-isoxazolium-3'-sulphonate) can be used in place of carbodiimides in the foregoing reaction.

According to another embodiment, a salt of an acid of formula II (e.g. a trialkylammonium salt such as the triethylammonium salt) is reacted with a reactive functional derivative of an acid of formula R^3OH as mentioned earlier in an inert solvent (e.g. one of the aforementioned solvents).

According to a further embodiment, an acid halide, preferably the chloride, of an acid of formula R^3OH is reacted with an amine of formula II. The reaction is preferably carried out in the presence of an acid-binding agent, for example in the presence of aqueous alkali, preferably sodium hydroxide, or in the presence of an alkali metal carbonate such as potassium carbonate or in the presence of a lower alkylamine such as triethylamine. As the solvent there is preferably used water, optionally in admixture with an inert organic solvent such as tetrahydrofuran or dioxan. The reaction can also be carried out in an aprotic organic solvent such as dimethylformamide, dimethyl sulphoxide or hexamethylphosphoric acid triamide. When a silylated compound of formula II is used, the reaction is carried out in an anhydrous medium.

Advantageous alternatives for acylation, where an amino group present in the group R^3 need not be protected, involves the use of a 2-benzothiazolyl thioester or a 1-hydroxybenzotriazole ester of the acid R^3OH. For instance, the 2-benzthiazolyl thioester may be reacted with

the compound II in an inert organic solvent such as a chlorinated hydrocarbon e.g. methylene chloride, in acetone, ethyl acetate or in a mixture of such solvents with water. The 1-hydroxybenzotriazole ester can be employed by reacting the acid R^3OH with 1-hydroxybenzotriazole and a carbodiimide, especially N,N'-dicyclohexylcarbodiimide or N,N'-diisopropylcarbodiimide in an inert organic solvent, preferably methylene chloride, dimethylformamide, tetrahydrofuran, acetonitrile or ethyl acetate.

The reaction of a 7-amino compound of formula II with an acid of formula R^3OH or a reactive derivative thereof can conveniently be carried out at a temperature between about -40°C and +60°C, e.g. at room temperature.

The reaction of compounds III and their readily hydrolyzable esters and salts with the piperazine derivatives IV or IVa according to alternative (b) of the present process is preferably effected by initially protecting the starting compounds III and their readily hydrolyzable esters and salts, preferably with a trimethylsilylating agent such as N-methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA) thereby protecting amino, hydroxy and carboxy groups present. The leaving group X in compound III is preferably a halogen atom (e.g. a chlorine, bromine, or, in particular, an iodine atom) a lower alkyl- or aryl-sulfonyloxy group (e.g. the mesyloxy or tosyloxy group) or the azido group. Compound III can also be protected as described above for the starting materials of formula II. The piperazine reactants IV and IVa are preferably N-protected, e.g. with MSTFA. The reaction is preferably carried and at about 0°C to room temperature and in an inert organic solvent such as chloroform, methylene chloride or acetonitrile. Zwitterionic forms of compounds I are obtainable by treating a halogenide salt obtained with a base such as sodium bicarbonate or sodium hydroxide or with sodium phosphate buffer.

The reaction of compounds V with a base and phosgene and, subsequently, with compounds $R^{10}H$ according to alternative (c) of the present process is preferably carried out in an inert organic solvent such as methylene chloride or chloroform and at a temperature of about 0°C to about 30°C. Amino groups present may be protected e.g. as trimethylsilyl derivatives as described above and carboxy groups may be protected, e.g. as the readily hydrolyzable esters described above or as esters used in the ester saponification step (d) described below, e.g. as p-nitrobenzyl esters.

The deprotection of the esters VI according to embodiment (d) is effected using agents compatible with the ester protecting group utilized. As ester protecting groups R one may utilize an ester form which can be easily converted into a free carboxyl group under mild conditions, the ester protecting group being exemplified by, for example, t-butyl, p-nitrobenzyl, benzhydryl, allyl, etc. Also the residue of the readily hydrolyzable esters mentioned above as end products may be employed. For example the following reagents and their corresponding compatible esters are utilized: p-nitrobenzyl removed by hydrolysis in the presence of sodium sulfide at about or below 0°C to room temperature in a solvent, such as dimethylformamide (aqueous); t-butyl and benzhydryl removed by reaction with trifluoroacetic acid, optionally in the presence of anisole, at about 0°C to room temperature with or without a co-solvent such as methylene chloride; or allyl removed by a palladium (O) catalyzed transallylation reaction in the presence of sodium or potassium salt of 2-ethyl hexanoic acid, see for example J. Org. Chem. 1982, 47, 587.

The reduction of the sulfoxides VII according to embodiment (e) is effected utilizing one of a variety of reactions, for example, treatment with phosphorus trichloride in dimethylformamide or trifluoroacetic

anhydride in the presence of sodium iodide in acetone/methylene chloride. Both of the above reactions can be carried out at about 0°C to -20°C with about 0°C preferred.

The oxidation of the compounds VIII according to embodiment (f) isomerizes any Δ2 isomer VIII to the corresponding Δ3 isomer of formula I wherein n is 1 or 2. The oxidation is carried out by treatment with an organic or inorganic oxidizing agent. Various compounds which readily yield oxygen can be used as the oxidizing agent; for example, organic peroxides such as monosubstituted organic peroxides (e.g. C_1-C_4 alkyl- or alkanoylhydroperoxides such as t-butylhydroperoxide), performic acid and peracetic acid, as well as phenyl-substituted derivatives of these hydroperoxides such as cumenehydroperoxide and perbenzoic acid. The phenyl substituent can, if desired, carry a further lower group (e.g. a C_1-C_4 alkyl or alkoxy group), a halogen atom or a carboxy group (e.g. 4-methyl-perbenzoic acid, 4-methoxy-perbenzoic acid, 3-chloroperbenzoic acid and monoperphthalic acid). Various inorganic oxidizing agents can also be used as the oxidizing agent; for example, hydrogen peroxide, ozone, permanganates such as potassium or sodium permanganate, hypochlorites such as sodium, potassium or ammonium hypochlorite, peroxymonosulphuric and peroxydisulphuric acid. The use of 3-chloroperbenzoic acid is preferred. The oxidation is advantageously carried out in an inert solvent, for example, in an aprotic inert solvent such as tetrahydrofuran, dioxan, methylene chloride, chloroform, ethyl acetate or acetone or in a protic solvent such as water, a lower alkanol (e.g. methanol or ethanol) or a lower alkanecarboxylic acid which may be halogenated (e.g. formic acid, acetic acid or trifluoroacetic acid). The oxidation is generally carried out at a temperature in the range of -20°C to +50°C.

When the oxidizing agent is used in equimolar amounts or

in slight excess in relation to the starting material there is mainly obtained the corresponding sulfoxide, i.e. a compound of formula I in which m stands for 1. When the amount of oxidizing agent is increased to double the stoichiometric ratio or more, there is obtained the corresponding sulfone, i.e. a compound of formula I in which m stands for 2. It is also possible to obtain the sulfone from the corresponding sulfoxide by treatment with an equimolar or greater amount of the oxidizing agent. The process conditions are essentially the same as in the manufacture of the sulfoxides.

The cleavage of the amino-protecting group in the substituent R^{30} of a compound IX (or an ester or salt thereof) according to embodiment (g) gives corresponding compounds of formula I (and esters an salts thereof) carrying a free amino group. Possible amino-protecting groups are those employed in peptide chemistry, such as an alkoxycarbonyl group, e.g., t-butoxycarbonyl, etc., a substituted alkoxycarbonyl group, e.g., trichloroethoxy-carbonyl etc., a substituted aralkyloxycarbonyl group, e.g., p-nitrobenzyloxycarbonyl, an aralkyl group such as trityl or benzhydryl or a halogen-alkanoyl group such as chloroacetyl, bromoacetyl, iodoacetyl or trifluoroacetyl.

Preferred protecting groups are t-butoxycarbonyl (t-BOC) and trityl.

The amino protecting groups may be cleaved off by acid hydrolysis (e.g. the t-butoxycarbonyl or trityl group), e.g. aqueous formic acid, or by basic hydrolysis (e.g. the trifluoroacetyl group). The chloroacetyl, bromoacetyl and iodoacetyl groups are cleaved off by treatment with thiourea.

Amino-protecting groups which are cleavable by acid hydrolysis are preferably removed with the aid or a lower

alkanecarboxylic acid which may be halogenated. In particular, formic acid or trifluoroacetic acid is used. The acid hydrolysis is generally carried out at room temperature, although it can be carried out at a slightly higher or slightly lower temperature (e.g. a temperature in the range of about 0°C to +40°C). Protecting groups which are cleavable under basic conditions are generally hydrolyzed with dilute aqueous caustic alkali at 0°C to 30°C. The chloroacetyl, bromoacetyl and iodoacetyl protecting groups can be cleaved off using thiourea in acidic, neutral or alkaline medium at about 0°C-30°C.

In order to manufacture a readily hydrolyzable ester of the carboxylic acids of formula I in accordance with embodiment (h) of the process provided by the present invention, a carboxylic acid of formula I is preferably reacted with a corresponding halide, preferably an iodide, containing the desired ester group. The reaction can be accelerated with the aid of a base such as an alkali metal hydroxide, an alkali metal carbonate or an organic amine such as triethylamine. The esterification is preferably carried out in an inert organic solvent such as dimethylacetamide, hexamethylphosphoric acid triamide, dimethyl sulfoxide or, especially, dimethylformamide. The reaction is preferably carried out at a temperature in the range of about 0-40°C.

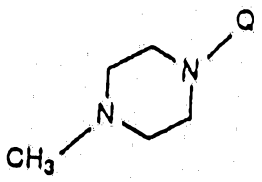
The manufacture of the salts and hydrates of the compounds of formula I or the hydrates of said salts in accordance with embodiment (i) of the process provided by the present invention can be carried out in a manner known per se; for example, by reacting a carboxylic acid of formula I or a salt thereof with an equivalent amount of the desired base, conveniently in a solvent such as water or an organic solvent (e.g. ethanol, methanol, acetone and the like). Correspondingly, salt formation is brought about by the addition of an organic or inorganic salt. The

temperature at which the salt formation is carried out is not critical. The salt formation is generally carried out at room temperature, but it can be carried out at a temperature slightly above or below room temperature, for example in the range of 0°C to +50°C.

The manufacture of th hydrates usually takes place automatically in the course of the manufacturing process or as a result of the hygroscopic properties of an initially anhydrous product. For the controlled manufacture of a hydrate, a completely or partially anhydrous carboxylic acid of formula I or salt thereof can be exposed to a moist atmosphere (e.g. at about +10°C to +40°C).

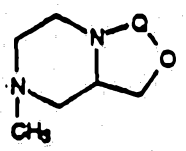
Exemplary of the process for obtaining products in accordance with the invention are the following reaction schemes.

The compound of formula IV, referred to in the schemes, is a substituted piperazine of the formula



IV

in which the piperazine nucleus may be substituted with one or more lower alkyl groups of 1-8, preferably 1-4 carbon atoms. It shall be understood that in these reaction schemes substituted piperazines of the structure



IVa

may similarly be used as starting materials in place of IV.

In the following reaction sequences, R' represents an easily removable amine-protecting group, such as t-butoxycarbonyl; R, R^1 and R^2 are a previously defined. Where a substituent group is present which may be attacked during the reaction it should be in protected form, utilizing well known protecting groups. For example, amino groups may be protected with easily removable protective groups employed in peptide chemistry, such as an alkoxycarbonyl group, e.g., t-butoxycarbonyl, and the like, a substituted alkoxycarbonyl group, e.g., trichloroethoxycarbonyl, and the like, a substituted alkylcarbonyl, e.g., monochloromethylcarbonyl, a substituted aralkyloxycarbonyl group, e.g., p-nitrobenzyloxycarbonyl, or an aralkyl group, e.g., triphenylmethyl.

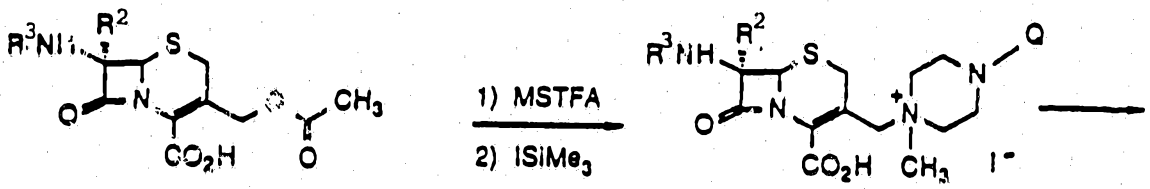
A preferred protecting group is t-butoxycarbonyl (t-BOC) or triphenylmethyl.

As carboxylic acid protecting groups one may utilize an ester form which can be easily converted into a free carboxyl group under mild conditions. The ester protecting group can be, for example, t-butyl, p-nitrobenzyl, benzhydryl, allyl, etc. Also suitable are trimethylsilyl ester groups.

The compounds of formulas X and IIIa, which are starting materials for Schemes IV and V, are known and can be made by established procedures; some are items of commerce, e.g., 7-aminocephalosphoranic acid. See Gordon, E.M., and Sykes, R.B. in "Chemistry and Biology of ß-Lactam Antibiotics," Volume 1, Morin, R.B. and Gorman, M., Editors; Academic Press: New York, 1982; Chapter 3, and references therein, and Ponsford, R.J. et al. in "Recent Advances in the Chemistry of ß-Lactam Antibiotics, Proceedings of the Third International Symposium," Brown A.G. and Roberts, S.M., Editors; Royal Society of Chemistry, Burlington House: London, 1985; Chapter 3, and references therein.

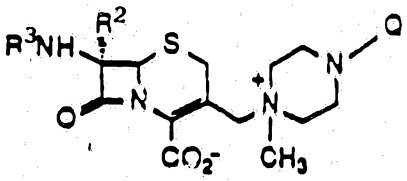
Compounds of formula I with m=O can be converted, if desired, into compounds in which m is 1 or 2 by oxidation according to general methods known in the art, e.g., by reaction with m-chloroperbenzoic acid.

Scheme I



IIIa

Ic

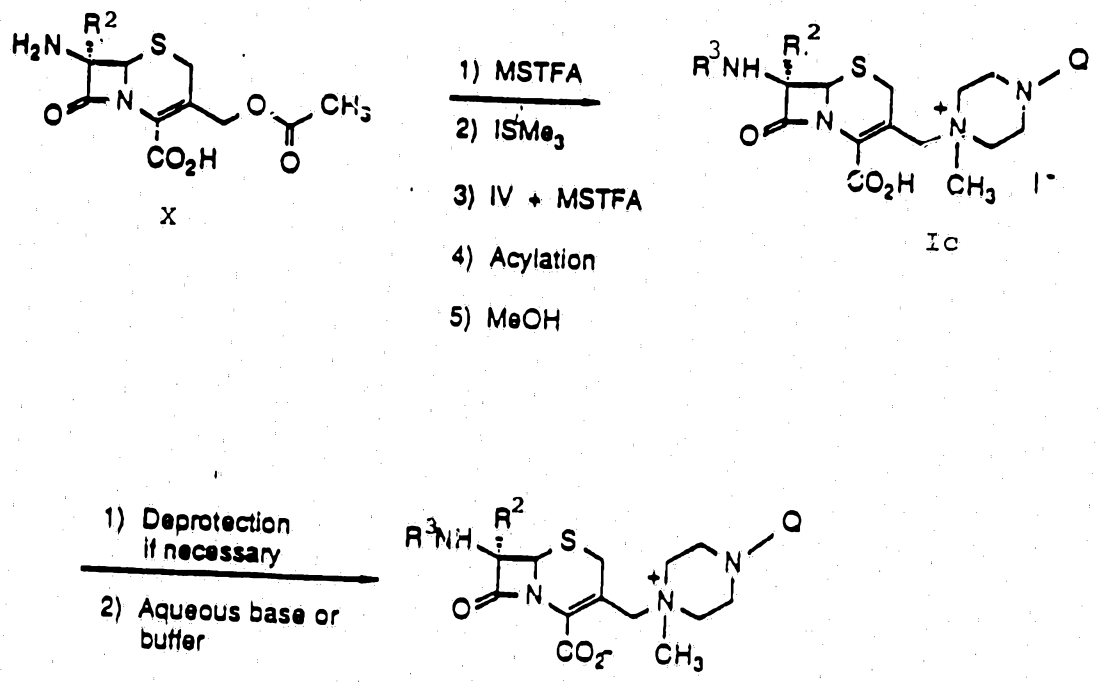


Id

Scheme I

The compound of formula IIIa is initially protected by reaction with a trimethylsilylating agent such as N-methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA) in an inert solvent such as chloroform or methylene chloride. The resulting trimethylsilyl ester, in which all potentially reactive sites, such as amino, hydroxy, and carboxylic acid functions, are protected by trimethylsilyl groups, is then subjected to a reaction with iodotrimethylsilane at about 0°C to room temperature, over a period of about twenty minutes to about two hours. The reaction mixture is then concentrated to dryness under reduced pressure, and the residue is dissolved in a suitable non-hydroxylic solvent such as acetonitrile. A small amount of tetrahydrofuran (THF) is introduced to decompose any residual traces of iodotrimethylsilane. The resulting protected iodo intermediate is then further reacted in situ with a protected form of the piperazine derivative IV which is obtained from IV by treatment with a trimethylsilylating agent such as MSTFA in a compatible solvent such as acetonitrile. The quaternization reaction is conducted at about room temperature over a period of about 30 minutes to 24 hours, preferably about 2 hours. Addition of a hydroxylic solvent such as methanol, with ice-cooling, then causes solvolysis of the trimethylsilyl protecting groups, and the quaternary iodide of formula Ic precipitates. Further treatment under aqueous conditions with a base such as sodium bicarbonate or sodium hydroxide, or with sodium phosphate buffer, converts Ic to the zwitterionic form Id, in which, depending upon the amount of base added, or the pH of the buffer, other acidic functions in the R_3 and Q substituents can be converted to salts.

Scheme II



X

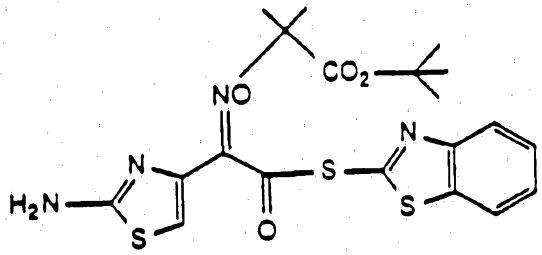
Ic

Id

Scheme II

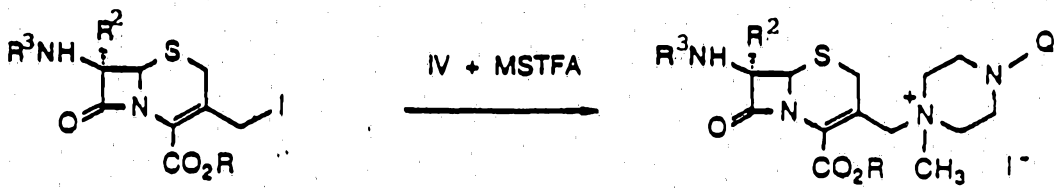
Starting material of structure X is subjected initially to reaction with a trimethylsilylating agent such as MSTFA in an inert solvent such as acetonitrile under anhydrous conditions at room temperature for a period of about 10 minutes to two hours, preferably about 30 minutes. Iodotrimetylsilane is then added and allowed to react for from 15 minutes to three hours, preferably about 30 minutes, at room temperature. A small amount of THF is then added to decompose any residual iodotrimethylsilane. The quaternization step is then carried out by adding a protected form of the piperazine derivative of IV which is obtained from a compound of formula IV by treatment with a trimethylsilylating agent such as MSTFA in a suitable solvent such a acetonitrile. The quaternization reaction is allowed to

proceed for about 30 minutes to 24 hours, preferably about two to four hours, and most preferably at room temperature. Then, an acylating agent consisting of an activated form of a carboxylic acid, for example, a thio ester such as

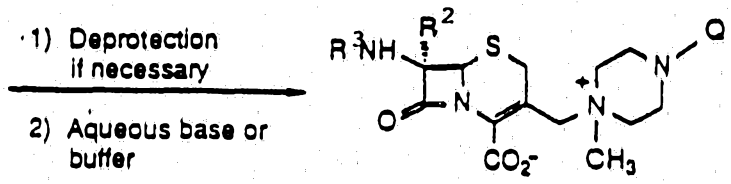


is added. The reaction mixture is then stirred for a period of from 2 to 24 hours. The mixture is then concentrated to dryness under reduced pressure, and the residue is redissolved in acetonitrile. Addition of methanol then solvolyzes the trimethylsilyl protecting groups and precipitates the quaternary iodide of formula Ic. In the case where other protecting groups are present, for example, in the substituent R_3, those protecting groups are then removed by methods known in the art. For example, if a t-butyl ester is present, it is cleaved by treatment with trifluoroacetic acid-anisole. Finally, as in Scheme I, the product of formula Id is obtained after aqueous reaction with a base such as sodium bicarbonate or sodium phosphate buffer.

Scheme III



IIIb Ic

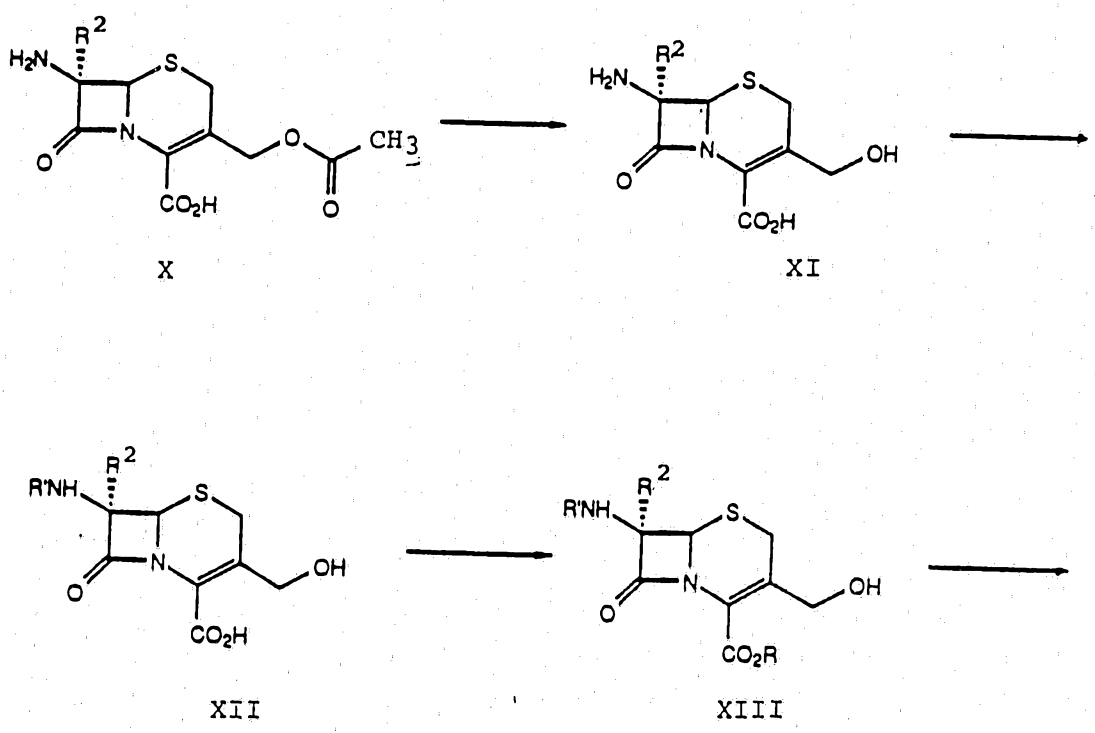


Id

Scheme III

Compounds of formula IIIb which are starting materials for this scheme are prepared by the procedures described in U.S. Patent No. 4,266,049 (R. Bonjouklian, May 5, 1981). In this sequence, the piperazine derivative of formula IV is converted to a protected form by reaction with a trimethylsilylating agent such as MSTFA in a suitable solvent, such as acetonitrile, under anhydrous conditions. Alternatively, conventional protecting groups which are readily removable under mild conditions can be used to protect reactive functionalities in the piperazine derivative of formula IV. For example, a carboxylic acid can be protected as a t-butyl or p-nitrobenzyl ester. The reaction of IIIb with the protected form of IV in an inert solvent such as acetonitrile provides the quaternary iodide Ic. Further treatment as necessary removes the protecting groups; for example, when R is t-butyl, the ester is cleaved with trifluoroacetic acid-anisole. Subsequent treatment with aqueous sodium bicarbonate or sodium phosphate buffer gives a compound of formula I, in which other carboxylic acid functions in R_3 and Q may be converted to salts, depending upon the pH.

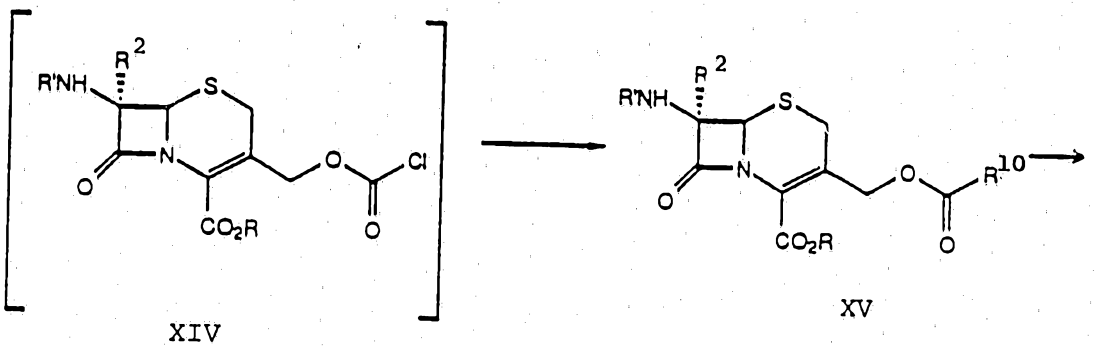
Scheme IV



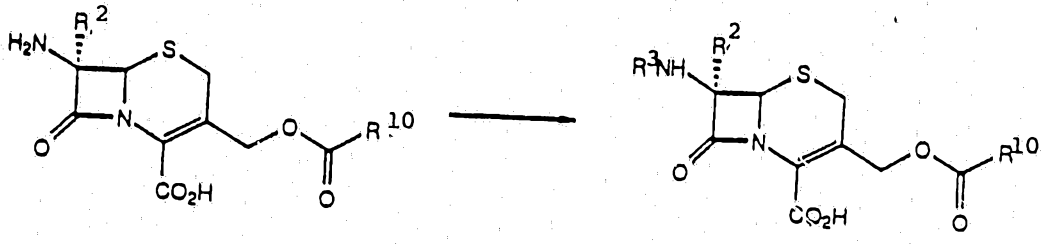
X XI

XII XIII

Scheme IV (cont'd)



XIV XV



IIa Id

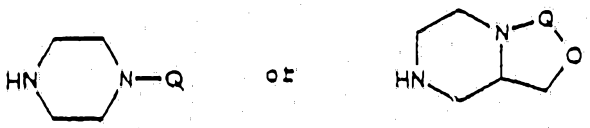
Scheme IV

X → XIII

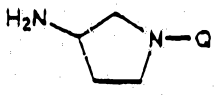
The compound of formula X is hydrolyzed under controlled conditions at -5 to +5°C with aqueous sodium hydroxide to produce compound XI, which is not isolated, but is subjected to further reaction to introduce a readily removable protecting group R' onto the amino nitrogen. For example, reaction with di-t-butyl dicarbonate over a period of from one to four days gives the compound of formula XII, in which R' is t-butoxycarbonyl. Esterification by methods known in the art provides compound XIII, in which R is a protecting group which is readily removable under mild conditions. For example, reaction of compound XII with diphenyldiazomethane gives compound XIII in which R is diphenylmethyl.

XIII → XV

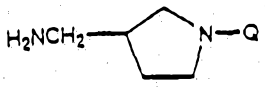
Reaction of compound XIII with phosgene in the presence of a base such as N,N-diisopropylethylamine or triethylamine in an inert solvent such as methylene chloride or chloroform at a temperature of about 0°C to about 30°C gives the intermediate chloroformate ester of formula XIV, with is not isolated, but used in situ. Reaction of compound XIV with a substituted piperazine of the formula



or a substituted pyrrolidineamine of the formula



or a substituted pyrrodinylmethylamine of the formula



where the piperazine or pyrrolidine nucleus may be optionally substituted with one or more lower alkyl groups, and where Q represents a substituted quinolinyl or naphthyridinyl group in which any carboxylic acid function is suitably protected as an ester, e.g. as a p-nitrobenzyl ester which can be easily converted to the free acid by hydrogenolysis, gives the carbamate of formula XV. Alternatively, any carboxylic acid functions in the Q group can be protected as trimethylsilyl esters, and the amino functions of the piperazine, pyrrolidineamine, or pyrrolidinylmethylamine can be trimethylsilylated before reaction with XIV to obtain XV.

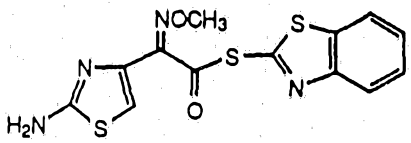
XV → IIa

R', R, and any other protecting groups in R^{10} are then removed by appropriate methods known in the art. More than one reaction may be necessary for this deprotection procedure, depending upon the nature and diversity of protecting groups involved. For example, if R is diphenylmethyl and R' is t-butoxycarbonyl, these groups are removed by reaction with trifluoroacetic acid-anisole at temperature of from 0°C to about room temperature in solvents such as methylene chloride or chloroform. If R^{10} contains, for example, a p-nitrobenzyl ester group, this can be removed by hydrogenolysis in a separate step, preferably prior to removal of R and R'.

IIa → Id

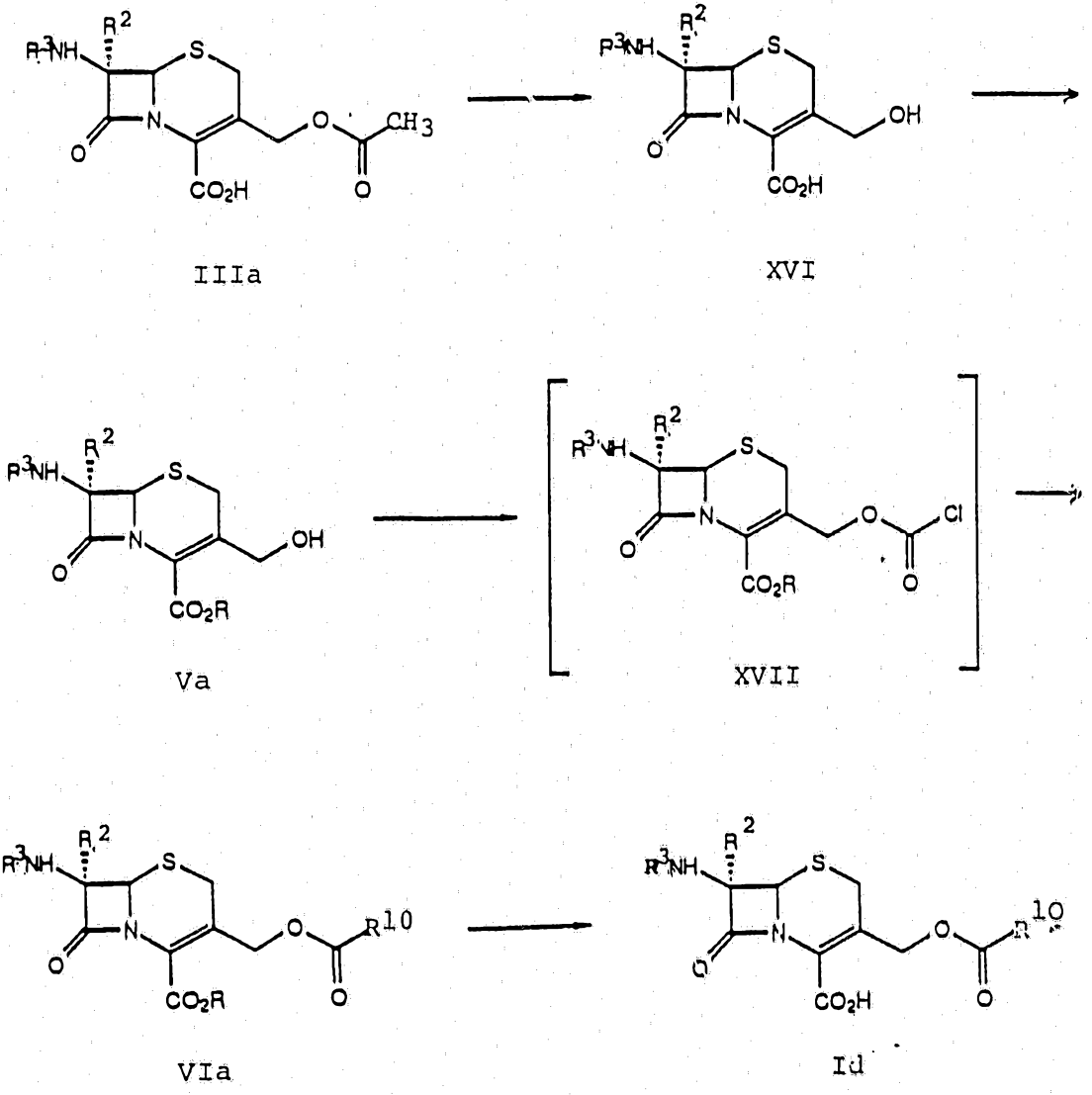
In the final step of Scheme IV the amino group in the compound of formula IIa is acylated by reaction with an

activated carboxylic acid, according to methods known in the art and as described above, in order to introduce R^3 and to obtain compound Id. For example, utilizing suitable solvents such as aqueous acetone or aqueous tetrahydrofuran, compound IIa is subjected to reaction with an acylating agent such as an acid chloride, or a thio ester such as, for example,



in the presence of a base, such as sodium bicarbonate or triethylamine. Reactions are carried out at about 0°C to about 30°C for about 2 to 24 hours. If R^3 itself is introduced in a form which contains protected functionalities, the protecting groups are subsequently removed by appropriate methods known in the art.

Scheme V



Scheme V

IIIa → XVI

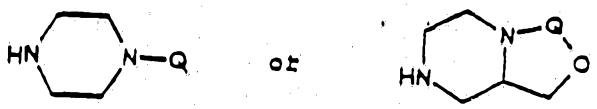
A compound of formula IIIa is hydrolyzed to a compound of formula XVI either with aqueous sodium hydroxide, or enzymatically, by reaction with an esterase such as citrus acetylesterase, or an esterase from Bacterium subtilis, or wheat bran, according to known procedures: See, for example, the following:
H. Peter and H. Bickel, Helvetica Chimica Acta, 57, 2044 (1974); and U.S. Patent 4,406,899. For example, a compound of formula IIIa in which R^2 is H and R^3 is phenylacetyl is hydrolyzed in an aqueous mixture with acetylesterase from orange peel, purchased from Sigma Chemical Company, over a period of about 18 to 72 hours, at room temperature.

XVI → Va

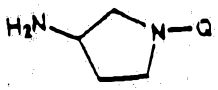
The compound of formula XVI is esterified to obtain compound Va by methods known in the art, e.g., by reaction with diphenyldiazomethane to prepare the diphenylmethyl ester. Also, if group R^3 should contain reactive functionalities, such as an amino group, a suitable protecting group should be introduced before the subsequent step.

Va → VIa

Reaction of the compound of formula Va with phosgene in the presence of a base such as N,N-diisopropylethylamine or triethylamine in an inert solvent such as chloroform, methylene chloride, dioxane, or acetonitrile, at a temperature of about 0 to about 30°C, yields the intermediate chloroformate ester of formula XVII, which is not isolated but utilized in situ. Reaction of compound XVII with a substituted piperazine of the formula



or a substituted pyrrolidineamine of the formula



or a substitute pyrrodinylmethylamine of the formula



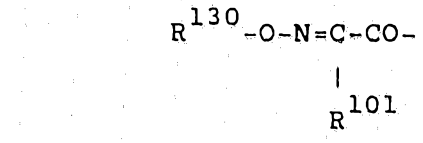
where the piperazine or pyrrolidine nucleus may be optionally substituted with one or more lower alkyl groups, and where Q represents a substituted quinolinyl or naphthyridinyl group in which any carboxyl function is protected as an ester, e.g., as a p-nitrobenzyl ester which can be readily converted to the free acid, gives the carbamate of formula VIa. Alternatively, a carboxylic acid function in the Q group can be protected as a trimethylsilyl ester, and the amino function of the piperazine, pyrrolidineamine or pyrrolidinylmethylamine can be trimethylsilylated before reacting with compound XVII to obtain compound VIa.

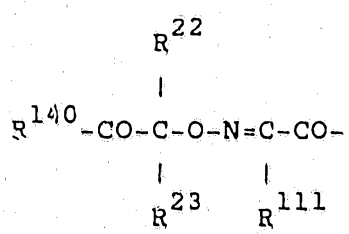
VIa → Id

In the final step of Scheme V, deprotection procedures known in the art are applied to remove R and any other protecting groups in R^{10} and R^{3}. For example, a

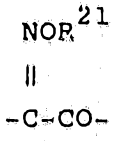
p-nitrobenzyl ester group is removed by hydrolysis, a t-butyl or diphenylmethyl ester group by reaction with trifluoroacetic acid-anisole, and an N-triphenylmethyl (trityl) group by acid hydrolysis, e.g. reaction with aqueous formic acid. The compound of formula Id is obtained.

Compounds of formula I containing the groupings





and



preferably exist as syn-forms. Such syn-forms can be obtained by utilizing starting materials containing this grouping pre-formed in the syn-form. Alternatively, a syn/anti mixture obtained can be separated into the corresponding syn and anti forms in usual manner, e.g. by recrystallization or by chromatographic methods using suitable solvents or solvent mixtures.

The compounds of formula I, their pharmaceutically acceptable salts and esters and hydrates of these compounds possess antibiotic, in particular bactericidal, activity and can be used as agents to combat bacterial infections

(including urinary tract infections and respiratory infections) in mammalian species, for example, dogs, cats, horses, etc., and humans. These compounds exhibit activity against a broad range of both Gram-negative and Gram-positive bacteria.

The in vitro activity of the compounds of the present invention as measured by the Minimum Inhibitory Concentration (MIC) in micrograms/ml utilizing the Broth Dilution Method against a variety of Gram-positive and Gram-negative organisms is as follows:

Compound A: [6R-[6α,7ß(Z)]]-1-[7-[[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]-methyl]-4-[3-carboxy-6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-quinolinyl]-1-methylpiperazinium iodide

Compound B: (6R-trans)-4-[3-carboxy-1-(2-fluoroethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinolin-7-yl]-1-[[2-carboxy-8-oxo-7-[(phenoxyacetyl)amino]-5-thia-1-azabicyclo-[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-piperazinium iodide

Compound C: [6R-[6α,7ß(Z)]]-1-[[7-[[[(2-amino-4-thiazolyl)[1-(1-carboxy-1-methyl)ethoxy]-imino]acetyl]amino]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-en-3-yl]methyl]-4-[3-carboxy-1-(2-fluoroethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinolin-7-yl]-1-methylpiperazinium hydroxide inner salt monosodium salt

Compound D: [6R-[6α,7ß(Z)]]-1-[[7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methyl]-4-(3-carboxy-1-ethyl-6-fluoro-1,4-

dihydro-4-oxo-7-quinolinyl)-1-methylpiperazinium iodide

Compound E: (6R-trans)-4-[3-carboxy-6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-quinolinyl]-1-[[2-carboxy-7-(formylamino)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpiperazinium trifluoroacetate

Table 1

In Vitro MIC (µg/ml), Broth Dilution Method

Culture	Compounds A	B	C	D	E
E. coli ATCC 25922	0.25	0.5	0.25	0.5	0.5
E. coli TEM 1	0.25	0.5	0.5	0.5	0.5
E. cloacae 5699	0.5	0.5	0.5	1	0.5
E. cloacae P99	0.5	0.5	2	1	0.5
S. marcescens 1071	0.5	0.5	0.5	0.5	1
P. aeruginosa 8710	8	8	8	8	8
P. aeruginosa 18 S/H	8	4	8	32	8
E. faecalis ATCC 29212	64	32	32	32	32
S. pneumoniae 6301	0.063	0.25	1	0.063	1
S. aureus 1059B	2	0.5	8	2	0.5
S. aureus 95	4	1	4	4	1
S. aureus ATCC 29213	4	0.5	4	4	0.5

The in vitro activity of the compounds of the present invention as measured by the Minimum Inhibitory Concentration (MIC) in micrograms/ml utilizing the Agar Dilution Method against a variety of Gram-positive and Gram-negative organisms, is as follows:

Compound F: [6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)-(methoxyimino)acetyl]amino]-3-[[[[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid disodium salt.

Compound G: [6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[[[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid disodium salt.

Table 2

in Vitro MIC (µg/ml), Agar Dilution Method

Culture	Compounds F	G
E.coli 257	0.25	0.0625
E.coli ATCC 25922	0.25	0.0625
E.coli TEM-1	0.25	0.0625
Cit. freundii BS-16	0.5	0.125
K. pneumoniae A	0.5	0.0625
Enter. cloacae 5699	0.5	0.125
Enter. cloacae P99	0.5	0.0313
Ser. marcescens SM	0.25	0.125
Ser. marcescens 1071	0.5	0.25
Prot. vulgaris ATCC 6380	0.0625	0.0625
Prot. vulgaris 1028 BC	0.125	0.0625
Prot. mirabilis 90	0.25	0.25
Ps. aeruginosa ATCC 27853	8	1
Ps. aeruginosa 5712	16	4
Ps. aeruginosa 8780	4	2
Ps. aeruginosa 765	8	1
Ps. aeruginosa 18SH	4	1

Staph. aureus Smith	1	0.5
Staph. aureus ATCC 29213	2	1
Staph. aureus 10598	2	1
Staph. aureus 67	4	2
Staph. aureus 753	4	1
Str. pneumoniae 6301	0.0157	0.0157
Str. pyogenes 4	0.0157	0.0157
Str. faecalis ATCC 29212	0.5	0.25

For combatting bacterial infections in mammals a compound of this invention (more precisely, a compound of formula I or a corresponding readily hydrolyzable ester or pharmaceutically acceptable salt or hydrate) can be administered to a mammal in an amount of about 5 mg/kg/day to about 500 mg/kg/day, preferably about 10 mg/kg/day to 100 mg/kg/day, most preferably about 10 mg/kg/day to about 55 mg/kg/day.

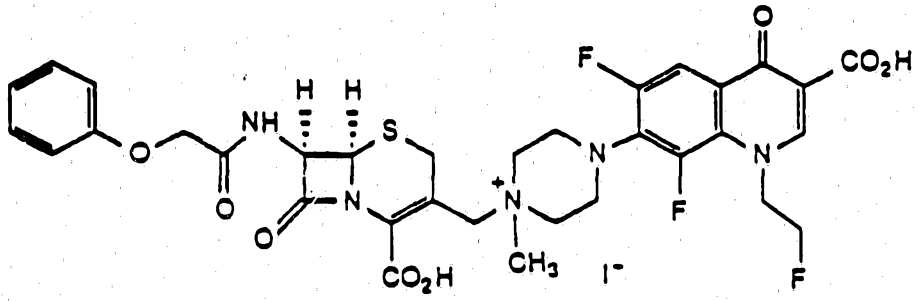
Modes of administration which have been used in the past to deliver penicillins and cephalosporins to the site of the infection are also contemplated for use with the compounds of the present invention. By way of illustration, such methods of administration include parenteral, e.g. intravenous or intramuscular, and enteral, e.g., as a suppository.

The cephalosporin derivatives provided by the present invention can be used as medicaments; for example, in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier material. This carrier material can be an organic or inorganic inert carrier material which is suitable for enteral or parenteral administration such as, for example, water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkyleneglycols, petroleum jelly etc. The pharmaceutical preparations can be made up in solid form (e.g. as tablets, dragées,

suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). The pharmaceutical preparations may be sterilised and/or may contain adjuvants such as preserving, stabilising, wetting or emulsifying agents, salts for varying the osmotic pressure, anaesthetics or buffers. The pharmaceutical preparations can also contain other therapeutically valuable substances. The carboxylic acids of formula I as well as their salts and hydrates are especially suitable for parenteral administration and for this purpose they are preferably made up in the form of lyophilisates or dry powders for dilution with customary agents such as water of isotonic sodium chloride solution as well as solvent aids such as propylene glycol. The readily hydrolyzable esters of formula I are also suitable for enteral administration.

EXAMPLE 1

Preparation of [6R-trans]-4-[3-carboxy-1-(2-fluoroethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinolin-7-yl]-1-[[2-carboxy-8-oxo-7-[(phenoxyacetyl)amino]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methyl]-1-methylpiperazinium iodide

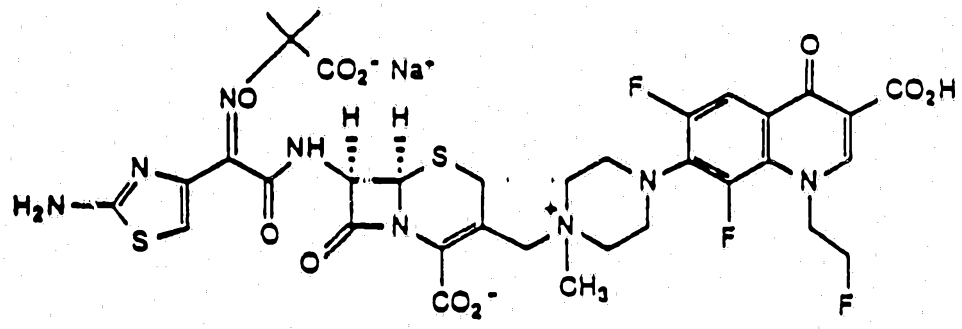


Under an argon atmosphere, a mixture of 406 mg (1 mmol) of [6R-trans]-3-(acetyloxy)methyl]-8-oxo-7-[(phenoxyacetyl)amino]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-2-carboxylic acid, 2 ml of dry methylene chloride and 0.60 ml (3 mmol) of N-methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA) was stirred for one hour; 0.28 ml (2 mmol) of iodotrimethylsilane was then added, and the mixture stirred for 2 hours. The solution was then concentrated to dryness under reduced pressure, and the residual oil dissolved in 2 ml of acetonitrile. Five drops of anhydrous tetrahydrofuran (THF) were added, and the mixture was stirred for 5-10 minutes. A solution prepared from 111 mg (0.3 mmol) of 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, 0.11 ml (0.6 mmol) of MSTFA and 1 ml of acetonitrile was added, and stirring was continued for 2 hours. The mixture was chilled in ice, and approximately 100 mg of methanol were added. The solid which precipitated was filtered, washed with acetonitrile, and dried under reduced pressure to obtain the

title compound: NMR (Me_2SO-d_6) δ 3.15 (s, 3H, NCH_3), 3.45-3.85 (m, 9H, 4 x NCH_2 and CH of SCH_2), 3.95 (d, 1H, J gem = 16.5 Hz, CH of SCH_2), 4.39 and 4.77 (AB, 2H, J gem = 13Hz, NCH_2), 4.61 and 4.64 (AB, 2H, J gem = 15 Hz, OCH_2CO), 4.83-5.07 (m, 4H, NCH_2CH_2F), 5.24 (d, 1H, J = 5Hz, CH), 5.82 (dd, 1H, J = 5 and 7 Hz, CH), 6.95 (d, 2H, J = 8 Hz, Ar), 6.97 (t, 1H, J = 8 Hz, Ar), 7.29 (t, 2H, J = 8 Hz), 7.96 (d, 1 H, J = 12 Hz, Ar), 8.91 (s, 1H, =CH-), 9.18 (d, 1H, J = 7 Hz, NH); IR (KBr) 3400, 1788, 1728, 1700, 1612, cm^{-1}; mass spectrum m/z 716 (cation).

EXAMPLE 2

Preparation of [6R-[6α,7β(Z)]]-1-[[7-[[[(2-amino-4-thiazolyl)[1-(1-carboxy-1-methyl)ethoxyl]imino]acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-4-[3-carboxy-1-(2-fluoroethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinolin-7-yl]-1-methylpiperazinium hydroxide inner salt monosodium salt

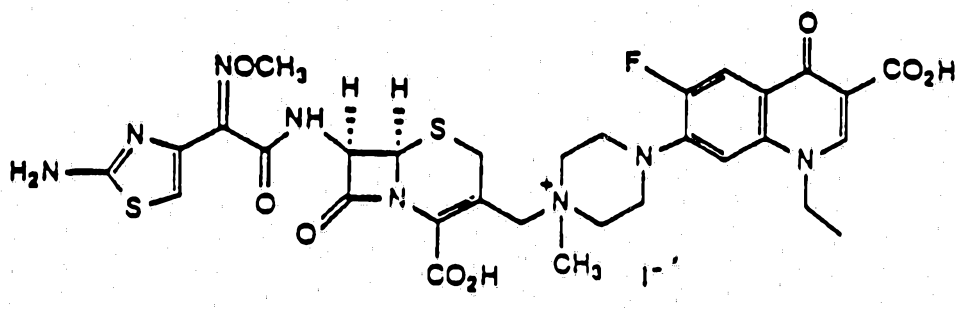


Under an argon atmosphere, a mixture of 5.12 g (8 mmol) of [6R-[6α,7β(Z)]]-3-[(acetyloxy)methyl]-7-[[[(2-amino-4-thiazolyl)[1-(1-carboxy-1-methyl)ethoxy]imino]acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid trifluoroacetic acid salt, 48 ml of dry acetonitrile, and 12 ml (64 mmol) of MSTFA was stirred for 30 minutes; 2.0 ml (14 mmol) of iodotrimethylsilane was added dropwise, and the mixture was stirred for 30 minutes. With momentary cooling in ice, 1.12 ml (14 mmol) of dry THF was added.

After 10 minutes, a solution prepared from 2.27 g (6 mmol) of 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, 24 ml of acetonitrile, and 1.28 ml (7.2 mmol) of MSTFA was added, and the mixture stirred for 1.5 hours. The mixture was concentrated under reduced pressure, and the residual oil was dissolved in 40 ml of acetonitrile. With ice-cooling, 4 ml of methanol were added, resulting in a thick precipitate. After settling for a few minutes, the precipitate was filtered and washed with four 10 ml portions of acetonitrile. After drying the solid was triturated with 60 ml of methanol, filtered and washed with four 10 ml portions of methanol. The solid (5.7 g) thus obtained, was suspended in water, and aqueous sodium bicarbonate was added to bring the pH to 7. The solution of crude product was purified by C_{18} reverse phase HPLC (High Pressure Liquid Chromatography) in three steps First a column of 50 g of Waters C_{18}-silica was used with water followed by 30% acetonitrile in water as eluant. Then, using a 0.025 molar pH 7 buffer-acetonitrile gradient, the product was further purified by HPLC on a Waters Prep 500Å with C_{18} columns. Finally, the product was desalted on a flash column of 60 g of C_{18} silica with water and 20% acetonitrile in water as eluants. After concentrating under reduced pressure to eliminate the organic solvent, and freeze-drying, 1.0 g of the title compound was obtained: NMR (Me_2SO-d6-D_2O) δ 1.37 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.10 (s, 3H, NCH_3), 3.39 and 3.88 (AB, 2H, J gem = 16.5 Hz, SCH_2), 3.40-3.70 (m, 8H, 4 x NCH_2), 4.12 and 5.17 (AB, 2H, J gem = 12.5 Hz, NCH_2) 4.62-4.94 (m, 4H, NCH_2CH_2F), 5.15 (d, 1H, J = 5Hz, CH), 5.73 (d, 1H, J = 5Hz, CH) 6.74 (s, 1H, Ar), 7.83 (d, 1H, J = 12 Hz, Ar), 8.47 (brs, 1H, = CH-); IR (KBr) 3400, 1772, 1618, 1595 cm^{-1}; mass spectrum m/z = 859 $(M + H)^+$.

EXAMPLE 3

Preparation of [6R-[6α,7β(Z)]]-1-[[7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methyl]-4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-methyl-piperazinium iodide

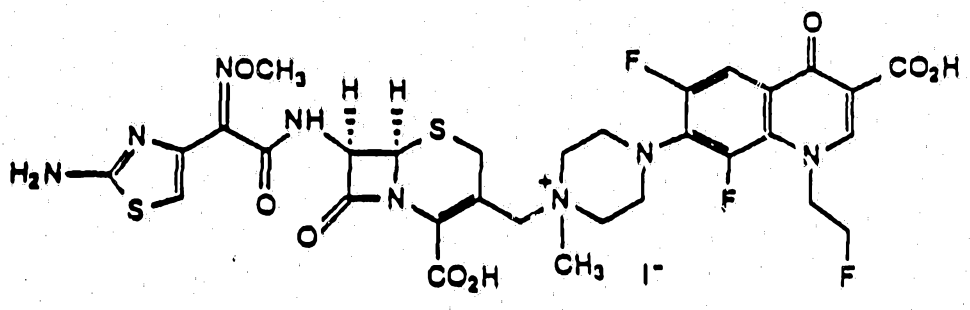


Under an argon atmosphere, a mixture of 273 mg (0.6 mmol) of [6R-[6α,7β(Z)]]-3-[(acetyloxy)methyl]-7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 2 ml of dry methylene chloride, and 0.45 ml (2.4 mmol) of MSTFA was stirred for 2 hours; 0.17 ml (1.2 mmol) of iodotrimethylsilane was added, and stirring was continued for another 2 hours. The mixture was concentrated under reduced pressure, and the residual oil was dissolved in 2 ml of dry acetonitrile. A few drops of dry THF were added and the mixture stirred for 15 minutes. A solution prepared from 60 mg (0.18 mmol) of 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, 1 ml of dry acetonitrile, and 0.07 ml (0.36 mmol) of MSTFA was added, and stirring was continued for 2 hours. Dropwise addition of 125 mg of methanol caused the product to precipitate. The solid was filtered, washed with four 1-ml portions of acetonitrile and dried under reduced pressure. After trituration with methanol and drying under reduced pressure the title compound was obtained: NMR (Me_2SO-d6)

δ 1.45 (brt, 3H, CH_3 of NEt), 3.15 (s, 3H, NCH_3), 3.50-3.95 (m, 9H, 4 x NCH_2 and CH of SCH_2), 3.85 (s, 3H, OCH_3), 3.99 (d, 1H, J gem = 16.5 Hz, CH of SCH_2), 4.43 and 4.70 (AB, 2H, J gem = 14 Hz, NCH_2), 4.61 (brq, 2H, CH_2 of NEt), 5.31 (d, 1H, J = 5 Hz, CH), 5.94 (dd, 1H, J = 5 and 8 Hz, CH), 6.76 (s, 1H, Ar), 7.30 (br, 2H, NH_2), 7.31 (d, 1H, J = 6.5 Hz, Ar), 8.03 (d, 1H, J = 12.5 Hz, Ar), 9.03 (s, 1H, = CH-), 9.68 (d, 1H, J = 8 Hz, NH); IR (KBr) 1785, 1720, 1680, 1628, cm^{-1}; mass spectrum m/z = 729 (cation).

EXAMPLE 4

Preparation of [6R-[6α,7β(Z)]]-1-[7-[[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-4-[3-carboxy-6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-quinolinyl]-1-methylpiperazinium iodide

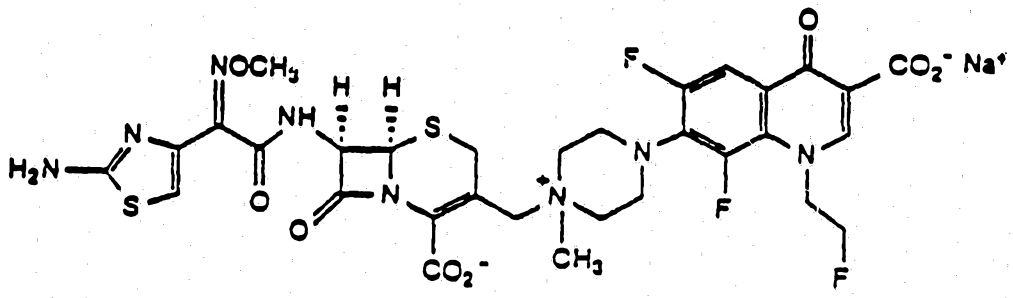


A mixture of 84.6 mg (0.186 mmol) of [6R-[6α,7β(Z)]]-3-[(acetyloxy)methyl]-7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 4 ml of dry methylene chloride, and 0.148 ml (0.8 mmol) of MSTFA was stirred for one hour. To the

resulting solution was added 0.0625 ml (0.46 mmol) of iodotrimethylsilane. The mixture was stirred for 2 hours, and concentrated to dryness under reduced pressure. The residue was dissolved in 2 ml of dry acetonitrile, and a few drops of dry THF were added. The mixture was stirred for 3 minutes, and then a solution prepared from 36.9 mg (0.10 mmol) of 6,8-difluro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid, 0.040 ml (0.215 mmol) of MSTFA, and 2.0 ml of dry acetonitrile was added. The mixture was stirred for 3 hours. After addition of 0.50 ml of methanol, a precipitate formed. The solid was filtered, washed repeatedly with acetonitrile, and dried to obtain 87.5 mg of the title compound: NMR (Me_2SO-d6) δ 3.15 (s, 3H, NCH_3), 3.50-3.90 (m, 9H, 4 x NCH_2 and CH of SCH_2), 3.86 (s, 3H, OCH_3), 3.96 (d, 1H, J gem = 17 Hz, CH of SCH_2), 4.42 and 4.73 (AB, 2H, J gem = 14 Hz, NCH_2), 4.85-5.10 (m, 4H, NCH_2CH_2F), 5.29 (d, 1H, J = 5 Hz, CH), 5.93 (dd, 1H, J = 5 and 7 Hz, CH), 6.86 (s, 1H, Ar), 7.24 (s, 2H, NH_2), 7.98 (d, 1H, J = 12 Hz, Ar), 8.94 (s, 1H = CH-), 9.67 (d, 1H, J = 7Hz, NH); IR (KBr) 3420, 1775, 1720, 1675, 1618 cm^{-1}.

EXAMPLE 5

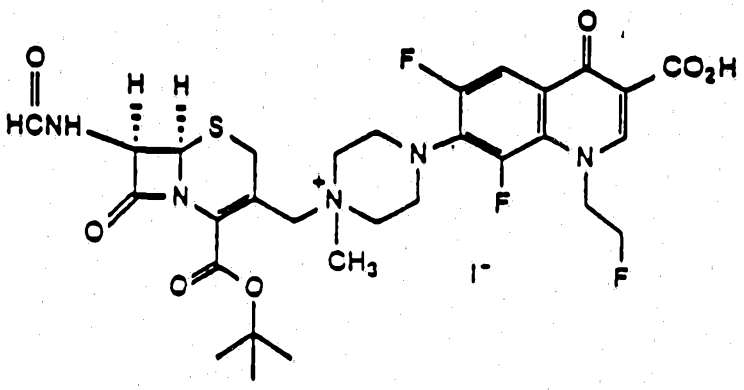
Preparation of 6R-[6α,7β(Z)]-1-[7-[[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-4-[3-carboxy-6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-quinolinyl]-1-methylpiperazinium hydroxide inner salt monosodium salt



A suspension of 900 mg of the compound prepared in Example 4 in water was neutralized with 0.1 N aqueous sodium hydroxide, and the resulting solution was freeze-dried. The residue was purified by C_{18} reverse phase HPLC on a Waters Prep 500Å, eluting with a water-acetonitrile gradient (0-40%). Evaporation and lyophilization of the appropriate fractions afforded 344 mg of the title compound: NMR (Me_2SO-d6) δ 3.10 (s, 3H, NCH_3), 3.40-3.76 (m, 9H, 4 x NCH_2 and CH of SCH_2), 3.84 (d, 1H, J = 16 Hz, CH of SCH_2), 3.84 (s, 3H, OCH_3), 4.10 and 5.19 (AB, 2H, J gem = 14Hz), 4.70-4.94 (m, 4H, NCH_2CH_2F), 5.13 (d, 1H, J = 5Hz, CH), 5.65 (dd, 1H, J = 5 and 7Hz, CH), 6.74 (s, 1H, Ar), 7.23 (s, 2H, NH_2), 7.82 (d, 1H, J = 12Hz, Ar), 8.55 (s, 1H, =CH-), 9.58 (d, 1H, J = 7Hz, NH); IR (KBr) 3410, 1772, 1665, 1618 cm^{-1}; mass spectrum m/z 787 $(M + H)^+$.

EXAMPLE 6

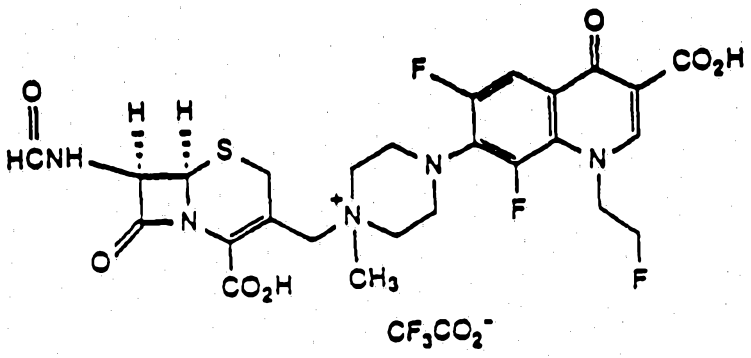
Preparation of (6R-trans)-4-[3-carboxy-6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-quinolinyl]-1-[[2-(1,1-dimethylethoxy)carbonyl-7-(formylamino)-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methyl]-1-methylpiperazinium iodide



A mixture of 0.87 g (2.35 mmol) of 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, 0.51 ml (2.6 mmol) of MSTFA and 5 ml of dry acetonitrile was stirred for 30 minutes; 1.00 g of [6R(6α,7ß]-7-formylamino-3-iodomethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1,1-dimethylethyl ester was added, and stirring was continued for 24 hours. The resulting precipitate was filtered and discarded. The mother liquor was absorbed onto a column of 5 g of C_{18}-silica. After elution with water, 10%- and 20%- aqueous methanol the appropriate fractions were combined and concentrated under reduced pressure to yield a precipitate. After filtration and drying 380 mg of the title compound was obtained: IR (KBr) 3440, 1785, 1720, 1610 cm^{-1}; mass spectrum m/z = 666 (cation).

EXAMPLE 7

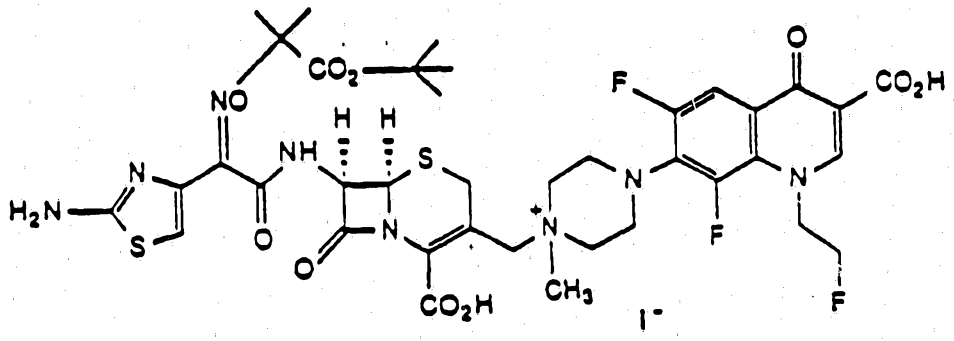
Preparation of (6R-trans)-4-[3-carboxy-6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-quinolinyl]-1-[[2-carboxy-7-(formylamino)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]-methyl]-1-methylpiperazinium trifluoroacetate salt



A mixture of 200 mg of the compound from Example 6, 0.2 ml anisole, and 2.5 ml of trifluoroacetic acid was stirred for 3 hours at room temperature. After filtration of the insoluble portion, the solution was concentrated under reduced pressure. The residue was dissolved in 10 ml of acetonitrile, and 200 ml of ether was added to precipitate the product. After filtration and drying, 135 mg of the title compound was obtained: NMR (Me_2SO-d6) δ 3.14 (s, 3H, NCH_3), 3.50-3.85 (m, 9H, 4 x NCH_2 and CH of SCH_2), 3.95 (d, 1H, J gem = 16.5 Hz, CH of SCH_2), 4.35 (d, 1H, J gem = 13Hz, CH of NCH_2), 4.82-5.05 (m, 5H, NCH_2CH_2F and CH of NCH_2), 5.23 (d, 1H, J = 5Hz, CH), 5.84 (dd, 1H, J = 5 and 7Hz, CH), 7.96 (d, 1H, J = 13Hz, Ar), 8.17 (s, 1H, NCHO), 8.92 (s, 1H, =CH-), 9.11 (d, 1H, J = 7Hz, NH); IR 3400, 1780, 1720, 1685 cm^{-1}; mass spectrum m/z = 610 (cation).

Example 8

Preparation of [6R-[6α,7β(Z)]]-1-[[7-[[(2-amino-4-thiazolyl)[[1,1-dimethyl-2-(1,1-dimethylethoxy)-2-oxoethoxy]imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-en-3-yl]methyl]-4-[3-carboxy-(2-fluoroethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinolin-7-yl]-1-methyl-piperazinium iodide

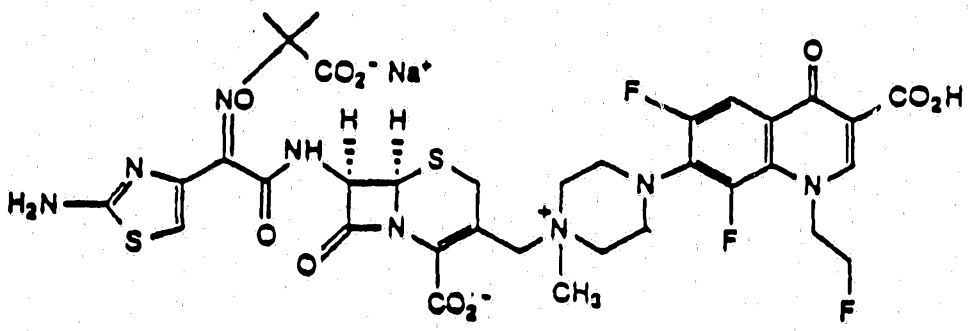


Under an argon atmosphere, a mixture of 272 mg (1 mmol) of 7-aminocephalosporanic acid, 0.67 ml (3.6 mmol) of MSTFA and 3 ml of dry acetonitrile was stirred for 30 minutes; 0.25 ml (1.75 mmol) of iodotrimethylsilane was then added and stirring was continued for another 30 minutes. The mixture was cooled momentarily, and 0.14 ml (1.75 mmol) of anhydrous THF was added. After 10 minutes, a solution prepared from 277 mg (0.75 mmol) of 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, 0.17 ml (0.9 mmol) of MSTFA and 3 ml of dry acetonitrile was added. Stirring at room temperature was continued for 2.5 hours; 478 mg (1 mmol) of 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-benzothiazolyl)thio]-2-oxoethylidene]amino]oxy]methylpropanoic acid 1,1-dimethylethyl ester and 4 ml of dry acetonitrile were added, and the mixture was stirred overnight. After filtration to remove a small amount of insoluble solid, the mixture was concentrated to dryness under reduced pressure. The residual oil was redissolved in 4 ml of acetonitrile, and with ice cooling, 0.16 ml of methanol was added. After stirring for one minute and standing for 3 minutes, the precipitated solid was filtered. After washing with three 3-ml portions of acetonitrile and drying under reduced pressure 530 mg of the title compound was obtained: NMR (Me_2SO-d6), δ 1.36 (s, 12H, t-Bu and CH_3), 1.40 (s, 3H, CH_3), 3.12 (s, 3H, NCH_3), 3.40-3.86 (m, 9H, 4 x

NCH_2 and CH of SCH_2), 3.96 (d, 1H, J gem = 16Hz, CH of SCH_2), 4.40-4.66 (AB, 2H, J gem = 13Hz, NCH_2), 4.62-5.06 (m, 4H, NCH_2CH_2F), 5.26 (d, 1H, J = 5Hz, CH), 5.93 (dd, 1H, J = 5 and 7Hz, CH), 6.68 (s, 1H, Ar), 7.25 (s, 2H, NH_2), 7.92 (d, 1H, J = 12Hz, Ar), 8.88 (s, 1H, =CH-), 9.44 (d, 1H, J = 7Hz, NH).

Example 9

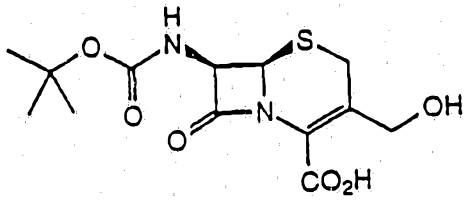
Alternate Synthesis of [6R-[6α,7β(Z)]]-1-[[7-[[[(2-amino-4-thiazolyl)[1-(1-carboxy-1-methyl)ethoxy]imino]acetyl]-amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-4-[3-carboxy-1-(2-fluoroethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinolin-7-yl]-1-methylpiperazinium hydroxide inner salt monosodium salt



A solution of 102 mg of the compound prepared in Example 8 in 0.4 ml of anisole, 1.5 ml of methylene chloride and 1.5 ml of trifluoroacetic acid was kept overnight at 0°C. After filtering, concentrating to dryness under reduced pressure, adding methylene chloride and again concentrating to dryness the residue was triturated with ether to obtain a solid. The solid was dissolved in aqueous sodium phosphate buffer of pH 7 and purified by reverse phase HPLC to obtain the title compound having an NMR spectrum similar to that of the product obtained by the previously described route (Example 2).

EXAMPLE 10

Preparation of (6R-trans)-3-hydroxymethyl-7-[[(1,1-dimethylethoxy)carbonyl]amino]-8-oxo-5-thia-1-azabicyclo [4,2,0]oct-2-ene-2-carboxylic acid

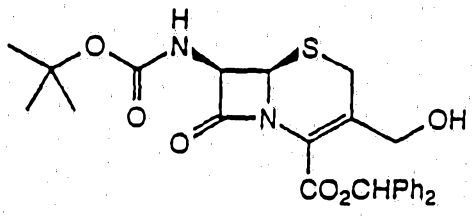


A solution of 19.2 g (0.48 mol) of sodium hydroxide in 240 ml of water was stirred and cooled to -5°C in a bath of dry-ice and acetone. All at once, 54.4g (0.20 mol) of 7-aminocephalosporanic acid was added. The reaction temperature was controlled at -5 to 0°C by raising and lowering the bath as necessary, until the initial heat of reaction was dissipated. Then the cold bath was replaced with an ice bath and stirring was continued at 0-5°C for the remainder of a total reaction time of 30 minutes. The pH was adjusted to 9-9.5 by addition of approximately 2 ml of 6 N aqueous hydrochloric acid. Dioxane (700 ml) was added followed by a solution of 87.5 g (0.40 mol) of di-t-butyl dicarbonate in 200 ml of dioxane, added all at once. Sodium bicarbonate (33.6 g, 0.40 mol) was added, and the mixture stirred for 70 hours. Ethyl acetate (750 ml) was added, the layers were separated, and the organic phase was extracted with water (2 x 125 ml). The combined aqueous phase and extracts was washed with ethyl acetate (2 x 300 ml). Then the aqueous solution was layered with 750 ml of ethyl acetate, and 80 ml of 6 N aqueous HCl was added to bring the

pH to 2.5. A precipitate formed which was removed by filtration through a bed of Hyflo. The aqueous phase was separated and extracted with 300 ml of ethyl acetate. The organic extracts were combined, washed with 300 ml of water, dried (Na_2SO_4), and concentrated under reduced pressure to about 100 ml of volume. As the volume was reduced, solid material began to precipitate. The precipitate was filtered and washed with ether. The product was dried under reduced pressure; 24.1 g (36%) of the title compound was obtained. This was used directly in the next Example.

EXAMPLE 11

Preparation of (6R-trans)-3-hydroxymethyl-7-[[(1,1-dimethylethoxy)carbonyl]amino]-8-oxo-5-thia-1-azabicyclo-[4,2,0]oct-2-ene-carboxylic acid diphenylmethyl ester

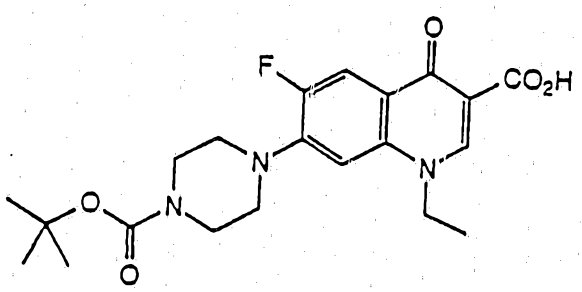


A suspension of 44.67 g (0.135 mol) of the product (hydroxy acid) from Example 10 in 270 ml of dry tetrahydrofuran (THF) was stirred mechanically. A solution of 32.51 g (0.167 mol) of diphenyldiazomethane in 390 ml of n-hexane was added, and the mixture was stirred vigorously for 20 hours. The precipitate was filtered, washed with n-hexane, and dried under reduced pressure to obtain 45.74 g

(68.2%) of the title compound: ^{1}H NMR (Me_2SO-d_6) δ1.41 (s, 9H), 3.59 (s, 2H), 4.22 (t, J=6Hz, 2H), 5.08 (d, J=5Hz), 5.51 (dd, J=5 and 8 Hz, 1H), 6.88 (s, 1H), 7.26-7.51 (m, 10H), 8.03 (d, J=8Hz, 1H).

EXAMPLE 12

Preparation of 1-ethyl-6-fluoro-1,4-dihydro-7-[4-[(1,1-dimethylethoxy)carbonyl]-1-piperazinyl-4-oxo-3-quinoline carboxylic acid

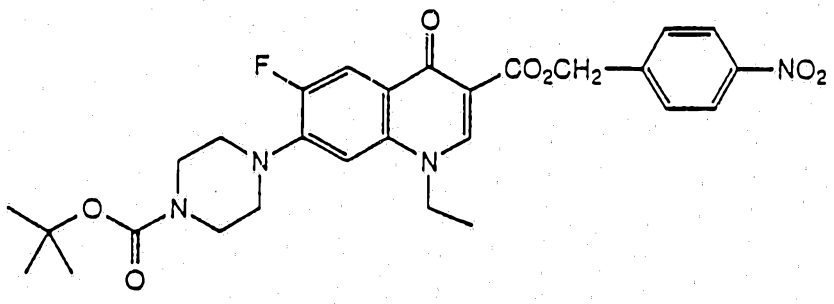


To a stirred suspension of 24.0 g (0.075 mol) of 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolone-carboxylic acid in 240 ml of dioxane were added 130 ml of water and 80 ml (0.080 mol) of 1N aqueous sodium hydroxide. The mixture was heated at 100°C for approximately 30 minutes until a clear solution resulted. The solution was cooled to 0°C, and a solution of 19.2 g (0.088 mol) of di-t-butyl dicarbonate in 50 ml of dioxane was added. The mixture was stirred at 0°C for 30 minutes and then for a further three hours at ambient temperature. The resulting precipitate was filtered and suspended in 520 ml of 10% aqueous acetic acid. The mixture was heated to 100°C briefly, and then allowed to cool before filtering the product. After drying under reduced pressure over P_2O_5 27.0 g (86%) of the title compound was obtained; ^{1}H NMR (Me_2SO) δ1.39

(t,3H, J=7Hz), 1.40 (S, 9H), 3.25 (m, 4H), 3.48 (m, 4H), 4.54 (q,2H, J=7Hz), 7.08 (d, 1H, J_{HF}=7.5Hz), 7.91 (d, 1H, J_{HF}=14Hz), 8.94 (s,1H).

EXAMPLE 13

Preparation of 1-ethyl-6-fluoro-1,4-dihydro-7-[4-[(1,1-dimethylethoxy)carbonyl]-1-piperazinyl]-4-oxo-3-quinoline-carboxylic acid (4-nitrophenyl)methyl ester

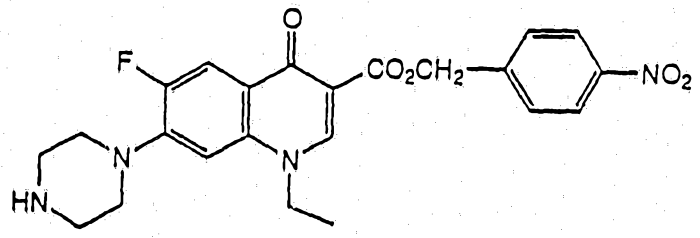


To a stirred suspension of 1.0 g (2.4 mmol) of the N-t-Boc product of the previous procedure (Example 12) in 40 ml of water were added 2.5 ml (2.5 mmol) of 1N aqueous sodium hydroxide. The mixture was warmed until complete solution occurred. The solution was filtered and freeze-dried to afford the sodium salt, which was dissolved in 10 ml of dimethylformamide (DMF) and stirred for 2 hours with 4Å molecular sieves; 0.55 g (2.5 mmol) of 4-nitrobenzyl bromide was then added. The mixture was stirred for three days. The sieves were removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, methylene chloride: ethyl acetate 1:2 as elutant) to afford 1.0 g (77%) of the title compound as a white solid: ^{1}H NMR($CDCl_3$), δ1.46 (s, 9H), 1.52 (t, 3H, J=7.5 Hz), 1.57 (s, 3H), 3.17 (m, 4H), 3.62 (m, 4H), 4.18 (q, 2H, J=7.5 Hz),

5.46 (s, 2H), 6.74 (d, 1H, J_{HF}=7Hz), 7.71 (d, 2H, J=8.5Hz), 8.12 (d, 1H, J_{HF}=13Hz), 8.23 (d, 2H, J=8.5Hz), 8.45 (s,1H).

EXAMPLE 14

Preparation of 1-ethyl-6-fluoro-1,4-dihydro-oxo-7-(1-piperazinyl)-3-quinolonecarboxylic acid (4-nitrophenyl)-methyl ester

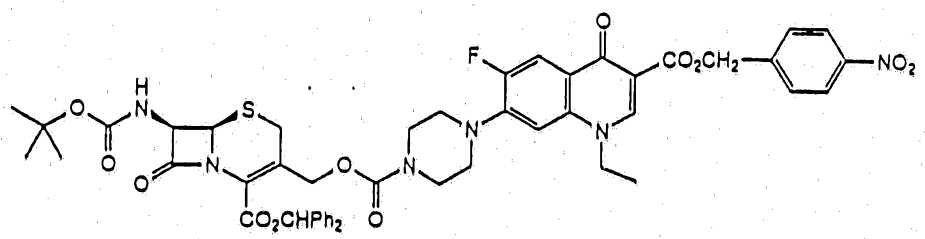


A mixture of 10 g (0.018 mol) of the N-t-Boc (4-nitrophenyl)methyl ester prepared as in Example 13, 40 ml of anisole, and 40 ml of trifluoroacetic acid was stirred at 0°C for 3 hours. The mixture was concentrated to dryness under reduced pressure; the residue was triturated with ether (2 x 100 ml). The ether extract was washed with water (2 x 100 ml) and the water washings combined with the residue from the trituration. Aqueous 1N NaOH was added to adjust the pH to 11, and the product was extracted with methylene chloride (7 x 100 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated to yield 7.70 g (95%) of the title compound: ^{1}H NMR ($CDCl_3$) δ1.57 (t, 3H, J=7.5 Hz), 3.11 (m,4H) 3.24 (m,4H), 4.23 (q, 2H, J=7.5 Hz), 5.51 (s, 2H), 6.78 (d, 1H, J_{HF}=7Hz), 7.75 (d, 2H, J=8.5 Hz), 8.15 (d, 1H, H_{HF}=14Hz, 8.26 (d, 2H,

J=8.5 Hz), 8.49 (s, 1H).

EXAMPLE 15

Preparation of (6R,trans)-3-[[[[4-[1-ethyl-6-fluoro-1,4-dihydro-3-[[(4-nitrophenyl)methoxy]carbonyl]-4-oxo-7-quinolinyl]-1-piperazinyl]carbonyl]oxy]methyl]-7-[[(1,1-dimethylethoxy)carbonyl]amino]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid diphenylmethyl ester



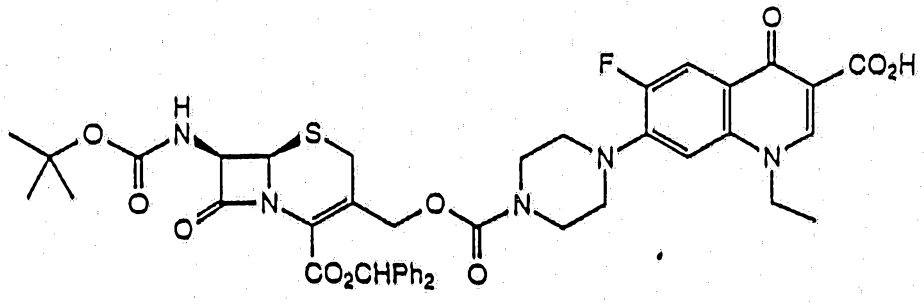
Under an argon atmosphere, a solution of 2.00 ml (3.84 mmol) of 20% phosgene in toluene and 68 ml of dry methylene chloride was cooled to 3-4°C. A solution of 1.71 g (3.44 mmol) of (6R-trans)-3-hydroxymethyl-7-[[(1,1-dimethylethyoxy)carbonyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid diphenylmethyl ester (Example 11) in 30 ml of methylene chloride was then added, along with 0.66 ml (3.85 mmol) of N,N-diisopropylethylamine and 5 ml of methylene chloride wash. The mixture was stirred cold for 15 minutes, and then for two hours at room temperature. The resulting solution was added to a solution prepared from 1.88 g (4.14 mmol) of 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid (4-nitrophenyl)-methyl ester (Example 14), 0.71 ml (4.15 mmol) of N,N-diisopropylethyl-amine and 68 ml of methylene chloride. After stirring under argon for 2 1/2 to 3 hours

the solution was concentrated under reduced pressure to a volume of approximately 20 ml and applied directly to a 5.0 x 14 cm silica column for chromatographic purification under pressure. The column was eluted first with 20 ml of methylene chloride, and then with ethyl acetate, collecting fractions of 20-25 ml each. Fractions 26-30, containing pure product, were combined and concentrated to dryness under reduced pressure to obtain a residue of 0.716 g. Fractions 31-55 were re-chromatographed and the additional pure product obtained combined with the above residue to provide a total of 1.125 g (33.5% yield) of the title compound : IR (KBr) 1789, 1712, 1622 cm^{-1}.

Anal. Calcd. for $C_{50}H_{49}N_6O_{12}FS$: C, 61.47; H,5.06; N,8.60; S, 3.28; F, 1.94. Found: C, 61.23; H, 5.03; N, 8.50; S, 3.35; F, 1.65.

EXAMPLE 16

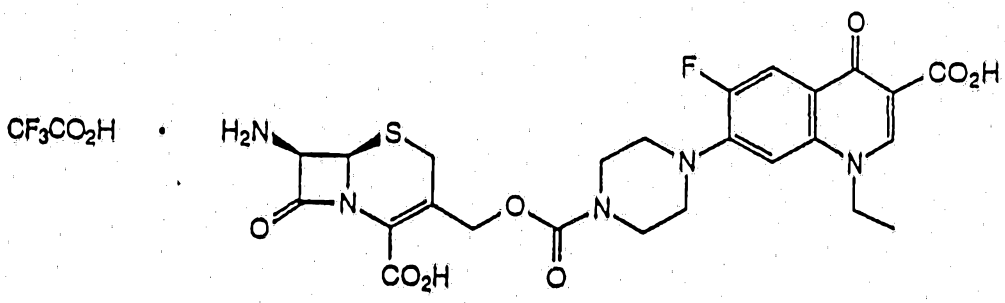
Preparation of (6R,trans)-3-[[[[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl]-1-piperazinyl]carbonyl]oxy]methyl]-7-[[(1,1-dimethylethoxy)carbonyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid diphenylmethyl ester



A mixture of 1.125 g (1.15 mmol) of the p-nitrobenzyl ester from Example 15, 1.54 g of 10% Pd on carbon catalyst and 115 ml of dry THF (distilled from sodium benzophenone ketyl) was stirred under hydrogen at atmospheric pressure for approximately three hours. After filtration of the catalyst the solvent was evaporated under reduced pressure. The residue was purified chromatographically on a 2.2 x 11 cm silica column using ethyl acetate followed by EtoAc-acetone-MeOH-water (70:5:2.5:2.5) as eluant. The appropriate fractions were combined and concentrated to dryness under reduced pressure to obtain 0.817 g (86.3% yield) of the title compound: IR(KBr) 1785, 1715, 1625, 698 cm^{-1}.

EXAMPLE 17

Preparation of (6R,trans)-7-amino-3-[[[[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid trifluoroacetic acid salt

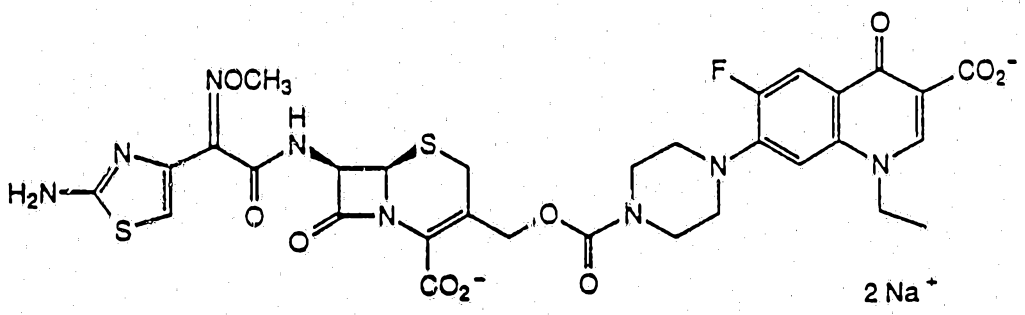


A solution of 0.811 g (0.963 mmol) of the diphenylmethyl ester prepared in Example 16 and 1.80 ml of anisole in 15 ml of dry methylene chloride was cooled to 0°C under an atmosphere of argon; 11.8 ml of cold trifluoroacetic acid

was then added and the mixture was stirred at 0°C for 2 hours. The mixture was then concentrated under reduced pressure at 0-5°C. Methylene chloride (5ml), ethyl acetate (20 ml), and ether (60 ml) were added to the residue. The mixture was stirred 5-10 minutes before filtering the solid and washing with ether. After drying under reduced pressure, 0.591 g (89.0% yield) of the title compound was obtained.

EXAMPLE 18

Preparation of [6R[6α,7β(z)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[[[4-(3-carboxyl-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl]-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid disodium salt

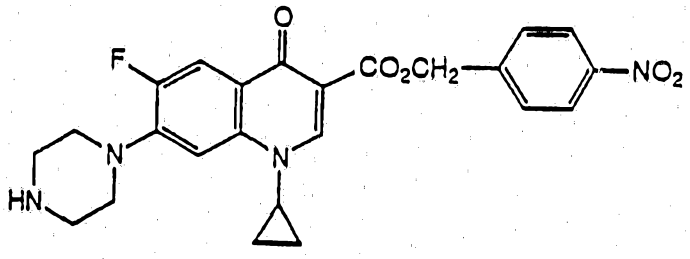


A mixture of 59.4 mg (0.086 mmol) of the trifluoroacetic acid salt prepared in Example 17 and 1.5 ml of THF was stirred and cooled at 0-5°C. A solution of 26.0 mg (0.309 mmol) of sodium bicarbonate in 2 ml of water was added, followed by a solution of 38.0 mg (0.108 mmol) of (Z)-2-amino-α-(methoxyimino)-4-thiazoleethanethioic acid S-2-benzothiazolyl ester in 0.75 ml of THF. The cooling bath was removed after 25 minutes, and the reaction mixture

was stirred for 16.5 hours. Under reduced pressure the mixture was concentrated to remove THF. The remaining aqueous solution was washed with ethyl acetate and then adjusted to pH 7.55 by the addition of 0.025 molar aqueous sodium dihydrogen phosphate solution before chromatographing on a column of 1.75 g of C_{18}-silica (from Waters). The product was eluted using a step-wise gradient of 0.025 molar sodium phosphate buffer-acetonitrile containing from 0 to 30% of acetonitrile. The appropriate fractions were combined and partially evaporated under reduced pressure to remove acetonitrile. Acidification to pH 2 with 1N aqueous HCl gave a precipitate which was centrifuged, and twice washed with water, centrifuging each time. The precipitate was dissolved in water by adding sodium bicarbonate to bring the pH to 7.5. Adding acetone caused the sodium salt to precipitate. The product was isolated and washed with acetone by centrifuging. After drying under reduced pressure, 36.2 mg of the title compound was obtained: IR(KBr) 3420, 1762, 1675, 1622 cm^{-1}; mass spectrum (FAB) m/z 803 $(M+H)^+$

EXAMPLE 19

Preparation of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid (4-nitrophenyl) methyl ester

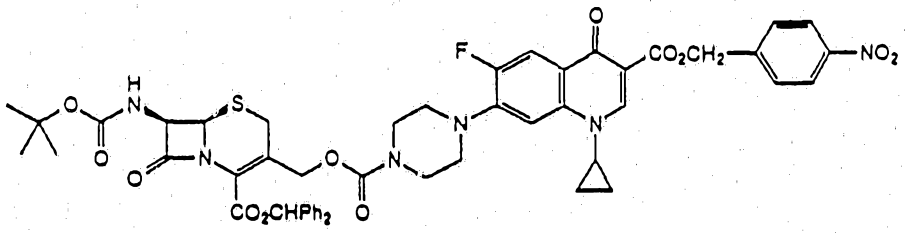


This compound was prepared from 1-cyclopropyl-6-fluoro-

-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid using procedures similar to those above described (in Examples 12, 13, and 14) for the synthesis of 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl-3-quinolinecarboxylic acid (4-nitrophenyl)methylester.

EXAMPLE 20

Preparation of (6R,trans)-[[7-(1,1-dimethylethoxy)carbonyl]-amino]-3-[[[[4-[1-cyclopropyl-6-fluoro-1,4-dihydro-3-[[(4-nitrophenyl)methoxy]carbonyl]-4-oxo-7-quinolinyl]-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid diphenylmethyl ester

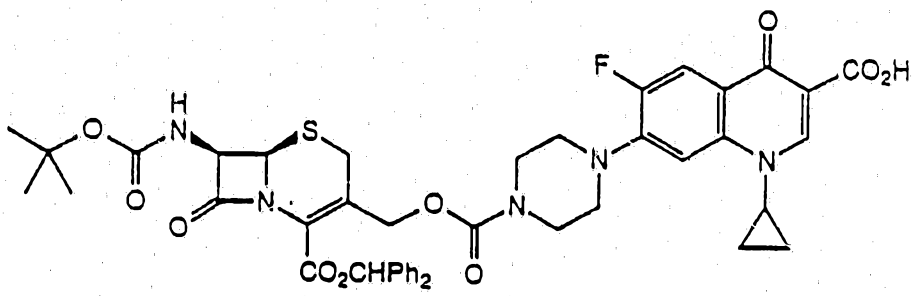


Under an argon atmosphere, a solution of 0.58 ml (1.12 mmol) of 20% phosgene in toluene and 20 ml of methylene chloride was cooled at 0-5°C. A solution of 0.497 g (1 mmol) of (6R-trans)-3-hydroxymethyl-7-[[(1,1-dimethyl-ethoxy)carbonyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid diphenylmethyl ester in 8 ml of methylene chloride was added along with 0.195 ml (1.14 mmol) of N,N-diisopropylethylamine. The mixture was stirred for 15 minutes at 0-5°C before removing the ice bath. Stirring was continued for one hour and 40 minutes at ambient temperature. The resulting solution was added to a solution of 0.550 g (1.18 mmol) of 1-cyclopropyl-6-fluoro-1,4-dihydro-

-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid (4-nitrophenyl)methyl ester and 0.205 ml (1.20 mmol) of N,N-diisopropylethylamine in 17 ml of methylene chloride. The mixture was stirred at room temperature under argon for three hours and five minutes. The mixture was then concentrated and purified by flash chromatography on 29 g of silica gel in a column approximately 2.2 cm in diameter. The mixture was applied to the column as a solution in methylene chloride and was eluted with ethyl acetate-n-hexane and then ethyl acetate. The appropriate fractions were combined and concentrated to dryness under reduced pressure to provide 0.425 g (42.9%) of the title compound: IR (KBr) 1789, 1720, 1622, 1520, 1345, 702 cm^{-1}; mass spectrum (FAB) m/z 989 $(M+H)^+$.

EXAMPLE 21

Preparation of (6R-trans)-3-[[[[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-7-[[(1,1-dimethylethoxy)carbonyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid diphenylmethyl ester



A mixture of 0.414 g (0.418 mmol) of the p-nitrobenzyl

ester (prepared in Example 20), 0.602 g of 10% Pd on carbon catalyst, and 40 ml of THF (distilled from sodium benzophenone ketyl) was hydrogenated at atmospheric pressure over a period of about 3.5 hours. After filtration of the catalyst the solvent was evaporated under reduced pressure. The residue was chromatographically purified on a Chromatron Model 7924 preparative, centrifugally-accelerated, radial Thin Layer Chromatography (TLC) apparatus, using ethyl acetate followed by ethyl acetate-acetone-methanol-water (70:10:5:5) as eluant, to obtain 251.6 mg (70.4%) of the title compound: IR (KBr) 1788, 1720, 1628, 702 cm^{-1}; mass spectrum (FAB) m/z 854 $(M + H)^+$.

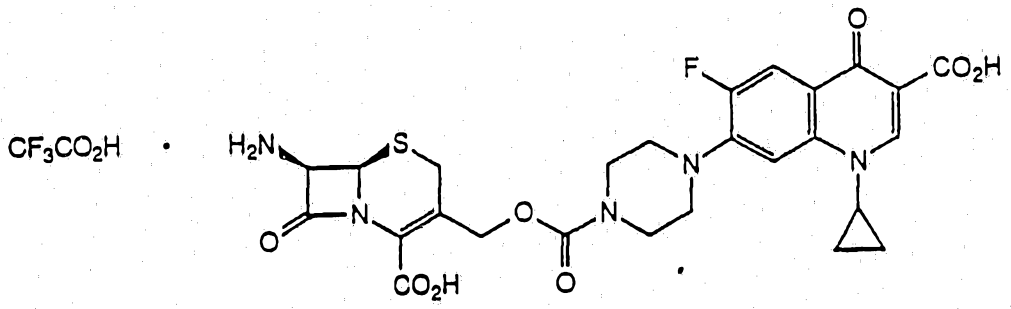
Alternate synthesis of (6R-trans)-3-[[[[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-7-[[(1,1-dimethylethoxy)-carbonyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid diphenylmethyl ester

Under an atmosphere of argon, 124 mg (0.25 mmol) of (6R-trans)-3-hydroxymethyl-7-[[(1,1-dimethylethoxy)carbonyl]-amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid diphenylmethyl ester was dissolved in 3 ml of methylene chloride and stirred for 45 minutes with 4Å molecular sieves. The solution was then cooled in ice and added simultaneously with 36 mg (0.28 mmol) of N,N-diisopropylethylamine to a cold solution of 0.14 ml of 20% phosgene in toluene in 1.5 ml of methylene chloride. The solution was stirred at 0-5°C for 30 minutes, and at room temperature for 45 minutes. The solution was then cooled again in ice and added at 0-5°C to an ice-cooled solution which had been prepared at room temperature by stirring 83 mg (0.25 mmol) of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid (previously dried under reduced pressure at 100°C) and 125 mg (0.62 mmol) of N-methyl-N-(trimethylsilyl)trifluoro-

acetamide (MSTFA) with 3 ml of methylene chloride for 30 minutes. After stirring for 30 minutes at 0-5°C and one hour at room temperature, the mixture was concentrated under reduced pressure. The residue was purified chromatographically to yield 63 mg (30%) of the title compound with spectral qualities similar to those of the product obtained above.

EXAMPLE 22

Preparation of (6R-trans)-7-amino-3-[[[[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid trifluoroacetic acid salt

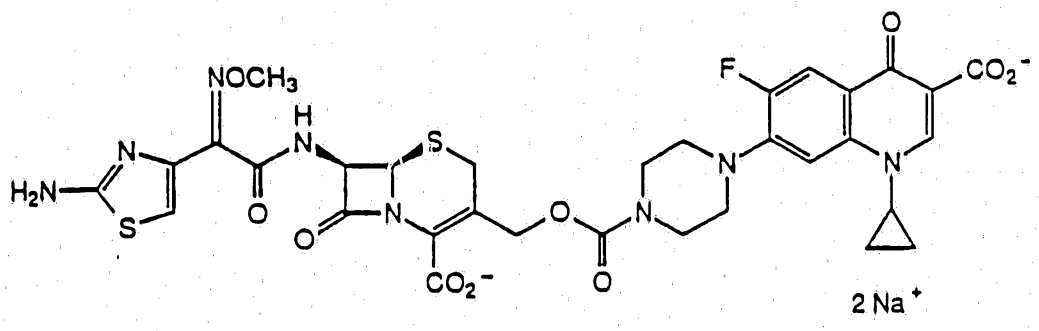


A solution of 0.251 g (0.294 mmol) of the diphenylmethyl ester prepared in Example 21 and 0.55 ml of anisole in 4.5 ml of dry methylene chloride was cooled to 0°C. Cold trifluoroacetic acid (3.6 ml) was added, and the mixture was stirred cold under argon for 1 hour and 45 minutes. The mixture was concentrated to dryness under reduced pressure. The residue was treated with 1.5 ml of methylene chloride followed by 6 ml of ethyl acetate. The resultant gummy

precipitate gradually solidified. Ether (23 ml) was then added, and the mixture was stirred cold for 10-15 minutes before filtering. The product was washed with ether and dried under reduced pressure, obtaining 186.2 mg of the title compound, with an additional 9.0 mg which adhered to the walls of the flask (total 93.3%).

EXAMPLE 23

Preparation of [6R-[6α,7ß(Z)]]-7-[[(2-amino-4-thiazolyl)-(methoxyimino)acetyl]amino]-3-[[[[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]-carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid disodium salt

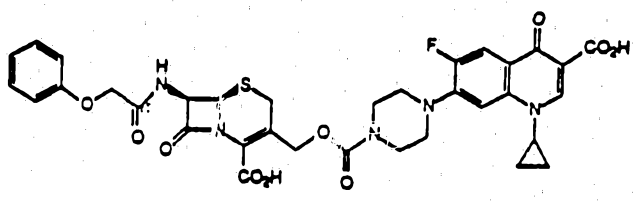


The trifluoroacetic acid salt (183.7 mg, 0.262 mmol) prepared by the preceding procedure (Example 22) was suspended in 4.5 ml of THF and cooled to 0°C. A solution of 79.9 mg (0.95 mmol) of sodium bicarbonate in 4.5 ml of water was added, followed by 1.5 ml of water wash. The mixture was stirred for 18 minutes. A solution of 93.9 mg (0.268 mmol) of (Z)-2-amino-α-(methoxyimino)-4-thiazole-ethanethioic acid S-2-benzothiazolyl ester in 1.5 ml of THF was then added along with 0.7 ml of THF wash. After 15 minutes the cooling bath was removed, and the reaction

mixture was stirred at ambient temperature for 17 hours. The mixture was concentrated under reduced pressure to remove the organic solvent. The remaining aqueous solution was extracted with ethyl acetate. The ethyl acetate was back-washed twice with water. The aqueous phase and water washes were combined. The pH of this solution was 8.70; 0.025 molar aqueous sodium dihydrogen phosphate solution was added to bring the pH to 7.80. The solution was concentrated slightly under reduced pressure to remove residual ethyl acetate before chromatography on a column containing 9 g of C_{18}-silica (from Waters). The column was washed with pH 7.8 aqueous sodium phosphate buffer and then eluted with a stepwise gradient of water-acetonitrile (from 0 to 30% acetonitrile) under pressure. Appropriate fractions were combined, concentrated and freeze dried to obtain 127.6 mg (59.7%) of the title compound. Of this material 52 mg were dissolved in 0.5 ml of water, and the pH was adjusted to 8.0 by addition of sodium bicarbonate. Cold acetone (24 ml) was added to re-precipitate the product. After centrifuging the supernatant liquid was removed; the residual solid was triturated with cold acetone, filtered and dried under reduced pressure over P_2O_5 to provide 39 mg of product: IR (KBr) 3410, 2540, 1762, 1672, 1622; mass spectrum (FAB) 837 $(M + Na)^+$, 815 $(M + H)^+$.

EXAMPLE 24

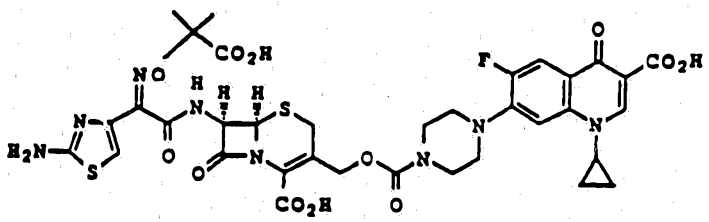
Preparation of (6R-trans)-3[[[[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]-carbonyl] oxy]methyl]-8-oxo-7-[(phenoxyacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



A suspension of 184 mg (0.262 mmol) of the trifluoroacetic acid salt, prepared as in Example 22, in 5 ml of THF was stirred at 0-5°C, and a solution of 101 mg (1.2 mmol) of sodium bicarbonate in 4.5 ml of water was added. A cold solution of 54 mg (0.314 mmol) of phenoxyacetyl chloride in 1.5 ml of THF was added dropwise. Stirring was continued at 0-5°C for twenty minutes and then for three hours at ambient temperature. The mixture was concentrated under reduced pressure to remove THF. The aqueous residue was diluted with water, washed with ethyl acetate, cooled in ice and acidified to pH 2.5 to precipitate the product. After filtration the solid was washed on the filter with water and ethyl acetate to obtain 130 mg of the title compound. Further purification was accomplished by reverse-phase HPLC on C_{18}-silica using a pH 7.5 sodium phosphate buffer-acetonitrile gradient. The residue obtained after evaporation and freeze-drying of the appropriate fractions was dissolved in water. The solution was filtered, and then acidified to pH 2.5 to precipitate the product: mass spectrum (FAB) m/z 722 $(M + H)^+$.

EXAMPLE 25

Preparation of [6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)-[(1-carboxy-1-methyl-ethoxy)imino]acetyl]amino]-3-[[[[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

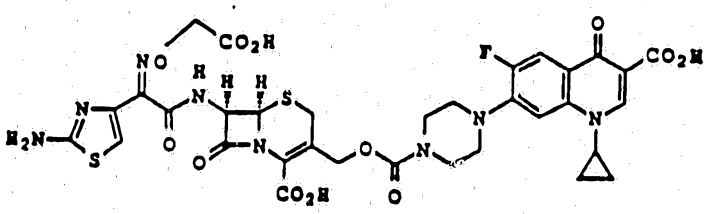


A suspension of 552 mg (0.786 mmol) of the trifluoroacetic acid salt, prepared according to Example 22, in 14 ml of THF was cooled in ice. A solution of 240 mg (2.85 mmol) of sodium bicarbonate in 15 ml of water was added and the mixture stirred for 20 minutes. A solution of 384 mg (0.804 mmol) of 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-benzothiazolyl)thio]-2-oxoethylidene]amino]oxy]methyl-propanoic acid 1,1-dimethylethyl ester in 6 ml of THF was then added. The mixture was stirred for 15 minutes with ice cooling and then overnight at room temperature. Under reduced pressure the mixture was concentrated to remove THF. The remaining aqueous solution was washed with ethyl acetate and acidified to pH 2.7. The solid precipitate was filtered, washed with water and dried under reduced pressure over calcium sulfate. The intermediate thus obtained (540 mg) was dissolved with cooling in 2.4 ml of anisole and 6 ml of trifluoroacetic acid and kept overnight at 0°C. The mixture was concentrated under reduced pressure. Methylene chloride (10 ml) was added and the mixture again evaporated under reduced pressure. On addition of 4 ml of methylene chloride and 16 ml of ethyl acetate, the residue solidified. After filtering, washing with ethyl acetate and air drying, 520 mg of product was obtained in the form of a trifluoro-acetic acid salt. This product was dissolved along with four equivalents of sodium bicarbonate in 0.025 molar pH 7.5 sodium phosphate buffer and purified chromatographically on C18-silica, using pH 7.5 buffer-acetonitrile as eluant. The

appropriate fractions were combined and acidified to pH 3 to precipitate the title compound, which was filtered, washed with water, and dried under reduced pressure: IR 1782, 1703, 1628 cm^{-1}; mass spectrum (FAB) m/z 843 (M + H)+.

EXAMPLE 26

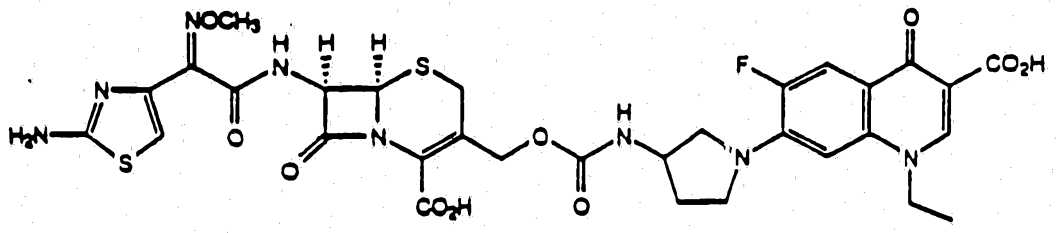
Preparation of [6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)-[(carboxymethoxy)imino]acetyl]amino]-3-[[[[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid



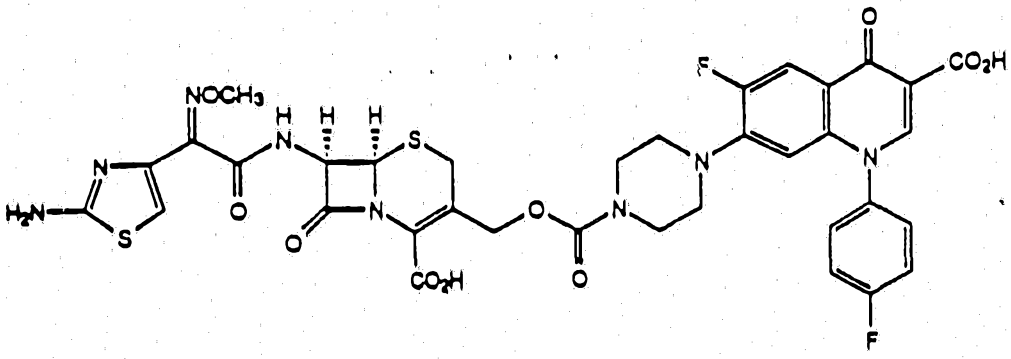
Using procedures similar to those in Example 25, but substituting the appropriate thio ester, the title compound was prepared: IR 1780, 1698, 1628 cm^{-1}; mass spectrum (FAB) 815 (M + H)+.

Following the procedures set forth in the foregoing examples, there can be prepared the following additional compounds:

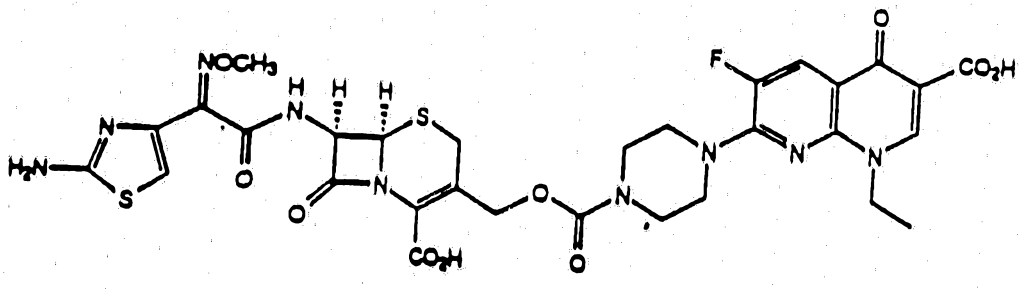
[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[[[[1-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-3-pyrrolidinyl]amino]carbonyl]-oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



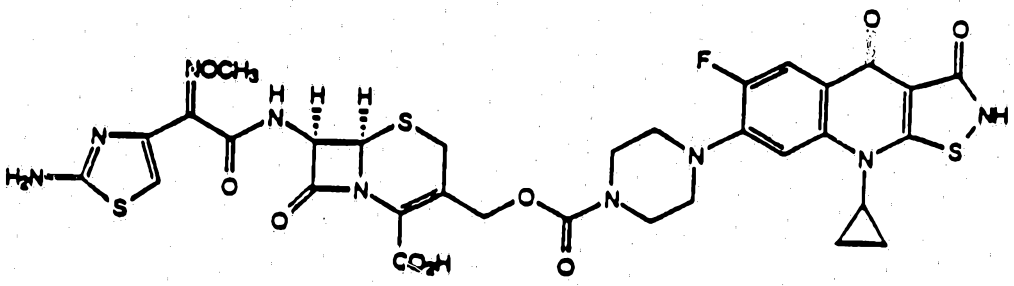
[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[[[4-[3-carboxy-6-fluoro-1-(4-fluorophenyl)-1,4-di-hydro-4-oxo-7-quinolinyl]-1-piperazinyl]carbonyl]oxy]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-carboxylic acid



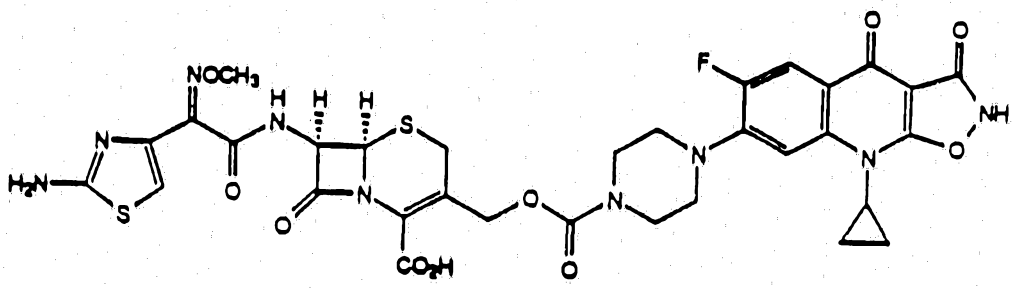
[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[[[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridin-7-yl)-1-piperazinyl]carbonyl]-oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



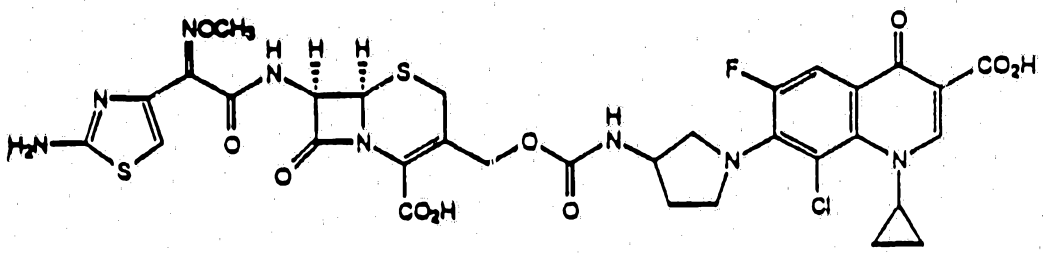
[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[[[4-(9-cyclopropyl-6-fluoro-2,3,4,9-tetra-hydro-3,4-dioxoisothiazolo[5,4-b]quinolin-7-yl)-1-pipera-zinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid



[6R-[6α,7ß(Z)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[[[4-(9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-3,4-dioxoisoxazolo[5,4-b]quinolin-7-yl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid

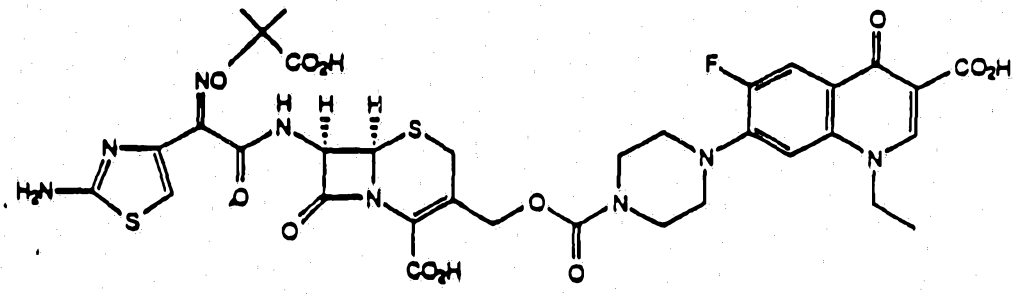


[6R-[6α,7ß(Z)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[[[1-(3-carboxy-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-3-pyrrolidinyl]amino]-carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

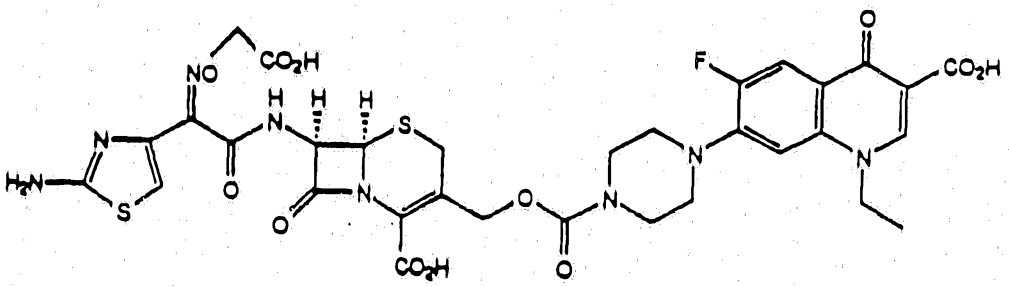


[6R-[6α,7ß(Z)]]-7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-3-[[[[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]-

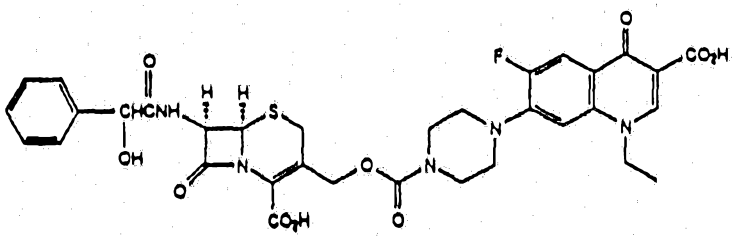
carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



[6R-[6α,7ß(Z)]]-7-[[(2-amino-4-thiazolyl)[(carboxymethoxy)-imino]acetyl]amino]-3-[[[[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

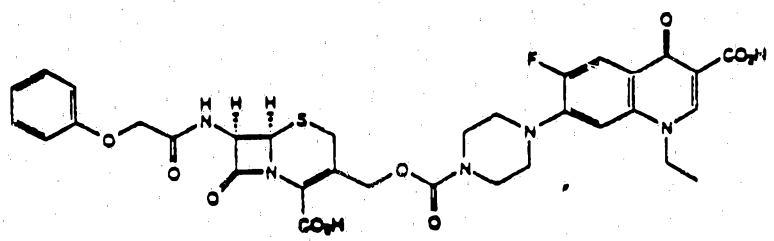


(6R-trans)-3-[[[[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-7-[(hydroxyphenylacetyl)amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

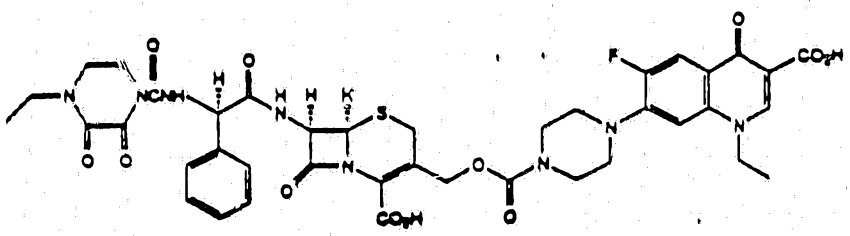


(6R-trans)-3-[[[[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-7-[(phenoxyacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-

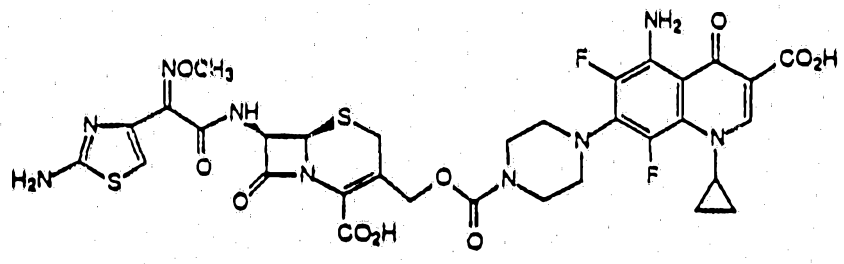
carboxylic acid



[6R-[6α,7ß(R)]]-3-[[[[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]-methyl]-7-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]-amino]phenylacetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



[6R-[6α,7ß(Z)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[[[4-(5-amino-3-carboxy-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]-carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



~~The following Example illustrates pharmaceutical~~

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~~preparations containing the cephalosporin derivatives provided by the present invention:~~

Example 27

Preparation of Diphenylmethyl (6R,7R)-7-(1-tert-butoxyformamido)-3-chlorocarbonyloxy-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

A solution of 855 mg (1.72mmol) of diphenylmethyl (6R,7R)-7-(1-tert-butoxyformamido)-3-(hydroxymeth,.)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate in 15 mL of dry CH_2Cl_2 was added dropwise over a period of approximately one minute, to a cold solution (ice-bath) of 4 mL (7.72 mmol) of phosgene solution (1.93 M in toluene), with stirring at 0°C. At the same time, a solution of 0.32 mL (1.87 mmol) of diisopropylethylamine in 10 mL of CH_2Cl_2 was added also over a period of five minutes. The clear reaction solution was stirred at 0°C for 2 h under argon. It was then taken into 50 mL of cold CH_2Cl_2, washed with cold 3 x mL H_2O, and dried over anhydrous Na_2SO_4 at 0°C. After filtration, the CH_2Cl_2 was evaporated at 0°C to 5°C to yield Diphenyl (6R,7R)-7-(1-tert-butoxyformamido)-3-chlorocarbonyloxy-methyl -8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate as a yellowish solution in toluene. (NMR spectrum 18035-136) M.W.: 559.042, E.F.: $C_{27}H_{27}C_1N_2O_7S$.

Example 28

Preparation of [6R-[5α,7β(Z)]]-7-(1-tert-butoxyformamido)-3-[[[4-(9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-3,4-dioxoisothiazolo[5,4-b]quinoline-7-yl)-1-piperazinyl]carbonyl]oxymethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid diphenylmethyl ester

A sample of 1.4 mL (7.52 mmol) of N-methyl-N-(trimethylsilyl) trifluoroacetamide (MSTFA) was added to a suspension of 600 mg

KWK:275X

(1.55 mmol) of 9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-7-(1-piperazinyl)isothiazolo-[5.4b]quinolone-3,4-dione in 10 mL dry CH_2Cl_2 with stirring under argon at 23°C. After 30 minutes, the clear yellow solution was chilled in an ice-bath, and treated dropwise with a cold toluene solution (ca. 3 mL) of the chloroformate prepared in Example 27 above. The resultant clear yellow solution was stirred at 0°C under argon for 1.0 h. To the reaction mixture 0.25 mL of CH_3OH was added and stirring was continued at 0°C for 20 min. The resultant yellow precipitate was filtered, washed with 3 x 2 mL 5% CH_3OH in CH_2Cl_2, and dried under vacuo to give 175 mg of 9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-7-(1-piperazinyl) isothiazolo[5.4b]quinoline-3,4-dione. To the filtrate, 200 mL of diethylether was added to precipitate the product. The solid was collected by filtration, washed with 3 x 5 mL ether, and dried in vacuo to give 809 mg (65% yield) of [6R-[5α,7β(Z)]]-7-(1-tert-butoxyformamido)-3-[[[4-(9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-3,4-dioxoisothiazolo[5,4-b]quinoline-7-yl)-1-piperazinyl]carbonyl]oxymethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid diphenylmethyl ester as a tan solid (NMR, UV, PC24977) M.W.: 882.995, E.F.: $C_{44}H_{43}FN_6O_9S_2$.

Example 29

Preparation of [6R-[6α,7β(Z)]]-7-amino-3-[[[4-(9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-3,4-dioxoisothiazolo[5,5-b]quinolin-7-yl)-1-piperazinyl]carbonyl]oxymethyl]-8-oxo-5-thia-1-azabicyclo[4.3.0]oct-2-ene-2-carboxylic acid (1:1) trifluoroacetic acid salt

A mixture of 15 mL dry nitromethane, 20 mL trifluoroacetic acid, and 0.3 mL of anisole was cooled to 0°C. To this mixture, under an argon atmosphere, with stirring, 1.6g (1.81 mmol) of [6R-[5α,7β(Z)]]-7-(1-tert-butoxyformamido)-3-[[[4-(9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-3,4-dioxoisothiazolo-[5,4-b]quinoline-7-yl-1-piperazinylcarbonyl]

PATENT OFFICE
KWK:275x

oxymethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]act-2-ene-carboxylic acid diphenylmethyl ester, was added in portions. The resultant solution was stirred at 0°C under argon for 3h. The reaction was stopped by adding first 30 mL hexane, followed by 160 mL diethyl ether. After 10 minutes at 0°C with vigorous stirring, the precipitate was filtered, washed with 3 x 50 mL ether, and dried in vacuo to give 1.16g (87,6% yield) of [6R-[6α,7β(Z)]]-7-amino-3-[[[4-(9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-3,4-dioxoisothiazolo-[5.5-b]quinolin-7-yl)-1-piperazinyl] carbonyl]oxy-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (1:1)trifluoroacetic acid salt as a pale yellow solid (NMR PC 249944), M.W.: 730.676, E.F.: $C_{26}H_{25}FN_6O_7S_2$. 1:1 $C_2HF_3O_2$.

Example 30

Preparation of [6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino) acetyl]amino]-3-[[[[4-9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-3,4-dioxoisothiazolo[5.4-b]quinolin-7-yl)-1-piperaz-inyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid disodium salt trihydrate.

A solution of approximately 7 mL saturated $NaHCO_3$ was added to a mixture of 1.53 g (2.09 mmol) of [6R-[6α,7β(Z)]]-7-amino-3- [[[4-(9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-3,4-dioxoisothiazolo[5,4-b]quinolin-7-yl)-1-piperaz-inyl]carbonyl]oxymethyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid (1:1) trifluoroacetic acid salt in 60 mL of 1:1 tetrahydrofural-water until the pH was 8.0 - 8.5. It was stirred vigourously for 15 minutes and then cooled to 0°C. To this mixture, a solution of 0.91 g (2.6 mmol) of S-(2-benzothiazoyl)-2-amino-4-thiazoleglyoxylate (E)-O-methyloxime in 10 mL of THF was added over a period of 15 minutes. The reaction mixture was stirred at 0°C - 5°C for 2.0 h, and at 23°C for 1.0 h. Acetone (800 mL) was then added and the resultant precipitate was collected by filtration, washed with acetone

AUSTRALIAN PATENT OFFICE

(4 x 20 mL), and dried under vacuum to yield 1.9 g of solid. This material was taken into 50 mL of 2.5% CH_3CN in water and treated with saturated sodium bicarbonate (20 mL) until the pH reached 9.5. After dilution with water (100 mL), the solution was passed through a C_{18} column (75 g of YMC-gel, 120). Elution with 15% to 20% CH_3CN in water gave fractions containing the product. The CH_3CN was evaporated in vacuo and the aqueous solution was lyophilized to give [6R-[6α,7β(Z)]]-7-[[2-amino-4-thiazolyl)(methoxyimino)acetyl]amino] -3-[[[[4-9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-3,4-dioxoisothiazolo[5,4-b]quinolin-7-yl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-carboxylic acid disodium salt trihydrate as a white solid. Calcd. for $C_{32}H_{28}FN_9O_9S_3$ 2Na $3H_2O$ (897.84); C42.8, H 3.81,N 14.04, F 2.11, Na 5.12. Found: C 42.8, H 3.46, N 13.71, F 2.17, Na 5.04.

In Vitro and In Vivo Data

[6R-[6α,7β(Z)]]-7-[[2-amino-4- thiazolyl)(methoxyimino)acetyl]amino]-3-[[[[4-(9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-3,4-dioxoisothiazolo[5,4-b]-quinolin-7-yl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2- ene-carboxylic acid shows excellent in vitro antibacterial activity and also demonstrated impressive activity subcutaneously in the murine streptococcal pneumonia model with an ED_{50} of 4.1 mg/kg as described below.

		MIC[a]	ED_{50}[b]
Escherichia coli	257	0.0157	
	DCO	0.25	
	DC2	0.0313	
Pseudomonas aeruginosa	56	0.5	
Staphylococcus aureus	Smith	0.125	
Streptococcus pneumonae	6301	0.0019	4.1

[a] MIC in >g/ml

[b] ED_{50} in mg/kg

KWK:275X

The following Example illustrates pharmaceutical preparations containing the cephalosporin derivatives provided by the present invention:

Example A

Production of dry ampoules for intramuscular administration:

A lyophilisate of 1 g of active ingredient is prepared in the usual manner and filled into an ampoule. The sterile water ampoule contains 10% propylene glycol. Prior to the administration, the lyophilisate is treated with 2.5 ml of a 2% aqueous lidocaine hydrochloride solution.

As active ingredient can be used one of the end products prepared according to the above Examples.

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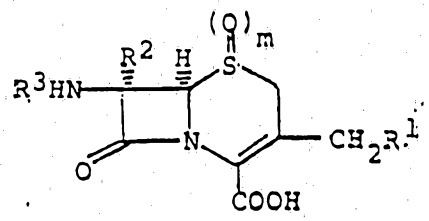
~~Claims~~

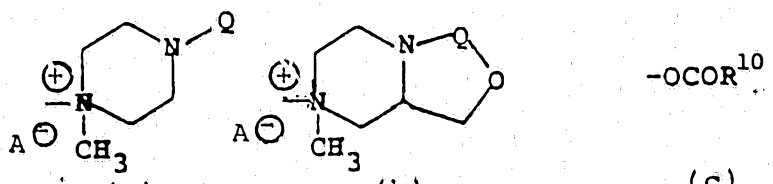
The claims defining the invention are as follows:

1. Acyl derivatives of the general formula



I

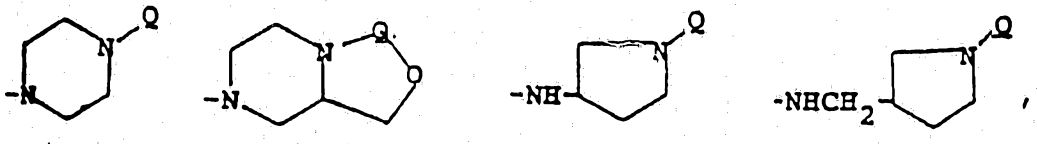
wherein R^1 is a substituted N-heterocyclus of the formulas



(a) (b) (c)

Ortho Fusion

where R^{10} is one of the groups



(c_1) (c_2) (c_3) (c_4)

Ortho Fusion

Q represents a substituted quinolinyl or naphthyridinyl group and the N-heterocyclic nucleus may optionally be substituted with one or more lower alkyl groups; R^2 is selected from the group consisting of hydrogen, lower alkoxy, lower alkylthio and lower alkanoylamino; R^3 is an acyl groups; m is zero, 1 or 2; and A is a

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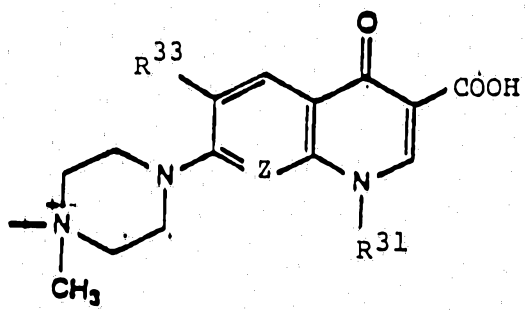
pharmaceutically acceptable anion,
and readily hydrolyzable esters and pharmaceutically acceptable salts of these compounds and hydrates of the compounds of formula I or of their esters or salts.

2. A compound as in claim 1, wherein R^1 is one of group (a) and (b).

3. A compound as in claim 2 wherein m is zero and R^2 is hydrogen.

4. A compound as in claim 2 or 3 wherein R^1 is of the formula



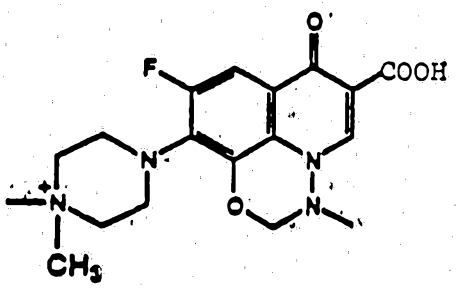
wherein Z represents R^{30}-C or nitrogen; R^{30} represents hydrogen, halogen or an oxymethylene ($-CH_2O-$) bridge to the piperazine nucleus to form a fused six-membered ring; R^{31} represents hydrogen, lower alkyl, lower alkenyl, C_3-C_7 cycloalkyl, halo-lower alkyl or mono-, di- or tri-halophenyl; R^{30} and R^{31} when taken together represent a C_3-C_5 alkylene group, a C_2-C_4 alkylene mono-oxy group, a C_1-C_2 alkylene dioxy group or a group of the formula $-OCH_2N(CH_3)-$, and R^{33} represents hydrogen or halogen.

5. A compound as in claim 4, wherein Z is R^{30}-C in which R^{30} is hydrogen, bromine, chlorine or fluorine,

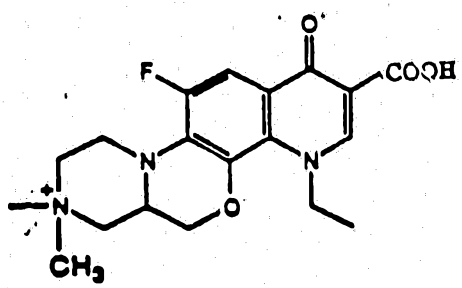
R^{31} is lower alkyl, halo-lower alkyl or C_3-C_7 cycloalkyl, and R^{33} is hydrogen, chlorine or fluorine.

6. A compound as in claim 5, wherein R^{30} is hydrogen or fluorine, R^{31} is ethyl, fluoroethyl or cyclopropyl, and R^{33} is hydrogen or fluorine.

7. A compound as in claim 2 or 3, wherein R^1 is of the formula



8. A compound as in claim 2 or 3, wherein R^1 is of the formula

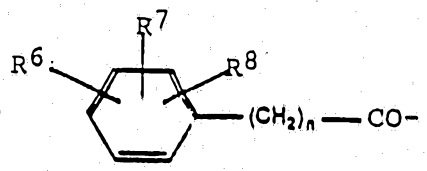


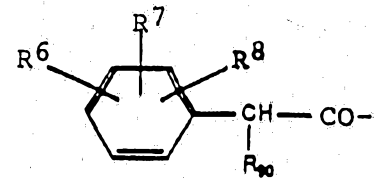
9. A compound as in any one of claims 2-8 wherein R^3 is an aliphatic acyl group of the formula

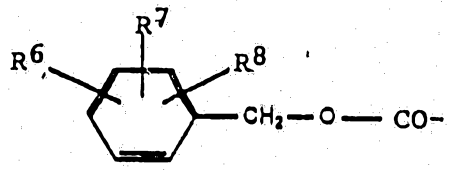
R^5CO-

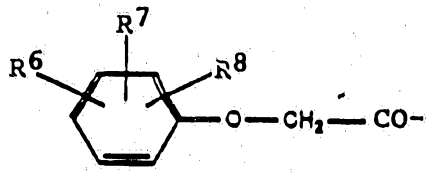
wherein R^5 is selected from the group consisting of hydrogen, lower alkyl, C_3-C_7 cycloalkyl, lower alkoxy, lower alkenyl, C_3-C_7 cycloalkenyl or cyclohexadienyl, or lower alkyl or alkenyl substituted with one or more halogen, cyano, nitro, amino, mercapto, lower alkylthio, or cyanomethylthio groups.

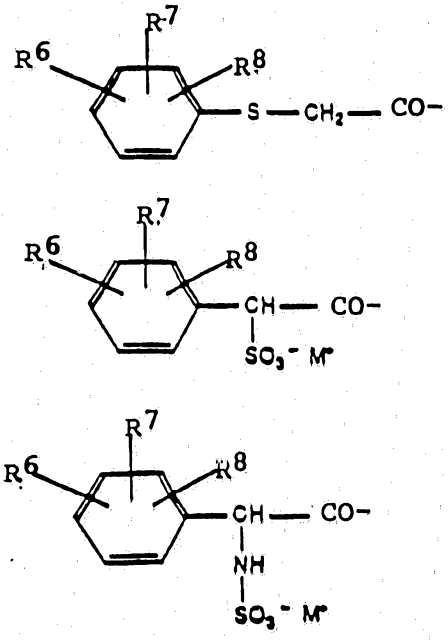
10. A compound as in any one of claims 2-8 wherein R^3 is an aromatic acyl group selected from the group consisting of











wherein n is 0, 1, 2 or 3; R^6, R^7, and R^8 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms and aminomethyl; and R^{90} is selected from the group consisting of amino, acylamino, hydroxy, a carboxy salt, protected carboxy, formyloxy, azido and a sulfo salt, and M is a cation.

11. A compound as in any one of claims 2-8 wherein R^3 is a heteroaromatic acyl group selected from the group consisting of

$$R^{101}-(CH_2)_n-CO-$$

R^{101}-CH(R^{90})-CO-

R^{101}-O-CH_2-CO-

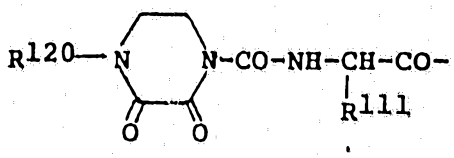
R^{101}-S-CH_2-CO-

and

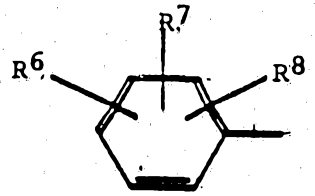
R^{101}-CO-CO-

wherein n is 0, 1, 2 or 3; R^{90} is selected from the group consisting of amino, acylamino, hydroxy, a carboxy salt, protected carboxy, azido and a sulfo salt; and R^{101} is a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur.

12. A compound as in any one of claims 2-8 wherein R^3 is a [[(4-substituted-2,3-dioxo-1-piperazinyl)carbonyl]-amino]acetyl group of the formula



wherein R^{111} is lower alkyl, hydroxy-lower alkyl or an aromatic group of the formula



wherein R^6, R^7, and R^8 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, aminomethyl or a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, and R^{120} is lower alkyl or substituted lower alkyl (wherein the lower alkyl group is substituted with one or more halogen, cyano, nitro, amino or mercapto groups).

13. A compound as in any one of claims 2-8 wherein R^3 is an (acylamino)acetyl group of the formula

$$R^{140}\text{-CO-NH-CH(}R^{111}\text{)-CO-}$$

wherein R^{111} is lower alkyl, hydroxy-lower alkyl or an aromatic group of the formula

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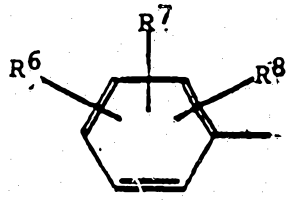
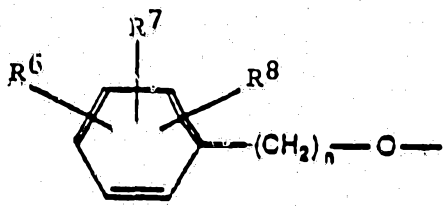
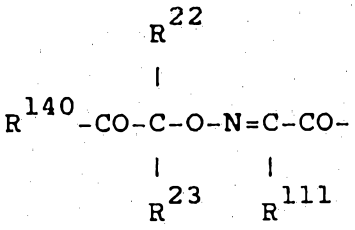


wherein R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl or 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms and aminomethyl, and a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, and R^{140} is

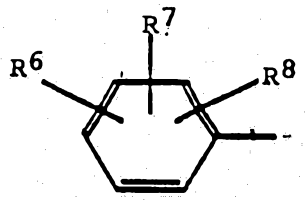


(where R^6, R^7 and R^8 are as previously defined and n is 0, 1, 2 or 3), hydrogen, lower alkyl, substituted lower alkyl, amino, lower alkylamino, di-lower alkylamino, (cyano-lower alkyl)amino, hydrazino, lower alkyl-hydrazino, aryl-hydrazino or acyl-hydrazino.

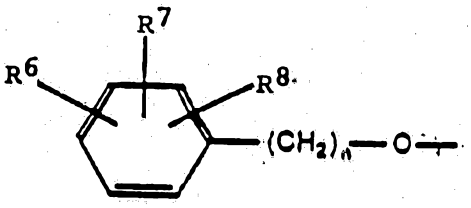
14. A compound as in any one of claims 2-8 wherein R^3 is a (substituted oxyimino)acetyl group having the formula



wherein R^{111} is lower alkyl, hydroxy-lower alkyl or an aromatic group of the formula

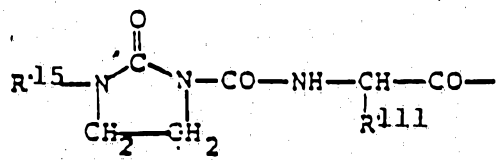


wherein R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl or 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms and amino-methyl, or a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, and R^{140} is

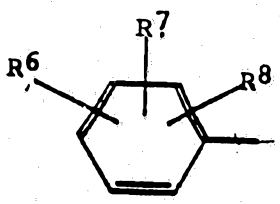


(wherein R^6, R^7 and R^8 are as defined above and n is 0, 1, 2 or 3), hydrogen, lower alkyl, substituted lower alkyl, amino, lower alkylamino, di-lower alkylamino, (cyano-lower alkyl) amino, hydrazino, lower alkyl-hydrazino, aryl-hydrazino and acyl-hydrazino, and R^{22} and R^{23} are independently selected from the group consisting of hydrogen and lower alkyl, or R^{22} and R^{23} taken together with the carbon atom to which they are attached form a C_3-C_7 carbocyclic ring.

15. A compound as in any one of claims 2-8 wherein R^3 is a [[[3-substituted-2-oxo-1-imidazolidinyl]carbonyl]-amino]acetyl group of the formula



wherein R^{111} is lower alkyl, hydroxy-lower alkyl or an aromatic group of the formula



wherein R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, halogen, hydroxy,

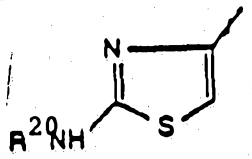
nitro, amino, cyano, trifluoromethyl, alkyl or 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, aminomethyl, or a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, and R^{15} is hydrogen, lower alkylsulfonyl, arylmethyleneamino (i.e., $-N=CHR^{111}$ wherein R^{111} is as defined above), $R^{16}CO-$ (wherein R^{16} is hydrogen, lower alkyl or halogen substituted lower alkyl), aromatic group (as defined by R^{111} above), lower alkyl or substituted lower alkyl (wherein the lower alkyl group is substituted with one or more halogen, cyano, nitro, amino or mercapto groups).

16. A compound as in any one of claims 2-8 wherein acyl group R^3 is of the formula

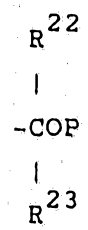
$$R^{130}-O-N=C-CO-$$
$$\quad\quad\quad

hydroxy(phenylmethoxy)phosphinyl, di-lower-alkoxyphosphinyl substituents].

17. A compound as in claim 16 wherein R^{101} is of the formula



wherein R^{20} is hydrogen or an amino protecting group, and R^{130} is hydrogen, lower alkyl or a group of the formula



wherein R^{22} and R^{23} are selected from the group consisting of hydrogen and lower alkyl or taken together with the carbon atom to which they are attached form a C_3-C_7 carbocyclic ring, and P is hydroxy or $-NHR^{19}$ where R^{19} is hydrogen, lower alkyl, amino, lower alkyl-amino, arylamino or acylamino.

18. A compound as in claim 17 wherein R^{20} is hydrogen and R^{130} is methyl or a group of the formula



wherein R^{22} and R^{23} are selected from the group consisting of hydrogen and methyl.

19. A compound as in any one of claims 14 and 16-18 which is in the syn-form or as a mixture in which the syn-form predominates.

20. A compound as in claim 2, wherein R^1 is group (a) and R^3 is phenoxyacetyl.

21. A compound as in claim 2 selected from the group consisting of

(6R-trans)-4-[3-carboxy-1-(2-fluoroethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinolin-7-yl]-[[2-carboxy-8-oxo-7-[(phenoxyacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpiperazinium iodide,

[6R-[6α,7ß(Z)]]-1-[[7-[[[(2-amino-4-thiazolyl)[1-(1-carboxy-1-methyl)ethoxy]imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-4-[3-carboxy-1-(2-fluoroethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinolin-7-yl]-1-methylpiperazinium hydroxide inner salt monosodium salt and

[6R-[6α,7ß(Z)]]-1-[[7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-en-3-yl]methyl]-4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-methylpiperazinium iodide.

22. [6R-[6α,7ß(Z)]]-1-[[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-en-3-yl]methyl]-4-[3-carboxy-6,8-difluoro-

1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-quinolinyl]-1-methylpiperazinium iodide.

23. [6R-[6α,7β(Z)]]-1-[[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-4-[3-carboxy-6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-quinolinyl]-1-methylpiperazinium hydroxide inner salt monosodium salt.

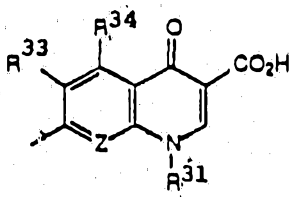
24. (6R-trans)-4-[3-Carboxy-6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-quinolinyl]-1-[[2-carboxy-7-(formylamino)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]-methyl]-1-methylpiperazinium trifluoroacetate.

25. [6R-[6α,7β(Z)]]-1-[[7-[[(2-Amino-4-thiazolyl)[[1,1-dimethyl-2-(1,1-dimethylethoxy)-2-oxo-ethoxy]imino]acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]-methyl]-4-[3-carboxy-(2-fluoroethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinolin-7-yl]-1-methylpiperazinium iodide.

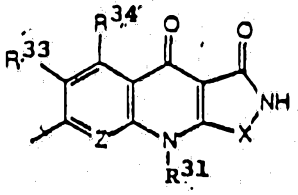
26. A compound as in claim 1 wherein R^1 is group (c).

27. A compound as in claim 26 wherein m is zero or 1.

28. A compound as in claim 26 or 27 wherein Q is



or

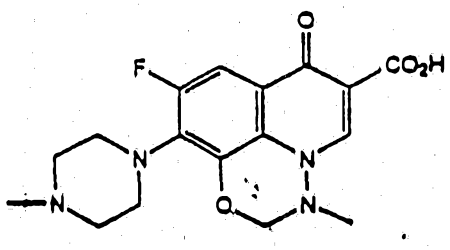


wherein Z represents R^{30}-C or nitrogen, X represents oxygen or sulfur, R^{30} represents hydrogen, halogen or an oxymethylene ($-CH_2O-$) bridge to the piperazine nucleus to form a fused six-membered ring; R^{31} represents hydrogen, lower alkyl, lower alkenyl, C_3-C_7 cycloalkyl, halo-lower alkyl or mono-, di- and tri-halophenyl; R^{30} and R^{31} when taken together represent a C_3-C_5 alkylene group, a C_2-C_4 alkylene mono-oxy group, a C_1-C_2 alkylene dioxy group or a group of the formula $-OCH_2N(CH_3)-$; R^{33} is hydrogen or halogen; and R^{34} is hydrogen or amino.

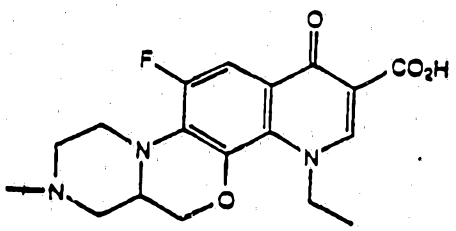
29. A compound as in claim 28, wherein Z is R^{30}-C wherein R^{30} is hydrogen, chlorine, bromine or fluorine, R^{31} is lower alkyl, halo-lower alkyl or C_3-C_7 cycloalkyl, and R^{33} is hydrogen, chlorine or fluorine.

30. A compound as in claim 29, wherein R^{30} is hydrogen or fluorine, R^{31} is ethyl, fluoroethyl or cyclopropyl, and R^{33} is hydrogen or fluorine.

31. A compound as in claim 28, wherein R^1 is of the formula



32. A compound as in claim 28 wherein R^1 is of the formula

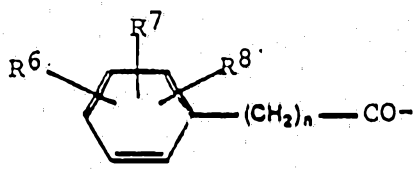


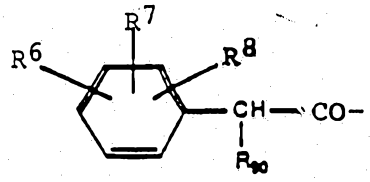
33. A compound as in any one of claims 26-32 wherein R^3 is an aliphatic acyl group of the formula

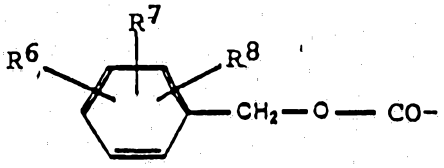
$$R^5CO-$$

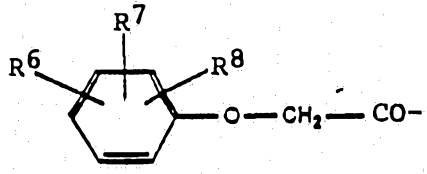
wherein R^5 is selected from the group consisting of hydrogen, lower alkyl, C_3-C_7 cycloalkyl, lower alkoxy, lower alkenyl, C_3-C_7 cycloalkenyl or cyclohexadienyl, or lower alkyl or alkenyl substituted with one or more halogen, cyano, nitro, amino, mercapto, lower alkylthio, or cyanomethylthio groups.

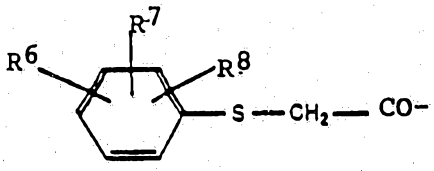
34. A compound as in any one of claims 26-32 wherein R^3 is an aromatic acyl group selected from the group consisting of

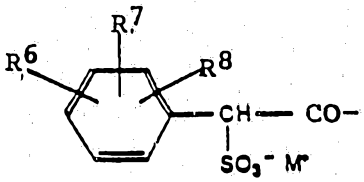


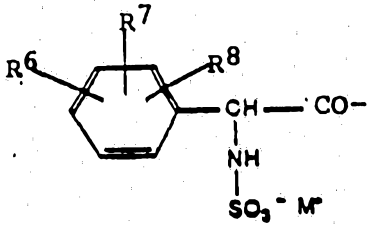












wherein n is 0, 1, 2 or 3; R^6, R^7, and R^8 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms and aminomethyl; and R^{90} is selected from the group consisting of amino, acylamino, hydroxy, a carboxy salt, protected carboxy, formyloxy, azido and a sulfo salt, and M is a cation.

35. A compound as in any one of claims 26-32 wherein R^3 is a heteroaromatic acyl group selected from the group consisting of

$$R^{101}\text{-}(CH_2)_n\text{-}CO\text{-}$$

$$R^{101}\text{-}\underset{\displaystyle R^{90}}{\underset{|}{CH}}\text{-}CO\text{-}$$

$$R^{101}\text{-}O\text{-}CH_2\text{-}CO\text{-}$$

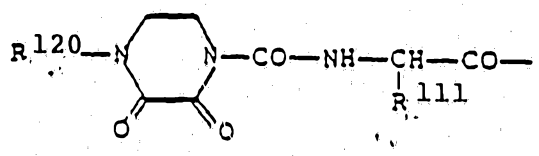
$$R^{101}\text{-}S\text{-}CH_2\text{-}CO\text{-}$$

and

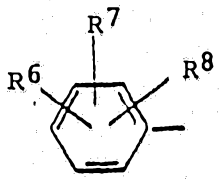
$$R^{101}\text{-}CO\text{-}CO\text{-}$$

wherein n is 0, 1, 2 or 3; R^{90} is selected from the group consisting of amino, acylamino, hydroxy, a carboxy salt, protected carboxy, azido and a sulfo salt; and R^{101} is a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur.

.36. A compound as any one of claims 26-32 wherein R^3 is a [[(4-substituted-2,3-dioxo-1-piperazinyl)carbonyl]-amino]-acetyl group of the formula



wherein R^{111} is lower alkyl, hydroxy-lower alkyl or an aromatic group of the formula

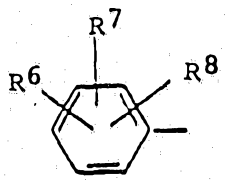


wherein R^6, R^7, and R^8 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, amino-methyl, or a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, and R^{120} is lower alkyl or substituted alkyl (wherein the lower alkyl group is substituted with one or more halogen, cyano, nitro, amino or mercapto groups).

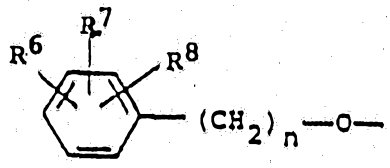
37. A compound as any one of claims 26-32 wherein R^3 is an (acylamino)acetyl group of the formula

$$R^{140}\text{-CO-NH-CH(}R^{111}\text{)-CO-}$$

wherein R^{111} is lower alkyl, hydroxy-lower alkyl or an aromatic group of the formula

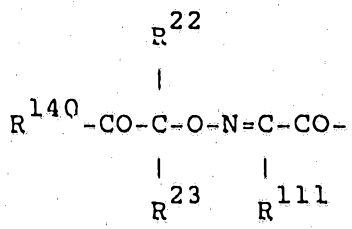


wherein R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl or 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms and aminomethyl, and a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, and R^{140} is

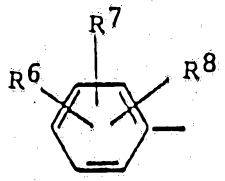


(where R^6, R^7 and R^8 are as previously defined and n is 0, 1, 2 or 3), hydrogen, lower alkyl, substituted lower alkyl, amino, lower alkylamino, di-lower alkylamino, (cyano-lower alkyl)amino, hydrazino, lower alkyl-hydrazino, aryl-hydrazino or acyl-hydrazino.

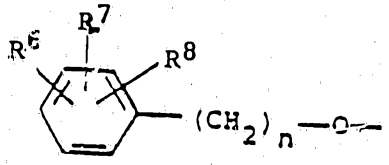
38. A compound as any one of claims 26-32 wherein R^3 is a (substituted oxyimino)acetyl group having the formula



wherein R^{111} is lower alkyl, hydroxy-lower alkyl or an aromatic group of the formula

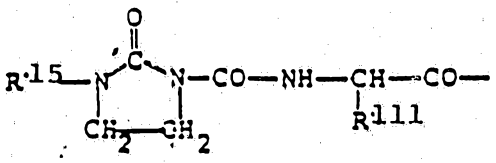


wherein R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl or 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms and aminomethyl, or a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, and R^{140} is

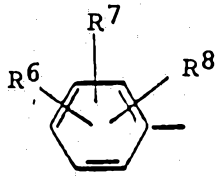


(wherein R^6, R^7 and R^8 are as defined above and n is 0, 1, 2 or 3), hydrogen, lower alkyl, substituted lower alkyl, amino, lower alkylamino, di-lower alkylamino, (cyano-lower alkyl) amino, hydrazino, lower alkyl-hydrazino, aryl-hydrazino and acyl-hydrazino, and R^{22} and R^{23} are independently selected from the group consisting of hydrogen and lower alky, or R^{22} and R^{23} taken together with the carbon atom to which they are attached form a C_3-C_7 carboxylic ring.

39. A compound as any one of claims 26-32 wherein R^3 is a [[[3-substituted-2-oxo-1-imidazolidinyl]carbonyl]-amino]acetyl group of the formula



wherein R^{111} is lower alkyl, hydroxy-lower alkyl or an aromatic group of the formula



wherein R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, aminomethyl, or a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, and R^{15} is hydrogen, lower alkylsulfonyl, arylmethyleneamino (i.e., $-N=CHR^{111}$ wherein R^{111} is as defined above), $R^{16}CO-$ (wherein R^{16} is hydrogen, lower alkyl or halogen substituted lower alkyl), aromatic group (as defined by R^{111} above), lower alkyl or substituted lower alkyl (wherein the lower alkyl group is substituted with one or more halogen, cyano, nitro, amino or mercapto groups).

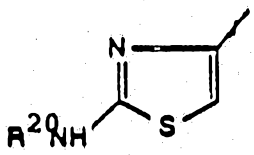
40. A compound as any one of claims 26-32 wherein acyl group R^3 is of the formula

$$R^{130}-O-N=\underset{\displaystyle R^{101}}{\overset{\displaystyle |}{C}}-CO-$$

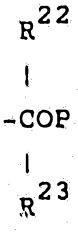
wherein R^{101} is an unsubstituted or substituted 5, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 hetero atoms selected from the group consisting of

nitrogen, oxygen and sulfur wherein the heterocyclic ring is substituted by halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, C_1-C_4 alkyl or C_1-C_4 alkoxy and R^{130} is hydrogen, lower alkyl, C_3-C_7 cycloalkyl, carboxy-C_3-C_7-cycloalkyl or substituted lower alkyl [wherein the lower alkyl is substituted with one or more halogen, cyano, nitro, amino, mercapto, lower alkylthio, aromatic group (as defined by R^{111} in claim 39), carboxy (including salts thereof), lower alkanoylamino, carbamoyl, lower alkoxycarbonyl, phenylmethoxycarbonyl, diphenylmethoxycarbonyl, hydroxy-lower alkoxyphosphinyl, dihydroxyphosphinyl, hydroxy(phenylmethoxy)phosphinyl, di-lower-alkoxyphosphinyl substituents].

41. A compound as in claim 40 wherein R^{101} is of the formula



wherein R^{20} is hydrogen or an amino protecting group, and R^{130} is hydrogen, lower alkyl or a group of the formula



wherein R^{22} and R^{23} are selected from the group consisting of hydrogen and lower alkyl or taken together with the carbon atom to which they are attached form a C_3-C_7 carboxylic ring, and P is hydroxy or $-NHR^{19}$ where R^{19} is hydrogen, lower alkyl, amino, lower alkyl-amino, arylamino or acylamino.

42. A compound as in claim 41 wherein R^{20} is hydrogen or triphenylmethyl.

43. A compound as in any one of claims 38 and 40-42 which is in the syn form or as a mixture in which the syn form predominates.

44. A compound as in claim 26 selected from the group consisting of

[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)-(methoxyimino)acetyl]amino]-3-[[[[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]-carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)methoxyimino)-acetyl]amino]-3-[[[[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid,

(6R-trans)-3[[[[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]-methyl]-8-oxo-7-[(phenoxyacetyl)amino]-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid,

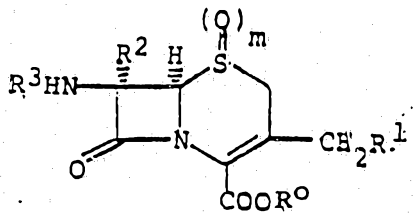
[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)-[(1-carboxy-1-methyl-ethoxy)imino]acetyl]amino]-3-[[[[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid and

[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)-[(carboxy-methoxy)imino]acetyl]amino]-3-[[[[4-(3-carboxy-1-cyclo-

propyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
as well as salts of these compounds and hydrates of these compounds and salts.

45. Salts of the compounds according to claim 44 which are sodium salts.

46. Compounds of the formula

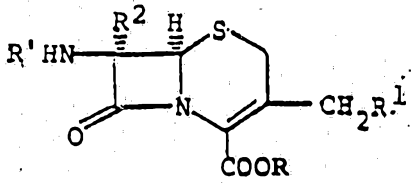


VIb

wherein R^1, R^2, R^3 and m are as above and R^o is t-butyl, benzhydryl, p-nitrobenzyl or allyl.

47. (6R-trans)-4-[3-carboxy-6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-quinolinyl]-1-[[2-(1,1-dimethylethoxy)carbonyl-7-(formylamino)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpiperazinium iodide.

48. Compounds of the formula



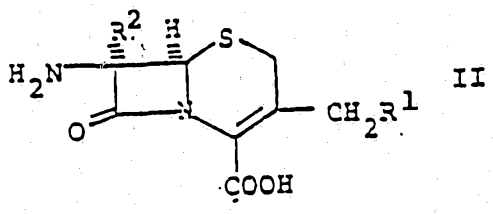
IIb

wherein R^1 and R^2 are as above, R is hydrogen or a carboxylic acid protecting group and R' is hydrogen or a readily removable amino protecting group.

49. (6R-trans)-3-[[[[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyl]oxy]methyl]-7-[[(1,1-dimethylethoxy)carbonyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid diphenylmethyl ester.

50. Process for the manufacture of the compounds according to any one of claims 1-45, which process comprises

a) for the manufacture of a compound of formula I, in which m is zero, reacting a compound of the general formula



II

wherein R^1 and R^2 are as above,

or a readily hydrolyzable ester or salt thereof with a carboxylic acid of the general formula R^3OH or a reactive derivative thereof, or

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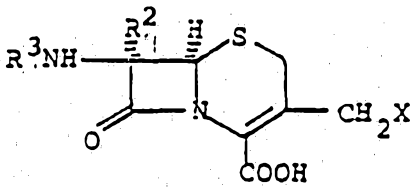
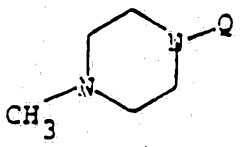
b) for the manufacture of a compound of formula I, in which m is zero and R^1 is one of the groups (a) and (b), reacting a compound of the formula



III

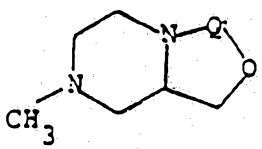
wherein R^2 and R^3 are as above and X is a leaving group, and amino, hydroxy and carboxy groups present may be protected,

or a readily hydrolyzable ester or salt thereof with a compound of the formula



IV

or

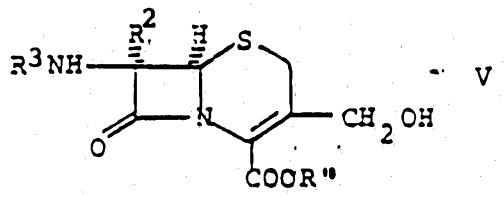


IVa

wherein Q is as above and the nitrogen groups may be protected,

or

c) for the manufacture of a readily hydrolyzable ester of a carboxylic acid of formula I, in which m is zero and R^1 is group (c), reacting a compound of the formula

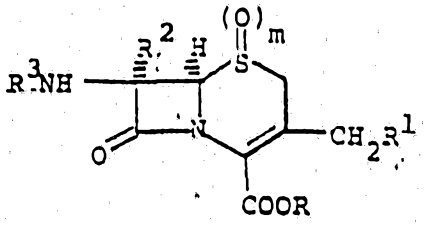


V

wherein R^2 and R^3 are as above and R'' is the residue of a readily hydrolyzable ester,

in the presence of a base with phosgene an reacting the reaction product obtained with a compound of formula $R^{10}H$, in which R^{10} is as above, except that amino, hydroxy and/or carboxy functions thereof may be protected, followed by cleavage of any protecting group present, or

d) for the manufacture of a carboxylic acid of formula I converting an ester of the formula

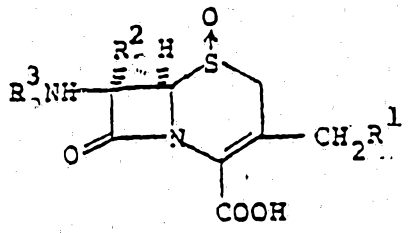


VI.

wherein R^1, R^2, R^3 and m are as above, and R is a carboxylic acid protecting group,

to the carboxylic acid of formula I, or

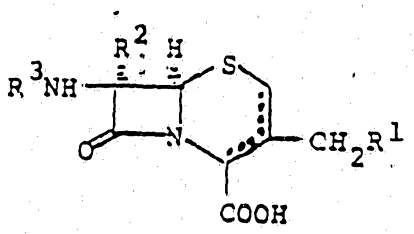
e) for the manufacture of the compound of formula I, in which m is zero, or a readily hydrolyzable ester or salt thereof reducing a compound of the formula



VII

wherein R^1, R^2 and R^3 are as above,
or a readily hydrolyzable ester or salt thereof, or

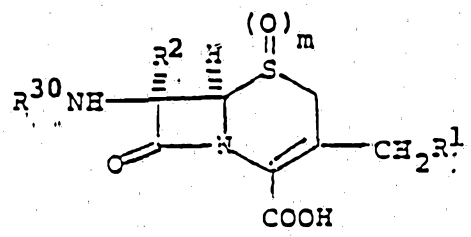
f) for the manufacture of a compound of formula I in which m is 1 or 2; or a readily hydrolyzable ester or salt thereof oxidizing a compound of the formula



VIII

wherein R^1, R^2 and R^3 are as above and the dotted lines indicates the presence of a Δ2 or Δ3 double bond,
or a readily hydrolyzable ester of salt thereof, or

g) for the manufacture of a compound of formula I, in which R^3 contains an amino substituent, or a readily hydrolyzable ester or salt thereof cleaving off an amino protecting group in the substituent R^{30} of a compound of the formula



IX

wherein R^1, R^2 and m are as above and R^{30} is an acyl group containing a protected amino substituent,

or of a readily hydrolyzable ester or salt thereof, or

h) for the manufacture of a readily hydrolyzable ester of a compound of formula I subjecting a carboxylic acid of formula I to a corresponding esterification, or

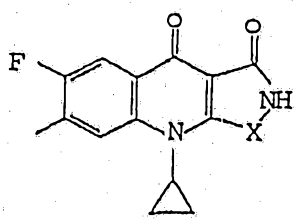
i) for the manufacture of salts or hydrates of a compound of formula I or hydrates of said salts converting a compound of formula I into a salt or hydrate or into a hydrate of said salt.

51. Process according to claim 50 which comprises carrying out process alternative (b).

52. Process according to claim 50 which comprises carrying out process alternative (a), (c), (d), (f), (g) or (i).

53. End products according to any one of claims 1-45 whenever prepared according to the process claimed in claim 52 or by an obvious chemical equivalent thereof.

54. A compound as in any one of Claims 26-30, wherein Q is



wherein X is oxygen or sulfur.

55. A compound as in Claim 54, wherein X is oxygen.

56. A compound as in Claim 54, wherein X is sulfur.

TMS/275x

57. [6R-[6α,7β(Z)]]-7-[[(2-Amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[[[4-(9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-3,4-dioxoisothiazolo[5,4-b]quinolin-7-yl)-1-piperazinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid as well as salts thereof and hydrates of this compound and of its salts.

58. [6R-[6α,7β(Z)]]-7-[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[[[4-(9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydro-3,4-dioxoisothiazolo[5,4-b]quinolin-7-yl)-1-piperaz-inyl]carbonyl]oxy]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid as well as salts thereof and hydrates of this compound and of its salts.

59. Acyl derivatives of the formula I as set out in claim 1 substantially as hereinbefore described with reference to any one of the Examples.

60. A pharmaceutical preparation for the treatment or prophylaxis of bacterial infectious disease comprising a compound according to any one of claims 1 to 45 or any one of claims 53 to 59 together with a pharmaceutically acceptable carrier, diluent and/or excipient.

61. A method for the treatment or prophylaxis of bacterial infectious disease in a patient requiring said treatment or prophylaxis, which method comprises administering to said patient an effective amount of at least one compound according to any one of claims 1 to 45, or any one of claims 53 to 59, or of a composition according to claim 60.

62. A process for preparing acyl derivatives of the formula I as set out in claim 1 substantially as hereinbefore described with reference to any one of the Examples.

DATED this TWENTY-SEVENTH day of FEBRUARY 1992

F. Hoffmann-La Roche & Company Aktiengesellschaft

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AUSTRALIAN PATENT OFFICE TMS/275X