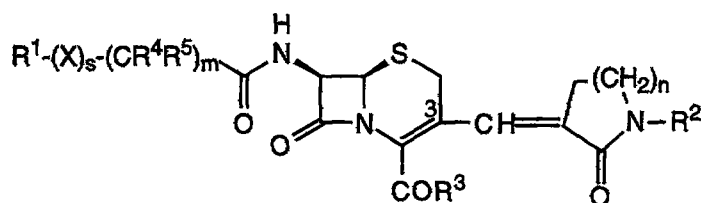


RAN 4410/257

Vinylpyrrolidinon Cephalosporin Derivatives ✓

The present invention relates to cephalosporin derivatives of the general formula



I

5 where

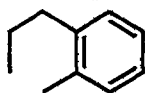
- |                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>R¹</p> <p>10</p> <p>R⁴, R⁵</p> <p>X</p> <p>15</p> <p>n</p> <p>m</p> <p>s</p> <p>R²</p> <p>20</p> | <p>is halogen, lower alkyl, phenyl, benzyl, styryl, naphthyl or heterocyclyl; the lower alkyl, phenyl, benzyl, styryl, naphthyl and heterocyclyl being optionally substituted by at least one of halogen, hydroxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted phenyl, amino, lower alkylamino, di-lower alkylamino, carboxy, lower alkyl-carboxy, carbamoyl or lower alkylcarbamoyl;</p> <p>independently are hydrogen, lower alkyl or phenyl;</p> <p>is S, O, NH or CH₂;</p> <p>is 0, 1 or 2;</p> <p>is 0 or 1;</p> <p>is 0 or 1;</p> <p>is hydrogen, hydroxy, -CH₂-CONHR⁶, lower alkyl-Q<sub>r</sub>, cycloalkyl-Q<sub>r</sub>, lower alkoxy, lower alkenyl, cycloalkenyl-Q<sub>r</sub>, lower alkynyl, aralkyl-Q<sub>r</sub>, aryl-Q<sub>r</sub>, aryloxy, aralkoxy, a heterocyclic ring or a heterocyclyl-Q<sub>r</sub>, the lower alkyl, cyclo-</p> |
|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Kj/ 10.9.97

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alkyl, lower alkoxy, lower alkenyl, cycloalkenyl, lower alkynyl, aralkyl, aryl, aryloxy, aralkoxy and the heterocyclic ring may be substituted with at least one group selected from carboxy, amino, nitro, cyano,  $-\text{SO}_2\text{NHR}^6$ , optionally fluoro substituted lower alkyl, lower alkoxy, hydroxy, halogen,  $-\text{CONR}^6\text{R}^7$ ,  $-\text{CH}_2\text{CONR}^6\text{R}^7$ ,  $-\text{N}(\text{R}^7)\text{COOR}^8$ ,  $\text{R}^7\text{CO}-$ ,  $\text{R}^7\text{OCO}-$ ,  $\text{R}^7\text{COO}-$ ,  $-\text{C}(\text{R}^7\text{R}^9)\text{CO}_2\text{R}^8$ ,  $-\text{C}(\text{R}^7\text{R}^9)\text{CONR}^7\text{R}^{10}$ , wherein  $\text{R}^6$  is hydrogen, lower alkyl, cycloalkyl or aryl;  $\text{R}^7$  and  $\text{R}^9$  are independently hydrogen or lower alkyl;  $\text{R}^8$  is hydrogen, lower alkyl, lower alkenyl or a carboxylic acid protecting group; and  $\text{R}^{10}$  is hydrogen,  $\omega$ -hydroxy-alkyl, phenyl, naphthyl or heterocyclyl, the phenyl, naphthyl or heterocyclyl being unsubstituted or substituted with at least one of the groups of optionally protected hydroxy, halogen, optionally substituted lower alkyl or  $\omega$ -hydroxyalkyl, optionally substituted lower alkoxy and/or cyano, or  $\text{R}^7$  and  $\text{R}^{10}$  form together group of



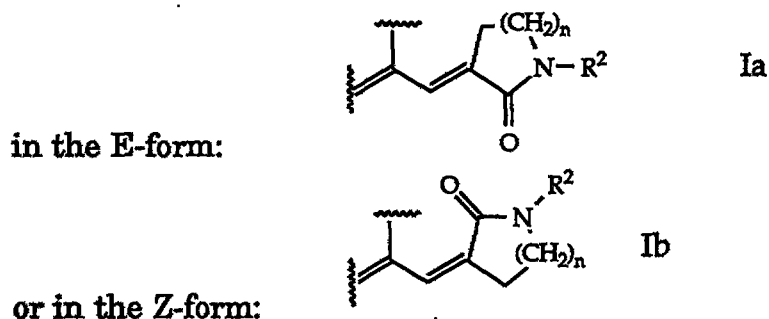
formula

$\text{Q}$  is  $-\text{CHR}-$ ,  $-\text{CO}-$  or  $-\text{SO}_2-$ ;  
 $r$  is 0 or 1;  
 $\text{R}$  is hydrogen or lower alkyl; and  
 $\text{R}^3$  is hydroxy,  $-\text{O}-$ , lower-alkoxy, or  $-\text{OM}$  and  $\text{M}$  represents an alkali metal;

as well as readily hydrolyzable esters thereof, pharmaceutically acceptable salts of said compounds and hydrates of the compounds of formula I and of their esters and salts.

The compounds of the present formula I are useful in the treatment of infectious diseases caused by gram-positive bacteria, especially infectious diseases caused by sensitive and resistant staphylococci, pneumococci, enterococci and the like.

In above compounds of formula I the substituent in position 3 can be present



Compounds of formula I i.e. wherein the substituent in position 3 is in the E-form are generally preferred.

In a particular embodiment of the compounds of formula I n is 1.

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

As used herein, the terms "alkyl" and "lower 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.

By the term "optionally substituted lower alkyl" is meant a "lower alkyl" moiety as defined above substituted by, for example, halogen, amino, hydroxy, cyano, carboxy etc., such as carboxymethyl, 2-fluoroacetyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-chloroethyl, 2-hydroxyethyl and like.

As used herein, the term "lower 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 "alkyl" portion may be substituted as defined above.

As used herein, "alkenyl" and "lower alkenyl" refer to unsubstituted or substituted hydrocarbon chain radical having from 2 to 8 carbon atoms, preferably from 2 to 4 carbon atoms, and having at least one olefinic double bond, e.g. allyl, vinyl etc.

As used herein, "lower alkynyl" refers to unsubstituted or substituted hydrocarbon chain radical having from 2 to 8 carbon atoms, preferably 2 to 4 carbon atoms, and having at least one triple bond.

By the term "cycloalkyl" is meant a 3-7 membered saturated carbocyclic moiety, e.g., cyclopropyl, cyclobutyl, cyclohexyl, etc.

As used herein, "cycloalkenyl" refers to a carbocyclic ring radical having at least one olefinic double bond.

5 By the term "aryl" is meant a radical derived from an aromatic hydrocarbon by the elimination of one atom of hydrogen and can be substituted or unsubstituted. The aromatic hydrocarbon can be mononuclear or polynuclear. Examples of aryl of the mononuclear type include phenyl, tolyl, xylyl, mesityl, cumenyl, and the like. Examples of aryl of the  
10 polynuclear type include naphthyl, anthryl, phenanthryl, and the like. The aryl group can have at least one substituent selected from, as for example, halogen, hydroxy, cyano, carboxy, nitro, amino, lower alkyl, lower alkoxy, carbamoyl, such as in 2,4-difluorophenyl, 4-carboxyphenyl, 4-nitrophenyl, 4-aminophenyl, 4-methoxyphenyl.

15 By the term "aralkyl" is meant an alkyl group containing an aryl group. It is 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., phenyl, tolyl, etc.

As used herein, "aryloxy" is an oxygen radical having an aryl  
20 substituent (i.e., -O-aryl).

As used herein, "aralkoxy" is an oxygen radical having an aralkyl substituent.

As used herein, the term "lower alkylamino and di-lower alkylamino" refers to mono and dialkylamino residues wherein lower alkyl is as defined  
25 above, for example methylamino, 2-ethylamino,  $-\text{CH}_2\text{NHCH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{NHCH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ , N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

As used herein, "heterocyclic ring" refers to an unsaturated or saturated, unsubstituted or substituted 4-, 5-, 6-, or 7-membered heterocyclic  
30 ring containing at least one hetero atom selected from the group consisting of oxygen, nitrogen, or sulfur. Exemplary heterocyclic rings include, but are not limited to, for example, the following groups: azetidyl, pyridyl, pyrazinyl, piperidyl, piperidino, N-oxido-pyridyl, pyrimidyl, piperazinyl, pyrrolidinyl, pyridazinyl, N-oxide-pyridazinyl, pyrazolyl, triazinyl,

imidazolyl, thiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl; furyl, 1H-azepinyl, thiophenyl, tetrahydrothiophenyl, isoxazolyl, isothiazolyl, oxazolidinyl, etc. Substituents for  
5 the heterocyclic ring include, for example, lower alkyls such as methyl, ethyl, propyl, etc., lower alkoxys such as methoxy, ethoxy, etc., halogens such as fluorine, chlorine, bromine, etc., halogen substituted alkyls such as trifluoromethyl, trichloroethyl, etc., amino, mercapto, hydroxyl, carbamoyl, or carboxyl groups. A further substituent is oxo, such as in 2-oxo-oxazolidin-  
10 3-yl, 1,1-dioxo-tetrahydrothiophen-3-yl. Further examples of substituted heterocycles are 6-methoxy-pyridin-3-yl, 5-methyl-isoxazol-3-yl, 1-methyl-pyridinium-2-yl, -3-yl, -4-yl, 1-carbamoylmethyl-pyridinium-2-yl, 1-carbamoylmethyl-pyridinium-3-yl, 1-carbamoylmethyl-pyridinium-2-yl, -3-yl, -4-yl, 1-[N-(3-fluoro-4-hydroxy)phenyl]-carbamoylmethyl-pyridinium-2-yl.

15 By the term "substituted phenyl" is meant phenyl mono or di-substituted by halogen, optionally substituted lower alkyl, optionally protected hydroxy or amino, nitro or trifluoromethyl.

The term "optionally protected hydroxy" refers to hydroxy or hydroxy protected, for example with t-butyloxycarbonyl, trimethylsilyl, t-butyl-  
20 dimethylsilyl, tetrahydropyranyl, trifluoroacetyl, and the like, or refers to an ester group, for example, phosphate or sulfonate.

The term "optionally protected amino" refers to amino or amino protected with, for example, BOC [t-butoxycarbonyl; other name: (1,1-dimethylethoxy)carbonyl], benzyloxycarbonyl and allyloxycarbonyl.

25 As used herein pharmaceutically acceptable salts useful in this invention include salts derived from metals, the ammonium salt, quaternary ammonium salts derived from organic bases and amino acid salts. Examples of preferred metal salts are those derived from the alkali metals, for example, lithium ( $\text{Li}^+$ ), sodium ( $\text{Na}^+$ ) and potassium ( $\text{K}^+$ ).  
30 Examples of quaternary ammonium salts derived from organic bases include tetramethylammonium ( $\text{N}^+(\text{CH}_3)_4$ ), tetraethylammonium ( $\text{N}^+(\text{CH}_2\text{CH}_3)_4$ ), benzyltrimethylammonium ( $\text{N}^+(\text{C}_6\text{H}_5\text{CH}_2)(\text{CH}_3)_3$ ), phenyltriethylammonium ( $\text{N}^+(\text{C}_6\text{H}_5)(\text{CH}_2\text{CH}_3)_3$ ), and the like, etc. Those salts derived from amines include salts with N-ethylpiperidine, procaine,  
35 dibenzylamine, N,N'-dibenzylethylenediamine, alkylamines or

dialkylamines as well as salts with amino acids such as, for example, salts with arginine or lysine. Especially preferred are hydrochlorides, sulfates, phosphates, lactates, mesylates or the inner salt.

The term "amino protecting groups" refers to protecting groups  
5 conventionally used to replace an acidic proton of an amino group. Examples of such groups are described in Green, T., Protective Groups in Organic Synthesis, Chapter 7, John Wiley and Sons, Inc. (1981), pp. 218-287, herein incorporated by reference. Preferably these examples include carbamates, e.g fluorenylmethyl, 2,2,2-trichloroethyl, 2-haloethyl, 2-(trimethylsilyl)ethyl,  
10 t-butyl, allyl, benzyl. Further protecting groups are 3,5-dimethoxybenzyl, p-nitro-benzyl, diphenylmethyl, triphenylmethyl, benzyl, formyl, acetyl, trifluoroacetyl, chloro-acetyl, the cyclic imides of N-phthaloyl, N-trimethylsilyl, N-benzenesulfonyl, N-toluenesulfonyl, N-p-methylbenzyl-sulfonyl. Preferred is BOC [t-butoxycarbonyl, other name (1,1-dimethyl-  
15 ethoxy)carbonyl], benzyloxycarbonyl and allyloxycarbonyl.

The term "carboxylic acid protecting group" refers to protecting groups conventionally used to replace the acidic proton of a carboxylic acid. Examples of such groups are described in Greene, T., Protective Groups in Organic Synthesis, Chapter 5, pp. 152-192 (John Wiley and Sons, Inc. 1981),  
20 incorporated herein by reference. Preferably these examples include methoxymethyl, methylthiomethyl, 2,2,2-trichloroethyl, 2-haloethyl, 2-(trimethylsilyl)ethyl, t-butyl, allyl, benzyl, triphenylmethyl (trityl), benzhydryl, p-nitrobenzyl, p-methoxybenzyl, trimethylsilyl, triethylsilyl, t-butyl dimethylsilyl, i-propyl-dimethylsilyl. Preferred are benzyhydryl, t-butyl,  
25 p-nitrobenzyl, p-methoxybenzyl and allyl.

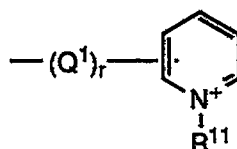
The term "hydroxy protecting group" refers to protecting groups as conventionally used in the art such as trimethylsilyl, t-butyl-dimethylsilyl, dimethylphenylsilyl, triphenylmethyl, lower alkanoyl, acetyl, tetrahydro-pyranyl, benzyl, p-nitrobenzyl or t- butyloxycarbonyl.

30 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 (for example, 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 alkanoyloxy-alkyl esters (e.g., the  
35 acetoxymethyl, pivaloyloxymethyl, 1-acetoxyethyl and 1-pivaloyloxyethyl ester), the lower alkoxycarbonyloxyalkyl esters (e.g., the methoxycarbonyl-

oxymethyl, 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  
 5 (e.g., the benzyl and cyanomethyl esters) can also be used. Other examples of such esters are the following: (2,2-dimethyl-1-oxopropoxy)methyl ester; 2-[(2-methylpropoxy)carbonyl]-2-pentenyl ester; 1-[[[(1-methylethoxy)carbonyl]oxy]ethyl ester; 1-(acetyloxy) ethyl ester; (5-methyl-2-oxo-1,3-dioxol-4-yl) methyl ester; 1-[[[(cyclohexyloxy)carbonyl]oxy] ethyl ester; and 3,3-dimethyl-2-oxo-  
 10 butyl ester. It will be appreciated by those of ordinary skill in the art that the readily hydrolyzable esters of the compounds of the present invention can be formed at a free carboxy group of the compound.

Examples of salts of the compounds of formula I are defined under "pharmaceutically acceptable salts" above.

15 A preferred embodiment of the invention are compounds of formula I wherein  $R^1$  is selected from the groups phenyl, 2,4,5-trichlorophenyl, 3,4-dichlorophenyl, 2,5-dichlorophenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-hydroxymethylphenyl, 3,4-dimethoxyphenyl, 4-methyl-1,2,4-triazol-5-yl, 1-methyl-tetrazol-5-yl, pyrimidin-2-yl, optionally substituted  
 20 pyridinium-1-yl, 2-yl, -3-yl or -4-yl, benzimidazol-2-yl, 2-benzthiazolyl, 4-pyridinyl, (2-amino)-thiazol-4-yl, 2-naphthyl, benzyl and  $R^2$  is methylcyclopropyl, 2-, 3- or 4-hydroxybenzyl, pyrrolidin-3-yl or a group of formula



wherein

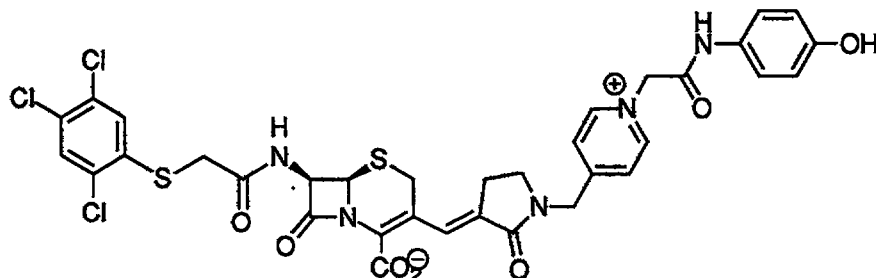
- 25  $Q^1$  is  $-\text{CH}_2-$   
 $r$  is 0 or 1;  
 $R^{11}$  is hydrogen, lower alkyl,  $\omega$ -hydroxy alkyl, benzyl or alkyl-heterocyclyl, the benzyl and the heterocyclyl group being unsubstituted or substituted with at least one of the groups  
 30 cyano, carboxy or hydroxy; or is  $-\text{CH}_2\text{CONR}^7\text{R}^{10}$ ; wherein  $R^7$  and  $R^{10}$  are as defined above.

The compounds of formula I as well as their salts and readily hydrolyzable esters can be hydrated. The hydration can be effected in the

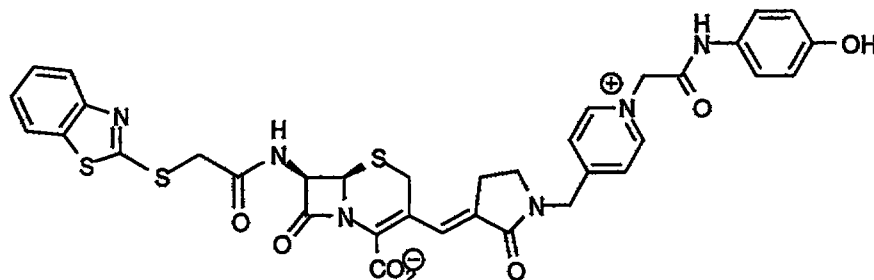
course of the manufacturing process or can occur gradually as a result of hygroscopic properties of an initially anhydrous product.

Especially preferred compounds of formula I are

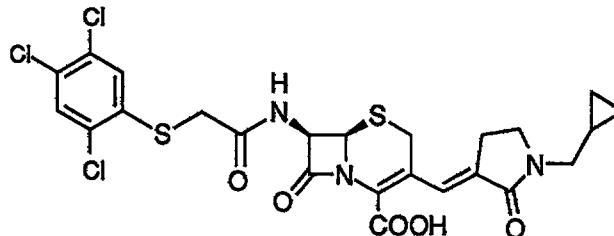
- (E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



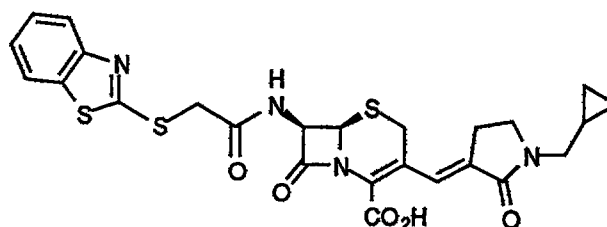
- 10 (E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(1-benzothiazol-2-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



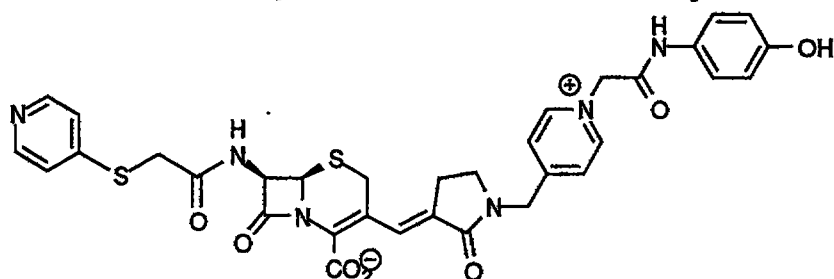
- 15 (E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



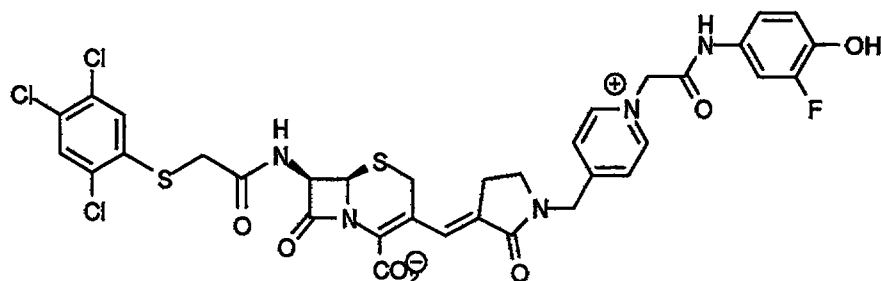
- 20 (E)-(6R,7R)-7-[2-(Benzothiazol-2-ylsulfanyl)-acetylamino]-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



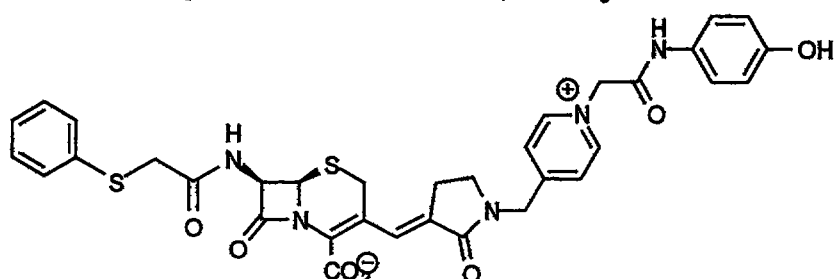
(E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(pyridin-4-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



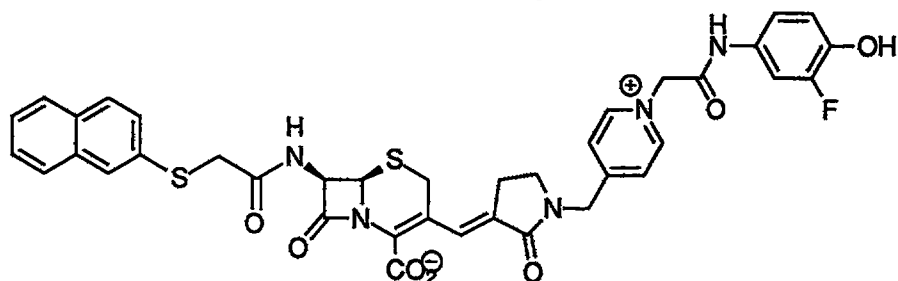
(E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



(E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

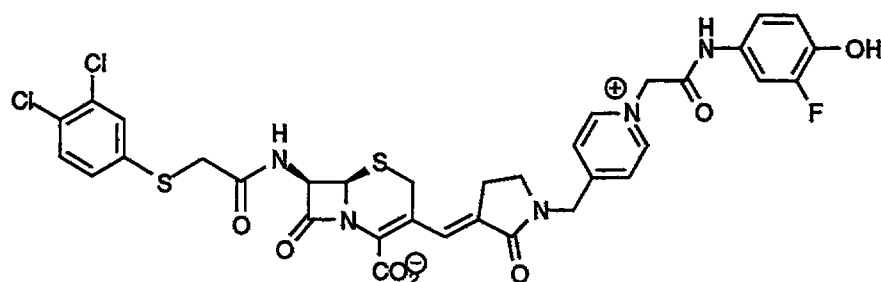


(E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-7-[2-(naphthalen-2-yl-sulfanyl)-acetyl-amino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



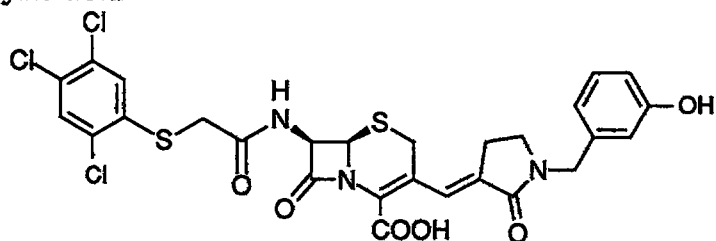
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(E)-(6R,7R)-7-[2-(3,4-Dichloro-phenylsulfanyl)-acetyl-amino]-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



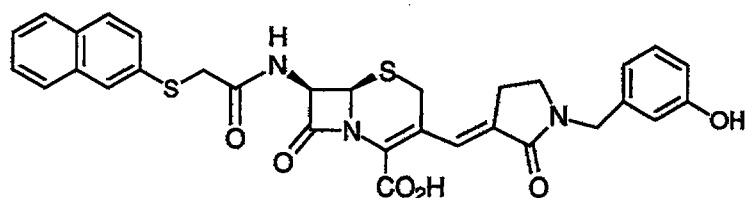
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(E)-(6R,7R)-3-[1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetyl-amino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



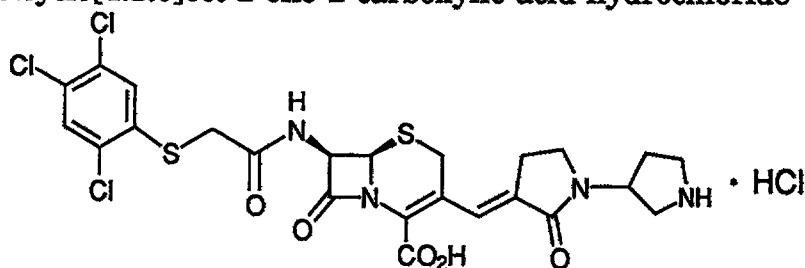
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(E)-(6R,7S)-3-[1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-naphthalen-2-ylsulfanyl)-acetyl-amino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



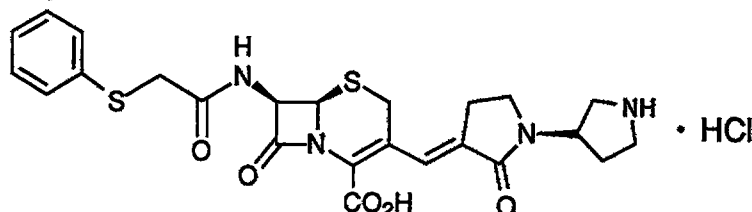
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Mixture of (E)-(6R,7R)-8-oxo-3-[(R)- and -(S)-2-oxo-[1,3']Bipyrrolidiny-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid hydrochloride



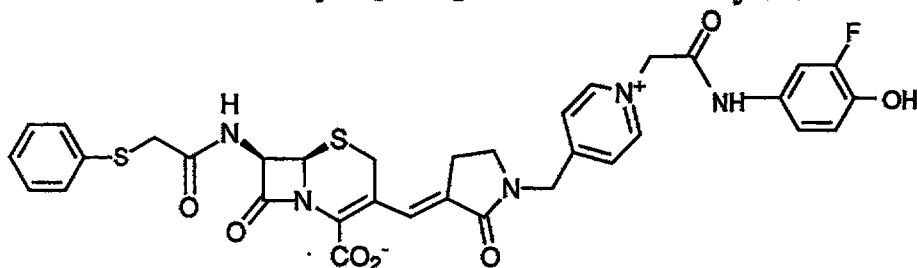
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(E)-(6R,7R)-8-Oxo-3-[(R)-2-oxo-[1,3']bipyrrolidiny-3-ylidenemethyl]-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid hydrochloride (1:1)

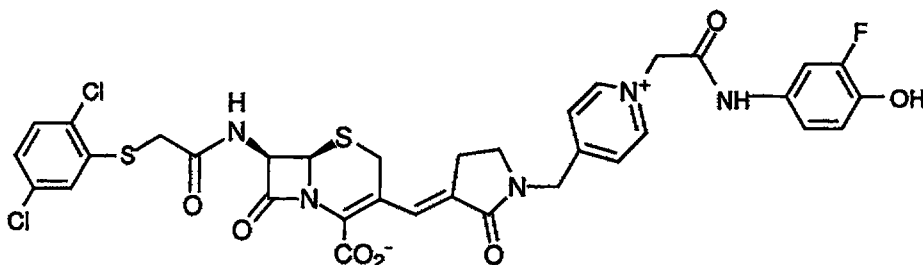


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(E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

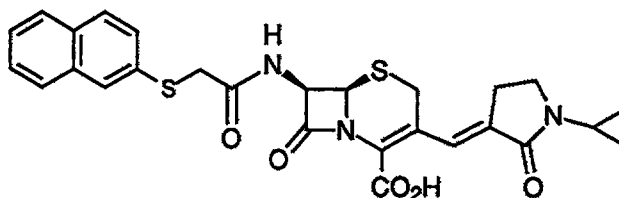


15 (E)-(6R,7R)-7-[2-(2,5-Dichloro-phenylsulfanyl)-acetylamino]-3-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



20

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(naphthalen-1-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)



5

The compounds of the present invention are useful as antibiotics having potent and broad antibacterial activity; especially against gram-positive organisms, e.g. methicillin-resistant staphylococci (MRSA).

The products in accordance with the invention can be used as  
10 medicaments, for example, in the form of pharmaceutical preparations for parenteral administration, and for this purpose are preferably made into preparations as lyophilisates or dry powders for dilution with customary agents, such as water or isotonic common salt solution.

Depending on the nature of the pharmacologically active compound the  
15 pharmaceutical preparations can contain the compound for the prevention and treatment of infectious diseases in mammals, human and non-human, a daily dosage of about 10 mg to about 4000 mg, especially about 50 mg to about 3000 mg, is usual, with those of ordinary skill in the art appreciating that the dosage will depend also upon the age, conditions of the mammals,  
20 and the kind of diseases being prevented or treated. The daily dosage can be administered in a single dose or can be divided over several doses. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg, and 2000 mg can be contemplated.

Representative compounds (A to F, below) of the present invention were  
25 tested. In vitro activity was determined by minimum inhibitory concentration in a microorganism spectrum by the agar dilution method in Mueller Hinton agar, inoculum =  $10^4$  CFU/spot.

A: (E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-  
30 phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

B: (E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(1-benzothiazol-

- 2-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate
- C: (E)-(6R,7R)-7-[2-(Benzothiazol-2-ylsulfanyl)-acetylamino]-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid
- 5 D: (E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(pyridin-4-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate
- E: (E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-7-[2-(naphthalen-2-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate
- 10 F: (E)-(6R,7R)-3-[1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid
- 15 G: (E)-(6R,7S)-3-[1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-naphthalen-2-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid
- H: Mixture of (E)-(6R,7R)-8-oxo-3-[(R)- and -[(S)-2-oxo-[1,3']Bipyrrolidinyl-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid hydrochloride
- 20 I: (E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetyl-amino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate
- 25

### In vitro activity against sensitive and resistant *S. aureus*

MIC [ $\mu\text{g/ml}$ ]

|                                  | A           | B    | C    | D   | E    | F    | G    | H           | I           |
|----------------------------------|-------------|------|------|-----|------|------|------|-------------|-------------|
| MIC <i>S. aureus</i> 6538 (MSSA) | $\leq 0.06$ | 0.12 | 0.25 | 0.5 | 0.25 | 0.12 | 0.12 | $\leq 0.06$ | $\leq 0.06$ |
| MIC <i>S. aureus</i> 270A (MRSA) | 1           | 1    | 2    | 4   | 1    | 2    | 1    | 1           | 1           |

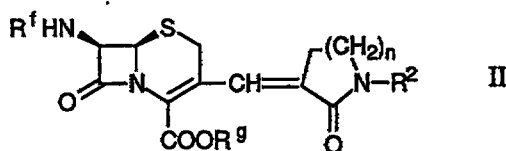
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Agar dilution method on Mueller-Hinton agar, inoculum:  $10^4$  CFU/spot

The compounds of the formula I in accordance with the invention as well as their pharmaceutical acceptable salts, hydrates, or readily hydrolyzable esters can be manufactured in accordance with the invention by

(a) treating a compound having the formula II

5



in which

R<sup>2</sup> and n are defined above;

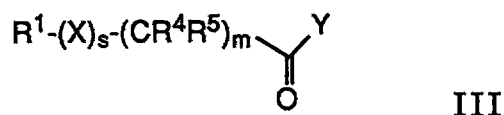
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R<sup>f</sup> is hydrogen or trimethylsilyl; and

R<sup>g</sup> is hydrogen, benzhydryl, p-methoxybenzyl, t-butyl, trimethylsilyl or allyl or salt thereof,

with a carboxylic acid of the general formula III

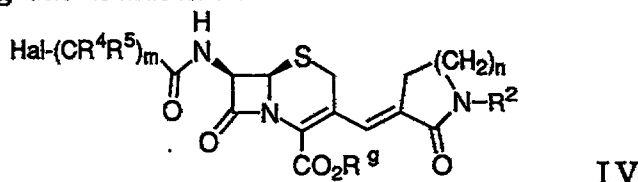
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in which R<sup>1</sup>, X, s, R<sup>4</sup>, R<sup>5</sup> and m are as defined above and Y is -OH, or a reactive functional derivative thereof wherein Y is, for example a  
 20 halogen as chloride or bromide, or 1-imidazolyl, 2-mercaptobenzotriazolyl, 1-hydrox- benzotriazolyl or pivaloyloxy, or an activating agent as HBTU (ortho-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium-hexafluorophosphat), DCC (N,N'-dicyclohexylcarbodiimid), CDI (1,1'-carbonyl-diimidazole), CDT (1,1'-carbonyl-1,2,4-ditriazole) or  
 25 thionylchloride and the like.

(b) for compounds of formula I wherein X is S, O or NH, by treating a compound having the formula IV

30



wherein R<sup>4</sup>, R<sup>5</sup>, m, n, R<sup>2</sup> and R<sup>g</sup> are as defined above and Hal stands for halogen as bromine or chlorine or iodide preferably bromine,

with an appropriate thiol or thiolate or an appropriate alcohol or alcoholate or an appropriate amine in the presence of a base,

(c) for the manufacture of a readily hydrolysable ester of a compound of formula I subjecting a carboxylic acid of formula I to a corresponding  
5 esterification or

(d) for the manufacture of salt 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 salts.

10

The reaction of a compound of formula II prepared according to embodiment (a) with a compound of formula III, or a reactive derivative thereof can be carried out in a manner known per se. The carboxy groups in compounds of formula II (carboxy group in position 2 and/or carboxy groups  
15 optionally present in  $R^2$ ) in compounds of formula III (carboxy groups optionally present in  $R^1$ ) can be protected intermediately or in situ, for example, by esterification to form readily cleavable esters such as a silyl ester (e.g. trimethylsilylester), a p-methoxy-benzylester or benzhydryl ester.

Furthermore the amino groups present in compounds of formula II (in  
20 position 7 and/or optionally present in  $R^2$ ) and/or optionally present in  $R^1$  of compounds of formula III can be protected, for example, with protecting groups which are cleavable by acid hydrolysis (e.g. the t-butoxycarbonyl or triphenylmethyl groups), by basic hydrolysis (e.g. the trifluoroacetyl group), by hydrazinolysis (e.g. the phthalimido group) or by catalytic cleavage in  
25 presence of Pd (the allyloxycarbonyl group). Preferred protecting groups are the t-butyloxy-carbonyl, allyloxycarbonyl, the chloroacetyl, bromoacetyl and iodoacetyl groups, especially the chloroacetyl group. These last-mentioned protecting groups can be cleaved off by treatment with thiourea. Another preferred protecting group is phenylacetyl which can be cleaved off by  
30 treatment with  $PCl_5$  or enzymatic.

The 7-amino group in compounds II can be protected in situ, for example, by a silyl protecting group such as the trimethylsilyl group.

In reacting a 7-amino compound of formula II with a carboxylic acid of formula III or a reactive functional derivative thereof, for example, a free  
35 carboxylic acid can be reacted with an aforementioned ester of a compound of formula II in the presence of a carbodiimide such as dicyclohexylcarbo-

diimide in an inert solvent such as ethyl acetate, acetonitrile, dioxane, chloroform, methylene chloride, benzene, dimethylformamide or dimethylacetamide, and subsequently the ester group can be cleaved off.

Prepared 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 a carboxylic acid of formula III in an inert solvent (e.g. dimethylformamide, dimethylacetamide, dimethylsulfoxide and the like).

The reaction of a 7-amino compound of formula II with the carboxylic acid of formula III 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.

Embodiment (b) of the process of the present invention involves treating a compound of formula IV with an appropriate thiol or thiolate or an appropriate alcohol or alcoholate or an appropriate amine in presence of a base, for example, trialkylamine such as trimethylamine, triethylamine sodium bicarbonate, DBU (1,8-diazabicyclo[5,4,0]undec-7-en(1,5-5)) to form the corresponding thioether, ether or amine. Optionally present amino, hydroxy or carboxyl groups can be intermediatly protected with groups as described above.

Deprotection (removal) of protected amino, hydroxy or carboxylic groups present in a compound of formulae II, III and IV can be carried out as follows:

#### Removal of amino protecting groups

Possible amino-protecting groups are those employed in peptide chemistry, such as the protecting groups mentioned above. Preferably these examples include carbamates, e.g. fluorenylmethyl, 2,2,2-trichloroethyl, t-butyl, triphenylmethyl, allyl, benzyl. Further protecting groups are p-nitrobenzyl, diphenylmethyl, triphenylmethyl, benzyl, formyl, trifluoroacetyl, chloro-acetyl, the cyclic imides of N-phthaloyl, N-trimethylsilyl, N-benzenesulfonyl, N-toluenesulfonyl. Preferred is BOC [t-butoxycarbonyl; other name: (1,1-dimethylethoxy)carbonyl], benzyloxycarbonyl, allyloxycarbonyl or trimethylsilyl

The amino protecting groups may be cleaved off by acid hydrolysis (e.g. the t-butoxycarbonyl or triphenylmethyl group), e.g. aqueous formic acid,

trifluoroacetic acid or by basic hydrolysis (e.g. the trifluoroacetyl group). The chloroacetyl, bromoacetyl and iodoacetyl groups are cleaved off by treatment with thiourea. The trimethylsilyl group is cleaved off by hydrolysis or alcoholysis.

- 5        Amino-protecting groups which are cleavable by acid hydrolysis are preferably removed with the aid of a lower alkanecarboxylic acid which may be halogenated. In particular, formic acid or trifluoroacetic acid is used. The reaction is carried out in the acid or in the presence of a co-solvent such as a halogenated lower alkane, e.g. methylene chloride. The acid hydrolysis is  
10 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  $-30^{\circ}\text{C}$  to  $+40^{\circ}\text{C}$ ). Protecting groups which are cleavable under basic conditions are generally hydrolyzed with dilute aqueous caustic alkali at  $0^{\circ}\text{C}$  to  $30^{\circ}\text{C}$ . The chloroacetyl, bromoacetyl and iodoacetyl protecting  
15 groups can be cleaved off using thiourea in acidic, neutral or alkaline medium at about  $0^{\circ}\text{C}$ - $30^{\circ}\text{C}$ . The phthalimido group can be cleaved off with hydrazine at  $-20^{\circ}\text{C}$  to  $+50^{\circ}\text{C}$ .

#### Removal of hydroxy protecting groups

- Possible hydroxy protecting groups are such as are commonly known in  
20 the art, such as trimethylsilyl, t-butyl-dimethylsilyl, dimethylphenylsilyl, triphenylmethyl, lower alkanoyl, acetyl, trifluoroacetyl, tetrahydropyranyl, benzyl, p-nitrobenzyl or t-butoxycarbonyl. These groups are removed in the presence of acidic solvents, weak organic acids or weak inorganic bases like sodium bicarbonate, respectively.

#### 25 Removal of protecting groups at the carboxy function

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

These protecting groups may be removed as follows:

- |                 |                                                                                                                                                                                                                                             |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| benzhydryl      | trifluoroacetic acid with anisol, phenol, cresol or triethylsilane at about -40°C to room temperature; hydrogen with Pd/C in an alcohol such as ethanol or in tetrahydrofuran; BF <sub>3</sub> -etherate in acetic acid at about 0 to 50°C; |
| 5 t-butyl       | formic acid or trifluoroacetic acid with or without anisol, phenol, cresol or triethylsilane and a solvent such as dichloromethane at about -10°C to room temperature;                                                                      |
| p-nitrobenzyl   | sodium sulfide in acetone/water at about 0 to room                                                                                                                                                                                          |
| 10              | temperature; or hydrogen with Pd/C in an alcohol such as ethanol or in tetrahydrofuran;                                                                                                                                                     |
| p-methoxybenzyl | formic acid at about 0 to 50°C; or trifluoroacetic acid and anisol, phenol or triethylsilane at about -40°C to room temperature;                                                                                                            |
| 15 allyl        | palladium(0) catalyzed transalkylation reaction in the presence of sodium or potassium salt of 2-ethyl hexanoic acid, see for example J. Org. Chem. 1982, <u>47</u> , 587.                                                                  |
| trimethylsilyl  | by hydrolysis or alcoholysis at room temperature.                                                                                                                                                                                           |

20 In order to manufacture a readily hydrolysable ester of the carboxylic acids of formula I in accordance with embodiment (c) 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.

30 The manufacture of the salts and hydrates of the compounds of formula I or the hydrates of said salts in accordance with embodiment (d) 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

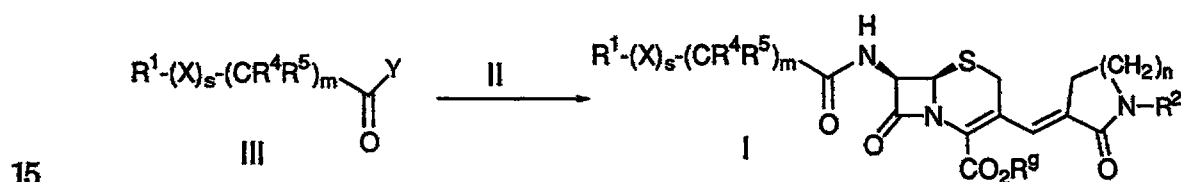
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addition of an organic or inorganic salt or an acid. The temperature at which the salt formation is carried out is not critical. The salt formation is generally carried out at room temperature, but it can be carried out at a temperature slightly above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

The manufacture of the 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  
10 or salt thereof can be exposed to a moist atmosphere (e.g. at about +10°C to +40°C).

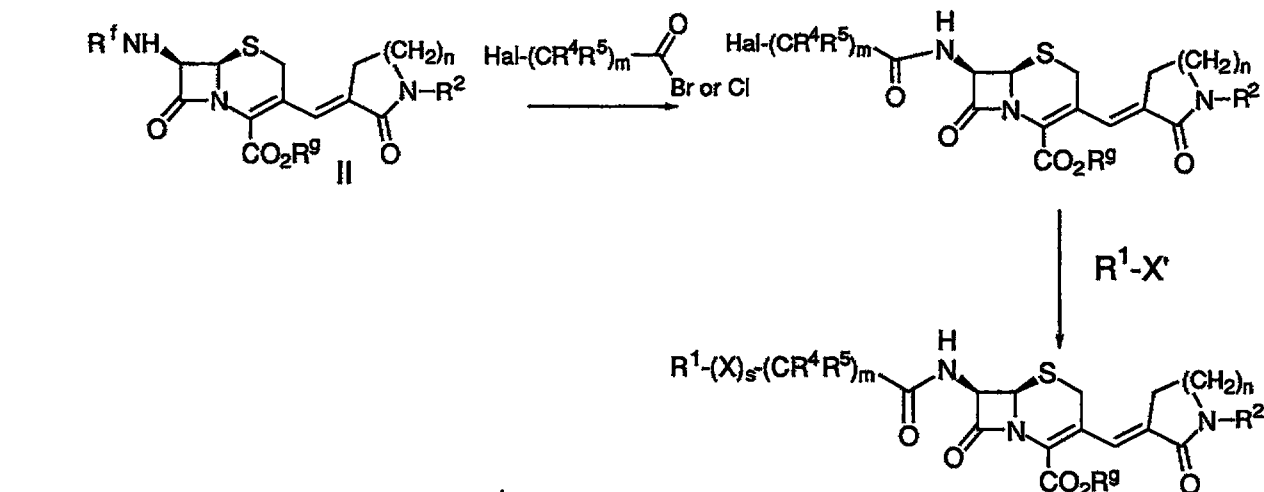
Exemplary of the process for obtaining products in accordance with the invention are the following reaction schemes 1 and 2 below.

Scheme 1, embodiment (a)



wherein X is -CH<sub>2</sub>-, O, S or NH and the remaining symbols are as defined above.

Scheme 2, embodiment (b)



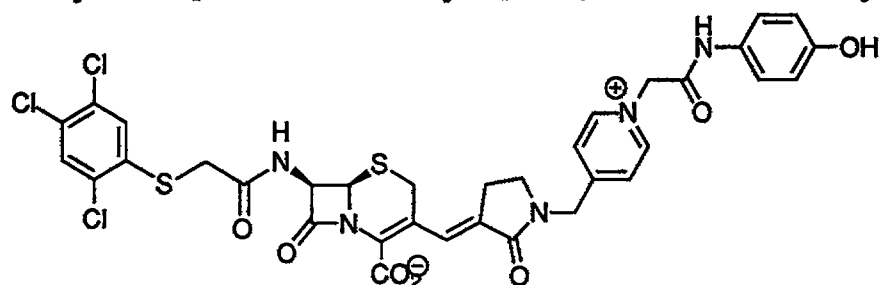
wherein X is O, S, NH and X' accordingly OH or O<sup>-</sup>, SH or S<sup>-</sup> or NH<sub>2</sub> and the remaining substituent are as defined above.

## Examples

### Method A

#### Example A1

(E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-yl-  
5 methyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenyl-  
sulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



To a solution of 68.4 mg (0.25 mmol) (2,4,5-trichloro-phenylsulfanyl)-acetic  
acid in 3 ml N,N-dimethylacetamide were added under stirring and Argon  
10 atmosphere 40.9 mg (0.25 mmol) 1,1'-carbonyldiimidazole. After 30 min,  
136.4 mg (0.21 mmol) (E)-(6R,7R)-7-amino-3-[1-[1-[(4-hydroxy-phenyl-  
carbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidene-  
methyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoro-  
acetate was added in a single portion. After 3h the reaction mixture was  
15 poured on diethyl ether. The solid material was collected by filtration and  
trituated with ethyl acetate.

Yield: 112.0 mg (67.5%) beige powder

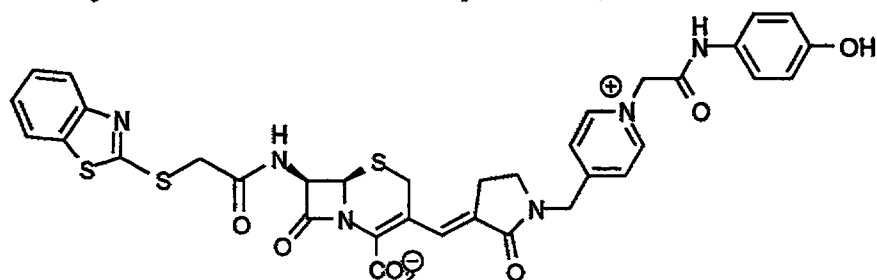
IR(KBr): 1770, 1678, 1642  $\text{cm}^{-1}$

MS(ISP): 790.2 ( $\text{M}^+$ )

20 According to the procedure in example A1 the following additional  
compounds were prepared:

#### Example A2

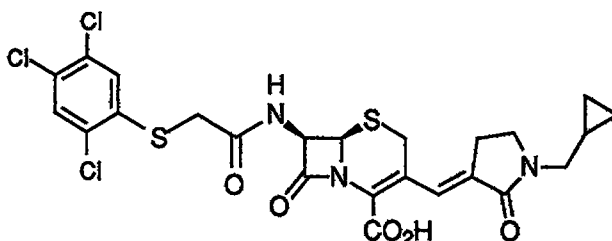
(E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-  
ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(1-benzothiazol-2-  
25 ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



- With 70.0 mg (0.43 mmol) 1,1'-carbonyldiimidazole, 96.0 mg (0.43 mmol) (benzothiazol-2-ylsulfanyl)-acetic acid and 233.8 mg (0.36 mmol) (E)-(6R,7R)-7-amino-3-[1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-yl-methyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetate in 4 ml N,N-dimethylacetamide.
- Yield: 92.0 mg (34.4%) yellow powder
- IR(KBr): 1769, 1679, 1643, 1625  $\text{cm}^{-1}$
- MS(ISP): 743.3 ( $\text{M}+\text{H}^+$ )

#### Example A3

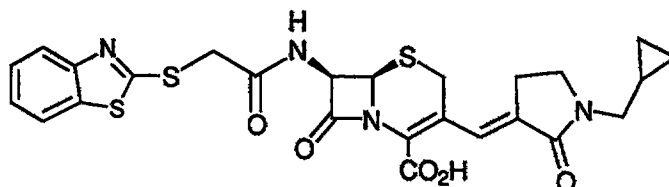
- 10 (E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetyl-amino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



- With 180.0 mg (1.11 mmol) 1,1'-carbonyldiimidazole, 301.4 mg (1.11 mmol) (2,4,5-trichloro-phenylsulfanyl)-acetic acid and 323.2 mg (0.92 mmol) (E)-(6R,7R)-7-amino-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid in 8 ml N,N-dimethylformamide.
- Yield: 337.0 mg (60.4%) brown powder
- 20 IR(KBr): 1773, 1668, 1621  $\text{cm}^{-1}$
- MS(ISP): 602.2 ( $\text{M}+\text{H}^+$ )

#### Example A4

- (E)-(6R,7R)-7-[2-(Benzothiazol-2-ylsulfanyl)-acetyl-amino]-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid
- 25



- With 220.0 mg (1.35 mmol) 1,1'-carbonyldiimidazole, 304.1 mg (1.35 mmol) (benzothiazol-2-ylsulfanyl)-acetic acid and 394.8 mg (1.13 mmol) (E)-(6R,7R)-7-amino-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-

thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid in 7 ml N,N-dimethylformamide.

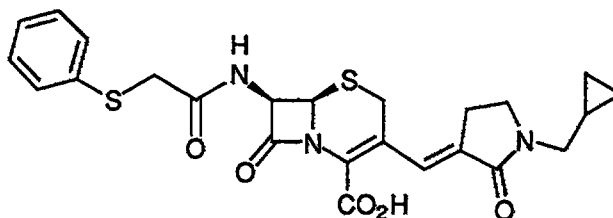
Yield: 173.0 mg (27.5%) orange powder

IR(KBr): 1772, 1665, 1623  $\text{cm}^{-1}$

5 MS(ISP): 557.1 ( $\text{M}+\text{H}^+$ )

#### Example A5

(E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-(2-phenylsulfanyl-acetyl-amino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



10

With 167.0 mg (1.03 mmol) 1,1'-carbonyldiimidazole, 173.0 mg (1.03 mmol) 2-(phenylthio)acetic acid and 300.0 mg (0.86 mmol) (E)-(6R,7R)-7-amino-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid in 6 ml N,N-dimethylformamide.

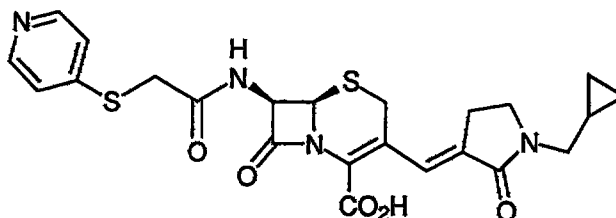
15 Yield: 271.5 mg (63.1%) brown powder

IR(KBr): 1773, 1662, 1624  $\text{cm}^{-1}$

MS(ISP): 500.3 ( $\text{M}+\text{H}^+$ )

#### Example A6

(E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-(2-pyridin-4-ylsulfanyl-acetyl-amino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



25 With 111.0 mg (0.68 mmol) 1,1'-carbonyldiimidazole, 116.0 mg (0.68 mmol) (pyridin-4-ylsulfanyl)-acetic acid and 200.0 mg (0.57 mmol) (E)-(6R,7R)-7-amino-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid in 4 ml N,N-dimethylformamide.

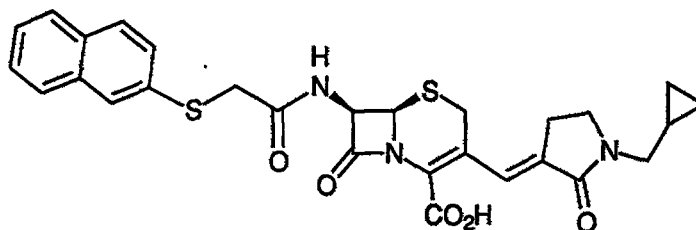
Yield: 79.0 mg (27.5%) beige solid

IR(KBr): 1769, 1667, 1624

30 MS(ISP): 501.1 ( $\text{M}+\text{H}^+$ )

### Example A7

(E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(naphthalen-2-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



5

With 167.0 mg (1.03 mmol) 1,1'-carbonyldiimidazole, 225.0 mg (1.03 mmol) (naphthalen-2-ylsulfanyl)-acetic acid and 300.0 mg (0.86 mmol) (E)-(6R,7R)-7-amino-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid in 4 ml N,N-dimethyl-

10 formamide.

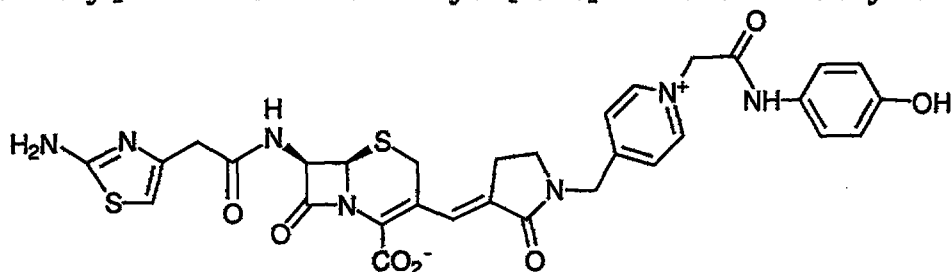
Yield: 320.0 mg (62%) brown powder

IR(KBr): 1769, 1662, 1623  $\text{cm}^{-1}$

MS(ISP): 550.2 ( $\text{M}+\text{H}^+$ )

### Example A8

15 (E)-(6R,7R)-7-[2-(2-Amino-thiazol-4-yl)-acetylamino]-3-[1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



20 With 54.5 mg (0.34 mmol) 1,1'-carbonyldiimidazole, 53.0 mg (0.34 mmol) (2-aminothiazole-4-yl)-acetic acid and 182.0 mg (0.28 mmol) (E)-(6R,7R)-7-amino-3-[1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetate in 4 ml N,N-dimethylformamide. The resulting solid was purified by reversed phase  
25 chromatography (RP-18 LiChroPrep gel, water : acetonitrile = 9 : 1). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

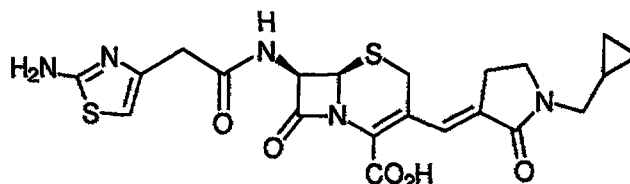
Yield: 49.0 mg (24.7%) beige lyophilisate

IR(KBr): 1775, 1680, 1650  $\text{cm}^{-1}$

MS(ISP): 676.2 ( $M^+$ )

### Example A9

(E)-(6R,7R)-7-[2-(2-Amino-thiazol-4-yl)-acetylamino]-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



With 167.0 mg (1.03 mmol) 1,1'-carbonyldiimidazole, 163.0 mg (1.03 mmol) (2-aminothiazole-4-yl)-acetic acid and 300.0 mg (0.86 mmol) (E)-(6R,7R)-7-amino-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid in 6 ml N,N-dimethylformamide. The resulting solid was purified by reversed phase chromatography (RP-18 LiChroPrep gel, water : acetonitrile = 9 : 1). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

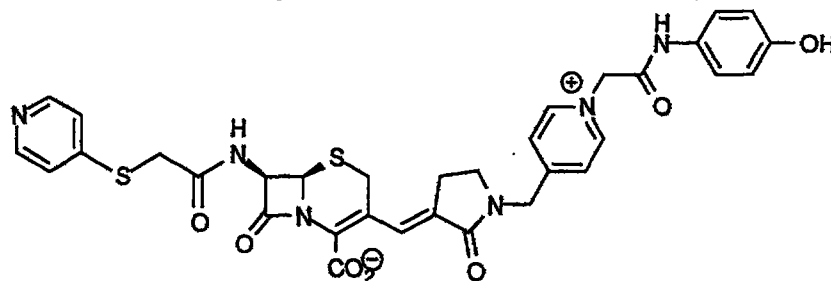
Yield: 120.0 mg (28.6%) beige lyophilisate

IR(KBr): 1769, 1664, 1620  $\text{cm}^{-1}$

MS(ISP): 490.2 ( $M+H^+$ )

### Example A10

(E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(pyridin-4-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



With 70.0 mg (0.43 mmol) 1,1'-carbonyldiimidazole, 72.8 mg (0.43 mmol) (pyridin-4-ylsulfanyl)-acetic acid and 232.8 mg (0.36 mmol) (E)-(6R,7R)-7-amino-3-[1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetate in 4 ml ml N,N-dimethylacetamide. The brown solid was purified by column chromatography on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (1:0, 4:1,

3:1, 2:1, 1:1). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

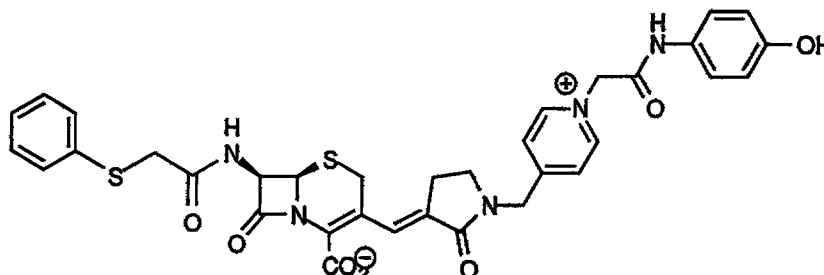
**Yield: 58.0 mg (30.0%) beige lyophilisate**

IR(KBr): 1772, 1670, 1625  $\text{cm}^{-1}$

5 MS(ISP): 687.3 (M+H<sup>+</sup>)

### Example A11

(E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetyl-amino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



10

With 70.0 mg (0.43 mmol) 1,1'-carbonyldiimidazole, 71.0 mg (0.43 mmol) 2-(phenylthio)acetic acid and 188.4 mg (0.29 mmol) (E)-(6R,7R)-7-amino-3-[1-[1-[(4-hydroxy-phenyl)carbamoyl]-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxopyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-

15 carboxylate trifluoroacetate in 4 ml ml N,N-dimethylacetamide. The  
resulting solid was suspended in 6 ml water : acetonitrile (1 : 1) and HCl was  
added until all compound dissolved. After column chromatography on MCI  
gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water :  
acetonitril (1:0, 4:1, 3:1, 2:1, 1:1) the organic solvent was stripped off at a  
20 rotary evaporator and the aqueous phase was freeze-dried.

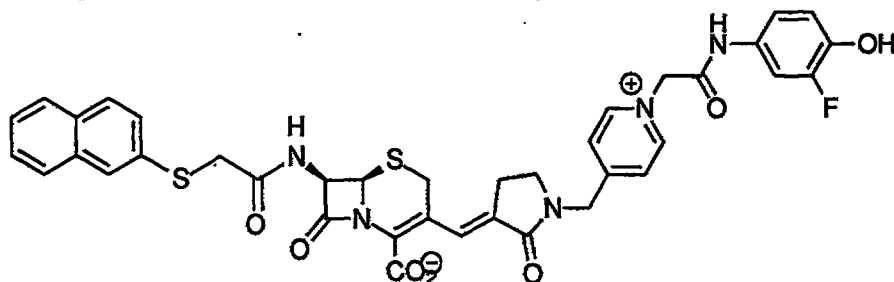
**Yield: 105.6 mg (64.4%) beige lyophilisate**

IR(KBr): 1770, 1680, 1643  $\text{cm}^{-1}$

MS(ESI): 686.3 (M+H<sup>+</sup>)

### Example A12

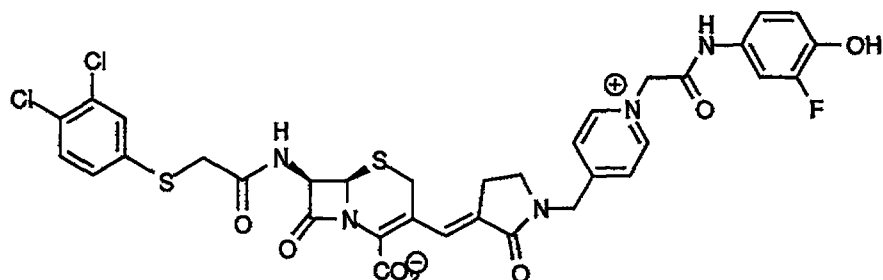
(E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-7-[2-(naphthalen-2-yl-sulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



- 5 With 58.3 mg (0.36 mmol) 1,1'-carbonyldiimidazole, 78.5 mg (0.36 mmol) (naphthalen-2-ylsulfanyl)-acetic acid and 200.0 mg (0.30 mmol) (E)-(6R,7R)-7-amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo-
- 10 [4.2.0]oct-2-ene-2-carboxylate trifluoroacetate in 4 ml N,N-dimethylacetamide. The resulting solid was purified by column chromatography on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (1:0, 4:1, 3:1, 2:1, 1:1). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.
- 15 Yield: 55.0 mg (24.0%) beige lyophilisate  
 IR(KBr): 1770, 1680, 1650, 1628  $\text{cm}^{-1}$   
 MS(ISP): 754.3 ( $\text{M}+\text{H}^+$ )

### Example A13

- 20 (E)-(6R,7R)-7-[2-(3,4-Dichloro-phenylsulfanyl)-acetylamino]-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



- 25 With 60.0 mg (0.36 mmol) 1,1'-carbonyldiimidazole, 85.0 mg (0.36 mmol) [(3,4-dichlorophenyl)thio]acetic acid and 200.0 mg (0.30 mmol) (E)-(6R,7R)-7-amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo-
- [4.2.0]oct-2-ene-2-carboxylate trifluoroacetate in 4 ml N,N-dimethylacet-

amide. The resulting solid was purified by column chromatography on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (1:0, 4:1, 3:1, 2:1, 1:1). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

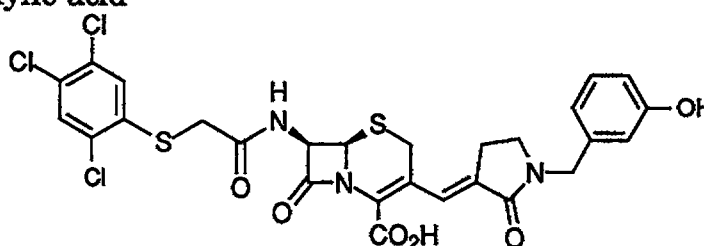
5 Yield: 70.0 mg (30.2%) beige lyophilisate

IR(KBr): 1772, 1680, 1642, 1617  $\text{cm}^{-1}$

MS(ISP): 772.3 ( $\text{M}+\text{H}^+$ )

#### Example A14

(E)-(6R,7R)-3-[1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-  
10 [2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



With 146.0 mg (0.90 mmol) 1,1'-carbonyldiimidazole, 244.4 mg (0.90 mmol) (2,4,5-trichloro-phenylsulfanyl)-acetic acid and 301.0 mg (0.73 mmol) (E)-  
15 (6R,7R)-7-amino-3-[1-(3-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid trifluoroacetate in 5 ml N,N-dimethylacetamide.

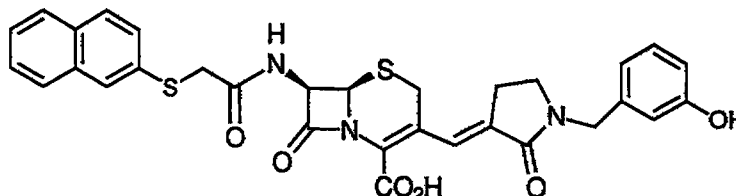
Yield: 180.0 mg (37.7%) beige powder

IR(KBr): 1767, 1664, 1614  $\text{cm}^{-1}$

20 MS(ISP): 654.1 ( $\text{M}+\text{H}^+$ )

#### Example A15

(E)-(6R,7S)-3-[1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-  
[2-naphthalen-2-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-  
2-carboxylic acid



25

With 146.0 mg (0.90 mmol) 1,1'-carbonyldiimidazole, 196.5 mg (0.90 mmol) (naphthalen-2-ylsulfanyl)-acetic acid and 301.0 mg (0.73 mmol) (E)-(6R,7R)-7-amino-3-[1-(3-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid trifluoroacetate in 5 ml N,N-  
30 dimethylacetamide. The resulting solid was purified by column chromato-

graphy on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (1:0, 4:1, 3:1, 2:1, 1:1). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

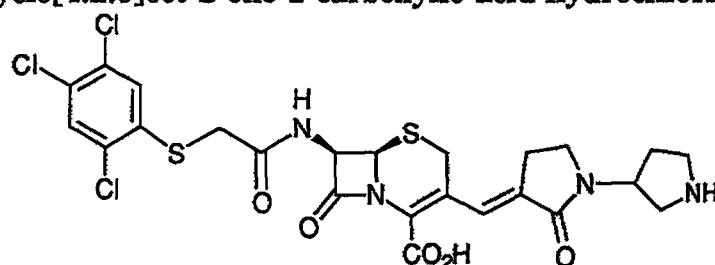
Yield: 65.0 mg (14.6%) beige lyophilisate

5 IR(KBr): 1771, 1663, 1589  $\text{cm}^{-1}$

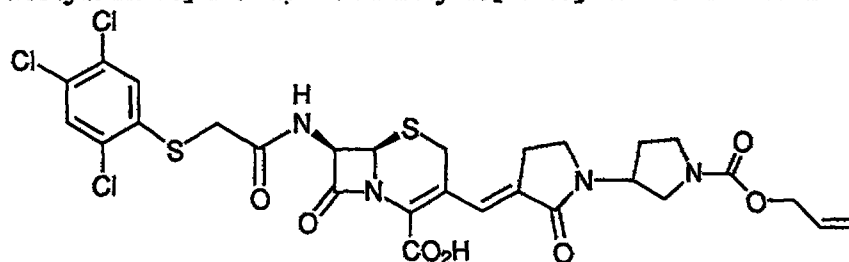
MS(ISP): 602.2 ( $\text{M}+\text{H}^+$ )

### Example A16

Mixture of (E)-(6R,7R)-8-oxo-3-[(R)- and -[(S)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-  
10 thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid hydrochloride



**Step a:** Mixture of (E)-(6R,7R)-3-[(R)- and -[(S)-1'-allyloxycarbonyl-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



15

With 115.2 mg (0.71 mmol) 1,1'-carbonyldiimidazole, 193.4 mg (0.71 mmol) (2,4,5-trichloro-phenylsulfanyl)-acetic acid and 329.1 mg (0.59 mmol) of a mixture of (E)-(6R,7R)-3-[(R)- and -[(S)-1'-allyloxycarbonyl-2-oxo-[1,3']bipyrrolidin-3-ylidenemethyl)-7-amino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid trifluoroacetate in 6 ml N,N-dimethylacetamide  
20 Prepared according to example A1.

Yield: 220.0 mg (66.0%) beige powder

IR(KBr): 1774, 1678, 1624  $\text{cm}^{-1}$

MS(ISP): 703.2 ( $\text{M}+\text{H}^+$ )

25 **Step b:** Mixture of (E)-(6R,7R)-8-oxo-3-[(R)- and -[(S)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid hydrochloride

The product prepared in step a (220.0 mg, 0.31 mmol) was suspended in 12 ml dichloromethane and 124  $\mu$ l (0.50 mmol) N,O-bis-(trimethylsilyl)-acetamide was added. After a clear solution had formed, 5.60 mg (8.56  $\mu$ mol) palladium-bis-(triphenylphosphine)-dichloride, 0.36 ml (6.30 mmol) acetic acid and 0.8 ml (3.0 mmol) tributyltinhydride were added. After 45 min 40  $\mu$ l water was added to the suspension and the reaction mixture was poured under stirring on 200 ml diethyl ether, containing 2 ml of a hydrochloric acid-saturated diethyl ether solution. The solid was collected by filtration and triturated with 40 ml ethyl acetate.

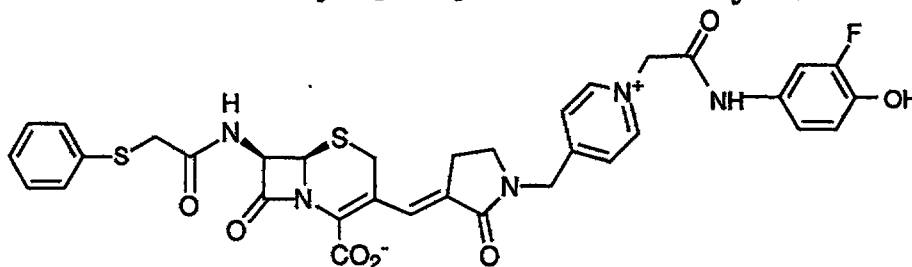
Yield: 180.0 mg (87.8%) beige powder

IR(KBr): 1771, 1661, 1582  $\text{cm}^{-1}$

MS(ISP): 619.1 ( $\text{M}+\text{H}^+$ )

### Example A17

(E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



With 175.0 mg (1.08 mmol) 1,1'-carbonyldiimidazole, 182.0 mg (1.08 mmol) 2-(phenylthio)acetic acid and 500.0 mg (0.75 mmol) (E)-(6R,7R)-7-amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetate in 4 ml N,N-dimethylacetamide. The resulting solid was purified by column chromatography on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (1:0, 4:1, 3:1, 2:1). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

Yield: 90.0 mg (20.6%) beige lyophilisate

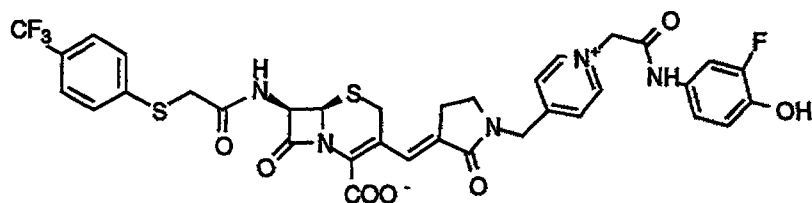
IR(KBr): 1772, 1680, 1648  $\text{cm}^{-1}$

MS(ISP): 704.4 ( $\text{M}^+$ )

### Example A18

(E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(4-trifluoro-

methyl-phenylsulfanyl)-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



With 66.8 mg (0.41 mmol) 1,1-carbonyldiimidazole, 97.3 mg (0.41 mmol) 2-[4-  
5 (trifluoromethyl)phenylthio]acetic acid and 250.0 mg (0.37 mmol) (E)-(6R,7R)-  
7-amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-  
ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetate in 4 ml N,N-  
dimethylacetamide. The resulting solid was purified by column  
10 chromatography on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a  
gradient of water : acetonitrile (1 : 0, 4 : 1, 3 : 1, 2 : 1, 1 : 1). The organic  
solvent was stripped off at a rotary evaporator and the aqueous phase was  
freeze-dried.

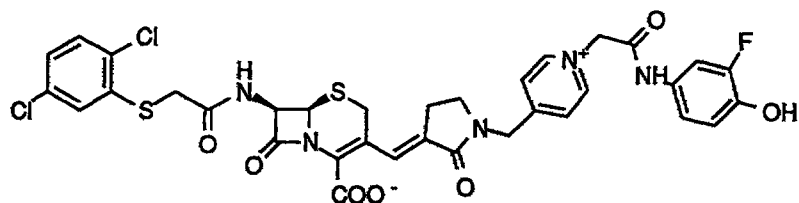
Yield: 89.0 mg (30.8%) pale yellow lyophilisate

15 IR(KBr): 1777, 1678, 1650  $\text{cm}^{-1}$

MS(ISP): 772.3 ( $\text{M}+\text{H}^+$ )

### Example A19

(E)-(6R,7R)-7-[2-(2,5-Dichloro-phenylsulfanyl)-acetylamino]-3-[1-[(3-fluoro-4-  
20 hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-  
pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-  
carboxylate



With 72.9 mg (0.45 mmol) 1,1-carbonyldiimidazole, 106.5 mg (0.45 mmol)  
25 (2,5-dichloro-phenylsulfanyl)acetic acid and 250.0 mg (0.37 mmol) (E)-  
(6R,7R)-7-amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-  
pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-  
aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetate in 4 ml N,N-  
dimethylacetamide. The resulting solid was purified by column chromato-  
30 graphy on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient  
of water : acetonitrile (1 : 0, 4 : 1, 3 : 1, 2 : 1, 1 : 1). The organic solvent was  
stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

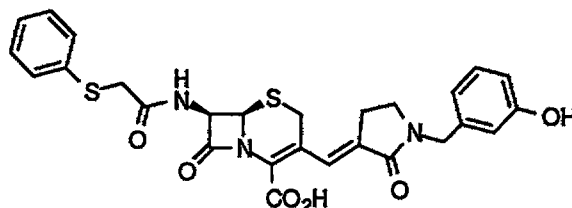
Yield: 74.5 mg (21.3%) beige lyophilisate

IR(KBr): 1772, 1680, 1650  $\text{cm}^{-1}$

MS(ISP): 772.3 ( $\text{M}+\text{H}^+$ )

### 5 Example A20

(E)-(6R,7R)-3-[1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



- 10 With 121.1 mg (0.75 mmol) 1,1-carbonyldiimidazole, 125.6 mg (0.75 mmol) (phenylthio)acetic acid and 250.0 mg (0.62 mmol) (E)-(6R,7R)-7-amino-3-[1-(3-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid trifluoroacetate in 4 ml N,N-dimethyl-acetamide. The resulting solid was purified by column chromatography on
- 15 MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (1 : 0, 4 : 1, 3 : 1). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

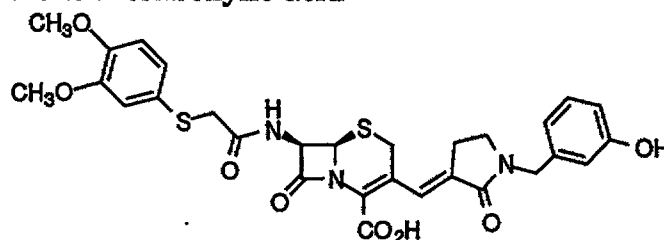
Yield: 189.5 mg (55.2%) yellow lyophilisate

IR(KBr): 1764, 1664, 1612  $\text{cm}^{-1}$

- 20 MS(ISP): 552.2 ( $\text{M}+\text{H}^+$ )

### Example A21

(E)-(6R,7R)-7-[2-(3,4-Dimethoxy-phenylsulfanyl)-acetylamino]-3-[1-(3-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



- With 121.1 mg (0.75 mmol) 1,1-carbonyldiimidazole, 170.6 mg (0.75 mmol) 2-(3,4-dimethoxyphenylthio)acetic acid and 250.0 mg (0.62 mmol) (E)-(6R,7R)-7-amino-3-[1-(3-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-
- 30 1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid trifluoroacetate in 4 ml N,N-dimethylacetamide. The resulting solid was purified by column chromato-

graphy on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (1 : 0, 4 : 1, 3 : 1). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

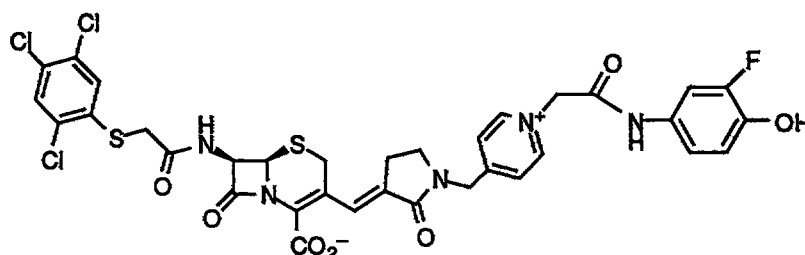
Yield: 175.6 mg (46.1%) pale yellow lyophilisate

5 IR(KBr): 1766, 1664, 1588  $\text{cm}^{-1}$

MS(ISP): 612.2 ( $\text{M}+\text{H}^+$ )

### Example A22

(E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



With 60.0 mg (0.36 mmol) 1,1-carbonyldiimidazole, 99.0 mg (0.36 mmol) (2,4,5-trichloro-phenylsulfanyl)-acetic acid and 200.0 mg (0.30 mmol) (E)-(6R,7R)-7-amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetate in 4 ml N,N-dimethylacetamide. The resulting solid was purified by column chromatography on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitril (2 : 1, 1 : 1). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

Yield: 140.0 mg (57.8%) beige lyophilisate

IR(KBr): 1763, 1666, 1645  $\text{cm}^{-1}$

MS(ISP): 806.3, 808.3 ( $\text{M}+\text{H}^+$ )<sup>+</sup>

25

The following compounds were prepared according to Example A1

### Example A23

(E)-(6R,7R)-7-[2-(Benzothiazol-2-ylsulfanyl)-acetylamino]-3-[1-(4-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

30 Yield: 66.0% beige solid

MS(ISP): 609.4 ( $\text{M}+\text{H}^+$ )<sup>+</sup>

IR(KBr): 1772, 1669, 1613  $\text{cm}^{-1}$

**Example A24**

(E)-(6R,7R)-3-[1-(1H-Benzoimidazol-2-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(phenylsulfanylcarbonylmethyl-amino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazol salt (1:1)

5 Yield: 91.6% brown solid

MS(ISP): 576.1 (M+H)<sup>+</sup>

IR(KBr): 1770, 1673, 1625 cm<sup>-1</sup>

**Example A25**

10 (E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(naphthalen-1-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 41.6% beige solid

MS(ISP): 536.3 (M+H)<sup>+</sup>

15 IR(KBr): 1769, 1664, 1624 cm<sup>-1</sup>

**Example A26**

(E)-(6R,7R)-3-[1-(4-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-7-[2-(naphthalen-2-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

20

Yield: 67.7% beige solid

MS(ISP): 602.2 (M+H)<sup>+</sup>

IR(KBr): 1771, 1667, 1614 cm<sup>-1</sup>

25 **Example A27**

(E)-(6R,7R)-7-[2-(Benzothiazol-2-ylsulfanyl)-acetylamino]-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 78.5% light yellow solid

30 MS(ISP): 543.2 (M+H)<sup>+</sup>

IR(KBr): 1769, 1665, 1624 cm<sup>-1</sup>

**Example A28**

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(3,5-dimethyl-phenylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

35

Yield: 67.0% beige solid

MS(ISP): 514.3 (M+H)<sup>+</sup>

IR(KBr): 1765, 1653, 1621 cm<sup>-1</sup>

**Example A29**

(E)-(6R,7R)-7-[2-(4-Bromo-phenylsulfanyl)-acetylamino]-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)  
Yield: 75.5% light yellow solid  
MS(ISP): 566.1 (M+H)<sup>+</sup>  
IR(KBr): 1767, 1661, 1622 cm<sup>-1</sup>

10 **Example A30**

(E)-(6R,7R)-7-[2-(Benzooxazol-2-ylsulfanyl)-acetylamino]-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)  
Yield: 67.2% beige solid  
15 MS(ISP): 527.1 (M+H)<sup>+</sup>  
IR(KBr): 1770, 1670, 1625 cm<sup>-1</sup>

**Example A31**

(E)-(6R,7R)-7-[2-(4-Bromo-phenylsulfanyl)-acetylamino]-8-oxo-3-[2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)  
Yield: 86.3% yellow powder  
MS(ISP): 608.3 (M+H)<sup>+</sup>  
IR(KBr): 1769, 1682, 1611 cm<sup>-1</sup>

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**Example A32**

(E)-(6R,7R)-8-Oxo-3-[2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidenemethyl]-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)  
Yield: 78.6% yellow powder  
30 MS(ISP): 528.3 (M+H)<sup>+</sup>  
IR(KBr): 1771, 1681, 1612 cm<sup>-1</sup>

**Example A33**

35 (E)-(6R,7R)-3-(1-Benzyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)  
Yield: 85.0% brown solid  
MS(ISP): 536.4 (M+H)<sup>+</sup>

IR(KBr): 1767, 1667, 1622  $\text{cm}^{-1}$

**Example A34**

(E)-(6R,7R)-3-[1-(4-Fluoro-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 91.0% beige solid

MS(ISP): 554.5 (M+H)<sup>+</sup>

IR(KBr): 1766, 1665, 1622  $\text{cm}^{-1}$

10

**Example A35**

(E)-(6R,7R)-3-[1-(4-Methoxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

15 Yield: 87.1% beige solid

MS(ISP): 566.5 (M+H)<sup>+</sup>

IR(KBr): 1773, 1672, 1611  $\text{cm}^{-1}$

**Example A36a**

20 (E)-(6R,7R)-3-[1-(4-Allyloxycarbonylamino-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1) **RO-65-2011**

Yield: 82.3% brown solid

MS(ISP): 652.5 (M+NH<sub>4</sub>)<sup>+</sup>

25 IR(KBr): 1770, 1726, 1667, 1613  $\text{cm}^{-1}$

**Example A36b**

(E)-(6R,7R)-3-[1-(4-Amino-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

30

(E)-(6R,7R)-3-[1-(4-allyloxycarbonylamino-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1) (400.0 mg, 0.57 mmol) was suspended in 20 ml dichloromethane and treated with N,O-bis(trimethylsilyl)-trifluoroacetamide (240.7 ml, 9.11 mmol). After 15 min, bis(triphenylphosphine)palladium(II) chloride (10.0 mg, 0.014 mmol), acetic acid (0.65 ml, 11.4 mmol) and tributyltin hydride (1.53 ml, 5.70 mmol) were added. After 45 min the suspension was poured under stirring on 250 ml diethyl ether, containing 3 ml of a hydrochloric acid-saturated diethyl ether

35

solution and was stirred for 1h. The solid material was collected by filtration, suspended in 4 ml water : acetonitrile (1 : 1) and the pH was adjusted to 2 with 1M hydrochloric acid. To the suspension an equal amount of MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) was added, the organic solvent was  
5 evaporated and the residue was chromatographed on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (9 : 1, 4 : 1, 2 : 1, 1 : 1, 1 : 3). The organic solvent was evaporated and the aqueous phase was freeze-dried.

Yield: 18.0% beige lyophilisate

10 MS(ISP): 551.5 (M+H)<sup>+</sup>

IR(KBr): 1769, 1667, 1626 cm<sup>-1</sup>

#### Example A37

(E)-(6R,7R)-3-[1-(1,1-Dioxo-tetrahydro-thiophen-3-yl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-  
15 bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1) (1:1 mixture of epimers)

Yield: 56.1% beige solid

MS(ISP): 581.4 (M+H)<sup>+</sup>

20 IR(KBr): 1771, 1673, 1618 cm<sup>-1</sup>

#### Example A38a

(E)-(6R,7R)-3-[1-(1-Allyloxycarbonyl-azetidin-3-yl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-  
25 bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 74.5% beige lyophilisate

MS(ISP): 585.5 (M+H)<sup>+</sup>

IR(KBr): 1775, 1678, 1626 cm<sup>-1</sup>

#### 30 Example A38b

(E)-6R,7R)-3-(1-Azetidin-1-ium-3-yl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

(E)-(6R,7R)-3-[1-(1-allyloxycarbonyl-azetidin-3-yl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-  
35 bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1) (448.0 mg, 0.69 mmol) was dissolved in 20 ml dichloromethane. Acetic acid (0.79 ml, 3.70 mmol), bis(triphenylphosphine)palladium(II) chloride (11.9 mg, 0.017 mmol) and tributyltin hydride (1.86 ml, 6.90 mmol) were added successively.

After 45 min the suspension was poured under stirring on 250 ml diethyl ether, containing 3 ml of a hydrochloric acid-saturated diethyl ether solution and was stirred for 1h. The solid material was collected by filtration, suspended in water : acetonitrile (1 : 1) and the pH was adjusted to 2 with 1N hydrochloric acid. To the suspension an equal amount of MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) was added, the organic solvent was evaporated and the residue was chromatographed on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (9 : 1, 4 : 1, 2 : 1, 1 : 1, 1 : 3). The organic solvent was evaporated and the aqueous phase was freeze-dried.

Yield: 23.2% beige lyophilisate  
MS(ISP): 501.4 (M+H)<sup>+</sup>  
IR(KBr): 1766, 1673, 1620 cm<sup>-1</sup>

15 **Example A39**

(E)-(6R,7R)-3-[1-(4-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 68.0% yellow solid

20 MS(ISP): 552.5 (M+H)<sup>+</sup>

IR(KBr): 1773, 1667, 1614 cm<sup>-1</sup>

**Example A40**

(E)-(6R,7R)-8-Oxo-3-(2-oxo-1-phenylcarbamoylmethyl-pyrrolidin-3-ylidenemethyl)-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 52.0% brown solid

MS(ISP): 579.4 (M+H)<sup>+</sup>

IR(KBr): 1770, 1665, 1599 cm<sup>-1</sup>

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**Example A41a**

(E)-(6R,7R)-3-[(R)-1'-Allyloxycarbonyl-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

35 Yield: 81.3% brown solid

MS(ISP): 562.3 (M+H)<sup>+</sup>

IR(KBr): 1776, 1670, 1631 cm<sup>-1</sup>

**Example A41b**

(E)-(6R,7R)-8-Oxo-3-[(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid hydrochloride (1:1)

- 5 (E)-(6R,7R)-3-[(R)-1'-allyloxycarbonyl-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid (370.0 mg, 0.62 mmol) was dissolved in 20 ml dichloromethane and treated successively with
- 10 bis(triphenylphosphine)palladium(II) chloride (10.9 mg, 0.015 mmol), acetic acid (0.71 ml, 12.4 mmol) and tributyltin hydride (1.67 ml, 6.20 mmol). After 40 min, the suspension was poured on 250 ml diethyl ether containing 3 ml of a hydrochloric acid-saturated diethyl ether solution and stirred for 1h. The suspension was filtered, the solid material was triturated with ethyl acetate for 1h and dried in high vacuum.
- 15 Yield: 25.5% beige solid  
MS(ISP): 515.3 (M+H)<sup>+</sup>  
IR(KBr): 1776, 1666, 1632 cm<sup>-1</sup>

**Example A42**

- 20 (E)-(6R,7R)-7-[2-(4-Chloro-phenylsulfanyl)-acetylamino]-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)  
Yield: 70.7% light yellow solid  
MS(ISP): 520.4 (M+H)<sup>+</sup>
- 25 IR(KBr): 1775, 1667, 1625 cm<sup>-1</sup>

The following compounds were prepared according to Example A10

**Example A43**

- (E)-(6R,7R)-8-Oxo-3-[2-oxo-1-(2-oxo-oxazolidin-3-yl)-pyrrolidin-3-ylidenemethyl]-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)
- 30 Yield: 36.0% beige lyophilisate  
MS(ISP): 548.4 (M+H)<sup>+</sup>  
IR(KBr): 1770, 1689, 1612 cm<sup>-1</sup>

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**Example A44**

(E)-(6R,7R)-8-Oxo-3-(2-oxo-1-pyridin-2-yl-pyrrolidin-3-ylidenemethyl)-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 18.0% brown lyophilisate

MS(ISP): 523.5 (M+H)<sup>+</sup>

IR(KBr): 1770, 1680, 1610 cm<sup>-1</sup>

**5 Example A45**

(E)-(6R,7R)-3-[1-(6-Methoxy-pyridin-3-yl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 12.0% beige lyophilisate

10 MS(ISP): 553.5 (M+H)<sup>+</sup>

IR(KBr): 1769, 1677, 1619 cm<sup>-1</sup>

**Example A46**

15 (E)-(6R,7R)-7-[2-(1H-Benzoimidazol-2-ylsulfanyl)-acetylamino]-3-[1-(4-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 11.2% beige lyophilisate

MS(ISP): 592.5 (M+H)<sup>+</sup>

IR(KBr): 1769, 1664, 1614 cm<sup>-1</sup>

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**Example A47**

(E)-(6R,7R)-3-(1-Isobutyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

25 Yield: 15.8% colorless lyophilisate

MS(ISP): 502.4 (M+H)<sup>+</sup>

IR(KBr): 1768, 1660, 1625 cm<sup>-1</sup>

**Example A48**

30 (E)-(6R,7R)-3-(1-Cyclohexylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 10.0% colorless lyophilisate

MS(ISP): 542.4 (M+H)<sup>+</sup>

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**Example A49**

(E)-(6R,7R)-3-[1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(3-phenyl-propionylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Yield: 17.0% beige lyophilisate

MS(ISP): 534.4 (M+H)<sup>+</sup>

IR(KBr): 1778, 1662, 1602 cm<sup>-1</sup>

**5 Example A50**

(E)-(6R,7R)-3-[(3-Hydroxy-benzyl)-oxo-pyrrolidin-3-ylidenemethyl]-7-[2-(4-hydroxymethyl-phenoxy)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 21.2% beige lyophilisate

10 MS(ISP): 566.4 (M+H)<sup>+</sup>

IR(KBr): 1773, 1665, 1588 cm<sup>-1</sup>

**Example A51**

15 (E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]]-2-oxo-pyrrolidin-3-ylidenemethyl]-7-[2-(4-hydroxymethyl-phenoxy)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

Yield: 14.1% beige lyophilisate

MS(ISP): 718.3 (M+H)<sup>+</sup>

20 IR(KBr): 1769, 1681, 1613 cm<sup>-1</sup>

**Example A52**

25 (E)-(6R,7R)-7-(2-Benzoylamino-acetylamino)-3-[1-(3-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 32% beige lyophilisate

MS(ISP): 562.0 (M+H)<sup>+</sup>

IR(KBr): 1771, 1658, 1602 cm<sup>-1</sup>

**30 Example A53**

(E)-(6R,7R)-3-[1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylamino-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 20.5% beige lyophilisate

35 MS(ISP): 535.4 (M+H)<sup>+</sup>

IR(KBr): 1780, 1670, 1608 cm<sup>-1</sup>

**Example A54**

(E)-(6R,7R)-3-[1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenoxy-acetyl-amino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:0.8)

5 Yield: 34.6% beige lyophilisate

MS(ISP): 536.2 (M+H)<sup>+</sup>

IR(KBr): 1776, 1673, 1600 cm<sup>-1</sup>

**Example A55**

10 (6R,7R)-3-[(E)-1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[(Z)-2-styrylsulfanyl-acetyl-amino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Yield: 31.6% beige lyophilisate

MS(ISP): 578.4 (M+H)<sup>+</sup>

15 IR(KBr): 1775, 1663, 1619 cm<sup>-1</sup>

**Example A56**

(6R,7R)-3-[(E)-1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[(Z)-2-

20 styrylsulfanyl-acetyl-amino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

Yield: 14.2% beige lyophilisate

MS(ISP): 730.5 (M+H)<sup>+</sup>

IR(KBr): 1769, 1677, 1642 cm<sup>-1</sup>

25 **Example A57**

(E)-(6R,7R)-7-[2-(4-Chloro-phenylsulfanyl)-acetyl-amino]-3-[1-(3-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 29.0% light yellow lyophilisate

30 MS(ISP): 586.3 (M+H)<sup>+</sup>

IR(KBr): 1769, 1669, 1600 cm<sup>-1</sup>

**Example A58**

(E)-(6R,7R)-7-[2-(4-Bromo-phenylsulfanyl)-acetyl-amino]-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

Yield: 13.3% beige lyophilisate

MS(ISP): 748.1 (M+H)<sup>+</sup>

IR(KBr): 1769, 1676, 1642  $\text{cm}^{-1}$

**Example A59**

(E)-(6R,7R)-7-[2-(3,5-Dimethyl-phenylsulfanyl)-acetyl-amino]-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

Yield: 24.0% light brown lyophilisate

MS(ISP): 732.4 (M+H)<sup>+</sup>

10 IR(KBr): 1766, 1667, 1644  $\text{cm}^{-1}$

**Example A60**

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(pyridin-4-ylsulfanyl)-acetyl-amino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 46.0% light yellow lyophilisate

MS(ISP): 486.4 (M+H)<sup>+</sup>

IR(KBr): 1769, 1664, 1619  $\text{cm}^{-1}$

20 **Example A61**

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(pyridin-4-ylsulfanyl)-acetyl-amino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 41.0% light yellow lyophilisate

25 MS(ISP): 487.2 (M+H)<sup>+</sup>

IR(KBr): 1772, 1672, 1623  $\text{cm}^{-1}$

**Example A62**

(E)-(6R,7R)-7-[2-(4-Fluoro-phenylsulfanyl)-acetyl-amino]-8-oxo-3-(2-oxo-1-phenylcarbamoylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

(4-Fluorophenylthio)acetic acid (102.7 mg, 0.55 mmol) was dissolved in N,N-dimethylacetamide and 1,1'-carbonyldiimidazole (89.0 mg, 0.55 mmol) was added in a single portion. The solution was stirred for 20 min, then (E)-35 (6R,7R)-7-amino-8-oxo-3-(2-oxo-1-phenylcarbamoylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid was added. After 6h the mixture was poured on 250 ml diethyl ether and the solid material was collected by filtration. The solid was converted into its sodium salt by suspending it in 6 ml water and adjusting the pH to 7 with 1M sodium

hydroxide solution. The solution was chromatographed on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (10 : 1, 8 : 2, 7 : 3). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

5 Yield: 75.2% yellow lyophilisate

MS(ISP): 597.2 (M+H)<sup>+</sup>

IR(KBr): 1770, 1668, 1630 cm<sup>-1</sup>

The following compounds were prepared according to Example A62

10 **Example A63**

(E)-(6R,7R)-8-Oxo-3-(2-oxo-1-phenyl-pyrrolidin-3-ylidenemethyl)-7-(2-phenylsulfanyl-acetyl-amino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 56.3% beige lyophilisate

15 MS(ISP): 522.2 (M+H)<sup>+</sup>

IR(KBr): 1765, 1682, 1622 cm<sup>-1</sup>

**Example A64**

20 (E)-(6R,7R)-3-[1-(2-Methyl-allyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetyl-amino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 40.8% beige lyophilisate

MS(ISP): 500.2 (M+H)<sup>+</sup>

IR(KBr): 1765, 1667, 1614 cm<sup>-1</sup>

25

**Example A65**

(E)-(6R,7R)-7-[2-(Benzooxazol-2-ylsulfanyl)-acetyl-amino]-3-[1-(4-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

30 Yield: 43.3% beige lyophilisate

MS(ISP): 593.2 (M+H)<sup>+</sup>

IR(KBr): 1770, 1670, 1615 cm<sup>-1</sup>

**Example A66**

35 (E)-(6R,7R)-7-(2-Benzylsulfanyl-acetyl-amino)-3-[1-(4-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 38.7% beige lyophilisate

MS(ISP): 583.3 (M+H)<sup>+</sup>

IR(KBr): 1764, 1664, 1614  $\text{cm}^{-1}$

**Example A67**

(E)-(6R,7R)-7-[2-(5-Acetylamino-[1,3,4]thiadiazol-2-ylsulfanyl)-acetylamino]-  
5 3-[1-(4-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 40.4% yellow lyophilisate

MS(ISP): 617.2 (M+H)<sup>+</sup>

IR(KBr): 1766, 1657, 1614  $\text{cm}^{-1}$

10

**Example A68**

(E)-(6R,7R)-3-[1-(4-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-7-(2-  
methylsulfanyl-acetylamino)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-  
carboxylic acid sodium salt (1:1)

15 Yield: 43.0% beige lyophilisate

MS(ISP): 490.3 (M+H)<sup>+</sup>

IR(KBr): 1764, 1664, 1614  $\text{cm}^{-1}$

**Example A69**

20 (E)-(6R,7R)-7-[2-(4-Bromo-phenylsulfanyl)-acetylamino]-8-oxo-3-(2-oxo-1-  
phenyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-  
carboxylic acid sodium salt

Yield: 53.0% yellow lyophilisate

MS(ISP): 602.1 (M+H)<sup>+</sup>

25 IR(KBr): 1764, 1673, 1618  $\text{cm}^{-1}$

**Example A70**

(E)-(6R,7R)-7-[2-(Naphthalen-2-ylsulfanyl)-acetylamino]-8-oxo-3-[2-oxo-1-  
(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidenemethyl]-5-thia-1-aza-  
30 bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1); compound with  
imidazole (1:0.5)

Yield: 28.3% yellow lyophilisate

MS(ISP): 578.1 (M+H)<sup>+</sup>

IR(KBr): 1770, 1682, 1620  $\text{cm}^{-1}$

35

The following compound was prepared according to Example A1

**Example A71**

1:1 Mixture of (E)-(6R,7R)-8-Oxo-3-[2-oxo-1-[(R)- and -(S)-tetrahydro-furan-2-

ylmethyl]-pyrrolidin-3-ylidenemethyl]-7-(2-phenylsulfanyl-acetyl-amino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

Yield: 88.0% yellow lyophilisate

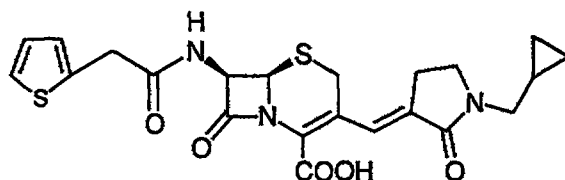
MS(ISP): 530.2 (M+H)<sup>+</sup>

5 IR(KBr): 1772, 1672, 1619 cm<sup>-1</sup>

## Method B

### Example B1

- 10 (E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-(2-thiophen-2-yl-acetyl-amino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



- To a suspension of 300.0 mg (0.86 mmol) (E)-(6R,7R)-7-amino-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid in 8 ml N,N-dimethylformamide was added 80.0 mg (0.95 mmol) sodium bicarbonate. After cooling to 0°C 101.0 µl (0.95 mmol) 2-thiopheneacetyl chloride were added. After 1.5 h the solvent was stripped off at a rotary evaporator and the residue was poured on diethyl ether. The solid was collected by filtration and was triturated with 25 ml ethyl acetate and 15 ml water for 1.5 h.

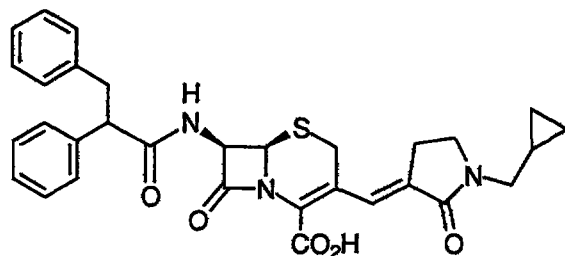
Yield: 150.0 mg (36.9%) beige powder

IR(KBr): 1779, 1669, 1626, 1540 cm<sup>-1</sup>

MS(ISP): 474.2 (M+H)<sup>+</sup>

### 25 Example B2

Mixture of (E)-(6R,7R)-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidene-methyl)-7-[(R)- and [(S)-2,3-diphenyl-propionyl-amino]]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



- 30 From 100.0 mg (0.29 mmol) (E)-(6R,7R)-7-amino-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-

carboxylic acid, 26.4 mg (0.31 mmol) sodium bicarbonate and 77.0 mg (0.31 mmol) 2,3-diphenylpropionyl chloride in 8 ml N,N-dimethylformamide.

Yield: 82.0 mg (51.4%) yellow powder

IR(KBr): 1782, 1671  $\text{cm}^{-1}$

5 MS(ISP): 558.4 ( $\text{M}+\text{H}^+$ )

### Example B3

(E)-(6R,7R)-7-[2-(4-Chloro-phenylsulfanyl)-2-methyl-propionylamino]-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

10 Prepared according to example B1.

The beige solid was suspended in water and the pH was adjusted to 7 with 1M sodium hydroxide solution. The resulting solution was chromatographed on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (9 : 1, 8 : 2, 7 : 3). The organic solvent was

15 stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

Yield: 56.0% beige lyophilisate

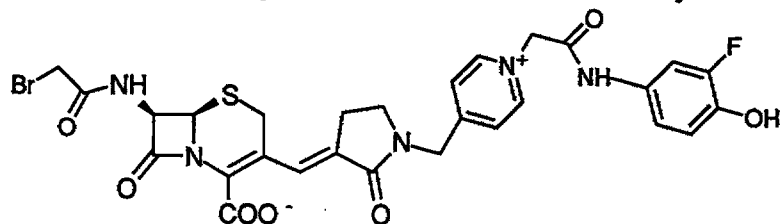
IR(KBr): 1765, 1669, 1620  $\text{cm}^{-1}$

MS(ISP): 562.3 ( $\text{M}+\text{H}^+$ )

## 20 Method C

### Example C1a

(E)-(6R,7R)-7-(2-Bromo-acetyl-amino)-3-(1-[1-[(3-fluoro-4-hydroxy-phenyl-carbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidene-methyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



25

To a suspension of 280.0 mg (0.42 mmol) (E)-(6R,7R)-7-amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetate in 4 ml dichloromethane were added 0.37  $\mu$ l (1.40 mmol) N,O-bis-(trimethylsilyl)-trifluoroacetamide. After a clear solution had formed, 36.8  $\mu$ l (0.42 mmol) bromoacetyl bromide were added and the reaction mixture was stirred for 3 h. To this solution 25.6  $\mu$ l (1.42 mmol) water and 25 ml diethyl ether was added. The precipitate was filtered off and washed with diethyl ether.

30

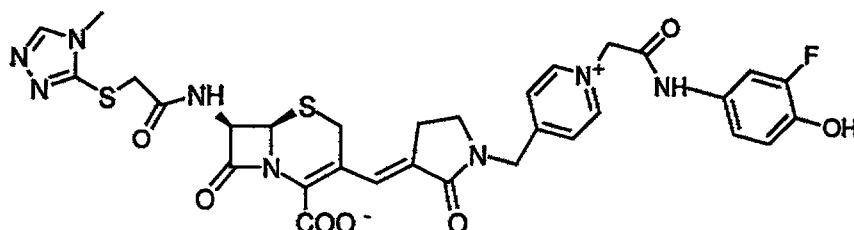
Yield: 210.0 mg (77.8%) beige powder

IR(KBr): 1782, 1686, 1643  $\text{cm}^{-1}$

MS(ISP): 676.2 ( $\text{M}+\text{H}^+$ )

### Example C1b

- 5 (E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-7-[2-(4-methyl-4H-[1,2,4]-triazol-3-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



- 10 To a solution of 230.0 mg (0.34 mmol) (E)-(6R,7R)-7-(2-Bromo-acetylamino)-3-(1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate in 5 ml N,N-dimethylformamide was added 40.0 mg (0.37 mmol) 4-methyl-4H-[1,2,4]triazole-3-thiol. After 1 h 47.0  $\mu\text{l}$  (0.34 mmol)
- 15 triethyl amine was added and stirring was continued for 12 h. The solution was poured on diethyl ether and the resulting solid was purified by column chromatography on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (1 : 0, 4 : 1, 3 : 1, 2 : 1). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.
- 20 Yield: 48.4 mg (20.0%) beige lyophilisate  
IR(KBr): 1780, 1660, 1647  $\text{cm}^{-1}$   
MS(ISP): 709.3 ( $\text{M}+\text{H}^+$ )

### Example C2

- 25 (E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-7-[2-(4-hydroxy-phenylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate
- (E)-(6R,7R)-7-(2-bromo-acetylamino)-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate (see
- 30 ex. C1a) (300.0 mg, 0.45 mmol) was dissolved in 3 ml N,N-dimethylformamide, then 4-mercaptophenol (58.0 mg, 0.45 mmol), followed by triethylamine (62.7 ml, 0.45 mmol) was added. After 22h the reaction

mixture was poured on diethyl ether and the solid was collected by filtration. The brown solid material was suspended in water : acetonitrile (1 : 1) and chromatographed on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (9 : 1, 4 : 1, 3 : 1). The organic solvent was  
5 stripped off at a rotary evaporator and the aqueous phase was freeze-dried.  
Yield: 14.0% beige solid  
MS(ISP): 720.4 (M+H)<sup>+</sup>  
IR(KBr): 1769, 1671, 1643 cm<sup>-1</sup>

10 **Example C3**

(E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(thiophen-2-ylsulfanyl)-acetyl-amino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Prepared according to example C1

15 Yield: 24.2% beige lyophilisate  
MS(ISP): 506.2 (M+H)<sup>+</sup>  
IR(KBr): 1781, 1719, 1667 cm<sup>-1</sup>

**Example C4a**

20 (E)-(6R,7R)-7-(2-Bromo-acetyl-amino)-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)  
(E)-(6R,7R)-7-amino-3-[(1-cyclopropyl-2-oxo-3-pyrrolidinylidene)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid trifluoroacetate (1 :  
25 0.25) (8.0 g, 22.0 mmol) was suspended in 100 ml dichloromethane and N-methyl-N-(trimethylsilyl)trifluoroacetamide (9.0 ml, 48.4 mmol) was added. After 45 min a solution had formed which was cooled to 0°C and treated with bromoacetyl bromide (2.10 ml, 24.2 mmol). After 30 min the ice-bath was removed and the reaction was stirred at ambient temperature for 2.5h. The  
30 volatile components were evaporated and the residue was converted into its sodium salt by suspending it in water and adjusting the pH to 6.5 with 1M sodium hydroxide solution. The solution was freeze-dried and the crude lyophilisate was purified by reversed phase chromatography (RP-18 LiChroPrep gel) with a gradient of water : acetonitril (10 : 0, 9 : 1). The  
35 organic solvent was evaporated and the aqueous phase was freeze-dried.  
Yield: 60.0% light yellow lyophilisate  
MS(ISP): 465.2 (M+H)<sup>+</sup>  
IR(KBr): 1766, 1672, 1620 cm<sup>-1</sup>

**Example C4b**

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(1H-imidazol-2-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

- 5 (E)-(6R,7R)-7-(2-bromo-acetylamino)-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1) (200.0 mg, 0.42 mmol) was dissolved in 4 ml N,N-dimethylformamide and 2-mercaptoimidazole sodium salt (56.2 mg, 0.46 mmol) was added in a single portion. After 15h the solvent was stripped off
- 10 at a rotary evaporator. The residue was dissolved in water and purified by reversed phase chromatography (RP-18 LiChroPrep gel) with a gradient of water : acetonitril (10 : 0, 9 : 1, 8 : 2). The organic solvent was evaporated and the aqueous phase was freeze-dried.
- Yield: 82.2% colorless lyophilisate
- 15 MS(ISP): 476.1 (M+H)<sup>+</sup>  
IR(KBr): 1764, 1664, 1620 cm<sup>-1</sup>

The following compounds were prepared according to Example C4

**Example C5**

- 20 (E)-(6R,7R)-7-[2-(4-Carboxy-phenylsulfanyl)-acetylamino]-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:2)
- Yield: 57.6% yellowish lyophilisate
- MS(ISP): 530.2 (M+H)<sup>+</sup>
- 25 IR(KBr): 1755, 1658, 1589 cm<sup>-1</sup>

**Example C6**

- (E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(4-hydroxy-phenylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-
- 30 ene-2-carboxylic acid sodium salt (1:1)
- Yield: 72.2% yellow lyophilisate
- MS(ISP): 502.0 (M+H)<sup>+</sup>
- IR(KBr): 1764, 1661, 1620 cm<sup>-1</sup>

35 **Example C7**

(E)-(6R,7R)-7-[2-(1-Carboxymethyl-1H-tetrazol-5-ylsulfanyl)-acetylamino]-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid disodium salt

Yield: 49.1% beige lyophilisate

MS(ISP): 558.2 (M+H)<sup>+</sup>

IR(KBr): 1764, 1622 cm<sup>-1</sup>

**Example C8**

- 5 (E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(1-phenyl-1H-tetrazol-5-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 81.8% colorless lyophilisate

MS(ISP): 554.2 (M+H)<sup>+</sup>

- 10 IR(KBr): 1764, 1672, 1619 cm<sup>-1</sup>

**Example C9**

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(2-oxo-3,7-dihydro-2H-purin-6-ylsulfanyl)-acetylamino]-5-thia-1-aza-

- 15 bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 40.6% light beige lyophilisate

MS(ISP): 544.4 (M+H)<sup>+</sup>

IR(KBr): 1762, 1625 cm<sup>-1</sup>

- 20 **Example C10**

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(pyrimidin-2-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 27.0% colorless lyophilisate

- 25 MS(ISP): 488.4 (M+H)<sup>+</sup>

IR(KBr): 1763, 1671, 1618 cm<sup>-1</sup>

**Example C11**

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(1-methyl-

- 30 1H-tetrazol-5-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 38.1% colorless lyophilisate

MS(ISP): 492.4 (M+H)<sup>+</sup>

IR(KBr): 1764, 1678, 1618 cm<sup>-1</sup>

35

**Example C12**

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(4-hydroxy-pyrimidin-2-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 47.3% light yellow lyophilisate

MS(ISP): 504.4 (M+H)<sup>+</sup>

IR(KBr): 1762, 1670, 1616 cm<sup>-1</sup>

**5 Example C13**

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-[2-(3,4-dihydroxy-phenyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ylsulfanyl]-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

10 Yield: 27.3% colorless lyophilisate

MS(ISP): 650.4 (M+H)<sup>+</sup>

IR(KBr): 1768, 1660, 1618 cm<sup>-1</sup>

**Example C14**

15 (E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(4-methyl-5-trifluoromethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 48.6% light yellow lyophilisate

MS(ISP): 559.4 (M+H)<sup>+</sup>

20 IR(KBr): 1763, 1672, 1618 cm<sup>-1</sup>

**Example C15a**

(E)-(6R,7R)-7-(2-Bromo-acetylamino)-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt

25 (E)-(6R,7R)-7-amino-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (3.50 g, 10.0 mmol) was suspended in 50 ml dichloromethane and N-methyl-N-trimethylsilyltrifluoroacetamide (4.62 ml, 25.0 mmol) was added dropwise. After 1h a solution had formed which was cooled to 0°C. To this  
30 solution bromoacetyl bromide (1.04 ml, 12.0 mmol) was added. After 30 min the ice-bath was removed and the solution was stirred for 4h at room temperature. After evaporation of the volatile components, the residue was suspended in water and the pH was adjusted to 6.8 with 1N sodium  
35 hydroxide solution and freeze-dried. The crude lyophilisate was purified by reversed phase chromatography (RP-18 LiChroPrep gel) with a gradient of water : acetonitrile (9 : 1, 8 : 2, 7 : 3). The organic solvent was evaporated and the aqueous phase was freeze-dried.

Yield: 67.1% yellow lyophilisate

MS(ISP): 470.0 (M+H)<sup>+</sup>

IR(KBr): 1766, 1665, 1622 cm<sup>-1</sup>

The following compounds were prepared according to Example C4

5 **Example C15b**

(E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(3H-[1,2,3]triazol-4-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 52.1% yellowish lyophilisate

10 MS(ISP): 491.4 (M+H)<sup>+</sup>

IR(KBr): 1764, 1664, 1619 cm<sup>-1</sup>

**Example C16**

15 (E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-[2-(3,4-dihydroxy-phenyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ylsulfanyl]-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 38.3% colorless lyophilisate

MS(ISP): 664.1 (M+H)<sup>+</sup>

20 IR(KBr): 1766, 1665, 1593 cm<sup>-1</sup>

**Example C17**

25 (E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(1H-[1,2,4]triazol-3-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 51.2% yellowish lyophilisate

MS(ISP): 491.4 (M+H)<sup>+</sup>

IR(KBr): 1765, 1664, 1619 cm<sup>-1</sup>

30 **Example C18**

(E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 20.1% yellowish lyophilisate

35 MS(ISP): 542.3 (M+H)<sup>+</sup>

IR(KBr): 1764, 1666, 1625 cm<sup>-1</sup>

**Example C19**

(E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(4-

methyl-5-trifluoromethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 52.2% yellowish lyophilisate

MS(ISP): 573.3 (M+H)<sup>+</sup>

5 IR(KBr): 1763, 1665, 1612 cm<sup>-1</sup>

**Example C20**

(E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(1-methyl-1H-tetrazol-5-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza

10 bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 50.8% yellowish lyophilisate

MS(ISP): 506.3 (M+H)<sup>+</sup>

IR(KBr): 1763, 1667, 1615 cm<sup>-1</sup>

15 **Example C21a**

Mixture of (E)-(6R,7R)-7-[(R)- and -[(S)-2-bromo-propionylamino]-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1), see ex. D1a

20 **Example C21b**

Mixture of (E)-(6R,7R)-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[(R)- and -[(S)-2-(4-methyl-5-trifluoromethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-propionylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

25 Prepared according to example C4

Yield: 55.0% colorless lyophilisate

MS(ISP): 587.3 (M+H)<sup>+</sup>

IR(KBr): 1765, 1670, 1618 cm<sup>-1</sup>

30 **Example C22**

Mixture of (E)-(6R,7R)-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[(R)- and -[(S)-2-(3H-[1,2,3]triazol-4-ylsulfanyl)-propionylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

35 Yield: 63.3% beige lyophilisate

MS(ISP): 505.2 (M+H)<sup>+</sup>

IR(KBr): 1764, 1657, 1621 cm<sup>-1</sup>

**Example C23**

(E)-(6R,7R)-7-[2-(1H-Benzoimidazol-2-ylsulfanyl)-acetylamino]-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

- 5 (E)-(6R,7R)-7-(2-bromo-acetylamino)-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1) (see ex. C4a) (200 mg, 0.42 mmol) was dissolved in 4 ml N,N-dimethylformamide and 2-mercaptobenzimidazole sodium salt (79.2 mg, 0.46 mmol) was added in a single portion. After completion of the
- 10 reaction, the solvent was stripped off at a rotary evaporator. The residue was dissolved in water and chromatographed on MCI gel (75-150 $\mu$ , Mitsubishi Kasei Corporation) with a gradient of water : acetonitril (10 : 1, 9 : 1). The organic solvent was evaporated and the aqueous phase was freeze-dried. Yield: 57.0% beige lyophilisate
- 15 MS(ISP): 526.0 (M+H)<sup>+</sup>  
IR(KBr): 1763, 1668, 1617 cm<sup>-1</sup>

The following compounds were prepared according to Example C23

**Example C24**

- 20 (E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)  
Yield: 20.0% light yellow lyophilisate  
MS(ISP): 528.4 (M+H)<sup>+</sup>
- 25 IR(KBr): 1764, 1667, 1618 cm<sup>-1</sup>

**Example C25**

- (E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(2,6-dimethyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanyl)-acetylamino]-8-oxo-5-
- 30 thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)  
Yield: 33.3% beige lyophilisate  
MS(ISP): 533.4 (M+H)<sup>+</sup>  
IR(KBr): 1762, 1629, 1478 cm<sup>-1</sup>

35 **Example C26**

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(2-hydroxymethyl-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 45.5% colorless lyophilisate

MS(ISP): 572.5 (M+H)<sup>+</sup>

IR(KBr): 1765, 1668, 1598 cm<sup>-1</sup>

5 **Example C27**

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-[2-(4-hydroxy-phenyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ylsulfanyl]-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

10 Yield: 22.5% colorless lyophilisate

MS(ISP): 634.4 (M+H)<sup>+</sup>

IR(KBr): 1765, 1666, 1613 cm<sup>-1</sup>

**Example C28**

15 (E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 53.5% beige lyophilisate

20 MS(ISP): 491.4 (M+H)<sup>+</sup>

IR(KBr): 1764, 1673, 1615 cm<sup>-1</sup>

**Example C29**

(E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-  
25 [2-(pyrimidin-2-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 55.2% yellowish lyophilisate

MS(ISP): 502.1 (M+H)<sup>+</sup>

IR(KBr): 1762, 1664, 1614 cm<sup>-1</sup>

30

**Example C30a**

Mixture of (E)-(6R,7R)-7-[(R)- and -[(S)-2-bromo-propionylamino]-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt, see ex. D1a

35

The following compounds were prepared according to Example C4

**Example C30b**

Mixture of (E)-(6R,7R)-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[(R)- and -[(S)-2-(1H-pyrazolo[3,4-d]pyrimidin-4-

ylsulfanyl)-propionylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 56.2% yellow lyophilisate

MS(ISP): 556.2 (M+H)<sup>+</sup>

5 IR(KBr): 1764, 1666, 1621 cm<sup>-1</sup>

### Example C31

Mixture of (E)-(6R,7R)-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[(R)- and -[(S)-2-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-

10 propionylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

Yield: 64.0% beige lyophilisate

MS(ISP): 519.2 (M+H)<sup>+</sup>

IR(KBr): 1764, 1667, 1619 cm<sup>-1</sup>

15

### Example C32

Mixture of (E)-(6R,7R)-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[(R)- and -[(S)-2-(2,4,5-trichloro-phenylsulfanyl)-

propionylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

20

Yield: 60.2% colorless lyophilisate

MS(ISP): 617.0 (M+H)<sup>+</sup>

IR(KBr): 1760, 1670, 1618 cm<sup>-1</sup>

### 25 Example C33

(E)-(6R,7R)-7-[2-[2-(3,4-Dihydroxy-phenyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ylsulfanyl]-acetyl-amino]-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

30 (E)-(6R,7R)-7-(2-bromo-acetyl-amino)-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate (see ex. C1a) (337.0 mg, 0.50 mmol) was dissolved in 4 ml N,N-

dimethylformamide and 4-[7-mercapto-5-methyl-s-triazolo[1,5-a]pyrimidin-

35 2-yl]pyrocatechol sodium salt (162.4 mg, 0.55 mmol) was added. After 6h the reaction mixture was poured on diethyl ether and the solid material was filtered. The brown powder was suspended in 8 ml water : acetonitrile (3 : 1), the pH was adjusted to 3 with 1M hydrochloric acid and the suspension was chromatographed on MCI gel (75-150μ, Mitsubishi Kasei Corporation) with a

gradient of water : acetonitrile (4 : 1, 3 : 1, 2 : 1, 1 : 1 1 : 2, 1 : 3). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

Yield: 12.0% brown lyophilisate

5 MS(ISP): 868.4 (M+H)<sup>+</sup>

IR(KBr): 1774, 1680, 1644 cm<sup>-1</sup>

#### Example C34a

(E)-(6R,7R)-7-(2-Bromo-acetylamino)-3-[1-(4-hydroxy-benzyl)-2-oxo-pyrrolidin-  
10 3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2 carboxylic acid  
(E)-(6R,7R)-7-amino-3-[1-(4-hydroxy-benzyl)-2-oxo-pyrrolidin-3-  
ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid  
(736.0 mg, 1.83 mmol) was suspended in 20 ml dichloromethane and N,O-  
bis(trimethylsilyl)-trifluoroacetamide (1.94 ml, 7.32 mmol) was added. After  
15 45 min bromoacetyl bromide (167 ml, 1.92 mmol) was added dropwise. After  
1h the reaction mixture was poured on 200 ml diethyl ether containing 160  
ml water. After 15 min the solid material was collected by filtration, washed  
with diethyl ether and dried in high vacuum.

Yield: 84.1% yellowish solid

20 MS(ISP): 522.3 (M+H)<sup>+</sup>

IR(KBr): 1779, 1667, 1615 cm<sup>-1</sup>

#### Example C34b

(E)-(6R,7R)-7-[2-(4-Carboxy-phenylsulfanyl)-acetylamino]-3-[1-(4-hydroxy-  
25 benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-  
2-ene-2-carboxylic acid sodium salt (1:2)  
4-Mercaptobenzoic acid disodium salt (83.0 mg, 0.42 mmol) was dissolved in  
4 ml N,N-dimethylformamide and (E)-(6R,7R)-7-(2-bromo-acetylamino)-3-[1-  
(4-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-  
30 bicyclo[4.2.0]oct-2-ene-2 carboxylic acid (200.0 mg, 0.40 mmol) was added in a  
single portion. After 2h the reaction mixture was poured on diethyl ether  
and the solid material was collected by filtration. The beige solid was  
suspended in water and the pH was adjusted to 7 with 1M sodium hydroxide  
solution. The resulting solution was chromatographed on MCI gel (75-150μ,  
35 Mitsubishi Kasei Corporation) with a gradient of water : acetonitrile (9 : 1, 8 :  
2, 7 : 3). The organic solvent was stripped off at a rotary evaporator and the  
aqueous phase was freeze-dried.

Yield: 50.0% beige lyophilisate

MS(ISP): 569.1 (M+H)<sup>+</sup>

IR(Nujol): 1763, 1663, 1592  $\text{cm}^{-1}$

The following compounds were prepared according to Example C34

**Example C35**

- 5 (E)-(6R,7R)-7-[2-[5-Carboxy-2-(3,4-dihydroxy-phenyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ylsulfanyl]-acetylamino]-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate sodium salt (1:1)
- 10 Yield: 20.0% beige lyophilisate  
MS(ISN): 896.3 (M-Na)<sup>-</sup>  
IR(Nujol): 1775, 1673, 1643  $\text{cm}^{-1}$

**Example C36**

- 15 (E)-(6R,7R)-7-[2-(4-Carboxy-phenoxy)-acetylamino]-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate sodium salt (1:2)
- Yield: 20.0% brown lyophilisate
- 20 MS(ISP): 748.4 (M+H)<sup>+</sup>  
IR(Nujol): 1766, 1668, 1643  $\text{cm}^{-1}$

**Example C37**

- (E)-(6R,7R)-7-[2-[2-(3,4-Dihydroxy-phenyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ylsulfanyl]-acetylamino]-3-[1-(4-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid
- 25 (E)-(6R,7R)-7-(2-bromo-acetylamino)-3-[1-(4-hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid
- 30 (see ex. C34a) (200.0 mg, 0.38 mmol) was dissolved in 4 ml N,N-dimethylformamide and 4-[7-mercapto-5-methyl-s-triazolo[1,5-a]pyrimidin-2-yl]pyrocatechol sodium salt (124.0 mg, 0.42 mmol) was added. After 5h the reaction mixture was poured on diethyl ether and the suspension was filtered. The solid material was digested with 10 ml ethyl acetate : water (1 :
- 35 1) for 1h, filtered and dried in high vacuum.
- Yield: 70.0% beige solid  
MS(ISP): 716.3 (M+H)<sup>+</sup>  
IR(KBr): 1774, 1670, 1596  $\text{cm}^{-1}$

The following compound was prepared according to Example C23

**Example C38**

(E)-(6R,7R)-7-[2-(4-Amino-phenylsulfanyl)-acetyl-amino]-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-

5 carboxylic acid sodium salt (1:1)

Yield: 37.0% beige lyophilisate

MS(ISP): 501.2 (M+H)<sup>+</sup>

IR(KBr): 1782, 1623, 1599 cm<sup>-1</sup>

10 The following compounds were prepared according to Example C33

**Example C39**

(E)-(6R,7R)-7-[2-(2,6-Dichloro-phenylsulfanyl)-acetyl-amino]-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-

15 carboxylate

Yield: 19.0% beige lyophilisate

MS(ISP): 772.3 (M+H)<sup>+</sup>

IR(KBr): 1768, 1663, 1643 cm<sup>-1</sup>

20 **Example C40**

(E)-(6R,7R)-7-[2-(3,5-Dichloro-phenylsulfanyl)-acetyl-amino]-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

25 Yield: 19.0% beige lyophilisate

MS(ISP): 772.3 (M+H)<sup>+</sup>

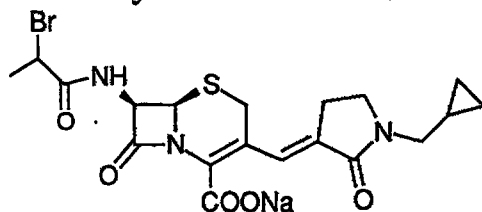
IR(KBr): 1769, 1677, 1643 cm<sup>-1</sup>

30 **Method D**

**Example D1a**

Mixture of (E)-(6R,7R)-7-[(R)- and -(S)-2-bromo-propionyl-amino]-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-

35 bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt



A suspension of (E)-(6R,7R)-7-amino-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (3.50 g, 10.0 mmol) in 50 ml dichloromethane was treated with N-methyl-N-trimethylsilyl-trifluoroacetamide (4.40 ml, 24.0 mmol). After 1 h a yellow solution was formed to which 2-bromo-propionyl bromide (1.30 ml, 12.0 mmol) was added dropwise at 0°C. The reaction mixture was stirred for 30 min at 0°C and for 3 h at room temperature and then concentrated in vacuo. The oily residue was suspended in water and the pH was adjusted to 6.8 using 1 N sodium hydroxide solution. The resulting solution was purified by reversed-phase chromatography (RP-18 LiChroPrep gel, water : acetonitrile = 1 : 0, 4 : 1).

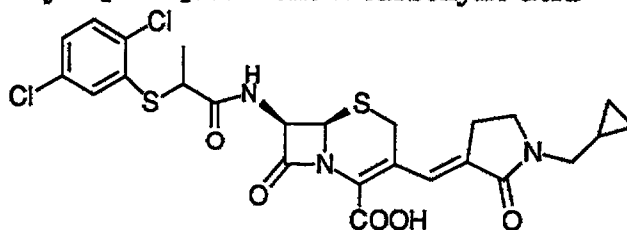
Yield: 2.80 g (55.0 %)

IR(KBr): 1765, 1667 cm<sup>-1</sup>

MS(ISN): 482.1 (M-Na)<sup>+</sup>

#### Example D1b

Mixture of (E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidene-methyl)-7-[(R)- and- [(S)-2-(2,5-dichloro-phenylsulfanyl)-propionylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



A 0.05 N solution of a mixture of (E)-(6R,7R)-7-[(R)- and -[(S)-2-bromo-propionylamino]-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt in DMSO (500 µl) was treated with with a 0.05 N solution of 2,5-

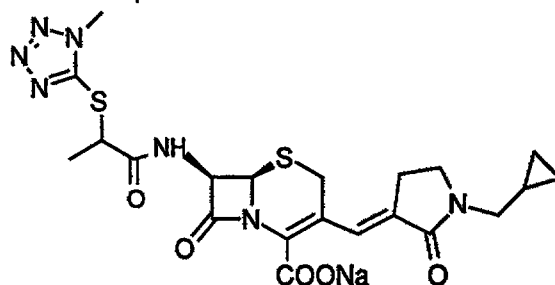
dichlorobenzenethiol in DMSO (500 µl) at room temperature for 24 h.

MS(ISP): 599.2 (M+NH<sub>4</sub>)<sup>+</sup>

The following compounds were synthesized according to the procedure described above:

#### Example D2

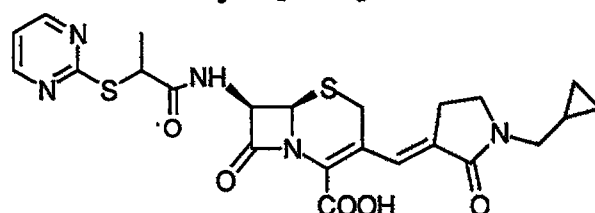
Mixture of (E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidene-methyl)-7-[(R)- and- [(S)- [2-(1-methyl-1H-tetrazol-5-ylsulfanyl)-propionyl-amino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt



MS(ISP): 537.3 (M+NH<sub>4</sub>)<sup>+</sup>

### Example D3

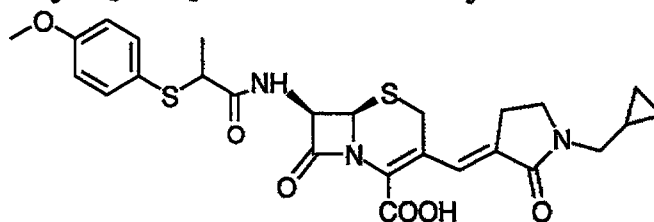
- 5 Mixture of (E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[(R)- and- [(S)- [2-(pyrimidin-2-ylsulfanyl)-propionylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



MS(ISP): 533.2 (M+NH<sub>4</sub>)<sup>+</sup>

### Example D4

- 10 Mixture of (E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidene-methyl)-7-[(R)- and- [(S)- [2-(4-methoxy-phenylsulfanyl)-propionylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

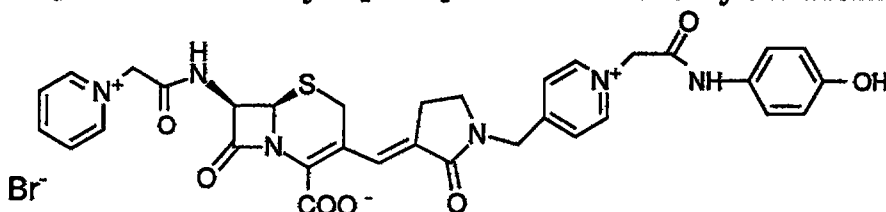


MS(ISP): 561.2 (M+NH<sub>4</sub>)<sup>+</sup>

## Method E

### Example E1

(E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(pyridin-1-ium-1-yl)-acetyl-amino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate bromide



To a suspension of 260.0 mg (0.40 mmol) (E)-(6R,7R)-7-amino-3-[1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetate in 3 ml dichloromethane were added 212  $\mu$ l (0.80 mmol) N,O-bis-(trimethylsilyl)-trifluoroacetamide. After a clear solution had formed, 65  $\mu$ l (0.80 mmol) pyridine and 35  $\mu$ l (0.40 mmol) bromoacetyl bromide were added and the reaction mixture was stirred for 6 h. To this solution 3 ml diethyl ether and 10  $\mu$ l water were added. The precipitate was filtered off, dissolved in 250  $\mu$ l water : acetonitrile (3 : 2) and purified by reversed phase chromatography (RP-18 LiChroPrep gel, water : acetonitrile = 9 : 1). The organic solvent was stripped off at a rotary evaporator and the aqueous phase was freeze-dried.

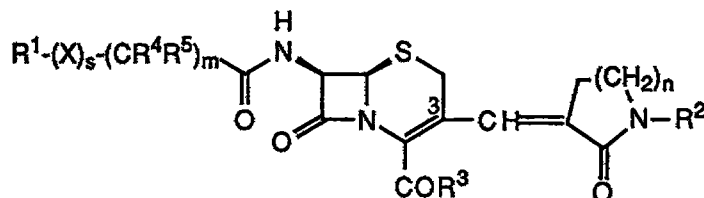
Yield: 110.0 mg (45.3%) beige lyophilisate

IR(KBr): 1768, 1682, 1635, 1574  $\text{cm}^{-1}$

MS(ISP): 655.4 ( $\text{M}+\text{H}^+$ )

# Claims

## 1. Cephalosporin derivatives of the general formula



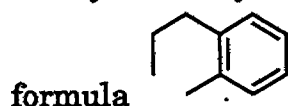
I

5 where

- $R^1$  is halogen, lower alkyl, phenyl, benzyl, styryl, naphthyl or heterocyclyl; the lower alkyl, phenyl, benzyl, styryl, naphthyl and heterocyclyl being optionally substituted by at least one of halogen, hydroxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted phenyl, amino, lower alkylamino, di-lower alkylamino, carboxy, lower alkyl-carboxy, carbamoyl or lower alkylcarbamoyl;
- $R^4, R^5$  independently are hydrogen, lower alkyl or phenyl;
- $X$  is S, O, NH or  $CH_2$ ;
- 15  $n$  is 0, 1 or 2;
- $m$  is 0 or 1;
- $s$  is 0 or 1;
- $R^2$  is hydrogen, hydroxy,  $-CH_2-CONHR^6$ , lower alkyl- $Q_r$ , cycloalkyl- $Q_r$ , lower alkoxy, lower alkenyl, cycloalkenyl- $Q_r$ , lower alkynyl, aralkyl- $Q_r$ , aryl- $Q_r$ , aryloxy, aralkoxy, a heterocyclic ring or a heterocyclyl- $Q_r$ , the lower alkyl, cyclo-alkyl, lower alkoxy, lower alkenyl, cycloalkenyl, lower alkynyl, aralkyl, aryl, aryloxy, aralkoxy and the heterocyclic ring may be substituted with at least one group selected from carboxy, amino, nitro, cyano,  $-SO_2NHR^6$ , optionally fluoro substituted lower alkyl, lower alkoxy, hydroxy, halogen,  $-CONR^6R^7$ ,  $-CH_2CONR^6R^7$ ,  $-N(R^7)COOR^8$ ,  $R^7CO-$ ,  $R^7OCO-$ ,  $R^7COO-$ ,  $-C(R^7R^9)CO_2R^8$ ,  $-C(R^7R^9)CONR^7R^{10}$ , wherein  $R^6$  is hydrogen, lower alkyl, cycloalkyl or aryl;
- 20  $R^7$  and  $R^9$  are independently hydrogen or lower alkyl;
- 25  $R^8$  is hydrogen, lower alkyl, lower alkenyl or a carboxylic acid
- 30



protecting group; and  
 $R^{10}$  is hydrogen,  $\omega$ -hydroxy-alkyl, phenyl, naphthyl or heterocyclyl, the phenyl, naphthyl or heterocyclyl being  
 5 optionally protected hydroxy, halogen, optionally substituted lower alkyl or  $\omega$ -hydroxyalkyl, optionally substituted lower alkoxy and/or cyano, or  $R^7$  and  $R^{10}$  form together group of



$Q$  is -CHR-, -CO- or -SO<sub>2</sub>;  
 10  $r$  is 0 or 1;  
 $R$  is hydrogen or lower alkyl; and  
 $R^3$  is hydroxy, -O-, lower-alkoxy, or -OM and M represents an alkali metal;

as well as readily hydrolyzable esters thereof, pharmaceutically acceptable  
 15 salts of said compounds and hydrates of the compounds of formula I and of their esters and salts.

## 2. Cephalosporin derivatives according to claim 1 wherein

$R^1$  is halogen, phenyl, benzyl, naphthyl or heterocyclyl, the  
 20 phenyl, benzyl, naphthyl and heterocyclyl being optionally substituted by at least one of halogen, hydroxy, optionally substituted lower alkyl or lower alkoxy, or amino, lower alkylamino, di-lower alkylamino, carboxy, lower alkylcarboxy or carbamoyl;  
 25  $R^4, R^5$  independently are hydrogen, lower alkyl or phenyl;  
 $X$  is S, O, NH or CH<sub>2</sub>;  
 $n$  is 0, 1 or 2;  
 $m$  is 0 or 1;  
 $s$  is 0 or 1;  
 30  $R^2$  is hydrogen, hydroxy, lower alkyl- $Q_r$ , cycloalkyl- $Q_r$ , lower alkoxy, lower alkenyl, cycloalkenyl- $Q_r$ , lower alkynyl, aralkyl- $Q_r$ , aryl- $Q_r$ , aryloxy, aralkoxy, a heterocyclic ring or a heterocyclyl- $Q_r$ , the lower alkyl, cycloalkyl, lower alkoxy, lower alkenyl, cycloalkenyl, lower alkynyl, aralkyl, aryl, aryloxy, aralkoxy and the heterocyclic ring may be substituted with at  
 35



- least one group selected from carboxy, amino, nitro, cyano, optionally fluoro substituted lower alkyl, lower alkoxy, hydroxy, halogen,  $-\text{CONR}^6\text{R}^7$ ,  $-\text{N}(\text{R}^7)\text{COOR}^8$ ,  $\text{R}^7\text{CO}-$ ,  $\text{R}^7\text{OCO}-$ ,  $\text{R}^7\text{COO}-$ ,  $-\text{C}(\text{R}^7\text{R}^9)\text{CO}_2\text{R}^8$ ,  $-\text{C}(\text{R}^7\text{R}^9)\text{CONR}^7\text{R}^{10}$ , wherein
- 5  $\text{R}^6$  is hydrogen, lower alkyl, or cycloalkyl;  
 $\text{R}^7$  and  $\text{R}^9$  are independently hydrogen or lower alkyl;  
 $\text{R}^8$  is hydrogen, lower alkyl, lower alkenyl or a carboxylic acid protecting group; and  
 $\text{R}^{10}$  is hydrogen,  $\omega$ -hydroxy-alkyl, phenyl, naphthyl or
- 10 heterocyclyl, the phenyl, naphthyl or heterocyclyl being unsubstituted or substituted with at least one of the groups of optionally protected hydroxy, halogen, optionally substituted lower alkyl or  $\omega$ -hydroxyalkyl, optionally substituted lower alkoxy and/or cyano, or  $\text{R}^7$  and  $\text{R}^{10}$  form together group of



- $\text{Q}$  is  $-\text{CHR}-$ ,  $-\text{CO}-$  or  $-\text{SO}_2-$ ;  
 $r$  is 0 or 1;  
 $\text{R}$  is hydrogen or lower alkyl; and  
 $\text{R}^3$  is hydroxy,  $-\text{O}-$ , lower-alkoxy, or  $-\text{OM}$  and  $\text{M}$  represents an
- 20 alkali metal;

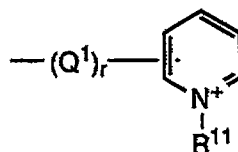
as well as readily hydrolyzable esters thereof, pharmaceutically acceptable salts of said compounds and hydrates of the compounds of formula I and of their esters and salts.

- 25 3. Compounds according to claims 1 or 2, wherein  $n$  is 1.

4. Compounds according to claims 1, 2 or 3 wherein  $\text{R}^1$  is selected from the groups phenyl, 2,4,5-trichlorophenyl, 3,4-dichlorophenyl, 2,5-dichlorophenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-hydroxymethylphenyl, 3,4-dimethoxyphenyl, 4-methyl-1,2,4-triazol-5-yl, 1-
- 30 methyl-tetrazol-5-yl, pyrimidin-2-yl, optionally substituted pyridinium-1-yl, 2-yl, -3-yl or -4-yl, benzimidazol-2-yl, 2-benzthiazolyl, 4-pyridinyl, (2-amino)-thiazol-4-yl, 2-naphthyl, benzyl.

5. Compounds according to any one of claims 1 to 4 wherein  $\text{R}^2$  is methylcyclopropyl, 2-, 3- or 4-hydroxybenzyl, pyrrolidin-3-yl or a group of
- 35 formula





wherein

Q<sup>1</sup> is -CH<sub>2</sub>-

r is 0 or 1;

5 R<sup>11</sup> is hydrogen, lower alkyl, ω-hydroxy alkyl, benzyl or alkyl-heterocyclyl, the benzyl and the heterocyclyl group being unsubstituted or substituted with at least one of the groups cyano, carboxy or hydroxy; or is -CH<sub>2</sub>CONR<sup>7</sup>R<sup>10</sup>; wherein

R<sup>7</sup> and R<sup>10</sup> are as defined in claim 1.

10

6. The compounds according to claim 1

(E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetyl-amino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-

15 carboxylate

(E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(1-benzothiazol-2-yl-sulfanyl)-acetyl-amino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

20 (E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(pyridin-4-ylsulfanyl)-acetyl-amino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

(E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2,4,5-trichloro-phenylsulfanyl)-acetyl-amino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-

25 carboxylate

(E)-(6R,7R)-3-[1-[1-[(4-Hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetyl-amino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

30 (E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-7-[2-(naphthalen-2-yl-sulfanyl)-acetyl-amino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

(E)-(6R,7R)-7-[2-(3,4-Dichloro-phenylsulfanyl)-acetyl-amino]-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-

35 carboxylate



(E)-(6R,7R)-3-[1-[1-[(3-Fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

(E)-(6R,7R)-3-(1-Cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

(E)-(6R,7R)-7-[2-(Benzothiazol-2-ylsulfanyl)-acetylamino]-3-(1-cyclopropylmethyl-2-oxo-pyrrolidin-3-ylidenemethyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

10 (E)-(6R,7R)-3-[1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

(E)-(6R,7S)-3-[1-(3-Hydroxy-benzyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-7-[2-naphthalen-2-ylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Mixture of (E)-(6R,7R)-8-oxo-3-[(R)- and -(S)-2-oxo-[1,3']Bipyrrolidinyl-3-ylidenemethyl]-8-oxo-7-[2-(2,4,5-trichloro-phenylsulfanyl)-acetylamino]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid hydrochloride.

(E)-(6R,7R)-8-Oxo-3-[(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-7-(2-phenylsulfanyl-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid hydrochloride (1:1)

(E)-(6R,7R)-7-[2-(2,5-Dichloro-phenylsulfanyl)-acetylamino]-3-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

(E)-(6R,7R)-3-(1-Cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-7-[2-(naphthalen-1-ylsulfanyl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid imidazole salt (1:1)

30 7. Compounds as in any one of claims 1 to 5 for use as pharmaceutically active substances, particularly for the treatment and prophylaxis of infectious diseases.

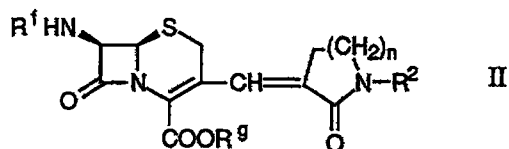
8. Process for the manufacture of the compounds prepared according to any one of claims 1 to 6, which process comprises

35 (a) treating a compound having the formula II

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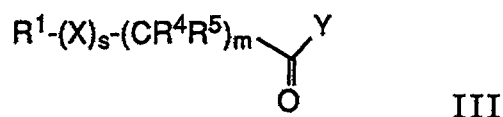
in which

$R^2$  and  $n$  are as defined in claim 1;

5  $R^f$  is hydrogen or trimethylsilyl; and

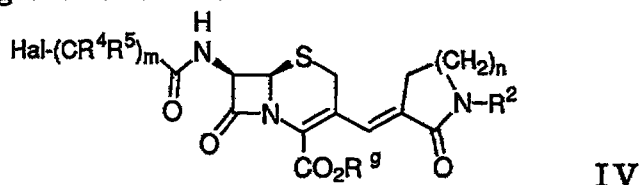
$R^g$  is hydrogen, benzhydryl, p-methoxybenzyl, t-butyl, trimethylsilyl or allyl or salt thereof,

with a carboxylic acid of the general formula III



in which  $R^1$ ,  $X$ ,  $s$ ,  $R^4$ ,  $R^5$  and  $m$  are as defined in claim 1 and  $Y$  is  $-OH$ , or a reactive functional derivative thereof.

15 (b) for compounds of formula I wherein  $X$  is  $S$ ,  $O$  or  $NH$ , by treating a compound having the formula IV



wherein  $R^4$ ,  $R^5$ ,  $m$ ,  $R^2$  and  $R^g$  are as defined above and  $Hal$  stands for halogen,

20 with an appropriate thiol or thiolate or an appropriate alcohol or alcoholate or an appropriate amine in the presence of a base,

(c) for the manufacture of a readily hydrolysable ester of a compound of formula I subjecting a carboxylic acid of formula I to a corresponding  
25 esterification or

(d) for the manufacture of salt 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 salts.

30



9. A pharmaceutical preparation containing a compound prepared according to any one of claims 1 to 6 and a therapeutically inert carrier, particularly for the treatment and prophylaxis of infectious diseases.

10. Compounds prepared according to any one of claims 1 to 6,  
5 whenever prepared Prepared according to the process claimed in claim 8 or by an obvious chemical equivalent thereof.

11. The use of the compounds prepared according to any one of claims 1 to 6 in the treatment and prophylaxis of infectious diseases or for the manufacture of medicaments for the treatment and prophylaxis of infectious  
10 diseases.

12. The novel compounds, formulations, processes and methods substantially as described herein.

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