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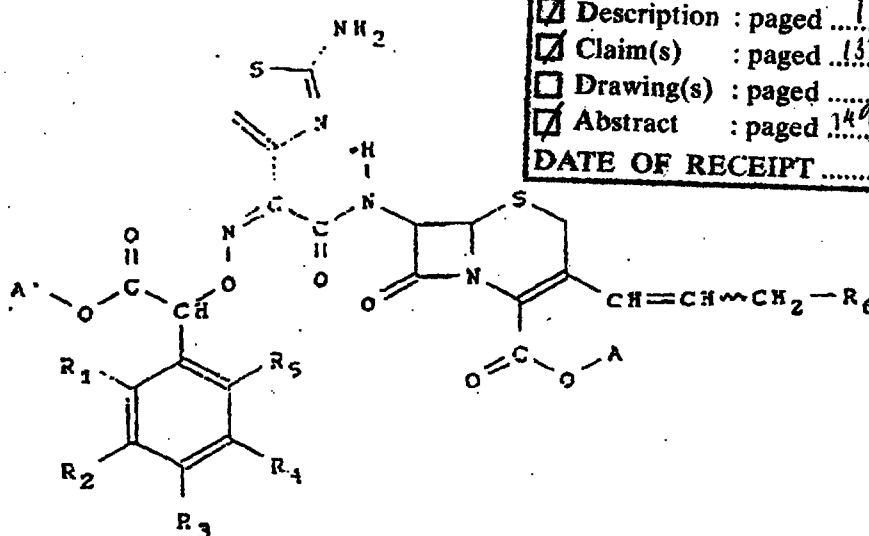


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9607288-9

The present invention relates to new cephalosporins containing a substituted benzyloxyimino radical on the side chain in position 7, their preparation process, their use as medicaments, the compositions containing them and the new intermediates obtained.

A subject of the invention is the products of general formula (I):



(I)

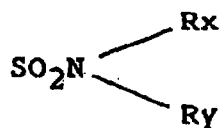
syn isomer, in (R) or (S) form or an (R,S) mixture, in the form of an internal salt or their salts with mineral or organic acids, in which formula:

R₁, R₂, R₃ and R₅, identical or different, represent a hydrogen atom, a halogen atom or one of the radicals chosen from the following radicals: hydroxy, alkyl containing 1 to 4 carbon atoms, optionally substituted by one or more halogen atoms, alkoxy containing 1 to 4 carbon atoms, mercapto, alkylthio containing 1 to 4 carbon atoms, nitro, cyano, amino, alkylamino containing 1 to 4 carbon atoms, dialkylamino containing 2 to 8 carbon atoms, carbamoyl, (alkylamino) carbonyl containing 2 to 5 carbon atoms, (dialkylamino) carbonyl containing 3 to 9 carbon atoms, carboxy, alkoxycarbonyl containing 2 to 5 carbon atoms, acyloxy containing 1 to 8 carbon atoms,

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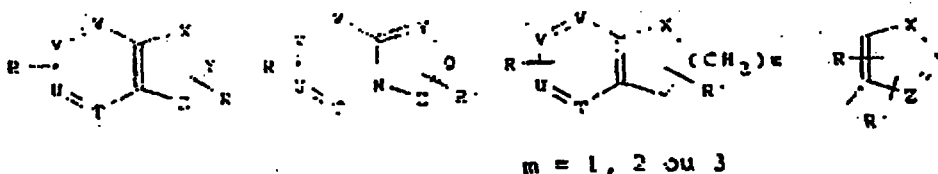
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- 5 in which Rx and Ry, identical or different, represent a hydrogen atom or a alkyl radical containing 1 to 4 carbon atoms,
- R₄ represents a hydroxy radical or an alkyloxy radical containing 1 to 8 carbon atoms,
- 10 it being understood that when R₃ represents a hydroxy radical, or an alkyloxy radical containing 1 to 8 carbon atoms, R₁, R₂ and R₅ do not all represent a hydrogen atom, A and A', identical or different, represent a hydrogen atom, an equivalent of an alkali or alkaline-earth metal,
- 15 magnesium, ammonium or an amino organic base, or one only or each of the groups CO₂A or CO₂A' represent CO₂⁻, the wavy line signifies that the CH₂R₆ group can be in the E or Z position and R₆ represents, in the quaternary ammonium form, one of the following radicals:

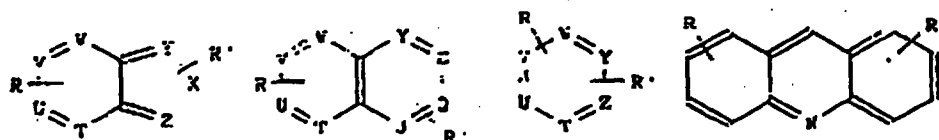
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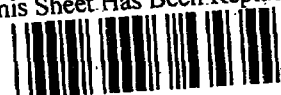


in which X represents CH₂, NH, O or S;

- 35 Q, J, Y, T, U, V, W and Z, identical or different, represent independently of each other CH or N, it being understood that each of these cyclic radicals contains 1 to 5 hetero-atoms, that at least one of these heteroatoms is the nitrogen atom

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and that these cyclic radicals can be substituted by one or more R or R' radicals;

R and R', identical or different, represent a halogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkyloxy radical containing 1 to 4 carbon atoms, a halogen atom, a cyano radical, one of the following radicals: $\text{CO}_2\text{-Q}_1$, $\text{CO-NQ}_1(\text{Q}_2)$, $\text{NQ}_1(\text{Q}_2)$, $\text{SO}_2\text{-NQ}_1(\text{Q}_2)$, CS-NH_2 , NH-CO-Q_1 , CH=N-OH , CH=N-O-Q_1 , $\text{CH}_2\text{-CN}$, $\text{CH}_2\text{-S-Q}_1$ in which Q_1 and Q_2 , identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, P_1 , P_2 and P_3 , identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the dotted line indicates that P_1 and P_2 can optionally form with the nitrogen atom to which they are linked, a heterocycle with 5 or 6 members.

By alkyl radical containing 1 to 4 carbon atoms is meant methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl radicals.

By alkyloxy radical containing 1 to 4 carbon atoms is meant methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy or tert-butoxy radicals.

By alkylthio radical containing 1 to 4 carbon atoms is meant methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio or tert-butylthio radicals.

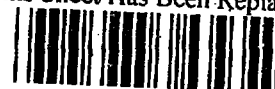
By alkylamino radical containing 1 to 4 carbon atoms is meant methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, sec-butylamino or tert-butylamino radicals.

By dialkylamino radical containing 2 to 8 carbon atoms is meant notably dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, ethyl methylamino, propyl methylamino, butyl methylamino, propyl ethylamino radicals.

By (alkylamino) carbonyl radical containing 2 to 5 carbon atoms is meant notably (methylamino) carbonyl, (ethylamino) carbonyl, (propylamino) carbonyl,

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(isopropylamino) carbonyl, (butylamino) carbonyl radicals.

By alkoxycarbonyl radical containing 2 to 5 carbon atom is meant notably methoxycarbonyl, ethoxycarbonyl radicals.

By (dialkylamino) carbonyl radical containing 3 to 9
5 carbon atoms is meant notably (dimethylamino) carbonyl, (diethylamino) carbonyl, (dipropylamino) carbonyl radicals.

By acyloxy radical containing 1 to 8 carbon atoms is meant notably acetoxy, propionyloxy or benzoyloxy radicals.

10 By halogen atom is meant a fluorine, chlorine, bromine or iodine atom.

When P_1 and P_2 form a heterocycle with the nitrogen atom to which they are linked, it may be a pyrrolidine, a morpholine or a piperidine.

15 When R_4 represents an alkyloxy radical, it may be in particular an acetoxy, propionyloxy or benzoyloxy radical.

Among the values of A' there can be mentioned an equivalent of sodium, potassium, lithium, calcium, magnesium or ammonium. There can be mentioned, among the organic
20 bases, methylamine, propylamine, trimethylamine, diethylamine, triethylamine, N,N-dimethylethanolamine, tris-[(hydroxymethyl)-amino]-methane, ethanolamine, pyridine, picoline, dicyclohexylamine, morpholine, benzylamine, procaine, lysine, arginine, histidine, N-methylglucamine.

25 The products of formula (I) can also appear in the form of a pure internal salt, in salified form or in a combined form with the acids of the solution. Among the acids with which the product or products of formula (I) can be salified, there can be mentioned amongst others, the following acids:
30: acetic, trifluoroacetic, maleic, tartaric, methanesulphonic, benzenesulphonic, para-toluenesulphonic, phosphoric, sulphuric, hydrochloric, hydrobromic, hydroiodic.

In a preferred method of the invention, A' represents a hydrogen atom and CO_2A represents CO_2^- .

35 The expression in the form of quaternary ammonium, indicates that the R_6 radical is linked by the or one of the nitrogen atoms that it contains.

A particular subject of the invention is the products of

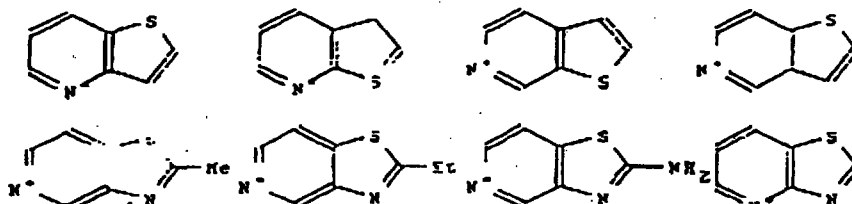
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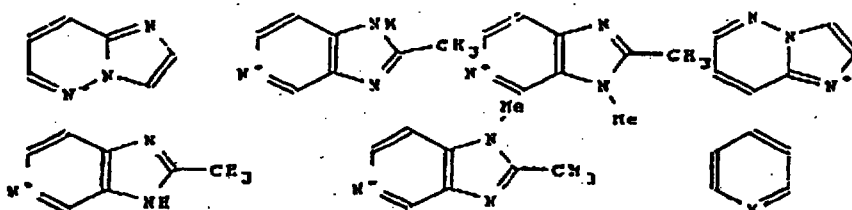
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general formula (I) as defined above in which R_6 represents one of the following radicals:

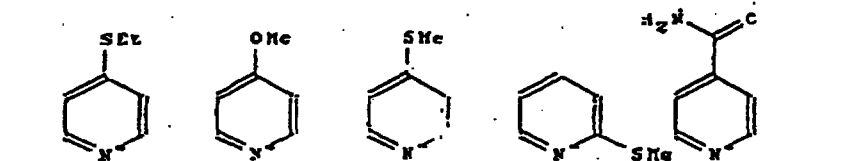
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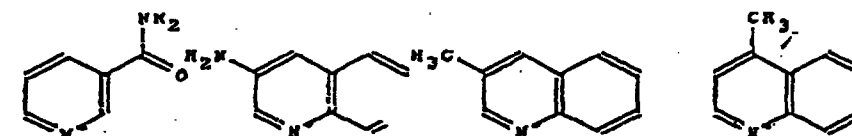
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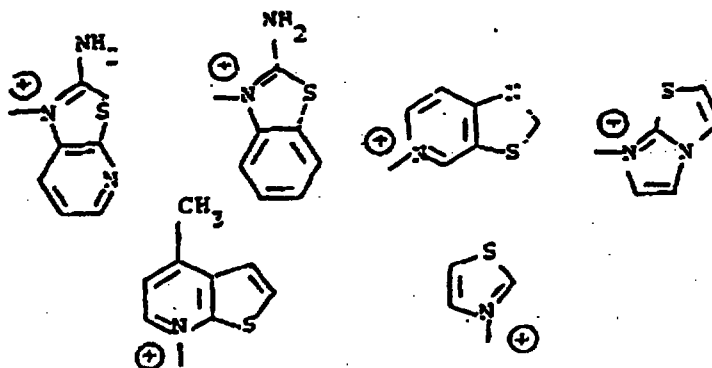
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or also one of the following radicals:

25

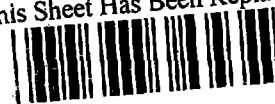
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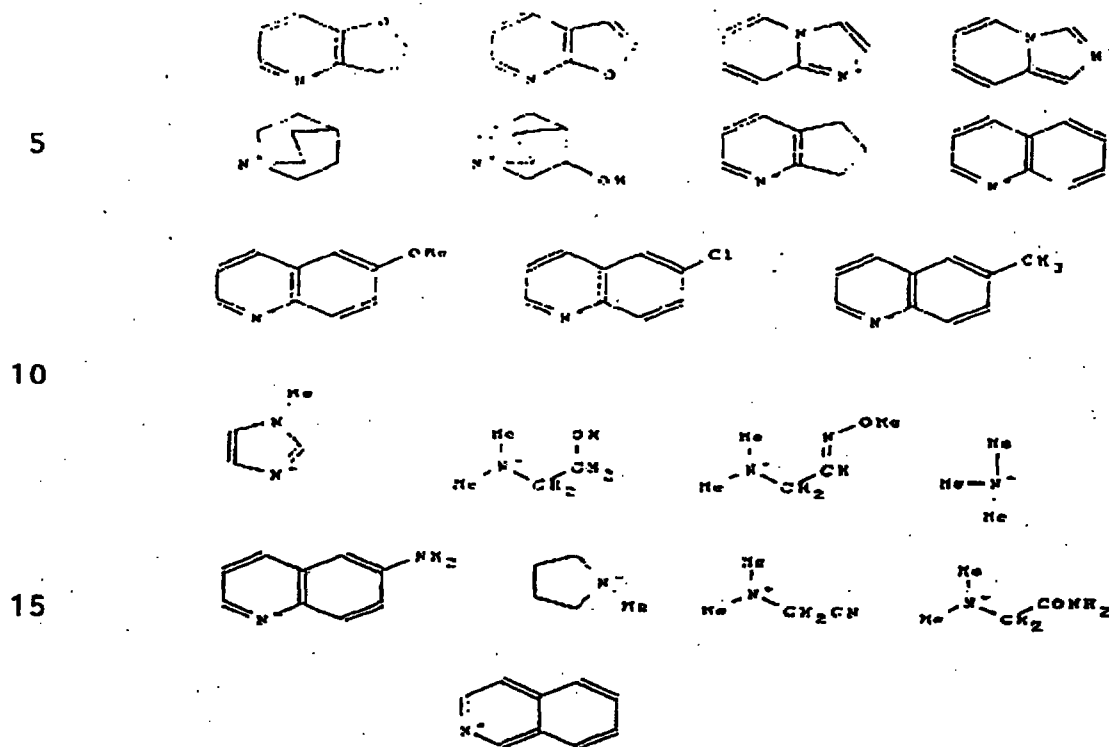
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A more particular subject of the invention is the products of general formula (I) as defined above, in which R_6 represents the quinolinium, isoquinolinium, 4-(methylthio)-pyridinium, thieno[2,3-b]pyridinium, imidazo(1,2-a)pyridinium radical or the 6,7-dihydro-5H-pyrindinium radical, those in which R_3 and R_4 each represent a hydroxy radical and those in which R_2 and R_5 each represent a chlorine or fluorine atom, those in which R_1 and R_2 represent a fluorine atom and those in which R_2 represents a methoxy radical and one of R_1 or R_5 represents a chlorine atom.

A quite particular subject of the invention is the products of which the names follow:

- the internal salt of (6R-(3-(E) 6alpha, 7beta(Z)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,3-difluoro-4,5-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) imidazo(1,2-a) pyridinium,
- the internal salt of (6R-(3-(E) 6alpha, 7beta(Z)))-1-(3-

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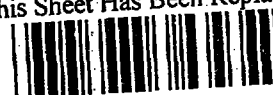


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- (7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-difluoro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a) pyridinium,
- 5 - the internal salt of (6R-(3-(E) 6alpha, 7beta(Z)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2-chloro-4,5-dihydroxy-3-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)quinolinium,
- 10 - the internal salt of (6R-(3-(E) 6alpha, 7beta(Z)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-6,7-dihydro-5-H-pyridinium,
- 15 - the internal salt of (6R-(3-(E) 6alpha, 7beta(Z(S*))))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3,4-dihydroxy-5-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-quinolinium,
- 20 - the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(2-chloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium (R) or (S) or an (R+S) mixture,
- 25 - the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(3-cyano-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium (R) or (S) or an (R+S) mixture,
- 30 - the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(3-fluoro-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium (R) or (S) or an (R+S) mixture,
- 35 - the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-

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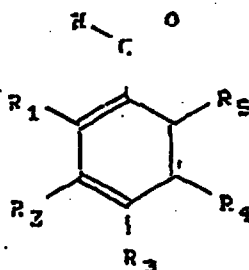
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propenyl]thieno[2,3-b]pyridinium (R) or (S) or an (R+S) mixture,

- the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(2,5-dichloro-3,4-
- 5 dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium (R) or (S) or an (R+S) mixture,
- the internal salt of [6R-[3(E), 6alpha, 7beta[Z(S*)]]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(3-cyano-4,5-
- 10 dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-thieno[2,3-b]pyridinium,
- the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(2,5-dichloro-3,4-
- 15 dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-isoquinolinium (R) or (S) or an (R+S) mixture,
- the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(2,5-dichloro-3,4-
- 20 dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-4-(methylthio)-pyridinium (R) or (S) or an (R+S) mixture.

Also a subject of the invention is a preparation process for the products of formula (I) as defined above,

- 25 characterized in that the aromatic aldehyde of formula (II):



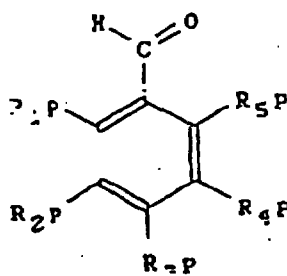
(II)

in which R_1 , R_2 , R_3 , R_4 and R_5 are as defined above, is if necessary protected in its reactive functions and thus

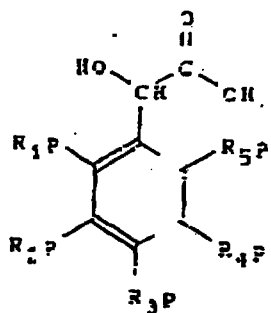
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converted into an aromatic aldehyde of formula (II)_p:

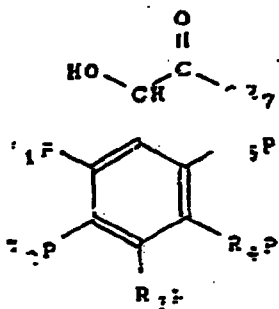
(II)_p

in which R_{1p}, R_{2p}, R_{3p}, R_{4p} and R_{5p} represent respectively the values of R₁, R₂, R₃, R₄ and R₅ as defined previously or a protected reactive function, said aldehyde of formula (II)_p is homologated into an alpha-hydroxy acid of formula (III):



(III)

which acid is esterified into an alpha-hydroxy ester of formula (IV):



(IV)

in which R₇ represents the remainder of an easily-cleavable ester, said alpha-hydroxy ester is treated with N-hydroxy

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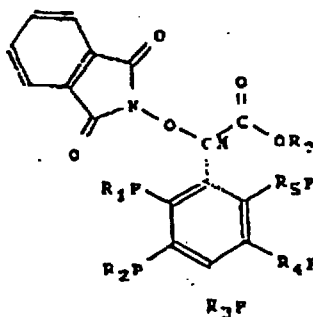


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phthalimide to give a derivative of formula (V):

5

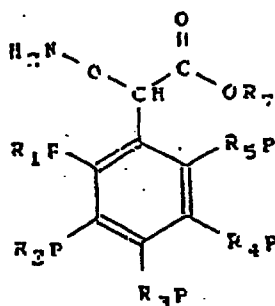


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(V)

which derivative of formula (V) is reduced into an O-substituted hydroxylamine of formula (VI):

15

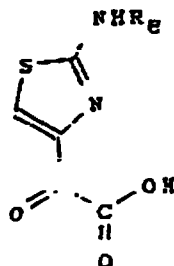


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(VI)

which product of formula (VI) is condensed with a derivative of (2-amino-thiazolyl)-glyoxylic acid of formula (VII):

30

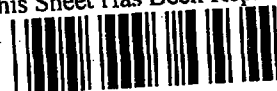


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(VII)

in which R_8 represents a hydrogen atom or a protective group of the amine function, in order to form the derivative of the

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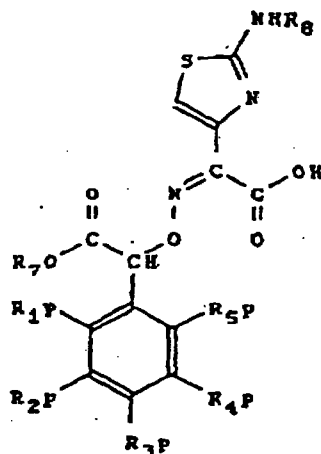
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alpha-hydroximino acetic acid of formula (VIII):

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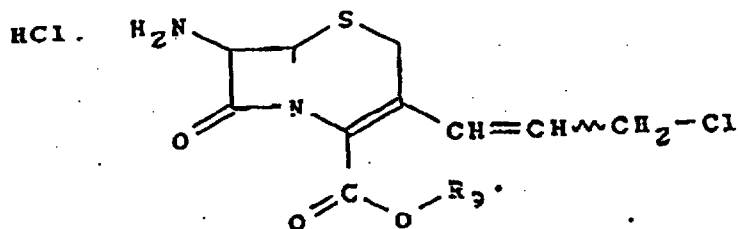
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(VIII)

which product of formula (VIII) is amidified with an ester of
 15 7-amino-3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo-
 [4,2,0]oct-2-en-2-carboxylic acid hydrochloride of formula
 (IX):

20



(IX)

25 or its salts, in which R_9 represents the remainder of an
 easily-cleavable ester, to give a derivative of 7-(N-
 substituted amido) 3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-
 azabicyclo[4,2,0]oct-2-en-2-carboxylic acid of formula (X):

30

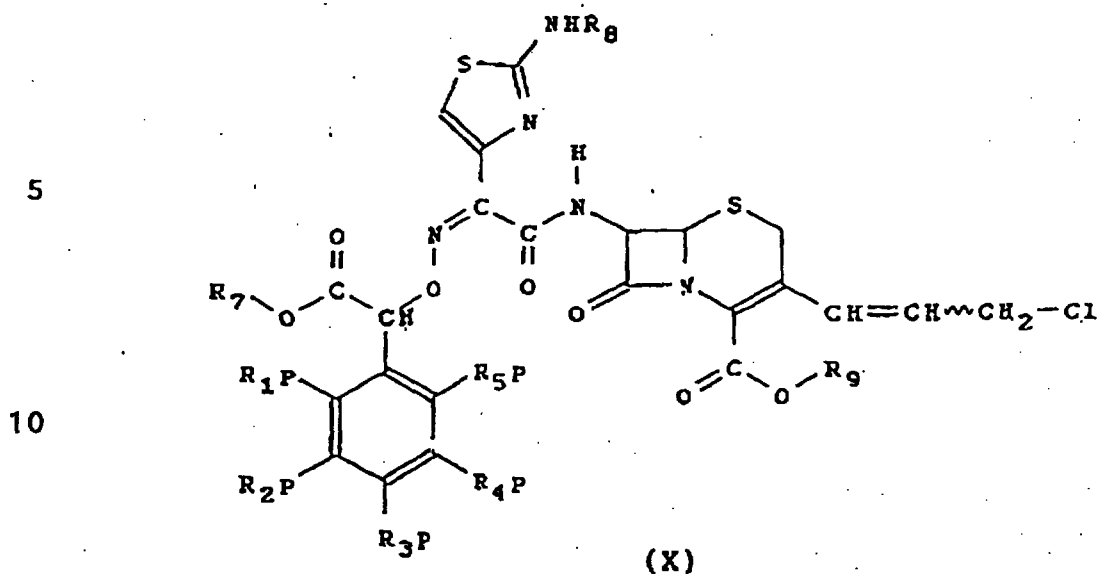
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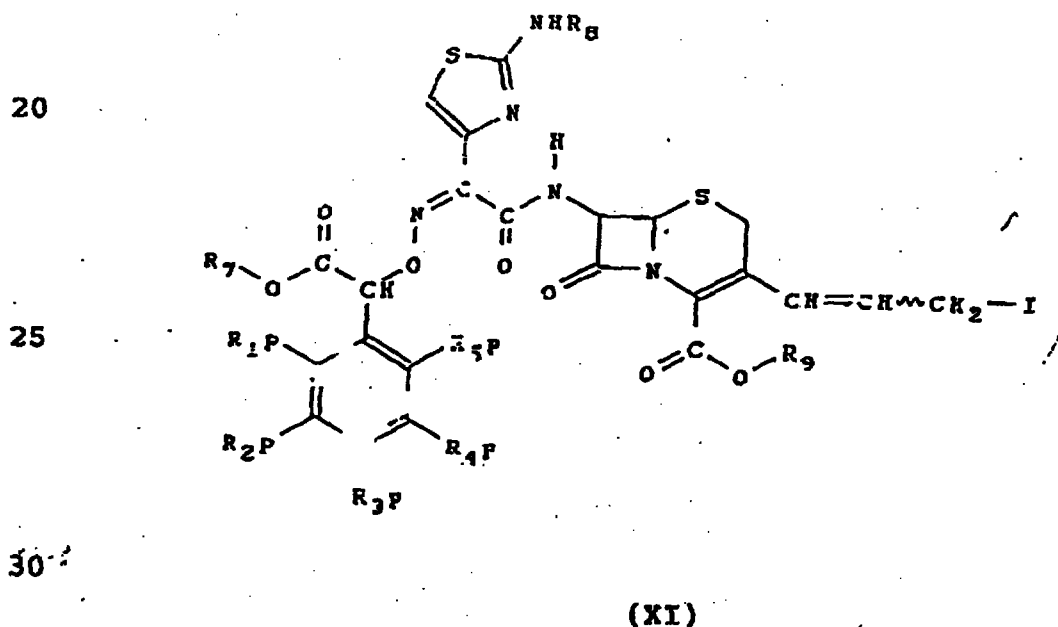


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15 which product of formula (X) is converted into an analogous 3-(3-iodo-propenyl) of formula (XI):

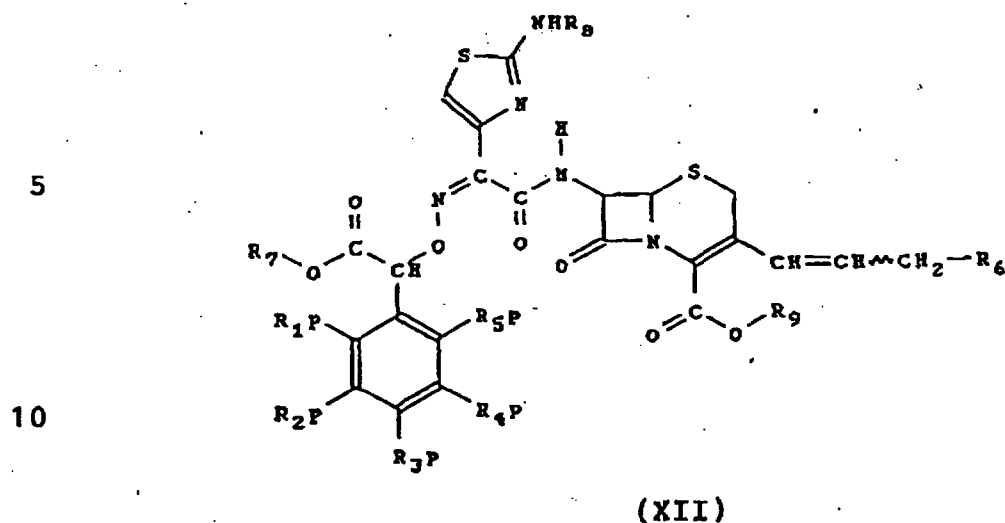


which product of formula (XI) is treated with a base of formula R_6 in order to obtain the product of formula (XII):



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from which product of formula (XII), if desired, the (E) or (Z) isomers are isolated or the (Z) isomers are converted into (E) isomers and which product of formula (XII) is subjected to one or more of the following reactions, in any order:

- a) cutting by hydrolysis or by the action of thiourea of all or part of the ester groups or the protective groups of the amino radical or the hydroxyl radicals,
- b) esterification or salification of the carboxylic radical or radicals by a base,
- c) salification of the amino radical by an acid,
- d) separation of the products in the form of an R,S mixture into R or S.

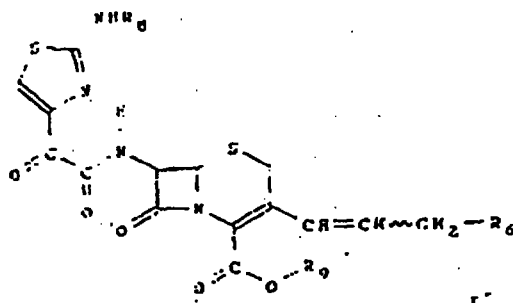
Also a subject of the invention is a variant of the process described above, characterized in that the O-substituted hydroxylamine of formula (VI) is condensed with the product of formula (XIII):



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(XIII)

to give the product of formula (XII) as defined previously.

The protected hydroxy functions that can be represented by R_{1p} , R_{2p} , R_{3p} , R_{4p} and R_{5p} , are chosen from acyloxy groups such as for example formyloxy, acetoxy, propionyloxy, chloroacetoxy, bromoacetoxy, dichloroacetoxy, trichloroacetoxy, trifluoroacetoxy, methoxyacetoxy, phenoxyacetoxy, benzoyloxy, benzoylformoxy, p-nitro benzoyloxy. The following groups can also be mentioned: ethoxycarbonyloxy, methoxycarbonyloxy, propoxycarbonyloxy, 2,2,2-trichloro ethoxycarbonyloxy, benzyloxycarbonyloxy, tert-butoxycarbonyloxy, 1-cyclopropyl ethoxycarbonyloxy, phthaloyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, oxalyloxy, succinyloxy and pivaloyloxy, phenylacetoxo, phenylpropionyloxy, mesyloxy, chlorobenzoyloxy, para-nitrobenzoyloxy, para-tert-butyl benzoyloxy, caprylyloxy, acryloyloxy, methylcarbamoyloxy, phenylcarbamoyloxy, naphthylcarbamoyloxy.

The following radicals can also be mentioned: phenoxy, 4-chloro phenoxy, tolyloxy or tert-butyl phenoxy, tetrahydropyrannyloxy, tetrahydrothiopyrannyloxy, methoxytetrahydropyrannyloxy, trityloxy, benzyloxy, 4-methoxy benzyloxy, benzhydryloxy, trichloroethoxy, 1-methyl-1-methoxyethoxy, or alkoxy alkoxy-methyl radicals such as methoxy ethoxy methyl.

Two adjacent hydroxy radicals can be protected by forming a methylenedioxy, isopropylendioxy, 1,1-cyclohexyl bis(oxy), diphenylmethylenedioxy, carbonate or hydroxy borannylbis(oxy) radical.

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The protected hydroxy functions that can be represented by R_{1p} , R_{2p} , R_{3p} , R_{4p} and R_{5p} , are preferably chosen from the following groups: methoxyethoxymethoxy, propionyloxymethoxy, acetoxymethoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, 5 hexyloxy, butyryloxymethoxy, valeryloxymethoxy, pivaloyloxymethoxy, 2-acetoxy ethoxy, 2-propionyloxy ethoxy, 2-butyryloxy ethoxy, 2-iodoethoxy, 2,2,2-trichloro ethoxy, vinyloxy, allyloxy, ethynyloxy, propynyloxy, benzyloxy, 4-methoxy benzyloxy, 4-nitro benzyloxy, phenylethoxy, 10 trityloxy, diphenylmethyloxy or 3,4-dimethoxyphenoxy.

The 2-methoxy ethoxymethoxy (MEM-O) group is particularly preferred.

The remainders of the easily-cleavable ester groups that are represented by R_7 and R_9 are chosen from the following 15 groups: butyl, isobutyl, tert-butyl, pentyl, hexyl, methoxymethyl, ethoxymethyl, isopropylloxymethyl, alpha-methoxy ethyl, alpha-ethoxy ethyl, methylthiomethyl, ethylthiomethyl, isopropylthiomethyl, pivaloyloxymethyl, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, 20 isobutyryloxymethyl, valeryloxymethyl, isovaleryloxymethyl, tert-butylcarbonyloxymethyl, hexadecanoyloxymethyl, pivaloyloxymethyl, propionyloxyethyl, isovaleryloxyethyl, 1-acetoxy ethyl, 2-acetoxy ethyl, 1-propionyloxy ethyl, 2-propionyloxy ethyl, 1-butyryloxy ethyl, 2-butyryloxy ethyl, 25 1-(tert-butylcarbonyloxy) ethyl, 1-acetoxy propyl, 1-hexadecanoyloxy ethyl, 1-propionyloxy propyl, 1-methoxycarbonyloxy ethyl, methoxycarbonyloxymethyl, 1-acetoxy butyl, 1-acetoxy hexyl, 1-acetoxy heptyl, phthalidyl, 5,6-dimethoxy phthalidyl, tert-butylcarbonylmethyl, vinyl, allyl, 2-chloro 30 allyl, ethynyl, propynyl, methoxycarbonylmethyl, benzyl, 4-methoxy benzyl, 4-nitro benzyl, phenethyl, trityl, diphenyl methyl, phenyl, 4-chloro phenyl, tolyl, tert-butyl phenyl, 3,4-dimethoxy phenyl, methoxyethoxymethyl, dimethylamino-ethyl, cyanomethyl, tert-butoxycarbonylmethyl, 2,2- 35 ethylenedioxy ethyl, cyanoethyl, 2,2-dimethoxy ethyl; 2-chloro ethoxymethyl, (2-hydroxy ethoxy) ethyl, 2,3-epoxy propyl, 3-dimethylamino 2-hydroxy propyl, 2-hydroxy ethyl, 2-methylaminoethoxymethyl, (2-amino ethoxy) methyl, 3-methoxy

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2,4-thiadiazol-5-yl, tetrahydropyrann-2-yl, 1-methoxy 1-methyl ethyl, 2-hydroxy 1-methyl ethyl, isopropyl, carbamoylmethyl, chloromethyl, 2-chloro ethyl, 2,2,2-trichloro ethyl, 2-iodo ethyl, acetyl, methyl, 2-methylthio ethyl, thiocyanatomethyl, 2-chloro 1-acetoxy ethyl, 2-bromo 1-acetoxy ethyl, 2-fluoro 1-acetoxy ethyl, 2-methoxy 1-acetoxy ethyl, 2-methyl 1-acetoxy propyl, 1-methyl 1-acetoxy ethyl, 1-(methoxyacetoxy) ethyl, 1-acetyl carbonyloxyethyl, 1-hydroxy acetoxyethyl, 1-(2-thienyl) carbonyloxyethyl, 1-(2-furyl) carbonyloxyethyl, 1-(5-nitro-2-furyl) carbonyloxyethyl, 1-(2-pyrrolyl) carbonyloxyethyl, 1-(propionyloxycarbonyloxy) ethyl, 1-(propoxycarbonyloxy) ethyl, 1-(isopropoxycarbonyloxy) ethyl, 1-(methoxyethoxycarbonyloxy) ethyl, 1-(allyloxycarbonyloxy) ethyl, 15 isopropoxycarbonyl methyl, 1-[(2,3-epoxy propyl) oxycarbonyloxy] ethyl, 1-[(2-furyl) methoxycarbonyloxy] ethyl, 1-[(2-fluoro ethoxy)-carbonyloxy] ethyl, 1-(methoxycarbonyloxy) propyl, 1-(methoxycarbonyloxy) 1-methyl ethyl, (methoxycarbonyloxy) chloromethyl, 1-(methoxycarbonyl-oxy)-2-20 chloro ethyl, 1-(methoxy carbonyloxy) 2-methoxy ethyl, 1-(methoxycarbonyloxy) allyl or a 5-methyl 2-oxo 1,3-dioxol-4-yl remainder.

The diphenylmethyl radical is preferred for R₇ and 4-benzyl methoxy or diphenylmethyl is preferred for R₉.

25 The protective group of the amino radical that can be represented by R₈ can be for example a carbamoyl methyl carbamoyl, phenylcarbamoyl, naphthylcarbamoyl group, as well as the corresponding thiocarbamoyls, an alkyl radical having 1 to 6 carbon atoms, substituted or non-substituted, such as, 30 preferably, trichloroethyl, tert-butyl or tert-amyl, an aralkyl radical such as benzyl, 4-methoxy benzyl, phenethyl, trityl, 3,4-dimethoxy benzyl or benzhydryl, a substituted or non-substituted aliphatic, aromatic or heterocyclic acyl radical, such as for example formyl, acetyl, propionyl, 35 butyryl, isobutyryl, valeryl, isovaleryl, chloroacetyl, dichloroacetyl, trichloroacetyl, bromoacetyl, trifluoroacetyl benzoyl, toluoyl, naphthoyl, chlorobenzoyl, para-nitro benzoyl, para-tert-butyl benzoyl, phenoxyacetyl, caprylyl,

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decanoyl, acryloyl, phthaloyl, mesyl, phenyl-acetyl, phenylpropionyl, oxalyl, succinyl, pivaloyl, a lower alkoxycarbonyl or cycloalkoxycarbonyl such as for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 1-cyclopropylethoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, trichloroethoxy carbonyl, an aralkoxycarbonyl group, such as benzyloxycarbonyl.

The trityl group is preferred.

10 The above list is not limitative, it is evident that other amine protective groups, groups known in particular in the chemistry of the peptides, can also be used.

The functional derivative of the acid of formula (VIII) can be for example a halide, a symmetrical or mixed anhydride, the amide, the azide or an activated ester.

15 As an example of a mixed anhydride there can be mentioned for example that formed with isobutyl chloroformate and that formed with pivaloyl chloride and the carboxylic-sulphonic mixed anhydrides formed for example with 20 paratoluene sulphonyl chloride.

As an example of an activated ester, there can be mentioned the ester formed with 2,4-dinitrophenol and that formed with hydroxybenzothiazole.

25 As an example of a halide, there can be mentioned chloride or bromide.

The anhydride can be formed in situ by the action of N,N'-disubstituted carbodiimide, for example N,N'-dicyclohexylcarbodiimide.

30 The acylation reaction is preferably carried out in an organic solvent such as methylene chloride. Other solvents can however be used such as tetrahydrofuran, chloroform or dimethylformamide.

35 When an acid halide is used and in a general manner when a hydrohalic acid molecule is released during the reaction, the reaction is preferably carried out in the presence of a base such as soda, potash, sodium or potassium carbonates and acid carbonates, sodium acetate, triethylamine, pyridine, morpholine or N-methylmorpholine.

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The reaction temperature is in general lower than or equal to ambient temperature.

A product of formula (VIII) can also be reacted directly with a product of formula (IX) in the presence of a carbodiimide such as diisopropylcarbodiimide or 1-(3-dimethylamino propyl)-3-ethyl carbodiimide (EDC). An example of such a preparation is given further on in the experimental part.

The action of the reagent capable of introducing the R_6 radical onto the product of formula (IV) is carried out under the following conditions:

When Hal represents for example a chlorine atom, a substitution of the chlorine atom by an iodine atom in the presence sodium iodide can be carried out in situ or separately, then the desired reagent is added, in the presence or not of an organic solvent such as dichloromethane, acetonitrile or tetrahydrofuran.

The desired reagent of formula R_6 can also be reacted directly on the product of formula (X) in the presence of silver tetrafluoroborate.

The isomerism of the products of formula (XII) can be different from that of the products of formula (X) or (XI) used at the start. When the Z isomer is isolated, this isomer can be converted into the E isomer according to the usual methods, notably by the action of iodine.

According to the values of R_7 , R_8 , R_9 , R_{1p} , R_{2p} , R_{3p} , R_{4p} and R_{5p} , the action of one or more hydrolysis, hydrogenolysis agents or of thiourea on the product of formula (XII) is intended to eliminate the R_8 radical when the latter represents a protective radical of the amino radical, to convert the R_{1p} , R_{2p} , R_{3p} , R_{4p} and R_{5p} radicals into R_1 , R_2 , R_3 , R_4 and R_5 radicals respectively when these represent a protective group of the hydroxyl radicals and/or to eliminate radicals R_7 and R_9 when these represent, amongst the easily-cleavable ester groups, one of those that is desired to eliminate.

However, it is of course possible to eliminate R_8 and to convert the R_{1p} , R_{2p} , R_{3p} , R_{4p} and R_{5p} radicals into the R_1 ,

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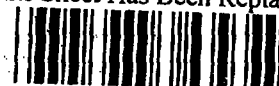


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- R_2 , R_3 , R_4 and R_5 radicals respectively when these represent a protective group of the hydroxyl radicals without affecting substituents R_7 and R_9 when these have to be preserved. The nature of the reagents to be used in such a case is well known to a man skilled in the art. Examples of such reactions are given further on in the experimental part. A description of the methods for eliminating the different protective groups will be found for example in the French Patent Application B.F. 2,499,995.
- Given the nature of the preferred protective groups used: trityl for R_8 , 2-methoxy ethoxy methyl to protect the hydroxy functions that can be represented by one or more of the substituents R_1 , R_2 , R_3 , R_4 and R_5 , diphenylmethyl for R_7 and 4-methoxy benzyl or diphenylmethyl for R_9 , trifluoroacetic acid is preferably used without a solvent or in a solvent such as anisole or a mixture of solvents such as anisole/methylene chloride. A salt is then obtained with trifluoroacetic acid. The free base can be returned to by the action of a base such as triethylamine carbonate.
- The salification of the products can be carried out according to the usual methods; it can, for example, be obtained by the action, on a product in the acid form or on a solvate, for example the ethanolic solvate or a hydrate of this acid, of a mineral base such as sodium or potassium hydroxide, sodium or potassium carbonate or acid carbonate. Mineral acid salts can also be used such as trisodium phosphate. Organic acid salts can also be used such as, for example, sodium salts of saturated or unsaturated, linear or branched aliphatic carboxylic acids having 1 to 18 and preferably 2 to 10 carbon atoms. The aliphatic chains of these acids can be interrupted by one or more heteroatoms such as oxygen or sulphur or substituted by aryl radicals such as phenyl, thienyl or furyl, by one or more hydroxyl radicals or by one or more halogen atoms such as fluorine, chlorine or bromine, preferably chlorine, by one or more lower carboxylic or alkoxycarbonyl radicals, preferably methoxycarbonyl, ethoxycarbonyl or propyloxycarbonyl, by one or more aryloxy radicals, preferably phenoxy.

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Moreover, sufficiently soluble aromatic acids can be used as the organic acids, such as, for example, benzoic acids substituted, preferably by lower alkyl radicals.

As examples of such organic acids, the following acids can be mentioned: formic, acetic, acrylic, butyric, adipic, isobutyric, n-caproic, isocaproic, chloropropionic, crotonic, phenyl acetic, (2-thienyl) acetic, (3-thienyl) acetic, (4-ethyl phenyl) acetic, glutaric, the monoethylic ester of adipic acid, hexanoic, heptanoic, decanoic, oleic, stearic, palmitic, 3-hydroxy propionic, 3-methoxy propionic, 3-methyl thiobutyric, 4-chloro butyric, 4-phenyl butyric, 3-phenoxy butyric, 4-ethyl benzoic, 1-propyl benzoic.

Sodium acetate, sodium 2-ethyl hexanoate or sodium diethyl acetate are however preferably used as sodium salts.

The salification can also be obtained by the action of an organic base such as triethylamine, diethylamine, trimethylamine, propylamine, N,N-dimethyl ethanolamine, tris[(hydroxymethyl)-amino] methane, methylamine, ethanolamine, pyridine, picoline, dicyclohexyl amine, morpholine and benzylamine.

It can also be obtained by the action of arginine, lysine, procaine, histidine, N-methyl glucamine.

This salification is preferably carried out in a solvent or a mixture of solvents such as water, ethyl ether, methanol, ethanol or acetone.

The salts are obtained in amorphous or crystallized form according to the reaction conditions used.

The crystallized salts are preferably prepared by reacting the free acids with one of the salts of the aliphatic carboxylic acids mentioned above, preferably with sodium acetate.

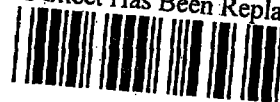
The salification of the products by mineral or organic acids is carried out under the usual conditions.

The optional esterification of the products is carried out under standard conditions. The operation is generally carried out by reacting the acid of formula (I) or a functional derivative of this acid with a derivative of formula:

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Z-Re

in which Z represents a hydroxyl radical or a halogen atom
5 such as chlorine, bromine, iodine and Re designates the ester
group to be introduced, a non-exhaustive list of which group
is given above. In certain cases, it may be advantageous to
carry out an esterification on a product of which the amine
and/or reaction groups present on the oxyimino are blocked
10 before removing the protective group of the amine and of the
reaction group present on the oxyimino.

The products of formula (I) contain several asymmetrical
carbons. In the cepHEME nucleus, which contains two
asymmetrical carbons, the two carbons are in R configuration..
15 Furthermore the radical present on the oxyimino function also
contains an asymmetrical carbon which can be in R or S form
or in the form of an R + S mixture. The separation of the
two diastereoisomers can be carried out by means known to a
man skilled in the art, for example by chromatography.

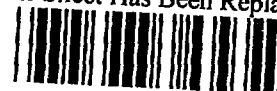
20 The products of general formula (I) have a very good
antibiotic activity on gram (+) bacteria such as
staphylococci, streptococci and notably on penicillin-
resistant staphylococci. Their effectiveness on gram (-)
bacteria, in particular on coliform bacteria, klebsiella,
25 salmonella, proteus and pseudomonas, is particularly
remarkable.

These properties make the said products as well as their
pharmaceutically acceptable acid salts suitable to be used as
medicaments in the treatment of germ-sensitive diseases,
30 and in particular in that of staphylococci, such as
staphylococcic septicemias, malignant staphylococcia of the
face or skin, pyodermatitis, septic or suppurative sores,
anthrax, phlegmon, erysipelas, acute primary or post-
influenzal staphylococcia, broncho-pneumonia, pulmonary
35 suppurations.

These products can also be used as medicaments in the
treatment of colibacilloses and associated infections, of
proteus, klebsiella and salmonella infections and of other

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diseases caused by gram (-) bacteria.

Therefore a subject of the present invention is also, as medicaments and notably as antibiotic medicaments, the products of formula (I) as defined above as well as their
5 pharmaceutically acceptable acid salts.

A more particular subject of the invention is, as medicaments, the products of formula (I) as described above in which R₆ is chosen from quinolinium, isoquinolinium, 4-(methylthio) pyridinium, thieno-[2,3-b]-pyridinium, imidazo
10 (1,2-a) pyridinium and 6,7-dihydro 5H-pyrindinium radicals.

A particular subject of the invention is, as medicaments and in particular as antibiotic medicaments, the products of which the names follow:

- the internal salt of (6R-(3-(E) 6alpha, 7beta(Z)))-1-(3-
15 (7-(((2-amino-4-thiazolyl) ((carboxy-(2,3-difluoro-4,5-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) imidazo(1,2-a) pyridinium,
- the internal salt of (6R-(3-(E) 6alpha, 7beta(Z)))-1-(3-
20 (7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-difluoro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a) pyridinium,
- the internal salt of (6R-(3-(E) 6alpha, 7beta(Z)))-1-(3-
25 (7-(((2-amino-4-thiazolyl) ((carboxy-(2-chloro-4,5-dihydroxy-3-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)quinolinium,
- the internal salt of (6R-(3-(E) 6alpha, 7beta(Z)))-1-(3-
30 (7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-6,7-dihydro-5-H-pyrindinium,
- the internal salt of (6R-(3-(E) 6alpha, 7beta(Z(S*))))-1-
35 (3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3,4-dihydroxy-5-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-quinolinium,

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- the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl] [[carboxy-(2-chloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium (R) or (S) or an (R+S) mixture,
- 5 - the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl] [[carboxy-(3-cyano-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium (R) or (S) or an (R+S) mixture,
- 10 - the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl] [[carboxy-(3-fluoro-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium (R) or (S) or an (R+S) mixture,
- 15 - the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[2-amino-4-thiazolyl] [[carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]thieno[2,3-b]pyridinium (R) or (S) or an (R+S) mixture,
- 20 - the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl] [[carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium (R) or (S) or an (R+S) mixture,
- 25 - the internal salt of [6R-[3(E), 6alpha, 7beta(Z(S*))]]-1-[3-[7-[[2-amino-4-thiazolyl] [[carboxy-(3-cyano-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-thieno[2,3-b]pyridinium,
- 30 - the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl] [[carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-isoquinolinium (R) or (S) or an (R+S) mixture,
- 35 - the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl] [[carboxy-(2,5-dichloro-3,4-

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dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-4-(methylthio)-pyridinium (R) or (S) or an (R+S) mixture, as well as their pharmaceutically acceptable salts.

- 5 The invention extends to pharmaceutical compositions containing, as active ingredient, at least one of the medicaments defined above.

These compositions can be administered by buccal, rectal, parenteral route, in particular by intramuscular route or by local route as a topical application on the skin and mucous membranes.

The products of formula (I) and notably those in which A represents a cleavable ester can be administered by oral route.

- 15 The compositions according to the invention can be solid or liquid and can be presented in the pharmaceutical forms commonly used in human medicine such as, for example, plain or sugar-coated tablets, capsules, granules, suppositories, injectable preparations, ointments, creams, gels; they are prepared according to the usual methods. The active ingredient or ingredients can be incorporated with the excipients usually employed in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents, and preservatives.

These compositions can notably be presented in the form of a powder intended to be dissolved extemporaneously in an appropriate vehicle, for example, apyrogenic sterile water.

- The dose administered is variable according to the disease being treated, the patient in question, the administration route and the product considered. It may be, for example, comprised between 0.250 g and 4 g per day, by oral route for man, with the product described in Example 1 or also comprised between 0.500 g and 1 g three times per day by intramuscular route.

The products of formula (I) can also be used as

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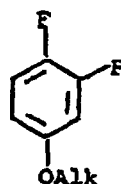
disinfectants for surgical instruments.

Finally a subject of the invention is, as new industrial products and in particular as intermediate products necessary for the preparation of the products of formula (I), the products of formulae (III), (IV), (V), (VI), (VIII), (X), (XI), (XII) and (XIII) as defined previously.

The products of formula (VI) in which R_1p and R_2p each represent a fluorine atom and R_3p and R_4p each represent a hydroxy radical protected for example by a methoxyethoxy-methyl function (MEM hereafter products of formula (VIa)) can in particular be prepared as follows:

Butyllithium and trimethylborate then hydrogen peroxide are reacted on a product of formula (A):

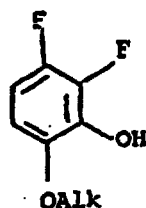
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(A)

20 in which Alk represents an alkyl radical, preferably methyl, in order to obtain the product of formula (B):

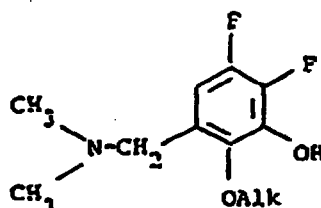
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(B)

on which dimethylamine is reacted in the presence of formic anhydride in order to obtain a product of formula (C):

30



(C)

35

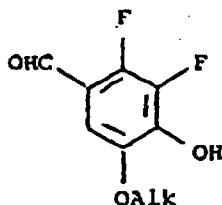
on which methyl iodide and hexamethylene tetramine is reacted in the presence of acetic acid in order to obtain a product

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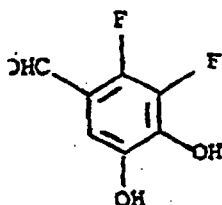
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of formula (II_D):

5

(II_D)

from which product of formula (II_D) the alkyl radical is
 10 eliminated in the presence of boron tribromide in order to
 obtain a product of formula (E):

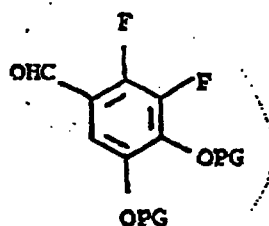
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(E)

of which product of formula (E) the hydroxyl functions are
 protected, for example using an (MEM) group in order to
 20 obtain a product of formula (F):

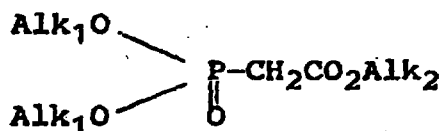
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(F)

in which G_p represents a protective group of the hydroxyl
 radical, which product is treated with an organophosphate
 derivative of formula:

30.:



35 in which Alk₁ and Alk₂ identical or different represent an
 alkyl radical having 1 to 4 carbon atoms in order to obtain a
 product of formula (G):

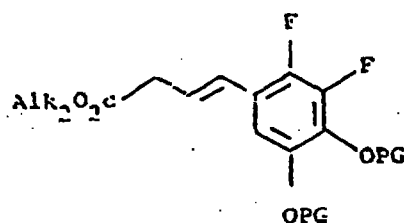
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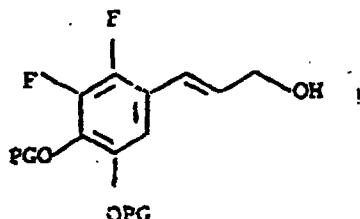
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(G)

which is treated with a reducing agent, for example
 10 diisobutylaluminium hydride in order to obtain a product of
 formula (H):

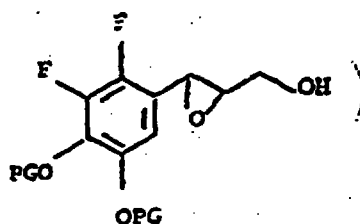
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(H)

which product is treated with an epoxidation agent for
 20 example metachloroperbenzoic acid in order to obtain a
 product of formula (J):

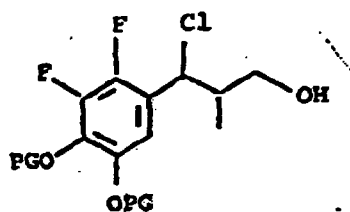
25



(J)

which product is treated with cuprous chloride in the
 presence of lithium chloride in order to obtain a product of
 30 formula (K):

35

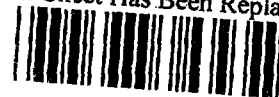


(K)

which product is treated with an oxidizing agent for example

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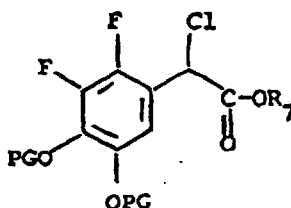
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sodium metaperiodate then with an esterification agent in order to obtain a product of formula (L):

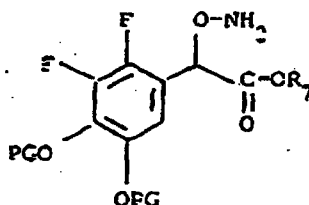
5



(L)

10 in which R₇ has the previous meaning, which product is treated with N-hydroxyphthalimide then with hydrazine in order to obtain a product of formula (VI_a):

15

(VI_a)

20 The products of formulae (II) and (A) are known in a general manner; most are commercially available; others can be prepared from commercially-available products, according to the methods described in the preparations below. For the products of formula (II) the methods described in the
25 literature can also be used, notably the so-called Rosemund reduction, the reduction of benzoic acids or the formylation of aromatic rings such as for example the Vilsmeier-Haack reaction, the Gatterman-Koch reaction, the Reimer-Tiemann reaction or the reaction with formyl fluoride (J. Am. Chem.
30 Soc. 82, 2380 (1960)).

The products of formulae (VII) and (IX) are also known in the literature, notably in the Belgian Patent Application BE864828 and the European Patent Application EP0333154.

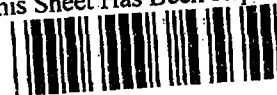
35 The following examples illustrate the invention without however limiting it.

PREPARATION 1: 2-chloro-3,4-bis[(2-methoxy-ethoxy)-methoxy]-benzaldehyde

Stage A: 2-chloro-3,4-dihydroxy benzaldehyde

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27.62 g of 3,4-dihydroxy benzaldehyde (commercial) is dissolved in 450 cm³ of acetic acid and chlorine is bubbled through the solution at an ordinary temperature until 4.48 dm³ of the gas has been consumed. Agitation is maintained for 16 hours then the solution is concentrated, cooled down to 0°C and the precipitate is filtered, washed and dried. In this way 7.5 g of the expected product is collected which is recrystallized from ethyl acetate. Melting point (MP) = 196°C.

10 Stage B: 2-chloro-3,4-bis[(2-methoxy-ethoxy)-methoxy]-benzaldehyde

46 cm³ of diisopropyl ethylamine is added to a suspension containing 11.42 g of the product prepared in the previous stage in 120 cm³ methylene chloride, the mixture is cooled down to -10°C then 30.14 cm³ of chloro-(2-methoxy-ethoxy)-methane is added, agitation is carried out for one hour, the mixture is diluted with 100 cm³ water, separated, then the organic phase is washed, dried and concentrated. In this way 22.6 g of the expected product is recovered. Rf = 0.6 (eluant: ethyl acetate)

NMR Analysis of the proton (CDCl₃ 250 MHz in ppm)

3.36 (s), and 3.38 (s): -OCH₃

3.58 (m) (4 H), 3.84 (m) (2 H) and 4.06 (m) (2 H): O-CH₂-CH₂-O

5.29 (s) (2 H) and 5.38 (s) (2 H): -O-CH₂-O

25 7.21 (d) and 7.71 (d): aromatic protons (Ar-H)

10.36 (s): -CH=O

PREPARATION 2: 3-formyl-5,6-bis[(2-methoxy-ethoxy)-methoxy] benzonitrile

Stage A: 3-formyl-6-hydroxy-5-methoxy benzonitrile

30 A mixture constituted by 23.1 g of 3-bromo-4-hydroxy-5-methoxy benzaldehyde, 9.3 g of cuprous cyanide and 140 cm³ of dimethyl acetal (DMA) is taken to reflux for 2 hours under agitation.

After cooling down the mixture, it is poured over ice, extracted with an ethyl acetate - methanol mixture (90+10), the organic phase is washed and dried and the solvents are eliminated. 18 g of crude product is collected which is used as it is for the following stage. MP = 180°C.

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Stage B: 3-formyl-5,6-dihydroxy benzonitrile

- 18 g of the product prepared in the previous stage and 400 cm³ of dichloromethane are mixed together under nitrogen, the mixture is cooled down to 0°C, 150 cm³ of a molar
- 5 solution of boron tribromide in dichloromethane is added, the whole mixture is left for 16 hours at ambient temperature, concentrated, cooled down again to 0°C and 250 cm³ of a normal solution of hydrochloric acid is added. The crystallized product is separated out, washed with water,
- 10 dried then recrystallized from an isopropanol - water mixture (1-2). In this way 12 g of the expected product is collected.

Infrared analysis (Nujol)

Strong and complex absorption in the -NH/OH region

- 15 2245 cm⁻¹: C≡N

1700 cm⁻¹: C=O

1602, 1597, 1520 cm⁻¹: aromatic nucleus

NMR analysis of the proton (DMSO 250 MHz in ppm)

7.45 (d) (J = 2): Ar-H

- 20 7.73 (d) (J = 2): Ar-H

9.74: CH=O

11.15: mobile absorption

Stage C: 3-formyl-5,6-bis[(2-methoxy-ethoxy)-methoxy]-benzonitrile

- 25 53.6 cm³ of diisopropyl ethylamine is added to a suspension containing 12.6 g of the product prepared in the previous stage in 500 cm³ of dichloromethane, the mixture is cooled down to -10°C then 35.3 cm³ of chloro-(2-methoxy-ethoxy)-methane is added, agitation is carried out for one
- 30 hour, the medium is diluted with 100 cm³ water, separated, then the organic phase is washed, dried and concentrated. In this way 21.4 g of the expected product is recovered.

Infrared analysis (CHCl₃)

Absence of OH

- 35 2235 cm⁻¹: C≡N

1702 and 2730 cm⁻¹: CH=O

1592, 1582 and 1485 cm⁻¹: aromatic nucleus

NMR analysis of the proton (CDCl₃ 250 MHz in ppm)

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3.37 (s): $-\text{OCH}_3$ 3.58 (m) (4 H), 3.85 (m) (2 H) and 4.06 (m) (2 H): $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$ 5.39 (s) (2 H) and 5.49 (s) (2 H): $-\text{O}-\text{CH}_2-\text{O}$ 7.76 (d) (1 H) and 7.92 (d) (1 H): $\text{Ar}-\text{H}$ 5 9.90 (s): $-\text{CH}=\text{O}$ PREPARATION 3: 3-fluoro-4,5-bis[(2-methoxy-ethoxy)-methoxy] benzaldehyde

Stage A: 3-fluoro-4-hydroxy-5-methoxy benzaldehyde

A mixture constituted by 30.4 g of 4-hydroxy-5-methoxy benzaldehyde (vanillin), 100 cm³ of acetonitrile and 250 cm³ of Freon is agitated for two and a half hours at 0°C and under nitrogen, nitrogen mixed with 10% fluorine, then nitrogen alone are then bubbled through for 2 hours and 30 minutes. After treatment with thiosulphate, acidification by a solution of 2N hydrochloric acid and extraction with ethyl acetate, the organic phase is washed, dried, concentrated and chromatographed on silica eluting with dichloromethane; 2.1 g of the desired product is collected.

Rf = 0.3

20 Microanalysis MF = $\text{C}_7\text{H}_7\text{FO}_3$

	C	H	F
% calculated	56.47	4.14	11.16
% found	56.4	4.1	11.0

Stage B: 3-fluoro-4,5-dihydroxy benzaldehyde

25 3.72 g of the product prepared in the previous stage and 60 cm³ of dichloromethane are mixed together under nitrogen, the mixture is cooled down to 0°C, 32 cm³ of a molar solution of boron tribromide in dichloromethane is added and the whole is left for 16 hours at ambient temperature, then

30 concentrated, cooled down again to 0°C and acidified. The crystallized product is separated out, washed with water and dried. In this way 2.83 g of the expected crude product is collected which is used as it is for the following stage.

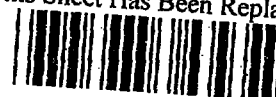
Rf = 0.2 [eluant: acetone - dichloromethane (1-9)]

35 Stage C: 3-fluoro-4,5-bis[(2-methoxy-ethoxy)-methoxy] benzaldehyde

17 cm³ of diisopropyl ethylamine is added to a suspension containing 2.8 g of the product prepared in the

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previous stage in 5.6 cm³ of dichloromethane, the mixture is cooled down to -10°C then 6.5 cm³ of chloro-(2-methoxy-ethoxy)-methane is added. Agitation is carried out for one hour, the medium is diluted with 100 cm³ water, separated then the organic phase is washed, dried and concentrated. In this way 5.5 g of the expected product is recovered. Rf = 0.55 [eluant: dichloromethane - acetone (9-1)]

Infrared analysis (CHCl₃)

Absence of OH

10 1696 and 2730 cm⁻¹: conjugated CH=O

NMR analysis of the proton (CDCl₃ 200 MHz in ppm)

3.36 (s) and 3.37 (s): -OCH₃

3.60 (m) (4 H), 3.85 (m) (2 H) and 3.96 (m) (2 H): O-CH₂-CH₂-O

5.33 (s) and 5.36 (s): O-CH₂-O

15 7.32 (dd) 7.51 (m): Ar-H

9.90 (m): -CH=O

PREPARATION 4: 3-chloro-4,5-bis[(2-methoxy-ethoxy)-methoxy] benzaldehyde

Stage A: 3-chloro-4,5-dihydroxy benzaldehyde

20 37.2 g of commercial 5-chloro vanillin and 800 cm³ of dichloromethane are mixed together under nitrogen, cooled down to 0°C, 300 cm³ of a molar solution of boron tribromide in dichloromethane is added, the resultant mixture is left for 16 hours at ambient temperature, concentrated, cooled down again to 0°C and acidified. The crystallized product is separated out, washed with water, dried and recrystallized from an isopropanol - water mixture (1-2 by volume). In this way 26.6 g of the expected product is collected. Melting point (MP) 260°C

30 Infrared analysis (Nujol)

3425 cm⁻¹: -OH + general absorption

1672-1660 cm⁻¹: C=O

1595, 1588, 1534, 1500 cm⁻¹: aromatic ring

NMR analysis of the proton (DMSO 250 MHz in ppm)

35 7.24 (d J=2Hz) and 7.44 (d J=2Hz): Ar-H

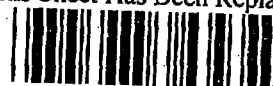
9.90 (m): -CH=O

10.40: mobile absorption

Stage B: 3-chloro-4,5-bis[(2-methoxy-ethoxy)-methoxy]

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benzaldehyde

- 60.5 cm³ of diisopropyl ethylamine is added to a suspension containing 15 g of the product prepared in the previous stage in 150 cm³ of dichloromethane, the mixture is
- 5 cooled down to -10°C then 39.7 cm³ of chloro-(2-methoxy-ethoxy)-methane is added over 45 minutes. The mixture is agitated for half an hour, diluted with 100 cm³ of water, separated, then the organic phase is washed, dried, concentrated and chromatographed on silica, eluting with a
- 10 dichloromethane - methanol mixture (99-1). In this way 15.9 g of the expected product is recovered.

Infrared analysis (CHCl₃)1698 and 2735 cm⁻¹: conjugated CH=O1591, 1579, 1498 cm⁻¹: aromatic ring

- 15 NMR analysis of the proton (CDCl₃ 250 MHz in ppm)

3.38 (s): -OCH₃3.57 (m) (4 H), 3.87 (m) (2 H) and 4.03 (m) (2 H): O-CH₂-CH₂-O5.36 (s) and 5.38 (s): O-CH₂-O

7.59 (d) 7.62 (d): Ar-H

- 20 9.85: -CH=O

PREPARATION 5: 3-nitro-4,5-bis[(2-methoxy-ethoxy)-methoxy] benzaldehyde**Stage A: 3-nitro-4,5-dihydroxy benzaldehyde**

- 35 g of 5-chloro vanillin (commercial) and 1200 cm³ of
- 25 dichloromethane are mixed together under nitrogen, the mixture is cooled down to 0°C, 533 cm³ of a molar solution of boron tribromide in dichloromethane is added, the whole is left for 2 days at ambient temperature, then concentrated, the residue is taken up cold (ice bath + methanol) in 300 cm³
- 30 of 2N hydrochloric acid, agitated for two to three hours at this temperature then left for 16 hours at ambient temperature. Extraction is carried out with ethyl acetate, the organic phase is washed, dried and concentrated. In this way 18 g of the expected product is collected. (MP) 260°C

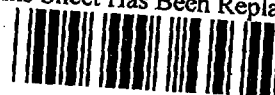
- 35 Infrared analysis (Nujol)

general absorption NH/OH

1682 cm⁻¹: C=O1620, 1590, 1580, 1548 and 1525 cm⁻¹: aromatic ring + -NO₂

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Stage B: 3-nitro-4,5-bis[(2-methoxy-ethoxy)-methoxy]
benzaldehyde

13.6 cm³ of diisopropyl ethylamine is added to a suspension containing 18 g of the product prepared in the previous stage in 50 cm³ of dichloromethane, the mixture is cooled down then 39.6 cm³ of chloro-(2-methoxy-ethoxy)-methane is added over 45 minutes, the whole is agitated for two hours at 0°C, diluted with 100 cm³ of water, separated, then the organic phase is washed, dried, concentrated and chromatographed on silica, eluting with a dichloromethane - acetone mixture (9-1). In this way 22.1 g of the expected product is obtained. R_f = 0.3

Infrared analysis (CHCl₃)

1704 cm⁻¹: CH=O

15 1608, 1578, 1546, 1496 cm⁻¹: aromatic ring + NO₂

NMR analysis of the proton (CDCl₃ 300 MHz in ppm)

3.36 and 3.38: -OCH₃

3.55 (m), 3.87 (m): O-CH₂-CH₂-O

5.41: O-CH₂-O

20 7.92: Ar-H

9.93: -CH=O

PREPARATION 6: 3-iodo-4,5-bis[(2-methoxy-ethoxy)-methoxy]
benzaldehyde

Stage A: 3-iodo-4,5-dihydroxy benzaldehyde

25 37.2 g of 5-iodo vanillin (commercial) and 360 cm³ of dichloromethane are mixed together under nitrogen, the mixture is cooled down to 0°C, 135 cm³ of a molar solution of boron tribromide in dichloromethane is added, the whole is left for 16 hours at ambient temperature, concentrated, cooled down again to 0°C and acidified. The crystallized product is separated out, washed with water, dried and recrystallized from an isopropanol - water mixture (1-2 by volume). In this way 23.4 g of the expected product is collected.

35 Infrared analysis (Nujol)

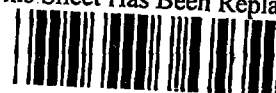
general absorption NH/OH

1662 (m) 1640 (F) cm⁻¹: C=O

1588, 1578, 1516 cm⁻¹: aromatic ring

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NMR analysis of the proton (DMSO 250 MHz in ppm)

7.25 (sl) and 7.44 (sl): Ar-H

9.68 (m): -CH=O

10.46, 10.43 cm^{-1} : mobile absorption

5 Stage B: 3-iodo-4,5-bis[(2-methoxy-ethoxy)-methoxy]
benzaldehyde

67 cm^3 of diisopropyl ethylamine is added to a suspension containing 25.4 g of the product prepared in the previous stage in 640 cm^3 of dichloromethane, the mixture is
10 cooled down to 10°C then 44 cm^3 of chloro-(2-methoxy-ethoxy)-methane is added over 45 minutes, the whole is agitated for half an hour, diluted with 100 cm^3 of water, separated, then the organic phase is washed, dried, concentrated and chromatographed on silica, eluting with an
15 ethyl acetate - hexane mixture (1/1). In this way 25.5 g of the expected product is recovered.

Infrared analysis (CHCl_3)

Absence of OH

1698 and 2730 cm^{-1} : CH=O

20 1588, 1562, cm^{-1} : aromatic ring

NMR analysis of the proton (CDCl_3 250 MHz in ppm)

3.38 (sl) (6 H): -OCH₃

3.58 (m) (4 H), 3.84 (m) (2 H) and 4.05 (m) (2 H): O-CH₂-CH₂-O

5.33 (sl) and 5.39 (sl): O-CH₂-O

25 7.68 (sl) and 7.96 (sl): Ar-H

9.82: -CH=O

PREPARATION 7: 3,4,5-tris[(2-methoxy-ethoxy)-methoxy]
benzaldehyde

52 cm^3 of diisopropyl ethylamine is added to a
30 suspension containing 8 g of 3,4,5-trihydroxy benzaldehyde (commercial) in 160 cm^3 of dichloromethane, the mixture is cooled down to 0-5°C then 35 cm^3 of chloro-(2-methoxy-ethoxy)-methane is added over one and a half hours, the whole is agitated, diluted with 100 cm^3 of water, separated, then
35 the organic phase is washed, dried and concentrated. In this way 21.75 g of crude product is recovered which is used as it is for what follows.

Infrared analysis (CHCl_3)



Absence of OH

1696 cm^{-1} : $\text{CH}=\text{O}$

1590, 1498 cm^{-1} : aromatic ring

NMR analysis of the proton (CDCl_3 250 MHz in ppm)

5 3.36 and 3.38 (9 H): $-\text{OCH}_3$

3.57 (m) (6 H), 3.85 (m) (4 H) and 3.99 (m) (2 H): $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$

5.31 (s) (2 H) and 5.34 (s) (4 H): $\text{O}-\text{CH}_2-\text{O}$

7.43 (s): $\text{Ar}-\text{H}$

9.82: $-\text{CH}=\text{O}$

10 PREPARATION 8: 2,5-dichloro-3,4-bis[(2-methoxy-ethoxy)-methoxy] benzaldehyde

Stage A: 2,5-dichloro-3,4-dihydroxy benzaldehyde

27.6 g of 3,4-dihydroxy benzaldehyde (commercial) is dissolved in 300 cm^3 of acetic acid and chlorine is bubbled through the solution at an ordinary temperature until 31.24 g of the gas has been consumed. Agitation is maintained for 42 hours, then the solution is concentrated, cooled down to 0°C and the precipitate is filtered, washed and dried. In this way 13.7 g of the expected product is collected. Melting point (MP) $176-178^\circ\text{C}$; $R_f = 0.1$ [eluant: ethyl acetate - cyclohexane (5-5)]

20 NMR analysis of the proton (DMSO 250 MHz in ppm)

7.24 (d $J=2\text{Hz}$) and 7.44 (d $J=2\text{Hz}$): $\text{Ar}-\text{H}$

9.90 (m): $-\text{CH}=\text{O}$

25 10.40: mobile absorption

Stage B: 2,5-dichloro-3,4-bis[(2-methoxy-ethoxy)-methoxy] benzaldehyde

60.5 cm^3 of diisopropyl ethylamine then 11.27 cm^3 of chloro-(2-methoxy-ethoxy)-methane are added to a solution containing 6.83 g of the product prepared in the previous stage in 265 cm^3 of acetonitrile, the whole mixture is agitated for two hours at 35°C and evaporated to dryness, the residue is taken up in dichloromethane, washed, dried and the solvent is evaporated off, chromatography is carried out on silica, eluting with an ethyl acetate - cyclohexane mixture (6-4). In this way 10.9 g of the expected product is recovered. MP 50°C ; $R_f = 0.3$

Infrared analysis (PE580)



1690 cm^{-1} : $\text{CH}=\text{O}$

1572, 1551 cm^{-1} : aromatic ring

NMR analysis of the proton (CDCl_3 250 MHz in ppm)

3.37 and 3.38: $-\text{OCH}_3$

5 3.58 and 4.01 (m) (2 H): $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$

5.29 and 5.36 (s): $\text{O}-\text{CH}_2-\text{O}$

7.78 (s): $\text{Ar}-\text{H}$

10.36 (s): $-\text{CH}=\text{O}$

PREPARATION 9: 3-methoxy-4,5-bis[(2-methoxy-ethoxy)-methoxy]

10 benzaldehyde

34 cm^3 of diisopropyl ethylamine is added to a suspension containing 8 g of 3,4-dihydroxy-5-methoxy benzaldehyde (commercial) in 80 cm^3 of dichloromethane, the mixture is cooled down to $-5^\circ\text{C}/-10^\circ\text{C}$ then 23 cm^3 of chloro-

15 (2-methoxy-ethoxy)-methane is added over half an hour, the whole is agitated for 16 hours, the organic phase is washed, dried, filtered, concentrated and chromatographed on silica, eluting with a hexane - ethyl acetate mixture (50-50). The expected product is recovered. $R_f = 0.4$ [eluant: hexane -
20 ethyl acetate (30-70)].

Infrared analysis (CHCl_3 on PE 580)

Absence of OH

1696 cm^{-1} : $\text{CH}=\text{O}$

1588, 1498 cm^{-1} : aromatic ring

25 NMR analysis of the proton (CDCl_3 250 MHz in ppm)

3.36 (s) (3 H) and 3.38 (s) (3 H): $\text{O}-\text{CH}_2-\text{CH}_2-\text{OCH}_3$

3.57 (m) (4 H), 3.87 (m) (2 H) and 4.00 (m) (2 H): $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$

3.90 (s) (3 H): $\text{Ar}-\text{OCH}_3$

5.31 (s) (2 H) and 5.35 (s) (2 H): $\text{O}-\text{CH}_2-\text{O}$

30 7.19 (d $J=2\text{Hz}$) (1 H) and 7.38 (d $J=2\text{Hz}$) (1 H): $\text{Ar}-\text{H}$ in the meta position

9.80 (s) (1 H): $-\text{CH}=\text{O}$

PREPARATION 10: 1-[3-[7beta-[[oxo-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0] [oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]pyridinium iodide

Stage A: 4-methoxy benzyl 7beta-[[oxo-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z+E)-3-chloro-1-



propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate.

5 g of 4-methoxy benzyl 7beta-amino-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate hydrochloride (described in the European Patent Application No. 0,333,154) and 0.72 g of oxo-[2-[(triphenylmethyl)-amino]-thiazol-4-yl] acetic acid (described in the Belgian Patent Application No. 864828) in 200 cm³ of dichloromethane are agitated under nitrogen, the mixture is cooled down to 0°C then 2.315 g of 1-(3-dimethylamino-propyl)-3-ethyl carbodiimide (EDC) is added, followed by agitating for 40 minutes, washing and drying, the solvents are evaporated and the residue is chromatographed, eluting with a dichloromethane - isopropyl ether mixture (9-1). 5.51 g of the expected product is collected. Rf = 0.3. Stage B: 4-methoxy benzyl 7beta-[[oxo-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z+E)-3-iodo-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate.

5.5 g of the product prepared in the previous stage is dissolved in 110 cm³ of acetone, 3.094 g of sodium iodide is added, the mixture is agitated for one and a half hours at 20°C, the solvent is evaporated, the residue is taken up in 350 cm³ of dichloromethane, washed, dried, filtered and brought to dryness. The foam obtained is filtered and the residue is chromatographed, eluting with a dichloromethane - isopropyl ether mixture (90-10); 3.93 g of the expected iodine derivative is collected. Rf = 0.3

Infrared analysis (CHCl₃)

1786, 1721, 1701 and 1663 cm⁻¹: C=O and beta-lactame
1613, 1586, 1535, 1516 cm⁻¹: aromatic + conjugated system

NMR analysis of the proton (CDCl₃ 300 MHz in ppm)

3.57: -S-CH₂-C(C=CH-)=C-

3.82 (s): Ar-OCH₃

3.98 (d, J=8): -CH=CH-CH₂-I

5.03 (d J=5) ppm: CO-NH-CH(C=O)-CH₂-(N-)-S-

5.25 (AB, J=12): CO-O-CH₂-Ar

5.75: CO-NH-CH₂(C=O)-CH(N-)-S-

6.14 (dt, J=16 and 8) ppm: $-\text{CH}=\text{CH}-\text{CH}_2-\text{I}$ E isomerism

6.8 to 7.4 (m): $-\text{S}-\text{CH}=\text{C}(\text{C}=\text{N}-)-\text{N}=\text{C}(\text{NH}-\text{trityl})-$ and $\text{Ar}-\text{H}$ of trityl

8.19 (d): $\text{CO}-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$

- 5 Stage C: 1-[3-[7beta-[[oxo-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0] [oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]pyridinium iodide

- 10 3.93 g of the iodine derivative obtained in the previous stage mixed with 6 g of thieno[2,3-b]pyridine is agitated for one and a half hours at 20°C. The mixture is precipitated from 400 cm³ of ether, filtered and dried under vacuum; in this way 4.12 g of the desired product is obtained. Rf = 0.1 [eluant: dichloromethane - methanol (92-8)]

- 15 Microanalysis MF = C₄₉H₄₀IN₅O₆S₃

	C	H	I	N	S
% calculated:	57.81	3.96	12.46	6.87	9.44
% found :	57.3	3.9	11.7	6.7	9.6

NMR analysis of the proton (CDCl₃, 300 MHz in ppm)

- 20 5.02 (d): $\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}-(\text{N}-)-\text{S}-$
 5.27 (s): $-\text{CO}-\text{O}-\text{CH}_2-\text{Ar}$
 5.6 (dd): $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$
 5.74 (dt): $\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$
 6.56 (d): $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$ E isomerism
 25 7.3: $\text{Ar}-\text{H}$ of the trityl
 8.3: $-\text{S}-\text{CH}=\text{C}(\text{C}=\text{N}-)-\text{N}=\text{C}(\text{NH}_2)-$
 7.89 (d): H in position 2 of thieno[2,3-b]pyridinium
 7.71 (d): H in position 3 of thieno[2,3-b]pyridinium
 8.8 (d) : H in position 4 of thieno[2,3-b]pyridinium
 30 8.10 (m): H in position 5 of thieno[2,3-b]pyridinium

PREPARATION 11: [4-fluoro-(2,3-bis-hydroxy)-phenyl] hydroxy acetic acid

- 51.2 g of 3-fluorocatechol and 36.8 g of glyoxylic acid are dissolved at 20°C in 160 cm³ of water. 34.8 g of soda in solution in 400 cm³ of water is added to this solution cooled down to 0°C. The resultant mixture is heated for 4 hours at 46°C, then cooled down to 0°C, the pH to brought to 4.6 by the addition of concentrated hydrochloric acid and extraction



is carried out with ethyl ether (after evaporation 14.7 g of the starting 9-fluorocatechol is collected), the aqueous phase is acidified with concentrated hydrochloric acid until a pH of 1.8 is achieved, extraction is carried out with ethyl acetate and after evaporation of the solvent, 47.7 g of the desired product is obtained (mixture of isomers, 2,3bis-hydroxy-4-fluoro; 3,4bis-hydroxy-5-fluoro; 2-fluoro-3,4bis-hydroxy) used as it is in Stage A of Example 16.

PREPARATION 12: 3-bromo 4,5-bis [(2-methoxyethoxy)methoxy] benzaldehyde.

By operating as in Preparation 4 starting with 5-bromo vanillin, the expected product used in Example 15 was prepared.

EXAMPLE 1: Internal salt of [6R-[3(E), 6alpha, 7beta (Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(2-chloro-3,4-dihydroxy-phenyl)-methoxy]-iminol]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium

Stage A: [2-chloro-3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-hydroxy acetic acid

2.42 g of lithium chloride and 7.02 g of potash are dissolved in 30 cm³ of water at 0°C; a solution containing 10 g of 2-chloro-3,4-bis[(2-methoxy-ethoxy)-methoxy] benzaldehyde (synthesized in Preparation 1), 2.8 cm³ of bromoform and 38 cm³ of dioxane are added to this mixture, the whole is left under agitation for 24 hours at 0°C, then another 2.8 cm³ of bromoform is added and the mixture is left for one night. After dilution in 100 cm³ of water, the solution is washed with ether, decanted, cooled down to 0°C, acidified until the pH = 2.5-3 and extraction is carried out with ether. The organic phase is washed with water, dried and the solvent is driven off in order to collect 11.4 g of the desired product in the form of an oil. R_f = 0.1 [eluant: methylene chloride - methanol - acetic acid (89-10-1)].

Infrared analysis (CHCl₃)

General absorption in the -OH region (acid + associated OH)

1726 cm⁻¹ complex: C=O of the acid function

1598-1489 cm⁻¹: aromatic nucleus

NMR analysis of the proton (CDCl₃ 250 MHz in ppm)

3.37 (s 1) (6 H): $-OCH_3$

3.57 (m) (4 H), 3.81 (m) (2 H) and 4.01 (m) (2 H): $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$

5.25 (m) (4 H) and 5.52 (s 1) (1 H): $-O-CH_2-O$ and $Ar-CH-CO$

5 7.11 (s 1) (2 H): Ar-H

Stage B: diphenylmethyl [2-chloro-3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-hydroxy acetate.

11.4 g of the acid prepared in Stage A is dissolved at ambient temperature and under nitrogen in 120 cm³ of dichloromethane, then 120 cm³ of a 0.3 molar solution of diphenyldiazomethane in dichloromethane is added at 15°C and the whole mixture is left under agitation for 16 hours at ambient temperature. Then 30 cm³ of water is added, followed by decanting and acidifying with 30 cm³ of acetic acid, washing with a saturated solution of sodium bicarbonate, drying and evaporating the solvents. After chromatography on silica, eluting with an ethyl acetate - hexane mixture (60-40), 8.1 g of the desired product is collected.

20 Infrared analysis (CHCl_3)

3528 cm^{-1} : non-phenolic -OH

1734 cm^{-1} : C=O of the ester function

1597, 1496, 1487 cm^{-1} : aromatic nucleus

NMR analysis of the proton (CDCl₃ 300 MHz in ppm)

25 3.36 (s): $-OCH_3$

3.55 (s) (4 H), 3.82 (s) (2 H) and 4.03 (s) (2 H): $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$

5.27 (s) and 5.29 (s): $-O-\underline{\text{CH}_2}-O$

5.67 (d after exchange): $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{OH}$

6.88 (s): CO-O-CHAr₂

30 7.0 (masked) and 7.08 (d): coupled Ar-H (ortho of the tetra-substituted ring

7.00 (2 H), 7.18 (3 H) and 7.30 (s) (5 H): Ar-H

Stage C: diphenylmethyl [2-chloro-3,4-bis[(2-methoxyethoxy)-methoxy]-phenyl]-phthalimidoxyl acetate.

35 2.47 g of N-hydroxy phthalimide and 7.55 g of triphenyl phosphine are added to a solution of 8.1 g of the ester prepared in Stage B in 90 cm³ of tetrahydrofuran, the mixture is cooled down to 10°C then 3.88 cm³ of diethyl



azodicarboxylate (DEAD) is poured into it and the whole is left under agitation for 16 hours.

After concentration of the solvents and chromatography on silica, eluting with an ethyl acetate - hexane mixture (60-40), 6.27 g of the desired product is collected in the form of an oil ($R_f = 0.25$).

Infrared analysis (CHCl_3)

1739, 1755 (sh) and 1795 cm^{-1} : C=O

1597, 1489 cm^{-1} : aromatic nucleus

10 NMR analysis of the proton (CDCl_3 300 MHz in ppm)

3.33 and 3.37: $-\text{OCH}_3$

3.54 (m) (4 H), 3.82 (m) (2 H) and 3.92 (m) (2 H): $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$

5.22 (AB sys.) and 5.30 (AB sys.): $-\text{O}-\text{CH}_2-\text{O}$

6.50: $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$

15 6.93 (s) ppm: $\text{CO}-\text{O}-\text{CH}-\text{Ar}_2$

7.09 (d), 7.41 (d): coupled Ar-H (ortho of the tetra-substituted ring)

7.44 (d) (4 H): Ar-H of the phthalimido

7.05 to 7.33 ppm: Ar-H aromatics

20 Stage D: Diphenylmethyl aminoxy [2-chloro-3,4-bis[(2-methoxyethoxy)-methoxy]-phenyl] acetate.

6.27 g of the product prepared in the previous stage is dissolved in 65 cm^3 of ethanol, the solution is cooled down to 5°C then 0.47 cm^3 of hydrazine hydrate is added, the mixture is maintained at 5°C for half an hour then returned to ambient temperature for 2 hours. After filtration, evaporation of the solvent and chromatography on silica, eluting with ethyl acetate, 3.64 g of the desired product is collected in the form of an oil. $R_f = 0.3$

30 Microanalysis MF = $\text{C}_{29}\text{H}_{34}\text{ClNO}_9$

	C	H	N
% calculated:	60.46	5.95	2.43
% found :	60.1	6.1	2.6

Infrared analysis (CHCl_3)

35 3235 cm^{-1} : $-\text{NH}_2$

1738 cm^{-1} : C=O of the ester function

1598, 1572, 1490 cm^{-1} : aromatic nucleus + NH_2

Stage E: [[[1-[2-chloro-3,4-bis[(2-methoxyethoxy)-methoxy]-



phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-
[(triphenylmethyl)-amino]-thiazol-4-yl] acetic acid.

0.69 g of the product prepared in the previous stage and
0.496 g of oxo-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]
5 acetic acid (described in the Belgian Patent Application No.
864828) are agitated for 3 hours under nitrogen and at
ambient temperature in the presence of 7 cm³ of methanol,
then the solvent is eliminated and the residue is
chromatographed on silica, eluting with a methylene chloride-
10 methanol mixture (95-5) in order to collect 0.726 g of the
expected product. RF = 0.3 [eluant: CHCl₂-MEOH (90-10)]
Microanalysis MF = C₅₃H₅₀ClN₃O₁₁S.

	C	H	N	S	Cl
% calculated:	65.45	5.18	4.32	3.29	3.64
15 % found :	63.7	5.1	4.2	3.2	3.1

Stage F: 4-methoxy benzyl 7beta-[[[[[1-[2-chloro-3,4-bis[(2-
methoxy-ethoxy)-methoxyl]-phenyl]-2-oxo-2-(diphenylmethoxy)-
ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]
acetyl]-amino]-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-1-
20 azabicyclo[4,2,0]oct-2-en-2-carboxylate.

0.322 g of 4-methoxy benzyl 7beta-amino-3-[(Z)-3-chloro-
1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-
carboxylate hydrochloride (described in the European Patent
Application No. 0,333,154) and 0.72 g of the product prepared
25 in the previous stage are agitated in 10 cm³, the mixture is
cooled down to 5°C then 0.1803 g of 1-(3-dimethylamino-
propyl)-3-ethyl carbodiimide (EDC) is added, agitation is
carried out for half an hour then the mixture is treated with
10 cm³ of potassium hydrogenophosphate in 10 cm³ of methylene
30 chloride, followed by decanting, washing and drying and
evaporating the solvents. 0.670 g of the expected product is
collected. Rf = 0.43 [eluant: methylene chloride-ethyl
acetate (80-20)].

Stage G: 4-methoxy benzyl 7beta-[[[[[1-[2-chloro-3,4-bis[(2-
35 methoxy-ethoxy)-methoxyl]-phenyl]-2-oxo-2-(diphenylmethoxy)-
ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-
yl]-acetyl]-amino]-3-[(Z)-3-iodo-1-propenyl]-8-oxo-5-thia-1-
azabicyclo[4,2,0]oct-2-en-2-carboxylate.



0.67 g of the product obtained in the previous stage in 10 cm³ of acetone and 0.223 g of sodium iodide are agitated for one hour at ambient temperature in the presence of an iodine crystal. After elimination of the solvent, the residue is taken up in methylene chloride, the organic phase is washed, dried, the solvent is eliminated and recrystallization is carried out from isopropyl ether in order to collect 0.579 g of iodated product. $R_f = 0.27$ [eluant: methylene chloride - methanol (90-10)].

- 10 Stage H: 1-[3-[7beta-[[[[[1-[2-chloro-3,4-bis[(2-methoxyethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0] [oct-2-en-3-yl]-2-propenyl]
- 15 quinolinium iodide

0.572 g of the product obtained in the previous stage is dissolved in 6 cm³ of methylene chloride and 0.234 g of quinoline is added. The solvent is evaporated off, the residue is taken up in ether, followed by crystallization and separation, and chromatography is carried out on silica, eluting with a methylene chloride - methanol mixture (9-1). In this way 0.235 g of the expected product is collected. $R_f = 0.27$ [eluant: methylene chloride - methanol (90-10)].

NMR analysis of the proton (CDCl₃ 250 MHz; ppm)

- 25 3.31 to 3.34: -OCH₃
 3.73 (s): Ar-O-CH₂
 3.42 to 4.01: CH₂-S and O-CH₂-CH₂-O
 4.92 (m): -CH(N-)-S-
 5.84 (m): -NH-CH-C-
 30 5.20 to 5.30: -O-CH₂-O and COO-CH₂-Ar
 5.93 to 6.15: =C-CH₂-N⁺
 6.40 to 6.55: =CH-CH₂- E isomerism and O-CH-Ar
 resolved 6.76: H in position 5 of the thiazole ring
 6.86 to 7.42: -CH-Ar, COO-CHAr₂, =C-CH=CH- E isomerism
 35 8.05 to 8.25 (3 H), 8.37 (m) (1 H), 8.92 (d (resolved)) (1 H),
 and 10.4 (d): hydrogens of the quinoline ring
 7.83 and 8.27: -CO-NH-

Stage I: Internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-

[7-[[[(2-amino-4-thiazolyl) [[carboxy-(2-chloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium isomer (R) and isomer (S)

- 5 A mixture containing 0.235 g of the product prepared in the previous stage and 5 cm³ of trifluoroacetic acid containing 10% anisole is agitated for one hour thirty minutes at ambient temperature. After the addition of ether, the mixture is subjected to ultrasonics, followed by
- 10 filtration, washing and drying for 16 hours under vacuum at ambient temperature, 0.118 g of the desired internal salt is isolated.

Microanalysis MF = C₃₂H₂₅ClN₆O₉S₂ + 1.5 C₂HF₃O₂ + 0.5 HI
for MW = 1014

- | | C | H | N | Cl | S | F | I |
|---------------|-------|------|------|------|------|------|------|
| % calculated: | 43.81 | 2.88 | 8.28 | 3.49 | 6.32 | 8.42 | 6.25 |
| % found : | 44.1 | 2.7 | 8.5 | 4.1 | 6.7 | 8.5 | 6.0 |
- NMR analysis of the proton (DMSO 300 MHz in ppm)
- S-CH₂-C(C=CH-)=C- masked by the water of DMSO
- 20 5.15 (resolved d) ppm: CO-NH-CH(C=O)-CH(N-)-S-
- 5.72 to 5.89 (4 H): CO-NH-CH(C=O)-CH(N-)-S-, Ar-CH(CO-O-)-O- and -CH=CH-CH₂-N⁺
- 6.38 (m) ppm: -CH=CH-CH₂-N⁺ E isomerism
- 6.7 to 6.82: -S-CH₂-C(C=N-)-N=C(NH₂)- and Ar-H of the catechol
- 25 6.98 ppm (d J=15.5): -CH=CH-CH₂-N⁺ E isomerism
- 7.30: NH₂
- 8.06 (t) (1 H), 8.25 (m) (2 H), 8.54 (m) (2 H) and
- 9.34 (d) (1 H): Ar-H of the quinoline
- 9.29 (s 1) and 9.94 (s 1): mobile H's
- 30 9.47 (d) and 9.58 (d): Ar-H and -CO-NH-CH(C=O)-CH(N-)-S-
- EXAMPLE 2:** the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(3-cyano-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium (R) or (S) or an (R+S) mixture,
- 35 Stage A: [3-cyano-4,5-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-hydroxy acetic acid.

Operating as in Stage A of Example 1, starting with



6.2 g of the product obtained in Stage C of preparation 2, 4.4 g of potash, 3.15 g of lithium bromide, 1.7 cm³ of bromoform and 15 cm³, after agitation for 48 hours at -5°C, 7.2 g of crude acid is obtained which, after chromatography on silica eluting with a dichloromethane - methanol - acetic acid mixture (90-7-3), yields 3.42 g of the desired product. R_f = 0.3 [eluant: methylene chloride - methanol - acetic acid (91-07-3)]

Infrared analysis (CHCl₃)

10 General absorption in the -OH region (acid + associated OH)
1721 cm⁻¹ max + 1750 cm⁻¹ sh.: C=O of the acid function
2235 cm⁻¹

1602-1586-1489 cm⁻¹: aromatic nucleus

15 Stage B: Diphenylmethyl [3-cyano-4,5-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-hydroxy acetate.

8.5 g of the acid prepared in Stage A is dissolved at ambient temperature and under nitrogen in 100 cm³ of dichloromethane then 75 cm³ of a 0.3 molar solution of diphenyldiazomethane in ether is added at 15°C and the mixture is left under agitation for 16 hours at ambient temperature. Then 30 cm³ of water is added, followed by decanting and acidifying with 30 cm³ of acetic acid, washing with a saturated solution of sodium bicarbonate, drying and evaporating the solvents. After chromatography on silica, eluting with an ethyl acetate - hexane mixture (50-50), 4.2 g of the desired product is collected. R_f = 0.3.

Infrared analysis (CHCl₃)

3525 cm⁻¹: non-phenolic -OH

2235 cm⁻¹: C≡N

30 1732 and 1750 cm⁻¹: C=O of the ester function

1600, 1585, 1495, 1490 cm⁻¹: aromatic nucleus

NMR analysis of the proton (CDCl₃ 300 MHz in ppm).

3.32 to 3.47: -OCH₃

3.58 and 3.72: O-CH₂-CH₂-O

35 5.15 to 5.40: -O-CH₂-O and Ar-CH(C=O)-OH

6.89 (s): CO-O-CHAr₂.

7.24 to 7.50: Ar-H

Stage C: Diphenylmethyl [3-cyano-4,5-bis[(2-methoxy-ethoxy)-



methoxy]-phenyl]-phthalimidoxy acetate.

0.134 g of N-hydroxy phthalimide and 0.409 g of triphenyl phosphine are added to a solution of 0.430 g of the ester prepared in Stage B in 10 cm³ of tetrahydrofuran, the resultant mixture is cooled down to -10°C then 0.21 cm³ of diethyl azodicarboxylate (DEAD) is poured into it and the whole is left under agitation for 16 hours. After concentrating the solvents and chromatography on silica eluting with a dichloromethane - acetone mixture (95-5), 0.2 g of the desired product is collected in the form of an oil. R_f = 0.25 [eluant: dichloromethane - acetone (97-3)].

Infrared analysis (CHCl₃)

1792 (m), 1775 (sh) 1760 (sh) and 1738 (max) cm⁻¹: C=O

2230 cm⁻¹: C=N

1604, 1586, 1490 cm⁻¹: aromatic nucleus

Stage D: Diphenylmethyl aminoxy [3-cyano-4,5-bis[(2-methoxy-ethoxy)-methoxy]-phenyl] acetate.

2.7 g of the product prepared in the previous stage is dissolved under nitrogen in 80 cm³ of ethanol, the solution is cooled down to -2°C then 0.20 cm³ of hydrazine hydrate is added, the mixture is maintained at -2°C for half an hour then returned to ambient temperature for one hour. After filtration, evaporation of the solvent and chromatography on silica eluting with an ethyl acetate - hexane mixture (7-3), 1.8 g of the desired product is collected in the form of an oil. R_f = 0.25

Microanalysis MF = C₃₀H₃₄N₂O₉

	C	H	N
% calculated:	63.53	6.04	4.94
% found :	63.3	6.4	4.6

Infrared analysis (CHCl₃)

3335 cm⁻¹: O-NH₂

2230 cm⁻¹: C≡N

1748 cm⁻¹: C=O of the ester function

1600, 1588, 1488 cm⁻¹: aromatic nucleus + NH₂

Stage E: [[[1-[3-cyano-4,5-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazolyl] acetic acid.

of dichloromethane, decanted, washed and dried and the solvents are evaporated off. After chromatography on silica, eluting with a dichloromethane - ethyl acetate mixture (8-2), 0.349 g of the expected product is collected. $R_f = 0.4$

5 [eluant: dichloromethane - ethyl acetate (8-2)].

Stage G: 4-methoxy benzyl 7beta-[[[[1-[3-cyano-4,5-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-iodo-1-propenyl]-8-oxo-5-thia-1-
10 azabicyclo[4,2,0]oct-2-en-2-carboxylate.

0.573 g of the product obtained in the previous stage in 7 cm³ of acetone and 0.192 g of sodium iodide are agitated for one hour at ambient temperature in the presence of an iodine crystal. After elimination of the solvent, the
15 residue is taken up in dichloromethane, the organic phase is washed, dried, the solvent is eliminated and the residue is recrystallized from isopropyl ether in order to collect 0.463 g of the iodated product. $R_f = 0.30$ [eluant: dichloromethane - methanol (9-2)]

20 Stage H: 1-[3-[7beta-[[[[1-[3-cyano-4,5-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0] [oct-2-en-3-yl]-2-propenyl]-quinolinium
25 iodide

0.463 g of the product obtained in the previous stage is dissolved in 4 cm³ of dichloromethane and 0.191 g of quinoline is added, the whole is agitated for one hour at ambient temperature, the solvent is evaporated off, the
30 residue is taken up in ether, crystallized, separation is carried out followed by chromatography on silica, eluting with a dichloromethane - methanol mixture (97-3). In this way 0.241 g of the expected product is collected. $R_f = 0.27$
NMR analysis of the proton (CDCl₃ 400 MHz; ppm)

35 3.25 (s), 3.27 (s) and 3.34: -OCH₃

3.26 to 4.04: CH₂-S and O-CH₂-CH₂-O

3.98 (s): Ar-O-CH₃

4.90 to 5.08 and 5.15 to 5.40: -CH(N-)-S-, =C-CH₂-N⁺, -O-CH₂-O

and

5.75 to 6.05: $\text{N}-\text{CH}(\text{C}=\text{O})-\text{CH}-(\text{N}-)-\text{S}$ and $-\text{O}-\text{CH}(\text{C}=\text{O})-\text{Ar}$ 6.38 (m) and 6.56 (m): $=\text{CH}-\text{CH}-$ E isomerism6.73 (m): $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N})-\text{N}$ 5 6.80 to 7.50: trityl's, $\text{COO}-\text{CHAr}_2$,7.9 to 8.56 (5 H), 8.56 (d) and 8.87 (d) resolved (1 H), 10.27 (d) and 10.83 (d): hydrogens of the quinoline ring and $-\text{NH}-$

Stage I: Internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-

[3-[7-[[2-amino-4-thiazolyl] [[carboxy-(3-cyano-4,5-

10 dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-

carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-

2-propenyl]-quinolinium isomer (R) and isomer (S)

A mixture containing 0.241 g of the product prepared in the previous stage and 5 cm³ of trifluoroacetic acid

15 containing 10% anisole is agitated for one and a half hours at ambient temperature. After the addition of ether, scraping, filtering, washing and drying for 16 hours under vacuum at ambient temperature, 0.128 g of the sought internal salt is isolated.

20 Microanalysis MF = $\text{C}_{33}\text{H}_{25}\text{N}_7\text{O}_9\text{S}_2 + 1.4 \text{ C}_2\text{HF}_3\text{O}_2 + 0.4 \text{ HI}$

	C	H	N	S	F	I
% calculated:	45.8	2.87	10.43	6.83	8.5	5.4
% found	: 44.1	2.7	8.5	7.0	8.4	4.1

NMR analysis of the proton (DMSO 300 MHz in ppm)

25 3.53 (d) and 3.74 (d): $-\text{S}-\text{CH}_2-\text{C}(\text{C}=\text{CH}-)=\text{C}-$ 5.14 (resolved d) ppm: $\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}-(\text{N}-)-\text{S}-$ 5.40 (s): $\text{Ar}-\text{CH}(\text{CO}-\text{O}-)-\text{O}-$ 5.76 (m): $\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$ to 5.89 (m): $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$,30 6.34 (m) ppm: $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$ E isomerism6.76 (s) and 6.79 (s): $-\text{S}-\text{CH}=\text{C}(\text{C}=\text{N}-)-\text{N}=\text{C}(\text{NH}_2)-$ 6.98 ppm (d J=16): $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$ E isomerism7.11 to 7.15 (m) (2 H): $\text{Ar}-\text{H}$

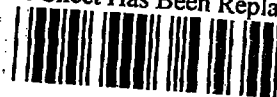
7.30 (m) and 10.38 (m): mobile H's

35 8.06 (t) (1 H), 8.26 (m) (2 H), 8.53 (m) (2 H), 9.33 (d) and 9.58 (d): $\text{Ar}-\text{H}$

9.60 (d) and 9.65 (d): $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$ **EXAMPLE 3:** the internal salt of [6R-[3(E), 6alpha,

This Sheet Has Been Replaced





7beta(Z)]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(3-fluoro-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium (R) or (S) or an (R+S) mixture.

Stage A: [3-fluoro-4,5-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-hydroxy acetic acid.

0.662 g of lithium bromide and 3.6 g of potash are dissolved in 13 cm³ of water at 0°C; a solution containing 5.5 g of 3-fluoro-4,5-bis[(2-methoxy-ethoxy)-methoxy benzaldehyde (synthesized in Preparation 3), 2.85 cm³ of bromoform and 13 cm³ of dioxane is added to this mixture, the whole is left under agitation for 24 hours at 0°C, then another 2.85 cm³ of bromoform is added and the mixture is left for 16 hours. After dilution in water and washing with ether, decanting takes place, followed by cooling down to 0°C, acidifying until the pH = 2.5-3 and extracting with ether. The organic phase is washed with water, dried and the solvent is driven off in order to collect 5.3 g of the desired product in the form of an oil.

Infrared analysis (CHCl₃)

3600 cm⁻¹: -OH region (acid + associated OH)

1715 cm⁻¹ complex: C=O of the acid function

1616, 1595 and 1510 cm⁻¹: aromatic nucleus

Stage B: Diphenylmethyl [3-fluoro-4,5-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-hydroxy acetate.

5.3 g of the acid prepared in Stage A is dissolved in 66 cm³ of dichloromethane, then 46 cm³ of a solution of diphenyldiazomethane at 6.5 g/cm³ in ether is added at 15°C, and the whole is left under agitation for 16 hours at ambient temperature. Then water is added, followed by decanting and acidifying with acetic acid, washing with a saturated solution of sodium bicarbonate, drying and evaporating the solvents. After chromatography on silica, eluting with an ethyl acetate - hexane mixture (50-50), 4.0 g of the desired product is collected. R_f = 0.17.

Infrared analysis (CHCl₃)

3520 cm⁻¹: non-phenolic -OH

This Sheet Has Been Replaced



17352 cm^{-1} : C=O of the ester function

1615, 1595 and 1509 cm^{-1} : aromatic nucleus

NMR Analysis of the proton (CDCl_3 250 MHz in ppm)

3.33 (s) and 3.37 (s): $-\text{OCH}_3$

5 3.46 (m), 3.57 (m), 3.78 (m) and 3.98 (m): $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$

5.19 to 5.30: $-\text{O}-\text{CH}_3-\text{O}$ and $\text{Ar}-\text{CH}(\text{C}=\text{O}-\text{O})-\text{O}-$

6.87 (s): $\text{CO}-\text{O}-\text{CHAr}_2$

6.87 (m) (1 H), 6.97 (m) (2 H), 7.07 (m) (1 H), 7.21 (m) (3 H)
and 7.32 (m) (5 H): $\text{Ar}-\text{H}$

10 Stage C: Diphenylmethyl [3-fluoro-4,5-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-phthalimidoxo acetate.

0.77 g of N-hydroxy phthalimide and 2.42 g of triphenyl phosphine are added to a solution of 2.6 g of the ester prepared in Stage B in 28 cm^3 of tetrahydrofuran, after
15 cooling down to -10°C 1.4 cm^3 of diethyl azodicarboxylate (DEAD) is added dropwise to the resultant mixture and the whole is left under agitation at 0°C for one and a half hours. After concentration of the solvents and chromatography on silica, eluting with a dichloromethane-acetone (95-5) mixture, 2.56 g of the desired product is
20 collected in the form of an oil. $R_f = 0.6$ [eluant: dichloromethane-acetone (85-15)].

Infrared analysis (CHCl_3)

1794, 1752 and 1738 (max) cm^{-1} : C=O

25 NMR analysis of the proton (CDCl_3 250 MHz in ppm)

3.34 (s) and 3.33 (s): $-\text{OCH}_3$

3.48 (m) (2 H), 3.56 (m) (2 H), 3.77 (m) (2 H) and

3.96 (m) (2 H): $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$

5.22 (m) (4 H): $-\text{O}-\text{CH}_2-\text{O}$

30 5.92 (s): $\text{Ar}-\text{CH}(\text{C}=\text{O}-\text{O})-\text{O}-$

6.92 (s): $\text{CO}-\text{O}-\text{CHAr}_2$

7.00 to 7.35 (m): $\text{Ar}-\text{H}$

7.75 (m) (4 H): $\text{Ar}-\text{H}$ of the phthalimide

35 Stage D: Diphenylmethyl aminoxy-[3-fluoro-4,5-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl] acetate.

2.4 g of the product prepared in the previous stage is dissolved under nitrogen in 25 cm^3 of ethanol, the mixture is cooled down to -5°C then 0.38 cm^3 of hydrazine hydrate is



- 53 -

added, the whole is kept at -5°C for two hours. After filtration, the solvent is evaporated and the residue is chromatographed on silica eluting with a mixture of ethyl acetate - hexane (7-3), and 1.67 g of the desired product is collected in the form of an oil. $R_f = 0.3$.

Infrared Analysis (CHCl_3)

3340 cm^{-1} : O-NH_2

1747 cm^{-1} : C=O of the ester function

$1616, 1596, 1581, 1508$ and 1497 cm^{-1} : aromatic nucleus + NH_2

NMR analysis of the proton (CDCl_3 300 MHz in ppm)

3.34 and 3.36: $-\text{OCH}_3$

3.48, 3.56, 3.77 and 3.97: $\text{O-CH}_2\text{-CH}_2\text{-O}$

5.17 (s): Ar-CH(C=O-O)-O-

5.20 and 5.21: $-\text{O-CH}_2\text{-O}$

5.79 (s): O-NH_2

6.82 (dd): Ar-H in ortho position of F

6.91 (s): CO-O-CHAr_2

7.02: Ar-H in para position of F

7.05 to 7.40: Ar-H

Stage E: $[[[1-[3\text{-fluoro-4,5-bis-}[(2\text{-methoxy-ethoxy})\text{-methoxy]}\text{-phenyl]}\text{-2-oxo-2-}[(\text{diphenylmethoxy})\text{-ethyl}]\text{-oxy}]\text{-iminol}]\text{-2-}[(\text{triphenylmethyl})\text{-aminol}]\text{-thiazol-yl}]\text{ acetic acid}$.

0.640 g of the product prepared in the preceding stage and 0.474 g of oxo- $[[2-[(\text{triphenylmethyl})\text{-aminol}]\text{-thiazol-4-yl}]\text{ acetic acid}$ (described in the Belgian Patent Application No. 864828) are agitated for 4 and a half hours under nitrogen and at ambient temperature in the presence of 20 cm^3 of methanol, then the solvent is eliminated, and the residue is chromatographed on silica eluting with a dichloromethane-methanol (95-5) mixture in order to collect a total of 0.612 g of the expected product. $R_f = 0.35$ [eluant: dichloromethane-methanol (9-1)].

Infrared analysis (CHCl_3)

3400 cm^{-1} : $=\text{C-NH}$

1755 (shoulder), 1736 (Max) cm^{-1} : C=O

$1695, 1527, 1509$ and 1496 cm^{-1} : aromatic, heterocycle,

1635 cm^{-1} : C=O

NMR analysis of the proton (CDCl_3 in ppm)

791249 90210

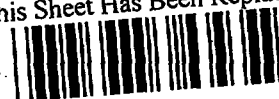
3.09 (s) and 3.22 (s): $-\text{OCH}_3$
3.30 (m), 3.55 (m), 3.60 (m), 3.92 (m),: $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$
5.15 (s), 5.10 (d) and 5.20 (d): $-\text{O}-\text{CH}_2-\text{O}$
5.81 (s): $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$
5 6.56 (s): $\text{CO}-\text{O}-\text{CHAr}_2,$
6.74 (s): $-\text{S}-\text{CH}=\text{C}(\text{C}=\text{N})-\text{N}$
7.10 to 7.33 (m): $\text{Ar}-\text{H}$

Stage F: 4-methoxy benzyl 7beta-[[[[[1-[3-fluoro-4,5-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate.

0.289 g of 4-methoxy benzyl 7beta-amino-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate hydrochloride (described in European Patent Application No. 0,333,154), and 0.641 g of the product prepared in the preceding stage in 6 cm³ of dichloromethane are agitated, cooled down to 5°C then 0.160 g of EDC is added, agitation takes place for half an hour then the whole is treated with potassium hydrogen phosphate in dichloromethane, followed by decanting, washing, drying and evaporating the solvents. After chromatographing on silica eluting with a dichloromethane - ethyl acetate (8-2) mixture, 0.678 g of expected product is collected. Rf = 0.4 [eluant: dichloromethane-ethyl acetate (8-2)]

Stage G: 4-methoxy benzyl 7beta-[[[[[1-[3-fluoro-4,5-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-iodo-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate.

0.678 g of the product obtained in the preceding Stage in 7 cm³ of acetone and 0.228 g of sodium iodide are agitated for one hour at ambient temperature in the presence of an iodine crystal. After elimination of the solvent, the residue is taken up in dichloromethane, the organic phase is washed, dried, the solvent is eliminated and the residue obtained is separated in order to collect 0.501 g of iodated product. Rf = 0.2 [eluant: dichloromethane - methanol (97-3)].



Stage H: 1-[3-[7beta-[[[1-[3-fluoro-4,5-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl quinolinium iodide.

0.500 g of the product obtained in the previous stage is dissolved in 2 cm³ of dichloromethane and 0.226 cm³ of quinoline is added, the solvent is concentrated, agitation takes place for one hour at ambient temperature, 2 cm³ of dichloromethane is added, then precipitation is carried out with ether and chromatography takes place on silica eluting with a dichloromethane-methanol (97-3) mixture. In this way 0.220 g of expected product is collected. Rf = 0.20

Stage I: Internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[(2-amino-4-thiazolyl)-[[carboxy-(3-fluoro-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-quinolinium (R) isomer and (S) isomer

A mixture containing 0.220 g of the product prepared in the preceding stage and 5 cm³ of trifluoroacetic acid containing 10% anisole is agitated at ambient temperature for one and a half hours. After 15 cm³ of ether is added, the precipitate formed is washed and dried, and leads to 0.0994 g of the desired internal salt.

Microanalysis MF = C₃₂H₂₅FN₆O₉S₂ + 1.2 C₂HF₃O₂ + 0.5 HI

	C	H	N	S	F	I
% calculated:	44.8	2.89	9.12	6.95	9.48	6.88
% found :	44.7	2.8	8.8	6.6	9.1	6.6

NMR Analysis of the proton (DMSO 300 MHz in ppm)

3.5 and 3.8: (masked by the water of the solvent)

5.14 (d resolved) ppm: CO-NH-CH(C=O)-CH(N)-S-

5.34 (s resolved): Ar-CH(CO-O)-O-

5.77 (dd resolved d resolved): CO-NH-CH(C=O)-CH(N)-S-

5.80 to 6.0: -CH=CH-CH₂-N⁺,

6.37 (m): -CH=CH-CH₂-N⁺ E isomerism

6.7 to 6.8: -S-CH=C(C=N)-N=C(NH₂)- and Ar-H in ortho and para position of F.

6.98 ppm (d resolved): $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$ E isomerism
 8.07 (t), 8.29 (t): H in positions 6 and 7 of the quinolinium
 8.24 (dd) : H in position 3 of the quinolinium
 8.53 : H in positions 5 and 8 of the quinolinium
 5 9.34 (d) : H in position 4 of the quinolinium
 9.58 (d) : H in position 2 of the quinolinium
 7.31-9.19 and 9.5 to 9.7: mobile H's

EXAMPLE 4: the internal salt of [(+)(cis)(Z)] 7-[3-[7-[(2-amino-4-thiazolyl)-[carboxy-(3-chloro-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-
 10 azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl]-thieno-[2,3-b]pyridinium (R) or (S) or an (R+S) mixture
 Stage A: [3-chloro-4,5-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-hydroxy acetic acid.

15 3.34 g of lithium chloride and 9.64 g of potash are dissolved in 36 cm³ of water at 0°C; a solution containing 13.77 g of 3-chloro-4,5-bis-[(2-methoxy-ethoxy)-methoxy benzaldehyde (synthesized in Preparation 3), 3.74 cm³ of bromoform and 34 cm³ of dioxane is added to this mixture, the
 20 whole is left under agitation for 24 hours at 0°C, then another 3.74 cm³ of bromoform is added and the resultant mixture is left for 16 hours. After dilution in 100 cm³ of water and washing with ether, decanting takes place, followed by cooling down to 0°C, acidifying to a pH = 2.5 - 3 and
 25 extracting with ether. The organic phase is washed with water, dried and the solvent driven off in order to collect 13.95 g of desired product in the form of a yellow oil.

Infrared analysis (CHCl₃)

1700 (max) and 1730 (shoulder) cm⁻¹: C=O
 30 1599, 1578, 1489 cm⁻¹: aromatic nucleus
 NMR analysis of the proton (CDCl₃ 250 MHz in ppm)
 3.38 (m) (6 H): $-\text{OCH}_3$
 5.09 to 5.35 (m): $-\text{O}-\text{CH}_2-\text{O}$ and $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}$
 7.05 to 7.78 ppm (m) (2 H): Ar-H

35 Stage B: Diphenylmethyl [3-chloro-4,5-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-hydroxy acetate.

13.95 g of the acid prepared in Stage A is dissolved in 150 cm³ of ether at ambient temperature and under nitrogen,



then 150 cm³ of a 0.3 molar solution of diphenyl-diazomethane in dichloromethane is added at 15°C and the mixture is left under agitation for 16 hours at ambient temperature. Then 30 cm³ of water is added, followed by decanting and acidifying with 30 cm³ of acetic acid, washing takes place again with a saturated solution of sodium bicarbonate, followed drying and evaporating the solvents. After chromatographing on silica eluting with a dichloromethane - methanol (99-1) mixture, 10 g of the desired product is collected.

10 Infrared analysis (CHCl₃)

3535 cm⁻¹: non-phenolic -OH

1738 cm⁻¹: C=O of the ester function

1600, 1580, 1489 cm⁻¹: aromatic nucleus

NMR analysis of the proton (CDCl₃ 250 MHz in ppm)

15 3.59 (m) and 3.47 (m) (4 H), 3.75 (m) (2 H) and 4.04 (m) (2 H): O-CH₂-CH₂-O

3.38, 3.33 and 3.25 (m) (6 H): -OCH₃

5.02 to 5.30 (m): O-CH₂-O and Ar-CH(C=O)-O

6.8 to 7.35 (m): Ar-H

20 Stage C: Diphenylmethyl [3-chloro-4,5-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-phthalimidoxo acetate.

1 g of N-hydroxy phthalimide and 1.54 g of triphenyl phosphine are added to a solution of 1 g of the ester prepared in Stage B in 35 cm³ of tetrahydrofuran, followed by cooling down to 10°C then 1.58 g of diethyl azodicarboxylate (DEAD) is added dropwise and the mixture is left under agitation for 16 hours.

After concentration of the solvents and chromatography on silica eluting with a dichloromethane-methanol (99-1) mixture, 3.09 g of desired product is collected in the form of a colourless oil (RF =0.3).

30 Infrared analysis (CHCl₃)

1738, 1755 (shoulder) and 1795 cm⁻¹: C=O

1600, 1578, 1488 cm⁻¹: aromatic nucleus

35 NMR analysis of the proton (CDCl₃ 250 MHz in ppm)

3.34 (s), and 3.36 (s): -OCH₃

3.49 (m) (2 H), 3.57 (m) (2 H), 3.77 (m) (2 H) and

4.02 (m) (2 H) ppm: O-CH₂-CH₂-O



- 5.22 (s) and 5.27 (s) ppm: $-O-CH_2-O$
 5.91 (s) and 5.92 (s) ppm: $Ar-CH(C=O)-O$
 6.92 (s) ppm: $CO-O-CH-Ar_2$
 7.75 ppm (m) (4 H): $Ar-H$ of the phthalimido
 5 7.11 (m) and 7.21 to 7.33 ppm: the other aromatic H 's
 Stage D: Diphenylmethyl aminoxy [3-chloro-4,5-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl] acetate.

3 g of the product prepared in the preceding stage is dissolved under a nitrogen atmosphere in 40 cm³ of ethanol,
 10 the mixture is cooled down to 5°C then 0.224 cm³ of hydrazine hydrate is added, the whole is maintained at 5°C for half an hour then returned to ambient temperature for 2 hours. After filtration and evaporation of the solvent the desired product is collected in the form of an oil. $R_f = 0.3$ [eluant:
 15 acetone - cyclohexane (3-7)].

Infrared analysis (CHCl₃)
 3330 cm⁻¹: $-NH_2$
 1745 cm⁻¹: $C=O$
 1600, 1578, 1488 cm⁻¹: aromatic nucleus + NH_2
 20 NMR analysis of the proton (CDCl₃ 250 MHz in ppm)
 3.34 (s) and 3.38 (s): $-OCH_3$
 3.48 (m), 3.58 (m), 3.76 (m) and 4.02 (m): $O-CH_2-CH_2-O$
 5.17: $Ar-CH(C=O)-O$
 5.19 (s) and 5.25 (s): $-O-CH_2-O$

25 5.80: mobile NH_2
 6.91 (s): $CO-O-CH-Ar_2$
 7.10 (m) (4 H) and 7.21 to 7.33 (8 H): $Ar-H$
 Stage E: 7-[3-[7beta-[[[[[1-[3-chloro-4,5-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino]-2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0][oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]pyridinium iodide

0.441 g of the product prepared in the preceding stage,
 35 24 cm³ of methanol and 145 mg of paratoluenesulphonic acid are mixed together under a nitrogen atmosphere for 5 minutes and a solution of 0.65 mg of 1-[3-[7beta-[[oxo-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-



methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0][oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]pyridinium iodide (synthesized in preparation 10) is added then the whole is left under agitation for 16 hours.

- 5 After evaporation of the solvent, the residue is taken up in ether, the precipitate is filtered, washed and dried and in this way 0.730 g of the desired product is collected.

Melting point (MP.) = 135°C (gum); Rf = 0.3 [eluant dichloromethane-methanol (9-1)]

- 10 Stage F: the internal salt of [(±)(cis)(Z)] 7-[3-[7-[(2-amino-4-thiazolyl)-[[carboxy-(3-chloro-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2(E)-propenyl]-thieno[2,3-b]pyridinium (R) or (S) or an (R+S) mixture,

- 15 A solution of 31 cm³ of trifluoroacetic acid in 8.5 cm³ of dichloromethane, is poured at 0°C into a mixture at 0°C containing 0.69 mg of the product prepared in the preceding stage, 17 cm³ of dichloromethylene and 3 cm³ of anisole, agitation takes place at this temperature for one hour, the
20 solvents are eliminated, followed by crystallizing, filtering, washing, drying, chromatography eluting with an acetonitrile - water (1-1) mixture and in this way 0.22 g of the desired product is isolated.

NMR analysis of the proton (DMSO 300 MHz in ppm)

- 25 3.19: C=C-CH₂-S-
5.01 (d) and 5.07 (d): CO-NH-CH (C=O)-CH₂-(N-)-S-
5.12 (s) and 5.17 (s): Ar-CH(CO-O-)-O-
5.52 (1): -CH=CH-CH₂-N⁺,
5.60: CO-NH-CH(C=O)-CH (N-)-S- (cis/H in position 6)
30 5.87 (m): -CH=CH-CH₂-N⁺ E isomerism
6.78 to 6.86: -S-CH=C(C=N-)-N=C(NH₂)- and Ar-H in ortho and para position of the Cl
7.21 and 7.41: -NH₂
7.87 (d): H in position 3 of the thieno[2,3-b]pyridinium
35 8.10 (1): H in position 5 of the thieno[2,3-b]pyridinium
8.26 (d): H in position 2 of the thieno[2,3-b]pyridinium
9.03 (1): H in position 4 of the thieno[2,3-b]pyridinium
9.23 (1): H in position 6 of the thieno[2,3-b]pyridinium

9.74 (d): $\text{CO-NH-CH(C=O)-CH(N-)-S}$

By operating in a similar manner to that of Example 4 and by using the products synthesized in Preparations 1 to 10, the following compounds were obtained:

5 **EXAMPLE 5:** the internal salt of $[[6R-[3(E),6\alpha,7\beta(Z)]]7-[3-[7-[[2\text{-amino-4-thiazolyl}]-[[\text{carboxy-(3,4-dihydroxy-5-nitro-phenyl)-methoxy]-imino]-acetyl]-amino]-2\text{-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl}]-2\text{-propenyl}]-\text{thieno}[2,3\text{-b}]\text{pyridinium (R) or (S) or an (R+S) mixture,$

10 NMR Analysis of the proton (DMSO 300 MHz in ppm)

3.49 to 3.9 (m): $\text{C=C-CH}_2\text{-S-}$

3.14 (d) and 5.18 (d): $\text{CO-NH-CH(C=O)-CH-(N-)-S -}$

5.47 (s), 5.50 (s), 5.60 (s), 5.63 (s): Ar-CH(CO-O-)-O-

5.67 (d): $-\text{CH=CH-CH}_2\text{-N}^+$,

15 5.77 (m): $\text{CO-NH-CH(C=O)-CH(N-)-S-}$

6.29 (m): $-\text{CH=CH-CH}_2\text{-N}^+$

6.80 (s), 6.83 (s),

7.64 (s) and 7.66 (s): $-\text{S-CH=C(C=N-)-N=C(NH}_2\text{)-}$

7.42 (d) and 7.47 (d): Ar-H in ortho position of the nitro

20 7.1 to 7.2 (m): $-\text{CH=CH-CH}_2\text{-N}^+$ and Ar-H in para position of the nitro

7.89 (d): H in position 3 of the thieno[2,3-b]pyridinium

8.15 (dd): H in position 5 of the thieno[2,3-b]pyridinium

8.29 (d): H in position 2 of the thieno[2,3-b]pyridinium

25 9.09 (d): H in position 4 of the thieno[2,3-b]pyridinium

9.23 (d): H in position 6 of the thieno[2,3-b]pyridinium

9.54 (d res.), 9.65 (d) and 9.69 (d): $\text{CO-NH-CH(C=O)-CH(N-)-S}$

10.42 (m): mobile $\text{H}'\text{s}$

30 **EXAMPLE 6:** the internal salt of $[(\pm)(\text{cis})(Z)]7-[3-[7-[[2\text{-amino-4-thiazolyl}]-[[\text{carboxy-(3,4-dihydroxy-5-iodo-phenyl)-methoxy]-imino]-acetyl]-amino]-2\text{-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl}]-2\text{-(E)-propenyl}]-\text{thieno}[2,3\text{-b}]\text{pyridinium (R) or (S) or an (R+S) mixture,$

Microanalysis $\text{MF} = \text{C}_{30}\text{H}_{23}\text{IN}_6\text{O}_9\text{S}_3 + 1 \text{ C}_2\text{HF}_3\text{O}_2 + 1 \text{ APTS}$

35

	C	H	N	S	I
% calculated:	41.78	2.85	7.5	11.43	11.3
% found :	46.6	2.8	7.8	12.0	10.9

NMR analysis of the proton (DMSO 300 MHz in ppm)

- 3.70: C=C-CH₂-S-
 5.11 (s) and 5.17 (s) (1 H): CO-NH-CH(C=O)-CH₂-(N-)-S-
 5.29 (s) and 5.32 (s): Ar-CH(CO-O)-O-
 5 5.67 (d): -CH=CH-CH₂-N⁺,
 5.75 (m): CO-NH-CH(C=O)-CH(N-)-S-
 6.29: -CH=CH-CH₂-N⁺ E isomerism
 6.77 (resolved) (1 H): -S-CH=C(C=N-)-N=C(NH₂)-
 6.90 (2 H): Ar-H in ortho and para position of I
 10 7.89 (d): H in position 3 of the thieno[2,3-b]pyridinium
 8.15 (dd): H in position 5 of the thieno[2,3-b]pyridinium
 8.29 (d): H in position 2 of the thieno[2,3-b]pyridinium
 9.08 (d): H in position 4 of the thieno[2,3-b]pyridinium
 9.13 (d): H in position 6 of the thieno[2,3-b]pyridinium
 15 9.37 (sl): CO-NH-CH(C=O)-CH(N-)-S

EXAMPLE 7: the internal salt of [(+)(cis)(Z)] 7-[3-[7-[(2-amino-4-thiazolyl)-[[carboxy-(3,4,5-trihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2(E)-propenyl]-thieno-[2,3-b]pyridinium (R) or (S) or an (R+S) mixture,

NMR analysis of the proton (DMSO 300 MHz in ppm)

- 5.15 (d) and 5.17 (d) (1 H): CO-NH-CH(C=O)-CH₂-(N-)-S-
 [2/5 < (R/S) < 3/5]
 5.22 and 5.34 (2 H): Ar-CH(CO-O)-O-
 25 5.67 (d): -CH=CH-CH₂-N⁺,
 5.76 (m), 6.20 to 6.40 (m): CO-NH-CH(C=O)-CH(N-)-S-,
 CH=CH-CH₂-N⁺ and Ar-H of the triphenol
 6.75, 6.77, 6.87 and 6.90 (1H): -S-CH=C(C=N-)-N=C(NH₂)-
 30 7.74 (d): H in position 5 of the thieno[2,3-b]pyridinium
 7.89 (d) and 8.28 (d): H in positions 4 and 3 of the thieno[2,3-b]pyridinium
 8.10 to 8.27, 9.09 and 9.23: H in positions 2 and 6 of the thieno[2,3-b]pyridinium
 35 9.6 to 9.85: CO-NH-CH(C=O)-CH(N-)-S

EXAMPLE 8: the internal salt of [(+)(cis)(Z)] 7-[3-[7-[(2-amino-4-thiazolyl)-[[carboxy-(2-chloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-



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azabicyclo[4,2,0]oct-2-en-3-yl]-2(E)-propenyl]-thieno-[2,3-b]pyridinium (R) or (S) or an (R+S) mixture,

Microanalysis MF = $C_{30}H_{23}IN_6O_9S_3 + 2 \text{ APTS}$

- | | C | H | N | S | Cl |
|------------|------|------|------|------|------|
| 5 % found: | 46.8 | 2.55 | 8.53 | 9.76 | 3.59 |
- NMR analysis of the proton (DMSO 300 MHz in ppm)
- 3.5 to 3.9 (m): $C=C-CH_2-S-$
- 5.17 (m) (1 H): $CO-NH-CH(C=O)-CH(N-)-S-$
- 5.67 (dl): $-CH=CH-CH_2-N^+$,
- 10 5.70 to 5.90 (2 H): $CO-NH-CH(C=O)-CH(N-)-S- + \text{other H}$
- 6.33 (m): $-CH=CH-CH_2-N^+$ E isomerism
- 6.79 (m) and 6.96 (m) (4 H): 4 H
- 7.89 (d) and 8.29 (d): H in positions 2 and 3 of the thieno[2,3-b]pyridinium
- 15 8.14 (m): H in position 5 of the thieno[2,3-b]pyridinium
- 9.08 (d): H in position 4 of the thieno[2,3-b]pyridinium
- 9.26 (d): H in position 6 of the thieno[2,3-b]pyridinium
- EXAMPLE 9: the internal salt of [[6R-[3(E), 6alpha, 7beta(Z)]] 7-[3-[7-[[[(2-amino-4-thiazolyl)-[[carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-thieno[2,3-b] pyridinium (R) or (S) or an (R+S) mixture.
- NMR Analysis of the proton (DMSO 300 MHz in ppm)
- 25 5.20: Ar-H in ortho position of the Cl
- 5.79: $Ar-CH(CO-O-)-O-$
- 5.78 (m): $-CH=CH-CH_2-N^+$,
- 6.31: $-CH=CH-CH_2-N^+$
- 7.88: H in position 3 of the thieno[2,3-b]pyridinium
- 30 8.15 (m): H in position 5 of the thieno[2,3-b]pyridinium
- 8.98 (m): H in position 2 of the thieno[2,3-b]pyridinium
- 9.08 (d): H in position 4 of the thieno[2,3-b]pyridinium
- 9.13 (d): H in position 6 of the thieno[2,3-b]pyridinium
- EXAMPLE 10: the internal salt of [[6R-[3(E), 6alpha, 7beta(Z)]] 7-[3-[7-[[[(2-amino-4-thiazolyl)-[[carboxy-(3-cyano-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-thieno[2,3-b] pyridinium (R) or (S) or an (R+S)

791213 990710

mixture.

NMR analysis of the proton (DMSO 300 MHz in ppm)

- 3.19: C=C-CH₂-S-
 5.15 (d) and 5.20 (d): CO-NH-CH(C=O)-CH(N-)-S-
 5 5.40 (s): Ar-CH(CO-O-)-O-
 5.67 (d): -CH=CH-CH₂-N⁺,
 5.81 (m): CO-NH-CH(C=O)-CH(N-)-S-
 6.67 (s): -S-CH=C(C=N-)-N=C(NH₂)-
 7.10 to 7.20 (m) (3 H): Ar-H and CH=
 10 7.34 (m), 10.27 to 10.42 (m): mobile H's
 7.89 (d): H in position 3 of the thieno[2,3-b]pyridinium
 8.15 (dd): H in position 5 of the thieno[2,3-b]pyridinium
 8.28 (d): H in position 2 of the thieno[2,3-b]pyridinium
 9.09 (d): H in position 4 of the thieno[2,3-b]pyridinium
 15 9.23 (d): H in position 6 of the thieno[2,3-b]pyridinium
 9.52 (d) and 9.62 (d): CO-NH-CH(C=O)-CH(N-)-S

EXAMPLE 11: the internal salt of [[6R-[3(E), 6alpha, 7beta (Z)]] 7-[3-[7-[[2-amino-4-thiazolyl)-[[carboxy-(3,4-dihydroxy-5-methoxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]pyridinium (R) or (S) or an (R+S) mixture.

The (R) and (S) isomers are separated by HPLC (Microbondapac column C18), solvent: Water/acetonitrile (85/15)

15 (S) Isomer

NMR analysis of the proton (DMSO 300 MHz in ppm)

- 3.71 (s): Ar-OCH₃
 5.16 (d J=5): CO-NH-CH(C=O)-CH(N-)-S-
 5.32 (s): Ar-CH(CO-O-)-O-
 30 5.68 (d): -CH=CH-CH₂-N⁺,
 5.79 (dd J=5 and 7.5): CO-NH-CH(C=O)-CH(N-)-S-
 6.28 (m): -CH=CH-CH₂-N⁺,
 6.55 (s) (2 H): Ar-H in ortho and para position of the -OMe
 6.78 (s): -S-CH=C(C=N-)-N=C(NH₂)-
 35 7.11 (d): -CH=CH-CH₂-N⁺,
 7.29 (m), 8.38 (m), 8.99 (m): mobile H's
 7.88 (d): H in position 3 of the thieno[2,3-b]pyridinium
 8.15 (dd): H in position 5 of the thieno[2,3-b]pyridinium



- 8.29 (d): H in position 2 of the thieno[2,3-b]pyridinium
 9.08 (d): H in position 4 of the thieno[2,3-b]pyridinium
 9.22 (d): H in position 6 of the thieno[2,3-b]pyridinium
 9.55 (d): CO-NH-CH(C=O)-CH(N-)-S

5 (R) Isomer

NMR analysis of the proton (DMSO 300 MHz in ppm)

- 3.50 (s) (partly masked): C=C-CH₂-S-
 3.72 (s): Ar-OCH₃
 5.19 (d J=5): CO-NH-CH(C=O)-CH(N-)-S-
 10 5.32 (s): Ar-CH(CO-O-)-O-
 5.68 (d J=6): -CH=CH-CH₂-N⁺,
 5.76 (dd J=5 and 7.5): CO-NH-CH(C=O)-CH(N-)-S-
 6.29 (m): -CH=CH-CH₂-N⁺,
 6.55 (s) and 6.57 (s) (2 H): Ar-H in ortho and para position
 15 of the -OMe
 6.74 (s): -S-CH=C(C=N-)-N=C(NH₂)-
 7.15 (d): -CH=CH-CH₂-N⁺,
 7.30 (m) (2 H), 8.39 (s) (1 H), 8.96 (s) (1 H): mobile H's
 7.89 (d): H in position 3 of the thieno[2,3-b]pyridinium
 20 8.15 (dd): H in position 5 of the thieno[2,3-b]pyridinium
 8.29 (d): H in position 2 of the thieno[2,3-b]pyridinium
 9.08 (d): H in position 4 of the thieno[2,3-b]pyridinium
 9.23 (d): H in position 6 of the thieno[2,3-b]pyridinium
 9.62 (d): CO-NH-CH(C=O)-CH(N-)-S

25 **EXAMPLE 12:** the internal salt of [[6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[(2-amino-4-thiazolyl)-[[carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl] quinolinium (R) or (S) or an (R+S) mixture.

30 **EXAMPLE 13:** the internal salt of [[6R-[3(E), 6alpha, 7beta (Z)]] 2-[3-[7-[(2-amino-4-thiazolyl)-[[carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl] isoquinolinium (R) or (S) or an (R+S)
 35 mixture.

Rf = 0.6 (eluant: acetone-water (8-2))

EXAMPLE 14: the internal salt of [[6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[(2-amino-4-thiazolyl)-[[carboxy-(2,5-



dichloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-4-(methylthio) pyridinium (R) or (S) or an (R+S) mixture.

5 Rf = 0.6 (eluant: acetone - water (8-2)).

EXAMPLE 15: the internal salt of [(±)(cis)(Z)] 7-[3-[7-[(2-amino-4-thiazolyl)-[[carboxy-(3-bromo-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-(E)-propenyl]-thieno-[2,3-b]pyridinium (R) or (S) or an (R+S) mixture.

EXAMPLE 16: internal salt of (6R (3(E), 6alpha, 7beta(Z))) 1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-4-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo(4,2,0)oct-2-en-3-yl)-2-propenyl)

15 quinolinium

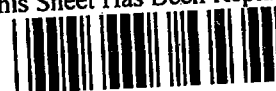
Stage A: Diphenylmethyl [4-fluoro-(2,3bis-hydroxy)-phenyl]-hydroxy acetate

480 cm³ of a 0.3M solution of diphenyl diazomethane is added over 2 hours to a solution of 47.7 g of the product obtained in Preparation 11 in 500 cm³ of ethyl ether cooled down to -10°C. The temperature is taken to -5°C and 10 cm³ of acetic acid is added. This solution is used as it is in the following stage.

Stage B: Diphenylmethyl [4-fluoro-[2,3bis[(2-methoxyethoxy)-methoxyl]-phenyl]-hydroxy acetate

238 cm³ of diisopropylethylamine is added to the solution obtained in the preceding stage. The ether is replaced by 500 cm³ of methylene chloride, then the whole is cooled down to 6-10°C and 53 cm³ of methoxy ethoxy methyl chloride is added over 75 minutes and agitation takes place again for 75 minutes.

500 cm³ of water is added, followed by decanting, the organic phase is washed with N hydrochloric acid then with N soda and with water, followed by drying and evaporating to dryness. The residue is chromatographed on silica eluting with an ethyl acetate - hexane (1-1) mixture. 26.1 g of crude product is obtained which is chromatographed again on silica, eluant methylene chloride - acetone (97-3) in order to obtain



14.58 g of desired product.

NMR spectrum: CDCl_3 300 MHz ppm

3.34-3.36: the C-O-Me's; 3.52-3.80-3.91: the O-CH₂-CH₂-O's;
4.06 (dJ = 6.5): mobile H; 5.17 to 5.27: the O-CH₂-O's; 5.49
5 (dJ = 7.5): the C₆H₅-CH-O's; 6.84 (dd: J = 9 and 10): H₆;
6.96 (dd J = 9 and 6): H₅; 7.20 to 7.40 and 6.94 (sl): the
aromatics.

Stage C: Diphenylmethyl [4-fluoro-2,3bis-[(2-methoxyethoxy)-methoxy]-phenyl]-phthalimidoxo acetate.

10 The operation is carried out as in Stage C of Example 4 starting with 14.42 g of the product obtained in Stage B above, and after chromatography on silica, eluant methylene chloride - methanol (99-1), 11.89 g of the desired product is obtained.

15 IR Spectrum: CHCl_3

1792-1756-1734 cm^{-1} : C=O; 1600-1492 cm^{-1} : aromatic.

NMR spectrum: CDCl_3 250 MHz: for 2 OMEM groups:

3.30 (s), 3.34 (s): OCH₃; 3.47 (m)-3.84 (m): O-CH₂-CH₂-O;
5.10-5.27: O-CH₂O; then 6.30 (s): Ar-CH(ON=)-CO₂⁻; 6.95 (s)
20 CO₂CH(C₆H₅)₂; 6.84 (t): H₅; 7.15 (2H)-7.19-7.32 (9H)-7.74
(4H): aromatic H's.

Stage D: Diphenylmethyl aminoxy [4-fluoro-2,3bis[(2-methoxy-ethoxy)-methoxy]-phenyl] acetate

0.88 cm^3 of hydrazine hydrate is added over one hour at -10°C
25 to a solution of 11.27 g of the product obtained in Stage C above in 112.7 cm^3 of tetrahydrofuran. Agitation takes place for one hour thirty minutes at -10°C, the insoluble part is filtered off and the filtrate is concentrated to dryness.
The residue is chromatographed on silica (eluant: methylene
30 chloride - ethyl acetate (80-20)) and in this way 4.72 g of desired product is obtained.

NMR spectrum: CDCl_3 200 MHz

3.35 (s)-3.36 (s): OCH₃; 3.54 (m) 4H-3.93 (m) 4H: O-CH₂-CH₂O;
5.20 (s)-5.27 (s): OCH₂O; 6.78 (dd. J = 9.5 and 9): H₅;
35 6.89 (m): H₆; 5.73 (s): Ar-CH(ONH₂)-CO₂; 6.94 (s):
CO₂-CH-(C₆H₅)₂; 7.10 (m) 2H - 7.21 (m) 5H: 10 aromatic H's
(C₆H₅ 2.

Stage E: [[1-[4-fluoro-2,3bis-[(2-methoxy-ethoxy)-methoxy]-



phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-iminol]-[2-
 [(triphenylmethyl)-amino]-thiazol-4-yl] acetic acid

The operation is carried out as in Stage E of Example 1
 starting with 4.65 g of the product obtained in Stage D
 5 above, using 3.45 g of oxo-[2-[(triphenylmethyl)-amino]-
 thiazol-4-yl] acetic acid (described in Belgian Patent
 Application No. 864828) and after chromatography on silica
 (eluant methylene chloride - methanol (96-4)) 6.5 g of the
 desired product is obtained.

10 IR Spectrum: CHCl_3

3410 cm^{-1} : $=\text{C}-\text{NH}-$; 1781 cm^{-1} : $\text{C}=\text{O}$; 1618, 1607, 1528,
 1496 cm^{-1} : CO_2 , aromatic and heteroaromatic.

NMR spectrum: DMSO 300 MHz

3.18 (s)-3.21 (s): OCH_3 ; 3.43 (m) 4H-3.81 (m) 4H:
 15 $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$; 5.17 (s) 2H-5.21 (s) 2H: $\text{O}-\text{CH}_2-\text{O}$; 5.87 (s)
 3/4H: $\text{ArCH}(\text{O}-\text{NH}_2)-\text{CO}_2-$; 6.68 (s) 3/4 H: H_5 thiazole; 6.84
 (s) 3/4H: $\text{CO}_2\text{CH}(\text{C}_6\text{H}_5)_2$; approx. 6.95-7.10: H_5, H_6 ;
 approx. 7.18-7.50: other aromatics; 8.65 (s, 1): $=\text{C}-\text{NH}$.

Stage F: 4-methoxy benzyl 7beta-[[[[1-[4-fluoro-2,3bis[(2-
 20 methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-
 ethyl]-oxy]-iminol]-[2-[(triphenyl-methyl)-amino]-thiazol-4-
 yl]-acetyl]-amino]-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-
 1-azabicyclo[4,2,0]oct-2-en-2 carboxylate

The operation is carried out as in Stage F of Example 1
 25 but at a temperature of -10°C , starting with 6.44 g of the
 product obtained in Stage E above. After chromatography on
 silica, eluant methylene chloride - ethyl acetate (90-10),
 5.35 g of desired product is obtained.

NMR spectrum: CDCl_3 400 MHz

30 3.05 (d, 1H)-3.20 (d, 1H): CH_2S ; [3.24 (s), 3.26 (s)] 3H-3.35
 (s, 3H): OCH_3 ; 3.43 (m, 2H)-3.55 (m, 2H)-3.70-4.15:
 $\text{OCH}_2\text{CH}_2\text{O}$ and $=\text{CH}-\text{CH}_2\text{Cl}$; 3.81 (s): CH_3OAr ; 4.96 (d)-4.97
 (d): H_6 cephalo; 5.12-5.31 (6-7H): OCH_2O , $\text{CO}_2\text{CH}_2\text{Ar}$,
 $\text{ArCH}(\text{ONH}_2)-\text{CO}_2-$; 5.81 (m): H_7 cephalo; 5.75 (m): $\text{CH}=\text{CH}-\text{CH}_2\text{Cl}$
 35 (AZ); 6.26 (d, $J = 11$) - 6.29 (d, $J = 11$): $-\text{CH}=\text{CH}-\text{CH}_2-\text{Cl}$
 (AZ); approx. 6.77: H_5 thiazole; approx. 6.85-7.45: aromatic
 $\text{H}'\text{s} + \text{CO}_2\text{CH}(\text{C}_6\text{H}_5)_2$; 7.85-8.20: NH.

Stage G: 4-methoxy benzyl 7beta-[[[[1-[4-fluoro-2,3bis[(2-



methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-[(triphenyl-methyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-iodo-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2 carboxylate

- 5 The operation is carried out as in Stage G of Example 1 starting with 1.2 g of the product obtained in the previous Stage. In this way 1.05 g of desired product is obtained.
NMR spectrum: 3.23 (s)-3.26 (s)-3.35 (s): CH₃O; approx. 3.50 to 3.95: O-CH₂-CH₂-O of which 3.81: CH₃OAr; approx. 4.0: =CH-CH₂-I; 4.92 (m): H₆ cephalo; 5.16-5.30: OCH₂O,
 10 CO₂CH₂Ar; 5.50 (m): H₇ cephalo; 6.12 (m): =CH-CH₂I (ΔE); 6.42 (s)-6.44 (s): Ar-CH(OH)₂CO₂⁻; 6.66 (t, J = 9, approx. = 0.5H): aromatic H in ortho position of F; 6.76 (s resolved): H₅ thiazole; 6.77-7.45: aromatic H's; 7.95 (d)-8.25 (d):
 15 NH.

Stage H: 1-[3-[7beta-[[[[[1-[4-fluoro-2,3bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-
 20 thia-1-azabicyclo[4,2,0]-[oct-2-en-3-yl]-2-propenyl quinolinium iodide

- The operation is carried out as in Stage H of Example 1 starting with 1.02 g of the product obtained in Stage G above using 0.46 g of quinoline. After chromatography on silica,
 25 eluant methylene chloride - methanol (97-3), 347 mg of the desired product is collected (50/50 mixture of the two R and S isomers of expected structure).

NMR spectrum: CDCl₃ 400 MHz
 3.20 (s)-3.26 (s)-3.34 (s)-3.35 (s): CH₃O; 3.79 (s)-
 30 3.80 (s): CH₃OAr; 3.42 (m)-3.54 (m)-3.79 (m)-3.90 (m): OCH₂CH₂O; 4.89 (d): H₆ cephalo; 5.12-5.28: OCH₂O, CO₂CH₂Ar; 5.77 (dd resolved) H₇ cephalo; 6.00 (dd)-6.13 (dd):

+
 =CH-CH₂-N =; 6.38 (s) - 6.44 (s): Ar-CH-(O-)CO₂⁻; 6.51 (m):
 35 =CH-CH₂ (ΔE); 6.72 (resolved): H₅ thiazole; 6.70 to 7.15: H₅-H₆ fluorophenyl, CH=CH-CH₂, CO₂CH(C₆H₅)₂; approx. 7.30: aromatic H's (C₆H₅)₃-C.

Stage I: internal salt of (6R(3(E), 6alpha, 7beta(Z))) 1-(3-



(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-4-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo(4,2,0)oct-2-en-3-yl)-2-propenyl)-quinolinium

- 5 The operation is carried out as in Sage I of Example 1 starting with 339 mg of the product obtained in Stage H above using 5 cm³ of a solution of trifluoroacetic acid with 10% anisole. 180 mg of the desired product is obtained.

NMR spectrum: DMSO 300 MHz

- 10 5.15 (d resolved): H₆ cephalo; 5.75 (dd) approx. 5.81-5.95: H₇ cephalo, =CH-CH₂N =, Ar-CH(-O-)CO₂; 6.38 (m): CH=CH-CH₂ (ΔE); 6.99 (d resolved J = 16): CH=CH-CH₂ (ΔE); 6.59 (d resolved J = 10): H₅ fluorophenyl; 6.75-6.81: H₆ and H₅ thiazole; 7.35 (wide): NH₂ and/or C₆H₅; 8.07 (t, 1H) 8.26 (m, 2H), 8.52 (d, 1H)
15 -8.56 (dd, 1H)-9.30 (d, 1H) 9.58 (sl, 1H): quinoline; approx. = 10.50: OH; 9.46 (d): CONH.

EXAMPLE 17: internal salt of (6R(3(E), 6alpha, 7beta (Z))) 7-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-4-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo(4,2,0)oct-2-en-3-yl)-2-propenyl)-thieno(2,3-b) pyridinium

- Stage A: 1-[3-[7beta-[[[[1-[4-fluoro-2,3bis[(2-methoxyethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl-25 amino]-2-[(4-methoxy-benzyloxy-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]-[oct-2-en-3-yl]-2-propenyl-thieno(2,3-b) pyridinium iodide.

- By operating as in Stage H of Example 16 starting with 944 mg of the product obtained in Stage G of Example 16 and
30 by using 0.45 g of thieno[2,3-b] pyridine, 339 mg of the desired product is obtained after chromatographing on silica (eluant methylene chloride-methanol (95-5)).

NMR spectrum: CDCl₃ 300 MHz

- 3.20 (s)-3.27 (s)-3.34 (s)-3.35 (s): OCH₃; 3.40-3.60 and
35 3.77-4.00: OCH₂CH₂O, CH₂S; 3.79 (s)-3.80 (s): ArOCH₃; 4.92 (d, J = 5)-4.99 (d, J = 5): H₆ cephalo; approx. 5.18-5.30: OCH₂O, CO₂CH₂Ar; approx. 5.77 (m): H₇ cephalo; 5.68 (m)-5.96 (m):



+
 =CH-CH₂N =; 6.39 (s)-6.45 (s): ArCH(-O-)CO₂⁻; 6.73 (s)-6.74 (s): H₅ thiazole; approx. 6.77 (t, resolved): H₅ fluorophenyl; 6.90 to 7.40: benzene H's, CO₂CH(C₆H₅)₂, CH=CH-CH₂(ΔE); 6.92 (m): CH=CH-CH₂(ΔE); 7.54 (d)-7.66 (d): H₃, and 7.83-7.87: H₂, and 8.06 (m): H₅, and 8.80 (d): H₄, and 10.05 (m): H₆, and 8.23 (d)-8.34 (d): CONH of the thieno[2,3-b]pyridine.

Stage B: internal salt of (6R(3(E), 6alpha, 7beta (Z))) -7-(3-
 10 (7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-4-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo(4,2,0)oct-2-en-3-yl)-2-propenyl)-thieno(2,3-b) pyridinium

By operating as in Stage I of Example 16, starting with
 15 332 mg of the product obtained above, 164 mg of the desired product is obtained.

NMR spectrum DMSO 300 MHz

+
 5.18 (d) resolved: H₆ cephalo; 5.67 (d) =CH-CH₂-N =; 5.77-5.90: H₇ cephalo, Ar-CH(-O-)CO₂⁻; 6.31 (m): CH=CH-CH₂(ΔE);
 20 7.14 (d, J = 15): CH=CH-CH₂(ΔE); approx. 6.80 (m): H₅ thiazole, H₅ fluorophenyl; 7.36 (wide): NH₂: 6.59 (t, J = 9): H₆; 7.89 (d, J = 6)-8.15 (dd)-8.28 (d, J = 6)-9.08 (d)-9.23 (d): H₃'-H₅'-H₂'-H₄'-H₆' of the thieno[2,3-b]pyridine.

EXAMPLE 18: internal salt of (6R(3(E), 6alpha, 7beta (Z))) -1-
 25 (3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-4-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo(4,2,0)oct-2-en-3-yl)-2-propenyl)-4-(methylthio) pyridinium

Stage A: 1-[3-[7beta-[[[[1-[4-fluoro-2,3bis[(2-methoxy-
 30 ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl-amino]-2-[(4-methoxy-benzyloxy-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]-[oct-2-en-3-yl]-2-propenyl-4-(methylthio) pyridinium iodide

35 By operating as in Stage H of Example 16, starting with 1.052 g of the product obtained in Stage G of Example 16 and by using 462 mg of 4-thiomethyl pyridine, 536 mg of the desired product is obtained after chromatography on silica

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(eluant methylene chloride - methanol (95-5)).

NMR spectrum: CDCl_3 400 MHz

2.61 (s): CH_3S ; 3.21 (s)-3.26 (s)-3.34 (s)-3.35 (s):
 OCH_3 ; 3.79 (s)-3.88 (s): CH_3OAr ; 3.43 (m)-3.54 (m)-3.80-
 5 4.00: CH_2S , $\text{OCH}_2\text{CH}_2\text{O}$; 4.92 (d): H_6 cephalo; 5.70 (dd)-

+
 5.77 (dd) H_7 cephalo; 5.33 (m)-5.54 (m): $\text{CH}_2\text{N} \equiv$; 5.17-
 5.30: OCH_2O , $\text{CO}_2\text{CH}_2\text{Ar}$; 6.33 (m): $\text{CH}=\text{CH}-\text{CH}_2(\Delta\text{E})$; 6.35 (s):
 $\text{ArCH}(\text{O}-)\text{CO}_2-$; 6.74 (s)-6.75 (s): H_5 thiazole; 6.72 to
 10 7.18: H_5 , H_6 fluorophenyl, $\text{CO}_2\text{CHC}_6\text{H}_5$, 4H aromatic, $\text{CH}=\text{CH}-\text{CH}_2$
 (ΔE) ; 7.20 to 7.38: aromatic H C-(C_6H_5)₃, (C_6H_5)₂- CH_2-CO_2 ;
 7.61 (d, 2H)-8.8 (m, 2H): H_3' , H_5' and H_2' , H_6' of the
 pyridinium; 7.83 (d), 8.15 (d): -CONH.

Stage B: internal salt of (6R(3(E), 6alpha, 7beta (Z))) -1-(3-
 15 (7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-4-
 fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-
 5-thia-1-azabicyclo(4,2,0)oct-2-en-3-yl)-2-propenyl)-4-
 (methylthio) pyridinium

By operating as in Stage I of Example 16 starting with
 20 500 mg of the product obtained in Stage A above, 251 mg of
 desired product is obtained.

NMR spectrum: DMSO 300 MHz

3.50-3.70: CH_2S ; 2.72 (s): CH_3S ; 5.18 (m): H_6 cephalo;
 +
 25 approx. = 5.77 (m): H_7 cephalo; 5.24 (m): $=\text{CH}-\text{CH}_2-\text{N} \equiv$; 5.83
 (s), 5.87 (s): OCH_2O , ArCO_2CH_2 ; 6.28 (m): $\text{CH}=\text{CH}-\text{CH}_2(\Delta\text{E})$; 6.98
 (d, $J = 16$): $\text{CH}=\text{CH}-\text{CH}_2$; 6.61 (t, resolved): H_6 fluorophenyl;
 6.77-6.82: H_5 and H_6 thiazole; 7.32: NH_2 ; 7.96 (d)-8.71
 (d): $\text{H}_3'-\text{H}_5'$ and $\text{H}_2'-\text{H}_6'$ of the pyridinium.

30 EXAMPLE 19: internal salt of (6R(3(E), 6alpha, 7beta (Z))) -2-
 (3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-4-
 fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-
 5-thia-1-azabicyclo(4,2,0)oct-2-en-3-yl)-2-propenyl)
 isoquinolinium

35 Stage A: 1-[3-[7beta-[[[[[1-[4-fluoro-2,3bis[(2-methoxy-
 ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-
 oxy]-imino]-[2-(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl-
 amino]-2-[(4-methoxy-benzyloxy-carbonyl)-8-oxo-5-thia-1-



azabicyclo[4,2,0]-[oct-2-en-3-yl]-2-propenyl isoquinolinium iodide

By operating as in Stage H of Example 16, starting with 917 mg of the product obtained in Stage G of Example 16 and by using 416 mg of isoquinoline, 473 mg of desired product is obtained, after chromatography on silica (eluant: methylene chloride - methanol (96-4)).

NMR spectrum: CDCl₃ 300 MHz

3.20 (s)-3.26 (s)-3.34 (s)-3.35 (s): CH₃O; 3.76 (s)-3.78 (s): ArOCH₃; 3.40-4.00: OCH₂-CH₂O, CH₂S; H₆ cephalo; 5.80 (m): H₇ cephalo; approx. 5.18-5.30: OCH₂O, ArCO₂CH₂; approx. 6.48 (m): CH₂-CH=(ΔE); 6.38 (s)-6.44 (s): Ar-CH(-O-)CO₂-; 6.73 (s)-6.75 (s): H₅ thiazole; approx. = 6.76 to 7.40: aromatic H's (phenyl groups), CO₂CH(C₆H₅)₂; 7.96 (m, 1H)-8.10 (m, 2H) - 8.26 (m, 2H)-8.49 (m, 1H)-8.69 (m, 1H)-10.90 (s resolved, 1H): of the isoquinoline.

Stage B: internal salt of (6R(3(E), 6alpha, 7beta (Z))) 2-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-4-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo(4,2,0)oct-2-en-3-yl)-2-propenyl) isoquinolinium

By operating as in Stage I of Example 16 starting with 460 mg of the product obtained above, 176 mg of expected product is obtained.

NMR spectrum: DMSO 400 MHz

3.72 (m): CH₂S; 5.18 (d, resolved): H₆ cephalo; 5.77 (dd, d after exchange) - H₇ cephalo; 5.52 (m): CH₂-N =; 5.83 (s), 5.87 (s): Ar-CH₂(-O-)CO₂-; 6.39 (m): CH=CH-CH₂(ΔE); 7.10 (d, J = 10): CH=CH-CH₂(ΔE); 6.59 (m), 6.80 (m): H₆, H₅ fluorophenyl; 6.77 (s)-6.80 (s): H₅ thiazole; 8.09 (t)-8.28 (t) and 8.37 (d)-8.53 (d)-8.61 (d)-8.74 (m)-10.06 (s): H₆'-H₇' and H₃'-H₄' and H₅' and H₈' and H₁' of the isoquinoline.

EXAMPLE 20: internal salt of (6R(3(E), 6alpha, 7beta (Z))) 1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-4-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo(4,2,0)oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a) pyridinium



Stage A: 1-[3-[7beta-[[[[[1-[4-fluoro-2,3bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl-amino]-2-[(4-methoxy-benzyloxy-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]-[oct-2-en-3-yl]-2-propenyl-imidazo-(1,2-a)pyridinium iodide

By operating as in Stage H of Example 16, starting with 955 mg of the product obtained in Stage G of Example 16, using 401 mg of imidazo[1,2-a] pyridine, 486 mg of expected product is obtained (after chromatography on silica, eluant methylene chloride - methanol (95-5)).

NMR spectrum: CDCl_3 300 MHz

3.20 (s)-3.26 (s)-3.34 (s)-3.35 (s): CH_3O ; 3.40-3.95: $\text{OCH}_2\text{-CH}_2\text{O}$, CH_2S ; 4.89 (d): H_6 cephalo; 5.74 (m): H_7 cephalo;

15

5.20-5.42 (9H, excess): $\text{ArCO}_2\text{CH}_2\text{-OCH}_2\text{O}$, $\text{CH-CH}_2\text{-N} \equiv$; 6.28 (m): $=\text{CH-CH}_2(\text{AE})$; 6.38 (s)-6.44 (s): Ar-CH(-O-)CO_2^- ; 6.88 (s)-6.90 (s): $\text{CO}_2\text{CH(C}_6\text{H}_5)_2$; approx. 6.75 to 7.35: aromatic H's (phenyl groups) + nitrogenous bicyclic H's; 7.85 (m, 1H)-8.03 (d, 1H)-8.36 (d, 1H)-9.09 (m, 1H); other nitrogenous bicyclic H's; 7.94 (d), 8.25 (d): CONH.

20

Stage B: internal salt of (6R(3(E), 6alpha, 7beta (Z))) 1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-4-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo(4,2,0)oct-2-en-3-yl)-2-propenyl)imidazo(1,2-a) pyridinium

25

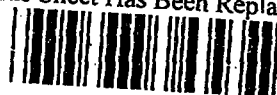
By operating as in Stage I of Example 16 starting with 476 mg of the product obtained in Stage A above, 215 mg of desired product is obtained.

30 NMR spectrum: DMSO 400 MHz

3.70 (m): CH_2S ; 5.15 (d, resolved): H_6 cephalo; 5.74 (dd, d after exchange)-5.82 (dd, d after exchange): H_7 cephalo;

35

5.28 (m): $\text{CH}_2\text{-N} \equiv$; 5.83 (s), 5.86 (s): Ar-CH(-O-)CO_2^- ; 6.25 (m): $\text{CH=CH-CH}_2(\text{AE})$; 6.89 (d, resolved, $J = 15.5$): $\text{CH=CH-CH}_2(\text{AE})$; 6.60 (m), 6.78 (m): H_6 , H_5 fluorophenyl; 6.76 (s)-6.80 (s): H_5 thiazole; 7.57 (m)-8.05 (m)-8.19 (m) and 8.28 (d, resolved, $J = 2.5$)-8.44 (d, resolved, $J = 2.5$)-8.96 (d,



$J = 6.5$): $H_5'-H_6'-H_7'-H_4'$ and H_2' , H_3' of the imidazo(1,2-a)pyridinium; 9.44 (d)-9.56 (d): $CONH-C$; 7.32 (m)-9.40 (m): mobile H's.

EXAMPLE 21: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z)))

5 1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-4-(methylthio) pyridinium

Stage A: Ethyl [(2,3-dihydroxy)-phenyl]-hydroxy acetate

10 10 cm³ of a molar solution of titanium chloride in methylene chloride is added to a solution of 1.1 g of pyrocatechol in 20 cm³ of methylene chloride cooled down to -20°C. Agitation takes place for 30 minutes at -20°C then a solution of 1.02 g of ethyl glyoxylate in 10 cm³ of methylene
15 chloride is added over 5 minutes. Agitation takes place for 2 hours at -20°C. The medium is left to return to ambient temperature, then it is poured into 50 cm³ of a saturated solution of ammonium chloride, extracted with methylene chloride, the extracts are washed, dried and evaporated to
20 dryness under reduced pressure. The residue is chromatographed on silica (eluant: methylene chloride - ethyl acetate (7-3)), and in this way 860 mg of desired product is obtained (M.p. = 86°C).

IR Spectrum: CHCl₃

25 3595 cm⁻¹, 3040 cm⁻¹ OH complex + associated, 1730 cm⁻¹ = C=O, 1602-1402 cm⁻¹: aromatic.

NMR spectrum: CDCl₃ 250 MHz ppm

5.33 (s): C-CH(OH)COOEt; 1.26 (t) - 4.27 (m): COOEt; 3.75-5.86-7.45: mobile H; 6.7 to 6.95: aromatic H's.

30 Stage B: Ethyl [2,3bis-[(2-methoxy ethoxy)-methoxy]-phenyl]-hydroxy acetate

15.69 g of methoxy ethoxy methyl chloride and 16.35 g of N-ethyl diisopropylamine are added to a solution of 8.1 g of the product obtained in Stage A in 750 cm³ of acetonitrile,
35 agitation takes place for 16 hours at 0°C, then the whole is poured into 100 cm³ of water and the acetonitrile is evaporated off, followed by taking up in methylene chloride, washing with 1N hydrochloric acid, with water then with a 10%



solution of sodium carbonate. After drying and evaporating to dryness under reduced pressure 12.3 g of product is collected which is chromatographed on silica (eluant: cyclohexane - ethyl acetate (5-5)), and in this way 6.7 g of
5 desired product is obtained.

IR Spectrum: CHCl_3

3315-3440 cm^{-1} : OH complex; 1735 cm^{-1} : C=O; 1601-1590 cm^{-1} : aromatics.

NMR spectrum: CDCl_3 250 MHz

10 1.21 and 4.22: CO_2Et ; 3.37: OCH_3 ; 3.57-3.83-3.93: CH_2 - CH_2 -O; 5.25-5.28: O- CH_2 -O; 4.07: OH; 5.39: C-CH(OH)- CO_2Et .

Stage C: Diphenylmethyl [2,3bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-hydroxy acetate

a) Saponification:

15 22 cm^3 of 2N soda is added to a solution of 8.54 mg of the product obtained in the preceding stage in 400 cm^3 of ethanol. Agitation takes place for 3 hours at ambient temperature, followed by acidifying to pH 2 with N
hydrochloric acid, concentrating to 1/2 volume under reduced
20 pressure, diluting with 200 cm^3 of water and extracting with methylene chloride and ethyl acetate. The extracts are dried and after evaporating to dryness under reduced pressure 8.2 g of [2,3bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-hydroxy
acetic acid is obtained.

25 b) Esterification

109 cm^3 of diphenyldiazomethane in a 0.3M solution in ethyl ether is added to a solution of 8.2 g of the acid obtained above in 300 cm^3 of methylene chloride cooled down to 0°C. Agitation takes place for 16 hours at ambient
30 temperature. Acetic acid is added at 0°C followed by evaporation to dryness under reduced pressure and 13 g of product is collected which is chromatographed on silica, eluant cyclohexane - ethyl acetate (6-4), in this way 10.2 g of desired product is obtained.

35 IR Spectrum: CHCl_3

3530-3520 cm^{-1} : OH complex; 1742 cm^{-1} : C=O; 1600-1585-1495 cm^{-1} : aromatics.

NMR spectrum: CDCl_3 300 MHz

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3.34-3.37: CH_3 ; 3.54-3.83: $\text{O}-\text{CH}_2-\text{CH}_2$; 4.08: OH ; 5.18-5.28: OCH_2O ; 5.53: $\text{C}-\text{CH}(\text{OH})\text{C}-(\text{C}_6\text{H}_5)_2$.

Stage D: Diphenylmethyl [2,3bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-phthalimidoxo acetate

- 5 226 mg of triphenyl phosphine and 77 mg of N-hydroxy phthalimide are added at ambient temperature to a solution of 227 mg of the product obtained in the previous stage in 25 cm^3 of tetrahydrofuran. The mixture is cooled down to -5°C and 136 μl (150 mg) of diethylazodicarboxylate is added over 10 2 hours. Agitation takes place for 2 hours while allowing the temperature to rise to ambient. The whole is poured into 25 cm^3 of ice-cooled water, extracted with methylene chloride then with ethyl acetate, the extracts are dried and 15 evaporated to dryness under reduced pressure, 760 mg of residue is collected which is chromatographed on silica (eluant: methylene chloride - acetone (97-3)), and in this way 230 mg of desired product is obtained.

IR Spectrum: CHCl_3 1794-1738 cm^{-1} : $\text{C}=\text{O}$; 1602-1588-1488 cm^{-1} : aromatic

NMR spectrum: CDCl_3 300 MHz

- 20 3.31 - 3.36: CH_3 ; 3.46-3.52-3.79-3.89: $\text{CH}_2-\text{CH}_2-\text{O}$; 5.24: $\text{O}-\text{CH}_2-\text{O}$; 6.43: $\text{C}-\text{CH}(\text{ON}=\text{C})\text{CO}_2\text{C}-(\text{C}_6\text{H}_5)_2$; 6.95: $\text{CH}-(\text{C}_6\text{H}_5)_2$; 7.72: Ar-H phthalimido; 7.0-7.35: Ar-H aromatic.

Stage E: Diphenylmethyl aminoxo [2,3bis-[(2-methoxy-ethoxy)-methoxy]-phenyl] acetate

- 25 1.42 cm^3 (1.47 g) of hydrazine hydrate is added to a solution of 6.2 g of the product obtained in the previous stage in 400 cm^3 of ethanol and 20 cm^3 of methylene chloride and agitation takes place for 3 hours at ambient temperature. After evaporating to dryness under reduced pressure, the dry 30 extract is taken up in methylene chloride, the insoluble part is filtered out and the filtrate is brought to dryness under reduced pressure, and 5.0 g of desired product is obtained.

IR Spectrum CHCl_3

- 3335 cm^{-1} : ONH_2 ; 1745 cm^{-1} : $\text{C}=\text{O}$; aromatics 1602, 1589, 1577, 35 1495 cm^{-1} : aromatics.

NMR spectrum: CDCl_3 250 MHz

- 3.35-3.37: OCH_3 ; 3.54-3.83-3.95: $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$; 5.26-5.29: $\text{O}-\text{CH}_2-\text{O}$; 5.75: $-\text{C}-\text{CH}(\text{ONH}_2)\text{CO}_2\text{C}-(\text{C}_6\text{H}_5)_2$; 5.86: $\text{O}-\text{NH}_2$; 6.95:



COO-CH(C₆H₅)₂.

Stage F: [[[[1-[2,3bis[(methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-[(triphenyl-methyl)-amino]-thiazol-4-yl] acetic acid

- 5 5.0 g of the product obtained in the previous stage in solution in 60 cm³ of methanol with 4.016 g of [2-[(triphenyl-methyl)-amino]-thiazol-4-yl] acetic acid (prepared as described in the Belgian Patent Application No. 864828) is agitated for 6 hours. After evaporating to
- 10 dryness, the residue is chromatographed on silica, eluant ethyl acetate - ethanol (7-3), and in this way 5.55 g of desired product is obtained.

IR Spectrum: CHCl₃

- =C-NH: 3405 cm⁻¹; C=O: 1735 cm⁻¹; C=N, aromatic and CO₂⁻:
- 15 1619-1602-1529-1494 cm⁻¹

NMR spectrum: CDCl₃ 250 MHz

- 3.13-3.31: CH₃; 3.34-3.49-3.76: O-CH₂-CH₂-O; 5.14- 5.18: O-CH₂-O; 6.11: -C-CH(ON=)CO₂C-; 6.46: -CO₂-CH(C₆H₅)₂; 6.81: CH thiazol; 6.75 to 7.3 aromatic H's.
- 20 Stage G: 4-methoxy benzyl 7beta-[[[[[1-[2,3bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-[(triphenyl-methyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate
- 25 3.55 g of 4-methoxy benzyl 7beta-amino-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate hydrochloride (prepared as described in the EP Application: 0333154) and 1.6 g of N-ethyl
- 30 dimethylaminopropyl carbodiimide (EDAC) are added to a solution of 6.18 g of the product obtained in Stage F in 150 cm³ of methylene chloride and cooled down to 0°C, agitation takes place for 10 minutes at 0°C then for 2 hours while allowing the temperature to rise to 20°C, and the whole is poured into a molar solution of potassium hydrogen phosphate.
- 35 Extraction takes place with methylene chloride then with ethyl acetate followed by drying and evaporating to dryness. After chromatography on silica eluting with methylene chloride - ethyl acetate (9-1), 5.1 g of desired product is



obtained.

IR Spectrum: CHCl_3

3404 cm^{-1} : $=\text{C}-\text{NH}$; $1790-1731-1684\text{ cm}^{-1}$: $\text{C}=\text{O}$; aromatics, heteroatom, amide II: $1613-1587-1526-1517-1496\text{ cm}^{-1}$.

5 NMR spectrum: CDCl_3 (300 MHz)

3.24 to 3.37: $\text{CH}_2-\text{O}-\text{CH}_3$ and $\text{C}-\text{S}-\text{CH}_2-$; 3.44 to 4.0: CH_2Cl and $\text{C}_6\text{H}_5\text{OCH}_3$; 3.44 to 4.0: $\text{O}-\text{CH}_2-\text{CH}_2-$; 5.15 to 5.28: $-\text{O}-\text{CH}_2-\text{O}$; 5.67 to 5.88, 6.29: $\text{C}-\text{CH}-\text{CH}_2\text{Cl}$; 6.77: CH thiazol; 6.7 to 7.4: aromatics; 8.01-8.37: NH .

10 Stage H: 4-methoxy benzyl 7beta-[[[[1-[2,3bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2[(triphenyl-methyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-iodo-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2 carboxylate

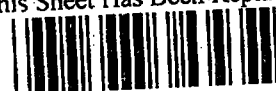
15 0.57 g of sodium iodide and 1 crystal of iodine are added to a solution of 1.25 g of the product obtained in Stage G (above) in 5 cm^3 of acetone and agitation takes place for 1 hour 30 minutes at ambient temperature. After evaporating to dryness under reduced pressure, the dry
20 extract is taken up in methylene chloride, washed with a 10% solution of sodium thiosulphate, then with salt water, followed by drying and evaporating to dryness under reduced pressure. 1.28 g of expected product is collected which is used as it is for the following stage.

25 Stage I: 1-[3-[7beta-[[[[1-[2,3bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]-[oct-2-en-3-yl]-2-propenyl]-4-methyl-thio
30 pyridinium iodide

1.28 g of the product obtained in Stage H, 1.15 g of thiomethyl pyridine and 3 cm^3 of methylene chloride are mixed together. After evaporating to dryness under reduced pressure, the residue is chromatographed on silica (eluant
35 methylene chloride - methanol (97-3) then (96-4) and (95-5)) and in this way 415 mg of desired product is obtained.

NMR Spectrum: CDCl_3 250 MHz

2.6: $\text{S}-\text{CH}_3$; 3.21-3.25-3.35-3.36-3.37: $-\text{OCH}_3$; 3.4 to 3.9:



-O-CH₂-CH₂-O; 3.77-3.79 C₆H₅-OCH₃.

Stage J: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z)))1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-4-(methylthio) pyridinium

400 mg of the product obtained in Stage I, 4.5 cm³ of trifluoroacetic acid and 0.5 cm³ of anisole are agitated for 2 hours at ambient temperature. Then 0.5 cm³ of water is added and agitation continues for 2 hours at ambient temperature, followed by filtering, rinsing with 2 times 3 cm³ of trifluoroacetic acid and 15 cm³ of ethyl ether is added. Agitation takes place for 15 minutes, followed by separating and drying under reduced pressure, and 222 mg of desired product is collected.

NMR spectrum: DMSO (300 MHz) ppm

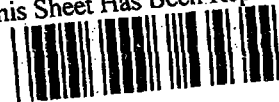
2.71: SCH₃; 3.72: C-S-CH₂-C; 5.19-5.76-5.83: -S-CH₂-(-N=)-CH-NH-; 5.22: -C=C-CH₂-N⁺; 5.91-5.95: H imino-carboxybenzyl; 6.28: -CH=CH-CH₂-N⁺; 6.98: -CH=CH-CH₂-N⁺; 6.59 - 6.79: aromatic H's; 6.79-6.83: H thiazol; 9.49: NH.

EXAMPLE 22: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z)))7-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-thieno(2,3-b) pyridinium

Stage A: 1-[3-[7beta-[[[[1-[2,3bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]-[oct-2-en-3-yl]-2-propenyl]-thieno(2,3-b) pyridinium iodide

The operation is carried out as in Stage I of Example 21 starting with 1.24 g of the product obtained as in Stage H of Example 21 using 1.28 g of thieno(2,3-b) pyridine, and after chromatography on silica, eluant methylene chloride - methanol (97-3 then 96-4 and 95-5), 450 mg of desired product is obtained.

IR Spectrum: CHCl₃



=C-NH: 3404 cm^{-1} ; C=O: $1790\text{--}1731\text{--}1684\text{ cm}^{-1}$; C=C, aromatics, heteroatoms, amide II: $1613\text{--}1587\text{--}1526\text{--}1517\text{--}1496\text{ cm}^{-1}$; thienopyridine: 1599 cm^{-1} .

NMR spectrum: CDCl_3 300 MHz

- 5 3.21-3.26-3.34-3.37: $\text{CH}_2\text{--O--CH}_3$; 3.43-3.55-3.82: $\text{--O--CH}_2\text{--O--CH}_2\text{--CH}_2$; 3.80: $\text{C}_6\text{H}_5\text{O--CH}_3$; 5.2 to 5.3: $\text{O--CH}_2\text{--O--CH}_2\text{--}$, $\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5\text{--O--}$; 5.90: $\text{--CH--CH}_2\text{--N}^{\oplus}$; 6.45 to 6.6: $\text{C--CH=CH--CH}_2\text{--N}^{\oplus}$; 6.51 to 6.56: $\text{CO}_2\text{--CH(C}_6\text{H}_5)_2$; 6.73: H thiazol; 6.85 to 8.78: aromatic H's.
- 10 Stage B: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) - 7-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-thieno(2,3-b) pyridinium

- 15 The operation is carried out as in Stage J of Example 21 starting with 430 mg of the product obtained in the previous stage and 206 mg of desired product is obtained.

IR Spectrum: nujol

- C=O: 1775 cm^{-1} (beta-lactame) 1670 cm^{-1} (complex); conjugated system, aromatic, NH_2 , amide: $1599\text{--}1580\text{--}1520\text{ cm}^{-1}$.

NMR spectrum: CDCl_3 400 MHz

- 3.69: $\text{--S--CH}_2\text{--C--}$; 5.18-5.78-5.86: --NH--CH--CH--S-- ; 5.67: $\text{=CH--CH}_2\text{--N}^{\oplus}$; 5.91-5.95: $\text{--C--CH(O--N=)CO}_2\text{H}$; 6.31 and 7.15: the H's of the propylene; 6.59 and 6.79: aromatic H's; 6.78 and 6.82: H thiazol; 7.89 to 9.22: thienopyridine; 9.49 and 9.61: amide.

- 25 EXAMPLE 23: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) - 7-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-

- 30 imidazo(1,2-a) pyridinium

- Stage A: 1-[3-[7beta-[[[[1-[2,3bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]-[oct-2-en-3-yl]-2-propenyl]-imidazo(1,2-a) pyridinium iodide

The operation is carried out as in Stage I of Example 21 starting with 1.24 g of the obtained product as in Stage H of

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Example 21 and using 1.28 g imidazopyr... In this way 270 mg of expected product is obtained.

NMR spectrum CDCl₃ 400 MHz

3.25-3.20-3.35-3.37: CH₂OCH₃; 3.30 to 3.90: OCH₂-CH₂-
 5 OCH₃; 3.30 to 3.90: -S-CH₂-C-; 3.78-3.79: -C₆H₅-OCH₃; 4.88
 and 5.72: NH-CH-CH-S; 5.10 to 5.50: C-O-CH₂-OCH₂-, =C-CH₂-N⁺;
 6.28: C-CH=CH-CH₂-; 6.51-6.56: -C-CH(O-N=)CO₂CH; 6.7 to
 7.4: aromatic H, H thiazol, H propylene; 7.93-8.20: NH.
 Stage B: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) 7-
 10 (3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-
 phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-
 thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-
 imidazo(1,2-a) pyridinium

The operation is carried out as in Stage J of Example 21,
 15 starting with 280 mg of the product obtained in the
 preceding stage. 140 mg of desired product is obtained.

IR Spectrum:

C=O: 1775-1670 cm⁻¹; conjugated system, aromatic, amide II:
 1598-1530-1510 cm⁻¹.

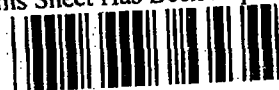
20 NMR spectrum: DMSO 300 MHz

3.45 to 4.20: -S-CH₂-; 5.16-5.76-5.82: -NH-CH-CH-S-;
 5.29: -CH₂-N⁺; 5.91-5.94: C-CH(-O-N=)CO₂H; 6.26: 1H
 propylene; 6.58-6.70 to 6.95: H thiazol, aromatic, 1H
 propylene; 9.47-9.58: NH; 7.58-8.06-8.20-8.96-8.29
 25 -8.44: bicycle.

EXAMPLE 24: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z)))
 7-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-
 phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-
 thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-
 30 quinolinium

Stage A: 1-[3-[7beta-[[[[1-[2,3bis[(2-methoxy-ethoxy)-
 methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-
 imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-
 amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo 5-thia-1-
 35 azabicyclo[4,2,0]-[oct-2-en-3-yl]-2-propenyl] quinolinium
 iodide

The operation is carried out as in Stage I of Example
 21, starting with 1.33 g of the product obtained as in Stage



H of Example 21, using 1.2 g of quinoline, and 475 mg of desired product is obtained after chromatography on silica (eluant methylene chloride - methanol (97-3 then 95-5)).

NMR spectrum:

- 5 3.42 to 3.95: $\text{OCH}_2\text{-CH}_2\text{-OCH}_3$; 3.78-3.79: $-\text{C}_6\text{H}_4\text{-OCH}_3$; 5.13 to 5.28: $-\text{OCH}_2\text{-O-CH}_2-$, $=\text{C-CH(O-N=)}$; 5.96-6.11: $-\text{CH}_2\text{-N}^{\oplus}$; 6.49-6.55: $-\text{CO}_2\text{-CH(C}_6\text{H}_5)_2$; 6.85-8.93: aromatics.
- Stage B: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) 7-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,3-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo [4,2,0]oct-2-en-3-yl)-2-propenyl) quinolinium
- 10

- The operation is carried out as in Stage J of Example 21, starting with 465 mg of the product obtained above.
- 15 255 mg of desired product is obtained.

NMR spectrum: DMSO 300 MHz

- 3.3 to 3.8: $-\text{S-CH}_2-$; 5.15 and 5.78: $-\text{NH-CH-CH-S-}$; 5.91: $-\text{C-CH(O-N=)CO}_2\text{H}$ and $\text{CH}_2\text{-N}^{\oplus}$; 6.39: $=\text{C-CH=CH-}$; 6.99: $=\text{C-CH-CH-}$; 6.7 to 6.9: aromatic H's; 8.07 to 9.58: bicyclic H.
- 20 EXAMPLE 25: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) 1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-N, N-dimethyl benzenaminium

- 25 Stage A: [[[1-[2,5-dichloro-3,4bis-[(2-methoxy ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl] acetic acid

- The operation is carried out as in Stage E of Example 1 starting with 3.5 g diphenyl methyl aminoxy [2,5-dichloro-3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-acetate (obtained intermediately in Example 9) with 2.37 g oxo [2-[(triphenylmethyl)-amino]-thiazol-4-yl] acetic acid (described in the Belgian Patent Application No. 864828). After chromatography on silica (eluant ethyl acetate - ethanol (9-1)) 5.14 g of
- 30
- 35 desired product is obtained.

NMR spectrum: 300 MHz CDCl_3

- 3.30 (s): OCH_3 ; 3.51-3.92 (m): $-\text{O-CH}_2\text{-CH}_2\text{-OCH}_3$; 5.16 (s)-5.18 (s): $\text{O-CH}_2\text{-O}$; 6.25: CH-CO-CH_2 , H_6 ; 7.20 to 7.30:



aromatic H's.

Stage B: 4-methoxy benzyl 7beta [[[[[1-[2,5-dichloro-3,4bis-
[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-
methoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-
5 thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-chloro-1-propenyl]-8-
oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate

The operation is carried out as in Stage F of Example 1
starting with 4.8 g of the product obtained above with 2.26 g
of 4-methoxy benzyl 7beta-amino-3-[(Z)-3-chloro-1-propenyl]-
10 8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate
hydrochloride (described in EP 0333154). After chromatography
on silica (eluant methylene chloride - ethyl ether (9-1)),
4.6 g of desired product is obtained.

NMR spectrum: 300 MHz CDCl₃

15 3.05 (m)-3.45 (m): -CH₂-Cl; 3.36-3.37 (s): -O-CH₃; 3.57
(m)-3.97 (m): O-CH₂-CH₂-O-; 3.81 (s,d): -OCH₃; 4.99- 5.02
(d): NH-CH-CH-S; 5.86-5.90: NH-CH-CH-S; 5.15 to 5.26: O-CH₂-
O-; 5.75 (m): H₂ propylene; 6.26 (J=11.5) (d)-6.35 (J=11.5)
(d): H₁ propylene; 6.47 to 6.50 (s) -CO₂-CH- Φ ₂; 6.85 to 7.40
20 the aromatic H's.

Stage C: 4-methoxy benzyl 7beta [[[[[1-[2,5-dichloro-3,4bis-
[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-
methoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-
thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-iodo-1-propenyl]-8-oxo-
25 5-thia-1-azabicyclo[4,2,0]oct-2-en-2 carboxylate

The operation is carried out as in Stage G of Example 1
starting with 150 mg of the product obtained in the stage
above, and 160 mg of desired product is obtained.

Stage D: 1-[3-[7beta-[[[[[1-[2,5-dichloro-3,4bis-[(2-methoxy-
30 ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-
oxyl-imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-
acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-
thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-N,N-
dimethyl benzeneaminium iodide

35 The operation is carried out as in Stage H of Example 1,
starting with 155 mg of the product obtained above, using
64 mg of N-N-dimethylaniline, after chromatography on silica
(eluant methylene chloride - methanol (96-4)), 55 mg of



desired product is obtained.

NMR spectrum: CDCl_3 300 MHz

2.95 (s): $\text{N}^{\oplus}(\text{CH}_3)_2$; 3.30 to 3.45: $-\text{S}-\text{CH}_2-$; 3.35 - 3.36 - 3.37

(s): $\text{O}-\text{CH}_3$; 3.82 (s,d) $\text{O}-\text{CH}_3$; 3.90 to 4.05: $-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-$,
 $=\text{C}-\text{CH}_2-\text{N}(\text{CH}_3)_2$; 4.94 (d) - 4.98 (d): $\text{NH}-\text{CH}-\text{CH}-\text{S}$; 5.87 (m):
 $\text{NH}-\text{CH}-\text{CH}-\text{S}$; 5.18 to 5.30 (m): $\text{O}-\text{CH}_2-\text{O}$ and $\text{O}-\text{CH}_2-\text{O}$; 6.14 (m) (ΔE) $\text{C}-\text{CH}=\text{CH}-\text{CH}_2-$; 6.70 to 7.40 (m) $\text{C}-\text{CH}-\text{CH}-\text{CH}_2-$, H thiazole,
 aromatic H's; 8.17-8.25 (d): NH.

Stage E: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) - 1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-N,N-dimethyl benzeneaminium

The operation is carried out as in Stage I of Example 1 starting with 50 mg of the product obtained above, and 22 mg of desired product is obtained.

EXAMPLE 26: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) -

1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a) pyridinium

Stage A: 1-[3-[7beta-[[[[1-[2,5-dichloro-3,4bis-[(2-methoxyethoxy)-methoxyl-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-imidazo(1,2-a) pyridinium iodide

The operation is carried out as in Stage H of Example 1, starting with 1.24 g of the product obtained as in Stage C of Example 25 using 0.497 g of imidazo(1,2-a) pyridine. After chromatography on silica (eluant methylene chloride - methanol (95-5)), 626 mg of desired product is obtained.

NMR spectrum: CDCl_3 400 MHz

3.34-3.36: $-\text{CH}_2-\text{O}-\text{CH}_3$; 3.50-3.87: $\text{O}-\text{CH}_2-\text{CH}_2-\text{OMe}$; 3.80 (s) $-\text{O}-\text{CH}_3$; 4.94 (d,d): $-\text{NH}-\text{CH}-\text{CH}-\text{S}$; 5.20-5.24: $-\text{O}-\text{CH}_2-\text{O}-$, $\text{CO}_2-\text{CH}_2-\text{O}$; 5.86: $\text{NH}-\text{CH}-\text{CH}-\text{S}$; 6.15-6.35: H propylene; 6.47

- 6.51: =N-O-CH-; 6.77: H thiazole; 6.90 to 7.40: the aromatic H's; 7.88-8.04: H of the imidazole; 7.88: -NH-CF₃.
 Stage B: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))-1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a) pyridinium

The operation is carried out as in Stage I of Example 1 starting with the product obtained in Stage A, and 327 mg of desired product is obtained.

NMR spectrum: CDCl₃ 300 MHz
 3.50 to 3.75: -S-CH₂-C≡; 5.16: -NH-CH-CH-S-; 5.79 (m): -NH-CH-CH-S-; 6.24 (m): =C-CH=CH-C-; 6.91 (dd): =C-CH=CH-C-; 6.83 (dd): H thiazole; 7.58-8.06 (t) and 8.21-8.96 (d): H pyridine; 8.29-8.45: H imidazole; 9.62: NH; 9.93: NH₂, CO₂H.

EXAMPLE 27: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))-1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-6,7-dihydro-5-H-pyrindinium

Stage A: 1-[3-[7beta-[[[[[1-[2,5-dichloro-3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyrindinium iodide

The operation is carried out as in Stage H of Example 1, starting with 1.13 g of the product obtained as in Stage C of Example 25 using 457 mg of cyclopentano[2,3]pyridine. After chromatography on silica (eluant methylene chloride - methanol (9-1)) 460 mg of desired product is obtained.

NMR spectrum: CDCl₃ 300 MHz ppm
 2.41-3.23-3.45: -S-CH₂ and CH₂ of the cyclopentane; 3.34 to 3.37: O-CH₃; 3.57 to 3.98: -O-CH₂-CH₂-O-; 3.81: ϕ -O-CH₃; 4.97-5.88: NH-CH-CH-S-; 5.12 to 5.25: -O-CH₂-O-; 6.22 and 6.45 (Δ E) =C-CH=CH-CH₂-; 6.85 to 7.35: =C-CH=CH-CH₂-; 6.46 - 6.50 (s) =N-O-CH-CO₂-; 6.72: H thiazole; 6.85 to 7.35:



aromatic H's; 7.97-8.23 (d): NH; 7.79-9.20: H pyridine.

Stage B: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z)))1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-6,7-dihydro-5-H-pyrindinium

The operation is carried out as in Stage I of Example 1, starting with 447 mg of the product obtained in the previous stage. 194 mg of desired product is obtained.

10 NMR spectrum: DMSO 300 MHz

2.23 (m): the central CH₂'s; 3.19 (t) the =C-CH₂'s; 5.17 (d): H₆; 5.33 (m): =CH-CH₂-N⁺; 5.78 (m) (2H): the H₇'s and O-CH- ϕ 's; 6.23 (m): CH₂-CH=ΔE; 6.82 (s) (d): H₅, thiazole's; 6.89 (d)d the =C-CH=CH (ΔE)'s; 7.01 (S,d) aromatic H; 7.91 (t):

15 H₅'; 8.42 (d): H₄'; 8.76 (d): H₆'; 7.35 (l): NH₂; 9.56 to 10.0 the mobile H's.

EXAMPLE 28: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z)))1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-1-methyl-pyrrolidinium

Stage A: 1-[3-[7beta-[[[[[1-[2,5-dichloro-3,4bis-[(2-methoxyethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium iodide

The operation is carried out as in Stage H of Example 1 starting with 605 g of the product obtained as in Stage C of Example 25, using 174 mg of N-methyl pyrrolidine. After chromatography on silica (eluant methylene chloride - methanol (9-1)), 210 mg of desired product is obtained.

NMR spectrum: 400 MHz in CDCl₃

3.49 to 3.72 and 3.97: the central CH₂'s and N⁺CH₃; 3.20-3.33-3.34: the OCH₃'s; 2.6: pyrrolidine; 4.01-4.28-4.52: N⁺-CH₂; 5.25: CO₂-CH₂- ϕ and O-CH₂-O; 6.09 and 6.17 =C-CH=CH-CH₂-; 6.85 to 7.42: =C-CH=CH₂- and CO₂-CH-o₂.

Stage B: Internal salt of (6R (3-(E) 6alpha, 7beta-(Z)))1-



(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-1-methyl pyrrolidinium

5 The operation is carried out as in stage I of Example 1, starting with 200 mg of the product obtained in the previous stage. 93 mg of desired product is obtained.

NMR spectrum: DMSO 300 MHz ppm

2.09 (sl): CH₂ in position 3' 4'; approx. = 3.45 (sl) CH₂ in
10 position 2' 5'; 2.99 (s): N⁺CH₃; 3.61 (d,d) and 3.80 (d)
3.86 (d): CH₂-S; 4.10 (d): =CH-CH₂-N⁺; 5.21 (d): H₆; 5.84
(m): H₇; 5.78 (s) 5.81 (s) =C-CH=O; 6.16 (m): CH=CH-CH₂ (ΔE);
7.03 (d, J=15) CH=CH-CH₂; 7.01 (s)-7.06 (s)-6.83 (s)-
6.84 (s): H₅ of the thiazole and aromatic 1H; 9.60 (d)-9.66
15 (d) CONH-CH; 9.95 (m)-7.40 (m): mobile H's.

EXAMPLE 29: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z)))

1-(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-
20 thieno(2,3-c) pyridinium

Stage A: 1-[3-[7beta-[[[[[1-[2,5-dichloro-3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino]-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-
25 thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-thieno(2,3-c) pyridinium iodide

The operation is carried out as in Stage H of Example 1 starting with 1 g of the product obtained as in Stage C of Example 25 using 458 mg of thieno[2,3-c] pyridine. After
30 chromatography on silica (eluant methylene chloride - methanol (9-1)) 520 mg of desired product is obtained.

NMR spectrum: CDCl₃ 300 MHz

3.56 (s)-3.98 (s): the central CH₂'s and S-CH₂; 3.79 (s): $\bar{O}$ -OCH₃; 5.20 to 5.30: O-CH₂-O and CO₂-CH₂- $\bar{O}$; 4.95-5.26 (m):
35 NH-CH=CH-S; 6.33-6.48 (m) ΔE: C-CH=CH-; 6.80 to 7.40: =C-CH=CH-; 5.59 (m) to 5.80 (m): =CH-CH₂-N=; 6.80 to 7.40: aromatic H; 6.77 (sd): H thiazole; 11.50 (sl,d) NH, -N=CH-.
Stage B: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z)))



(3-(7-(((2-amino-4-thiazolyl)-((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-thieno(2,3-c) pyridinium

5 The operation is carried out as in Stage I of Example 1 starting with the product obtained in Stage A above. 114 mg of desired product is obtained.

NMR spectrum: DMSO 300 MHz

5.19 (d): H₆; 5.46 (d) N⁺CH₂-CH=; 5.79 (m):
10 -O-CH₂-P, H₇; 6.35 (m): =CH-CH₂ (E); 6.81 (s)d: H₅ thiazole;
7.00 (s): H of the phenyl; 7.07 (dJ=16): =C-CH=CH (ΔE); 7.34
(l): NH₂; 7.94 (dJ=5.5).H₃'; 8.86 (dJ=5,5): H₂'; 8.53 (d,
J=6.5)-8.73 (d, J=6.5): H₄' and H₅'; 9.91 (s,l): H₆'; 9.59
(d,d) =C-NH-CH; 9.88: mobile H.

15 EXAMPLE 30: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-7-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(4-cyano-2,3-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-thieno(2,3-b)-pyridinium

20 Stage A: [4-cyano-2,3bis[(2-methoxy-ethoxy)-methoxy]-phenyl] bromoacetic acid

440 microlitres of bromoform is added at -5°C to a mixture of 4.26 mg of lithium bromide, 598 mg of potash and 5 cm³ of water, then, drop by drop, a solution of 825 mg of
25 4-cyano-2,3bis[(2-methoxy-ethoxy)-methoxy] benzaldehyde (preparation given hereafter) in 5 cm³ of dioxane is added, and the whole is agitated for 72 hours at 0°/-5°C. The reaction mixture is poured into a mixture, agitated at 0°/-5°C, of 15 cm³ of ethyl acetate and 11 cm³ of
30 hydrochloric acid, extraction is carried out with ethyl acetate, the extracts are washed, dried then evaporated to dryness under reduced pressure, and an oil is obtained which is used as it is for the following stage.

Stage B: Diphenylmethyl [4-cyano-2,3bis-[(2-methoxy-ethoxy)-
35 methoxy]-phenyl] bromoacetate

The product obtained in Stage A is dissolved in 10 cm³ of methylene chloride and 470 mg of diphenyl diazomethane is added. Evaporation is carried out followed by chromatography



on silica (eluant cyclohexane - ethyl acetate (2-1)) and in this way 450 mg of the desired product is obtained.

NMR Spectrum:

3.31 (s), 3.37 (s): OCH_3 's; 3.43 (m)-3.61 (m)-3.77 (m)-
 5 4.05 (m) central CH_2 's; 5.18 (d)-5.25 (d)-5.29 (AB) OCH_2O 's;
 6.02 (s): $=\text{CH}-\text{X}$

Stage C: Diphenylmethyl 4-cyano-[2,3bis-[(2-methoxy-ethoxy)-methoxy]-phenyl] phthalimidoxo acetate

326 mg of N-hydroxyphthalimide and 196 mg of potassium
 10 acetate are added to a solution of 820 mg of the product
 obtained above in 13 cm^3 of dimethyl formamide. The whole
 mixture is agitated for 3 hours at ambient temperature,
 evaporated to dryness and chromatographed on silica (eluant:
 cyclohexane - ethyl acetate (1-1)), and in this way 640 mg of
 15 the desired product is obtained, used as it is for the
 following stage.

Stage D: Diphenylmethyl 4-cyano-[2,3bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-aminox acetate

The operation is carried out as in Stage D of Example 1,
 20 starting with 640 mg of the product obtained above, using 50
 microlitres of hydrazine hydrate, and 320 mg of the expected
 product is obtained.

Stage E: [[[1-[4-cyano-2,3bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-
 25 [(triphenylmethyl)-amino]-thiazol-4-yl acetic acid

The operation is carried out as in Stage E of Example 1,
 starting with 320 mg of the product obtained above, using
 234 mg of triphenylamino-thiazol-4-yl acetic acid, and 550 mg
 of the desired product is obtained.

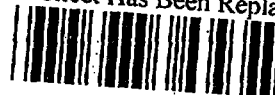
30 NMR Spectrum: CDCl_3 ppm

3.32 (s), 3.37 (s): OCH_3 's; 3.48 (t)-3.60 (t)-3.75 (m)-
 4.03 (m): central CH_2 's; 5.13 (AB)-5.24 (AB): $\text{O}-\text{CH}_2-\text{O}$'s;

6.27 (s): $\text{O}-\text{CH}-\begin{array}{l} \text{CO}_2 \\ \text{Ph} \end{array}$; 6.74 (s): H_5 thiazole;
 35

6.92 (s): $-\text{CO}_2-\text{CH}-\text{O}_2$; 7.09 to 7.32: aromatic H's;
 2.60 mobile H: NH.

Stage F: 4-methoxy benzyl 7beta-[[[[[1-[4-cyano-2,3bis-[(2-



methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-1-azabicyclo-oct-2-en-2-carboxylate

5 The operation is carried out as in Stage F of Example 1, starting with 550 mg of the product obtained above. After chromatography on silica (eluant: methylene chloride - ethyl acetate (8- 2)), 580 mg of the desired product is obtained.

10 Stage G: 4-methoxy benzyl 7beta[[[[[1-[4-cyano-2,3bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-iodo-1-propenyl]-8-oxo-5-thia-1-azabicyclo-oct-2-en-2-carboxylate

15 The operation is carried out as in Stage G of Example 1, starting with 580 mg of the product obtained above, and 615 mg of the desired product is obtained.

NMR Spectrum: CDCl₃

3.25 (s)-3.27 (s)-3.37 (s)-3.2 to 3.6 (m): OCH₃'s and CH₂S's;
3.44 (m)-3.60 (m)-3.80 (m): central CH₂'s; 4.01 (m): CH₂-I;
20 4.93 (d): H₆; 5.17 to 5.38 (m): O-CH₂-O's; 5.78 (dd)-5.86 (dd): H₇; 6.12 (m): CH=CH-CH₂; 6.43-6.46 (s): O-CH-Φ; 6.75 (s)-6.76 (s): H₅ thiazole; 6.83 to 7.45 (m): aromatic H's, HC=, CO₂-CH-Φ₂; 7.82-8.15 (d): mobile H: CONH.

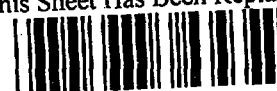
25 Stage H: 1-[3-[7beta[[[[[1-[4-cyano-2,3bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0] [oct-2-en-3-yl]-2-propenyl]-thieno(2,3-b) pyridinium iodide

30 The operation is carried out as in Stage H of Example 1, starting with 615 mg of the product obtained above and using 290 microlitres of thieno(2,3-b)pyridine.

35 After chromatography on silica (eluant: methylene chloride - methanol (9-1)), 300 mg of the desired product is obtained.

NMR Spectrum: CDCl₃ ppm

3.20 (s)-3.26 (s)-3.35 (s)-3.37 (s): the CH₃O's; 3.43 (m)-3.50 (m)-3.78 (m)-4.02 (m): central CH₂'s; 3.80-3.81 (s):



$\text{O}-\text{CH}_3$; 4.93 (d,d): H_6 ; 5.76-5.84 (m): H_7 ; 5.71-5.96 (m): $\text{C}-\text{CH}_2-\text{N}^+$; 6.40-6.45 (s): $\text{O}-\text{CH}-\text{CO}_2-\text{CH}-\text{O}_2$; 6.91 (m) $=\text{CH}-\text{CH}_2$ (ΔE); 6.73-6.74 (s): H_5 thiazole; 6.94 (m): aromatic H, $-\text{O}-\text{CH}-\text{O}_2$, $\text{CH}=\text{CH}-$ (ΔE); 7.05 to 7.45: the aromatic H's.

Stage I: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))) - 7-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(4-cyano-2,3-dihydroxyphenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-thieno-(2,3-b) pyridinium

The operation is carried out as in Stage I of Example 1, starting with 292 mg of the product obtained above, and 176 mg of the desired product is obtained.

NMR Spectrum: DMSO

5.18 (d,d): H_6 ; 5.82 (m): H_7 ; 5.68 (d): $=\text{C}-\text{CH}_2-\text{N}^+$; 5.93 (s,d): $\text{O}-\text{CH}-\text{O}_2$; 6.29 (m): $\text{CH}_2-\text{CH}=\text{CH}-$ (ΔE); 6.79 (s,d): H_5 thiazole; 6.94 (d,d), 7.03 (d): aromatic H; 7.89 (d) $\text{H}_{3'}$, 8.28 $\text{H}_{2'}$, 8.15 $\text{H}_{5'}$, 9.22 $\text{H}_{4'}$: thienopyridine; 9.54-9.69: $\text{CO}-\text{NH}-\text{CH}$; 10.33: mobile H.

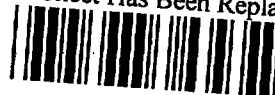
PREPARATION EXAMPLE 30: 4-cyano-2,3bis-[(2-methoxy-ethoxy)-methoxy]-benzaldehyde

Stage A: 1,4-dicyano-2,3-dihydroxyphenyl

46 g of sodium ethylate is added to a mixture of 400 cm³ of tetrahydrofuran, 50 g of dicyanoethyl sulphide and 52 g of diethyl oxalate. The mixture is agitated for one hour, concentrated under reduced pressure and the residue is taken up in 600 cm³ of water and 250 cm³ of ethyl acetate, washed with ethyl acetate and the aqueous phase is acidified with concentrated hydrochloric acid. Extraction is carried out with ethyl acetate and the extracts are evaporated to dryness under reduced pressure, dry extract obtained is taken up in 400 cm³ of nitromethane, followed by separation and washing with water. 12.46 g of the desired product is obtained. Rf 0.31 in CH_2Cl_2 -MeOH 85-15.

Stage B: 1,4-dicyano-2,3-dimethoxy phenyl

A mixture of 1 g of the product obtained above, 60 cm³ of acetone, 3.15 g of potassium acetate and 1.5 cm³ of dimethyl sulphate is agitated for 16 hours under reflux,



cooled down, filtered and evaporated to dryness under reduced pressure. The residue obtained is chromatographed on silica (eluant: methylene chloride - hexane (9-1)), and in this way 820 mg of the desired product is obtained.

5 IR Spectrum: (CHCl_3)

conjugated CN 2240 cm^{-1}

aromatic $1595\text{--}1555 \text{ cm}^{-1}$

Stage C: 4-cyano-2,3-dimethoxy benzaldehyde

900 cm^3 of toluene is added to a solution of 15.70 g of
10 the product obtained above, then 61 cm^3 of a 1.5M solution of diisobutylaluminium hydride in toluene is added over 15 minutes at -74°C , the resultant mixture is agitated for 30 minutes at $-70/-74^\circ\text{C}$, 20 cm^3 of acetone is added slowly, agitation is continued for 10 minutes and the reaction
15 mixture is poured into 700 cm^3 of 1N hydrochloric acid and 200 cm^3 of ethyl acetate, agitation is carried out for 30 minutes at ambient temperature, followed by decanting and extracting with ethyl acetate, the extracts are dried and evaporated to dryness, and 15.5 g of the desired product is
20 obtained.

4.9 g of a previous product is added to the dry extract obtained and the 20.4 g of crude product is chromatographed on silica three times, eluting with toluene - ethanol (95-5). In this way 7.5 g of the desired product is
25 collected.

NMR Spectrum: CDCl_3

4.06-4.10: the O- CH_3 's; 7.38 (d)-7.60 (d): aromatic 2H, ortho coupling; 10.42 (s): CHO.

30 Stage D: 4-cyano-2,3bis-[(2-methoxy-ethoxy)-methoxy] benzaldehyde

124 cm^3 of a molar solution of boron tribromide is added at -70°C to a solution of 5.9 g of the product obtained as above in 150 cm^3 of methylene chloride. The medium is agitated for 72 hours at ambient temperature, cooled down to
35 -30°C and 30 cm^3 of methanol is added slowly, agitation is carried out for 30 minutes followed by evaporation to dryness under reduced pressure and the residue is taken up in 200 cm^3 of ethyl acetate, washed with water, dried and evaporated to



dryness under reduced pressure, and 6.4 g of residue is obtained to which is added 190 cm³ of methylene chloride. After cooling down to 0°C, 21 cm³ of diisopropylethyl amine and 141 cm³ of methoxy ethoxy methyl chloride are added. The whole is agitated for 3 hours at ambient temperature, the reaction solution is washed with N hydrochloric acid, N soda and water, dried and evaporated to dryness. The residue is chromatographed on silica (eluant: methylene chloride - ethyl acetate (9-1)). 4.93 g of the desired product is obtained.

10 NMR Spectrum: CDCl₃

3.35-3.38 (s): the O-CH₃'s; 3.53-3.62-3.88-4.08 (m): central CH₂'s; 5.33-5.39 (s): O-CH₂-O; 7.45 (dd=J=8 and 0.5 Hz):

H₆; 7.67 (d=J=8 Hz): H₅; 10.39 (d, J = 0.5 Hz): CHO.

15 EXAMPLE 31: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))-7-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(4-cyano-2,3-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-quinolinium

20 Stage A: 1-[3-[7beta[[[[[1-[4-cyano-2,3bis-[(2-methoxyethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0] [oct-2-en-3-yl]-2-propenyl]

25 quinolinium iodide

The operation is carried out as in Stage H of Example 1, starting with 615 mg of the product obtained in Stage G of Example 30, using 200 microlitres of quinoline. After chromatography on silica (eluant: methylene chloride -

30 methanol (91-9)), 145 mg of the desired product is obtained.

Stage B: Internal salt of (6R-(3-(E)6alpha, 7beta-(Z))-7-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(4-cyano-2,3-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)

35 quinolinium

The operation is carried out as in Stage I of Example 1, starting with 230 mg of the product obtained as in the previous stage. 137 mg of the desired product is obtained.

NMR Spectrum: DMSO

- 3.30 to 3.80 (m): CH₂-S; 5.15 (d): H₆; 5.60 (dd): H₇;
 5.91-5.93 (s): O-CH₂-O; 5.90 (m): CH₂-N⁺; 6.37 (m):
 HC=CH-CH₂; 6.93 (d, J = 16) HC=CH-CH₂; 6.78-6.94 (d):
 5 H_{5'}, H_{6'}; 7.01 (s): H thiazole; 8.07-8.28 (t): H_{6''}, H_{7''};
 8.23 (dd) (J = 6 and 8 Hz): H_{3''}; 8.51 (d)-8.55 (dd):
 H_{5''} and H_{4''} or H_{8''}; 9.34 (d, J = 8 Hz) H_{4''} or H_{8''}; 9.59
 (d, J = 6 Hz): H_{2''}; 9.52 (d)-9.68 (d): HC-NH-CO.

- EXAMPLE 32: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-7-
 10 (3-(7-(((2-amino-4-thiazolyl) ((carboxy-(5-cyano-3,4-
 dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-
 oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-
 thieno(2,3b)pyridinium (RS isomer)

- Stage A: 1-[3-[7beta-[[[[[1-[5-cyano-3,4bis-[(2-methoxy-
 15 ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-
 oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-
 acetyl)-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-
 thia-1-azabicyclo[4,2,0] [oct-2-en-3-yl]-2-propenyl)-thieno-
 (2,3b)-pyridinium iodide (RS isomer)

- 20 The operation is carried out as in Stage H of Example 2
 starting with 1.5 g of the product obtained in Stage G of
 Example 2, using 1.35 g of thieno[2,3-b]pyridine.

1.22 g of the expected product is obtained (R/S mixture).

NMR Spectrum: CDCl₃ 300 MHz

- 25 3.27 (s)-3.29 (s)-3.35 (s)-3.36 (s): the C=OMe's; 3.80 (s)-
 3.81 (s): the =C-OMe's; 3.30 to 4.10: central CH₂'s and
 CH₂S's; approx. 5.00 to 5.11: the H₆'s; approx. 5.20 to 5.40:
 the O-CH₂-O's; 6.76 (s) and 6.77 (s): H₅ thiazoles; approx.
 6.90 to 7.50: COOCHO₂ and C₆H₅'s; 9.58 (d) resolved: the
 30 H_{6''}'s; 7.52 to 8.90 the other quinoline H's; 8.22 and 8.34
 (d): the =C-NH-CH's.

- Stage B: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-7-(3-
 (7-(((2-amino-4-thiazolyl) ((carboxy-(5-cyano-3,4-dihydroxy-
 phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-
 35 thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-thieno-
 (2,3b)-pyridinium (R/S mixture)

The operation is carried out as in Stage I of Example 1,
 starting with 1.2 g of the product obtained in Stage A, and



730 mg of the desired product is obtained.

NMR Spectrum: DMSO 300 MHz

5.17 (d) resolved: H_6 ; 5.41 (s): $O-CH-\phi$; 5.68 (d): $CH_2-N^{\oplus}$; 5.79 (m): H_7 ; 6.87 (m): $=C-CH=CH-CH_2$ (ΔE); 6.77 (s) and 6.79 (s): H_5 thiazole; 7.12 and 7.17: aromatic and $=C-CH=CH-$; 7.89 (d): H_3' ; 8.28 (d): H_2' ; 8.15 (dd): H_5' ; 9.09 (d): H_4' ; 9.23 (d) resolved H_6' ; 9.68 (d) resolved: NH; 10.38: mobile H; 7.39 (m): NH_2 .

EXAMPLE 33: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))) - 7-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(5-cyano-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-thieno(2,3b)pyridinium (S isomer)

240 mg of the product obtained is chromatographed on a microbondapack column, eluant: water - acetonitrile 82/18 (pH = 2.7). 45 mg of the desired product is obtained.

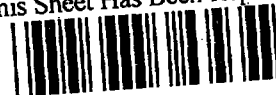
NMR Spectrum: DMSO 300 MHz

5.15 (d, $J = 5$): H_6 ; 5.40 (s): $O-CH-\phi$; 5.67 (d): $=CH-CH_2-N^{\oplus}$; 5.80 (dd, $J = 5$ and 8): H_7 ; 6.25 (m): $=CH-CH_2$; 6.79 (s): H_5 thiazole; 7.13 (m): aromatic and $=CH-CH$ (ΔE); 7.89 (d, $J = 6$) - 8.28 (d, $J = 6$): H_3' and H_2' ; 8.15 (m): H_5' ; 9.09 (d, $J = 8$): H_4' ; 9.22 (d, $J = 6$): H_6' ; 9.62 (d, $J = 8$): $=C-NH-CH$; 10.34-10.43: OH; 7.33: the NH_2 's.

EXAMPLE 34: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))) - 1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3-chloro-4,5-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)pyridinium

Stage A: [[[1-[3-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetic acid

The operation is carried out as in Stage E of Example 1, starting with 2.56 g of the product obtained in Stage D of Example 4 using 1.84 g of oxo-[2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetic acid (Belgian Patent Application No. 864,828). After chromatography on silica (eluant: methylene chloride - methanol (97-3)), 3.34 g of the desired product is obtained (R_f 0.54: CH_2Cl_2 -MeOH (9-1)).



Stage B: 4-methoxy benzyl 7beta-[[[[[1-[3-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-
5 1-azabicyclo[4,2,0]oct-2-2-carboxylate

The operation is carried out as in Stage F of Example 1, starting with 1.42 g of 4-methoxy benzyl 7beta-amino-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate hydrochloride (EP 0,333,154) and 3.34 g of
10 the product obtained in Stage A above. 2.88 g of the desired product is obtained. (Rf 0.44: CH₂Cl₂-ACOEt (8-2)).

Stage C: 4-methoxy benzyl 7beta-[[[[[1-[3-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-
15 yl]-acetyl]-amino]-3-[(Z)-3-iodo-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate

The operation is carried out as in Stage G of Example 1, starting with 1.88 g of the product obtained in Stage B. 1.75 g of the desired product is obtained (Rf 0.52 CH₂Cl₂-
20 ACOEt (8-2)).

Stage D: 1-[3-[7beta-[[[[[1-[3-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy-carbonyl]-8-oxo-5-
25 thia-1-azabicyclo[4,2,0] [oct-2-en-3-yl]-2-propenyl]-imidazo(1,2-a)pyridinium iodide

The operation is carried out as in Stage H of Example 1 starting with 876 mg of the product obtained in Stage C, using 0.308 cm³ of imidazo[1,2-a]pyridine. After
30 chromatography on silica (eluant: methylene chloride - methanol (97-3)), 450 mg of the desired product is obtained.

NMR Spectrum: CDCl₃ 300 MHz

3.25-3.29 (s)-3.35-3.36 (s): the OCH₃'s; 3.43-3.55-3.72-4.01 (m): the central CH₂'s and CH₂S's; 3.78 (s,d) ϕ -O-Me; 4.94
35 (d,d) and 5.83 (m): H₆ and H₇ (cis); 5.17 to 5.35 and 5.43 (dt): OCH₂O, CO₂CH₂- ϕ , NCH₂-CH=; 5.94 (s): O-CH- ϕ ; 6.25 (m): =CH-CH₂ (Δ E); 6.76 (s): H₅ thiazole; 6.89 -CH- ϕ ₂; 6.85 to 7.40: o-C, aromatic, CH=CH-C= (Δ E); 7.85 (d,d): H₅', H₆';



8.05 (d,d): H_4' ; 8.38 (d,d): H_3' ; 8.64 (d,d): H_1' ; 9.11 (d,d): H_7' ; 7.97 to 8.19 (d) the NH 's.

Stage E: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3-chloro-4,5-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)pyridinium

The operation is carried out as in Stage I of Example 1, starting with 489 mg of the product obtained in Stage D above, and 187 mg of the expected product is obtained.

NMR Spectrum: DMSO 300 MHz

3.62: CH_2S ; 5.29 (m): $N^{\oplus}-CH_2-CH=$; 5.34 (s,d): $O-CH-\Phi$; 6.22 (m): $=CH-CH_2 (\Delta E)$; 6.77 (s): H_5 thiazole; 6.85 (s)-6.90: $-CH-\Phi_2$, aromatic and $CH=CH-CH_2 (\Delta E)$; 7.33: NH_2 and $\Phi-C$; 5.13 and 5.75: H_6-H_7 ; 7.58 (t)-8.06 (t): $H_5'-H_6'$; 8.28 (m)-8.44 (sl): $H_3'-H_2'$; 8.96 (d): H_4' ; 9.59 (d,d): H_7' ; 9.29 (sl)-13.03-13.66: mobile H.

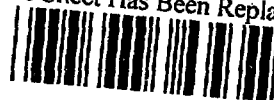
EXAMPLE 35: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3-chloro-4,5-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-4-methylthio pyridinium

Stage A: 1-[3-[7beta-[[[[[1-[3-chloro-4,5bis-[(2-methoxyethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy-carbonyl)-8-oxo-5-thia-1-azabicyclo[4,2,0] [oct-2-en-3-yl]-2-propenyl]-4-methylthio pyridinium iodide

The operation is carried out as in Stage H of Example 1, starting with 875 mg of the product obtained in Stage C of Example 34 using 385 mg of 4-S-methyl thiopyridine. After chromatography on silica (eluant: methylene chloride - methanol (97-3 then 90-10)), 389 mg of the desired product is obtained.

NMR Spectrum: $CDCl_3$ 300 MHz

2.61-2.63: $S-CH_3$; 3.25-3.28-3.36-3.37: the OCH_3 's; 3.78 (s)-3.79 (s): the ΦOMe 's; 3.44-3.58-3.72-4.01: the central CH_2 's and CH_2-S 's; 4.97 (d,d): H_6 ; 5.05 to 5.35: OCH_2O , $CO_2CH_2-\Phi$,



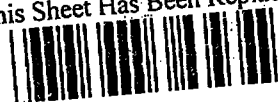
5 Stage B: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3-chloro-4,5-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-4-methylthio pyridinium

NMR Spectrum: DMSO 300 MHz

EXAMPLE 36: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3-chloro-4,5-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl))-2-propenyl) quinolinium

30 The operation is carried out as in Stage H of Example 1, starting with 900 mg of the product obtained in Stage C of Example 34, using 0.366 cm³ of quinoline. After chromatography on silica (eluant: methylene chloride - methanol (97-3)), 384 mg of the desired product is obtained.

3.24 (s)-3.29 (s)-3.36 (s,d): the O-CH₃'s; 3.78 (s): $\bar{\Phi}$ -OMe; 3.40 (m)-3.58 (m)-3.71 (m)-4.00 (m): the central CH₂'s; 5.07 and 5.26: CO₂CH₂ $\bar{\Phi}$ and O-CH₂-O; 4.94 (s): H₆;



5.04 (m): H₇; 6.00 to 6.20: =CH-CH₂-N[⊕]; 5.99 (s) resolved: Φ -CH-O; 6.38 (m)-6.55 (m): =CH-CH₂ (Δ E); 6.75 (s) resolved: H₅ thiazole; 6.85 to 7.40: aromatics and =C-CH=CH-CH₂; 7.91 (m)-8.08 to 8.26 (m)-8.42 (m)-8.95 (m)-10.49 (d): quinoline and mobile H.

Stage B: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))) -1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3-chloro-4,5-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) quinolinium

The operation is carried out as in Stage I of Example 1, starting with 384 mg of the product obtained in the previous stage. 192 mg of the desired product is obtained.

NMR Spectrum: DMSO 300 MHz

15 3.35 to 3.70: CH₂S; 5.11 (d, J = 5)-5.15 (d, J = 5): H₆; 5.32 (o)-5.34 (s): Φ -CH-CO; 5.74 (m): H₇; 5.89 (m): =CH-CH₂-N[⊕]; 6.36 (m): =CH-CH₂; 6.75 to 7.00 (m): other CH=, aromatic and H₅ thiazole; 7.33: mobile H's, 8.07-8.26-8.52-20 9.33: quinoline; 9.57-9.29-9.60-9.91 (m) 13.00 (eq)-13.70 (m): mobile H's.

EXAMPLE 37: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))) -1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3,4-dihydroxy-2-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-25 5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-quinolinium

Stage A: 1alpha-(hydroxy) (3,4bis-[(2-methoxy-ethoxy)-methoxy] phenyl acetic acid

The operation is carried out as in Stage A of Example 1, 30 starting with 15.5 g 2-fluoro-3,4bis-[(2-methoxy-ethoxy)-methoxy]-benzaldehyde, preparation given hereafter. 20.7 g of the desired product is obtained, used as it is for the following stage.

Stage B: Diphenylmethyl [2-fluoro-(3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl)-hydroxy acetate

The operation is carried out as in Stage B of Example 1, starting with 20.6 g of the product obtained in Stage A above, using 9.08 g of diphenyl diazomethane. After



chromatography on silica (eluant: cyclohexane - ethyl acetate (7-3)), 3.2 g of the desired product is obtained.

IR Spectrum: CHCl_3

OH 3600 cm^{-1} and 3530 cm^{-1}

5 C=O 1733 cm^{-1}

Aromatics 1620 - 1603 - 1588 - 1498 cm^{-1}

Stage C: Diphenylmethyl [2-fluoro-(3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-phthalimidoxy acetate

The operation is carried out as in Stage C of Example 1
10 starting with 3.2 g of the product obtained above. After chromatography on silica, (eluant: methylene chloride - acetone (95-5)), 2.9 g of the desired product is obtained.

IR Spectrum: CHCl_3

C=O 1794 - 1754 - 1737 cm^{-1}

15 Aromatics 1619 - 1597 - 1498 cm^{-1}

Stage D: Diphenylmethyl aminoxy-[2-fluoro-(3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-acetate

The operation is carried out as in Stage D of Example 1, and 1.05 g of the desired product is obtained.

20 IR Spectrum: CHCl_3

O-NH₂ 3340 cm^{-1}

C=O 1744 cm^{-1}

starting NH₂ + 1620 - 1580 - 1498 cm^{-1}

Aromatic

25 Stage E: [[1-[2-fluoro-(3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenyl)-amino]-thiazol-4-yl acetic acid

The operation is carried out as in Stage E of Example 1, starting with 1.05 g of the product obtained above, using
30 0.777 g of oxo-[2-[(triphenylmethyl)-amino]-thiazol-4-yl acetic acid (Belgian Application No. 864,828), and 1.74 g of the desired product is obtained, used as it is for the following stage.

35 Stage F: 4-methoxy benzyl 7beta-[[[[1-[2-fluoro-(3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-yl]-acetyl]-amino]-3-[(2)3-chloro-1-propenyl-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate



The operation is carried out as in Stage F of Example 1, starting with 1.74 g of the product obtained above, using 0.784 g of 4-methoxy benzyl 7beta-amino-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate, and after chromatography on silica (eluant: methylene chloride - ethyl acetate (8-2)), 1.77 g of the desired product is obtained, used as it is for the following stage.

Stage G: 4-methoxy benzyl 7beta-[[[[1-[2-fluoro-(3,4bis-
10 [(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-yl]-acetyl]-amino]-3-[(Z)-3-iodo-1-propenyl-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate

The operation is carried out as in Stage G of Example 1, starting with 840 mg of the product obtained above, and 814 mg of the desired product is obtained. Rf 0.45 (CH₂Cl₂-ACOEt (8-2)).

Stage H: 1-[3-[7beta-[[[[1-[2-fluoro-(3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl
20 quinolinium iodide

The operation is carried out as in Stage H of Example 1, starting with 814 mg of the product obtained above, using 0.337 cm³ of quinoline. After chromatography on silica (eluant: methylene chloride - methanol (98-2), 368 mg of the expected product is obtained.

NMR Spectrum: CDCl₃ 300 MHz

30 3.31 to 3.35: the O-CH₃'s; 3.45 (d, J = 16): CH₂S; 3.51-3.81-3.94: the central CH₂'s; 3.79 (s)-3.80 (s): the

Φ-O-CH₃'s; 4.91 (m): H₆; 5.15 to 5.30: CO-CH₂-Φ, O-CH₂-O;
5.83: H₇; 6.05 (ml): =C-CH₂-N[⊕]; 6.31 and 6.35 (m): the
35 O-CH₂-Φ's; 6.49 (ml): -CH₂-CH-CH; 6.72-6.75: H₅ thiazole;
6.87 to 7.40: aromatics, CO₂-CH-Φ₂, CH=CH-C; 7.90 to 8.20: quinoline, 8.40 (d,d): H₄'; 8.90 (d,d): H₂'.

Stage I: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))) -1-(3-



(7-(((2-amino-4-thiazolyl) ((carboxy-(3,4-dihydroxy-2-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) quinolinium

- 5 The operation is carried out as in Stage I of Example 1, starting with 357 mg of the product obtained above, and 176.9 mg of the desired product is collected.

NMR Spectrum: DMSO 300 MHz

- 5.14: the H₆'s; 5.41 (s) resolved: O-CH- ϕ ; 5.70 to 5.90: CH₂N⁺ and H₇; 6.54 (d, J = 8.5) and 6.70 to 6.80: aromatic and H₅ thiazole; 6.37 (m): -CH=CH-CH₂ (ΔE); 6.97 (d,d): -CH=CH-CH₂; 7.34 (l): NH₂; 8.07 to 9.58: quinoline; 9.16-9.49-9.69: mobile H's.

- PREPARATION OF EXAMPLE 37: 2-fluoro-3,4bis-[(2-methoxy-ethoxy)-methoxy] benzaldehyde

Stage A: 2-fluoro-3,4bis-dihydroxy benzaldehyde

- A mixture of 74.3 g of hexamethylene tetramine and 125 cm³ of trifluoroacetic acid is agitated for 2 hours at 80°C, then a solution of 34 g of 3-fluorocatechol in 130 cm³ of trifluoroacetic acid is added and agitation is continued for 2 hours at 80°C and for 16 hours at ambient temperature. The trifluoroacetic acid is distilled off under reduced pressure, the residue is taken up in water and neutralized by the addition of potassium carbonate until a pH of 7 is achieved. After filtration and extraction with ether, the extracts are dried and evaporated to dryness under reduced pressure, and 39 g of product is obtained, used as it is for the following stage.

- Stage B: 2-fluoro-3,4bis-[(2-methoxy-ethoxy)-methoxy] benzaldehyde

- 261 cm³ of N-ethyl diisopropylamine is added to a solution of 39 g of the product obtained above in 390 cm³ of acetonitrile, the resultant mixture is cooled down to -5°C and 113 cm³ of (2-methoxyethoxy) methyl chloride is added slowly, agitation is carried out for 16 hours at -5°C. The acetonitrile is evaporated off, the residue is taken up in 250 cm³ of methylene chloride then washed with N hydrochloric acid, with water, with N soda then with water, followed by



drying, filtering and evaporating to dryness under reduced pressure. 49.5 g of product is obtained which is chromatographed on silica (eluant: methylene chloride - acetone (96-4)) and 10.4 g of the desired product is obtained.

NMR Spectrum: CDCl_3 200 MHz

3.37-3.38 (s): the OCH_3 's; 5.24 (s)-5.37 (s): the $\text{O}-\text{CH}_2-\text{O}$'s; 3.56 (m)-3.83 (m)-4.00 (m): the central CH_2 's; 10.26 (s): CHO; 7.09 (dd $J = 1.5-9$): H_4 ; 7.59 (dd $J = 7.5-9$): H_3

10 EXAMPLE 38: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3,4-dihydroxy-2-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)pyridinium

15 Stage A: 1-[3-[7beta-[[[[[1-[2-fluoro-(3,4bis-[(2-methoxyethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl-
20 imidazo(1,2-a)pyridinium iodide

The operation is carried out as in Stage H of Example 1, starting with 704.5 g of the product obtained in Stage G of Example 37, using 0.25 cm^3 of imidazo(1,2-a)pyridine. After chromatography on silica (eluant: methylene chloride -
25 methanol (95-5)), 275 mg of the expected product is obtained.

NMR Spectrum: CDCl_3 400 MHz

3.32-3.33 (s): the $-\text{OCH}_3$'s; 3.46-3.47 (d): CH_2S ; 3.78 (m): the $\text{O}-\text{CH}_3$'s; 3.53-3.81-3.95: the central CH_2 's; 4.82: H_6 ; 5.78: H_7 ; 5.00 to 5.32: $\text{OCH}_2\text{O}-$, $\text{CO}_2\text{CH}_2\text{O}$, $=\text{CH}-\text{CH}_2\text{N}^+$; 5.40: 30 the other H of CH_2N^+ ; 6.32-6.37 (s): $\text{O}-\text{CH}-\text{O}$; 6.28 (m): $\text{CH}_2-\text{CH}=\text{CH}$ (ΔE); 6.74 (s)-6.76 (s): H_5 thiazole; 6.8 to 7.40: $\text{O}-\text{C}$, COCH_2-O_2 , aromatic, $=\text{CH}-\text{CH}=\text{CH}$ (ΔE); 7.84 (m) to 9.13 (5H) imidazo pyridinium.

35 Stage B: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3,4-dihydroxy-2-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)pyridinium



The operation is carried out as in Stage I of Example 1, starting with 275 mg of the product obtained in the previous stage, and 116.2 mg of the desired product is obtained.

NMR Spectrum: DMSO 300 MHz

- 5 3.60: CH₂S; 5.11-5.14 (d): H₆; 5.75 (dd)-5.79 (dd):
H₇; 5.30 (m): CH₂N⁺; 5.64-5.65 (s): O-CH₂-; 6.25 (m):
CH=CH-; 6.91-6.93 (d): CH=CH-CH₂; 6.57-6.74 (m): H₅" and
H₆"; 6.77 (s)-6.79 (s): H₅ thiazole; 7.57-8.05 (dd):
H₅' and H₆'; 8.22 (d)-8.98 (d,d): H₄', H₇'; 8.30-8.46
10 (m): H₂', H₃'; 9.48 (d)-9.55 (d): CH-NH-C=O; 7.32-9.13-
9.64 (m): mobile H's.

EXAMPLE 39: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-difluoro-3,4-
15 dihydroxyphenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-
oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-
imidazo(1,2-a)pyridinium

Stage A: Methyl [2,5-difluoro-3,4bis-dihydroxy]-phenyl-hydroxy acetate

- 20 The operation is carried out as in Stage B of Example 1, starting with 3.30 g of [2,5-difluoro-3,4bis-dihydroxy] phenyl hydroxy acetic acid and 2.77 g of diphenyl diazomethane. After chromatography on silica (eluant: cyclohexane - acetone (6-4)), 3.75 g of the desired product
25 is obtained.

IR Spectrum:

Complex absorptions OH/NH region

C=O 1752 cm⁻¹

Aromatic 1630-1535-1485 cm⁻¹

- 30 Stage B: Diphenylmethyl [2,5-difluoro-3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-hydroxy acetate

2.96 g of diisopropylethylamine and 10 cm³ of methylene chloride are added to a solution of 4.21 g of the product obtained as in Stage A in 45 cm³ of methylene chloride.

- 35 The mixture is cooled down to -5°C and 2.71 g of methoxyethoxymethyl chloride and 5 cm³ of methylene chloride are added slowly. The whole is agitated for 30 minutes at -5°C and poured into 0.1N hydrochloric acid (30 cm³),



followed by decanting and washing with a saturated solution of sodium hydrogen carbonate (pH 8), drying, filtering and concentrating to dryness under reduced pressure. 6.9 g of product is obtained which is chromatographed on silica (eluant: methylene chloride - ethyl acetate (85-15)), and 3.577 g of the desired product is obtained.

IR Spectrum: CHCl_3

approx. 3600 cm^{-1} (f) - 3530 cm^{-1} complex: OH

1734 cm^{-1} : C=O

10 $1624-1600-1589-1492\text{ cm}^{-1}$: aromatic.

NMR Spectrum ^{19}F

- 140.6 F^2 , $J_{\text{F1-F4}} = 14$, $J_{\text{F1H5}} = 6.5$

- 135.2 F^5 , $J_{\text{F4-H5}} = 11$.

Stage C: Diphenylmethyl 2,5-difluoro-3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-phthalimidoxy acetate

The operation is carried out as in Stage C of Example 1, starting with 4.419 g of product obtained as above, using 1.41 g of hydroxyphthalimide and 4.12 g of triphenylphosphine. After chromatography on silica (eluant: methylene chloride - acetone (97-3) then cyclohexane - ethyl acetate (1-1)), and 2.56 g of the desired product is obtained.

NMR Spectrum: CDCl_3 300 MHz

3.33 (s)-3.36 (s): OCH_3 ; 3.50 (m)-3.91 (m): $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$;

5.20 (A,B system)-5.26 (A,B system): OCH_2O ; 6.26 (s):

O
|
 $-\text{CH}-\text{CO}_2$; 6.94 (s): $\text{CO}_2\text{CH Ph}_2-$; 7.15-7.3 (m)-7.76 (m): aromatic H's.

Stage D: Diphenylmethyl aminoxy-[2,5-difluoro-3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl] acetate

The operation is carried out as in Stage D of Example 1, starting with 2.537 g of the product obtained above, using 0.21 cm^3 of hydrazine hydrate. After chromatography on silica (eluant: cyclohexane - ethyl acetate (1-1)), 1.67 g of the desired product is obtained.

NMR Spectrum ^{19}F : CDCl_3

135.5 (dd) F_5

139.8 (dd) F_2

This Sheet Has Been Replaced



J_{F5-F2} = 14

J_{F5-H6} = 10.5

J_{F2-H6} = 6

Stage E: [[[[1-[2,5-difluoro-3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl] acetic acid

The operation is carried out as in Stage E of Example 1, starting with 909 mg of the product obtained in the previous stage, using 652 mg of oxo[2-[(triphenylmethyl)-amino]-thiazol]-4-yl] acetic acid (described in the Belgian Application No. 864,828). After chromatography on silica (eluant: methylene chloride - methanol (96-4)), 1.138 g of the desired product is obtained.

IR Spectrum:

15 =C-NH + approx. 3405 cm⁻¹
 general absorption OH/NH
 C=O 1740 - 1727 cm⁻¹
 C=N
 Aromatic + 1615 - 1597 - 1526 - 1495 cm⁻¹
 20 Heteroaromatic

Stage F: 4-methoxy benzyl 7beta-[[[[[1-[2,5-difluoro-3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-2-carboxylate

The operation is carried out as in Stage F of Example 1, starting with 1.12 g of the product obtained above. After chromatography on silica (eluant: methylene chloride - ethyl acetate (9-1)), 979 mg of the expected product is obtained.

30 NMR Spectrum: CDCl₃ 400 MHz

3.08-3.20-3.40: CH₂S; 3.34-3.35 (s): the C-O-CH₃'s; 3.54-3.92 (m): the central CH₂'s; 3.80-3.81 (s): Ar-O-CH₃; 3.70-4.00: CH=CH₂Cl; 4.95-5.03: H₆ cephalo; 5.16-5.25: OCH₂O, CO₂CH₂Ar; 5.75 (m): =CH-CH₂ (ΔZ); 5.85-6.00: H₇ cephalo, 35 =CH-CH₂; 6.26 (d, J = 11)-6.35 (m): C-CH=CH-CH₂Cl, ArCHO; 6.70-6.78 (m): H₅ thiazole; approx. 7.00 to 7.35: aromatic H's; 7.80-8.30: NH-CH.

Stage G: 4-methoxy benzyl 7beta-[[[[[1-[2,5-difluoro-3,4bis-

[(2-methoxy-ethoxy)-methoxyl-phenyl]-2-oxo-2-(diphenyl-methoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(2)-3-iodo-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate

5 The operation is carried out as in Stage G of Example 1, starting with 969 mg of the product obtained above. 725 mg of the expected product is obtained.

Stage H: 1-[3-[7beta-[[[1-[2,5-difluoro-3,4bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-imidazo(1,2-a)pyridinium iodide

15 The operation is carried out as in Stage H of Example 1, starting with 717 mg of the product obtained above, using 313 mg of imidazo(1,2-a)pyridine. After chromatography on silica (eluant: methylene chloride - methanol (95-5)), 350 mg of the desired product is obtained.

NMR Spectrum: CDCl₃ 400 MHz

20 3.32-3.33-3.34 (s): C-O-CH₃; 3.53-3.92 (m): central CH₂'s; 3.30-3.80: CH₂S; 3.79-3.80 (s): Ar-O-CH₃; 4.94 (dd): H₆ cephalo; 5.80-5.88 (d) after exchange: H₇ cephalo;

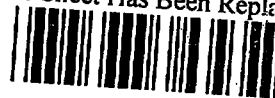
(td)-6.31 (td): =CH-CH₂N⁺; 6.31 (s)-6.37 (s): Ar-CH-CO₂; 25 7.84-8.18 (d): CO-NH-CH; 7.86-8.02 (m): heterocycle; 8.32 to 9.18: imidazopyridine; 6.75-7.45 (m): aromatic, H₅ thiazole, CH=CH-CH₂, CO₂-CH- $\overset{\text{O}}{\parallel}$ CH₂; 5.18-5.30-5.43: CH₂-N⁺,

OCH₂O, ArCH₂- $\overset{\text{O}}{\parallel}$ OC.

30 Stage I: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-difluoro-3,4-dihydroxyphenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)pyridinium

35 The operation is carried out as in Stage I of Example 1, starting with 344 mg of the product obtained above. 170 mg of the expected product is collected.

NMR Spectrum: DMSO 300 MHz



5.16 (dd): H_6 cephalo; 5.77 (m): H_7 cephalo; 5.29 (m):

$CH_2-N^{\oplus}$; 5.64 (s,d): $Ar\overset{O}{CH}$; 6.70 (dd): aromatic H coupled with 2F; 6.80 (s,d): H_5 thiazole; 6.87 (d,d): $CH=CH-CH_2$ (ΔE):
 5 7.33 (sl): NH_2 ; 8.28-8.44 (m): H_2' and H_3' ; 7.18 to 8.96 (4H) imidazopyridine; 9.03-9.63 (d): $C-NH-CH$; 9.84 other mobile H's.

PREPARATION OF EXAMPLE 39: 2,5-difluoro-3,4-dihydroxy]-phenyl hydroxy acetic acid

10 Stage A: 2,5-difluorophenol

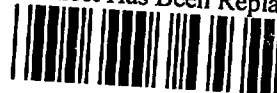
325 cm^3 of n-butyl lithium in a 1.6M solution of hexane is added at $-65^\circ C$ to a solution of 62.19 g of 1,4-difluorobenzene in 500 cm^3 of tetrahydrofuran. The resultant mixture is agitated for 2 hours 30 minutes then a solution of 53.8 g
 15 of trimethylborate in 250 cm^3 of ether is added over 30 minutes at $-65^\circ C$. The whole is agitated for one hour 30 minutes, allowing the temperature to rise to $-15^\circ C$. Agitation is carried out for 15 minutes and 350 cm^3 of 10% hydrochloric acid is added. After decanting, the residue is
 20 washed with water, dried and evaporated to dryness under reduced pressure. 63.5 g of product is obtained which is taken up in 400 cm^3 of toluene. After heating to $108^\circ C$ 180 cm^3 of 30% hydrogen peroxide is added drop by drop, heating is carried out for 2 hours at $90^\circ C$, the medium is
 25 left to cool down and is filtered. The filtrate is decanted, the organic phase is washed with water then with a 10% solution of ferrous ammonium sulphate then with water, the organic phase is extracted twice with 300 cm^3 of 2N soda. Acidification is carried out with concentrated hydrochloric
 30 acid, followed by extraction with methylene chloride, the extracts are dried and evaporated to dryness under reduced pressure.

NMR Spectrum: $CDCl_3$

5.21 (sl): OH; 6.55 (dddd): H_4 , $JH_4-H_2 = 9$, $JH_4-F_2 = 3.5$,
 35 $JH_4-H_6 = 3$, $JH_4-F_5 = 8$; 6.74 (ddd): H_6 , $JH_6-H_4 = 3$, $JH_6-F_2 = 7$; 7.01 (ddd): H_3 , $JH_3-H_4 = 9$, $JH_3-F_2 = 10$, $JH_3-F_5 = 5$.

Stage B: 2,5-difluoroanisole

35.0 g of the product obtained above, 350 cm^3 of



acetone, 44.6 g of potassium carbonate and 40.7 g of dimethyl sulphate (neutralized on potassium hydrogen carbonate). The mixture is left to return to ambient temperature, water is added, extraction is carried out with ether, the extracts are washed, dried and concentrated to dryness under reduced pressure, and 39.8 g of the desired product is obtained.

NMR Spectrum: ^{19}F CDCl_3 188 MHz

119.1 (dddd) F_5
 10 144.1 (dddd) F_2 $J_{\text{F}_2-\text{F}_5} = 15$
 $J_{\text{F}_5-\text{H}_3} = 5$ $J_{\text{F}_2-\text{H}_3} = 10.5$
 $J_{\text{F}_5-\text{H}_4} = 8$ $J_{\text{F}_2-\text{H}_4} = 3.5$
 $J_{\text{F}_5-\text{H}_6} = 10$ $J_{\text{F}_2-\text{H}_6} = 7$

Stage C: 3,6-difluoroguaiacol

15 The operation is carried out as in Stage A above, starting with 55.15 g of the product obtained in Stage B above, using 220 cm^3 of n-butyl lithium, 1.6 M in hexane, 36.4 g of trimethyl borate and 200 cm^3 of 30% hydrogen peroxide. 44.7 g of the desired product is obtained.

20 NMR Spectrum: CDCl_3 200 MHz

4.02 (d, $J = 2$) OCH_3
 5.56 (sl) OH
 6.57 (ddd) H_4
 6.75 (dt) H_5
 25 $J_{\text{H}_5-\text{H}_4} = 9.5$; $J_{\text{H}_5-\text{F}_3} = 5$; $J_{\text{H}_5-\text{F}_6} = 9.5$; $J_{\text{H}_4-\text{F}_3} = 10.5$;
 $J_{\text{H}_4-\text{F}_6} = 5$.

Stage D: 3,6-difluorocatechol

The operation is carried out as in Stage B of Preparation 2 starting with 21.15 g of the product obtained in Stage C above, using 260 cm^3 of a molar solution of boron tribromide. 17.62 g of the desired product is obtained.

Stage E: 2,5-difluoro-3,4-dihydroxy] phenyl hydroxy acetic acid

7.69 g of soda in solution in 80 cm^3 of water is added at $+10^\circ\text{C}$ to a solution of 11.7 g of the product obtained in the above stage and 7.37 g of monohydrated glyoxylic acid in 40 cm^3 of water. The mixture is agitated for 30 minutes at 10°C then for 3 hours 30 minutes at ambient temperature.



0.74 g of monohydrated glyoxylic acid is added and agitation is carried out for one hour at ambient temperature.

Concentrated hydrochloric acid is added until a pH of 1 is achieved. Extraction is carried out with ethyl acetate, the
5 extracts are dried, filtered and concentrated to dryness under reduced pressure. 17.0 g of the desired product is obtained.

IR Spectrum: Nujol

Complex absorption OH/NH region

10 C=O 1700 cm^{-1}

Aromatic 1640 - 1612 - 1526 - 1488 cm^{-1}

EXAMPLE 40: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))) -1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2-chloro-4,5-dihydroxy-3-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-
15 carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)-pyridinium

Stage A: [2-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-3-methoxy] benzaldehyde and 2-chloro-3,4bis-[(2-methoxy-ethoxy)-methoxy]-5-methoxy benzaldehyde

20 2.17 g of 3,4bis-[(2-methoxy-ethoxy)-methoxy]-5-methoxy benzaldehyde is agitated with 21.7 cm^3 of methylene chloride and 4 cm^3 of a solution of 1.76 g of calcium hypochlorite (at 65%) in 10 cm^3 of water, agitation is continued for 20
25 minutes at 0/+5°C, extraction is carried out with methylene chloride, the extracts are washed with water, dried and evaporated to dryness under reduced pressure. 2.34 g of a mixture of isomers (7/3) is obtained.

NMR Spectrum: CDCl_3 250 MHz

3.37: the OCH_3 's; 3.7 to 4.1: the central CH_2 's; 5.29 to 5.33: OCH_3 ; 3.91: OCH_3 ; 7.54 and 7.30: H_6 ; 10.38 and 10.40: CHO.
30

Stage B: [2-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-3-methoxy] styryl carboxylate and corresponding 5-methoxy isomer

2.97 cm^3 of triethylamine then a solution of 6.72 g of
35 the mixture of isomers obtained in the previous stage, in solution in 60 cm^3 of tetrahydrofuran, are added to a mixture, agitated at +5/+10°C, of 2.162 g of lithium bromide with 60 cm^3 of tetrahydrofuran and 4.03 cm^3 of



triphenylphosphoroacetate. The resultant mixture is agitated for 16 hours at ambient temperature and concentrated to dryness under reduced pressure. The residue is taken up in methylene chloride, washed with 1N hydrochloric acid then
 5 with water, dried and evaporated to dryness under reduced pressure, and 8.8 g of the expected product (mixture of 2 isomers 7/3) is obtained.

NMR Spectrum: CDCl_3 250 MHz

1.35 (t,d) 4.28 (q,d): CO_2Et ; 3.37-3.38: the OCH_3 's; 3.57
 10 (m)-3.84 to 4.04 (m): the central CH_2 's; 3.88 (s)-3.86 (s): OCH_3 ; 5.24 to 5.28: the OCH_2 's; 6.34 (d)-6.38 (d): $\text{CH}=\text{CH}-\text{CO}_2$; 8.03-8.05 (d): $-\text{CH}=\text{CH}-\text{CO}_2$; 6.93-7.30: aromatic H.
 Stage C: [2-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-3-methoxy] styrol and corresponding 5-methoxy isomer

15 11.7 cm^3 of a molar solution of diisobutyl aluminium hydride in hexane is added to a solution cooled down to -70°C of 2.83 g of the isomer mixture, obtained in the previous stage, in 20 cm^3 of methylene chloride. The resultant mixture is agitated for 20 minutes at -70°C and 2 cm^3 of
 20 water is added. Agitation is carried out for 30 minutes at 20°C , followed by drying, filtering and bringing to dryness under reduced pressure, and 1.95 g of the desired product (mixture of isomers 7/3) is obtained.

NMR Spectrum: CDCl_3 250 MHz

25 3.37-3.38: the OCH_3 's; 3.54-3.84-3.97 (m): the central CH_2 's; 3.87 (s): OCH_3 (in position 3); 4.34 (d): $-\text{CH}_2-\text{OH}$; 6.29 (t): $\text{CH}=\text{CH}-\text{CH}_2$; 6.93 (d): $-\text{CH}=\text{CH}-\text{CH}_2$; 7.19 (s): aromatic H.
 Stage D: [2-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-3-methoxy] (1,2-epoxy) styrol (isomer A) and [2-chloro-3,4bis-
 30 [(2-methoxy-ethoxy)-methoxy]-5-methoxy] (1,2-epoxy) styrol (isomer B)

A solution of 2.79 g of metachloroperbenzoic acid in 50 cm^3 of methylene chloride is added at $+5^\circ\text{C}$ to a solution of 4.78 g of the isomer mixture obtained in Stage C, in 50 cm^3
 35 of methylene chloride. The resultant mixture is agitated for 16 hours at 20°C and 20 cm^3 of a saturated solution of sodium hydrogen carbonate and 50 cm^3 of methylene chloride are added, followed by decanting, washing with water, drying and



evaporating to dryness under reduced pressure. The residue is chromatographed on silica (eluant: methylene chloride - acetone 85-15), and 2.12 g of isomer A product and 716 mg of isomer B are obtained.

5 NMR Spectrum: CDCl_3 250 MHz

3.07 (t,d): $\text{CH}-\text{CH}_2-\text{CH}_2$; 3.37-3.38 (s): the OCH_3 's; 3.57-3.83-3.97 (m): the central CH_2 's; 3.88 (s): OCH_3 (in position 3);

10 3.83-4.06 (ddd): $-\text{CH}_2\text{OH}$; 4.19 (d, $J = 2$): $-\text{CH}-\text{CH}_2$; 5.2-5.26 (s): the OCH_2 's; 1.94 (d,d, $J = 5.5-7.5$): OH.

Stage E: Diphenylmethyl [[2-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-3-methoxy]-phenyl] chloro acetate

a) Opening of the epoxide

15 A solution prepared at $+5^\circ\text{C}$ of 1.306 g of copper chloride, 20 cm^3 of tetrahydrofuran and 1 g of lithium chloride is agitated for 5 minutes then, 2.055 g of the isomer A epoxide (obtained in Stage D above) in solution in 10 cm^3 of tetrahydrofuran, is added to this solution at 20°C ,
20 agitation is carried out for 5 hours at 20°C , 10 cm^3 of water is added, followed by decanting, washing, drying and evaporating to dryness under reduced pressure. 2.09 g of intermediate diol is obtained.

b) Oxidation

25 9 cm^3 of water and 3.79 g of sodium periodate and 50 mg of hydrated ruthenium chloride (with 35/40% Ru) are added at $+5^\circ\text{C}/+10^\circ\text{C}$ to a solution of 2.035 g of the diol above with 6 cm^3 of carbon tetrachloride and 6 cm^3 of acetonitrile, the resultant mixture is agitated for one hour at 20°C , 20 cm^3 of
30 methylene chloride and 10 cm^3 of water are added, followed by decanting, washing, drying and evaporating to dryness under reduced pressure. 1.8 g of the desired product is obtained.

c) Esterification:

35 790 mg of diphenyl diazomethane is added to a solution of 1.8 g of the above product, in 20 cm^3 of methylene chloride. The mixture is agitated for one hour at 20°C and concentrated to dryness under reduced pressure. After chromatography on silica (eluant: methylene chloride (9-1)),



1.525 g of the desired product is obtained.

NMR Spectrum: CDCl_3 250 MHz

3.34-3.37: the OCH_3 's; 3.47-3.57-3.74-3.97 (m): the central CH_2 's; 3.87 (s): 3-methoxy; 5.12-5.24: the OCH_2 's;

5

5.94: $\text{C}-\overset{\text{Cl}}{\underset{|}{\text{CH}}}-\text{CO}_2-$; 6.89 (s): CO_2-CH

Stage F: Diphenylmethyl aminoxy [[2-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-3-methoxy] acetate

a) Phthalimidoxylation

10 1.48 g of the product obtained in the previous stage, 7.5 cm^3 of dimethylformamide with 363 mg of potassium acetate and 604 mg of N-hydroxyphthalimide are agitated together for 5 hours.

b) Hydrazinolysis

15 180 μl of hydrazine hydrate is added at 20°C , agitation is carried out for 20 minutes at 20°C , the phthalylhydrazide is separated out, washed with acetonitrile and the organic fractions are evaporated to dryness. After chromatography on silica (eluant: methylene chloride - ethyl acetate (3-1)),

20 1.11 g of the desired product is obtained.

NMR Spectrum: CDCl_3 250 MHz

3.33-3.37 (s): the OCH_3 's; 3.44-3.57-3.71-3.97 (m): the central CH_2 's; 3.88 (s): 3-methoxy; 5.09 and 5.23: the OCH_2 's;

25 5.73 (s): $-\overset{\text{O}}{\underset{|}{\text{CH}}}-\text{CO}_2-$; 5.84: NH_2 ; 6.91 (s)-6.94: $\text{CO}_2\text{CH}-\text{C}_2$; 7.07 to 7.35: aromatics.

Stage G: [[1-[2-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-3-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl] acetic acid

30 The operation is carried out as in Stage E of Example 1, starting with 1.1 g of the product obtained in Stage F above, using 835 mg of oxo-[2-[(triphenylmethyl)-amino]-thiazol-4-yl] acetic acid (described in the Belgian Application No. 35 864,828). The product is not isolated and treated as it is for the following stage.

Stage H: 4-methoxy benzyl 7beta-[[[[1-[2-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-3-methoxy]-phenyl]-2-oxo-2-



(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate

- 5 The operation is carried out as in Stage F of Example 1, starting with the crude product obtained in Stage G above, using 781 mg of 4-methoxy benzyl 7beta-amino-3-[(Z)-3-chloro-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate hydrochloride (EP 0,333,154). After chromatography on silica, (eluant: methylene chloride - ethyl acetate (9-1)), 1.36 g of the desired product is obtained.

NMR Spectrum: CDCl₃ 300 MHz

- 3.25-3.29-3.36-3.37-3.81: the OCH₃'s; 3.2 to 4.0: -SCH₂-, C-CH₂Cl, the central CH₂'s; 4.94 (d) to 5.25: CO₂CH₂, NH-CH-CH-S, the OCH₂O's; 5.75 (m): -CH=CH-CH₂ (ΔZ); 5.9 (m): NH-CH-CH-S; 6.28 (d): -CH=CH-CH₂ (ΔZ); 6.8 to 7.15: aromatics + H₅ thiazole.

- Stage I: 4-methoxy benzyl 7beta-[[[[[1-[2-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-3-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-3-[(Z)-3-iodo-1-propenyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylate

- 25 The operation is carried out as in Stage G of Example 1, starting with 1.33 g of the product obtained above. After chromatography on silica (eluant: methylene chloride - ethyl acetate (9-1)), 990 mg of the desired product is obtained.

NMR Spectrum: CDCl₃ 400 MHz

- 3.24 (s)-3.26 (s)-3.35 (s)-3.36 (s): the 2 OCH₃'s; 3.2 to 4.0 (m): -SCH₂-C and the central CH₂'s; 3.8 (s,d) 3.85-3.88 (s): the 2 =C-OCH₃'s; 4.9 to 5.07 (m) 5.18 to 5.25 (m): the O-CH₃'s; 4.97-5.02 (d): CH-CH-S-; 5.87 (ddd) NH-CH-CH-S-; 6.51-6.53 (s): =NH-O-CH=; 6.79-6.80 (s): H₅ thiazole; 6.84 to 7.37 (m): aromatics, other CH=C and CO₂-CH- Φ ₂; 7.78-8.3 (d):

- 35 0
-C-NH-CH

Stage J: 1-[3-[7beta-[[[[[1-[2-chloro-4,5bis-[(2-methoxy-ethoxy)-methoxy]-3-methoxy]-phenyl]-2-oxo-2-(diphenyl-



methoxy)-ethyl]-oxyl-iminol [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-imidazo(1,2-a)pyridinium iodide

- 5 The operation is carried out as in Stage H of Example 1, starting with 735 mg of the product obtained above, using 260 microlitres of imidazo(1,2-a)pyridine, and 750 mg of the expected product is obtained.

NMR Spectrum: CDCl₃ 300 MHz

- 10 3.14 to 3.38: -S-CH₂-C≡, the -C-O-CH₃'s; 3.78-3.79-3.85-3.87: =C-OCH₃; 3.3 to 4.0: the central CH₂'s; 4.9 to 5.02: NH-CH-CH-S-; 5.8 (m): =NH-CH-CH-S; 6.27 (m): -CH=CH-CH₂ (ΔE); 6.53-6.54: =N-O-CH; 6.76 to 7.3: CO₂-CH-Φ₂, -CH=CH-CH₂ and the aromatics; 7.6 to 9.10: imidazopyridine.

- 15 Stage K: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2-chloro-4,5-dihydroxy-3-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)pyridinium

- 20 The operation is carried out as in Stage I of Example 1, starting with 750 mg of the product obtained above, and 463 mg of the desired product is obtained.

NMR Spectrum: DMSO 300 MHz

- 5.12 (d,d): =NH-CH-CH-S-; 5.28 to 5.3: =CH-CH₂-N⁺; 5.74 (m): =NH-CH-CH-S; 5.75: =N-O-CH-; 6.23 (m): =C-CH=CH-; 6.78 (s): H₅ thiazole; 6.84 (d, J = 15): =C-CH=CH- (ΔE); 7.36: NH₂; 7.58 to 8.93: imidazopyridine; 9.55: mobile H's.

- EXAMPLE 41: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2-chloro-3,4-dihydroxy-5-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)pyridinium

- 35 Operating as in Stages E to K of Example 40, starting with isomer B obtained in Stage D of Example 40, the desired product was obtained.

NMR Spectrum: DMSO 300 MHz

3.5 to 3.7 (m): S-CH₂-C≡; 3.73-3.74 (s): OCH₃; 5.18: NH-CH-CH-S; 5.29: -CH₂N⁺; 5.79 (ddd): NH-CH-CH-; 5.83-5.85



(s): =N-O-CH=; 6.25 (m): CH=CH-; 6.6 (s)-6.78 (s)-6.82 (s): aromatic, H₅ thiazole; 6.88 (d,d) J=16): -CH=CH-CH₂ (ΔE); 7.58 to 8.96 (6H) imidazopyridine.

EXAMPLE 42: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2-chloro-4,5-dihydroxy-3-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) quinolinium

Stage A: 1-[3-[7beta-[[[[[1-[2-chloro-4,5bis-[(2-methoxyethoxy)-methoxy]-3-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] [2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl] quinolinium iodide

The operation is carried out as in Stage J of Example 40 starting with 700 mg of the product obtained in Stage I of Example 40, using 282 microlitres of quinoline. 706 mg of the desired product is obtained.

Stage B: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2-chloro-4,5-dihydroxy-3-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) quinolinium

The operation is carried out as in Stage K of Example 40, starting with 690 mg of the product obtained in Stage A above. 434 mg of the desired product is obtained.

NMR Spectrum: DMSO 300 MHz

3.4 to 3.8 (m): S-CH₂-; 3.65-3.73 (s): ≡C-OCH₃; 5.1-5.14 (d): -NH-CH-CH-; 5.73: -NH-CH-CH-; 5.75 (s): =N-O-CH=; 5.89 (m): -CH=CH-CH₂; 6.75-6.76-6.78-6.79 (s): H₅ thiazole, aromatic H; 6.35 (m): -CH=CH-C (ΔE); 6.97 (dl J = 16): -CH=CH-C (E); 8.07 to 9.58 (7H) quinoline; 9.53: -NH-CH-CH-; 7.35-9.24-13.0: mobile H's.

EXAMPLE 43: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2-chloro-3,4-dihydroxy-5-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) quinolinium

Stage A: 1-[3-[7beta-[[[[1-[2-chloro-3,4-dihydroxy-5-methoxy]-phenyl]-2-oxo-2-(diphenylmethoxy)-ethyl]-oxy]-imino] 2-[(triphenylmethyl)-amino]-thiazol-4-yl]-acetyl]-amino]-2-[(4-methoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-
5 [4,2,0]oct-2-en-3-yl]-2-propenyl] quinolinium iodide

The operation is carried out as in Stage J of Example 40 starting with 450 mg of the product obtained in Stage E of Example 41, and 440 mg of the desired product is obtained.

Stage B: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-1-(3-
10 (7-(((2-amino-4-thiazolyl) ((carboxy-(2-chloro-3,4-dihydroxy-5-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) quinolinium

The operation is carried out as in Stage K of Example
15 40, starting with 440 mg of the product obtained in Stage A above, and 256 mg of the desired product was obtained.

NMR Spectrum: DMSO 300 MHz

3.48 to 3.84 (m): S-CH₂; 3.71-3.73 (s): =C-OCH₃; 5.17 (d,d):
-NH-CH-CH-C; 5.8 (m): -NH-CH-CH-; 5.82-5.84 (s): N-O-CH=;
20 5.88 (m): -CH=CH-CH₂-; 6.38 (d,m): CH=CH-CH₂; 6.97 (d,d) dJ =
16): -CH=CH- (ΔE); 6.59 (s)-6.77 (s)-6.81 (s): H₅ thiazole,
aromatic; 8.06 to 9.58: quinoline (7H); 9.53-9.64 (d): C-NH-;
O

7.54 (m)-9.25 (m)-13.70 (m): mobile H's.

25 EXAMPLE 44: Internal salt of (6R-(3-(E)6alpha, 7beta-(Z(S*))))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3,4-dihydroxy-5-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) quinolinium

30 10 mg of the product obtained in Example 3 is chromatographed on a MICROBONDAPACK C₁₈ column (eluant: water (at pH 2.7 with trifluoroacetic acid) - acetonitrile (containing 0.025% trifluoroacetic acid) 86-14), and 1.5 mg of expected (S) isomer and 1.5 mg of (R) isomer are obtained.

35 NMR Spectrum: DMSO 400 MHz

3.40 to 3.60 (m): CH₂S; 5.13 (d, J = 5): H₆; 5.77 (dd, J = 5 and 8): H₇ (d, after exchange); 5.32 (s) $\overline{\text{H}}$ -CH-O; 5.87 (m): CH₂N⁺; 6.31 (m): CH=CH-CH₂; 7.00 (d, J = 16): CH=CH-CH₂;



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6.77 (s): H₅ thiazole; 6.72 (m): H_{4'} H_{6'}; 7.25 (s): mobile 2H's; 8.06 (dd, J = 7 and 8) and 8.28 (dd) J = 7 and 9): H_{6''}, H_{7''}; 8.22 (dd J = 6 and 8): H_{3''}; 8.50 (d, J = 8) and 8.55 (d, J = 9): H_{4''} and H_{5''}; 9.33 (d, J = 8): H_{8''}; 9.57 (d, J = 6): H_{2''}.

EXAMPLE 45: Internal salt of (6R-(3-(E)6alpha, 7beta-(Z(R*))) -1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3,4-dihydroxy-5-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) quinolinium

R isomer isolated during the chromatography in Example 44.

NMR Spectrum: DMSO 400 MHz

3.39 to 3.75 (m): CH₂S; 5.16 (d, J = 5): H₆; 5.32 (s) $\bar{\text{P}}\text{-CH-O}$; 5.74 (dd, J = 5 and 8) H₇; 5.88 (m): CH₂N⁺; 6.36 (dt): CH=CH-CH₂; 6.99 (d, J = 16): CH=CH-CH₂; 6.73 (m) (3H): H₅ thiazole and H_{2'} and H_{6'}; 7.26 (s): mobile 2H's; 8.07 (t, J = 8) and 8.28 (t, J = 8): H_{6''} and H_{7''}; 8.22 (dd, J = 6 and 8): H_{3''}; 8.50 (d, J = 8) and 8.55 (d, J = 9): H_{5''} and H_{4''}; 9.33 (d, J = 8): H_{8''}; 9.59 (d, J = 6): H_{2''}; 9.59 (d, m): CONH-CH; 9.14 (s): mobile 1H.

EXAMPLE 46: Internal salt of [[6R-[3-(E)6alpha, 7beta-(Z)(S*)]] -1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-4-(methylthio) pyridinium corresponding to the separation of the isomers of the product obtained in Example 14

NMR Spectrum: DMSO 300 MHz

2.71 (s): $\bar{\text{P}}\text{-SMe}$; approx. 3.57: =C-CH₂S; 5.15 to 5.25: H₆ and N⁺-CH₂-CH=; approx. 5.80 (sl): O-CH-o and H₇; 6.25 (m): =CH-CH₂; approx. 6.98 (d): =C-CH=CH; 6.81 (s): H₅ thiazole; 7.00: H₆; 7.32 (l) 2H: NH₂; 7.96-8.70 (d): H pyridine; 9.58 (d): C-NH-CH; 9.84 (s)-9.92 (s): the OH's; 13.28-13.78: the O

other mobile H's.

EXAMPLE 47: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)(S*)) -1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-

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(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)pyridinium

NMR Spectrum: DMSO 300 MHz

- 5 5.15 (d, J = 5): H₆; 5.29 5 (m): CH₂-N[⊕]; 5.79 (s): O-CH-; 5.79 (dd, d after exch.): H₇; 6.24 (dt, J = 15.5 and 6.5): =CH-CH₂, approx. 3/4 H; 6.81 (s)-6.99 (s): H₅ thiazole, aromatic 1H; 6.86 (d, J = 15.5) =C-CH=CH; 7.58 (t)-8.06 (t): H_{5'}, H_{6'}; 8.20 (d): H_{7'}; 8.96 (d): H_{4'}; 8.28 (d)-8.44 (d): H_{2'}, H_{3'}; 9.56 (d): CH-NH-CO; 7.35 (m): approx. 2H; 9.87 (sl): 1H; 9.96 (sl): 1H; mobile H.

EXAMPLE 48: Internal salt of (6R-(3-(E)6alpha,

7beta(Z)(R*)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-

- 15 amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)pyridinium

NMR Spectrum: DMSO 300 MHz

- 5.15 (d, J = 5): H₆; 5.27 (m): CH₂-N⁺; 5.78 (d, J = 5): H₇; 5.81 (s): O-CH-, approx. 1.7 H; 6.24 (dt, J = 16 and 6): =CH-CH₂, approx. 0.85 H; 6.84 (s)-6.99 (s): approx. 1.7 H, H₅ and aromatic 1H; 6.85 (d, J = 16): =C-CH=CH; 7.57 (dd, J = 6 and 7): H_{5'}; 8.05 (dd, J = 7 and 8.5): H_{6'}; 8.17 (d, J = 8.5): H_{7'}; 8.94 (d, J = 6): H_{4'}; 8.26 (d, J = 2)-8.42 (d, J = 2): H_{2'}, H_{3'}.

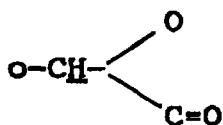
- 25 Operating in a similar manner to that described in the previous examples, starting with appropriate intermediates, the following products were obtained:

EXAMPLE 49: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))

- 30 (3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,3-dihydroxy-4-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) quinolinium

NMR Spectrum: DMSO 300 MHz

- 3.52 (d)-3.70: CH₂S; 3.72-3.74: C-OMe; 5.15 (d, resolved): H₆; 5.57 (dd)-5.80 (m): H₇; 5.83-5.87:



; 5.70 to 6.0: CH₂-N[⊕]; 6.42 (d, resolved)-6.75 (d,



resolved) aromatic H; 6.40 (m)-6.99 (d, resolved, J approx. 16): ethylene (ΔE); 6.78-6.82: H₅ thiazole; 8.07 (t)-8.26: H_{3'}, H_{6'}, H_{7'}; 8.53 (d)-8.56 (d)-9.34 (d): H_{4'}, H_{5'}; 9.53 (d): H_{8'}; 9.45 (d)-9.56 (d): NHC: 7.45 and 8.84: mobile H.

5

O.

EXAMPLE 50: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-7-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,3-dihydroxy-4-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-thieno-(2,3-b) pyridinium

10

NMR Spectrum: DMSO 400 MHz

3.54 (d) approx. 3.68 (d): =C-CH₂S; 5.18 (m): the H_{6'}'s; 5.76 (m)-5.96 (m): H₇; 5.72 (s)-5.74 (s): the Φ -OMe's; 5.67 (m): CH₂-CH=; 5.83 (s)-5.87 (s): C-CH- Φ ; approx. 6.80 (s)

15

resolved: the H thiazoles; 6.42 (m)-6.73 (m): H₅, H₆; 6.30 (m)-7.15 (d) resolved: =C-CH=CH-CH (ΔE); 7.88 (d): H_{3'}; 8.29 (d): H_{2'}; 8.15 (m) H_{5'}; 9.08 (d): H_{4'}; 9.22 (d): H_{6'}; 9.44 (d)-9.53 (d): =C-NH-CH; 7.44 (m)-8.60 to 8.90: mobile H's.

EXAMPLE 51: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,3-dihydroxy-4-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)pyridinium

20

NMR Spectrum: DMSO 300 MHz

25 7.35 (m)-8.69 (m)-8.82 (m): mobile H's; 3.52 (m) approx. 3.70 (m): CH₂S; 3.74 (s)-3.75 (s): CH₃O- Φ ; 5.15 (d, resolved): H₆; 5.74 (dd, d after exch.)-5.81 (dd, d after exch.): H₇; 5.29 (m): CH₂-N⁺: 5.83 (s)-5.86 (s): O-CH- Φ ; 6.25 (m)-6.90 (d, resolved): CH=CH-CH₂; 6.43 (d): H_{6'}; 6.72 to 6.80 (m): H_{5'} and H₅ thiazole; 7.58 (t): H_{5''}; 8.06 (t): H_{6''}; 8.21 (d)-8.96 (d): H_{4''}, H_{7''}; 8.29 (sl): H_{3''}; 8.44 (sl): H_{2''}; 9.44 (d)-9.54 (d): CO-NH-CH.

30

EXAMPLE 52: Internal salt of (6R-(3-(E)6alpha, 7beta(Z)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,3,4-trihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)pyridinium

35

NMR Spectrum: DMSO (300 MHz)



- 3.54 (m): CH_2S ; 5.15 (d): H_6 ; 5.82 (m): H_7 and $\text{O}-\text{CH}-\text{O}$;
 5.28 (m): $=\text{CH}-\text{CH}_2-\text{N}^+$; 6.26 (m): $\text{CH}=\text{}$; 6.5 to 7.4 (m): aromatic
 6H; 7.58 (t): H_5' ; 8.06 (t): H_6' ; 8.20 (d), 8.96 (d): H_4' ,
 H_7' ; 8.29 (sl)-8.44 (sl): H_2' , H_3' ; 9.41 (d)-9.53 (d):
 5 CO-NH-CH; 8.68 (m)-9.27 (m)-7.36 (m): mobile H's.

EXAMPLE 53: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,3-difluoro-4,5-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a)pyridinium

NMR Spectrum: DMSO (300 MHz)

- approx. 3.70: CH_2S ; 5.09 (d)-5.14 (d): H_6 ; 5.29 (m): CH_2-N^+ ;
 5.58 (s)-5.59 (s): $\text{O}-\text{CH}-\text{O}$; 5.72 (m): H_7 ; 6.22 (m):
 $\text{CH}=\text{CH}-\text{CH}_2$; 6.68 (m): H_6' ; 6.77 (s)-6.78 (s): H_5 thiazole;
 15 6.85 (d, J=16): $=\text{C}-\text{CH}=\text{CH}-$; 7.58 (t)-8.06 (t): H_5'' , H_6'' ; 8.19
 (d)-8.96 (d): H_4'' , H_7'' ; 8.28 (m)-8.44 (sl): H_2'' , H_3'' ; 7.32
 (m): 9.5 to 9.9 (m): mobile H's.

EXAMPLE 54: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,3-difluoro-4,5-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)quinolinium

NMR Spectrum: DMSO (300 MHz)

- 3.45 (m): CH_2S ; 5.09 (d)-5.14 (d): H_6 ; 5.72 (m): H_7 ;
 25 5.58 (s)-5.59 (s): $\text{O}-\text{CH}-\text{CO}$; 5.88 (m): CH_2-N^+ ; 6.34 (m):
 $\text{CH}=\text{CH}-\text{CH}_2$; 6.94 (d, J=16)-6.97 (d, J=16): $\text{CH}=\text{CH}-\text{CH}_2$; 6.67
 (m): H_6'' ; 6.76 (s)-6.77 (s): H_5 thiazole; 8.07 (m)-8.26 (m)-
 8.53 (m)-9.34 (d)-9.57 (d): quinoline; 7.32 (m)-9.5 to 9.9
 (m): mobile H's.

EXAMPLE 55: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-difluoro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)pyridinium

NMR Spectrum: DMSO (300 MHz)

- 3.58 (m): CH_2S ; 5.18 (d,d): H_6 ; 5.79 (m): H_7 ; 5.41
 (sl): CH_2N^+ ; 5.64 (s)-5.65 (s): $\text{O}-\text{CH}-\text{C}=\text{}$; 6.30 (m):
 $\text{CH}=\text{CH}-\text{CH}_2$; 7.02 (dd, J=16): $\text{CH}=\text{CH}-\text{CH}_2$; 6.70 (dd): H_6' ;



6.78 (s)-6.80 (s): H₅ thiazole; 8.18 (m): H₃", H₅";
 8.63 (m): H₄"; 9.05 (d): H₂", H₆"; 9.35 (d)-9.62 (d):
 CO-NHCH; 7.33 (m)-9.80 (m): mobile H.

EXAMPLE 56: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))) -1-
 5 (3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-difluoro-3,4-
 dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-
 oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-
 6,7-dihydro-5H-pyrindinium

NMR Spectrum: DMSO (300 MHz)

10 2.24 (m): CH₂ in position 6'; 3.14 (m)-3.37 (m): CH₂ in
 position 5' and 7'; 3.56 (m): CH₂S; 5.15 (d)-5.18 (d): H₆;
 5.79 (m): H₇; 5.33 (d): =CH-CH₂-N[⊕]; 5.63 (s)-5.65 (s):
 O-CH- Φ ; 6.23 (m): CH=CH-CH₂; 6.85 (d)-6.88 (d, J=16):
 CH=CH-CH₂; 6.71 (dd, J = 10.5 and 6): H₆"; 6.78 (s)-6.81 (s):
 15 H₅ thiazole; 7.91 (m): H₃'; 8.43 (d, J=8): H₄'; 8.76 (d,
 J=6): H₂'; 9.54 (d)-9.63 (d): CH-NH-CO; 7.35 (m)-9.85 (m):
 mobile H's.

EXAMPLE 57: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))) -1-
 (3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-difluoro-3,4-
 20 dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-
 oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)
 quinolinium

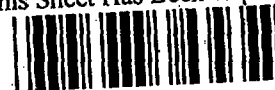
NMR Spectrum: DMSO (300 MHz)

3.4 to 3.7 (m): CH₂S; 5.15 (dd): H₆; 5.79 (m): H₇; 5.62
 25 (s)-5.64 (s): -O-CH- Φ ; 5.89 (m): =CH-CH₂-N[⊕]; 6.37 (m):
 CH=CH-CH₂; 6.97 (dd, J=15.5): CH=CH-CH₂; 6.76 (s)-6.80
 (s): H₅ thiazole; 6.70 (dd, J = 11 and 6): H₆"; 8.07 (m)-8.27
 (m)-8.53 (m)-9.34 (d): quinoline; 9.58 (d): H₂; 9.53 (d)-9.62
 (d): CO-NH-CH; 7.30 (m)-9.83 (m): mobile H.

30 **EXAMPLE 58:** Internal salt of (6R-(3-(E)6alpha, 7beta(Z))) -3-
 (3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-difluoro-3,4-
 dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-
 oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)
 thiazolium

35 NMR Spectrum: DMSO (300 MHz)

3.50 to 3.75 (m): CH₂S; 5.16 to 5.19 (d): H₆; 5.81 (m):
 H₇; 5.33 (m): =CH-CH₂-N[⊕]; 5.63 (s)-5.65 (s): O-CH- Φ ; 6.26
 (m): CH=CH-CH₂; 6.96 (dd, J=16): CH=CH-CH₂; 6.71 (dd,



J=6 and 11): H_6'' ; 6.78 (s)-6.81 (s): H_5 thiazole; 8.37 (m)-8.51 (m): H_4' , H_5' ; 10.20 (sl): H_2' ; 7.30 (m): 9.5 to 9.9 (m)-13.25 (m)-13.75 (m): mobile $H's$.

EXAMPLE 59: Internal salt of (6R-(3-(E)6alpha, 7beta(Z))) 2-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-difluoro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) isoquinolinium

NMR Spectrum: DMSO (300 MHz)

10 3.50 to 3.75 (m): CH_2S ; 5.18 (dd): H_6 ; 5.80 (m): H_7 ; 5.53 (d): $=CH-CH_2-N^+$; 5.63 (s)-5.65 (s): $O-CH-\Phi$; 6.37 (m): $CH=CH-CH_2$; 7.09 (dd, J=15.5): $CH=CH-CH_2$; 6.71 (dd, J=11 and 6): H_6'' ; 6.78 (s)-6.80 (s): H_5 thiazole; 8.09 (t)-8.28 (t): H_6' , H_7' ; 8.37 (d)-8.53 (d): H_5' , H_8' ; 8.61 (d)-8.74 (d): H_3' , H_4' ; 10.06 (s): H_1' ; 7.35 (m)-9.84 (m): mobile $H's$; 9.56 (d)-9.65 (d): $CH-NH-CO$.

EXAMPLE 60: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) 1-(3-(7-(((2-amino 4-thiazolyl) ((carboxy (2,5-difluoro 3,4-dihydroxy phenyl) methoxy) imino) acetyl) amino) 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl) 2-propenyl) 4-(methylthio) pyridinium

NMR spectrum: (DMSO) 300 MHz

2.71 (s): $OSMe$; 3.54 (d), 3.66 (d): $CH-S$; 5.17 (m): the $H_6's$; 5.22 (s,1): $=CH-CH_2-N^+$; 5.63 (s) resolved: $OCH-\Phi$; 5.79 (m): the $H_7's$; 6.26 (m) $CH=CH-CH_2$ E, 6.98 (d, J=16) resolved: $CH=CH-CH_2$; 6.71 (dd, J=6 and 11): H_6'' ; 6.78 (s) resolved: H_5 thiazole; 7.30 (s,1): NH_2 ; 7.95 (d), 8.70 (d): $N-S$; 9.62-9.67 (d), 9.85: the mobile $H's$; 19.49.

EXAMPLE 61: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) 4-(3-(7-(((2-amino 4-thiazolyl) ((carboxy (2,5-difluoro 3,4-dihydroxy phenyl) methoxy) imino) acetyl) amino) 2-carboxy 8-oxo 1-azabicyclo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl) 2-propenyl) 2-amino thiazolo (5,4-b)-pyridinium

NMR spectrum: (DMSO) 300 MHz

35 ~3.60: CH_2 ; 5.19 (d) resolved: H_6 ; 5.81 (d): H_7 ; 5.47 (d): $=CH-CH_2-N^+$; 5.63 (s), 5.65 (s): $O-CH-\Phi$; 6.21 (m): $CH=CH-CH_2$; 7.08 (d) resolved J=16: $CH=CH-CH_2$; 6.78 (s): H_5 thiazole; 6.70 (dd, J=6 and 11): H_6'' ; 7.83 (m): H_5' ; 8.29 (d, J=8):



H₄'; 8.64 (d, J=6): H₆'; 9.55 (d), 9.64 (d): CH-NH-CO; 8.73 (s), 9.84 (m), 7.33 (m): mobile H.

EXAMPLE 62: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) 7-(3-(7-(((2-amino 4-thiazolyl) ((carboxy (2,5-difluoro 3,4-dihydroxy phenyl) methoxy) imino) acetyl) amino) 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl) 2-propenyl) thieno (2,3-b)-pyridinium.

NMR spectrum: (DMSO)

3.4 to 3.8: CH₂S; 5.18 (d, resolved): H₆; 5.81 (dd, resolved): H₇; 5.66 (m) 3H=CH-CH₂-N⁺ and O-CH- ϕ ; 6.30 (m): CH=CH-CH₂; 7.14 (d, resolved, J=16): CH=CH-CH₂; 6.70 (dd, J=6 and 11): H₆"; 6.77 (s), 6.81 (s): H₅ thiazole; 7.89 (d, J=6): H₃'; 8.28 (d, J=6): H₂'; 8.16 (m): H₅'; 9.09 (d, J=8): H₄'; 9.23 (d, J=6): H₆'; 9.55 (d), 9.65 (d): CO-NH-CH; 7.32 (m), 9.83 (m): mobile H's.

EXAMPLE 63: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) 7-(3-(7-(((2-amino 4-thiazolyl) ((carboxy (3,4-dihydroxy 2,5-difluorophenyl) methoxy) imino) acetyl) amino) 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl) 2-propenyl) imidazo (2,1-b)-thiazolium

EXAMPLE 64: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) 3-(3-(7-(((2-amino 4-thiazolyl) ((carboxy (3,4-dihydroxy 2,5-difluorophenyl) methoxy) imino) acetyl) amino) 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl) 2-propenyl) 1-methyl 1H-benzimidazolium

EXAMPLE 65: Internal salt of (6R-(3-(E) 6alpha, 7beta-(Z))) 7-(3-(7-(((2-amino 4-thiazolyl) ((carboxy (3,4-dihydroxy 2,5-difluorophenyl) methoxy) imino) acetyl) amino) 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl) 2-propenyl) 4-methyl thieno (2,3-b)-pyridinium

In addition to the products described above in the examples, the following products constitute products which can be obtained according to the methods of the invention:



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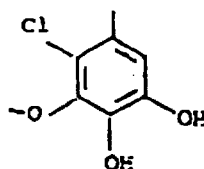
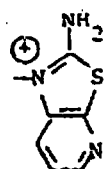
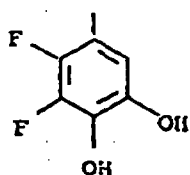
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Φ	Z	Φ	Z
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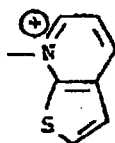


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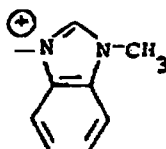


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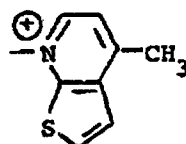


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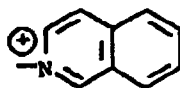


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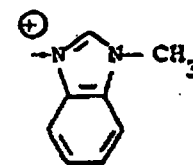


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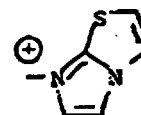


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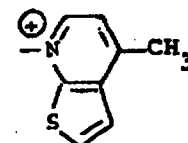


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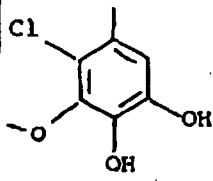
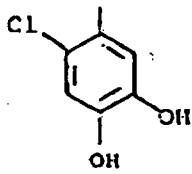
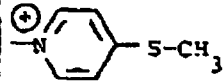
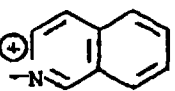
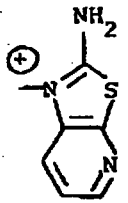
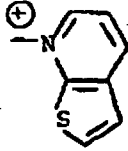
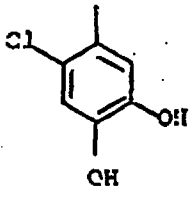
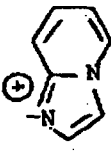
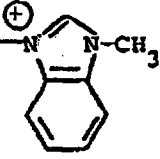
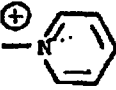
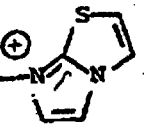
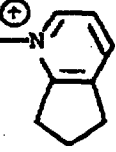
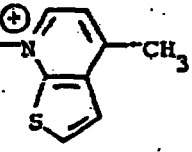
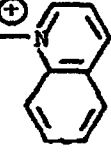
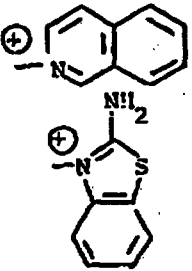
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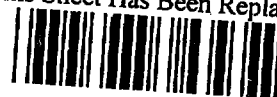
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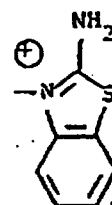
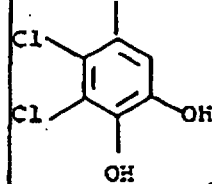
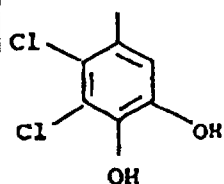
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Φ	Z	Φ	Z
			
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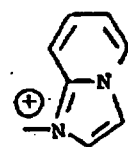
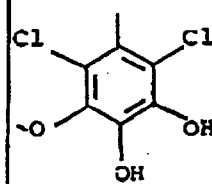
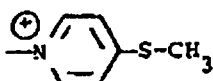


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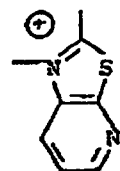
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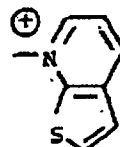


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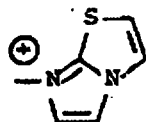


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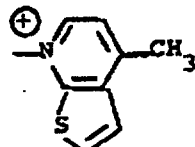


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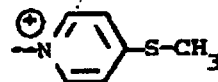


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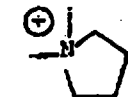


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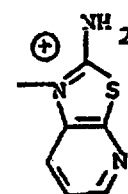


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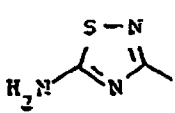
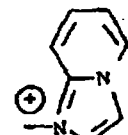
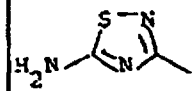
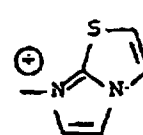
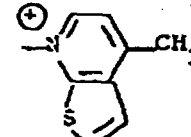
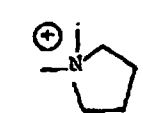
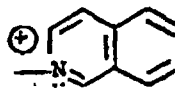
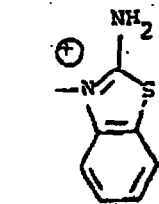
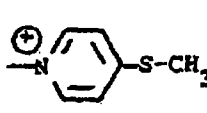
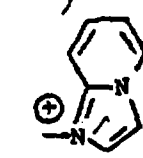
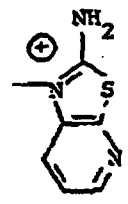
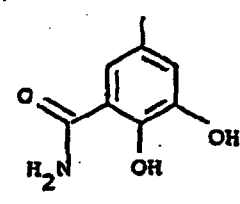
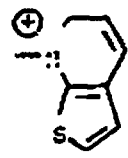
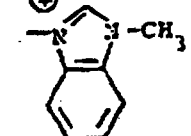
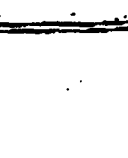
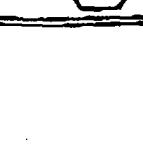


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	"		"	
10	"		"	
	"		"	
15	"		"	
	"		"	
20	"		"	
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25	"		"	
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30			"	
	"		"	
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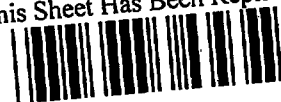
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15	"		"	
20			"	
25	"		"	
30	"		"	
35	"		"	



	Φ	Z	Φ	Z
5				
	"		"	
10	"		"	
15	"		"	
20	"		"	
	"			
25	"			
	"		"	
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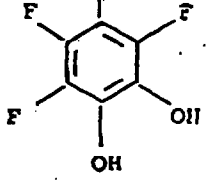
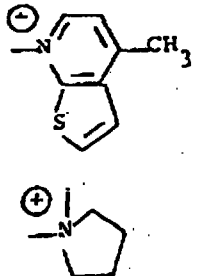
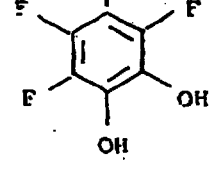
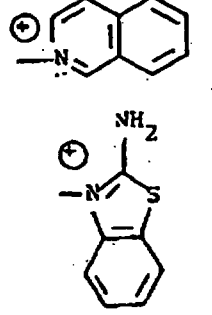


	Φ	Z	Φ	Z
5				
10	"			
15	"		"	
20	"		"	
25	"		"	
30	"		"	
35	"		"	



	Φ	Z	Φ	Z
5				
	"		"	
10	"		"	
15	"		"	
20	"		"	
25	"		"	
30			"	
35	"		"	



Φ	Z	Φ	Z
			

EXAMPLE 66: The following preparations for injections were made:

- Product of Example 2 500 mg
- Sterile aqueous excipient, sufficient quantity
- for 5 cm³

PHARMACOLOGICAL STUDY OF THE PRODUCTS OF THE INVENTION

In vitro activity, method of dilutions in liquid medium.

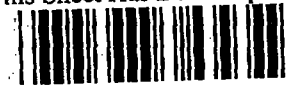
A series of tubes is prepared in which an equal quantity of sterile nutritional medium is distributed. Increasing quantities of the product to be studied is distributed into each tube, then each tube is seeded with a bacterial strain. After incubation in a heating chamber for twenty-four hours at 37°C, the growth inhibition is evaluated by transillumination, which allows the minimal inhibitory concentrations (M.I.C.) to be determined, expressed in µg/cm³ (TABLE I).

In vitro activity, method of dilutions in solid medium.

A series of dishes is prepared in which an equal quantity of sterile nutritional medium is distributed, containing increasing quantities of the product to be studied then each dish is seeded with several bacterial strains.

After incubation in a heating chamber for 24 hours at 37°C, the growth inhibition is evaluated by the absence of any bacterial development, which allows the minimal inhibitory concentrations (M.I.C.) to be determined, expressed in micrograms/cm³.

The results are expressed in M.I.C.90 which is the minimum concentration of antibiotic allowing the growth of



the strains studied to be inhibited by 90% (TABLE II).

The following results were obtained:

MIC 35 30 25 20 15 10 5

TABLE I

Product of Example	Enterobacteria Cloacae 1321E	Staphylococci aureus SG 5 11	Proteus A 235	Pseudomonas Aeruginosa 1771 m
9	0.04	0.08	0.04	0.3
3	0.08	0.15	0.04	0.6
1	0.08	0.15	0.04	0.6
2	0.15	0.30	0.02	0.3

TABLE II

MIC 90

Product of Example	oracillin-sensitive penicillin-resistant Staphylococci aureus (20 strains)	Enterobacteria producing cephalosporinases (20 strains)	Enterobacteria producing β lactamase with enlarged spectrum (16 strains)	Pseudomonas Aeruginosa (39 strains)
40	2.5	0.3	2.5	0.08
43	0.3	2.5	1.2	1.2
28	5	0.3	10	0.08



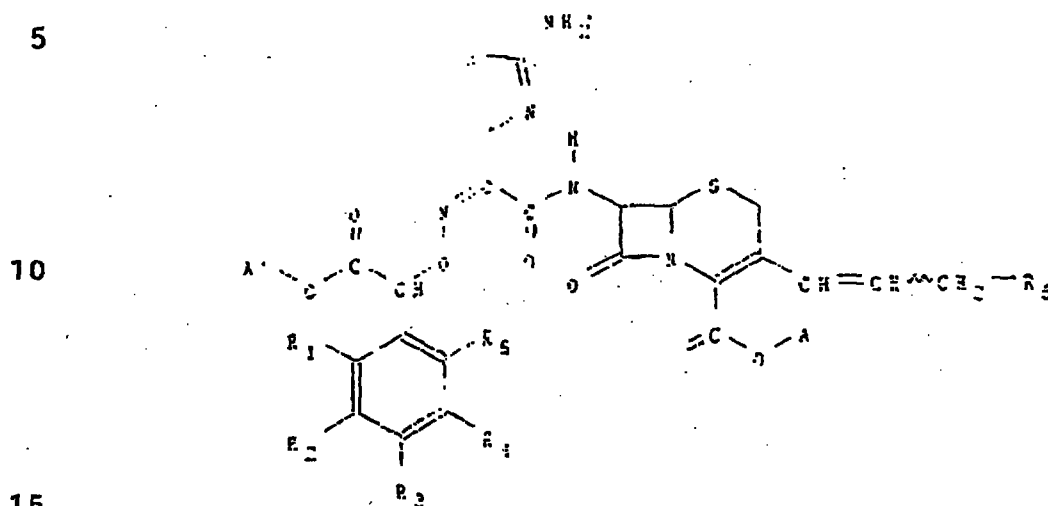
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CLAIMS

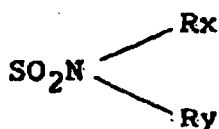
1) The products of general formula (I):



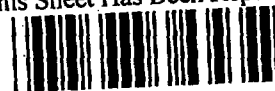
(I)

20 syn isomer, in (R) or (S) form or an (R,S) mixture, in the form of an internal salt or their salts with mineral or organic acids, in which formula:

R₁, R₂, R₃ and R₅, identical or different, represent a hydrogen atom, a halogen atom or one of the radicals chosen from the following radicals: hydroxy, alkyl containing 1 to 4
25 carbon atoms, optionally substituted by one or more halogen atoms, alkyloxy containing 1 to 4 carbon atoms, mercapto, alkylthio containing 1 to 4 carbon atoms, nitro, cyano, amino, alkylamino containing 1 to 4 carbon atoms, dialkylamino containing 2 to 8 carbon atoms, carbamoyl,
30 (alkylamino) carbonyl containing 2 to 5 carbon atoms, (dialkylamino) carbonyl containing 3 to 9 carbon atoms, carboxy, alkoxy carbonyl containing 2 to 5 carbon atoms, acyloxy containing 1 to 8 carbon atoms,
R₄ represents a hydroxy radical or an alkyloxy radical
35 containing 1 to 8 carbon atoms,



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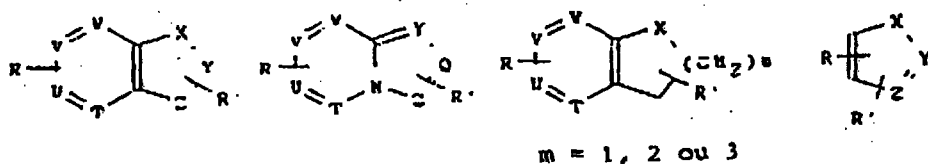


in which R_x and R_y , identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms,

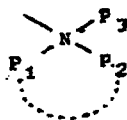
it being understood that when R_3 represents a hydroxy

- 5 radical, or an alkyloxy radical containing 1 to 8 carbon atoms, R_1 , R_2 and R_5 do not all represent a hydrogen atom, A and A' , identical or different, represent a hydrogen atom, an equivalent of an alkali or alkaline-earth metal, magnesium, ammonium or an amino organic base, or one only or
- 10 each of the groups CO_2A or CO_2A' represent CO_2^- , the wavy line signifies that the CH_2R_6 group can be in the E or Z position and R_6 represents, in the quaternary ammonium form, one of the following radicals:

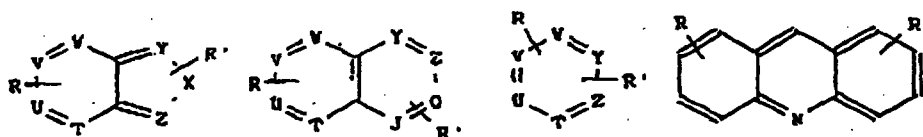
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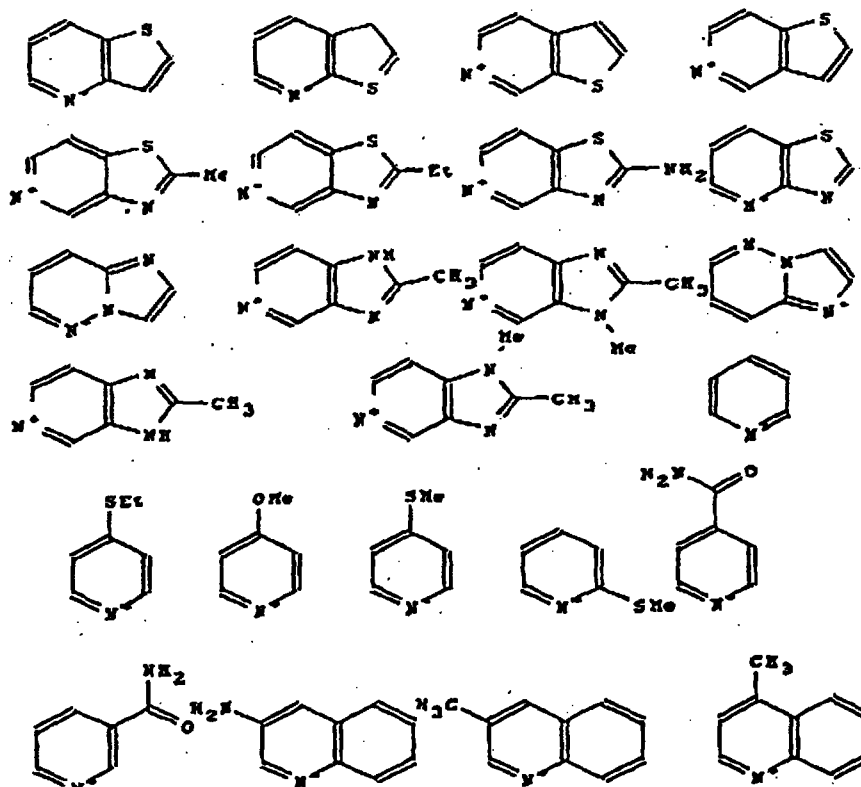
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- 30 in which X represents CH_2 , NH , O or S ;
 Q , J , Y , T , U , V , W and Z , identical or different, represent independently of each other CH or N , it being understood that each of these cyclic radicals contains 1 to 5 cyclic heteroatoms, that at least one of these heteroatoms is the nitrogen
- 35 atom and that these cyclic radicals can be substituted by one or more R or R' radicals;
 R and R' , identical or different, represent a halogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkyloxy

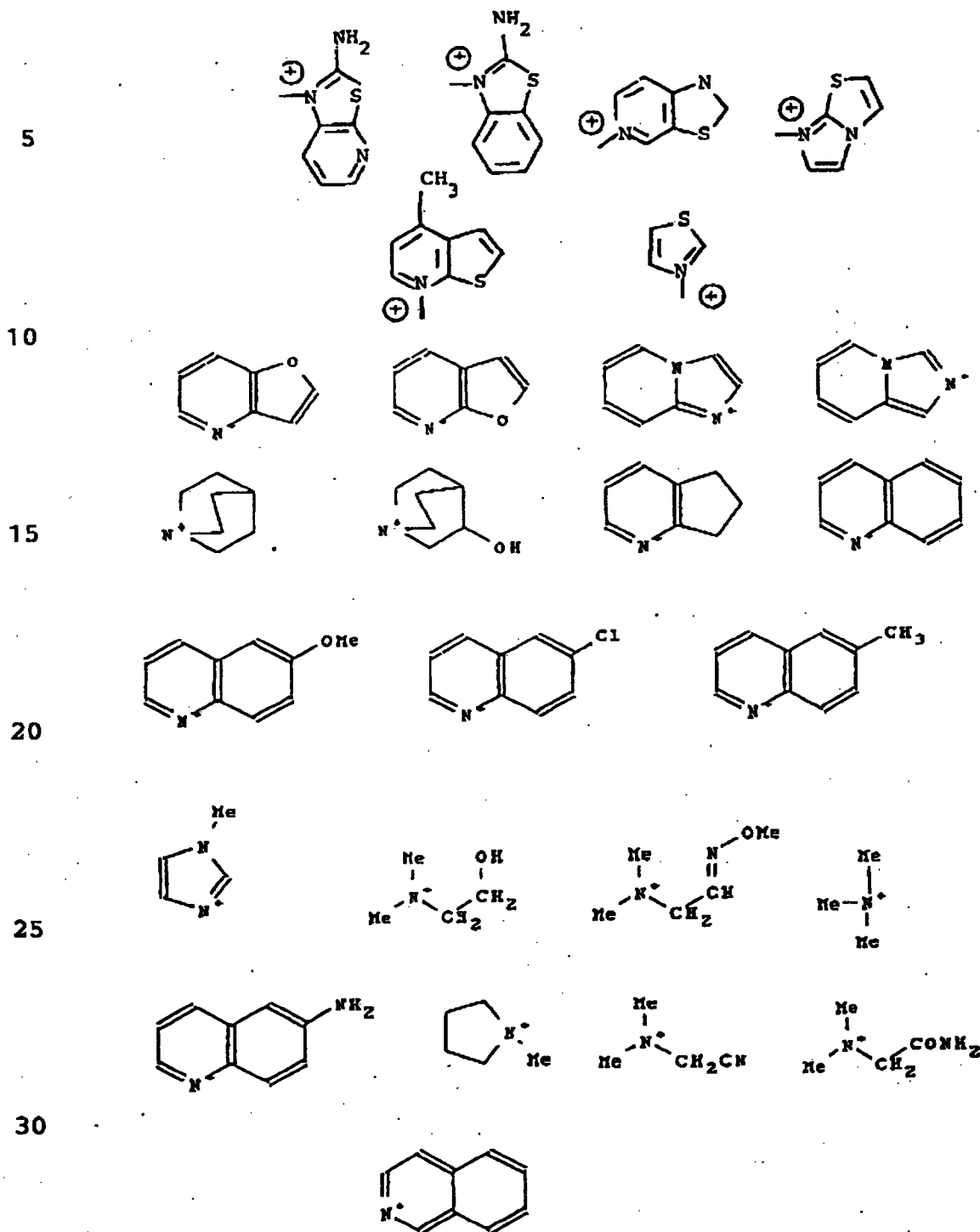
radical containing 1 to 4 carbon atoms, a halogen atom, a cyano radical, one of the following radicals: $\text{CO}_2\text{-Q}_1$, $\text{CO-NQ}_1(\text{Q}_2)$, $\text{NQ}_1(\text{Q}_2)$, $\text{SO}_2\text{-NQ}_1(\text{Q}_2)$, CS-NH_2 , NH-CO-Q_1 , CH=N-OH , CH=N-O-Q_1 , $\text{CH}_2\text{-CN}$, $\text{CH}_2\text{-S-Q}_1$ in which Q_1 and Q_2 , identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, P_1 , P_2 and P_3 , identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the dotted line indicates that P_1 and P_2 can optionally form with the nitrogen atom to which they are linked, a heterocycle with 5 or 6 members.

2) The products of general formula (I) as defined in claim 1 in which R_6 represents one of the following radicals:

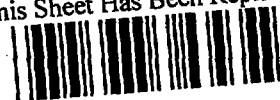




or also one of the following radicals:



3) The products of formula (I) as defined in one of claims
 35 1 and 2 in which R_6 represents the quinolinium,
 isoquinolinium, 4-(methylthio)-pyridinium, thieno[2,3-
 b]pyridinium, imidazo(1,2-a)pyridinium radical or the 6,7-
 dihydro-5H-pyridinium radical.



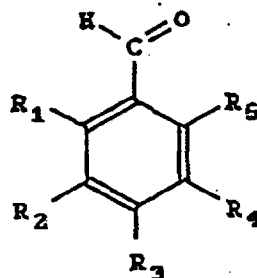
- 4) The products of general formula (I) as defined in any one of claims 1, 2 or 3 in which R_3 and R_4 each represent a hydroxy radical.
- 5) The products of general formula (I) as defined in any one of claims 1, 2, 3 or 4 in which R_2 and R_5 each represent a chlorine atom.
- 6) The products of general formula (I) as defined in any one of claims 1, 2, 3 or 4 in which R_2 and R_5 each represent a fluorine atom.
- 10 7) The products of general formula (I) as defined in any one of claims 1, 2, 3 or 4 in which R_1 and R_2 each represent a fluorine atom.
- 8) The products of general formula (I) as defined in any one of claims 1, 2, 3 or 4 in which R_2 represents a methoxy radical and one of R_1 or R_5 represents a chlorine atom.
- 15 9) The products of general formula (I) as defined in any one of claims 1, 2, 3, 4, 5, 6, 7 or 8 of which the names follow:
- the internal salt of (6R-(3-(E) 6alpha, 7beta(2)))--
 - 20 1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(2,3-difluoro-4,5-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)imidazo(1,2-a) pyridinium,
 - the internal salt of (6R-(3-(E) 6alpha, 7beta(2)))--1-(3-
 - 25 (7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-difluoro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-imidazo(1,2-a) pyridinium,
 - the internal salt of (6R-(3-(E) 6alpha, 7beta(2)))--1-(3-
 - 30 (7-(((2-amino-4-thiazolyl) ((carboxy-(2-chloro-4,5-dihydroxy-3-methoxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl) quinolinium,
 - the internal salt of (6R-(3-(E) 6alpha, 7beta(2)))--1-(3-
 - 35 (7-(((2-amino-4-thiazolyl) ((carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-6,7-dihydro-5-H-pyridinium,



- the internal salt of (6R-(3-(E) 6alpha, 7beta(Z(S*)))-1-(3-(7-(((2-amino-4-thiazolyl) ((carboxy-(3,4-dihydroxy-5-fluorophenyl)-methoxy)-imino)-acetyl)-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl)-2-propenyl)-
- 5 quinolinium,
- the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(2-chloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-
- 10 quinolinium (R) or (S) or an (R+S) mixture,
- the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(3-cyano-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-
- 15 quinolinium (R) or (S) or an (R+S) mixture,
- the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(3-fluoro-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-
- 20 quinolinium (R) or (S) or an (R+S) mixture,
- the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-
- 25 thieno[2,3-b]pyridinium (R) or (S) or an (R+S) mixture,
- the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-
- 30 quinolinium (R) or (S) or an (R+S) mixture,
- the internal salt of [6R-[3(E), 6alpha, 7beta(Z(S*))]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(3-cyano-4,5-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-
- 35 thieno[2,3-b]pyridinium,
- the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl) [[carboxy-(2,5-dichloro-3,4-dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-

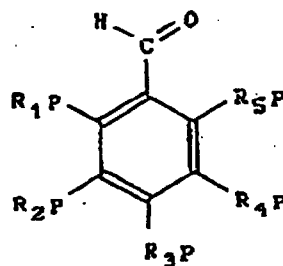


oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-
 isoquinolinium (R) or (S) or an (R+S) mixture,
 - the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-
 [[(2-amino-4-thiazolyl) [[carboxy-(2,5-dichloro-3,4-
 5 dihydroxy-phenyl)-methoxy]-imino]-acetyl]-amino]-2-carboxy-8-
 oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-
 4-(methylthio)-pyridinium (R) or (S) or an (R+S) mixture.
 10) Preparation process for the products of formula (I) as
 defined in claim 1, characterized in that the aromatic
 10 aldehyde of formula (II):



(II)

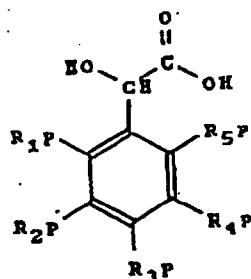
in which R_1 , R_2 , R_3 , R_4 and R_5 are as defined in claim 1, is
 if necessary protected in its reactive functions and thus
 25 converted into an aromatic aldehyde of formula (II)_p:

(II)_p

35 in which R_{1p} , R_{2p} , R_{3p} , R_{4p} and R_{5p} represent respectively
 the values of R_1 , R_2 , R_3 , R_4 and R_5 as defined in claim 1 or
 a protected reactive function, said aldehyde of formula (II)_p

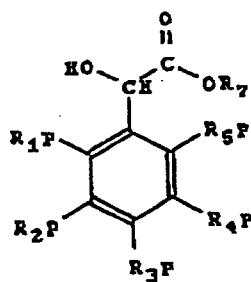


is homologated into an alpha-hydroxy acid of formula (III):



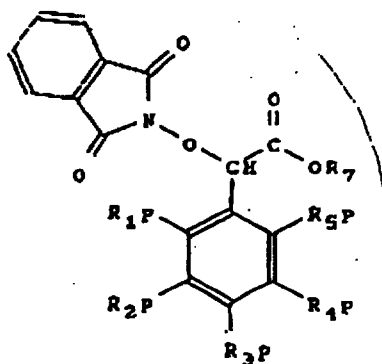
(III)

which acid is esterified into an alpha-hydroxy ester of formula (IV):



(IV)

in which R_7 represents the remainder of an easily-cleavable ester, said alpha-hydroxy ester is treated with N-hydroxy phthalimide to give a derivative of formula (V):



(V)

which derivative of formula (V) is reduced into an O-

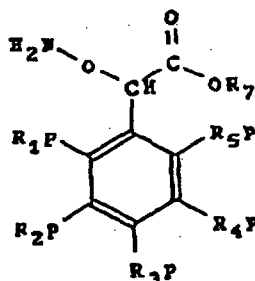


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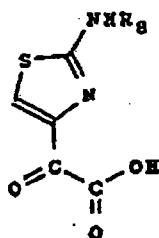
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substituted hydroxylamine of formula (VI):



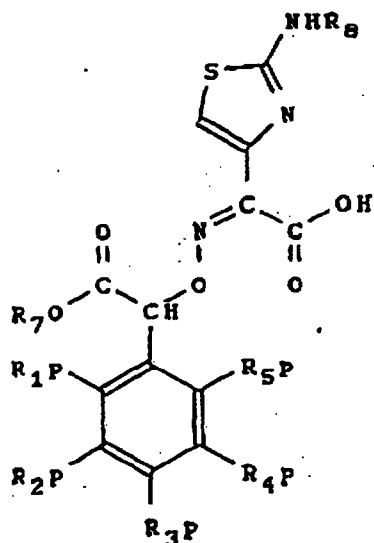
(VI)

which product of formula (VI) is condensed with a derivative of (2-amino-thiazolyl)-glyoxylic acid of formula (VII):



(VII)

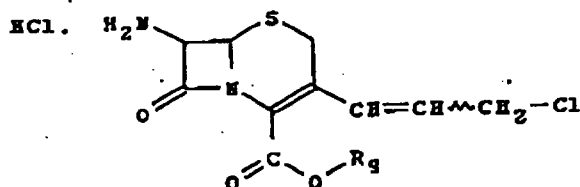
in which R₈ represents a hydrogen atom or a protective group of the amine function, in order to form the derivative of the alpha-hydroximino acetic acid of formula (VIII):



(VIII)

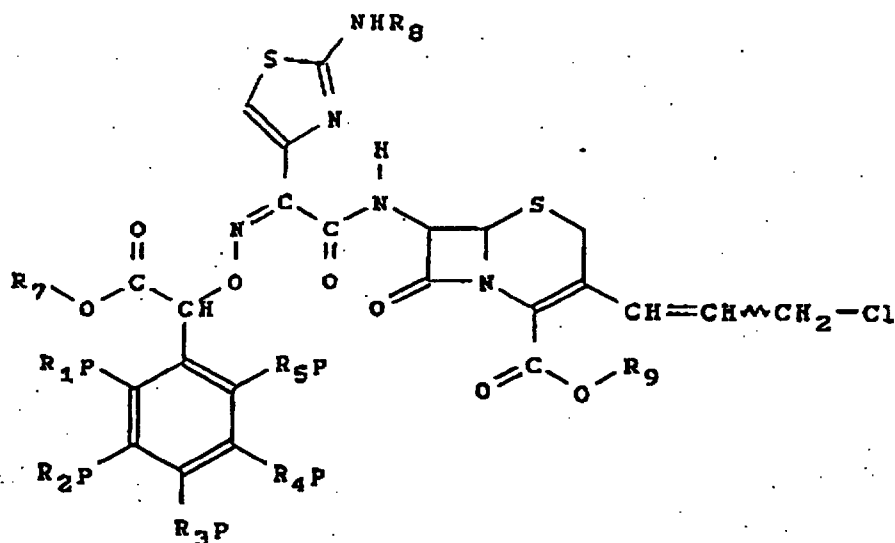


which product of formula (VIII) or a functional derivative of this acid is amidified with an ester of 7-amino-3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylic acid hydrochloride of formula (IX):



(IX)

or its salts, in which R₉ represents the remainder of an easily-cleavable ester, to give a derivative of 7-(N-substituted amido) 3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-2-carboxylic acid of formula (X):



(X)

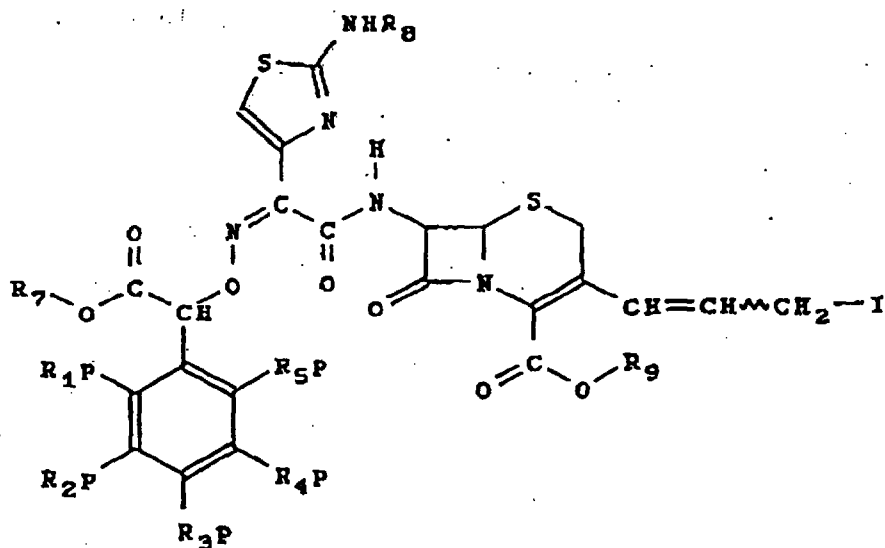
which product of formula (X) is converted into an analogous 3-(3-iodo-propenyl) of formula (XI):

35



5

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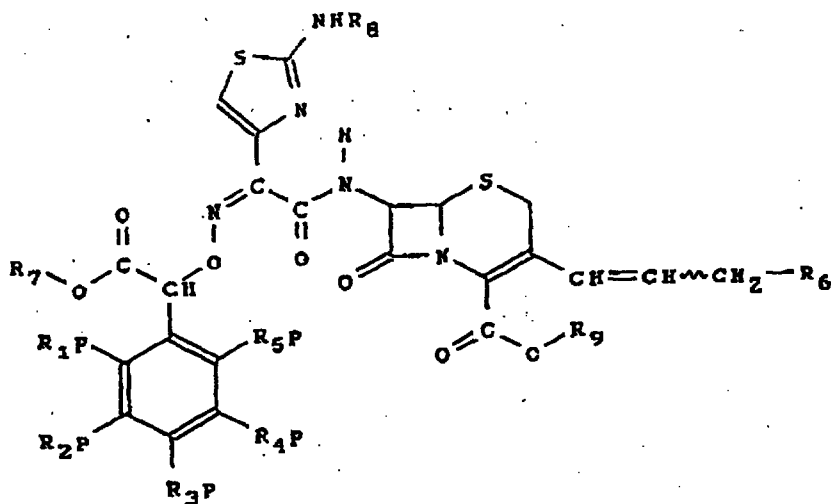


(XI)

which product of formula (XI) is treated with a base of
15 formula R_6 in order to obtain the product of formula (XII):

20

25



(XII)

30 from which product of formula (XII), if desired, the (E) or
(Z) isomers are isolated or the (Z) isomers are converted
into (E) isomers and which product of formula (XII) is
subjected to one or more of the following reactions, in any
order:

- 35 a) cutting by hydrolysis or by the action of thiourea of all
or part of the ester groups or the protective groups of the
amino radical or the hydroxyl radicals,
b) esterification or salification of the carboxylic radical



* C L M S *

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or radicals by a base,

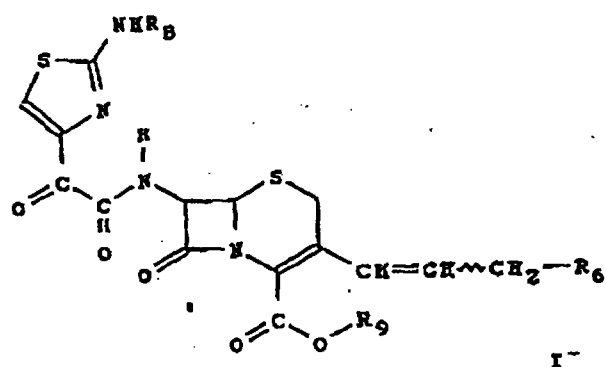
c) salification of the amino radical by an acid,

d) separation of the products in the form of an R,S mixture into R or S.

- 5 11) Variant of the process according to claim 10, characterized in that the O-substituted hydroxylamine of formula (VI) is condensed with the product of formula (XIII):

10

15



20

(XIII)

to give the product of formula (XII) as defined in claim 10.

- 12) As medicaments, the products corresponding to formula
25 (I) as defined in claim 1, as well as their pharmaceutically acceptable acid salts.

13) As medicaments, the products as defined in any one of claims 2 to 9 as well as their pharmaceutically acceptable acid salts.

- 30 14) Pharmaceutical compositions containing, as active ingredient, at least one medicament according to one of claims 12 or 13.

- 15) As new industrial products, the products of formulae (III), (IV), (V), (VI), (VIII), (X), (XI) and (XII) as
35 defined in claim 10.