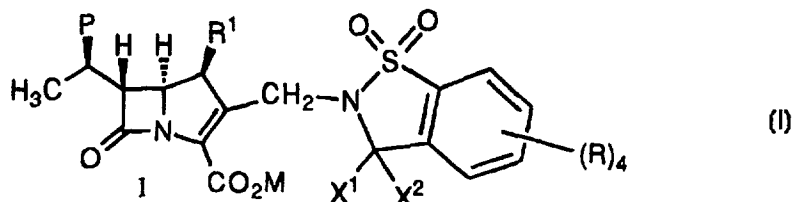




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(54) Title: CARBAPENEM ANTIBACTERIAL COMPOUNDS, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT



(57) Abstract

The present invention relates to carbapenem antibacterial agents in which the carbapenem nucleus is substituted at the 2-position with a naphthosultam linked through a CH₂ group. The naphthosultam is further substituted with various substituent groups including at least one cationic group. The compounds are represented by formula (I). Pharmaceutical compositions and methods of use are also included.

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TITLE OF THE INVENTION

CARBAPENEM ANTIBACTERIAL COMPOUNDS,
COMPOSITIONS CONTAINING SUCH COMPOUNDS AND
METHODS OF TREATMENT

5

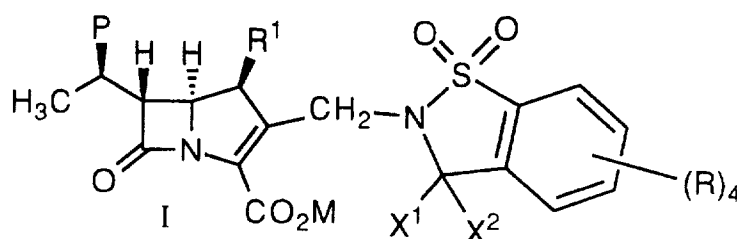
BACKGROUND OF THE INVENTION

The present invention relates to carbapenem
antibacterial agents in which the carbapenem nucleus is substituted at
the 2-position with a sulfonamide containing ring system, linked to
10 the carbapenem through a CH₂ group. The sulfonamide containing
ring system is further substituted with various substituents including
cationic groups.

The carbapenems of the present invention are useful
against gram positive microorganisms, especially methicillin resistant
15 *Staphylococcus aureus* (MRSA), methicillin resistant *Staphylococcus*
epidermidis (MRSE), and methicillin resistant coagulase negative
Staphylococci (MRCNS). The antibacterial compounds of the present
invention thus comprise an important contribution to therapy for
treating infections caused by these difficult to control pathogens.
20 There is an increasing need for agents effective against such pathogens
which are at the same time relatively free from undesirable side effects.

SUMMARY OF THE INVENTION

The compounds of the present invention are represented by
25 formula I:



or a pharmaceutically acceptable salt thereof, wherein:

30

R¹ represents H or methyl;

- 2 -

CO₂M represents a carboxylic acid, a carboxylate anion, a pharmaceutically acceptable ester group or a carboxylic acid protected by a protecting group;

5 P represents hydrogen, hydroxyl, F or hydroxyl protected by a hydroxyl-protecting group;

X¹ and X² represent hydrogen or X¹ and X² taken together represent a carbonyl group;

10

each R is independently selected from: -R*; -Q; hydrogen; halo; -CN; -NO₂; -NR^aR^b; -OR^c; -SR^c; -C(O)NR^aR^b; -C(O)OR^h; -S(O)R^c; -SO₂R^c; -SO₂NR^aR^b; -NR^aSO₂R^h; -C(O)R^a; -OC(O)R^a; -OC(O)NR^aR^b; -NR^aC(O)NR^bR^c; -NR^aCO₂R^h; -OCO₂R^h; -NR^aC(O)R^b; -C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four R^d groups; and -C₃₋₇ cycloalkyl, unsubstituted or substituted with one to four R^d groups;

15

each R^a, R^b and R^c independently represents hydrogen, -R*, -C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four R^d groups, or -C₃₋₇ cycloalkyl, unsubstituted or substituted with one to four R^d groups;

20

or R^a and R^b taken together with any intervening atoms represent a 4-6 membered saturated ring optionally interrupted by one or more of O, S, NR^c, with R^c as defined above, or -C(O)-, said ring being unsubstituted or substituted with one to four Rⁱ groups;

25

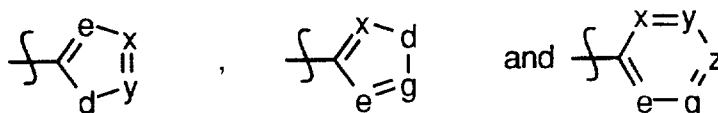
or R^b and R^c taken together with any intervening atoms represent a 4-6 membered saturated ring optionally interrupted by one to three of O, S, NR^a, with R^a as defined above, or -C(O)-, said ring being unsubstituted or substituted with one to four Rⁱ groups;

30

each R^d independently represents halo; -CN; -NO₂; -NR^eR^f; -OR^g; -SR^g; -CONR^eR^f; -COOR^g; -SOR^g; -SO₂R^g; -SO₂NR^eR^f; -NR^eSO₂R^f; -COR^e; -NR^eCOR^f; -OCOR^e; -OCONR^eR^f; -NR^eCONR^fR^g;

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R* is selected from the group consisting of:



wherein:

5 d represents O, S or NR^k;

e, g, x, y and z represent CR^m, N or N⁺R^k, provided that no more than one of e, g, x, y and z in any given structure represents N⁺R^k;

10 R^k represents hydrogen; -C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four Rⁱ groups; or -(CH₂)_nQ where n = 1, 2 or 3 and Q is as previously defined;

each R^m independently represents a member selected from the group consisting of: hydrogen; halo; -CN; -NO₂; -NRⁿR^o; -ORⁿ; -SRⁿ; -CONRⁿR^o; -COOR^h; -SORⁿ; -SO₂Rⁿ; -SO₂NRⁿR^o; -NRⁿSO₂R^o; -CORⁿ; -NRⁿCOR^o; -OCORⁿ; -OCONRⁿR^o; -NRⁿCO₂R^h; -NRⁿCONR^oR^h; -OCO₂R^h; -CNRⁿNR^oR^h; -NRⁿCNHNR^oR^h; -NRⁿC(NR^o)R^h; -C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four Rⁱ groups; -C₃₋₇ cycloalkyl, unsubstituted or substituted with one to four Rⁱ groups; and -(CH₂)_nQ where n and Q are as defined above;

25 Rⁿ and R^o represent hydrogen, phenyl; -C₁₋₆ straight- or branched-chain alkyl unsubstituted or substituted with one to four Rⁱ groups;

each R^s independently represents hydrogen; phenyl or -C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four Rⁱ groups;

each Rⁱ independently represents hydrogen; halo; phenyl;

- 5 -

-CN; -NO₂; -NR^uR^v; -OR^u; -SR^u; -CONR^uR^v; -COOR^h; -SOR^u; -SO₂R^u; -SO₂NR^uR^v; -NR^uSO₂R^v; -COR^u; -NR^uCOR^v; -OCOR^u; -OCONR^uR^v; -NR^uCO₂R^v; -NR^uCONR^vR^w; -OCO₂R^v; -C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four Rⁱ groups;

5

R^u and R^v represent hydrogen or -C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four Rⁱ groups;

or R^u and R^v together with any intervening atoms
10 represent a 4-6 membered saturated ring optionally interrupted by one or more of O, S, NR^w or -C(O)-, said ring being unsubstituted or substituted with one to four Rⁱ groups;

each R^w independently represents hydrogen; -C₁₋₆ straight-
15 or branched-chain alkyl, unsubstituted or substituted with one to four Rⁱ groups; C₃₋₆ cycloalkyl optionally substituted with one to four Rⁱ groups; phenyl optionally substituted with one to four Rⁱ groups, or heteroaryl optionally substituted with 1-4 Rⁱ groups;

or R^h and R^w taken together with any intervening atoms
20 represent a 5-6 membered saturated ring, optionally interrupted by one or two of O, S, SO₂, NH or NCH₃;

R^x represents hydrogen or a C₁₋₈ straight- or branched-chain alkyl, optionally interrupted by one or two of O, S, SO, SO₂,
25 NR^w, N⁺R^hR^w, or -C(O)-, said chain being unsubstituted or substituted with one to four of halo, CN, NO₂, OR^w, SR^w, SOR^w, SO₂R^w, NR^hR^w, N⁺(R^h)₂R^w, -C(O)-R^w, C(O)NR^hR^w, SO₂NR^hR^w, CO₂R^w, OC(O)R^w, OC(O)NR^hR^w, NR^hC(O)R^w, NR^hC(O)NR^hR^w, or a phenyl or heteroaryl group which is in turn optionally substituted with from
30 one to four Rⁱ groups or with one to two C₁₋₃ straight- or branched-chain alkyl groups, said alkyl groups being unsubstituted or substituted with one to four Rⁱ groups;

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R^y and R^z represent hydrogen; phenyl; -C₁₋₆ straight or branched chain alkyl, unsubstituted or substituted with one to four Rⁱ groups, and optionally interrupted by O, S, NR^w, N+R^hR^w or -C(O)-;

5 or R^x and R^y together with any intervening atoms represent a 4-8 membered saturated ring optionally interrupted by O, S, SO₂, NR^w, N+R^hR^w or -C(O)-, unsubstituted or substituted with 1 - 4 Rⁱ groups,

10 and when R^x and R^y together represent a 4-6 membered ring as defined above, R^z is as defined above or R^z represents an additional saturated 4-8 membered ring fused to the ring represented by R^x and R^y taken together, optionally interrupted by O, S, NR^w or -C(O)-, said rings being unsubstituted or substituted with one to four Rⁱ groups.

15

Pharmaceutical compositions and methods of treatment are also included herein.

DETAILED DESCRIPTION OF THE INVENTION

20 The invention is described herein in detail using the terms defined below unless otherwise specified.

Carboxylate anion refers to a negatively charged group -COO⁻.

25 The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 10 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, cyclopentyl and cyclohexyl. When substituted, alkyl groups may be substituted with up to four substituent groups, selected from R^d and
30 Rⁱ, as defined, at any available point of attachment. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group".

Cycloalkyl is a specie of alkyl containing from 3

- 7 -

to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings which are fused.

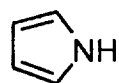
5 The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl.

10 The term "alkynyl" refers to a hydrocarbon radical straight or branched, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Preferred alkynyl groups include ethynyl, propynyl and butynyl.

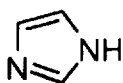
15 Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and the like, as well as rings which are fused, e.g., naphthyl, phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms or suitable heteroatoms. The preferred aryl groups are phenyl, naphthyl and phenanthrenyl. Aryl groups may likewise be substituted as defined. Preferred
20 substituted aryls include phenyl and naphthyl.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment,
25 and in which one or two additional carbon atoms is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms, said heteroaryl group being optionally substituted as described herein. Examples of this type are pyrrole, pyridine,
30 oxazole, thiazole and oxazine. Additional nitrogen atoms may be present together with the first nitrogen and oxygen or sulfur, giving, e.g., thiadiazole. Examples include the following:

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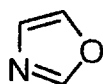
pyrrole (pyrrolyl)



imidazole (imidazolyl)



thiazole (thiazolyl)



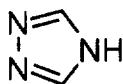
oxazole (oxazolyl)



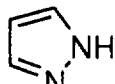
furan (furyl)



thiophene (thienyl)



triazole (triazolyl)



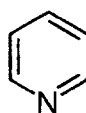
pyrazole (pyrazolyl)



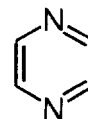
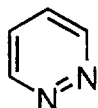
isoxazole (isoxazolyl)



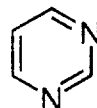
isothiazole (isothiazolyl)



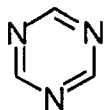
pyridine (pyridinyl)

pyrazine
(pyrazinyl)

pyridazine (pyridazinyl)



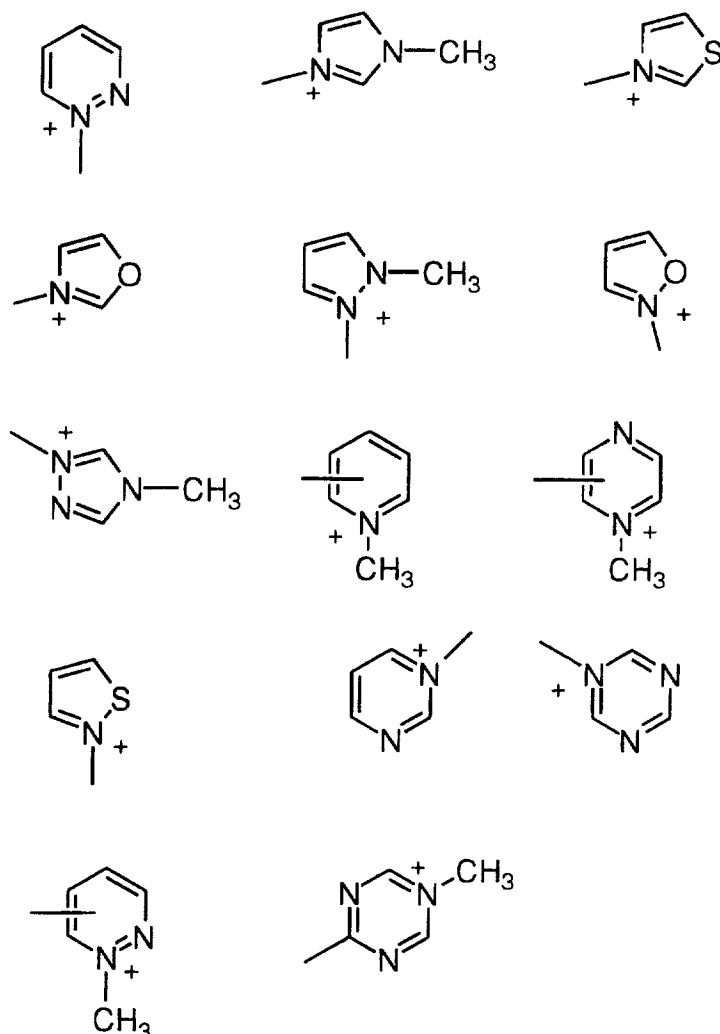
pyrimidine (pyrimidinyl)



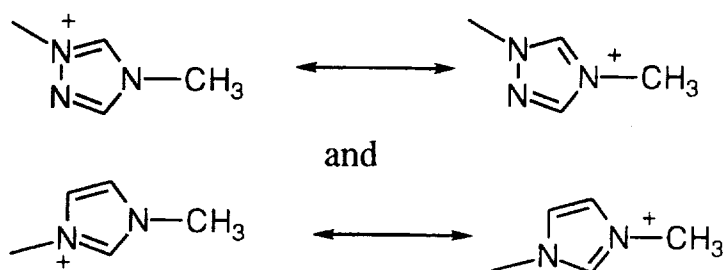
triazine (triazinyl)

Heteroarylium refers to heteroaryl groups bearing a quaternary nitrogen atom and thus a positive charge. Examples include the following:

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- When a charge is shown on a particular nitrogen atom in a ring which contains one or more additional nitrogen atoms, it is understood that the charge may reside on a different nitrogen atom in the ring by virtue of charge resonance that occurs.
- 5



- 10 -

The term "heterocycloalkyl" refers to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S or N, and in which up to three additional carbon atoms may be replaced by hetero atoms.

5 The terms "quaternary nitrogen" and "positive charge" refer to tetravalent, positively charged nitrogen atoms including, e.g., the positively charged nitrogen in a tetraalkylammonium group (e. g. tetramethylammonium), heteroarylium, (e.g., N-methylpyridinium), basic nitrogens which are protonated at physiological
10 pH, and the like. Cationic groups thus encompass positively charged nitrogen-containing groups, as well as basic nitrogens which are protonated at physiologic pH.

 The term "heteroatom" means O, S or N, selected on an independent basis.

15 Halogen and "halo" refer to bromine, chlorine, fluorine and iodine.

 Alkoxy refers to C₁-C₄ alkyl-O-, with the alkyl group optionally substituted as described herein.

 Ureido means the group -NHC(O)NH₂, the hydrogens
20 of which may be replaced with alkyl groups.

 GuanidinyI means the group -NHC(NH)NH₂, the hydrogens of which may be replaced with alkyl groups.

 Carbamimidoyl means the group -C(NH)NH₂, the hydrogens of which may be replaced with alkyl groups.

25 When a group is termed "substituted", unless otherwise indicated, this means that the group contains from 1 to 4 substituents thereon. With respect to R, R_a, R_b and R_c, the substituents available on alkyl groups are selected from the values of R^d. Many of the variable groups are optionally substituted with up to four Rⁱ groups.
30 With respect to R^e, R^f and R^g, when these variables represent substituted alkyl, the substituents available thereon are selected from the values of Rⁱ.

 When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side

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reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with reference to standard textbooks, such as Greene, T. W.
5 et al. Protective Groups in Organic Synthesis Wiley, New York (1991). Examples of suitable protecting groups are contained throughout the specification.

In some of the carbapenem compounds of the present invention, M is a readily removable carboxyl protecting group,
10 and/or P represents a hydroxyl which is protected by a hydroxyl-protecting group. Such conventional protecting groups consist of known groups which are used to protectively block the hydroxyl or carboxyl group during the synthesis procedures described herein. These conventional blocking groups are readily removable, i.e.,
15 they can be removed, if desired, by procedures which will not cause cleavage or other disruption of the remaining portions of the molecule. Such procedures include chemical and enzymatic hydrolysis, treatment with chemical reducing or oxidizing agents under mild conditions, treatment with a transition metal catalyst
20 and a nucleophile and catalytic hydrogenation.

Examples of carboxyl protecting groups include allyl, benzhydryl, 2-naphthylmethyl, benzyl, silyl such as t-butyldimethylsilyl (TBDMS), phenacyl, p-methoxybenzyl, o-nitrobenzyl, p-methoxyphenyl, p-nitrobenzyl, 4-pyridylmethyl
25 and t-butyl.

Examples of suitable C-6 hydroxyethyl protecting groups include triethylsilyl, t-butyldimethylsilyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, benzyloxycarbonyl, allyloxycarbonyl, t-butyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl and the like.
30

The carbapenem compounds of the present invention are useful per se and in their pharmaceutically acceptable salt and ester forms for the treatment of bacterial infections in animal and human subjects. The term "pharmaceutically acceptable ester, salt

- 12 -

or hydrate," refers to those salts, esters and hydrated forms of the compounds of the present invention which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which may favorably affect the pharmacokinetic properties of said compounds, such as palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, solubility, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers. Thus, the present invention is also concerned with pharmaceutical compositions and methods of treating bacterial infections utilizing as an active ingredient the novel carbapenem compounds.

With respect to $-\text{CO}_2\text{M}$, which is attached to the carbapenem nucleus at position 3, this represents a carboxylic acid group (M represents H), a carboxylate anion (M represents a negative charge), a pharmaceutically acceptable ester (M represents an ester forming group) or a carboxylic acid protected by a protecting group (M represents a carboxyl protecting group). The pharmaceutically acceptable salts referred to above may take the form $-\text{COOM}$, where M is a negative charge, which is balanced by a counterion, e.g., an alkali metal cation such as sodium or potassium. Other pharmaceutically acceptable counterions may be calcium, magnesium, zinc, ammonium, or alkylammonium cations such as tetramethylammonium, tetrabutylammonium, choline, triethylhydroammonium, meglumine, triethanolhydroammonium, etc.

The pharmaceutically acceptable salts referred to above also include acid addition salts. Thus, the Formula I compounds can be used in the form of salts derived from inorganic or organic acids. Included among such salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate,

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citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide,
5 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate.

The pharmaceutically acceptable esters are such as
10 would be readily apparent to a medicinal chemist, and include, for example, those described in detail in U.S. Pat. No. 4,309,438. Included within such pharmaceutically acceptable esters are those which are hydrolyzed under physiological conditions, such as pivaloyloxymethyl, acetoxymethyl, phthalidyl, indanyl and
15 methoxymethyl, and others described in detail in U.S. Pat. No. 4,479,947. These are also referred to as "biolabile esters".

Biolabile esters are biologically hydrolyzable, and may be suitable for oral administration, due to good absorption through the stomach or intestinal mucosa, resistance to gastric acid
20 degradation and other factors. Examples of biolabile esters include compounds in which M represents an alkoxyalkyl, alkylcarbonyloxyalkyl, alkoxycarbonyloxyalkyl, cycloalkoxyalkyl, alkenyloxyalkyl, aryloxyalkyl, alkoxyaryl, alkylthioalkyl, cycloalkylthioalkyl, alkenylthioalkyl, arylthioalkyl or alkylthioaryl
25 group. These groups can be substituted in the alkyl or aryl portions thereof with acyl or halo groups. The following M species are examples of biolabile ester forming moieties.: acetoxymethyl, 1-acetoxyethyl, 1-acetoxypentyl, pivaloyloxymethyl, 1-isopropoxyloxycarbonyloxyethyl, 1-cyclohexyloxycarbonyloxyethyl,
30 phthalidyl and (2-oxo-5-methyl-1,3-dioxolen-4-yl)methyl.

L⁻ can be present or absent as necessary to maintain the appropriate charge balance. When present, L⁻ represents a pharmaceutically acceptable counterion. Most anions derived from inorganic or organic acids are suitable. Representative examples of

- 14 -

such counterions are the following: acetate, adipate, aminosalicylate, anhydromethylenecitrate, ascorbate, aspartate, benzoate, benzenesulfonate, bromide, citrate, camphorate, camphorsulfonate, chloride, estolate, ethanesulfonate, fumarate, glucoheptanoate, gluconate, glutamate, lactobionate, malate, maleate, mandelate, methanesulfonate, pantothenate, pectinate, phosphate/diphosphate, polygalacturonate, propionate, salicylate, stearate, succinate, sulfate, tartrate and tosylate. Other suitable anionic species will be apparent to the ordinarily skilled chemist.

10 Likewise, when L^- represents a specie with more than one negative charge, such as malonate, tartrate or ethylenediaminetetraacetate (EDTA), an appropriate number of carbapenem molecules can be found in association therewith to maintain the overall charge balance and neutrality.

15 One subset of compounds which is of particular interest relates to compounds in which at least one of the R groups attached to the sulfonamide containing platform contains a positively charged moiety. Thus, it can include $-R^*$ or Q, or a moiety which in turn contains a positively charged group.

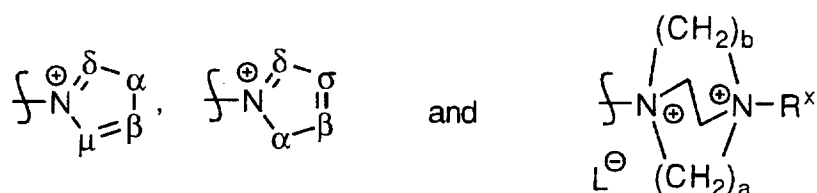
20 A further subset of compounds of formula I which is of interest relates to compounds of formula I wherein one R represents a group which contains a positively charged moiety, and the remaining R groups are selected from hydrogen, R^* and C_{1-6} straight or branched chain alkyl, unsubstituted or substituted with one to four R^d groups. More particularly, this subset of interest includes compounds of formula I wherein one R represents a group containing a positively charged moiety and the remaining R groups are hydrogen or R^* .

25 With respect to the positively charged moiety or
30 moieties that are contained in one or more R groups, it is preferred that from 1-3 positive charges be present, and most preferably two positive charges be present, balanced by the carboxylate anion and a negatively charged counterion.

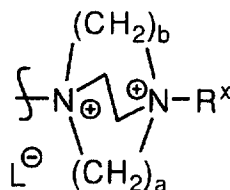
Another subset of compounds which is of interest is represented by formula I wherein one R group represents a -C₁₋₆ straight or branched chain alkyl group, substituted with one to four R^d groups, wherein one R^d group represents -R* or Q. Hence, a positively charged moiety -R* or Q is attached to an alkyl group.

Another subset of compounds of formula I which is of interest relates to those compounds where CO₂M represents a carboxylate anion. Hence, M in this instance represents a negative charge which is balanced by a positively charged group, such as in the positively charged R group. Likewise, if the positively charged R group contains more than one positive charge, a negatively charged counterion may be present which in combination with the carboxylate anion, provides overall charge neutrality.

Another group of compounds of interest is represented
15 by formula I wherein Q is selected from the group consisting of:



20 More particularly, the group of compounds which is of interest is represented by formula I wherein Q represents:



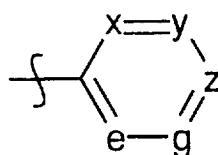
25 Within this subset of compounds, L⁻, a and b are as originally defined, and R^x is as originally defined, and represents a member selected from the group consisting of: hydrogen or a C₁₋₈ straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO₂, NR^w, N⁺R^hR^w, or -C(O)-, said chain being

- 16 -

unsubstituted or substituted with one to four of halo, CN, NO₂, OR^w, SR^w, SOR^w, SO₂R^w, NR^hR^w, N⁺(R^h)₂R^w, -C(O)-R^w, C(O)NR^hR^w, SO₂NR^hR^w, CO₂R^w, OC(O)R^w, OC(O)NR^hR^w, NR^hC(O)R^w, NR^hC(O)NR^hR^w, or a phenyl or heteroaryl group
 5 which is in turn optionally substituted with from one to four Rⁱ groups or with one to two C₁₋₃ straight- or branched- chain alkyl groups, said alkyl groups being unsubstituted or substituted with one to four Rⁱ groups.

Another group of compounds of interest is represented
 10 by formula I wherein Q represents -N⁺R^xR^yR^z, wherein R^x, R^y and R^z are as originally defined.

Another group of compounds of interest is represented by formula I wherein one R^{*} group is:



15

Within this subset, e, g, x, y and z represent CR^m, N or N⁺R^k, provided that no more than one of e, g, x, y and z in any given structure represents N⁺R^k. R^k and R^m are as originally defined.

20 A preferred subset of compounds of formula I which is of particular interest relates to compounds represented by formula I wherein:

CO₂M represents a carboxylate anion;

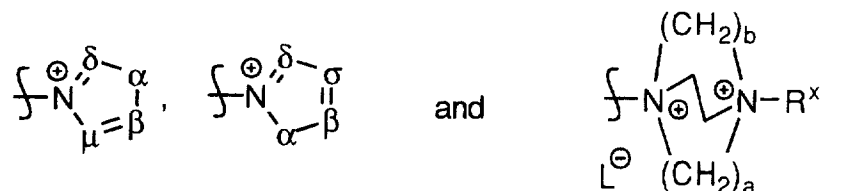
one R group which is attached to the sulfonamide
 25 containing ring system contains at least one positively charged moiety, and the remaining R groups are selected from hydrogen and C₁₋₆ straight or branched chain alkyl, unsubstituted or substituted with one to four R^d groups;

R^d is as originally defined;

30 R^h represents hydrogen or a C₁₋₆ straight or branched chain alkyl group;

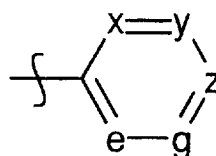
Q is selected from the group consisting of:

- 17 -



wherein L^- , a and b are as originally defined, and

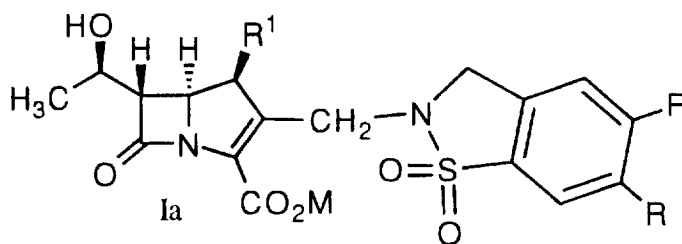
- 5 R^x represents a member selected from the group consisting of: hydrogen or a C₁-8 straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO₂, NR^w, N⁺R^hR^w, or -C(O)-, said chain being unsubstituted or substituted with one to four of halo, CN, NO₂, OR^w, SR^w, SOR^w, SO₂R^w, NR^hR^w,
 10 N⁺(R^h)₂R^w, -C(O)-R^w, C(O)NR^hR^w, SO₂NR^hR^w, CO₂R^w, OC(O)R^w, OC(O)NR^hR^w, NR^hC(O)R^w, NR^hC(O)NR^hR^w, or a phenyl or heteroaryl group which is in turn optionally substituted with from one to four Rⁱ groups or with one to two C₁-3 straight- or branched- chain alkyl groups, said alkyl groups being
 15 unsubstituted or substituted with one to four Rⁱ groups;
 one R* group is:



- 20 and e , g , x , y and z represent CR^m, N or N⁺R^k, provided that no more than one of e , g , x , y and z in any given structure represents N⁺R^k. R^k and R^m are as originally defined. Within this subset, all other variables are as originally defined with respect to formula I.

- 25 Another preferred subset of compounds of the invention is represented by formula Ia:

- 18 -



or a pharmaceutically acceptable salt thereof, wherein:

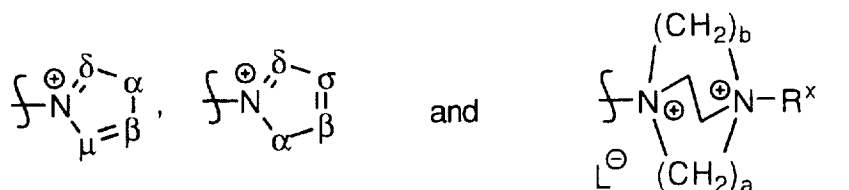
CO₂M represents a carboxylate anion;

- 5 one R group which is attached to the sulfonamide platform contains a positively charged moiety, and the other R groups are selected from hydrogen and R*;

R^d is as originally defined;

Q is selected from the group consisting of:

10



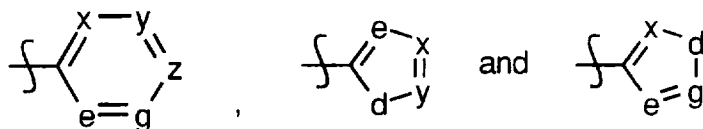
wherein L⁻, a and b are as originally defined, and

- R^x represents a member selected from the group consisting of:
- 15 hydrogen or a C₁-8 straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO₂, NR^w, N⁺R^hR^w, or -C(O)-, said chain being unsubstituted or substituted with one to four of halo, CN, NO₂, OR^w, SR^w, SOR^w, SO₂R^w, NR^hR^w, N⁺(R^h)₂R^w, -C(O)-R^w, C(O)NR^hR^w, SO₂NR^hR^w, CO₂R^w,
 20 OC(O)R^w, OC(O)NR^hR^w, NR^hC(O)R^w, NR^hC(O)NR^hR^w, or a phenyl or heteroaryl group which is in turn optionally substituted with from one to four Rⁱ groups or with one to two C₁-3 straight- or branched- chain alkyl groups, said alkyl groups being unsubstituted or substituted with one to four Rⁱ groups;
- 25 R^h represents hydrogen or a C₁-6 straight or branched chain alkyl group;

R^w is as originally defined;

- 19 -

R* is selected from:

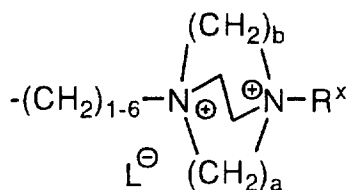


- 5 wherein d represents NR^k; R^k represents -C₁₋₆ straight or branched chain alkyl; and e, g, x and y represent CR^m or N⁺R^k, with R^k as defined above and R^m representing hydrogen.

Within this subset, all other variables are as originally defined with respect to formula I.

- 10 Another more preferred subset of compounds of the invention is represented by formula Ia wherein:

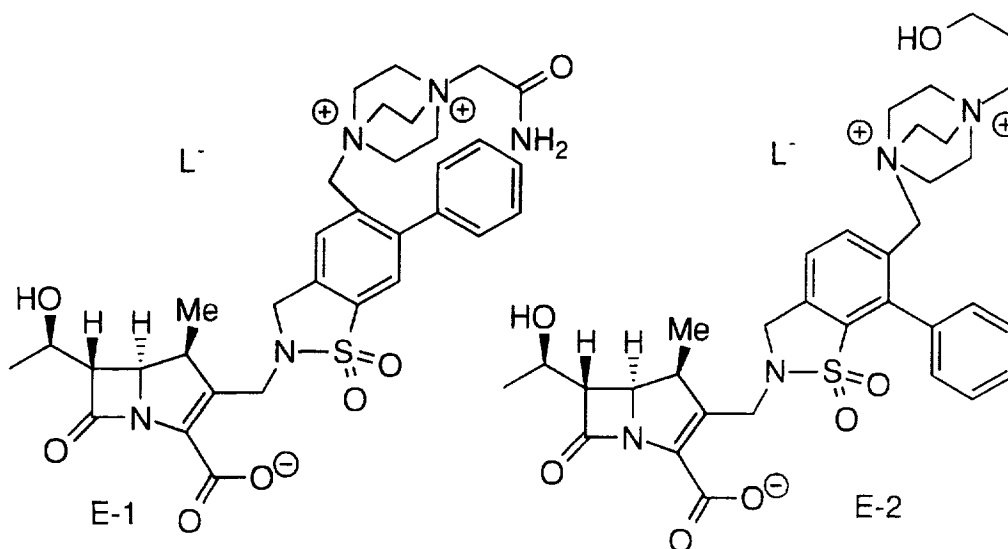
one R represents



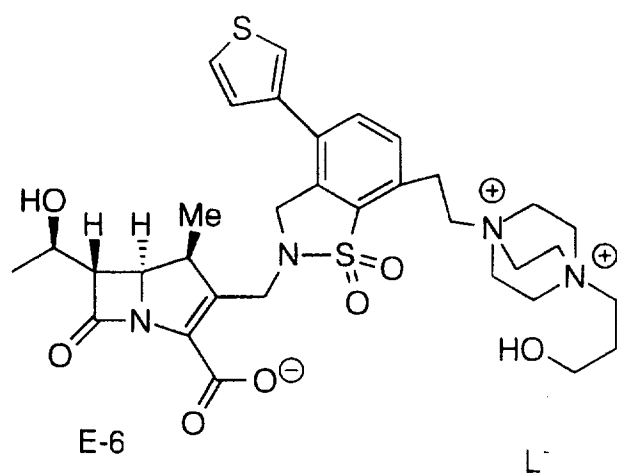
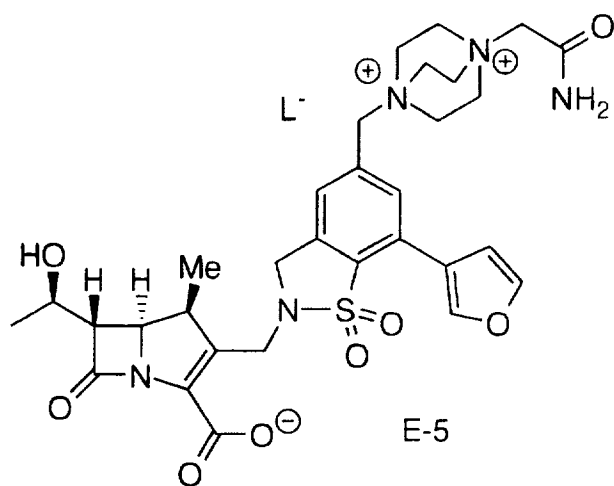
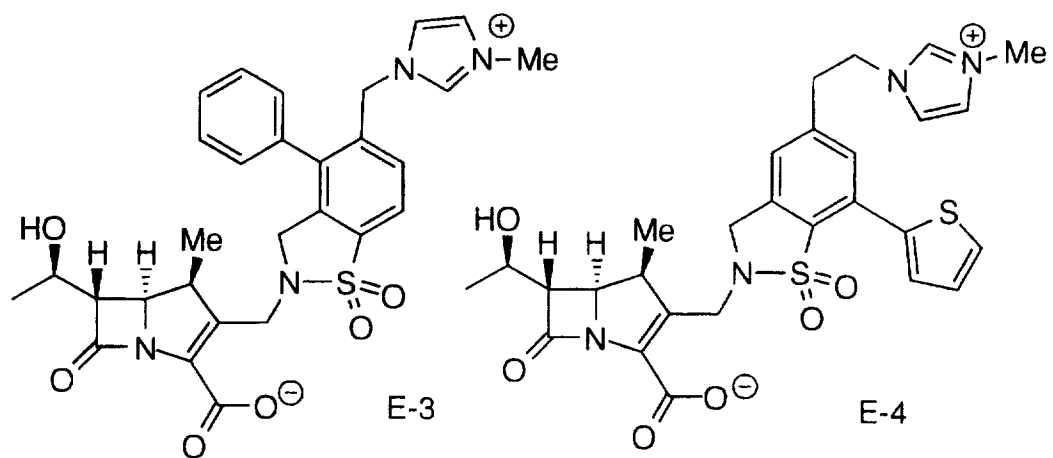
15

and R^x, a, b and L⁻ are as originally defined.

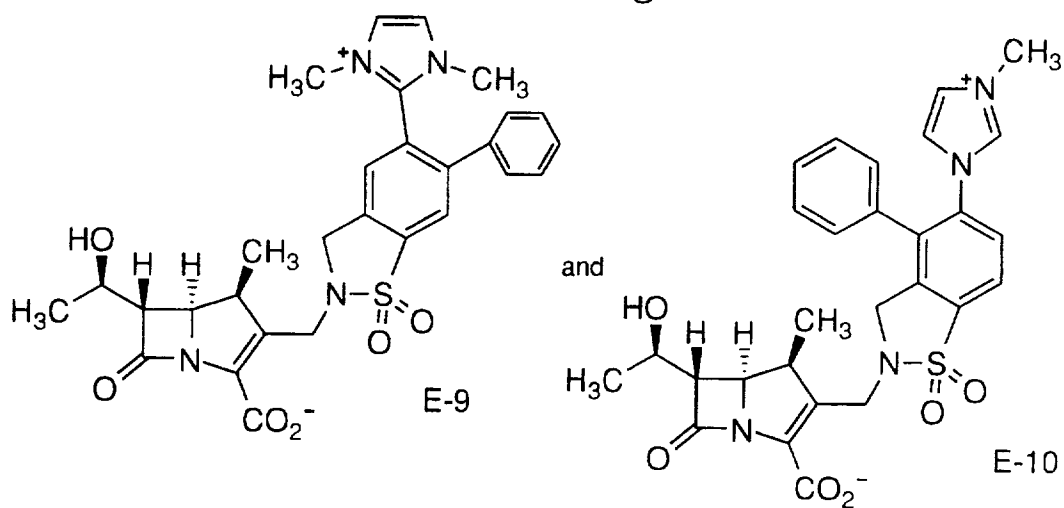
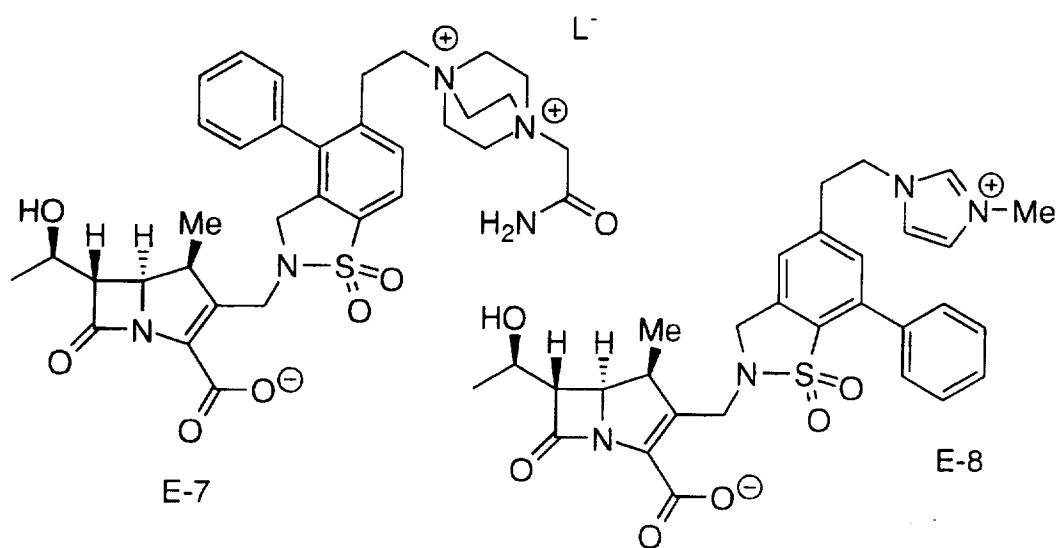
Representative examples of compounds of the invention are as follows:



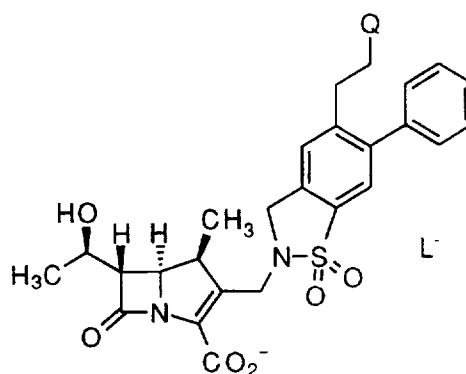
- 20 -



- 21 -



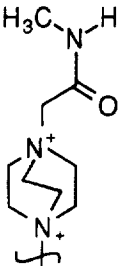
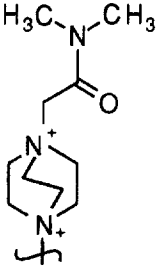
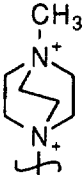
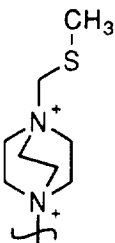
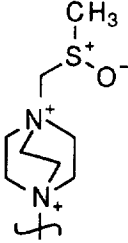
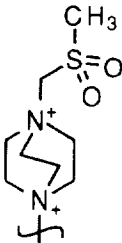
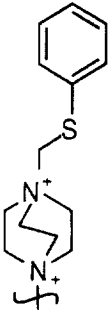
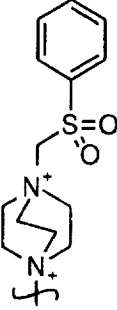
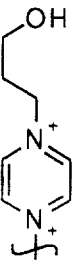
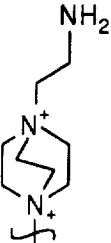
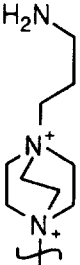
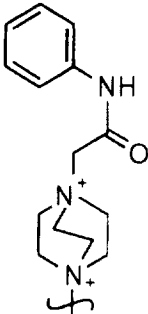
- 22 -



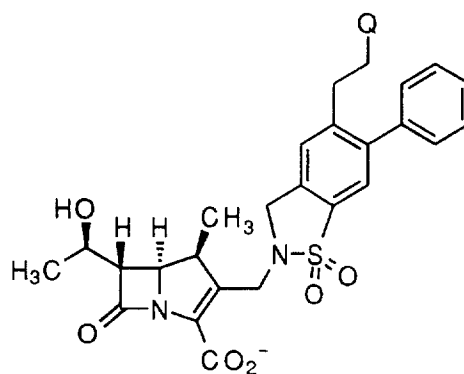
TABLE

#	Q	#	Q	#	Q
11		12		13	
		Ph = phenyl			
14		15		16	

- 23 -

17		18		19	
20		21		22	
23		24		25	
26		27		28	

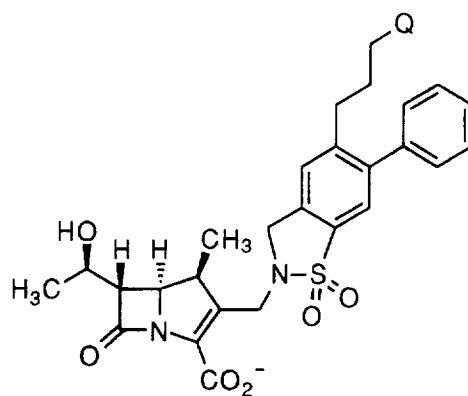
- 24 -



TABLE

#	Q	#	Q	#	Q
29		30		31	
32		33		34	

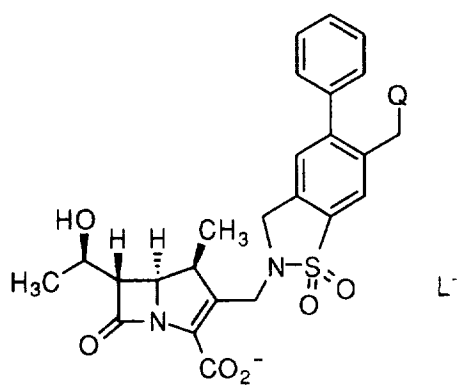
- 25 -



TABLE

#	Q	#	Q	#	Q
35		36		37	

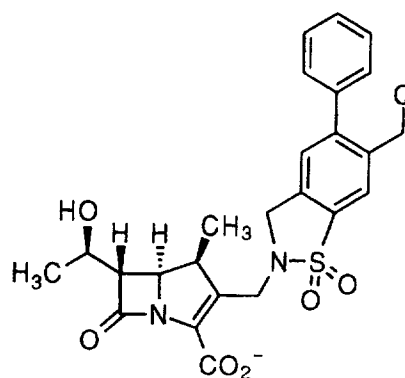
- 26 -



TABLE

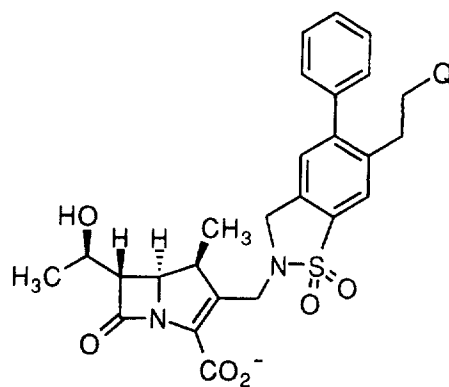
#	Q	#	Q	#	Q
38		39		40	

- 27 -



TABLE

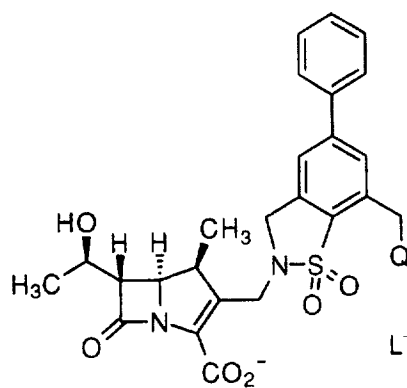
#	Q	#	Q	#	Q
41		42		43	



TABLE

#	Q	#	Q	#	Q
44		45		46	

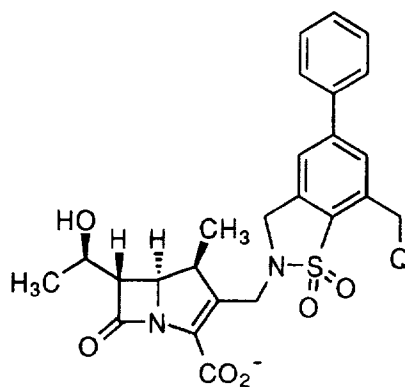
- 28 -



TABLE

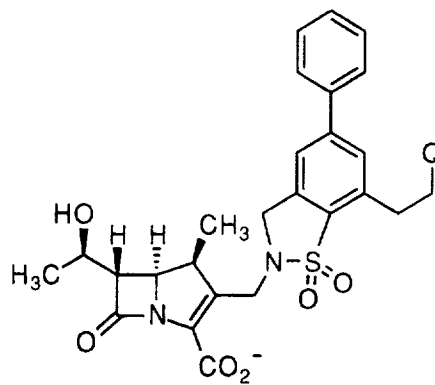
#	Q	#	Q	#	Q
47		48		49	

- 29 -



TABLE

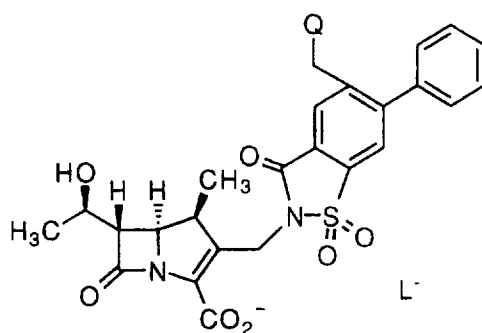
#	Q	#	Q	#	Q
50		51		52	



TABLE

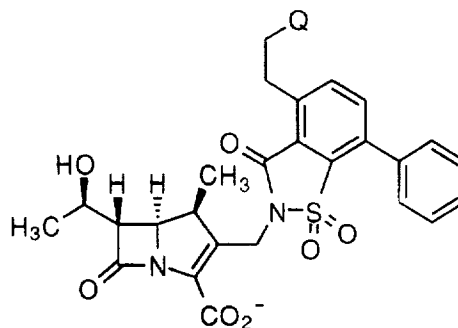
#	Q	#	Q	#	Q
53		54		55	

- 30 -



TABLE

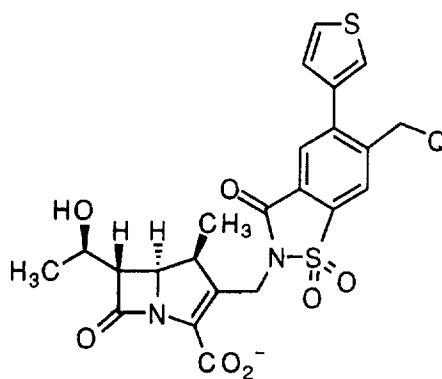
#	Q	#	Q	#	Q
56		57		58	



TABLE

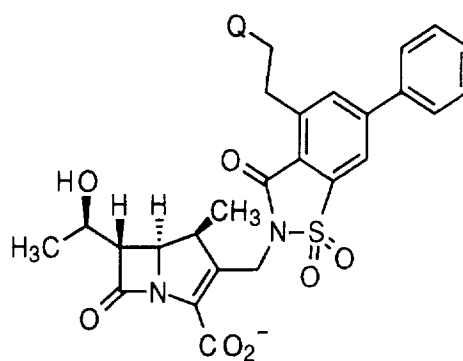
#	Q	#	Q	#	Q
59		60		61	

- 31 -

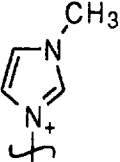
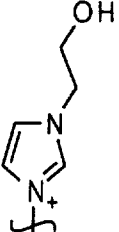
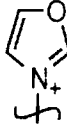


TABLE

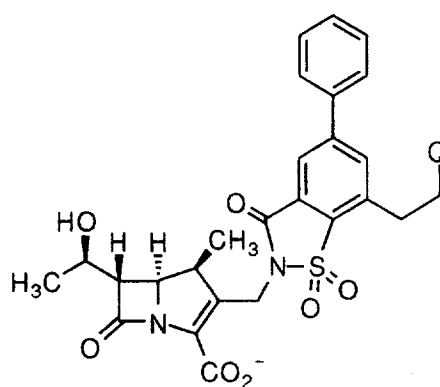
62		63		64	
----	--	----	--	----	--



TABLE

#	Q	#	Q	#	Q
65		66		67	

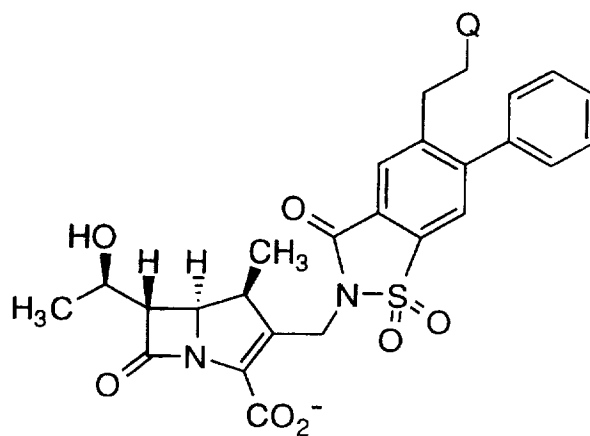
- 32 -



TABLE

#	Q	#	Q	#	Q
68	Chemical structure of a quaternary ammonium salt. The cation consists of a 1,4-bis(methylene)pyrrolidinium ring with a 2-aminoethyl group (-CH₂CH₂NH₂) attached to one of the methylene groups. The counterion is L⁻.	69	Chemical structure of a quaternary ammonium salt. The cation consists of a 1,4-bis(methylene)pyrrolidinium ring with a 2-hydroxyethyl group (-CH₂CH₂OH) attached to one of the methylene groups. The counterion is L⁻.	70	Chemical structure of a quaternary ammonium salt. The cation consists of a 2-methylpyridinium ring with a lithium counterion (L⁻).

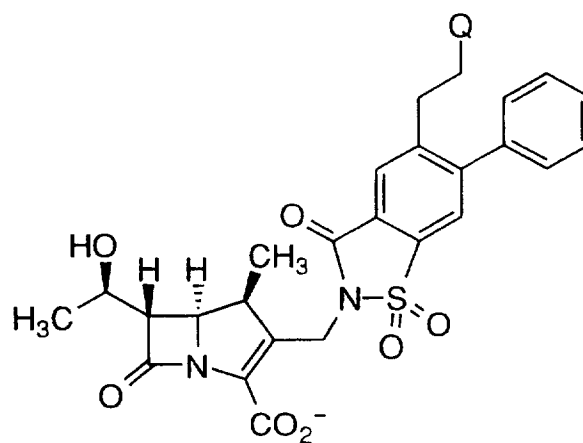
- 33 -



TABLE

#	Q	#	Q	#	Q
71	Chemical structure of a quaternary ammonium salt. The cation is a 1,4-bis(trimethylammonio)butane derivative. The Q group is a benzyl group attached to an amide group (NH_2).	72	Chemical structure of a quaternary ammonium salt. The cation is a 1,4-bis(trimethylammonio)butane derivative. The Q group is a 2-hydroxyethyl group.	73	Chemical structure of a quaternary ammonium salt. The cation is a 1,4-bis(trimethylammonio)butane derivative. The Q group is a 4-methylpyridinium group.

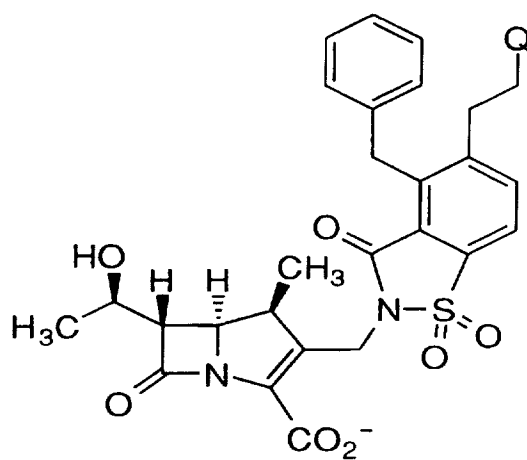
- 34 -



TABLE

#	Q	#	Q	#	Q
74		75		76	

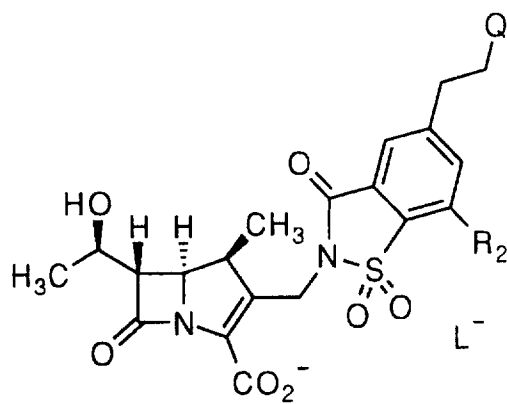
- 35 -



TABLE

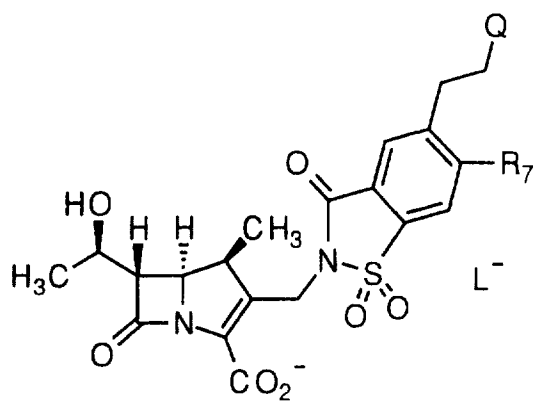
#	Q	#	Q	#	Q
77		78		79	

- 36 -



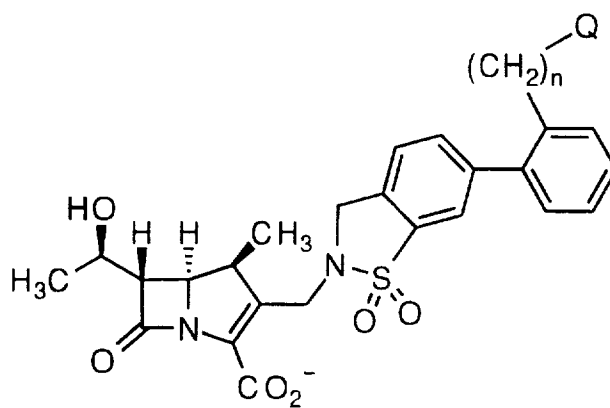
R_2	Q	R_2	Q	R_2	Q	R_2	Q
Cl		C_6H_5					

- 37 -



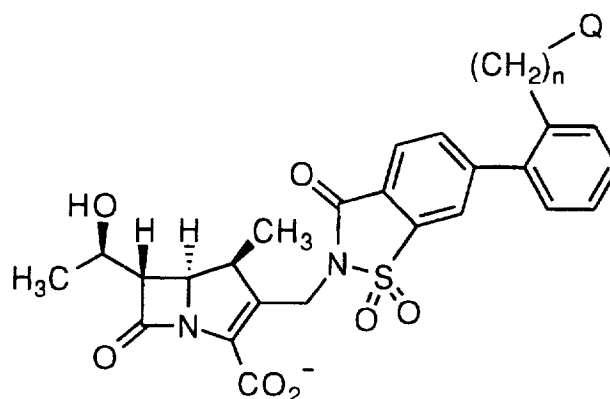
R_7	Q	R_7	Q	R_7	Q	R_7	Q
Cl							

- 38 -



n	Q	n	Q	n	Q	n	Q
1		2		1		2	

- 39 -

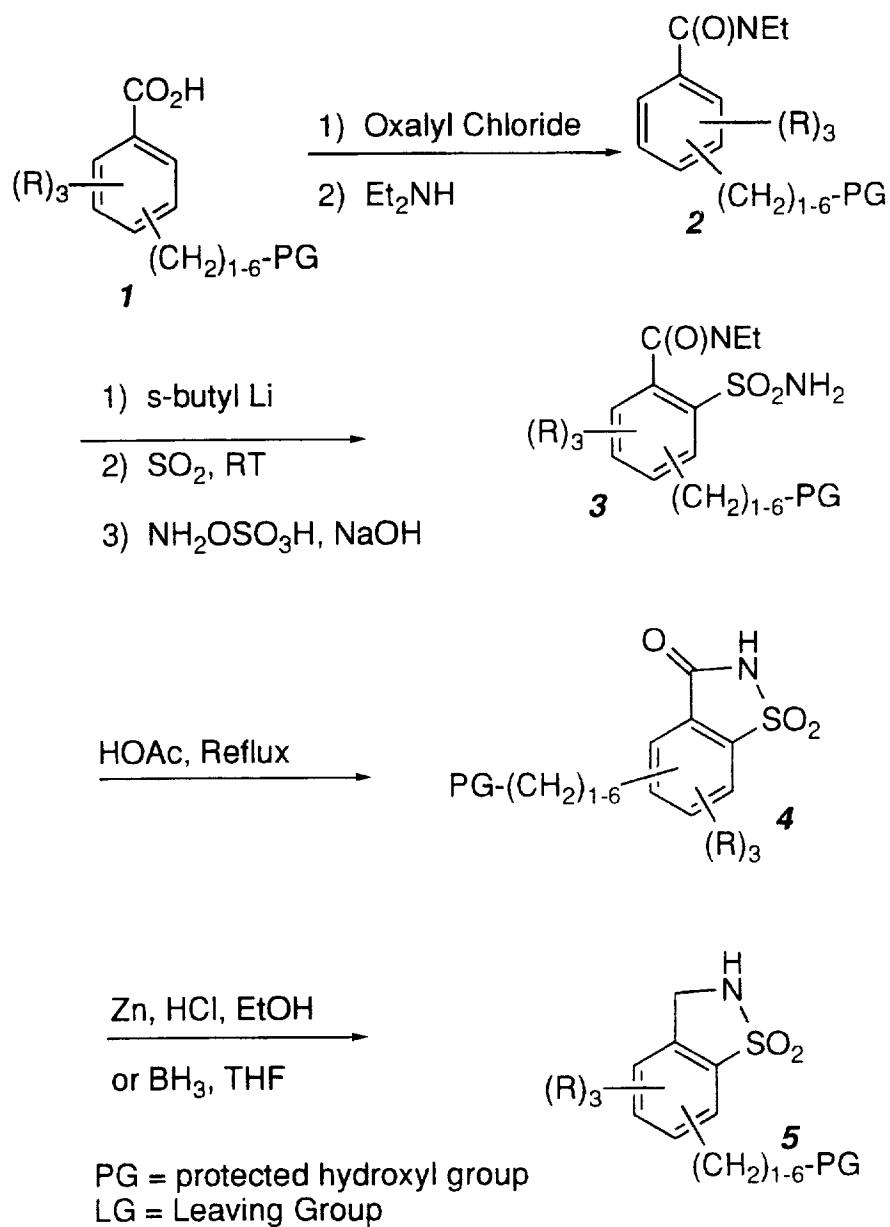


n	Q	n	Q	n	Q	n	Q
1		2		1		2	

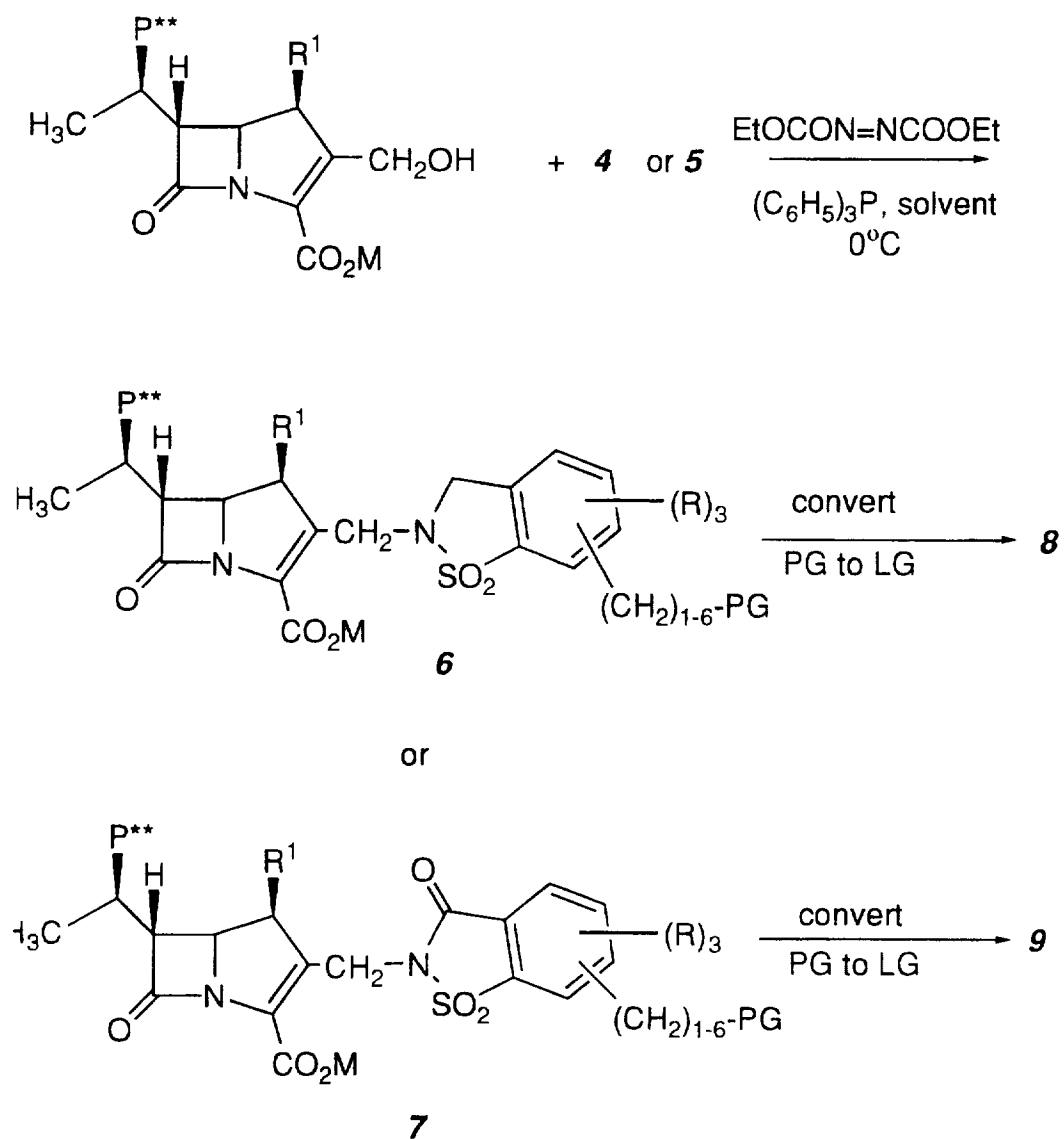
wherein Q is as defined in the tables and L^- represents a pharmaceutically acceptable counterion.

- 5 The compounds of the present invention are prepared by reacting a suitably protected, activated 2-hydroxymethyl-carbapen-2-em-3-carboxylate with a sulfonamide containing ring system, modifying the thus-introduced side chain as desired, and then removing any protecting groups which are present to afford the desired final
- 10 product. The process is illustrated by the following generic scheme:

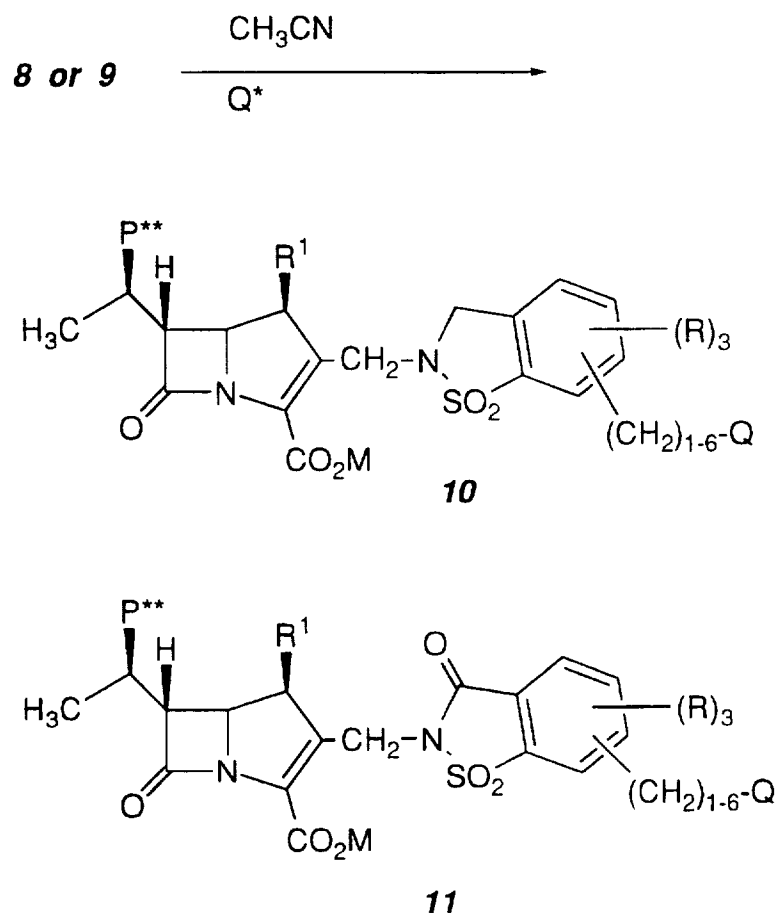
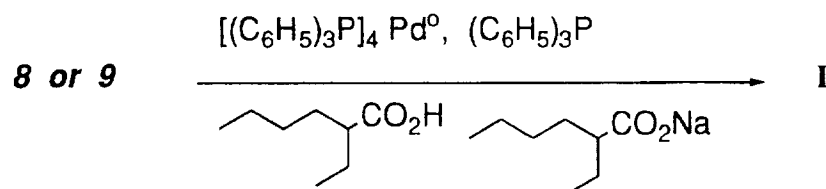
- 40 -

SCHEME 1

- 41 -

SCHEME 2

- 42 -

SCHEME 3**SCHEME 4**

5

With reference to the Schemes above, P, R¹, R and M are as defined with respect to the compounds of formula I. P** represents

- 43 -

a protected hydroxyl group. PG is also a protected hydroxyl group. LG is an appropriate leaving group. Also, the chain to which LG is attached can be varied within wide limits to include all other values of R which form a bridge between the cyclic sulfonamide aryl platform and the quaternary group.

The cyclic sulfonamide platform can be formed with a protected hydroxyl group in place on the ring *1*, producing *4*, which can be converted to the dihydro compound *5*. The cyclic sulfonamide is then reacted with a protected carbapen-2-em-3-carboxylate having an activated hydroxymethyl group at the 2-position, via a Mitsunobu reaction between the cyclic sulfonamide and the carbapenem alcohol.

The carbapenem nucleus having a -CH₂OH substituent at position 2 can be obtained in accordance with Schmitt, S. M. et al., J. Antibiotics 41(6): 780-787 (1988), the teachings of which are incorporated herein by reference. The carboxylic acid group at C-3 of the carbapenem is generally protected as a carboxyl protecting group such as p-nitrobenzyl (PNB), allyl, p-methoxybenzyl, trichloroethyl, 2-trimethylsilylethyl, and the like. Furthermore, the hydroxyl group of the 6-(hydroxyethyl) side-chain is protected with a hydroxyl protecting group such as trimethylsilyl (TMS), triethylsilyl (TES), tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), acetyl, allyloxycarbonyl, 2-trimethylsilylethoxy carbonyl, 2-trichloroethoxycarbonyl and the like.

Addition of the cyclic sulfonamide to the carbapenem is accomplished by treating a solution of the hydroxymethyl-carbapenem and the cyclic sulfonamide in a suitable solvent such as tetrahydrofuran (THF), ether, acetonitrile, dimethylformamide (DMF), benzene, dimethylsulfoxide (DMSO), and the like with a (premixed) suitable activating reagent such as diethyl azodicarboxylate (DEAD) / triphenylphosphine, diisopropyl azodicarboxylate (DIAD) / tributylphosphine, and the like, at a temperature between about -20°C and 35°C for about 5 to 90 minutes.

Alternatively, the side chain component and the carbapenem can be mixed together with either the azodicarboxylate or the phosphine

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reagent in a suitable solvent and the other component of the activating reagent (the phosphine or the azodicarboxylate, respectively) can be added to that mixture. Once the sulfonamide, carbapenem and activating reagent(s) have been mixed, the reaction is allowed to proceed at a temperature between about -20 °C and 35 °C for about 5 to 90 minutes.

The resulting mixture is then subjected to a standard work-up procedure familiar to those skilled in the art to afford a crude 2-methyl substituted carbapenem which is purified, if necessary, by recrystallization or by chromatography on silica gel, eluting with a suitable solvent or mixture of two or more solvents, such as hexane, ethyl acetate, ether, benzene, dichloromethane, chloroform, acetone, methanol and the like.

Modification of the side chain of compounds **6** or **7** is generally necessary to introduce the charged substituent Q. This may entail conversion of the protected hydroxyl group to a leaving group by deprotection, followed by activation, such as by converting the hydroxyl to a leaving group, e.g., a mesylate or triflate, followed by displacement with a heterocyclic or tertiary nitrogen containing species to give a quaternary compound. Quaternization is best accomplished before removal of the protecting groups. For compounds which contain a hydroxyl group in the side chain, a positively charged substituent may be introduced into the side chain by first activating the hydroxyl group by converting it to a suitable leaving group such as a triflate, mesylate, tosylate, iodide, chloride, bromide, and the like, and then displacing the resulting leaving group with a quaternary compound, such as N-methylimidazole, N-(2-hydroxyethyl)-imidazole, N-methyl-diazabicyclooctane, 1-(carbamoylmethyl)-4-aza-1-azoniabicyclo-[2.2.2.]-octane, 1-(3-hydroxyprop-1-yl)-4-aza-1-azoniabicyclo-[2.2.2.]-octane, pyridine, morpholine and the like which contains a nitrogen atom that can act as a nucleophile. Alternatively, in some cases, the charged substituent may be incorporated in the side chain before addition of the sulfonamide to the carbapenem or may be introduced after deprotection. However, introduction of the charged substituent by modification before deprotection as in Scheme 4 is greatly preferred.

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Conversion of the hydroxyl group to a suitable leaving group is accomplished by treating the hydroxyl substituted compound in a suitable solvent such as dichloromethane, tetrahydrofuran, ether, benzene, and the like with an activating reagent, such as trifluoromethanesulfonic anhydride, methanesulfonic anhydride, toluenesulfonic anhydride, methanesulfonyl chloride, benzenesulfonyl chloride, toluenesulfonyl chloride, and the like in the presence of a suitable base such as triethylamine, tributylamine, diisopropylethylamine, and the like at a temperature between about -100°C and 0°C for about 5 to 120 minutes. The intermediate thus obtained contains a leaving group, which may be converted to an alternative leaving group, iodide, by treating a solution of the intermediate in a suitable solvent such as acetone, methyl ethyl ketone, and the like at about -10°C to 50°C with an excess of sodium iodide or potassium iodide for about 0.25 to 24 hours.

In many cases, the iodide is obtained in sufficiently pure form that it may be used without further purification. For ease of handling, the iodide, if not crystalline, may be lyophilized from benzene to afford an amorphous, easily handled, solid.

The activated hydroxyl group or iodide is displaced by reacting the activated intermediate with reagent Q*. Q* represents a group which reacts with an activated intermediate in a manner which results in the incorporation in the product of a member of the group defined as Q above. Thus, Q* may be viewed as a precursor of Q. In some cases, activation and displacement of the hydroxyl group may be accomplished in a single step. The activating reagent is added to a solution of the hydroxyl substituted compound in the presence of a suitable base in a suitable solvent such as dichloromethane, tetrahydrofuran, ether, DMF, benzene, acetonitrile, DMSO, and the like as described in the preceding paragraphs. The resulting activated intermediate is treated with 1-3 molar equivalents of compound Q* at a temperature between about -78°C and 50°C for about 15 to 120 minutes. In some cases, it is desirable to form the activated intermediate in one solvent, isolate the activated intermediate, and conduct the

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displacement reaction in a different solvent. In other cases, the displacement may be conducted without isolation of the intermediate and, in cases where Q* is also used as a base, may even be concurrent with the formation of the activated intermediate.

5 In cases where the displacement reaction is best accomplished by using the iodide, a solution of the iodide is combined with an approximately equivalent amount (0.9 - 1.05 molar equivalents) of compound Q*. A silver salt of a non-nucleophilic acid, such as silver trifluoromethanesulfonate, silver tetrafluoroborate and the like is then
10 added. Although the reaction will proceed in the absence of the silver salt, the reaction proceeds more rapidly in the presence of the silver salt. In addition, the silver salt assists in the removal of the displaced iodide from the reaction mixture which can improve the efficiency of subsequent steps. The resulting mixture is then subjected to a standard
15 work-up procedure familiar to those skilled in the art to afford a crude product which is purified, if necessary, by recrystallization or chromatography.

 An alternative method for introducing a positive charge into the side chain may be applied to side chains that contain (Q) a
20 nitrogen atom which may be quaternized by reaction with a suitable alkylating reagent, such as methyl iodide, methyl bromide, benzyl trichloroacetimidate, methyl trifluoromethanesulfonate, triethyloxonium tetrafluoroborate, and the like. Quaternization of the nitrogen atom in the side chain is effected by treating a solution of the compound with a
25 slight excess (1.05 to 1.2 molar equivalents) of the alkylating reagent.

 The synthesis of the target compound is completed by removing any protecting groups which are present in the penultimate intermediate using standard techniques which are well known to those skilled in the art. This is shown in Scheme 4. The deprotected final
30 product is then purified, as necessary, using standard techniques such as ion exchange chromatography, HPLC on reverse phase silica gel, MPLC on reverse phase polystyrene gel, and the like or by recrystallization.

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The final product may be characterized structurally by standard techniques such as NMR, IR, MS, and UV. For ease of handling, the final product, if not crystalline, may be lyophilized from water to afford an amorphous, easily handled solid.

5 The compounds of the present invention are valuable antibacterial agents active against various Gram-positive and to a lesser extent Gram-negative bacteria, and accordingly find utility in human and veterinary medicine.

10 Many of the compounds of the present invention are biologically active against MRSA/MRCNS. In vitro antibacterial activity is predictive of in vivo activity when the compounds are administered to a mammal infected with a susceptible bacterial organism.

15 Using standard susceptibility tests, the compounds of the invention are determined to be active against MRSA.

 The compounds of the invention can be formulated in pharmaceutical compositions by combining the compound with a pharmaceutically acceptable carrier. Examples of such carriers are set forth below.

20 The compounds may be employed in powder or crystalline form, in liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically, orally and parenterally by injection (intravenously or intramuscularly).

25 Compositions for injection, a preferred route of delivery, may be prepared in unit dosage form in ampules, or in multidose containers. The injectable compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain various formulating agents. Alternatively,
30 the active ingredient may be in powder (lyophilized or non-lyophilized) form for reconstitution at the time of delivery with a suitable vehicle, such as sterile water. In injectable compositions, the carrier is typically comprised of sterile water, saline or another

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injectable liquid, e.g., peanut oil for intramuscular injections. Also, various buffering agents, preservatives and the like can be included.

Topical applications may be formulated in carriers such as hydrophobic or hydrophilic bases to form ointments, creams,
5 lotions, in aqueous, oleaginous or alcoholic liquids to form paints or in dry diluents to form powders.

Oral compositions may take such forms as tablets, capsules, oral suspensions and oral solutions. The oral compositions may utilize carriers such as conventional formulating agents, and
10 may include sustained release properties as well as rapid delivery forms.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated, the route and frequency of administration, the sensitivity of the pathogen
15 to the particular compound selected, the virulence of the infection and other factors. Such matters, however, are left to the routine discretion of the physician according to principles of treatment well known in the antibacterial arts. Another factor influencing the precise dosage regimen, apart from the nature of the infection and
20 peculiar identity of the individual being treated, is the molecular weight of the compound.

The compositions for human delivery per unit dosage, whether liquid or solid, may contain from about 0.01% to as high as about 99% of active material, the preferred range being from about
25 10-60%. The composition will generally contain from about 15 mg to about 2.5 g of the active ingredient; however, in general, it is preferable to employ dosage amounts in the range of from about 250 mg to 1000 mg. In parenteral administration, the unit dosage will typically include the pure compound in sterile water solution or in
30 the form of a soluble powder intended for solution, which can be adjusted to neutral pH and isotonic.

The invention described herein also includes a method of treating a bacterial infection in a mammal in need of such treatment

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comprising administering to said mammal a compound of formula I in an amount effective to treat said infection.

The preferred methods of administration of the Formula I antibacterial compounds include oral and parenteral, e.g., i.v.
5 infusion, i.v. bolus and i.m. injection.

For adults, about 5-50 mg of Formula I antibacterial compound per kg of body weight given one to four times daily is preferred. The preferred dosage is 250 mg to 1000 mg of the antibacterial given one to four times per day. More specifically, for
10 mild infections a dose of about 250 mg two or three times daily is recommended. For moderate infections against highly susceptible gram positive organisms a dose of about 500 mg three or four times daily is recommended. For severe, life-threatening infections against organisms at the upper limits of sensitivity to the antibiotic, a dose of
15 about 1000-2000 mg three to four times daily may be recommended.

For children, a dose of about 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg is typically recommended.

The compounds of Formula I are of the broad class
20 known as carbapenems. Many carbapenems are susceptible to attack by a renal enzyme known as dehydropeptidase (DHP). This attack or degradation may reduce the efficacy of the carbapenem antibacterial agent. Many of the compounds of the present invention, on the other hand, are less subject to such attack, and therefore may not require
25 the use of a DHP inhibitor. However, such use is optional and contemplated to be part of the present invention. Inhibitors of DHP and their use with carbapenems are disclosed in, e.g., [European Patent Application Nos. 79102616.4, filed July 24, 1979 (Patent No. 0 007 614); and 82107174.3, filed August 9, 1982 (Publication No.
30 0 072 014)].

The compounds of the present invention may, where DHP inhibition is desired or necessary, be combined or used with the appropriate DHP inhibitor as described in the aforesaid patents and published application. The cited European Patent Applications

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define the procedure for determining DHP susceptibility of the present carbapenems and disclose suitable inhibitors, combination compositions and methods of treatment. A preferred weight ratio of Formula I compound: DHP inhibitor in the combination

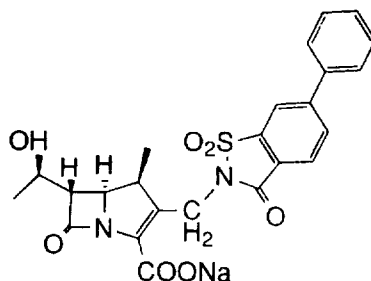
5 compositions is about 1:1.

A preferred DHP inhibitor is 7-(L-2-amino-2-carboxy-ethylthio)-2-(2,2-dimethylcyclopropanecarboxamide)-2-heptenoic acid or a useful salt thereof.

10 The invention is further described in connection with the following non-limiting examples.

EXAMPLE 1

15 SODIUM (1S, 5R, 6S) 2-(1,1-DIOXO-6-PHENYL-1,2-DIHYDRO-1-BENZO[D]ISOTHIAZOL-3-ONE-2-YL)METHYL-6-[1(R)-HYDROXYETHYL]-1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE



STEP 1

20 4-BIPHENYL-CARBOXYLIC ACID DIETHYLAMIDE

To 4-biphenyl carboxylic acid (1.98 g, 10 mmol) dissolved in methylene chloride (30 ml) and cooled to 0°, was added dropwise, oxalyl chloride (1.75 ml, 20 mmol) followed by DMF (0.1 ml). The mixture was allowed to stir at 0° for 0.5 hr., the ice bath was removed and stirring was continued for another 45 min. when reaction appeared to be complete. The solvent was removed under reduced pressure and the residue was treated with toluene (10 ml) and evaporated to dryness and the process was repeated to give the acid chloride.

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- The acid chloride was dissolved in methylene chloride (30 ml), cooled to 0° and treated with diethylamine (2.5 ml, 24 mmol) added dropwise. The mixture was stirred at 0° for 0.5 hr. then allowed to warm to room temp. The reaction mixture was diluted with
- 5 methylene chloride, and washed with water, 1N HCl then with satd. NaCl and dried over MgSO₄. Removal of the solvent gave the crude product which was chromatographed on silica gel using 30% EtOAc/hexane as eluant to give the pure product 2.0 g.
- 10 NMR (CDCl₃, 500 MHz) δ 1.17 and 1.27, (2t, broad, CH₂CH₃); 3.34 and 3.58 (broad q, CH₂CH₃); 7.15 to 7.65 (m, ArH)

STEP 2

3-SULFAMOYL-4-BIPHENYL-CARBOXYLIC ACID DIETHYLAMIDE

- 15 THF (3 ml) was cooled to -78°, under nitrogen, s-butyl lithium (0.92 ml, 1.3 M soln. in cyclohexane) was added, followed by N,N,N',N'-tetramethyl-ethylenediamine (0.165 ml, 1 mmol). To this was added dropwise 4-biphenyl-carboxylic acid diethylamide (0.253 g, 1 mmol) in THF (1.5 ml). The solution was stirred at -78° for 1.5 hr.
- 20 Sulfur dioxide (1 ml) was condensed into a dropping funnel under a dry-ice condenser, under nitrogen and added to the reaction mixture dropwise. The reaction mixture was allowed to stir overnight while allowing it to come to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in water/EtOH
- 25 4:1 and cooled to 0°.
- 30 Hydroxylamine-O-sulfonic acid (0.340 g, 3 mmol) was dissolved in water (2 ml) and cooled to 0°. NaOH (0.6 ml, 5N soln) was diluted to 2 ml with water and cooled to 0°. The two solutions were mixed and added to the solution of the sodium salt. The ice bath was removed and the reaction mixture was stirred at room temperature for 6 hr.. The solvent was evaporated to remove most of the EtOH and the residue was extracted with EtOAc. The organic phase was washed with water and satd. NaCl solution, dried over MgSO₄ and evaporated to give the crude product.

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NMR (CDCl₃, 500 MHz) δ 1.19 and 1.32, (2t, CH₂CH₃); 3.28, 3.5, 3.72 (broad q, CH₂CH₃); 7.42 (d, ArH); 7.45 (d, ArH); 7.51 (t, ArH); 7.64 (d, ArH); 7.82 (dd, ArH) 8.29 (d, ArH).

5 STEP 3

1,1-DIOXO-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-3-ONE

3-sulfamoyl-4-biphenyl-carboxylic acid diethylamide from the above reaction was dissolved in HOAc (8 ml) and gently refluxed overnight under nitrogen. The HOAc was removed under reduced pressure. The residue was treated with toluene (10 ml) and evaporated and the procedure was repeated once again. The residue was taken up in EtOAc, washed with HCl (1 N), water and satd. NaCl soln., dried and evaporated. The residue was treated with CHCl₃ to give the product (216 mg).

NMR (ACETONE ⁶D, 500 MHz) δ 7.53 (d, ArH); 7.58 (t, ArH); 7.89 (d, ArH); 8.12 (d, ArH); 7.26 (dd, ArH) 8.38 (d, ArH).

STEP 4

20 ALLYL (1S, 5R, 6S) 2-(1,1-DIOXO-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-3-ONE-2-YL) METHYL-6-[1(R)-(ALLYLOXYCARBONYL)OXYETHYL]-1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE

To a solution of allyl(1S, 5R, 6S)-2-hydroxymethyl)-6-[1(R)-(allyloxycarbonyl)oxyethyl]-1-methylcarbapen-2-em-3-carboxylate (0.035 g, 0.1 mmol), 1,1-dioxo-6-phenyl-1,2-dihydro-1-benzo[d]isothiazol-3-one (0.026 g, 0.11 mmol) and triphenylphosphine (0.032 mg, 0.12 mmol) in THF (0.5 ml), cooled to 0°, under nitrogen, was added diethylazodicarboxylate (0.019 ml, 0.12 mmol). After 30 min. the reaction mixture was evaporated to dryness and the residue was purified by preparative T.L.C. on a 1000 μ silica gel plate using 50% EtOAc/Hexane as eluant to give the title compound (0.032 g).

NMR (CDCl₃, 500 MHz) δ : 1.28 (d, 1-CH₃); 1.47 (d, CH₃CHO); 3.28 (dq, H-1); 3.44 (dd, H-6); 4.22 (dd, H-5); 4.61 and

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4.85 (2m, 2 $\underline{\text{CH}_2}$ -CH=CH $\underline{2}$); 5.13 (dq, H-8); 5.1 to 5.52 (m, -CH= $\underline{\text{CH}_2}$); 5.86 to 6.08 (m, $\underline{\text{CH}}$ =CH $\underline{2}$); 4.67 and 5.49 (2d, CH $\underline{2}$ N); 7.48 to 8.15 (m, ArH).

5 STEP 5

SODIUM (1S, 5R, 6S) 2-(1,1-DIOXO-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-3-ONE-2-YL)METHYL-6-[1(R)-HYDROXYETHYL]-1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE

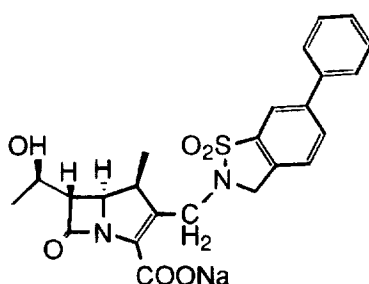
10 Allyl (1S, 5R, 6S) 2-(1,1-dioxo-6-phenyl-1,2-dihydro-1-benzo[d]isothiazol-3-one)methyl-6-[1(R)-(allyloxycarbonyl)oxyethyl]-1-methylcarbapenem-2-em-3-carboxylate (0.032 g, 0.052 mmol) was dissolved in methylene chloride (0.5 ml) and EtOAc (0.5 ml). Sodium 2-ethylhexanoate (0.009 g, 0.054 mmol), 2-ethylhexanoic acid (0.008 g, 15 0.055 mmol) and triphenylphosphine (0.008 g, 0.03 mmol) were added. The reaction was placed under nitrogen and treated with tetrakis (triphenylphosphine)palladium (0.012 g, 0.01 mmol). The reaction mixture was stirred at room temperature for 0.5 hr. The reaction mixture was diluted with ether (2 ml) and the precipitated solid was 20 centrifuged and the supernatant was decanted off. The residue was treated with ether (2 ml) and the solids centrifuged down and the supernatant liquid decanted off. The residual solid was dried under vacuum to give the crude product which was purified on a 1000 μ reverse phase TLC plate developed with 25% CH $\underline{3}$ CN/0.02M pH 7 25 sodium phosphate buffer. The product band was collected and eluted off the silica gel with 50% CH $\underline{3}$ CN/ water. The extract was washed twice with hexane and the aqueous phase was evaporated to about 1 ml and desalted on a 2 ml bed of Amberchrome-161-c resin eluting the product off the resin with 50% CH $\underline{3}$ CN/water. The eluate was freeze dried to 30 give the title compound.

NMR (D $\underline{2}$ O, 500 MHz) δ : 1.13 (d, 1-CH $\underline{3}$); 1.24 (d, $\underline{\text{CH}_3}$ CHO); 3.06 (dq, H-1); 3.41 (dd, H-6); 4.12 (dd, H-5); 4.18 (dq, H-8); 4.52 and 5.23 (2d, CH $\underline{2}$ N); 7.45 (m, ArH); 7.55 (m, ArH); 7.86 (d, ArH); 7.95 (d, ArH); 8.10 (s, ArH).

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EXAMPLE 2

5 SODIUM (1S, 5R, 6S) 2-(1,1-DIOXO-6-PHENYL-1,2-DIHYDRO-1-BENZO[D]ISOTHIAZOL-2-YL)METHYL-6-[1(R)-HYDROXYETHYL]-1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE.



10

STEP 11,1-DIOXO-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOLE

15 1,1-dioxo-6-phenyl-1,2-dihydro-1-benzo[d]isothiazol-3-one from Step 3, Example 1, (0.044 g, 0.17 mmol) was dissolved in THF (2 ml) under nitrogen. Diborane (0.34 ml, 1 M soln in THF) was added and the mixture refluxed for 5 hr. The reaction mixture was treated with MeOH (2 ml) and evaporated to dryness, the residue was taken up in toluene (5 ml) and evaporated to dryness to give the product.

20 NMR (ACETONE d_6 , 500 MHz) δ 4.58 (d, CH₂N); 7.43 (t, ArH); 7.51 (t, ArH); 7.65 (d, ArH); 7.76 (d, ArH); 7.96 (dd, ArH) 8.38 (s, ArH).

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STEP 2

- ALLYL (1S, 5R, 6S) 2-(1,1-DIOXO-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-2-YL)METHYL-6-[1(R)-(ALLYLOXYCARBONYL)OXYETHYL]-1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE

Following the procedure of Step 4, Example 1, but substituting the product of Step 1, Example 2 in place of the product of Step 3, Example 1, one obtains the title compound.

- NMR (CDCl₃, 500 MHz) δ : 1.29 (d, 1-CH₃); 1.48 (d, CH₃CHO); 3.42 (dq, H-1); 3.47 (dd, H-6); 4.24 (dd, H-5); 5.16 (dq, H-8); 4.22 and 4.74 (2d, CH₂N); 5.98 (m, CH=CH₂); 4.34 and 4.45 (2d, CH₂N); 7.46 (m, ArH); 7.6 (d, ArH); 7.84 (dd, ArH); 8.02 (d, ArH).

15 STEP 3

SODIUM (1S, 5R, 6S) 2-(1,1-DIOXO-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-2-YL)METHYL-6-[1(R)-HYDROXYETHYL]-1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE

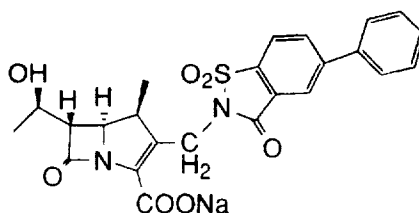
- 20 Following the procedure of Step 5, example 1, but substituting the product of step 2, Example 2 in place of the product of Step 4, Example 1, one prepares the title compound.

- NMR (D₂O, 500 MHz) δ : 1.15 (d, 1-CH₃); 1.25 (d, CH₃CHO); 3.21 (dq, H-1); 3.44 (dd, H-6); 4.18 (dd, H-5); 4.22 (dq, H-8); 4.13 and 4.64 (2d, CH₂N); 4.30 and 4.47 (2d, CH₂N); 7.48 (m, ArH); 7.62 (d, ArH); 7.89 (d, ArH); 8.02 (s, ArH).

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EXAMPLE 3

SODIUM (1S, 5R, 6S) 2-(1,1-DIOXO-5-PHENYL-1,2-
DIHYDRO-1-BENZO[D]ISOTHIAZOL-3-ONE-2-YL)
METHYL-6-[1(R)-HYDROXYETHYL]-1-
METHYLCARBAPENEM-2-EM-3-CARBOXYLATE

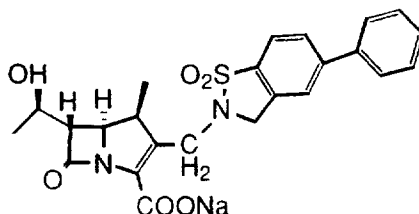


Starting with 3-biphenyl carboxylic acid and following the
 procedures of Example 1, Steps 1 to 5, one obtains the title compound.

NMR (D₂O, 500 MHz) δ : 1.17 (d, 1-CH₃); 1.25 (d, CH₃CHO); 3.12
 (dq, H-1); 3.43 (dd, H-6); 4.14 (dd, H-5); 4.21 (dq, H-8); 4.60 and 5.28
 (2d, CH₂N); 7.51 (m, ArH); 7.66 (d, ArH); 8.07 (d, ArH); 8.11 (s,
 ArH); 8.13 (d, ArH).

EXAMPLE 4

SODIUM (1S, 5R, 6S) 2-(1,1-DIOXO-5-PHENYL-
1,2-DIHYDRO-1-BENZO[D]ISOTHIAZOL-2-YL)
METHYL-6-[1(R)-HYDROXYETHYL]-1-
METHYLCARBAPENEM-2-EM-3-CARBOXYLATE

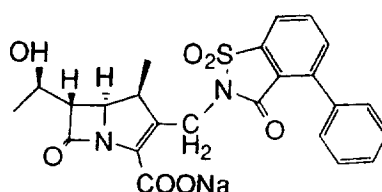


Starting with 3-biphenyl carboxylic acid and following the
 procedures of Example 1, Steps 1 to 3, followed by Example 2, steps 1
 to 3, one obtains the title compound.

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EXAMPLE 5

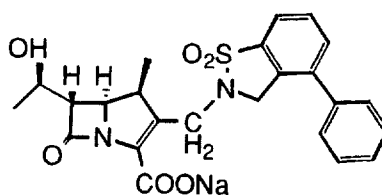
5 SODIUM (1S, 5R, 6S) 2-(1,1-DIOXO-4-PHENYL-1,2-DIHYDRO-1-BENZO[D]ISOTHIAZOL-3-ONE-2-YL)METHYL-6-[1(R)-HYDROXYETHYL]-1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE



10 Starting with 2-biphenyl carboxylic acid and following the procedures of Example 1, Steps 1 to 5, one obtains the title compound.

EXAMPLE 6

15 SODIUM (1S, 5R, 6S) 2-(1,1-DIOXO-4-PHENYL-1,2-DIHYDRO-1-BENZO[D]ISOTHIAZOL-2-YL)METHYL-6-[1(R)-HYDROXYETHYL]-1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE



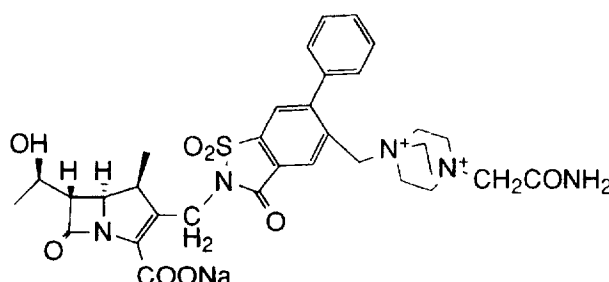
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Starting with 2-biphenyl carboxylic acid and following the procedures of Example 1, Steps 1 to 3, followed by Example 2, steps 1 to 3, one obtains the title compound.

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EXAMPLE 7

(1S, 5R, 6S)-2-[5-(4-CARBAMOYLMETHYL-1,4-DIAZONIABICYCLO[2.2.2]OCT-1-YL(METHYL)-1,1-DIOXO-6-PHENYL-1,2-DIHYDRO-1-BENZO[D]ISOTHIAZOL-3-ONE-2YL]METHYL-6-[(1R)-HYDROXY-ETHYL]-1-METHYLCARBAPEN-2-EM-3-CARBOXYLATE CHLORIDE

STEP 14-BROMO-3-METHYL BENZOIC ACID DIETHYLAMIDE

4-bromo-3-methyl benzoic acid (20 mmol) is converted to the diethylamide following the procedure of Step 1, Example 1.

STEP 23-METHYL-4-PHENYL BENZOIC ACID DIETHYLAMIDE

4-bromo-3-methyl benzoic acid diethylamide (15 mmol) and phenylboronic acid (16.5 mmol) are dissolved in toluene (10 ml), MeOH (2.5 ml) is added followed by sodium bicarbonate (33 mmol). The reaction is placed under nitrogen, tetrakis(triphenylphosphine) palladium (0.150 g) is added and the mixture is heated at 70° overnight. Ethyl acetates is added to the cooled reaction mixture and the organic phase is washed with water, dried over MgSO₄ and evaporated.

Chromatography on silica gel gives the purified title compound.

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STEP 3

2-SULFAMOYL-5-METHYL-4-PHENYLBENZOIC ACID
DIETHYLAMIDE

5 Following the procedure of Step 2, Example 1; the product
of Step 2, Example 7, is converted to the title compound.

STEP 4

1,1-DIOXO-5-METHYL-6-PHENYL-1,2-DIHYDRO-1-
BENZO[d]ISOTHIAZOL-3-ONE

10 Following the procedure of Step 3, Example 1 on the
product of Step 3, Example 7 one obtains the title compound.

STEP 5

1,1-DIOXO-5-BROMOMETHYL-6-PHENYL-
1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-3-ONE

15 1,1-dioxo-5-methyl-6-phenyl-1,2-dihydro-1-
benzo[d]isothiazol-3-one is dissolved in chloroform and treated with
N-bromosuccinimide (1.2 eq.). The reaction is refluxed until the N-
bromosuccinimide is completely reacted as shown by reaction to starch
20 iodide paper. The reaction mixture is washed with water and sodium
thiosulfate solution, dried over MgSO₄ and evaporated to give the title
compound.

STEP 6

25 ALLYL (1S, 5R, 6S) 2-(1,1-DIOXO-5-BROMOMETHYL-
6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-3-ONE-
2-YL)METHYL-6-[1(R)-(ALLYLOXYCARBONYL)OXYETHYL]-
1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE

30 Following the procedure of Step 4, Example 1; 1,1-
dioxo-5-bromomethyl-6-phenyl-1,2-dihydro-1-benzo[d]isothiazol-
3-one is reacted with allyl(1S, 5R, 6S)-2-hydroxymethyl)-6-[1(R)-
(allyloxycarbonyl)oxyethyl]-1-methylcarbapen-2-em-3-carboxylate
to give the title compound.

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STEP 7

ALLYL (1S, 5R, 6S) 2-(1,1-DIOXO-5-IODOMETHYL-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-3-ONE-2-YL)METHYL-6-[1(R)-(ALLYLOXYCARBONYL)OXYETHYL]-1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE

- 5 To a solution of allyl (1S, 5R, 6S) 2-(1,1-dioxo-5-bromomethyl-6-phenyl-1,2-dihydro-1-benzo[d]isothiazol-3-one-2-yl)methyl-6-[1(R)-(allyloxycarbonyl)oxyethyl]-1-methylcarbapenem-2-em-3-carboxylate in acetone (2 ml) and sodium iodide (5 eq.) is added
10 and the mixture is stirred at room temperature for 75 min. The reaction is partitioned between water and methylene chloride and the organic phase is washed with 5% aqueous NaHSO₃, dried over MgSO₄ and evaporated to give the title compound.

15 STEP 8

(1S, 5R, 6S)-2-[5-(4-CARBAMOYLMETHYL-1,4-DIAZONIABICYCLO[2.2.2]OCT-1-YL(METHYL)-1,1-DIOXO-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-3-ONE-2YL)METHYL-6-[(1R)-HYDROXY-ETHYL]-1-METHYLCARBAPEN-2-EM-3-CARBOXYLATE CHLORIDE

- 20 To a solution of allyl (1S, 5R, 6S) 2-(1,1-dioxo-5-iodomethyl-6-phenyl-1,2-dihydro-1-benzo[d]isothiazol-3-one-2-yl)methyl-6-[1(R)-(allyloxycarbonyl)oxyethyl]-1-methylcarbapenem-2-em-3-carboxylate in acetonitrile is added 1-carbamoylmethyl-4-aza-
25 1-azoniabicyclo-[2.2.2]octane trifluoromethane sulfonate (1.2 eq.) and silver trifluoromethane sulfonate (1.3 eq). The reaction is stirred at room temperature for 1 hr. then filtered and the solvent is evaporated under vacuum. The residue is dissolved in DMF and the solution is cooled in an ice bath. Sodium 2-ethylhexanoate (1.1 eq.), 2-
30 ethylhexanoic acid (1.1 eq.), triphenylphosphine (0.3 eq.) are added and the reaction is placed under nitrogen. Tetrakis(triphenylphosphine) palladium (0.3 eq) is added and the reaction is stirred for 1 hr. Diethyl ether is added to precipitate the product. The supernatant is decanted off and the solid is washed once with ether and dried under vacuum. The

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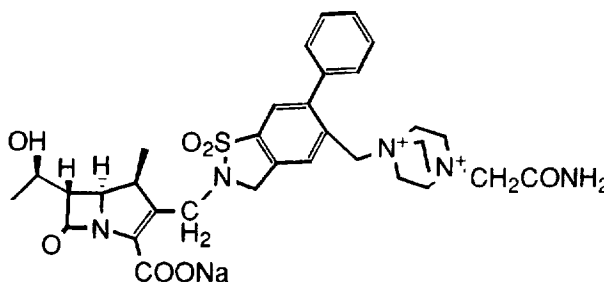
solid is purified by preparative HPLC, followed by desalting on Amberchrome CG-161 resin to give the title compound after freeze drying.

5

EXAMPLE 8

10

(1S, 5R, 6S)-2-[5-(4-CARBAMOYLMETHYL-1,4-DIAZONIABICYCLO[2.2.2]OCT-1-YL(METHYL)-1,1-DIOXO-6-PHENYL-1,2-DIHYDRO-1-BENZO[D]ISOTHIAZOL-2YL)METHYL-6-[(1R)-HYDROXY-ETHYL]-1-METHYLCARBAPEN-2-EM-3-CARBOXYLATE CHLORIDE



15

STEP 1

1,1-DIOXO-5-ACETOXYMETHYL-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-3-ONE

The product of Step 5, Example 7; 1,1-dioxo-5-bromomethyl-6-phenyl-1,2-dihydro-1-benzo[d]isothiazol-3-one is dissolved in DMF and treated with potassium acetate (2 eq.). the reaction is heated at 100° for 1 hour, allowed to cool to room temperature and diluted with EtOAc and washed with water, 5 times, dried over MgSO₄ and evaporated to give the title compound.

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STEP 21,1-DIOXO-5-HYDROXYMETHYL-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOLE

- 1,1-dioxo-5-acetoxymethyl-6-phenyl-1,2-dihydro-1-benzo[d]isothiazol-3-one is dissolved in THF under nitrogen. Diborane (2 molar eq., 1 M soln in THF) is added and the mixture refluxed for 5 hrs. The reaction mixture is treated with MeOH (2 ml) and evaporated to dryness, the residue is taken up in toluene (5 ml) and evaporated to dryness. The residue is taken up in MeOH and treated with sodium methoxide (0.2 eq.). The reaction mixture is stirred at room temperature for 1 hour, AcOH (0.3 eq.) is added and the mixture evaporated to dryness. The residue is chromatographed on silica gel to give the title compound.

STEP 31,1-DIOXO-5-TRIMETHYLSILYLOXYMETHYL-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOLE

- A solution of 1,1-dioxo-5-hydroxymethyl-6-phenyl-1,2-dihydro-1-benzo[d]isothiazol in THF is treated with N,O-Bis(trimethylsilyl)acetamide (2.5 eq.). The mixture is stirred at room temperature for 45 min. and evaporated. The residue is dissolved in methylene chloride and filtered through silica gel and evaporated to give the title compound.

STEP 4ALLYL (1S, 5R, 6S) 2-(1,1-DIOXO-5-HYDROXYMETHYL-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-2-YL)METHYL-6-[1(R)-(ALLYLOXYCARBONYL)OXYETHYL]-1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE

- Following the procedure of Step 4, Example 1; 1,1-dioxo-5-trimethylsilyloxymethyl-6-phenyl-1,2-dihydro-1-benzo[d]isothiazol-3-one is reacted with allyl(1S, 5R, 6S)-2-hydroxymethyl-6-[1(R)-(allyloxycarbonyl)oxyethyl]-1-methylcarbapen-2-em-3-carboxylate

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to give the silylated title compound. This is dissolved in a mixture of THF/water 4:1 and treated with aqueous trifluoromethane sulfonic acid (0.1 eq). After 5 min. the mixture is partitioned between methylene chloride and 1% aqueous sodium bicarbonate. The organic phase is
5 separated, dried over MgSO₄ and evaporated to give the title compound after preparative TLC on silica gel plates.

STEP 5

ALLYL (1S, 5R, 6S) 2-(1,1-DIOXO-5-IODOMETHYL-
10 6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-2-
YL)METHYL-6-[1(R)-(ALLYLOXYCARBONYL)OXYETHYL]-
1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE

To a solution of Allyl (1S, 5R, 6S) 2-(1,1-dioxo-5-hydroxymethyl-6-phenyl-1,2-dihydro-1-benzo[d]isothiazol-2-yl)methyl-
15 6-[1(R)-(allyloxycarbonyl)oxyethyl]-1-methylcarbapenem-2-em-3-carboxylate in dichloromethane cooled in an ice bath under nitrogen is added triethylamine (1.8 eq) followed by methane sulfonyl chloride (1.7 eq.). After 30 min. the reaction is diluted with methylene chloride and washed with 0.1N HCl soln. The organic phase is dried over MgSO₄ and
20 evaporated to give the mesylate. the mesylate is dissolved in acetone and sodium iodide (5 eq.) is added and the mixture is stirred at room temperature for 75 min. The reaction is partitioned between water and methylene chloride and the organic phase is washed with 5% aqueous NaHSO₃, dried over MgSO₄ and evaporated to give the title compound.

25

STEP 6

(1S, 5R, 6S)-2-[5-(4-CARBAMOYLMETHYL-1,4
DIAZONIABICYCLO[2.2.2]OCT-1-YL(METHYL)-1,1-
DIOXO-6-PHENYL-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-
2YL)METHYL-6-[(1R)-HYDROXY-ETHYL]-1-
30 METHYLCARBAPEN-2-EM-3-CARBOXYLATE CHLORIDE

To a solution of allyl (1S, 5R, 6S) 2-(1,1-dioxo-5-iodomethyl-6-phenyl-1,2-dihydro-1-benzo[d]isothiazol-2-yl)methyl-6-[1(R)-(allyloxycarbonyl)oxyethyl]-1-methylcarbapenem-2-em-

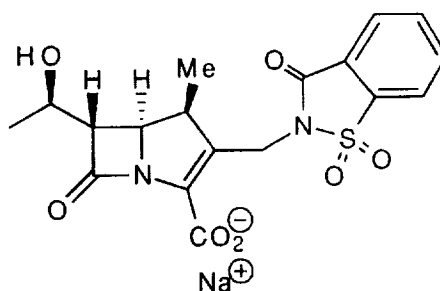
- 64 -

3-carboxylate in acetonitrile is added 1-carbamoylmethyl-4-aza-1-
azoniabicyclo-[2.2.2]octane trifluoromethane sulfonate (1.2 eq.)
and silver trifluoromethane sulfonate (1.3 eq). The reaction is
5 stirred at room temperature for 1 hr. then filtered and the solvent is
evaporated under vacuum. The residue is dissolved in DMF and the
solution is cooled in an ice bath. Sodium 2-ethylhexanoate (1.1 eq.),
2-ethylhexanoic acid (1.1 eq.), triphenylphosphine (0.3 eq.) are
added and the reaction is placed under nitrogen. Tetrakis
(triphenylphosphine)palladium (0.3 eq) is added and the reaction is
10 stirred for 1 hr. Diethyl ether is added to precipitate the product. The
supernatant is decanted off and the solid is washed once with ether and
dried under vacuum. The solid is purified by preparative HPLC,
followed by desalting on amberchrome CG-161 resin to give the title
compound after freeze drying.

15

EXAMPLE 9

SODIUM (1S,5R,6S)-2-((N-(1,2-BENZISOTHIAZOL-3(2H)-
ONE 1,1- DIOXIDE)METHYL)-6-[(1R)-HYDROXYETHYL]-
20 1-METHYLCARBAPEN-2-EM-3-CARBOXYLATE



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STEP 1

5 ALLYL (1S, 5R, 6S) 2-(1,1-DIOXO-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-3-ONE-2-YL)METHYL-6-[1(R)-(ALLYLOXYCARBONYL)OXYETHYL]-1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE

Sacharrin is reacted with allyl(1S, 5R, 6S)-2-hydroxymethyl)-6-[1(R)-(allyloxycarbonyl)oxyethyl]-1-methylcarbapen-2-em-3-carboxylate as described in Step 4, Example 1 to give the title compound.

10 ¹H NMR (CDCl₃, 500 MHz) δ 1.30 (d, 1-CH₃), 1.42 (d, CH₃CHO(ALLOC)), 3.25 (dq, H-1), 3.42 (dd, H-6), 4.20 (dd, H-5), 4.59 and 4.85 (2m's, 2CH₂vinyl), 5.16 (dq, H-8), 5.26- 5.53 (4m's, 4 vinyl H's), 4.62 and 5.45 (2d's, CH₂N), 5.95 and 6.05 (2m's, 2CH₂vinyl), 7.88 (dd, ArH), 7.90 (d, ArH), 7.93 (dd, ArH) and 8.10
15 (d, ArH).

STEP 2

20 SODIUM (1S,5R,6S)-2-((N-(1,2-BENZISOTHIAZOL-3(2H)-ONE 1,1- DIOXIDE)METHYL)-6-[1(R)-HYDROXYETHYL]-1-METHYLCARBAPEN-2-EM-3-CARBOXYLATE

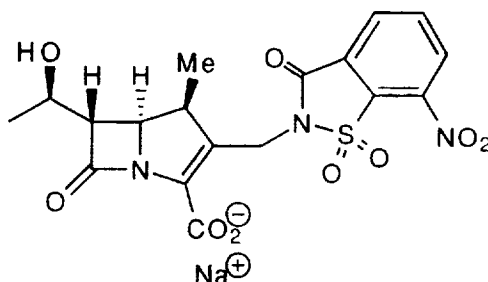
The product of Step 1, Example 9 is deblocked following the procedure of Step 5, Example 1, to give the title compound.

¹H NMR (3:1 D₂O/ CD₃CN, 500 MHz) δ 1.37 (d, 1-CH₃), 1.43 (d, CH₃CHOH), 3.34 (dq, H-1), 3.56 (dd, H-6), 4.31 (dd, H-5),
25 4.38 (dq, H-8), 4.82 and 5.61 (2d's, CH₂N), 8.20 (dd, ArH), 8.25 (dd, ArH) and 8.33 (2d, 2ArH).

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EXAMPLE 10

SODIUM (1S,5R,6S)-2-(((7-NITRO)-N-(1,2-BENZISOTHIAZOL-3(2H)-ONE 1,1- DIOXIDE)METHYL)-6-[(1R)-HYDROXYETHYL]-1-METHYLCARBAPEN-2-EM-3-CARBOXYLATE

STEP 1

ALLYL (1S, 5R, 6S) 2-(1,1-DIOXO-7-NITRO-1,2-DIHYDRO-1-BENZO[d]ISOTHIAZOL-3-ONE-2-YL)METHYL-6-[1(R)-(ALLYLOXYCARBONYLOXYETHYL)-1-METHYLCARBAPENEM-2-EM-3-CARBOXYLATE

Nitro-sacharrin is reacted with allyl(1S, 5R, 6S)-2-hydroxymethyl)-6-[1(R)-(allyloxycarbonyloxyethyl)-1-methylcarbapen-2-em-3-carboxylate as described in Step 4, Example 1 to give the title compound.

¹H NMR (CDCl₃, 500 MHz) d 1.26 (d, 1-CH₃), 1.46 (d, CH₃CHO(ALLOC)), 3.22 (dq, H-1), 3.44 (dd, H-6), 4.20 (dd, H-5), 4.59 and 4.85 (2m's, 2CH₂vinyl), 5.10 (dq, H-8), 5.26- 5.53 (4m's, 4 vinyl H's), 4.67 and 5.58 (2d's, CH₂N), 5.90 and 6.05 (2m's, 2CH₂vinyl), 8.13 (dd, ArH), 8.45 (d, ArH) and 8.68 (d, ArH).

STEP 2

SODIUM (1S,5R,6S)-2-(((7-NITRO)-N-(1,2-BENZISOTHIAZOL-3(2H)-ONE 1,1- DIOXIDE)METHYL)-6-[(1R)-HYDROXYETHYL]-1-METHYLCARBAPEN-2-EM-3-CARBOXYLATE

The product of Step 1, Example 10 is deblocked following the procedure of Step 5, Example 1, to give the title compound.

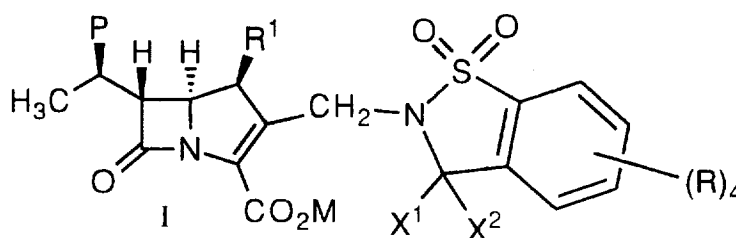
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^1H NMR (3:1 $\text{D}_2\text{O}/\text{CD}_3\text{CN}$, 500 MHz) δ 1.38 (d, 1- CH_3), 1.43 (d, CH_3CHOH), 3.38 (dq, H-1), 3.57 (dd, H-6), 4.32 (dd, H-5), 4.37 (dq, H-8), 4.87 and 5.69 (2d's, CH_2N), 8.44 (dd, ArH), 8.70 (dd, ArH) and 8.96 (d, ArH).

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WHAT IS CLAIMED IS:

1. A compound represented by formula I:



5

or a pharmaceutically acceptable salt or hydrate thereof,
wherein:

10 R^1 represents H or methyl;

CO_2M represents a carboxylic acid, a carboxylate anion, a
pharmaceutically acceptable ester group or a carboxylic acid protected
by a protecting group;

15

P represents hydrogen, hydroxyl, F or hydroxyl protected
by a hydroxyl-protecting group;

20 X^1 and X^2 represent hydrogen or X^1 and X^2 taken together
represent a carbonyl group;

each R is independently selected from: $-R^*$; $-Q$;
hydrogen; halo; $-CN$; $-NO_2$; $-NR^aR^b$; $-OR^c$; $-SR^c$; $-C(O)NR^aR^b$;
 $-C(O)OR^h$; $-S(O)R^c$; $-SO_2R^c$; $-SO_2NR^aR^b$; $-NR^aSO_2R^b$; $-C(O)R^a$;
25 $-OC(O)R^a$; $-OC(O)NR^aR^b$; $-NR^aC(O)NR^bR^c$; $-NR^aCO_2R^h$; $-OCO_2R^h$;
 $-NR^aC(O)R^b$; $-C_{1-6}$ straight- or branched-chain alkyl, unsubstituted
or substituted with one to four R^d groups; and $-C_{3-7}$ cycloalkyl,
unsubstituted or substituted with one to four R^d groups;

30 each R^a , R^b and R^c independently represents hydrogen, $-R^*$,
 $-C_{1-6}$ straight- or branched-chain alkyl, unsubstituted or substituted with

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one to four R^d groups, or $-C_{3-7}$ cycloalkyl, unsubstituted or substituted with one to four R^d groups;

or R^a and R^b taken together with any intervening atoms represent a 4-6 membered saturated ring optionally interrupted by one or more of O, S, NR^c , with R^c as defined above, or $-C(O)-$, said ring being unsubstituted or substituted with one to four R^i groups;

or R^b and R^c taken together with any intervening atoms represent a 4-6 membered saturated ring optionally interrupted by one to three of O, S, NR^a , with R^a as defined above, or $-C(O)-$, said ring being unsubstituted or substituted with one to four R^i groups;

each R^d independently represents halo; $-CN$; $-NO_2$; $-NR^eR^f$; $-OR^g$; $-SR^g$; $-CONR^eR^f$; $-COOR^g$; $-SOR^g$; $-SO_2R^g$; $-SO_2NR^eR^f$; $-NR^eSO_2R^f$; $-COR^e$; $-NR^eCOR^f$; $-OCOR^e$; $-OCONR^eR^f$; $-NR^eCONR^fR^g$; $-NR^eCO_2R^h$; $-OCO_2R^h$; $-C(NR^e)NR^fR^g$; $-NR^eC(NH)NR^fR^g$; $-NR^eC(NR^f)R^g$; $-R^*$ or $-Q$;

R^e , R^f and R^g represent hydrogen; $-R^*$; $-C_{1-6}$ straight- or branched-chain alkyl unsubstituted or substituted with one to four R^i groups;

or R^e and R^f taken together with any intervening atoms represent a 4-6 membered saturated ring optionally interrupted by one to three of O, S, $-C(O)-$ or NR^g with R^g as defined above, said ring being unsubstituted or substituted with one to four R^i groups;

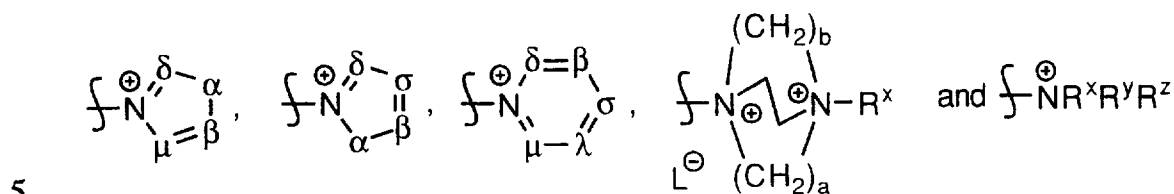
each R^i independently represents halo; $-CN$; $-NO_2$; phenyl; $-NHSO_2R^h$; $-OR^h$, $-SR^h$; $-N(R^h)_2$; $-N^+(R^h)_3$; $-C(O)N(R^h)_2$; $-SO_2N(R^h)_2$; heteroaryl; heteroarylium; $-CO_2R^h$; $-C(O)R^h$; $-OCOR^h$; $-NHCOR^h$; guanidinyl; carbamimidoyl or ureido;

each R^h independently represents hydrogen, a $-C_{1-6}$ straight or branched-chain alkyl group, a $-C_3-C_6$ cycloalkyl group or phenyl, or when two R^h groups are present, said R^h groups may be taken in

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combination and represent a 4-6 membered saturated ring, optionally interrupted by one or two of O, S, SO₂, -C(O)-, NH and NCH₃;

Q is selected from the group consisting of:



wherein:

a and b are 1, 2 or 3;

L⁻ is a pharmaceutically acceptable counterion;

α represents O, S or NR^s;

10 β, δ, λ, μ and σ represent CR^t, N or N⁺R^s, provided that
no more than one of β, δ, λ, μ and σ is N⁺R^s;

R* is selected from the group consisting of:



wherein:

d represents O, S or NR^k;

20 e, g, x, y and z represent CR^m, N or N⁺R^k, provided that
no more than one of e, g, x, y and z in any given structure represents
N⁺R^k;

R^k represents hydrogen; -C₁₋₆ straight- or branched-
chain alkyl, unsubstituted or substituted with one to four Rⁱ groups;
or -(CH₂)_nQ where n = 1, 2 or 3 and Q is as previously defined;

25

each R^m independently represents a member selected
from the group consisting of: hydrogen; halo; -CN; -NO₂; -NRⁿR^o;
-ORⁿ; -SRⁿ; -CONRⁿR^o; -COOR^h; -SORⁿ; -SO₂Rⁿ; -SO₂NRⁿR^o;
-NRⁿSO₂R^o; -CORⁿ; -NRⁿCOR^o; -OCORⁿ; -OCONRⁿR^o; -NRⁿCO₂R^h;
30 -NRⁿCONR^oR^h; -OCO₂R^h; -CNRⁿNR^oR^h; -NRⁿCNHNHNR^oR^h;

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-NRⁿC(NR^o)R^h; -C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four Rⁱ groups; -C₃₋₇ cycloalkyl, unsubstituted or substituted with one to four Rⁱ groups; and -(CH₂)_nQ where n and Q are as defined above;

5

Rⁿ and R^o represent hydrogen, phenyl; -C₁₋₆ straight- or branched-chain alkyl unsubstituted or substituted with one to four Rⁱ groups;

10 each R^s independently represents hydrogen; phenyl or -C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four Rⁱ groups;

15 each R^t independently represents hydrogen; halo; phenyl; -CN; -NO₂; -NR^uR^v; -OR^u; -SR^u; -CONR^uR^v; -COOR^h; -SOR^u; -SO₂R^u; -SO₂NR^uR^v; -NR^uSO₂R^v; -COR^u; -NR^uCOR^v; -OCOR^u; -OCONR^uR^v; -NR^uCO₂R^v; -NR^uCONR^vR^w; -OCO₂R^v; -C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four Rⁱ groups;

20 R^u and R^v represent hydrogen or -C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four Rⁱ groups;

25 or R^u and R^v together with any intervening atoms represent a 4-6 membered saturated ring optionally interrupted by one or more of O, S, NR^w or -C(O)-, said ring being unsubstituted or substituted with one to four Rⁱ groups;

30 each R^w independently represents hydrogen; -C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four Rⁱ groups; C₃₋₆ cycloalkyl optionally substituted with one to four Rⁱ groups; phenyl optionally substituted with one to four Rⁱ groups, or heteroaryl optionally substituted with 1-4 Rⁱ groups;

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or R^h and R^w taken together with any intervening atoms represent a 5-6 membered saturated ring, optionally interrupted by one or two of O, S, SO_2 , NH or NCH_3 ;

5 R^x represents hydrogen or a C_{1-8} straight- or branched-chain alkyl, optionally interrupted by one or two of O, S, SO , SO_2 , NR^w , $N^+R^hR^w$, or $-C(O)-$, said chain being unsubstituted or substituted with one to four of halo, CN, NO_2 , OR^w , SR^w , SOR^w , SO_2R^w , NR^hR^w , $N^+(R^h)_2R^w$, $-C(O)-R^w$, $C(O)NR^hR^w$, $SO_2NR^hR^w$, CO_2R^w ,
10 $OC(O)R^w$, $OC(O)NR^hR^w$, $NR^hC(O)R^w$, $NR^hC(O)NR^hR^w$, or a phenyl or heteroaryl group which is in turn optionally substituted with from one to four R^i groups or with one to two C_{1-3} straight- or branched-chain alkyl groups, said alkyl groups being unsubstituted or substituted with one to four R^i groups;

15 R^y and R^z represent hydrogen; phenyl; $-C_{1-6}$ straight or branched chain alkyl, unsubstituted or substituted with one to four R^i groups, and optionally interrupted by O, S, NR^w , $N^+R^hR^w$ or $-C(O)-$;

20 or R^x and R^y together with any intervening atoms represent a 4-8 membered saturated ring optionally interrupted by O, S, SO_2 , NR^w , $N^+R^hR^w$ or $-C(O)-$, unsubstituted or substituted with 1-4 R^i groups,

25 and when R^x and R^y together represent a 4-6 membered ring as defined above, R^z is as defined above or R^z represents an additional saturated 4-8 membered ring fused to the ring represented by R^x and R^y taken together, optionally interrupted by O, S, NR^w or $-C(O)-$, said rings being unsubstituted or substituted with one to four R^i groups.

30

2. A compound in accordance with claim 1 wherein at least one R is present which contains from one to three positively charged atoms.

- 73 -

3. A compound in accordance with claim 1 wherein CO_2M represents a carboxylate anion.

4. A compound in accordance with claim 1 wherein
 5 wherein one R represents a group which contains a positively charged moiety, and the remaining R groups are selected from hydrogen, R^* and C_{1-6} straight or branched chain alkyl, unsubstituted or substituted with one to four R^d groups.

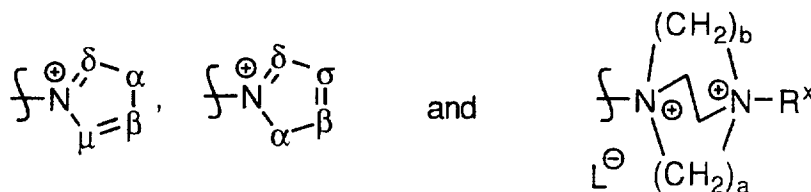
10 5. A compound in accordance with claim 4 wherein one R represents a group containing a positively charged moiety and the remaining R groups are hydrogen.

15 6. A compound in accordance with claim 1 wherein the R groups contain from 1-3 positive charges.

7. A compound in accordance with claim 6 wherein the R groups contain two positive charges, balanced by a carboxylate anion and a negatively charged counterion.

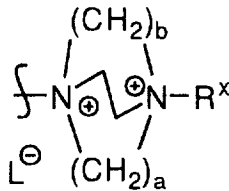
20 8. A compound in accordance with claim 1 wherein one R group represents a $-\text{C}_{1-6}$ straight or branched chain alkyl group, substituted with one to four R^d groups, wherein one R^d group represents $-\text{R}^*$ or Q.

25 9. A compound in accordance with claim 1 wherein Q is selected from the group consisting of:



30

10. A compound in accordance with claim 9 wherein
wherein Q represents:

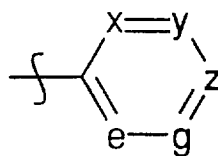


L⁻, a and b are as originally defined, and R^x represents a member selected from the group consisting of: hydrogen or a C₁₋₈ straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO₂, NR^w, N⁺R^hR^w, or -C(O)-, said chain being unsubstituted or substituted with one to four of halo, CN, NO₂, OR^w, SR^w, SOR^w, SO₂R^w, NR^hR^w, N⁺(R^h)₂R^w, -C(O)-R^w, C(O)NR^hR^w, SO₂NR^hR^w, CO₂R^w, OC(O)R^w, OC(O)NR^hR^w, NR^hC(O)R^w, NR^hC(O)NR^hR^w, or a phenyl or heteroaryl group which is in turn optionally substituted with from one to four Rⁱ groups or with one to two C₁₋₃ straight- or branched- chain alkyl groups, said alkyl groups being unsubstituted or substituted with one to four Rⁱ groups, and

R^h , R^i and R^w are as originally defined.

20 11. A compound in accordance with claim 1 wherein Q represents $-N^+R^xR^yR^z$, wherein R^x , R^y and R^z are as originally defined.

12. A compound in accordance with claim 1 wherein
25 one R* group is:



- 75 -

wherein e, g, x, y and z represent CR^m , N or N^+R^k , provided that no more than one of e, g, x, y and z represents N^+R^k , and R^k and R^m are as originally defined.

5 13. A compound in accordance with claim 1 wherein:
 CO_2M represents a carboxylate anion;

one R group contains at least one positively charged moiety, and the remaining R groups are selected from hydrogen and C_{1-6} straight or branched chain alkyl, unsubstituted or substituted

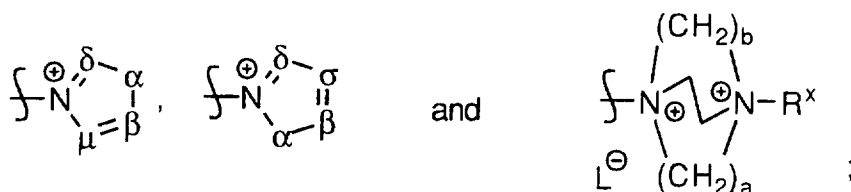
10 with one to four R^d groups.

R^d is as originally defined;

R^h represents hydrogen or a C_{1-6} straight or branched chain alkyl group;

Q is selected from the group consisting of:

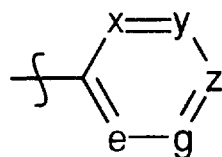
15



wherein L^- is as originally defined; a and b represent 2, and R^x represents a member selected from the group consisting of:
 20 hydrogen or a C_{1-8} straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO_2 , NR^w , $\text{N}^+\text{R}^h\text{R}^w$, or $-\text{C}(\text{O})-$, said chain being unsubstituted or substituted with one to four of halo, CN, NO_2 , OR^w , SR^w , SOR^w , SO_2R^w , NR^hR^w , $\text{N}^+(\text{R}^h)_2\text{R}^w$, $-\text{C}(\text{O})-\text{R}^w$, $\text{C}(\text{O})\text{NR}^h\text{R}^w$, $\text{SO}_2\text{NR}^h\text{R}^w$, CO_2R^w ,
 25 $\text{OC}(\text{O})\text{R}^w$, $\text{OC}(\text{O})\text{NR}^h\text{R}^w$, $\text{NR}^h\text{C}(\text{O})\text{R}^w$, $\text{NR}^h\text{C}(\text{O})\text{NR}^h\text{R}^w$, or a phenyl or heteroaryl group which is in turn optionally substituted with from one to four R^i groups or with one to two C_{1-3} straight- or branched- chain alkyl groups, said alkyl groups being unsubstituted or substituted with one to four R^i groups;

30 one R^* group is:

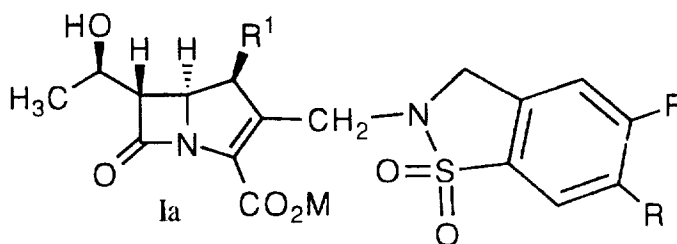
- 76 -



wherein e, g, x, y and z represent CR^m , N or N^+R^k , provided that no more than one of e, g, x, y and z represents N^+R^k ,

5 and R^k and R^m as originally defined.

14. A compound in accordance with claim 1 represented by formula Ia:



10

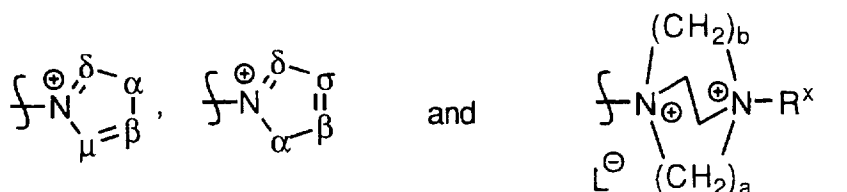
or a pharmaceutically acceptable salt thereof, wherein:

CO_2M represents a carboxylate anion;

one R group contains a positively charged moiety, and

15 the other R group is selected from hydrogen and R^* ;

Q is selected from the group consisting of:

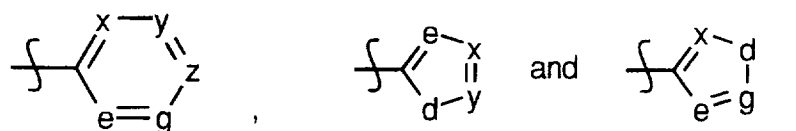


20

wherein L^- , a and b are as originally defined, and R^x represents a member selected from the group consisting of: hydrogen or a C1-8 straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO_2 , NR^w , $\text{N}^+\text{R}^h\text{R}^w$, or $-\text{C}(\text{O})-$, said chain being unsubstituted or substituted with one

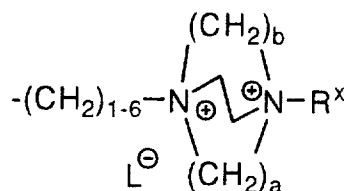
- 77 -

- to four of halo, CN, NO₂, OR^w, SR^w, SOR^w, SO₂R^w, NR^hR^w, N⁺(R^h)₂R^w, -C(O)-R^w, C(O)NR^hR^w, SO₂NR^hR^w, CO₂R^w, OC(O)R^w, OC(O)NR^hR^w, NR^hC(O)R^w, NR^hC(O)NR^hR^w, or a phenyl or heteroaryl group which is in turn optionally substituted with from one to four Rⁱ groups or with one to two C₁₋₃ straight- or branched- chain alkyl groups, said alkyl groups being unsubstituted or substituted with one to four Rⁱ groups;
- R^h represents hydrogen or a C₁₋₆ straight or branched chain alkyl group;
- R^w is as originally defined;
- R^{*} is selected from:



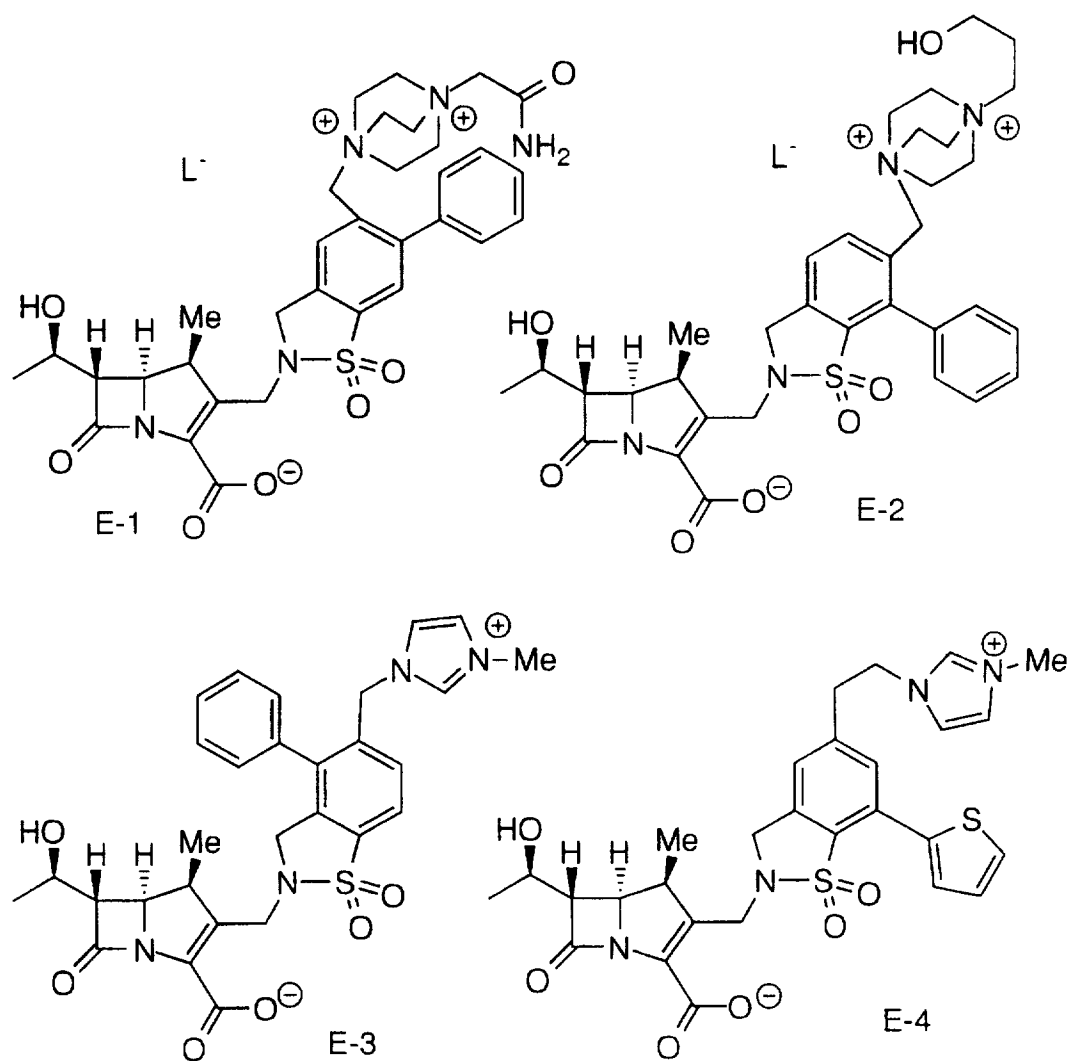
- wherein d represents NR^k; R^k represents -C₁₋₆ straight or branched chain alkyl; and e, g, x and y represent CR^m or N⁺R^k, with R^k as defined above and R^m representing hydrogen.

15. A compound in accordance with claim 14
- wherein:
- one R represents

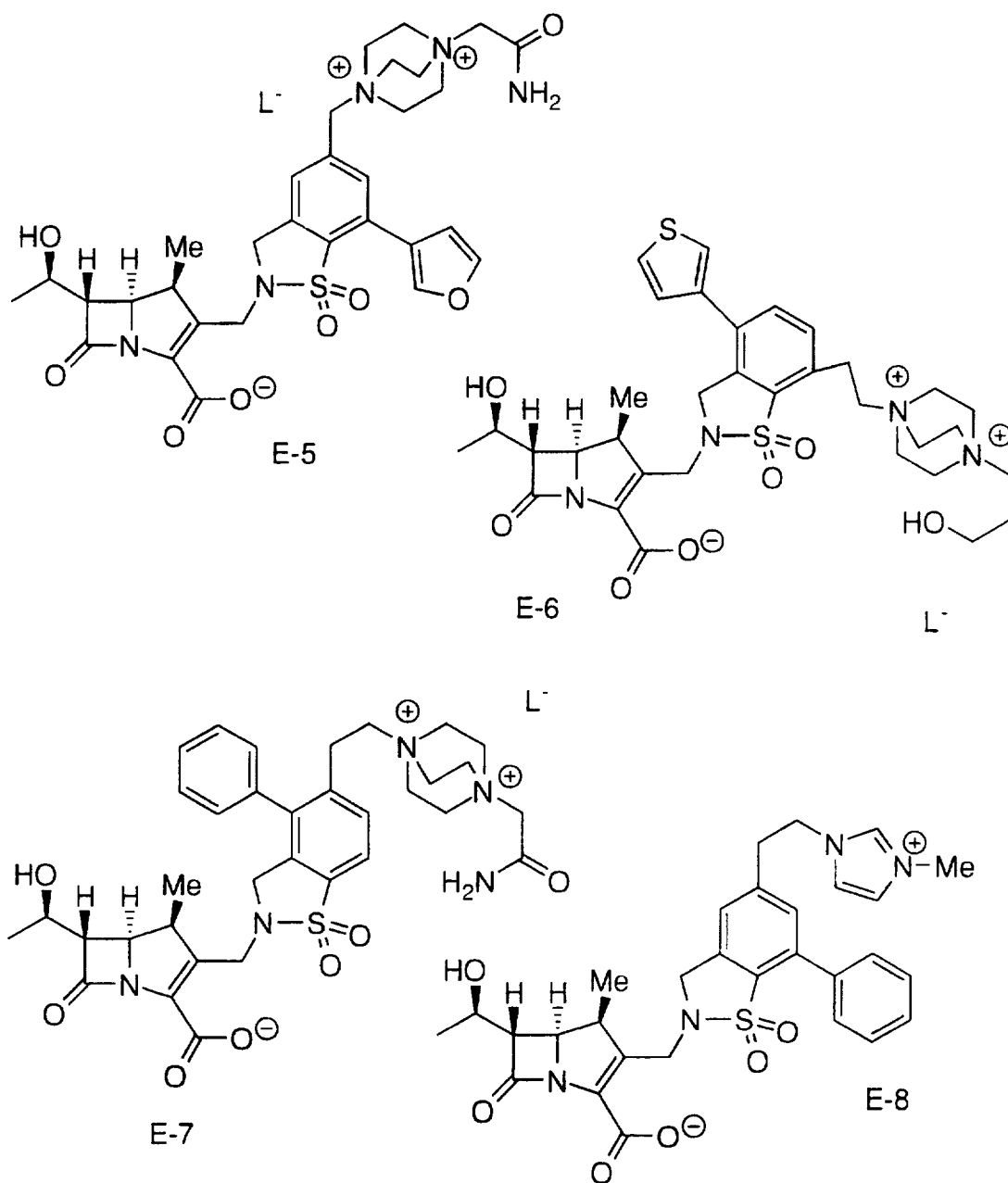


- and R^x, a, b and L⁻ are as originally defined.

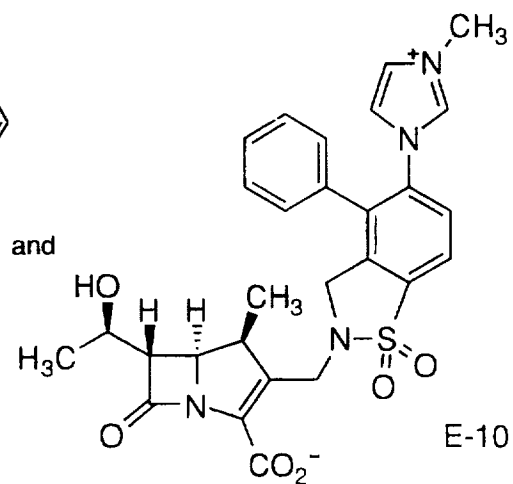
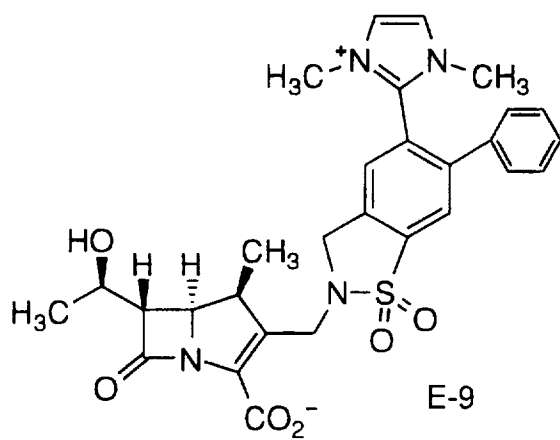
16. A compound in accordance with claim 1 represented by the formula:



- 79 -

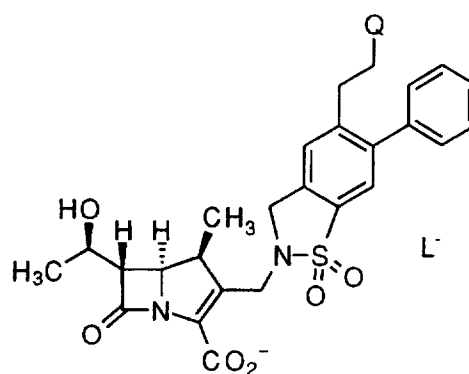


- 80 -



17. A compound in accordance with claim 1 falling
5 within one of the following tables:

- 81 -



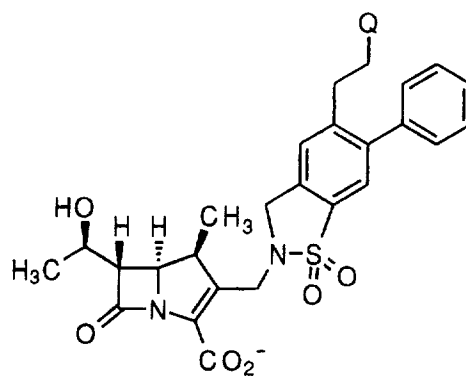
TABLE

#	Q	#	Q	#	Q
11		12		13	
		Ph = phenyl			
14		15		16	

- 82 -

17		18		19	
20		21		22	
23		24		25	
26		27		28	

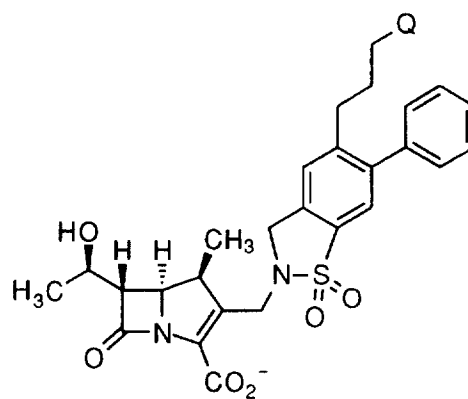
- 83 -



TABLE

#	Q	#	Q	#	Q
29		30		31	
32		33		34	

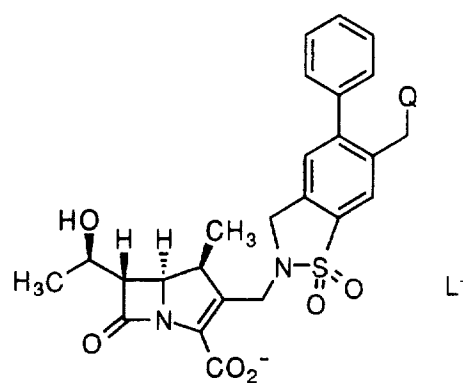
- 84 -



TABLE

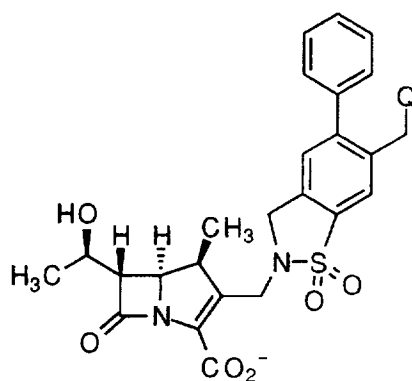
#	Q	#	Q	#	Q
35		36		37	

- 85 -

TABLE

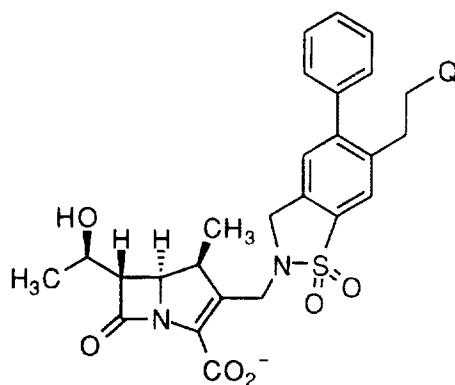
#	Q	#	Q	#	Q
38		39		40	

- 86 -



TABLE

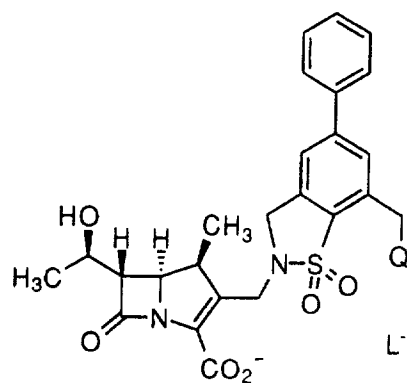
#	Q	#	Q	#	Q
41		42		43	



TABLE

#	Q	#	Q	#	Q
44		45		46	

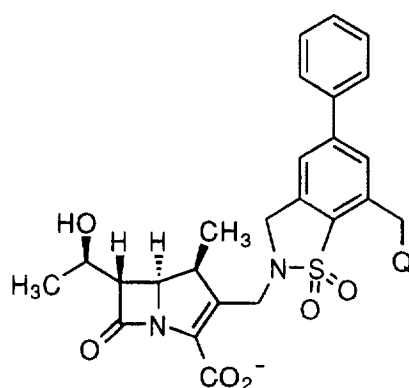
- 87 -



TABLE

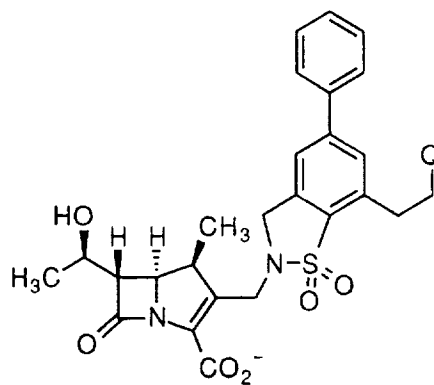
#	Q	#	Q	#	Q
47		48		49	

- 88 -



TABLE

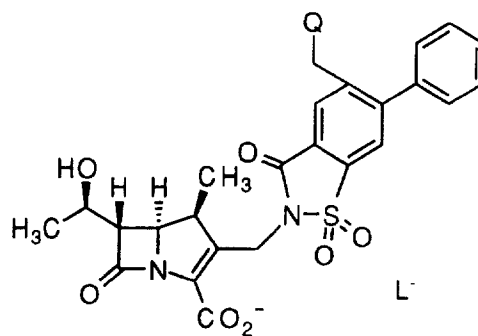
#	Q	#	Q	#	Q
50		51		52	



TABLE

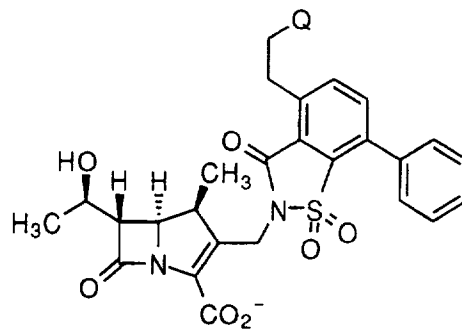
#	Q	#	Q	#	Q
53		54		55	

- 89 -



TABLE

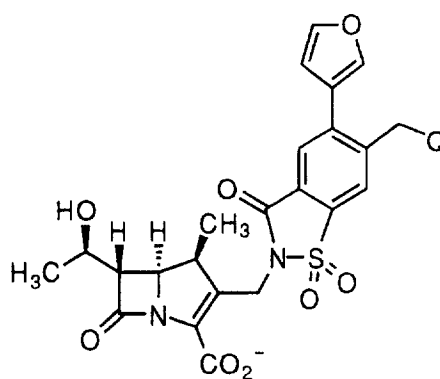
#	Q	#	Q	#	Q
56		57		58	



TABLE

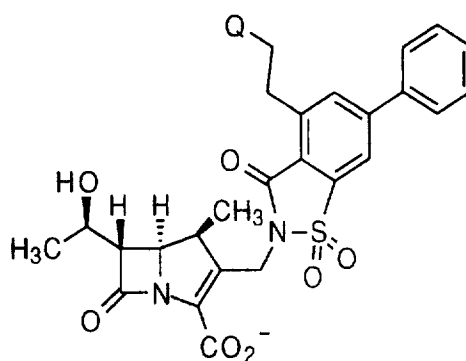
#	Q	#	Q	#	Q
59		60		61	

- 90 -



TABLE

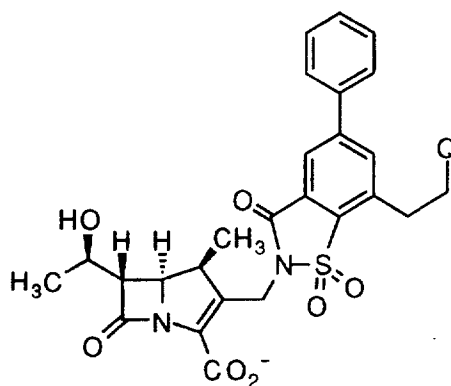
62		63	
----	--	----	--



TABLE

#	Q	#	Q
65		66	

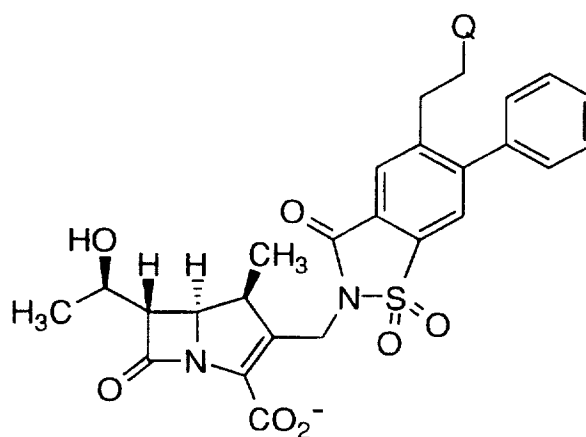
- 91 -



TABLE

#	Q	#	Q	#	Q
68	Chemical structure of a quaternary ammonium salt. The cation consists of a 1,4-diazabicyclo[2.2.2]octane ring system with a 2-aminoethyl group ($\text{CH}_2\text{CH}_2\text{NH}_2$) attached to one of the nitrogen atoms. The counterion is Li^+.	69	Chemical structure of a quaternary ammonium salt. The cation consists of a 1,4-diazabicyclo[2.2.2]octane ring system with a 2-hydroxyethyl group ($\text{CH}_2\text{CH}_2\text{OH}$) attached to one of the nitrogen atoms. The counterion is Li^+.	70	Chemical structure of a quaternary ammonium salt. The cation consists of a 1,4-diazabicyclo[2.2.2]octane ring system with a 2-methylpyridinium group ($\text{CH}_2\text{CH}_2\text{C}_5\text{H}_4\text{N}^+\text{CH}_3$) attached to one of the nitrogen atoms. The counterion is Li^+.

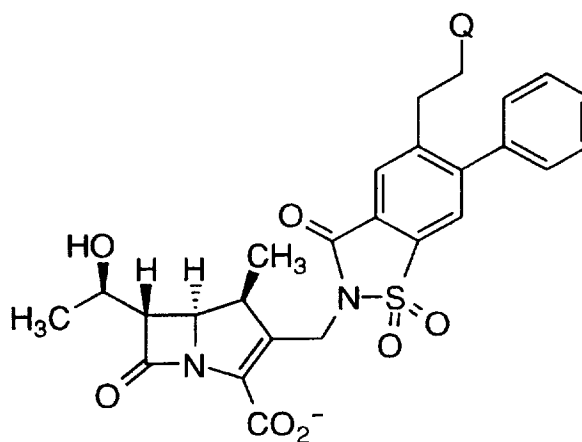
- 92 -



TABLE

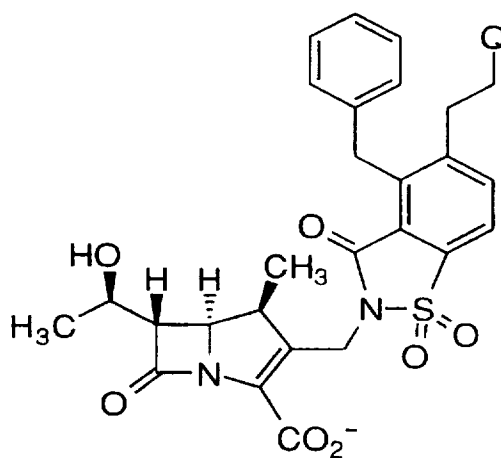
#	Q	#	Q	#	Q
71		72		73	

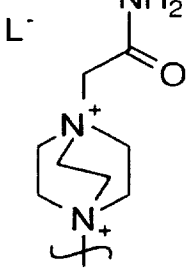
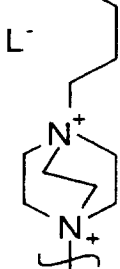
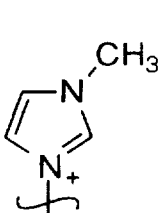
- 93 -



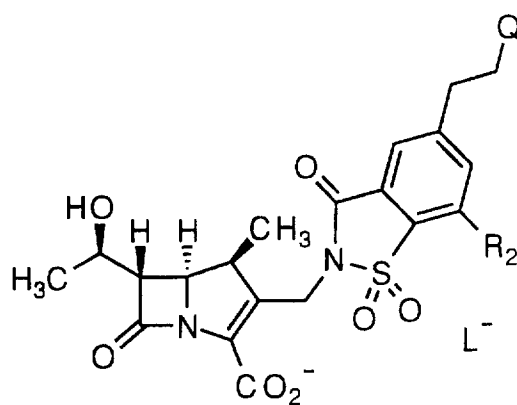
TABLE

#	Q	#	Q	#	Q
74	Chemical structure of a quaternary ammonium salt. The cation is a 1,4-diazabicyclo[2.2.2]octane derivative with a positive charge on one nitrogen. The counterion is a 2-aminoethyl group (NH₂CH₂CH₂-).	75	Chemical structure of a quaternary ammonium salt. The cation is a 1,4-diazabicyclo[2.2.2]octane derivative with a positive charge on one nitrogen. The counterion is a 2-hydroxyethyl group (HOCH₂CH₂-).	76	Chemical structure of a quaternary ammonium salt. The cation is a 1,4-diazabicyclo[2.2.2]octane derivative with a positive charge on one nitrogen. The counterion is a 2-methylimidazol-5-yl group (CH₃imidazol-5-yl).

TABLE

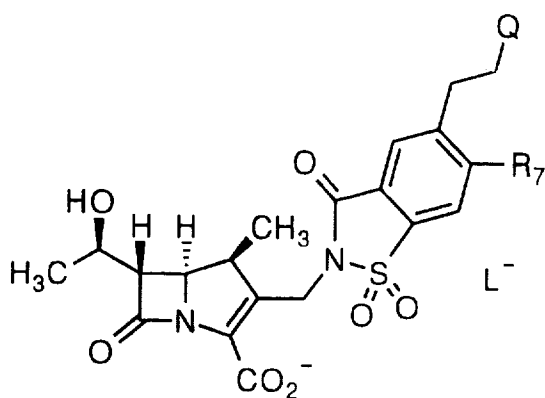
#	Q	#	Q	#	Q
77		78		79	

- 95 -



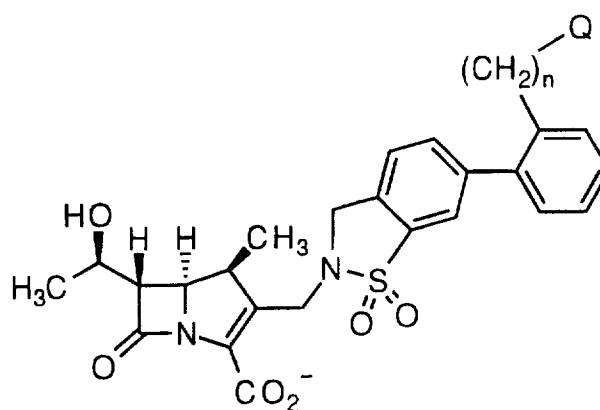
R_2	Q	R_2	Q	R_2	Q	R_2	Q
Cl		C_6H_5					

- 96 -



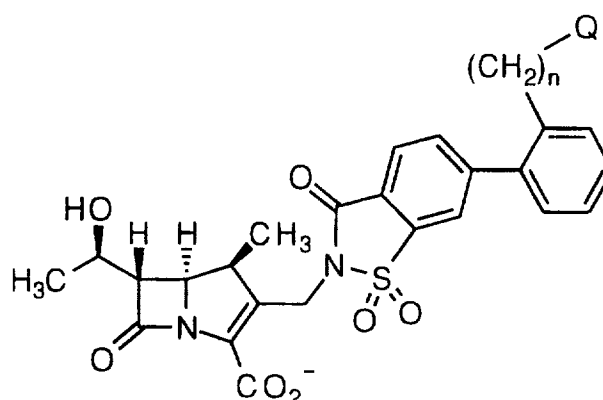
R_7	Q	R_7	Q	R_7	Q	R_7	Q
Cl							

- 97 -



n	Q	n	Q	n	Q	n	Q
1		2		1		2	

- 98 -



n	Q	n	Q	n	Q	n	Q
1		2		1		2	

wherein Q is as defined in the tables and L^- represents a pharmaceutically acceptable counterion.

5 18. A pharmaceutical composition comprised of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

10 19. A pharmaceutical composition produced by combining a compound in accordance with claim 1 with a pharmaceutically acceptable carrier.

15 20. A method of treating or preventing a bacterial infection in a mammalian patient in need thereof, comprising administering to said patient an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/16786

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/425; C07D 519/00

US CL : 540/302; 514/210

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 540/302; 514/210

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

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

REGISTRY, APS, CAPLUS, MARPAT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	US 5,578,722 A (SUNAGAWA et al) 26 November 1996, abstract.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
I document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

26 JANUARY 1998

Date of mailing of the international search report

23 FEB 1998

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