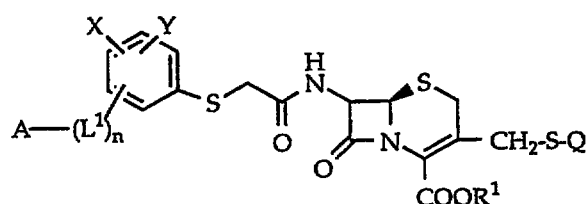


CEPHALOSPORIN DERIVATIVES

1. Field of the Invention

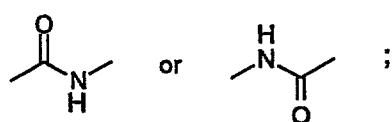
The present invention is directed to new cephem derivatives represented by the general formula



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wherein Q is an optionally substituted pyridinium group connected to the sulfur atom via a ring carbon atom; X is halogen; Y is hydrogen or halogen; A is CO₂H, PO₃H₂, SO₃H or tetrazole; L¹ is a furan group, a thiophene group, a C₂-C₁₀ alkyl group, or a C₂-C₁₀ alkyl group interrupted by one or more groups independently selected from vinyl, S, SO, SO₂, SO₂NH,

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n is 0 or 1; and R¹ is hydrogen or a carboxyl-protecting group; or pharmaceutically acceptable salts and/or prodrugs thereof. The derivatives are gram-positive antibacterial agents especially useful in the treatment of diseases caused by methicillin-resistant Staphylococcus aureus (also referred to below as MRSA or methicillin-resistant S. aureus).

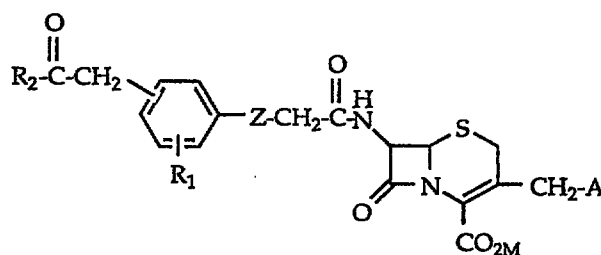
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2. Description of the Prior Art

The literature discloses a vast number of cephem derivatives having a wide variety of C-3 and C-7 substituents.

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With respect to the C-7 substituents of the present invention, U.S. Patent 3,345,366 discloses cephem derivatives of the type

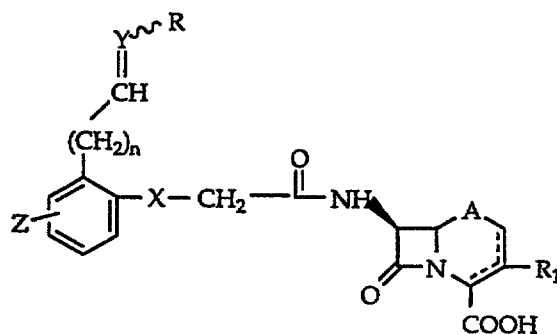


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wherein R_1 is hydrogen or chloro, R_2 is hydroxy or amino, Z is oxygen or sulfur, A is acetoxy or N-pyridinium and M is hydrogen, pharmaceutically acceptable non-toxic cations or an anionic charge when A is N-pyridinium. This approach was also discussed in Antimicrob. Ag. Chemother. Meeting, 1968, pgs 109-114 (Hobby, G.L.) and JP 50083383.

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EP 638,574 A1 discloses cephem derivatives of the general formula

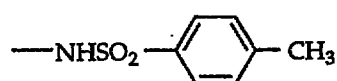


wherein X = absent, -O-, -S-, -SO-, -SO₂-, -NH-;

Y = -CH, N-;

Z = -H, halogen, -OH, C₁-C₅ O-alkyl, -OCH₂CONH₂,

5 -OCONH₂, -OSO₂NH₂, -OCH₂CN, -NH₂ either as such or substituted with C₁-C₆ alkyl radicals, -NHCOCH₃, -NHSO₂CH₃,



, amides of C₁-C₄ linear acids,

amides of benzene and toluene derivatives, -NO₂, -NO,

10 -CHO, -CH₂OH, -COOH, -SH, -SOH, -SO₂H, -SO₃H, -S-alkyl

where the alkyl residue is C₁-C₃, -CF₃;

R = -H, -OH, C₁-C₅-O-alkyl with the alkyl residue possibly

containing halogens, acid functionalities either free or

salified with alkaline or alkaline earth metals, basic

15 functions such as -OCH₂CH₂NH₂, -OCH₂CH₂NH-CH₃, -

OCH₂(o, m, p)-pyridinyl, -OCH₂CN, -OCH₂CONH₂, -

OCH₂SO₂NH₂;

n = 0 to 4;

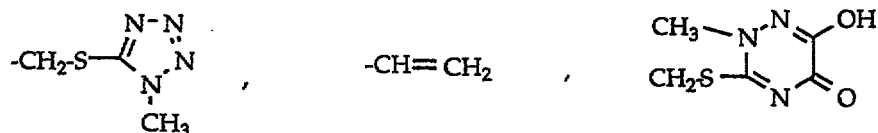
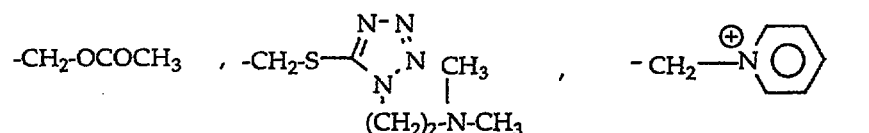
A = -S-, -O-, -CH₂-, -SO-, SO₂-;

20 R₁ = a structural group characteristic of cephalosporins such

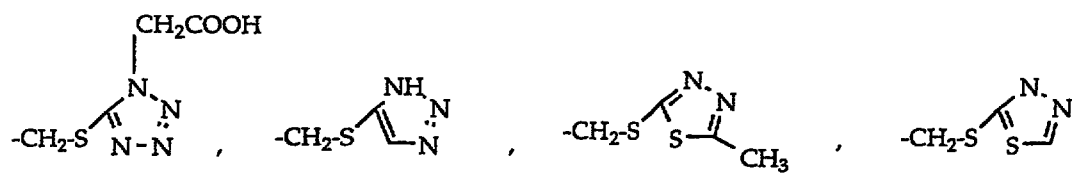
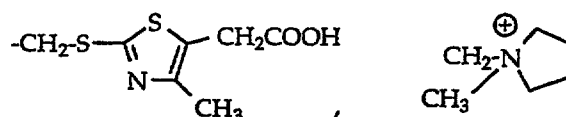
as -Cl, -H, -OCH₃, -CH₂OCH₂NH₂, -CH₂OCH₃, -CH₃, -CH=CH-

CH₃, -CF₃, -CO₂R₂, -SO₂R where R₂ is an alkyl or aryl radical

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their pharmaceutically acceptable salts and their C₆ and C₇ epimers.

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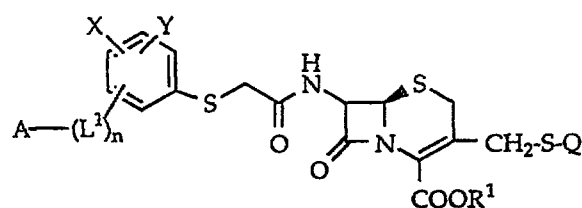
The C-3 substituents employed in the compounds of the present invention are known in the cephem art, but have not previously been combined with the C-7 substituents of the present invention. Applicants have discovered that the combination of C-3 and C-7 substituents provided in the compounds of the present invention unexpectedly gives the desired solubility, activity and toxicity profile needed for commercially viable anti-MRSA cephem products.

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SUMMARY OF THE INVENTION

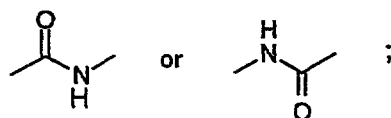
The present invention provides a novel series of cephem derivatives of the general formula

20



I

wherein Q is an optionally substituted pyridinium group connected to the sulfur atom via a ring carbon atom; X is halogen; Y is hydrogen or halogen; A is CO₂H, PO₃H₂, SO₃H or tetrazole; L¹ is a furan group, a thiophene group, a C₂-C₁₀ alkyl group, or a C₂-C₁₀ alkyl group interrupted by one or more groups independently selected from vinyl, S, SO, SO₂, SO₂NH,



n is 0 or 1; and R¹ is hydrogen or a carboxyl-protecting group; or pharmaceutically acceptable salts and/or a prodrugs thereof.

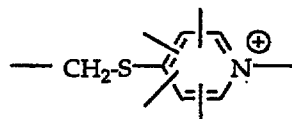
The compounds of formula I are antibacterial agents useful in the treatment of infections in humans and other animals caused by a variety of gram-positive bacteria, particularly methicillin-resistant *S. aureus*.

Also included in the invention are processes for preparing the compounds of formula I and pharmaceutical compositions containing said compounds in combination with pharmaceutically acceptable carriers or excipients.

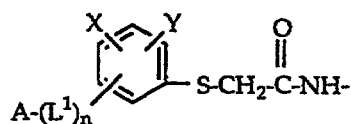
DETAILED DESCRIPTION

The present invention provides novel cephem derivatives of general formula I above which are antibacterial agents useful in the treatment of infectious diseases in humans and other animals. The compounds exhibit good activity against a wide variety of gram-positive microorganisms, e.g. S. pneumoniae, S. pyogenes, S. aureus, E. faecalis, S. epidermidis and S. hemolyticus, and are particularly useful against strains of methicillin-resistant S. aureus.

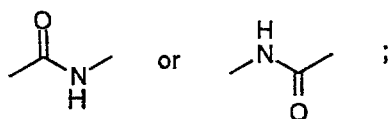
The compounds of formula I are characterized by an optionally substituted pyridinium thiomethyl group of the type



at the 3-position of the cephem ring and a 7-substituent of the type

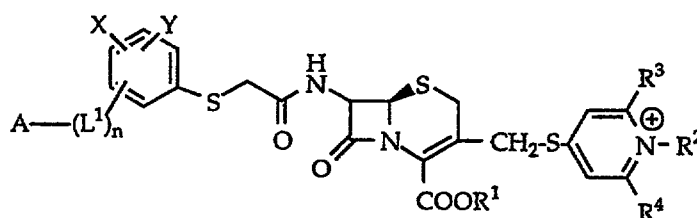


wherein X is halogen; Y is hydrogen or halogen; A is CO₂H, PO₃H₂, SO₃H or tetrazole; L¹ is a furan group, a thiophene group, a C₂-C₁₀ alkyl group, or a C₂-C₁₀ alkyl group interrupted by one or more (preferably 1 or 2) groups independently selected from vinyl, S, SO, SO₂, SO₂NH,



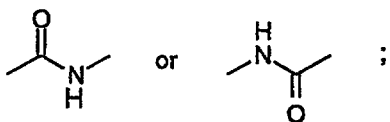
and n is 0 or 1.

A preferred embodiment of the present invention comprises a compound of the formula



IA

wherein X is halogen; Y is hydrogen or halogen; A is CO₂H, PO₃H₂, SO₃H or tetrazole; L¹ is a furan group, a thiophene group, a C₂-C₁₀ alkyl group, or a C₂-C₁₀ alkyl group interrupted by one or more groups independently selected from vinyl, S, SO, SO₂, SO₂NH,

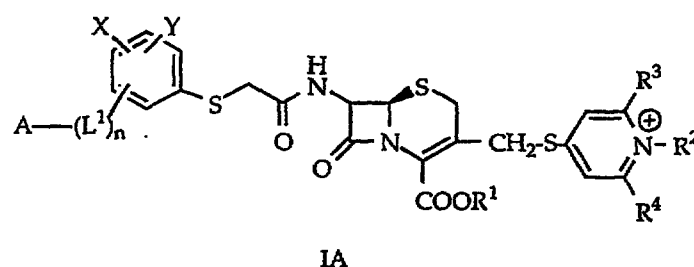


n is 0 or 1; R³ and R⁴ are each independently selected from hydrogen or C₁-C₆ alkyl; R² is hydrogen, NH₂, pyrrolidinyl, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₂-C₆ alkyl substituted by one or more substituents independently selected from OH, NR⁵R⁶ in which R⁵ and R⁶ are each independently hydrogen or C₁-C₆ alkyl, CO₂H, morpholinyl, morpholinyl quaternized by a C₁-C₆ alkyl

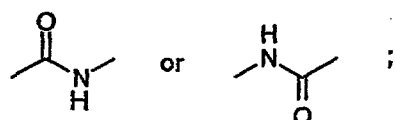
group, oxo (C=O), halogen, SO₃H, PO₃H₂, imidazolyl, imidazolyl substituted

by 1-2 C₁-C₆ alkyl groups, tetrazolyl, tetrazolyl substituted by 1-2 C₁-C₆ alkyl groups or N=CR⁷ in which R⁷ is a furan or thiophene ring optionally substituted by either -CO₂H or -SO₃H, phenyl or phenyl substituted by 1-3 substituents independently selected from OH, NR⁵R⁶ in which R⁵ and R⁶ are as defined above, CO₂H, morpholinyl, morpholinyl quaternized by a C₁-C₆ alkyl group, oxo, halogen, SO₃H, PO₃H₂, imidazolyl, imidazolyl substituted by 1-2 C₁-C₆ alkyl groups, tetrazolyl, tetrazolyl substituted by 1-2 C₁-C₆ alkyl groups or N=CR⁷ in which R⁷ is as defined above; and R¹ is hydrogen or a carboxyl-protecting group, or a pharmaceutically acceptable salt and/or a prodrug thereof.

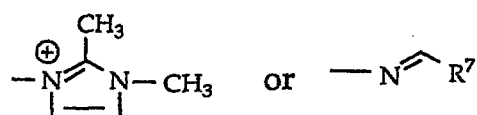
Another preferred embodiment comprises a compound of the formula



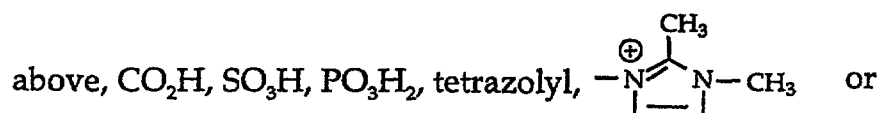
wherein X is halogen; Y is hydrogen or halogen; A is CO₂H, PO₃H₂, SO₃H or tetrazole; L¹ is a furan group, a thiophene group, a C₂-C₁₀ alkyl group or a C₂-C₁₀ alkyl group interrupted by one or two groups independently selected from vinyl, S, SO, SO₂, SO₂NH,



- n is 0 or 1; R³ and R⁴ are each independently selected from hydrogen or C₁-C₆ alkyl; R² is hydrogen, NH₂, pyrrolidinyl, C₁-C₆ alkyl, C₁-C₆ alkyl substituted by one or two substituents independently selected from OH, NR⁵R⁶ in which R⁵ and R⁶ are each independently hydrogen or
- 5 C₁-C₆ alkyl, CO₂H, morpholinyl, morpholinyl quaternized by a C₁-C₆ alkyl group, oxo, halogen, SO₃H, PO₃H₂, tetrazolyl,

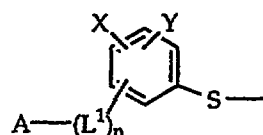


- 10 in which R⁷ is a furan or thiophene radical optionally substituted by a -CO₂H or -SO₃H group, phenyl or phenyl substituted by 1-2 substituents independently selected from OH, NR⁵R⁶ in which R⁵ and R⁶ are as defined



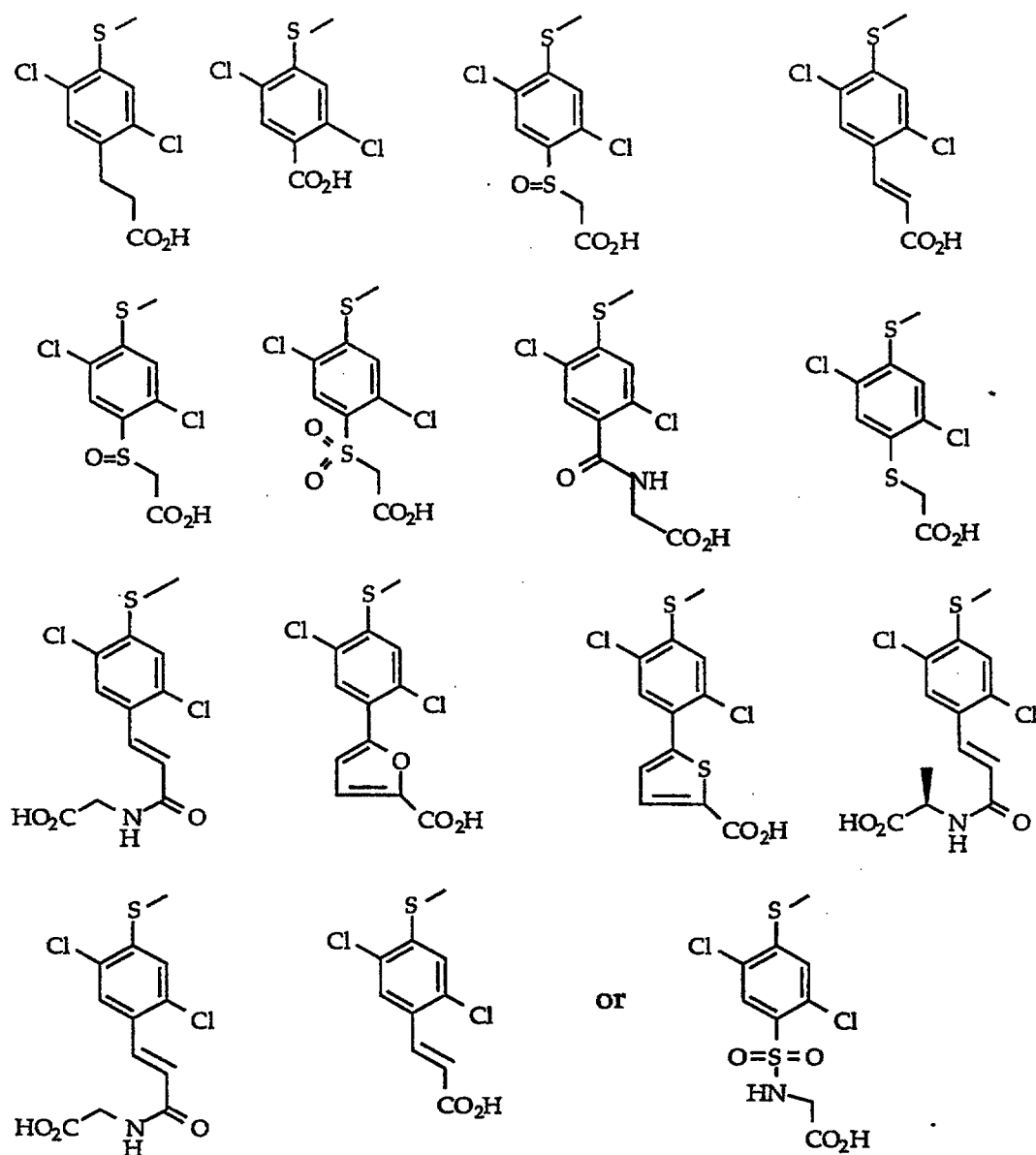
- halogen; and R¹ is hydrogen or a carboxyl-protecting group; or a
- 15 pharmaceutically acceptable salt and/or a prodrug thereof.

Particularly preferred groups of the formula

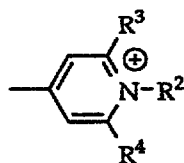


in the above-described compounds of formula I and formula IA include

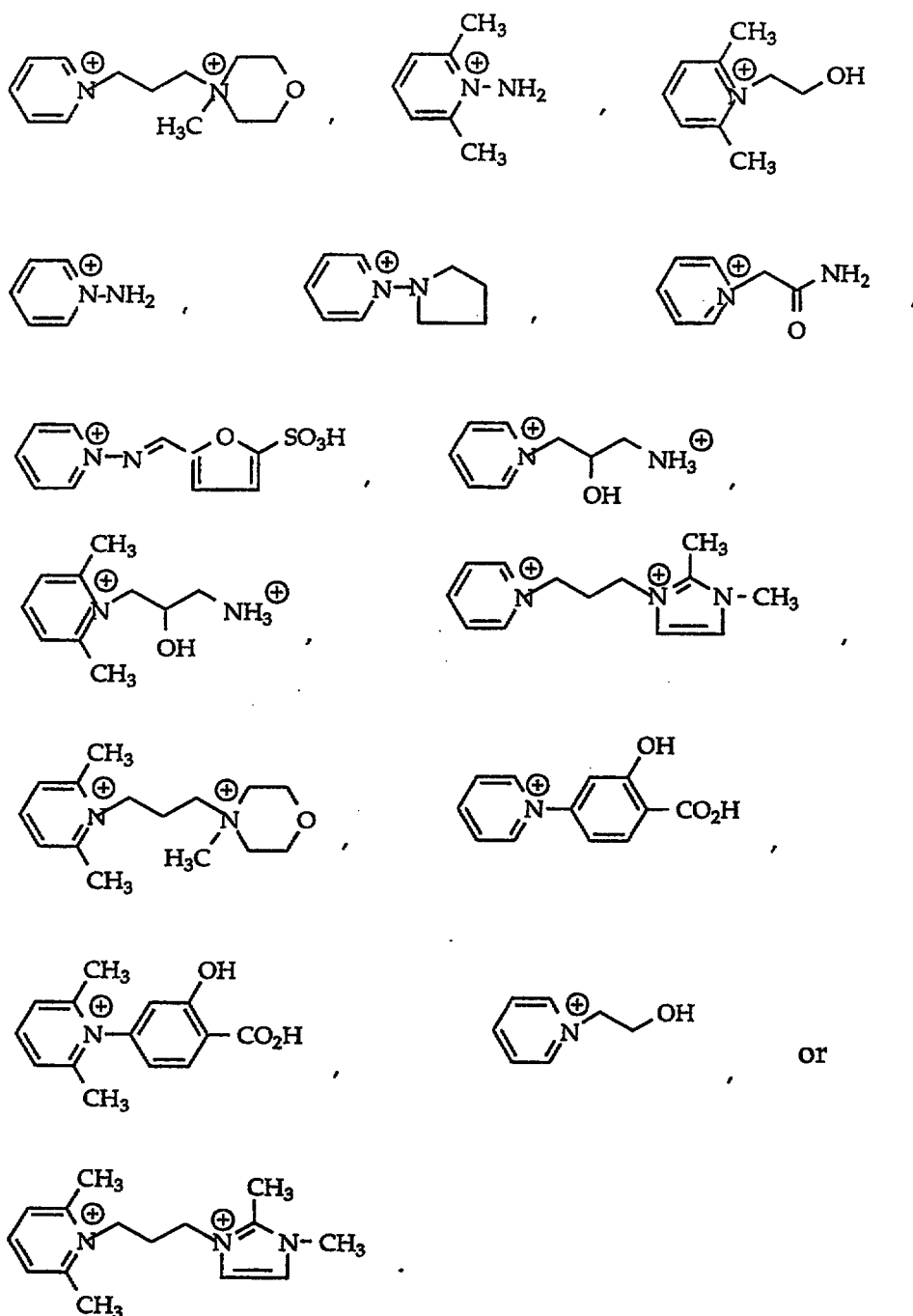
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Particularly preferred groups of the formula

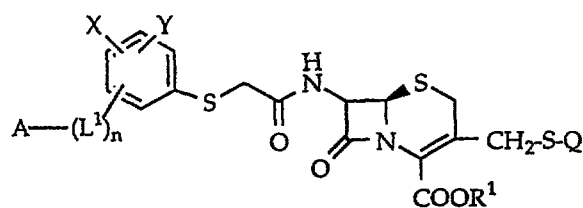


include

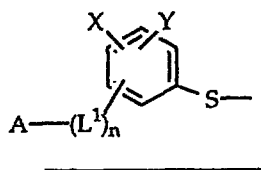
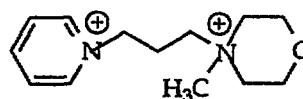
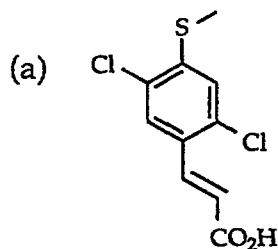


Specific preferred embodiments of the present invention include the following:

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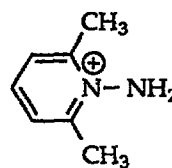
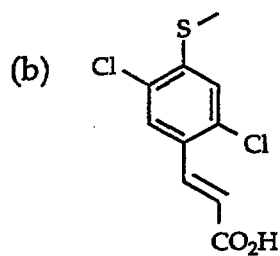
wherein R¹ is hydrogen or a carboxyl-protecting group

Q

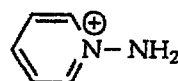
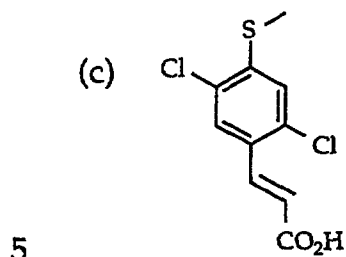
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1-[3-[N-(N-methyl) morpholino]-prop-1-yl]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(2-carboxyethenyl)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt

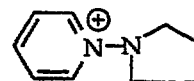
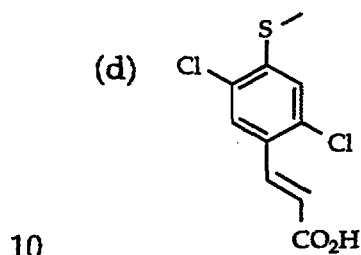
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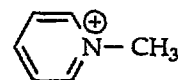
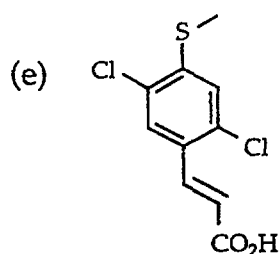
2,6-dimethyl-1-[amino]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(2-carboxyethenyl)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt



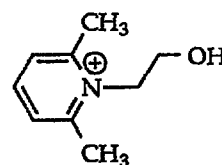
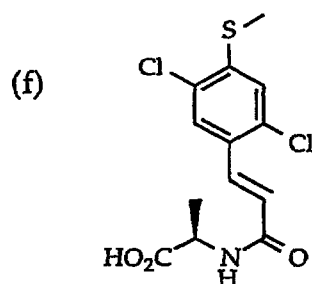
1-[amino]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(2-carboxyethenyl)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt



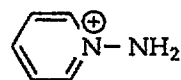
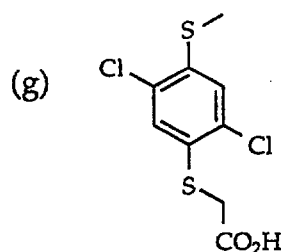
1-[N-pyrrolidino]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(2-carboxyethenyl)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt



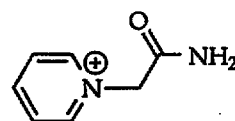
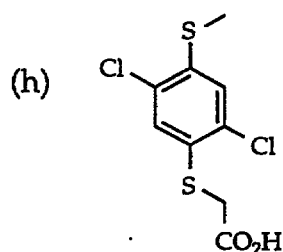
1-[methyl]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(2-carboxyethenyl)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt



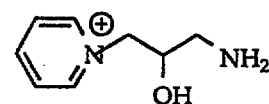
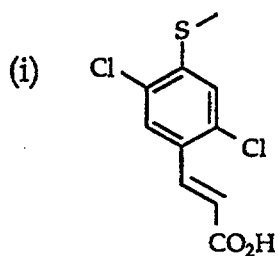
2,6 dimethyl-1-[2-hydroxy ethyl]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(2-[[[(1S)-(carboxy-1-ethyl(amino)carbonyl)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio] pyridinium inner salt



1-[amino]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(carboxymethyl
thio)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-
5 yl]methylthio]pyridinium inner salt

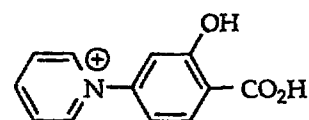
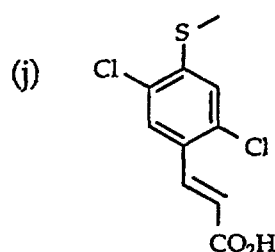


1-[aminocarbonyl methyl]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-
10 (carboxymethylthio)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-
en-3-yl]methylthio]pyridinium inner salt



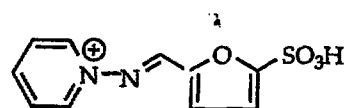
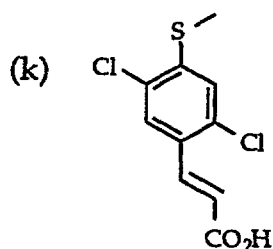
1-[2-hydroxy-3-amino-prop-1-yl]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(2-carboxyethenyl)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt

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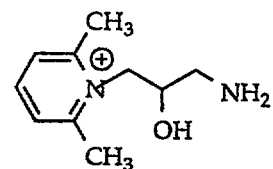
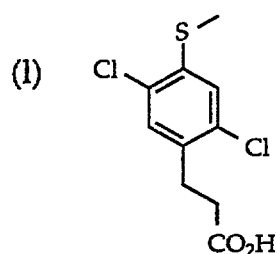
1-[3-hydroxy-4-carboxyphenyl]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(2-carboxyethenyl)phenylthio)acetamido]-5-thia-1-

10 azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt

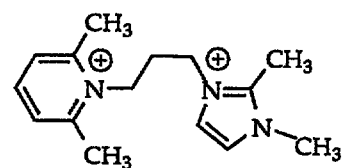
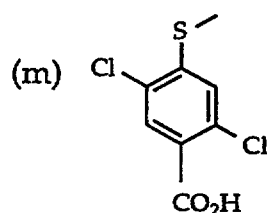


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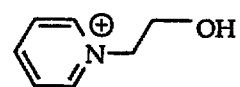
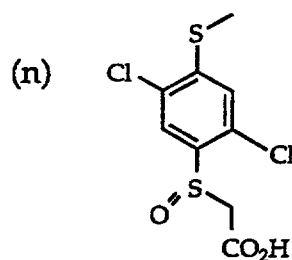
1-[5-(sulfonylfuran-2-yl)-methylimine]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(2-carboxyethenyl)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt



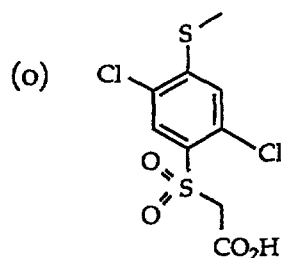
2,6-dimethyl-1-[2-hydroxy-3-amino-prop-1-yl]-4-[[[(6R)-trans-2-carboxy-8-
 5 oxo-7-[(2,5-dichloro-4-(2-carboxyethyl-1-yl)phenylthio)acetamido]-5-thia-1-
 azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt



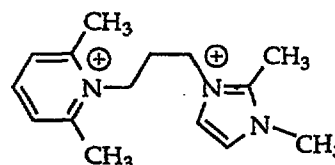
10 1-[3-(1,2 dimethyl-1H-imidazol-3)prop-1-yl]-4-[[[(6R)-trans-2-carboxy-8-oxo-
 7-[(2,5-dichloro-4-carboxyphenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-
 oct-2-en-3-yl]methylthio]pyridinium inner salt



1-[2-hydroxyethyl]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(carboxymethylsulfonyl)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt

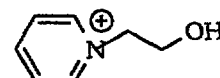
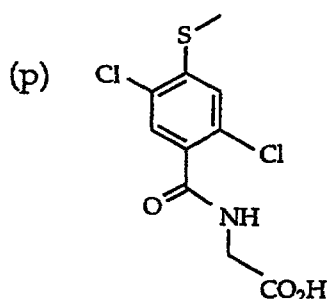


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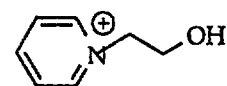
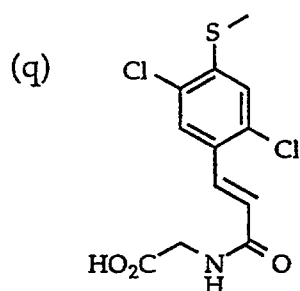
2,6-dimethyl-1-[3-(3-(1,2 dimethyl-1H-imidazol-3)prop-1-yl)-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(carboxymethylsulfonyl)phenylthio)acetamido]-5-thia-1-

10 azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt

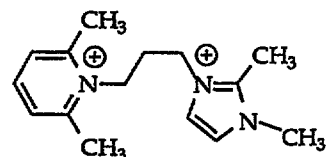
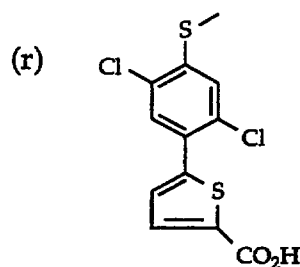


1-[2-hydroxyethyl]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(((carboxymethyl)amino)carbonyl)acetamido)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt

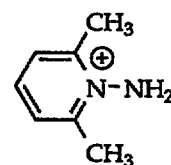
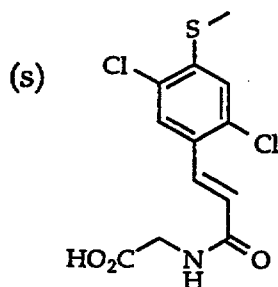
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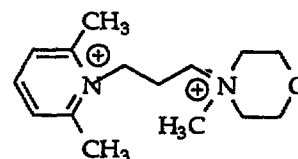
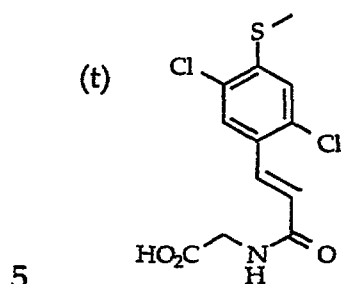
1-[2-hydroxyethyl]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(2-
 (((carboxymethyl)amino)carbonyl)ethenyl)phenylthio)acetamido]-5-thia-1-
 5 azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt



1-[3-(3-(1,2 dimethyl-1H-imidazol-3-yl)prop-1-yl)-4-[[[(6R)-trans-2-carboxy-8-
 oxo-7-[(2,5-dichloro-4-(5-carboxy-2-thiophene)phenylthio)acetamido]-5-
 10 thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt

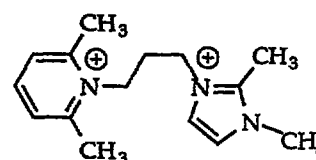
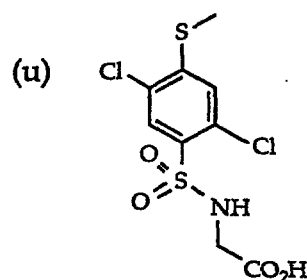


2,6-dimethyl-1-[amino]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(2-
 (((carboxymethyl)amino)carbonyl)ethenyl)phenylthio)acetamido]-5-thia-1-
 azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt



2,6-dimethyl-1-[N-(N-methyl) morpholino]-4-[[[(6R)-trans-2-carboxy-8-oxo-
 7-[(2,5-dichloro-4-(2-(((carbonylmethyl)amino)
 carbonyl)ethenyl)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-
 3-yl]methylthio]pyridinium inner salt

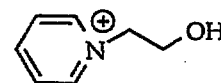
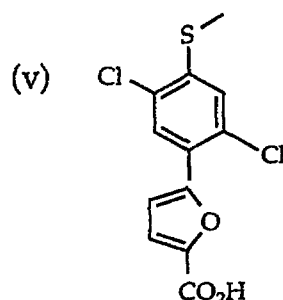
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2,6-dimethyl-1-[1,2-dimethyl-1H-imidazol-3-yl]prop-1-yl]-4-[[[(6R)-trans-2-
 carboxy-8-oxo-7-[(2,5-dichloro-4-(N-carboxymethyl
 aminosulfonyl)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-
 yl]methylthio]pyridinium inner salt

15

or



1-[2-hydroxyethyl]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(5-carboxy-2-furan)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt;
or pharmaceutically acceptable salts and/or prodrugs thereof.

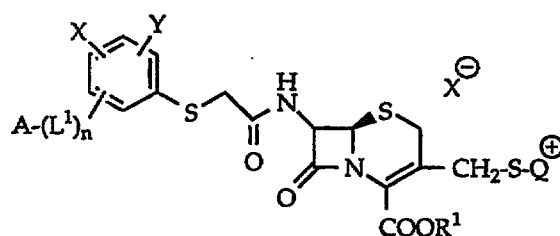
To elaborate on the definitions for substituents of the formula I and formula IA compounds:

- 10 (a) "Halogen" includes chloro, bromo, fluoro and iodo, and is preferably chloro or bromo and most preferably chloro.
- (b) The aliphatic "alkyl" groups may be straight or branched chains containing the specified number of carbon atoms.
- 15 The term "pharmaceutically acceptable salt" as used herein is intended to include the nontoxic acid addition salts with inorganic or organic acids, e.g. salts with acids such as hydrochloric, phosphoric, sulfuric, maleic, acetic, citric, succinic, benzoic, fumaric, mandelic, p-toluenesulfonic, methanesulfonic, ascorbic, lactic, gluconic, trifluoroacetic,

hydroiodic, hydrobromic, and the like. Some of the compounds of the present invention have an acidic hydrogen and can, therefore, be converted with bases in a conventional manner into pharmaceutically acceptable salts. Such salts, e.g. ammonium, alkali metal salts, particularly sodium or potassium, alkaline earth metal salts, particularly calcium or magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (e.g. hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or tris-(hydroxymethyl)amino-

methane), or with bases such as piperidine or morpholine, are also intended to be encompassed by the term "pharmaceutically acceptable salt".

Compounds of the present invention in the form of acid addition salts may be written as



where $X^{\ominus}$ represents an acid anion and R^1 is hydrogen or a carboxyl-protecting group. The counter anion $X^{\ominus}$ may be selected so as to provide pharmaceutically acceptable salts for therapeutic administration.

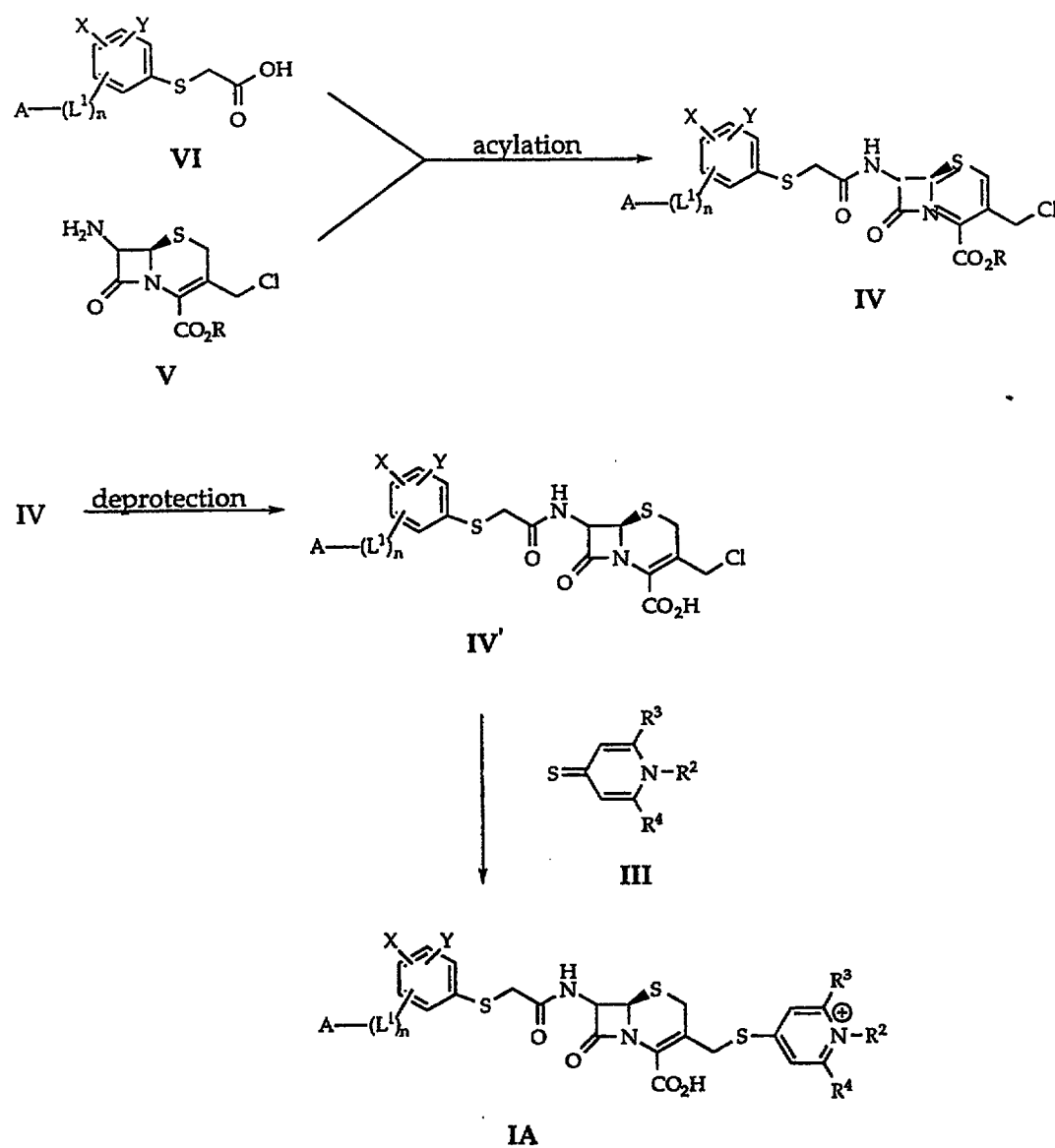
The carboxyl-protecting group R^1 is intended to include readily removable ester groups which have been conventionally employed to block a carboxyl group during the reaction steps used to prepare the compounds of the present invention and which can be removed by methods which do not result in any appreciable destruction of the remaining portion of the molecule, e.g. by chemical or enzymatic hydrolysis, treatment with chemical reducing agents under mild conditions, irradiation with ultraviolet light or catalytic hydrogenation.

Examples of such protecting groups include benzhydryl, p-nitrobenzyl, 2-naphthylmethyl, allyl, benzyl, p-methoxybenzyl, trichloroethyl, silyl such as trimethylsilyl, phenacyl, acetonyl, o-nitrobenzyl, 4-pyridylmethyl and C_1 - C_6 alkyl such as methyl, ethyl or t-butyl. Included within such protecting groups are those which are hydrolyzed under physiological conditions such as pivaloyloxymethyl, acetoxymethyl, phthalidyl, indanyl, α -acetoxylethyl, α -pivaloyloxyethyl and methoxymethyl.

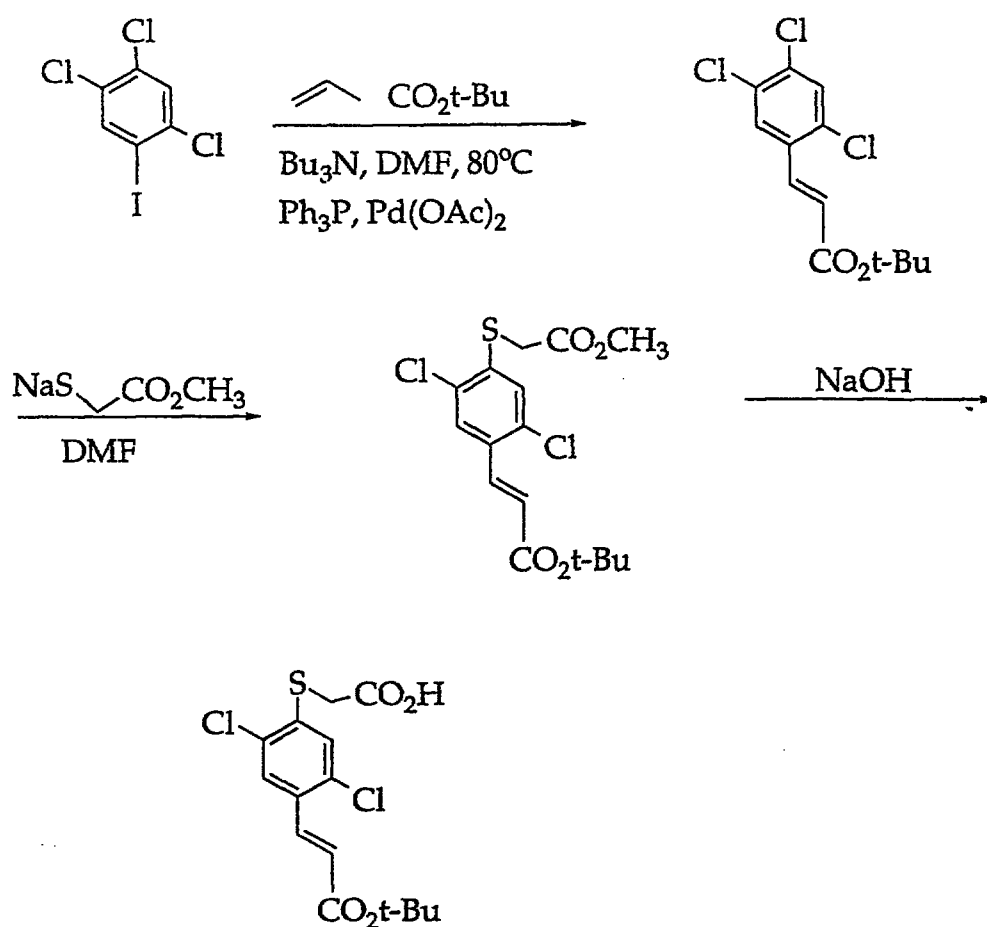
Compounds of the present invention with such physiologically hydrolyzable carboxyl protecting groups are also referred to herein as "prodrugs". Compounds of the present invention where R^1 is a physiologically removable protecting group are useful directly as antibacterial agents. Compounds where an R^1 protecting group is not physiologically removable are useful intermediates which can be easily converted to the bioactive form by conventional deblocking procedures well-known to those skilled in the art.

Compounds of the present invention wherein a hydroxyl substituent is esterified with a group hydrolyzable under physiological conditions are also included within the scope of the term "prodrug" as
5 used herein. Such hydroxyl-protecting groups may be employed, for example, to increase the solubility of a cephem derivative. Illustrative of suitable ester "prodrugs" of this type are compounds wherein one or more hydroxy substituent groups are converted to sulfate ($-\text{OSO}_3\text{H}$) or phosphate ($-\text{OPO}_3\text{H}_2$) groups.

10 The compounds of the present invention can be made by conventional methods. A suitable procedure is summarized by the following reaction scheme:



To elaborate on the above process, intermediates of type VI are first prepared, for example, analogous to the process illustrated below:



Acid intermediate VI is then coupled with a suitable cephem intermediate having a 3-substituent leaving group. For example, the leaving group may be acetoxy or halogen. In the preferred embodiment

5 leaving group may be acetoxy or halogen. In the preferred embodiment illustrated by the reaction scheme, the cephem intermediate is the 3-chloromethyl cephem V, but other suitable cephem intermediates with equivalent leaving groups at the 3-position could also be employed. The cephem intermediate V may be acylated with VI or a reactive derivative

10 thereof by conventional acylation procedures well-known in the cephalosporin art to give N-acylated intermediate IV. In addition to using the free arylthioacetic acid, e.g. with a suitable condensing agent such as

dicyclohexylcarbodiimide, acylating agent VI may also be employed in the form of equivalent acylating derivatives such as an acid anhydride, mixed anhydride, activated ester, or acid halide. The cephem intermediate preferably has the carboxyl group protected by a conventional carboxyl-protecting group which can be readily removed. Examples of such protecting groups are discussed above and include benzyl, 4-nitrobenzyl, 1,1 dimethylethyl, 4-methoxybenzyl, diphenylmethyl, allyl, and the like. Other examples of suitable protecting groups are disclosed in Protective Groups in Organic Synthesis, 2nd Ed., Theodora W. Greene (John Wiley & Sons, 1991), Chapter 5. In one embodiment, intermediate V may be acylated with acid VI in the presence of dicyclohexylcarbodiimide and in an inert solvent such as tetrahydrofuran or dichloromethane. The reaction temperature is typically between -20 °C and 50 °C. Upon completion of the reaction, insoluble material is removed by filtration, the filtrate is concentrated, and the residue is treated with a relatively non-polar solvent such as diethyl ether or ethyl acetate resulting in precipitation of the desired product. Alternatively, acid VI may be converted to the corresponding acid chloride, for example by treatment with thionyl chloride with or without a solvent such as dichloromethane, followed by coupling with cephem amine V in the presence of a base such as triethylamine or N-methylmorpholine to give intermediate IV. Cephem IV is typically isolated after aqueous work-up and evaporation of volatile solvents followed by trituration of the compound with a relatively non-polar solvent such as diethyl ether or ethyl acetate. This

intermediate may be used in the next reaction step as the X = chloride derivative, or can be converted to the X = bromide or X = iodide derivative by treatment with the appropriate metal halide in a solvent such as acetone.

5

To prepare the quaternary cephem I, intermediate IV is deprotected under acidic conditions, followed by reaction of the resulting intermediate IV' with a thiopyridone derivative III. For example, when R is diphenylmethyl or 4-methoxybenzyl, cephem acid IV' is obtained upon
10 treatment of IV with trifluoroacetic acid neat or in an inert solvent such as methylene chloride. A reagent such as anisole may also be employed to scavenge the liberated ester protecting group. The reaction temperature is usually at or below room temperature. The deprotection may also be carried out by treatment with other protic acids such as hydrochloric acid
15 in a solvent such as methanol. The final product is typically isolated by precipitation or crystallization. Reaction of IV' with a thiopyridone derivative III in a solvent such as dimethylformamide, dimethyl sulfoxide, ethanol, methanol, or other appropriate solvents at a temperature between -20 °C and 100 °C affords target quaternary cephem I.
20 The final product is isolated as described above. Thiopyridones III are typically prepared according to a method analogous to that described in T. Takahashi et al., European Patent Application No. 209751 and in I.E. El-Kholy et al., J. Heterocyclic Chem. Vol. 11, p. 487 (1974). This procedure entails reaction of 4-thiopyrone (European Patent No. 209751) with an

appropriate primary amine in a solvent such as aqueous methanol or ethanol at a temperature ranging between 0 °C and 78 ° C. The primary amine may be in the form of a zwitterion in examples where there is a free acid group present in the molecule. In these cases, a base such as sodium hydroxide, sodium bicarbonate, or pyridine is added to form the free amine in situ. The product may be isolated as its sodium salt by evaporation of volatile solvents, followed by trituration with a solvent such as diethyl ether or ethyl acetate. Alternatively, the reaction mixture may be acidified and extracted with an organic solvent to afford the product as the free carboxylic acid. If the carboxylate group is protected as an ester, the amine may be free or present as an acid salt. In the latter case, a base such as sodium hydroxide, sodium bicarbonate, or pyridine is added to form the free amine in situ. The product is typically isolated by precipitation or by reversed phase column chromatography following removal of volatile solvents.

Other representative intermediate VI groups may be prepared as described in the preparation of starting materials section below.

It will be understood that where the substituent groups used in the above reactions contain certain reaction-sensitive functional groups such as amino or carboxylate groups which might result in undesirable side-reactions, such groups may be protected by conventional protecting groups known to those skilled in the art. For example, thiopyridone

intermediates of formula III may have an amine functional group protected as the t-butyloxycarbamate. Suitable protecting groups and methods for their removal are illustrated, for example, in Protective Groups in Organic Synthesis, 2nd Ed., Theodora W. Greene (John Wiley & Sons, 1991). It is intended that such "protected" intermediates and end-products are included within the scope of the present disclosure and claims.

The desired end-product of formula I may be recovered either as the zwitterion or in the form of a pharmaceutically acceptable acid addition salt, e.g. by addition of the appropriate acid such as HCl, HI or methanesulfonic acid to the zwitterion. Compounds of formula I where R^1 is hydrogen or an anionic charge, or a pharmaceutically acceptable salt thereof, may be converted by conventional procedures to a corresponding compound where R^1 is a physiologically hydrolyzable ester group.

It will be appreciated that certain products within the scope of formula I may have a C-3 substituent group which can result in formation of optical isomers. It is intended that the present invention include within its scope all such optical isomers as well as epimeric mixtures thereof, i.e. R- or S- or racemic forms.

The novel cephalosporin derivatives of general formula I (including the IA compounds) wherein R^1 is hydrogen, an anionic charge

or a physiologically hydrolyzable carboxyl-protecting group, or the pharmaceutically acceptable salts or prodrugs thereof, are potent antibiotics active against many gram-positive bacteria. While they may be used, for example, as animal feed additives for promotion of growth, as
5 preservatives for food, as bactericides in industrial applications, for example in water-based paint and in the white water of paper mills to inhibit the growth of harmful bacteria, and as disinfectants for destroying or inhibiting the growth of harmful bacteria on medical and dental equipment, they are especially useful in the treatment of infectious
10 disease in humans and other animals caused by the gram-positive bacteria sensitive to the new derivatives. Because of their excellent activity against MRSA organisms, they are particularly useful in the treatment of infections resulting from such bacteria.

15 The pharmaceutically active compounds of this invention may be used alone or formulated as pharmaceutical compositions comprising, in addition to the active cephem ingredient, a pharmaceutically acceptable carrier or diluent. The compounds may be administered by a variety of means, for example, orally, topically or parenterally (intravenous or
20 intramuscular injection). The pharmaceutical compositions may be in solid form such as capsules, tablets, powders, etc. or in liquid form such as solutions, suspensions or emulsions. Compositions for injection, the preferred route of delivery, may be prepared in unit dose form in ampules or in multidose containers and may contain additives such as suspending,

stabilizing and dispersing agents. The compositions may be in ready-to-use form or in powder form for reconstitution at the time of delivery with a suitable vehicle such as sterile water.

5 The dosage to be administered depends, to a large extent, on the particular compound being used, the particular composition formulated, the route of administration, the nature and condition of the host and the particular situs and organism being treated. Selection of the particular preferred dosage and route of application, then, is left to the discretion of
10 the physician or veterinarian. In general, however, the compounds may be administered parenterally or orally to mammalian hosts in an amount of from about 50 mg/day to about 20 g/day. Administration is generally carried out in divided doses, e.g., three to four times a day, analogous to dosing with a cephalosporin such as cefotaxime.

15

IN VITRO ACTIVITY

Samples of the compounds prepared below in Examples 1 - 22 after solution in water and dilution with Nutrient Broth were found to exhibit
20 the following Minimum Inhibitory Concentrations (MIC) values versus the indicated microorganisms as determined by tube dilution. The MICs were determined using a broth micro dilution assay in accordance with that recommended by the National Committee for Clinical Laboratory Standards (NCCLS). Mueller-Hinton medium was used except for

Streptococci which was tested in Todd Hewitt broth. The final bacterial inoculate contained approximately 5×10^5 cfu/ml and the plates were incubated at 35°C for 18 hours in ambient air (Streptococci in 5% CO₂).

The MIC was defined as the lowest drug concentration that prevented
5 visible growth.

	<u>Microorganism</u>	<u>MIC value in ug/ml</u>
	<u>S. aureus</u> methicillin resistant A27223	≤8
10	<u>S. pneumoniae</u> A9585	≤2
	<u>S. pyogenes</u> A9604	≤2
	<u>E. faecalis</u> A20688	≤8
	<u>S. aureus</u> A9537, penicillinase negative	≤1
	<u>S. aureus</u> A15090, penicillinase positive	≤1
15	<u>S. epidermidis</u> A24548	≤1
	<u>S. epidermidis</u> A25783, methicillin resistant	≤2
	<u>S. hemolyticus</u> A21638	≤8

IN VIVO ACTIVITY

The in vivo therapeutic efficacy of the compounds prepared in Examples 1 - 22 below after intramuscular injection to mice

5 experimentally infected with the representative MRSA strain A27223 was also measured.

The determination of the effectiveness of antimicrobial agents in
Staphylococcus aureus systemic infection in mice

10

Organisms: The test organism, MRSA strain A27223 used to generate systemic infection in mice, is grown on two large Brain Heart Infusion Agar plates. On each plate, 0.5 ml of frozen stock culture is plated out. Plates are then incubated for 18 hours at 30°C. The next day each plate is

15 washed with 20 ml of Brain Heart Infusion Broth and then pooled together. A microscopic direct count of microorganism is done using a 1:1000 dilution of plate wash. After a direct count is obtained, the number of organisms per milliliter is calculated. The count is adjusted to the desired amount of inoculum by diluting in 4% hog mucin. The desired

20 challenge (amount of organisms given to mice) is 2.4×10^8 cfu/0.5 ml/mouse for MRSA strain A27223. The mice are infected intraperitoneally with 0.5 ml of challenge. Ten non-treated infected mice are used as controls.

Mice: Mice used are male ICR mice. The average weight of the animals is from 20 to 26 grams.

Drug preparation and treatment: Compounds are tested at 4 dose levels,
5 (25, 6.25, 1.56, and 0.39 mg/kg) and prepared in 5% cremophor, unless
otherwise specified. Vancomycin is used as the control compound, and is
dosed at 6.25, 1.56, 0.39, and 0.098 mg/kg. It is prepared in 0.1M phosphate
buffer. There are five infected mice per dose level, and they are treated
with 0.2 ml of the test compound, preferably by intramuscular injection.
10 Treatment begins 15 minutes and 2 hours post-infection.

Test duration: A PD₅₀ (the dose of drug given which protects 50% of
mice from mortality) experiment runs for 5 days. During this time,
mortality of mice are checked every day and deaths are recorded. The
15 cumulative mortality at each dose level is used to calculate a PD₅₀ value
for each compound. Surviving mice are sacrificed at the end of day 5 by
CO₂ inhalation.

Calculation: Actual calculation of PD₅₀ is performed with a computer
20 program using the Spearman-Kärber procedure.

Results: The in vivo efficacy, expressed as the PD₅₀ value, ranged from
about 0.8 to 22.0 mg/kg (for certain compounds, more than one test was

carried out; the indicated range is for at least one test result when multiple tests were done).

ILLUSTRATIVE EXAMPLES

5 The following examples illustrate the invention, but are not intended as a limitation thereof. The abbreviations used in the examples are conventional abbreviations well-known to those skilled in the art. Some of the abbreviations used are as follows:

10	h	=	hour(s)
	mol	=	mole(s)
	mmol	=	mmole(s)
	g	=	gram(s)
	THF	=	tetrahydrofuran
15	L	=	liter(s)
	mL	=	milliliter(s)
	Et ₂ O	=	diethyl ether
	EtOAc	=	ethyl acetate
	BOC	=	butoxycarbonyl
20	DCC	=	dicyclohexylcarbodiimide
	DPM	=	diphenylmethyl
	Ph ₃ P	=	triphenylphosphine
	t-Bu	=	tertiary-butyl
	EtOH	=	ethanol

	Bu ₃ N	=	tributylamine
	MeOH	=	methanol
	DMF	=	dimethylformamide
	DABCO	=	1,4-diazabicyclo[2.2.2]octane
5	TFA	=	trifluoroacetic acid
	DMS	=	dimethylsulfide
	m-CPBA	=	meta-chloroperoxybenzoic acid
	TFAA	=	trifluoroacetic anhydride
	TEA	=	triethylamine

10

In the following examples, all temperatures are given in degrees Centigrade. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker AM-300 or a Varian Gemini 300 spectrometer. All spectra were determined in CDCl₃, DMSO-d₆, CD₃OD, or D₂O unless

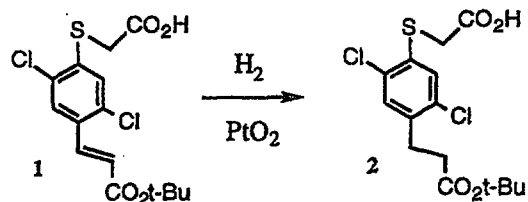
15 otherwise indicated. Chemical shifts are reported in δ units relative to tetramethylsilane (TMS) or a reference solvent peak and interproton coupling constants are reported in Hertz (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak; dd, doublet of doublets; dt, doublet of triplets;

20 and app d, apparent doublet, etc. Mass spectra were recorded on a Kratos MS-50 or a Finnegan 4500 instrument utilizing direct chemical ionization (DCI, isobutene), fast atom bombardment (FAB), or electron ion spray (ESI).

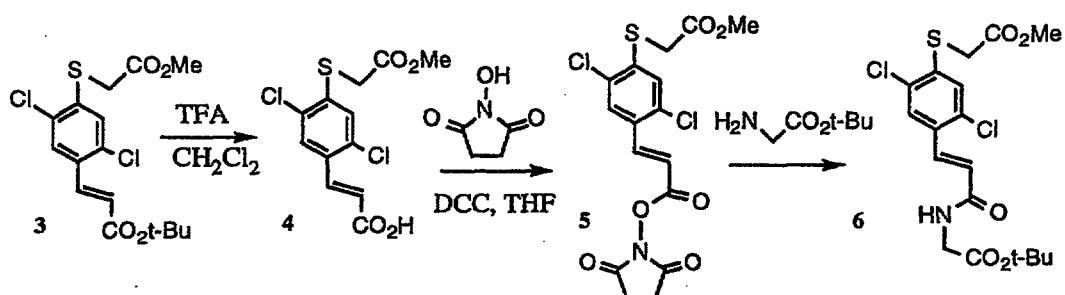
Analytical thin-layer chromatography (TLC) was carried out on precoated silica gel plates (60F-254) and visualized using UV light, iodine vapors, and/or staining by heating with methanolic phosphomolybdic acid. Column chromatography, also referred to as flash chromatography, was performed in a glass column using finely divided silica gel at pressures somewhat above atmospheric pressure with the indicated solvents. Reversed-phase analytical thin-layer chromatography was carried out on precoated reverse phase plates and visualized using UV light or iodine vapors. Reversed-phase column chromatography was performed in a glass column using Baker Octadecyl (C₁₈), 40 mm.

Preparation of Starting Materials

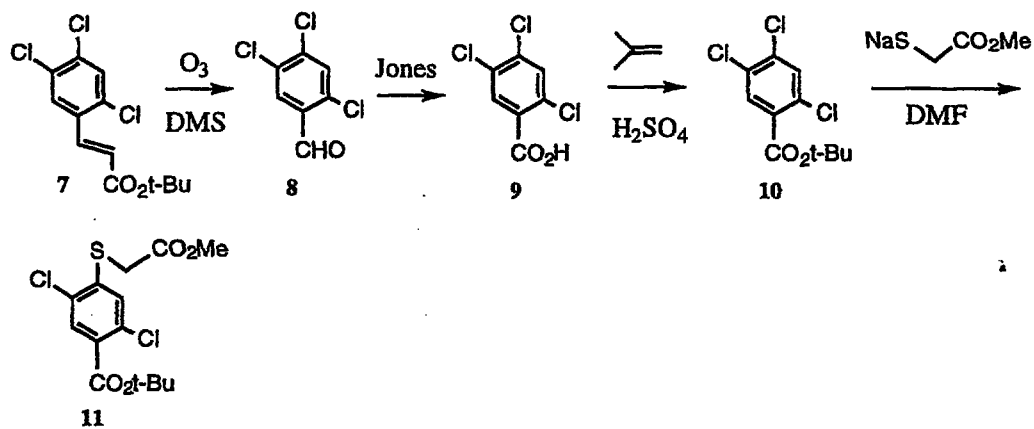
scheme 2



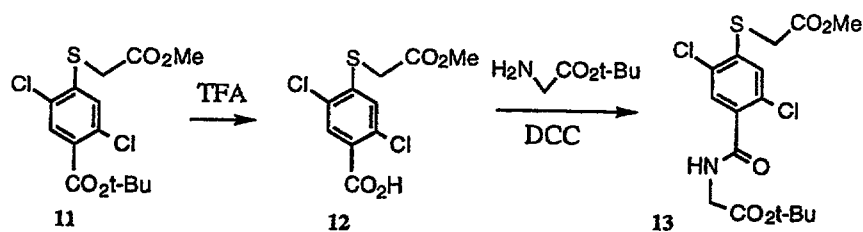
scheme 3



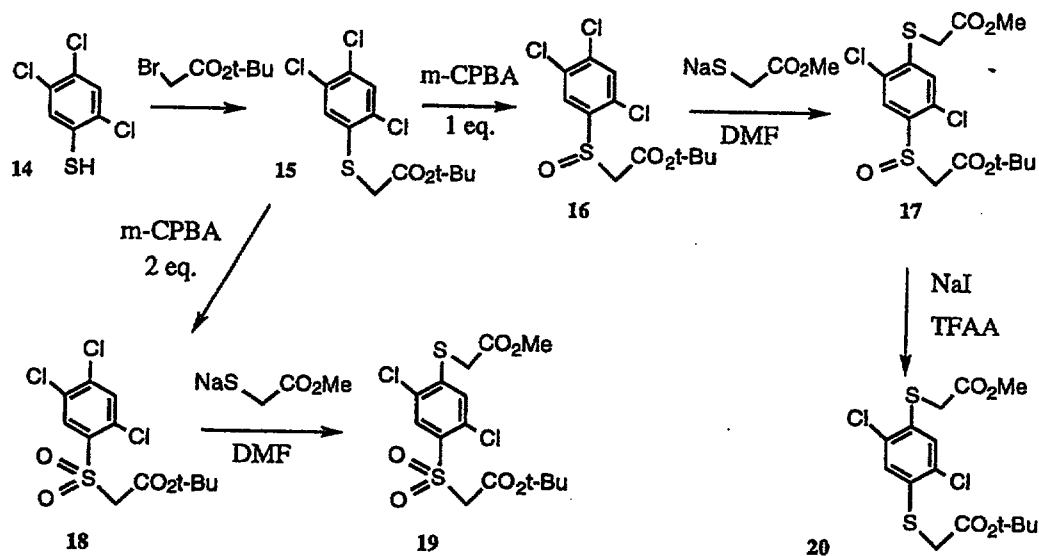
scheme 4



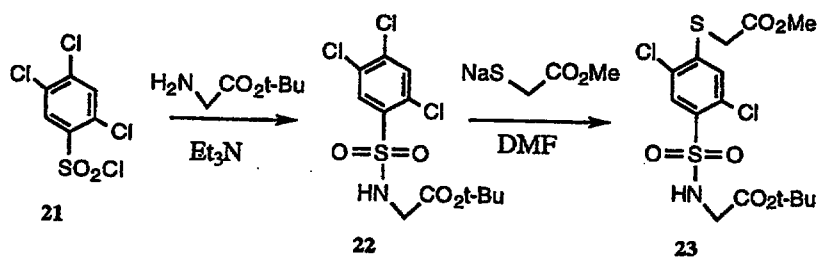
scheme 5



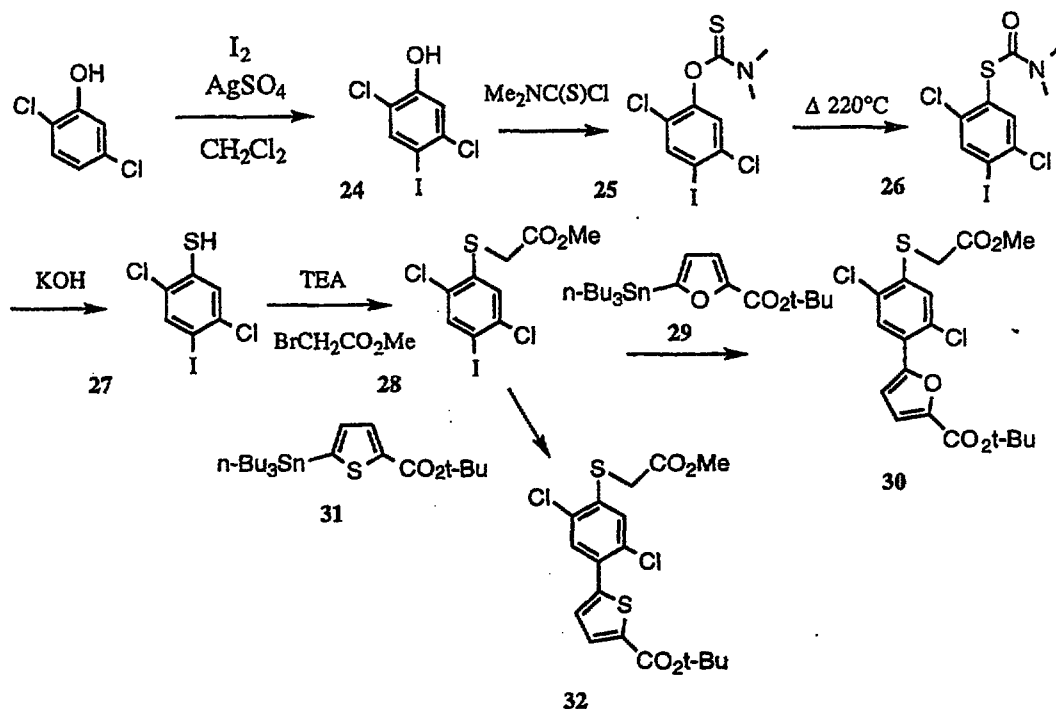
scheme 6



scheme 7



scheme 8



A. Synthesis of acid 2

Acid 1 (2.00 g., 0.006 mol) is dissolved in 50 mL EtOH, and PtO₂ (1.00 g., 0.004 mol) is added. The mixture is hydrogenated at 20 psi for 18 hours. ¹H-NMR analysis indicates that the reaction has only proceeded to 30% conversion. More PtO₂ (0.400 g., 0.002 mol) is added, and hydrogenation at 20 psi is continued another 6 hours. At this time the reaction is only 50% complete. The solids are filtered, and the filtrate is treated with fresh PtO₂ (1.00 g., 0.004 mol) and hydrogenated at 20 psi for another 20 hours. The reaction still shows some starting olefin. At this point the mixture is filtered, and the filtrate is concentrated. The residue is chromatographed on silica using CH₂Cl₂ as eluant, followed by a gradient elution with

methanol/CH₂Cl₂ (up to 15% MeOH). Acid 2 is obtained (0.750 g., 0.002 mol; 33% yield) as a white solid.

¹H-NMR (300 MHz, CDCl₃): δ 7.40 (s, 1H, ArH), 7.30 (s, 1H, ArH), 3.72 (s, 2H, SCH₂), 2.96 (t, 2H, J = 8 Hz, ArCH₂), 2.54 (t, 2H, J = 8 Hz, CH₂CO₂R), 1.43 (s, 9H, C(CH₃)₃).

B. Synthesis of acid 4

Diester 3 (7.00 g., 0.019 mol) is suspended in 40 mL CH₂Cl₂. Anisole (1 mL) is added, followed by 15 mL of trifluoroacetic acid. The mixture is stirred for 1 hour at room temperature. The solvents are concentrated to ~15 mL, and excess ether is added to precipitate a white solid. The solid is collected, washed with ether, and dried under vacuum to yield acid 4 (4.85 g., 0.015 mol; 79% yield).

¹H-NMR (300 MHz, DMSO-d₆): δ 8.08 (s, 1H, ArH), 7.71 (d, 1H, J = 16 Hz, ArCH=C), 7.43 (s, 1H, ArH), 6.69 (d, 1H, J = 16 Hz, C=CHCO₂), 4.19 (s, 2H, SCH₂), 3.66 (s, 3H, OCH₃).

C. Synthesis of hydroxysuccinimide ester 5

Acid 4 (8.75 g., 0.027 mol) is suspended in 55 mL THF under an atmosphere of nitrogen. Dicyclohexylcarbodiimide (1M in CH₂Cl₂, 28.7 mL, 0.029 mol) is added, followed by N-hydroxysuccinimide (3.14 g., 0.027 mol). The reaction is allowed to stir for 3 hours at room temperature. The mixture is diluted with ~30 mL acetone, filtered to remove dicyclohexylurea, and concentrated to ~25 mL. A solid forms which is filtered off, and the filtrate is evaporated to dryness. Crude 5 is obtained as a white solid (12.3 g.) which is of sufficient purity for use in subsequent reactions.

¹H-NMR (300 MHz, DMSO-d₆): δ 8.27 (s, 1H, ArH), 8.01 (d, 1H, J = 16 Hz, ArCH=C), 7.50 (s, 1H, ArH), 7.17 (d, 1H, J = 16 Hz, C=CHCO₂), 4.23 (s, 2H, SCH₂), 3.68 (s, 3H, OCH₃), 2.84 (m, 4H, CH₂CH₂).

D. Synthesis of amide 6

tert-Butylglycine hydrochloride (5.19 g., 0.031 mol) is suspended under a nitrogen atmosphere in 60 mL dry DMF. N-Methylmorpholine (3.90 mL, 0.036 mol) is added, and then the mixture is cooled to 0°C. Crude hydroxysuccinimide ester 5 (12.3 g.) is added, and the mixture allowed to stir for 10 minutes at 0°C. The cooling bath is removed and the reaction is stirred for 1 hour. The mixture is concentrated, and the residue dissolved in ethyl acetate and placed in a separatory funnel. The solution is washed with 0.4 N aqueous HCl, 0.1 N aqueous NaHCO₃,

water and then brine. The organic phase is dried (MgSO_4) and evaporated to afford clean amide 6 as a light yellow solid (10.4 g., 0.024 mol; 89% yield from acid 4).

5 ^1H -NMR (300 MHz, DMSO-d_6): δ 8.42 (t, 1H, $J = 8$ Hz, NH), 7.81 (s, 1H, ArH), 7.59 (d, 1H, $J = 16$ Hz, $\text{ArCH}=\text{C}$), 7.47 (s, 1H, ArH), 6.80 (d, 1H, $J = 16$ Hz, $\text{C}=\text{CHCONH}$), 4.20 (s, 2H, SCH_2), 3.85 (d, 2H, $J = 8$ Hz, NCH_2CO_2), 3.67 (s, 3H, OCH_3), 1.41 (s, 9H, $\text{C}(\text{CH}_3)_3$).

10 E. Synthesis of 2,4,5-trichlorobenzaldehyde 8

Ester 7 (1.03 g., 3.35 mmol) is dissolved in 200 mL CH_2Cl_2 and 100 mL methanol. The mixture is cooled to -78°C , and ozone is bubbled through the solution until it turns blue. The mixture is purged with oxygen, and then 1.3 mL of methyl sulfide is added. The mixture is
15 allowed to warm to room temperature, and the solvents are evaporated. The crude residue is partitioned between ether and water. The ether layer is washed with water and brine, and then dried (MgSO_4). Concentration of the ether layer, followed by chromatography on silica using 25% CH_2Cl_2 /hexane as eluant, affords 8 (0.55 g., 2.63 mmol; 79% yield) as a
20 white solid.

^1H -NMR (300 MHz, CDCl_3): δ 10.34 (s, 1H, CHO), 7.98 (s, 1H, ArH), 7.58 (s, 1H, ArH).

F. Synthesis of 2,4,5-trichlorobenzoic acid 9

2,4,5-Trichlorobenzaldehyde (0.275 g., 1.31 mmol) is dissolved in 8 mL acetone. A slight excess of Jones Reagent is added, and the mixture stirred at room temperature for 1 hour. Methanol (~6 mL) is added, and
5 after 5 minutes the mixture is partitioned between methylene chloride and water. The aqueous phase is extracted with chloroform (2X), and the combined organic extracts are washed with water, then brine. The organic phase is dried (MgSO₄), and concentrated to afford pure 2,4,5-trichlorobenzoic acid 9 (0.285 g., 1.26 mmol; 96% yield) as a white solid.

10

¹H-NMR (300 MHz, CDCl₃): δ 8.01 (s, 1H, ArH), 7.61 (s, 1H, ArH).

G. Synthesis of 2,4,5-trichlorobenzoic acid, tert-butyl ester 10

Acid 9 (2.93 g., 13.0 mmol) placed in a Parr hydrogenation bottle
15 (under an atmosphere of nitrogen) is dissolved in 55 mL of dioxane. The bottle is cooled to -78°C, and 5 mL conc. sulfuric acid is added cautiously, followed by ~50 mL liquid isobutylene (cooled to -78°C). The bottle is sealed and agitated on a Parr shaker overnight (~19.5 hours). The sealed
bottled is vented, and the solution slowly added to a separatory funnel
20 containing half-saturated aqueous NaHCO₃ and ether. The aqueous layer is extracted with ether, and the combined organic phase was dried (MgSO₄) and concentrated. Chromatography on silica using hexane, followed by 25% CH₂Cl₂/hexane, affords ester 10 as a pale yellow oil (2.56

g., 9.10 mmol; 70% yield) which solidifies overnight in the refrigerator to an off-white solid.

¹H-NMR (300 MHz, CDCl₃): δ 7.81 (s, 1H, ArH), 7.53 (s, 1H, ArH), 1.58 (s, 9H, C(CH₃)₃).

H. Synthesis of diester 11

Using the method described below for the synthesis of diester 3, ester 10 (2.5 g., 11.3 mmol) is converted to diester 11 (3.20 g., 9.12 mmol; 81% yield). Diester 11 was obtained as a white solid by chromatography on silica gel using 80% methylene chloride/hexane.

¹H-NMR (300 MHz, CDCl₃): δ 7.75 (s, 1H, ArH), 7.30 (s, 1H, ArH), 3.75 (s, 3H, OCH₃), 3.72 (s, 2H, SCH₂), 1.58 (s, 9H, C(CH₃)₃).

I. Synthesis of acid 12

Diester 11 (1.60 g., 4.56 mmol) is dissolved in 5 mL methylene chloride. Trifluoroacetic acid (2 mL) is added, and the mixture stirred for 4 hours at room temperature. The solvents are evaporated to provide 12 (1.24 g., 4.20 mmol; 92% yield) as a tan solid of sufficient purity for use in the next reaction.

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ 7.87 (s, 1H, ArH), 7.46 (s, 1H, ArH), 4.23 (s, 2H, SCH_2), 3.68 (s, 3H, OCH_3).

J. Synthesis of amide 13

5 Acid 12 (1.24 g., 4.20 mmol) is dissolved in 14 mL dry THF. Dicyclohexylcarbodiimide (0.866 g., 4.20 mmol) is added, followed by tert-butyl glycine (0.550 g., 4.20 mmol), and the mixture stirred at room temperature for 2 hours. Ether is added to the flask, and the solids removed by filtration. The filtrate is evaporated to yield 1.96 g. of crude
10 material. Chromatography on silica using 80% CH_2Cl_2 /hexane, followed by a second chromatography using 20% ethyl acetate/hexane affords amide 13 (0.844 g., 2.07 mmol; 49% yield) as a white solid.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.78 (s, 1H, ArH), 7.31 (s, 1H, ArH), 4.12 (d, 2H, $J = 6$ Hz, NCH_2CO_2), 3.77 (s, 3H, OCH_3), 3.72 (s, 2H, SCH_2), 1.48 (s, 9H, $\text{C}(\text{CH}_3)_3$).

K. Synthesis of ester 15

2,4,5-Trichlorothiophenol (35.0 g., 0.166 mol) is dissolved in 500 mL
20 methylene chloride and cooled to 0°C . Triethylamine (22.0 g., 0.217 mol) is added, followed by a solution tert-butyl bromoacetate (35.1 g., 0.180 mol) in 100 mL methylene chloride (over 5 minutes). After stirring for 20 minutes at 0°C , the ice-bath is removed, and stirring continued for

another hour. The mixture is placed in a separatory funnel and washed with water (2X), 10% aqueous H_3PO_4 , and then brine. The organic phase is dried (MgSO_4), and evaporated to afford a white solid, which is washed with hexane. Ester 15 (51 g., 0.156 mol; 94%) as obtained is of suitable
5 purity for subsequent reactions.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.47 (s, 1H, ArH), 7.45 (s, 1H, ArH), 3.66 (s, 2H, SCH_2), 1.43 (s, 9H, $\text{C}(\text{CH}_3)_3$).

10 L. Synthesis of sulfoxide 16

Ester 15 (50.0 g., 0.153 mol) is dissolved in 500 mL chloroform and cooled to 0°C . m-Chloroperoxybenzoic acid (50-60% from Aldrich, 48.0 g., 0.140-0.168 mol) is added in small portions over 30 minutes. The ice bath is removed and stirring continued for 2.5 hours at room temperature.
15 The solids were removed by filtration, and the filtrate washed with dilute aqueous NaHSO_3 , 5% aqueous Na_2CO_3 , saturated aqueous NaHCO_3 , and then brine. The organic phase is dried (MgSO_4), and evaporated. The crude material is chromatographed twice on silica gel using methylene chloride and then 3% methanol/methylene chloride to afford sulfoxide 16
20 (35.0 g., 0.102 mol; 67% yield) as a white solid.

^1H -NMR (300 MHz, CDCl_3): δ 7.95 (s, 1H, ArH), 7.53 (s, 1H, ArH), 4.05 (d, 1H, $J = 14$ Hz, $\text{CH}_2\text{S}(\text{O})$), 3.70 (d, 1H, $J = 14$ Hz, $\text{CH}_2\text{S}(\text{O})$), 1.43 (s, 9H, $\text{C}(\text{CH}_3)_3$).

5 M. Synthesis of diester 17

Using the procedure described below for the synthesis of diester 3, sulfoxide 16 (35.0 g., 105 mmol) is converted to diester 17 (32.5 g., 78.7 mmol; 75% yield). The compound is isolated as a white solid after chromatography on silica using methylene chloride then 3% methanol/methylene chloride.

^1H -NMR (300 MHz, CDCl_3): δ 7.83 (s, 1H, ArH), 7.28 (s, 1H, ArH), 3.92 (d, 1H, $J = 14$ Hz, $\text{CH}_2\text{S}(\text{O})$), 3.77 (s, 3H, OCH_3), 3.71 (s, 2H, SCH_2), 3.57 (d, 1H, $J = 14$ Hz, $\text{CH}_2\text{S}(\text{O})$).

15

N. Synthesis of diester 20

Diester 17 (28.0 g., 67.8 mmol) is dissolved in 500 mL acetone. Sodium iodide (48.7 g., 325 mmol) is added, followed by trifluoroacetic anhydride (40.0 g., 191 mmol) over 5 minutes. After stirring at room temperature for 1 hour, the solvents are evaporated. Methylene chloride is added and evaporated twice. The residue is taken up in methylene chloride and washed with aqueous NaHSO_3 solution (3X), water, and then brine. The organic phase is dried (MgSO_4), and evaporated.

20

Chromatography of the residue on silica using methylene chloride affords diester 20 (23.5 g., 59.2 mmol; 87 % yield) as a white solid.

¹H-NMR (300 MHz, CDCl₃): δ 7.38 (s, 1H, ArH), 7.35 (s, 1H, ArH), 3.74 (s,
5 3H, OCH₃), 3.66 (s, 2H, SCH₂), 3.60 (s, 2H, SCH₂).

O. Synthesis of sulfone 18

Ester 15 (7.00 g., 21.4 mmol) is dissolved in 40 mL chloroform and treated with m-chloroperoxybenzoic acid (~60% from Aldrich, 12.0 g., ~42
10 mmol). After stirring for 1 hour at room temperature, the solids are removed by filtration, and the filtrate is washed with dilute aqueous NaHSO₃, 5% aqueous Na₂CO₃, saturated aqueous NaHCO₃, and then brine. The organic phase is dried (MgSO₄), and evaporated.

Chromatography of the residue on silica using methylene chloride then
15 3% methanol/methylene chloride affords sulfone 18 (7.00 g., 19.5 mmol; 93% yield) as a white solid.

¹H-NMR (300 MHz, CDCl₃): δ 8.17 (s, 1H, ArH), 7.67 (s, 1H, ArH), 4.32 (s,
2H, SCH₂), 1.33 (s, 9H, C(CH₃)₃).

20

P. Synthesis of diester 19

Using the procedure described below for the synthesis of diester 3, sulfone 18 (7.20 g., 20.0 mmol) is converted to diester 19 (8.05 g., 18.8

mmol; 94% yield). The compound is isolated as a white solid after chromatography on silica using methylene chloride then 3% methanol/methylene chloride.

- 5 $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 8.05 (s, 1H, ArH), 7.40 (s, 1H, ArH), 4.28 (s, 2H, SO_2CH_2), 3.78 (s, 3H, OCH_3), 3.77 (s, 2H, SCH_2).

Q. Synthesis of sulfonamide 22

- tert-Butyl glycine (2.62 g., 20.0 mmol) and triethylamine (2.50 g., 25.0
10 mmol) are dissolved in 20 mL chloroform under a nitrogen atmosphere. The solution is cooled with an ice-bath, and 2,4,5-trichlorobenzenesulfonyl chloride (5.60 g., 20.0 mmol) dissolved in 30 mL chloroform is added over 5 minutes. The cooling bath is removed and the mixture allowed to stir at room temperature for 1 hour. The solution
15 is washed with 10% aqueous H_3PO_4 , water, and then brine. The organic phase is dried (MgSO_4), and evaporated to afford clean sulfonamide 22 (7.00 g., 18.8 mmol; 94% yield) as a white solid.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 8.10 (s, 1H, ArH), 7.63 (s, 1H, ArH), 3.72 (s, 2H, NCH_2CO_2), 1.33 (s, 9H, $\text{C}(\text{CH}_3)_3$).

20

R. Synthesis of diester 23

Using the procedure described above, sulfonamide 22 (3.70 g., 10.0 mmol) is converted to diester 23 (2.37 g., 7.40 mmol; 74% yield). The

compound is isolated as a white solid after chromatography on silica using methylene chloride then 5% methanol/methylene chloride.

¹H-NMR (300 MHz, CDCl₃): δ 7.96 (s, 1H, ArH), 7.36 (s, 1H, ArH), 5.65 (t, 1H, J = 5 Hz, NH), 3.85 (s, 3H, OCH₃), 3.78 (s, 2H, SCH₂), 3.71 (d, 2H, J = 5 Hz, NCH₂CO₂), 1.34 (s, 9H, C(CH₃)₃).

S. Synthesis of 2,5-dichloro-4-iodophenol 24

2,5-Dichlorophenol (20.4 g., 0.125 mol) is placed in a 1L round bottom flask equipped with a large egg-shaped stir bar and is dissolved in 307 mL CH₂Cl₂. With rapid stirring, iodine (46.6 g., 0.183 mol) is added, followed by silver sulfate (42.3 g., 0.136 mol). The purple solution is stirred 1 day, at which point NMR analysis of an aliquot indicates the reaction is complete.

The reaction is diluted with CH₂Cl₂ (~200 ml) and filtered through a fritted Buchner funnel to remove silver salts. The salts are washed with additional CH₂Cl₂ (~100 mL). The organic filtrate is transferred to a separatory funnel and is washed first with a solution of sodium thiosulfate (~40 g. in ~200 mL water; this removes excess I₂), and then brine. The organic phase is dried (MgSO₄), and evaporated to give 24 (34.59 g., 0.108 mol; 86% yield) as a pale pink/yellow solid. The material is sufficiently pure to carry forward.

^1H -NMR (300 MHz, CDCl_3): δ 7.75 (s, 1H, ArH), 7.14 (s, 1H, ArH), 5.62 (br, 1H, OH).

T. Synthesis of thiocarbamate 25

5 Iodophenol 24 (34.59 g., 0.108 mol) is placed into a 500 mL round bottom flask equipped with septa, N_2 inlet, and a stir bar. The phenol is then dissolved in 130 mL DMF. DABCO (24.2 g., 0.216 mol) is added followed by dimethylthiocarbamyl chloride (21.6 g., 0.175 mol). The mixture is stirred at room temperature for ~ 1 hour, then diluted with
10 EtOAc (~400 mL) and poured into a separatory funnel containing ~ 300 mL of ice-water. The phases are separated, and the aqueous extracted twice with ~ 200 mL of EtOAc. The combined organic extracts are washed twice with water (~ 100 mL), and then brine. The organic phase is dried (MgSO_4), and evaporated to afford 25 as a dark oil. This material is
15 dissolved in CH_2Cl_2 and dried again (MgSO_4). After evaporation a yellow solid (~35 g.) is obtained. The compound was of sufficient purity to be used in the next reaction.

^1H -NMR (300 MHz, CDCl_3): δ 7.90 (s, 1H, ArH), 7.24 (s, 1H, ArH), 3.46 (s,
20 3H, CH_3), 3.37 (s, 3H, CH_3).

U. Synthesis of 26

The crude material obtained above (~35 g.) was heated neat under N₂ at 220°C for two hours. After cooling, the material was dissolved in CH₂Cl₂ and filtered through a plug of silica gel. The fractions containing the product are evaporated to afford 30.2 g. of a brown solid. This material was chromatographed on silica (in portions) using a gradient elution starting with 1:1 CH₂Cl₂/hexane (material dissolved in a minimum amount of CH₂Cl₂ for column loading), and then ~70% CH₂Cl₂/hexane. Compound 26 is obtained as a yellow crystalline solid (13.0 g., 36.0 mmol; 33% yield from 2,5-dichlorophenol).

¹H-NMR (300 MHz, CDCl₃): δ 7.95 (s, 1H, ArH), 7.62 (s, 1H, ArH), 3.10 (br s, 3H, CH₃), 3.00 (br s, 3H, CH₃).

15 V. Synthesis of 2,5-dichloro-4-iodothiophenol 27

Carbamate 26 (9.80 g., 0.026 mol) is dissolved in 40 mL EtOH and treated with 30 mL 3N aqueous KOH. The mixture is heated to reflux with stirring under nitrogen for 3 hours. The solution is allowed to cool and is then acidified with 3 N HCl until pH ~3. The mixture is extracted with CH₂Cl₂ (thrice), and the combined organic phase washed with water and then brine. The extracts are dried (MgSO₄) and evaporated. The crude material is chromatographed on silica using 1:1 CH₂Cl₂/hexane. Thiol 27 (6.43 g., 0.021 mol; 81% yield) is obtained as a white solid.

^1H -NMR (300 MHz, CDCl_3): δ 7.83 (s, 1H, ArH), 7.56 (s, 1H, ArH).

W. Synthesis of ester 28

5 Thiol 27 (6.43 g., 0.021 mol) is dissolved in 50 mL CH_2Cl_2 and triethylamine (2.52 g., 0.025 mol) is added. Methyl bromoacetate (3.82 g., 0.025 mol) is then added over 5 minutes. The resultant mixture is stirred at room temperature for 1.5 hours, at which time ^1H -NMR analysis indicated the reaction was complete. The mixture was diluted with
10 CH_2Cl_2 (~200 mL) and was washed with water, 1N HCl, water, and then brine. The organic layer was dried (MgSO_4) and evaporated. The crude material is chromatographed on silica using 70% CH_2Cl_2 /hexane. Ester 28 is obtained as a white solid (7.20 g., 0.019 mol; 90% yield).

15 ^1H -NMR (300 MHz, CDCl_3): δ 7.82 (s, 1H, ArH), 7.42 (s, 1H, ArH), 3.75 (s, 3H, OCH_3), 3.68 (s, 2H, SCH_2).

X. Synthesis of stannane 29

Bis(tributyltin) (29.5 g., 50.9 mmol) is dissolved under a nitrogen
20 atmosphere in 70 mL dry THF. The solution is cooled to -20°C , and butyllithium (1.6 M in hexane, 31.2 mL, 49.9 mmol) is added dropwise over 20 minutes, maintaining the temperature of the bath at -20°C . The solution is then cooled to -50°C , and then copper(I) bromide

methyldisulfide complex (5.10 g., 24.8 mmol) is added. The mixture is allowed to stir at -40°C for 15 minutes, and is then cooled to -78°C. 5-Bromofuroic acid tert-butyl ester (4.10 g., 16.6 mmol) dissolved in 15 mL THF is added, and the mixture allowed to stir for 3 hours at -78°C. The reaction mixture is poured into 1 L of ether and ~300 mL half-saturated aqueous ammonium chloride solution. After stirring for 5 minutes the ether layer is decanted onto another ~300 mL of half-saturated aqueous ammonium chloride solution. After 5 minutes the biphasic mixture is separated, and the organic phase is washed with brine, dried (MgSO₄) and evaporated. Chromatography on silica using hexane, then 25% methylene chloride/hexane affords stannane 29 (5.05 g., 11.1 mmol; 67% yield) as a clear oil.

¹H-NMR (300 MHz, CDCl₃): δ 7.04 (d, 1H, J = 4 Hz, HetArH), 6.56 (d, 1H, J = 4 Hz, HetArH), 1.59-1.47 (m, 3 H, SnBu₃), 1.37-1.24 (m, 9 H, SnBu₃), 1.13-1.05 (m, 6 H, SnBu₃), 0.89 (t, 9H, J = 6 Hz, SnBu₃).

Y. Synthesis of diester 30

Stannane 29 (1.50 g., 3.28 mmol) is dissolved in 8 mL dry THF. Aryl iodide 28 (0.928 g., 2.46 mmol) is added, followed by bis(triphenylphosphine)-palladium(II) chloride (0.160 g., 0.228 mmol). The solution is heated to reflux for 6 hours. The mixture is diluted with ~15 mL THF, 4 mL conc. aqueous KF is added, and the mixture is stirred for 20 minutes. Ether is added, and the mixture is then filtered to remove

insoluble tin solids. The biphasic filtrate is separated, and the aqueous layer is extracted with ether. The combined organic phases are washed with brine, dried (MgSO_4) and evaporated. During evaporation crystals began to form, and when only ~5 mL of liquid remains it is decanted. The solids are washed with hexane and then pumped dry. Diester 30 (0.793 g., 1.91 mmol; 78% yield) is obtained as a white solid.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.99 (br s, 1H, ArH), 7.40 (br s, 1H, ArH), 7.19 (d, 1H, $J = 2$ Hz, HetArH), 7.13 (d, 1H, $J = 2$ Hz, HetArH), 3.75 (s, 3H, OCH_3), 3.71 (s, 2H, SCH_2), 1.60 (s, 9H, $\text{C}(\text{CH}_3)_3$).

Z. Synthesis of stannane 31

Using the method described above, 5-bromo-2-thiophenecarboxylic acid, tert-butyl ester (4.52 g., 17.2 mmol) is converted to stannane 31 (4.33 g., 9.16 mmol; 53% yield). The compound is isolated as a light yellow oil after chromatography on silica using 25% methylene chloride/hexane.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.80 (d, 1H, $J = 3$ Hz, HetArH), 7.12 (d, 1H, $J = 3$ Hz, HetArH), 1.58 (m, 15H, SnBu_3), 0.92 (t, 9H, $J = 6$ Hz, SnBu_3), 0.85-0.80 (m, 3H, SnBu_3).

AA. Synthesis of diester 32

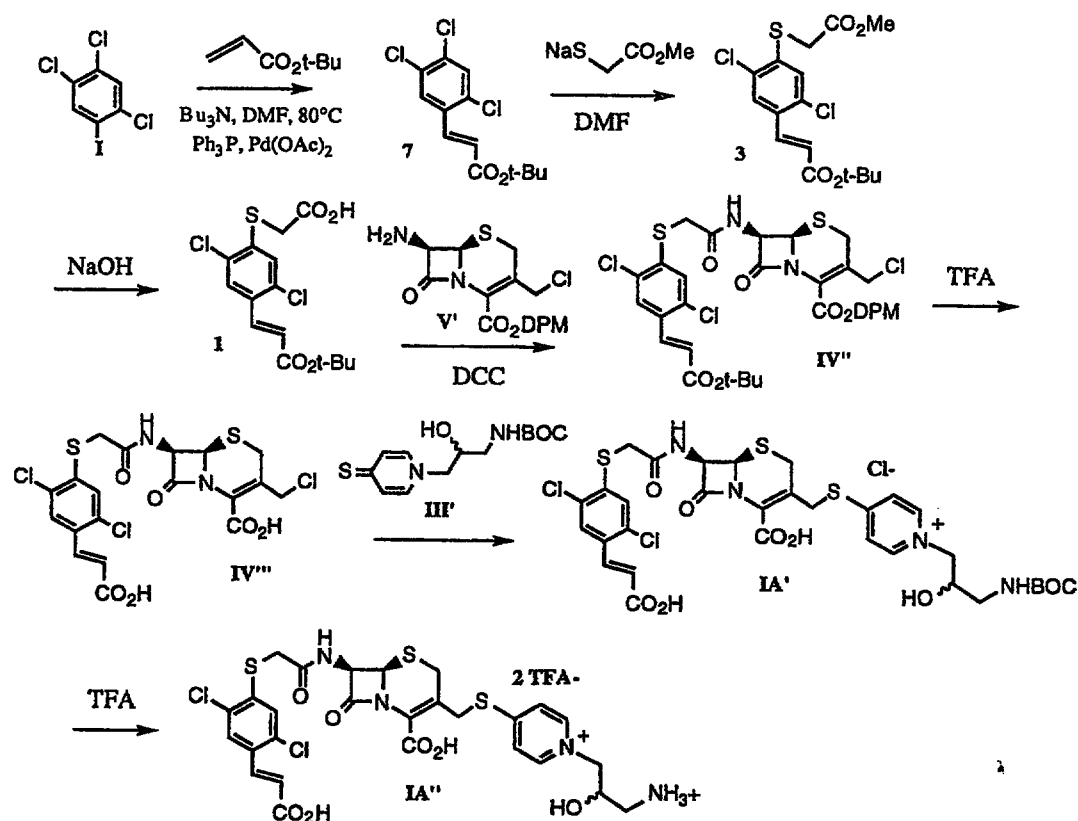
Using the method described above for the synthesis of diester 30, stannane 31 (1.70 g., 3.60 mmol) and aryl iodide 28 (1.03 g., 2.73 mmol) are converted to diester 32 (0.920 g., 2.13 mmol; 78% yield as a light yellow solid).

¹H-NMR (300 MHz, CDCl₃): δ 7.66 (d, 1H, J = 3 Hz, HetArH), 7.55 (s, 1H, ArH), 7.44 (s, 1H, ArH), 7.27 (d, 1H, J = 3 Hz, HetArH), 3.78 (s, 3H, OCH₃), 3.73 (s, 2H, SCH₂), 1.58 (s, 9H, C(CH₃)₃).

Example 1

1-[2-hydroxy-3-amino-prop-1-yl]-4-[[[(6R)-trans-2-carboxy-8-oxo-7-[(2,5-dichloro-4-(2-carboxyethenyl)phenylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]-oct-2-en-3-yl]methylthio]pyridinium inner salt.

scheme 1

**A. Synthesis of olefin 7**

2,4,5-Trichloriodobenzene (25 g., 81.3 mmol) is dissolved in 80 mL DMF. tert-Butyl acrylate (48 mL, 328 mmol), tributylamine (58 mL, 243 mmol), triphenylphosphine (4.08 g., 15.5 mmol), and palladium acetate (3.23 g., 14.4 mmol) are added, and the mixture heated to 80°C for three

hours. The solvents are evaporated and the residue is partitioned with EtOAc and water. The aqueous phase is extracted with EtOAc, and the combined organic phase is washed with brine, dried (MgSO₄), and evaporated. The dark red-brown oil is chromatographed on silica in a
5 fritted Buchner funnel using vacuum filtration, with 30% CH₂Cl₂/hexane followed by 50% CH₂Cl₂/hexane as eluant. Acrylate 7 is obtained (18.7 g., 60.8 mmol; 75% yield) as a mauve solid.

¹H-NMR (300 MHz, CDCl₃): δ 7.82 (d, 1H, J = 16 Hz, ArCH=C), 7.67 (s, 1H, ArH), 7.51 (s, 1H, ArH), 6.34 (d, 1H, J = 16 Hz, C=CHCO₂t-Bu), 1.51 (s, 9H, C(CH₃)₃).

B. Synthesis of diester 3

Acrylate 7 (21.23 g., 69 mmol) is dissolved in 131 mL DMF. The
15 sodium salt of methyl mercaptoacetate (17.7 g., crude: see note below) is added and the mixture stirred at room temperature for one hour. The mixture is partitioned with EtOAc and water. The aqueous phase is extracted with EtOAc, and the combined organic phase is washed with brine, dried (MgSO₄), and evaporated. Chromatography on silica in a
20 fritted Buchner funnel (vacuum filtration) using 50% CH₂Cl₂/hexane followed by 90% CH₂Cl₂/hexane as eluant affords diester 3 (19.6 g., 52.0 mmol; 75% yield).

^1H -NMR (300 MHz, CDCl_3): δ 7.86 (d, 1H, $J = 16$ Hz, $\text{ArCH}=\text{C}$), 7.60 (s, 1H, ArH), 7.36 (s, 1H, ArH), 6.35 (d, 1H, $J = 16$ Hz, $\text{C}=\text{CHCO}_2\text{t-Bu}$), 3.77 (s, 3H, OCH_3), 3.72 (s, 2H, SCH_2), 1.51 (s, 9H, $\text{C}(\text{CH}_3)_3$).

- 5 Note: The sodium salt of methyl mercaptoacetate is best made fresh before use. Approximately 30 mL of methyl mercaptoacetate is dissolved in ~250 mL THF. One equivalent of 5 N NaOH is added slowly in pipetfulls, and the mixture allowed to stir for 5 minutes. The solvents are removed in vacuo (including water) and the sticky solid is co-evaporated
- 10 with ether (~200 mLs) and then dry THF (2 x 200 mLs). The solid is pumped dry for several hours under high vacuum until the flask is no longer cool due to evaporation. The freely mobile white solid is used as obtained. Excess of this reagent (1.5 to 2 equivalents) is generally used.

15 C. Synthesis of acid 1

- Diester 3 (4.40 g., 0.012 mol) is dissolved in 30 mL THF. To this solution is added 13 mL of 1N NaOH, and the mixture is allowed to stir at room temperature for 1.5 hours. At this time ^1H -NMR analysis of an aliquot indicates that the reaction is complete. The THF is removed
- 20 under vacuum, and the concentrate is diluted with water and extracted with EtOAc. The aqueous layer is then acidified with 1N HCl to pH 4, and then extracted with CH_2Cl_2 . The organic phase is washed with brine, dried (MgSO_4), and then evaporated. Acid 1 is obtained as a tan solid (3.80 g., 0.011 mol; 92% yield).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.82 (d, 1H, $J = 16$ Hz, $\text{ArCH}=\text{C}$), 7.56 (s, 1H, ArH), 7.33 (s, 1H, ArH), 6.29 (d, 1H, $J = 16$ Hz, $\text{C}=\text{CHCO}_2\text{t-Bu}$), 3.72 (s, 2H, SCH_2), 1.51 (s, 9H, $\text{C}(\text{CH}_3)_3$).

5 D. Synthesis of cephem IV''

Cephem amine V' (15.04 g., 0.035 mmol) is suspended under a nitrogen atmosphere in 65 mL THF. A solution of DCC in methylene chloride (1M, 36.2 mL, 0.036 mmol) is added, and the mixture allowed to stir for 5 minutes. Acid 1 (13.15 g., 0.035 mmol) is added and the mixture
10 is stirred for 1.5 hours. Ether (~30 mL) is added, and the solids (mostly DCU) are filtered off. The red-colored filtrate is evaporated to ~25-30 mL and ether and pentane are added to precipitate the cephem product. The solid cephem is collected, washed with ether, and dried under vacuum to afford diester IV'' (14.2 g., 0.019 mmol; 54% yield).

15

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.53 (d, 1H, $J = 16$ Hz, $\text{ArCH}=\text{C}$), 7.45-7.20 (m, 12H, ArH), 6.98 (s, 1H, Ph_2CH), 6.35 (d, 1H, $J = 16$ Hz, $\text{C}=\text{CHCO}_2\text{t-Bu}$), 5.82 (dd, 1H, $J = 5, 8$ Hz, $\text{R}_1\text{R}_2\text{CHNR}_3$), 4.97 (d, 1H, $J = 5$ Hz, $\text{CH}(\text{NR})(\text{SR})$), 4.37 (m, 2H, CH_2Cl), 3.76 (d, 1H, $J = 16$ Hz, ArSCH_2), 3.55 (d, 1H, $J = 16$ Hz, ArSCH_2), 3.40 (d, 1H, $J = 16$ Hz, RSCH_2R), 1.54 (s, 9H, $\text{C}(\text{CH}_3)_3$).

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E. Synthesis of diacid IV'''

Diester IV'' (0.760 g., 1.00 mmol) is dissolved in 4 mL CH₂Cl₂ and 0.8 mL anisole. Trifluoroacetic acid (2 mL) is added, and the mixture is stirred for 4 hours. The solvents are evaporated, and the residue

5 triturated with CH₂Cl₂/ether. The solid is collected, washed with EtOAc and then dried under vacuum. Diacid IV''' is obtained (0.420 g., 0.780 mmol; 78% yield) as a light yellow solid.

¹H-NMR (300 MHz, DMSO): δ 9.30 (d, 1H, J = 8 Hz, RC(O)NH), 8.07 (s, 1H, ArH), 7.72 (d, 1H, J = 16 Hz, ArCH=C), 7.54 (s, 1H, ArH), 6.68 (d, 1H, J = 16 Hz, C=CHCO₂H), 5.71 (dd, 1H, J = 5, 8 Hz, R₁R₂CHNR₃), 5.13 (d, 1H, J = 5 Hz, CH(NR)(SR)), 4.55 (m, 2H, CH₂Cl), 3.97 (m, 2H, ArSCH₂), 3.70 (d, 1H, J = 16 Hz, RSCH₂R), 3.53 (d, 1H, J = 16 Hz, RSCH₂R).

15 F. Synthesis of cephem IA'

20 Diacid IV''' (0.780 g., 1.45 mmol) is dissolved in 3 mL methanol and 8 mL CH₂Cl₂. Thiopyridone III' (0.395 g., 1.45 mmol) is added, and the mixture is stirred at room temperature for 4 hours. The flask is then placed in a refrigerator at 4°C overnight. The solvents are concentrated, and the product precipitated with ether. The solid is filtered, then suspended in EtOAc and stirred for 30 minutes. The product is then filtered, and the solid dried under vacuum. Cephem IA' is obtained as a tan solid (0.690 g., 0.850 mmol; 59% yield of a mixture of two diastereomers).

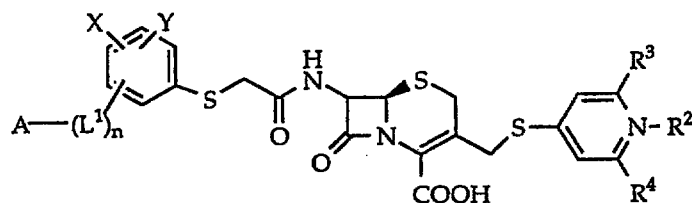
¹H-NMR (300 MHz, DMSO, partial): δ 9.31 (d, 1H, J = 8 Hz, RC(O)NH),
8.67 (d, 2H, J = 7 Hz, SpyrH), 7.98 (d, 2H, J = 7 Hz, SpyrH), 8.07 (s, 1H, ArH),
7.72 (d, 1H, J = 16 Hz, ArCH=C), 7.54 (s, 1H, ArH), 6.69 (d, 1H, J = 16 Hz,
C=CHCO₂H), 5.70 (dd, 1H, J = 5, 8 Hz, R₁R₂CHNR₃), 5.14 (d, 1H, J = 5 Hz,
5 CH(NR)(SR)), 4.59-4.45 (m, 2H, CH₂Spyr), 4.40-4.32 (m, 2H, pyrCH₂R), 4.05-
3.95 (m, 2H, ArCH₂S), 1.38 (s, 9H, C(CH₃)₃).

G. Synthesis of cephem IA''

Cephem IA' (0.605 g., 0.747 mmol) is suspended in 3 mL CH₂Cl₂,
10 and 1 mL of trifluoroacetic acid is added. The solution is stirred for two
hours and the solvents evaporated. The crude material is dissolved in
CH₂Cl₂ and precipitated with ether. The solids are collected, suspended
in EtOAc and stirred for 30 minutes. The solids are collected and dried
under vacuum (P₂O₅). Cephem IA'' is obtained (0.410 g., 0.609 mmol; 82%
15 yield).

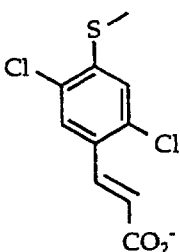
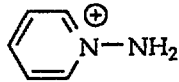
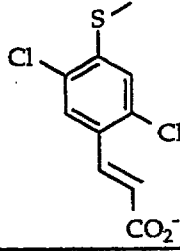
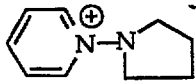
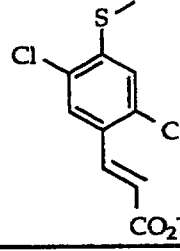
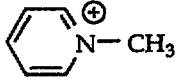
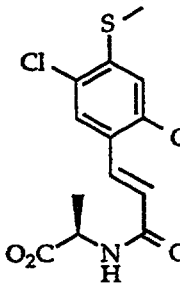
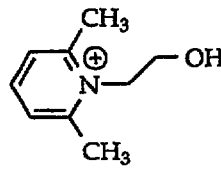
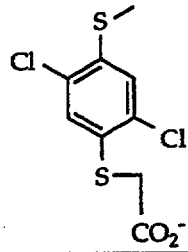
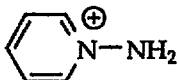
¹H-NMR (300 MHz, DMSO, partial): δ 9.40-9.35 (m, 1H, RC(O)NH), 8.77-
8.72 (m, 2H, SpyrH), 8.23-8.18 (m, 2H, SpyrH), 8.12 (s, 1H, ArH), 7.77 (d, 1H,
J = 16 Hz, ArCH=C), 7.62 (s, 1H, ArH), 6.75 (d, 1H, J = 16 Hz, C=CHCO₂H),
5.68-5.61 (m, 1H, R₁R₂CHNR₃), 5.11 (d, 1H, J = 5 Hz, CH(NR)(SR)), 4.07-
20 3.97 (m, 2H, ArSCH₂).

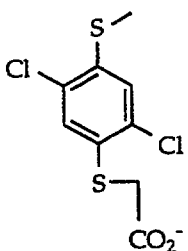
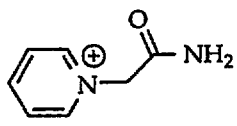
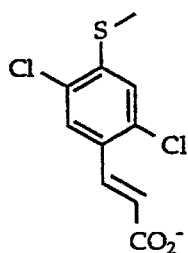
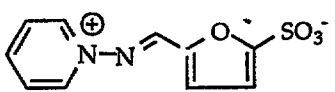
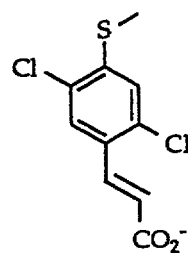
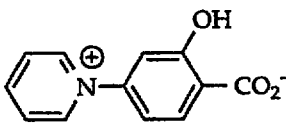
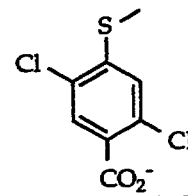
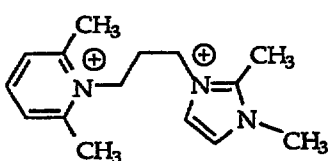
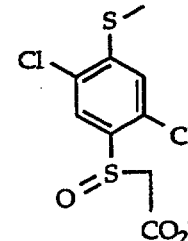
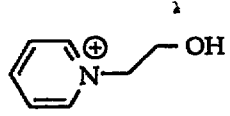
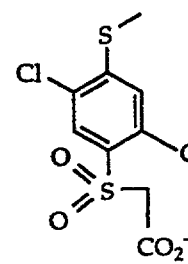
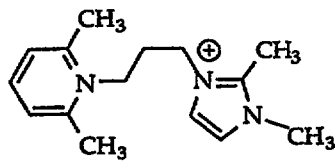
Following the general procedures and using the appropriate starting materials described above, the following additional compounds were prepared:

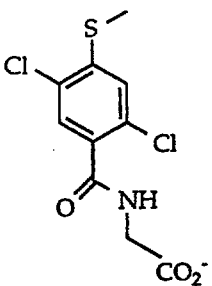
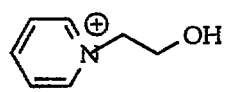
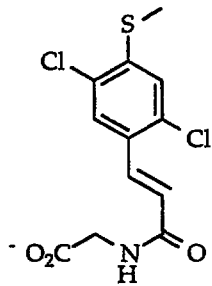
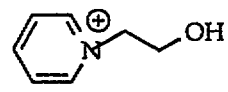
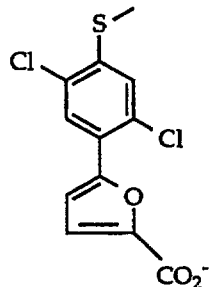
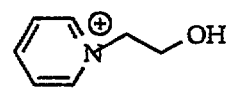
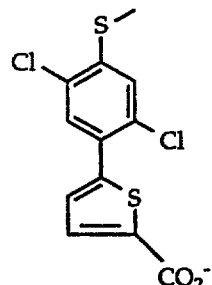
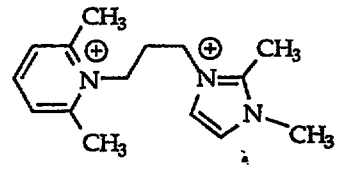
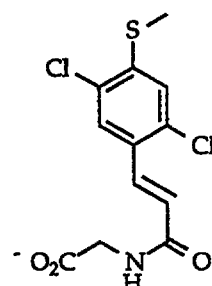
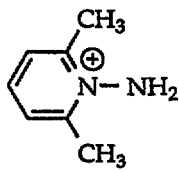


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<u>Example No.</u>		
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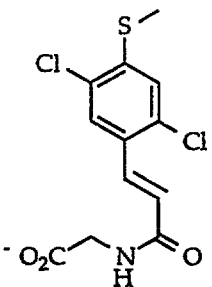
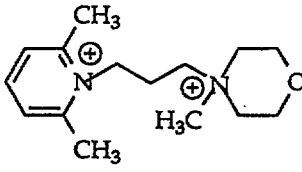
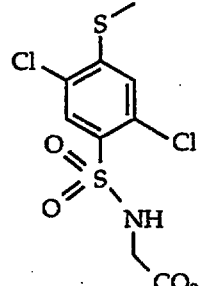
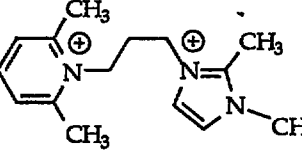
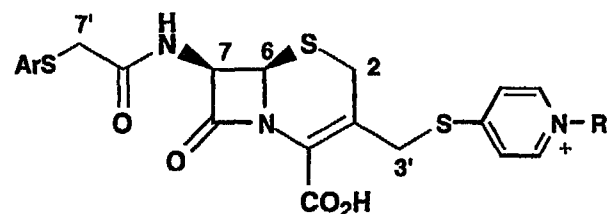
21	 <chem>CSC1=CC=C(Cl)C(Cl)=C1/C=C/C(=O)NCC(=O)[O-]</chem>	 <chem>CN1C=CC(=CC=C1)[NH+]CC[N+]1CCOCC1C</chem>
22	 <chem>CSC1=CC=C(Cl)C(Cl)=C1S(=O)(=O)NCC(=O)O</chem>	 <chem>CN1C=CC(=CC=C1)[NH+]CC[N+]2C=CN(C)C2=CN2C</chem>

TABLE: NMR DATA



Compd. of Ex. No.	H-2	H-6	H-7	H-3	H-7'	NH	ArH	S-PyrH	R	Isolated Form	MS Data
1	3.70-3.54 (m)	5.11 (d, J = 5)	5.68-5.61 (m)	4.40-4.39 (m)	3.97 (br s)	9.40-9.35 (m)	8.12 (s) 7.77 (d, J = 16) 7.62 (s) 6.75 (d, J = 16)	8.77-8.72 (m) 8.23-8.18 (m)	4.80-4.60 (m) 4.40-4.24 (m) 4.23-4.10 (m) 3.10-3.00 (m) 2.80-2.65 (m)	bis TFA salt	M ⁺ = 685
2	3.74 (d, J = 18) 3.49 (d, J = 18)	5.13 (d, J = 5)	5.69 (dd, J = 5, 8)	4.41-4.37 (m)	3.95-3.83 (m)	9.24 (d, J = 8)	7.47 (s) 7.45 (s) 2.84 (t, J = 7) 2.48 (t, J = 7)	8.62 (d, J = 6) 8.05 (d, J = 6)	4.62-4.57 (m) 4.30-4.23 (m) 4.09-3.98 (m) 3.10-2.98 (m) 2.80-2.64 (m)	bis TFA salt	MH ⁺ = 687
3	3.92-3.77 (m)	4.86 (d, J = 5)	5.39 (d, J = 5)	4.41 (d, J = 13) 4.29 (d, J = 13)	4.09 (br s)	D ₂ O exch.	7.74 (s) 7.41 (s) 7.39 (d, J = 16) 6.39 (d, J = 16)	8.54 (d, J = 7) 7.97 (d, J = 7)	4.50-4.40 (m) 3.92-3.77 (m) 3.49-3.21 (m) 2.40-2.30 (m)	bis zwitterion	M ⁺ = 752

4	3.44 (d, J = 17) 3.26 (d, J = 17)	4.90 (d, J = 5)	5.41 (dd, J = 5, 8)	4.37 (s)	3.96 (d, J = 15) 3.88 (d, J = 15)	9.23 (d, J = 8)	7.81 (s) 7.51 (s) 7.33 (d, J = 16) 7.02 (s) 6.51 (d, J = 16)	8.02 (s)		mono Na salt / zwitterion	M* = 654
5	3.45 (d, J = 17) 3.29 (d, J = 17)	4.94 (d, J = 5)	5.41 (dd, J = 5, 8)	4.64 (d, J = 14) 4.27 (d, J = 14)	3.92-3.83 (m)	9.23 (d, J = 8)	7.82 (s) 7.50 (s) 7.35 (d, J = 16) 6.53 (d, J = 16)	8.61 (d, J = 7) 8.23 (d, J = 7)		mono Na salt / zwitterion	M* = 626
6	3.46 (d, J = 17) 3.36 (d, J = 17)	4.95 (d, J = 5)	5.45 (dd, J = 5, 8)	4.65 (d, J = 14) 4.44 (d, J = 14)	3.95 (s)	9.21 (d, J = 8)	8.03 (s) 7.68 (d, J = 16) 7.56 (s) 6.68 (d, J = 16)	8.92 (d, J = 7) 8.33 (d, J = 7)	3.42-3.32 (m) 2.20-1.90 (m)	mono Na salt / zwitterion	M* = 680
7	3.76 (d, J = 18) 3.56 (d, J = 18)	5.16 (d, J = 5)	5.72 (dd, J = 5, 8)	4.18 (s)	4.00 (s)	9.27 (d, J = 8)	8.10 (s) 7.57 (s) 7.74 (d, J = 16) 6.72 (d, J = 16)	8.69 (d, J = 6) 8.00 (d, J = 6)	3.45 (s)	chloride salt	M* = 628
8	3.45 (d, J = 16) 3.24 (d, J = 16)	4.85 (d, J = 5)	5.40 (d, J = 5)	4.28-4.21 (m)	4.05 (br s)	obscured	7.83 (s) 7.55 (d, J = 16) 7.48 (s) 6.81 (d, J = 16) 3.83 (q, J = 8) 1.19 (d, J = 8)	7.75 (br s) 2.68 (s)	4.45-4.37 (m) 3.80-3.75 (m)	zwitterion sodium salt	MH* = 754
9	3.6-3.2 (m)	4.92 (d, J = 5)	5.39 (dd, J = 5, 8)	4.65 (d, J = 13) 4.25 (d, J = 13)	3.90-3.70 (m)	9.28 (d, J = 8)	7.47 (s) 7.36 (s)	8.58 (d, J = 7) 8.23 (d, J = 7)		mono Na salt / zwitterion	M* = 646
10	3.75 (d, J = 18) 3.53 (d, J = 18)	5.13 (d, J = 5)	5.68 (dd, J = 5, 8)	4.40 (d, J = 14) 4.36 (d, J = 14)	3.96 (s)	9.07 (d, J = 8)	7.65 (s) 7.39 (s) 3.87 (s)	8.63 (d, J = 7) 8.01 (d, J = 7)	7.65 (br s) 5.20 (s)	chloride salt	MH* = 689
11	3.6-3.2 (m)	4.96 (d, J = 5)	5.42 (d, J = 5)	4.42-4.19 (m)	3.95 (d, J = 14) 3.78 (d, J = 14)	D ₂ O exch.	7.60 (d, J = 16) 8.00-7.07 (m) 6.38 (d, J = 16)	8.62 (d, J = 7) 8.36 (d, J = 7)	8.88 (s)	mono Na salt / zwitterion	

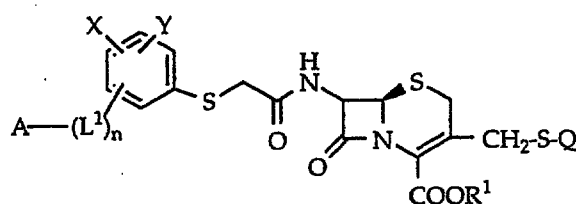
12	3.76 (d, J = 18) 3.56 (d, J = 18)	5.15 (d, J = 5)	5.69 (dd, J = 5, 8)	4.46 (d, J = 10) 4.44 (d, J = 10)	3.98 (s)	9.34 (d, J = 8)	8.07 (s) 7.71 (d, J = 16) 7.55 (s) 6.70 (d, J = 16)	9.34 (d, J = 6) 8.14 (d, J = 6)	8.04 (d, J = 8) 7.46 (d, J = 2) 7.31 (dd, J = 2, 8)	sodium salt	MH ⁺ = 748
13	3.74 (d, J = 12) other obscured	5.15 (d, J = 5)	5.70 (dd, J = 5, 8)	4.36-4.31 (m)	4.05-3.95 (m)	9.34 (d, J = 8)	7.86 (s) 7.56 (s)	7.83 (s) 2.75 (s)	7.80 (d, J = 2) 7.68 (d, J = 2) 4.40-4.31 (m) 3.77 (s) 2.66 (s)	zwitterion chloride salt	MH ⁺ = 752
14	3.75 (d, J = 18) 3.47 (d, J = 18)	5.14 (d, J = 5)	5.68 (dd, J = 5, 8)	4.40 (d, J = 14) 4.34 (d, J = 14)	4.02 (s)	9.35 (d, J = 8)	7.87 (s) 7.71 (s) 4.61 (s)	8.89 (d, J = 7) 8.01 (d, J = 7)	4.45 (br s) 3.80 (br s)	chloride salt	MH ⁺ = 710
15	3.50-3.20 (m)	5.13 (d, J = 5)	5.66 (dd, J = 5, 8)	4.40-4.25 (m)	4.08 (s)	9.35 (d, J = 8)	7.88 (s) 7.68 (s) 4.59 (s)	7.81 (s) 2.73 (s)	7.76 (d, J = 2) 7.66 (d, J = 2) 4.65-4.50 (m) 3.80-3.60 (m) 2.70-2.50 (m) 2.48 (s) 2.30-2.10 (m)	chloride salt	MH ⁺ = 829
16	3.69 (d, J = 16) 3.48 (d, J = 16)	5.12 (d, J = 6)	5.64 (dd, J = 6, 8)	4.41 (d, J = 13) 4.35 (d, J = 13)	3.96 (br s)	9.28 (d, J = 8)	8.83 (t, J = 8) 7.50 (s) 7.47 (s) 3.88 (d, J = 8)	8.67 (d, J = 8) 8.08 (d, J = 8)	4.51-4.45 (m) 3.83-3.77 (m)	chloride salt	MH ⁺ = 688
17	3.72 (d, J = 17) 3.49 (d, J = 17)	5.12 (d, J = 6)	5.66 (dd, J = 6, 8)	4.41 (d, J = 11) 4.34 (d, J = 11)	3.96 (br s)	9.30 (d, J = 8)	8.42 (t, J = 6) 7.81 (s) 7.56 (d, J = 16) 7.55 (s) 6.81 (d, J = 16) 3.86 (d, J = 6)	8.68 (d, J = 8) 8.02 (d, J = 8)	4.48-4.42 (m) 3.81-3.75 (m)	chloride salt	MH ⁺ = 714
18	3.76 (d, J = 17) 3.51 (d, J = 17)	5.15 (d, J = 5)	5.66 (dd, J = 5, 8)	4.42 (d, J = 12) 4.35 (d, J = 12)	4.03-3.93 (m)	9.31 (d, J = 8)	7.86 (s) 7.61 (s) 7.35 (d, J = 3) 7.24 (d, J = 3)	8.66 (d, J = 7) 8.02 (d, J = 7)	4.53-4.45 (m) 3.83-3.76 (m)	chloride salt	M ⁺ = 696

19	3.74 (d, J = 16) 3.49 (d, J = 16)	5.14 (d, J = 5)	5.70 (dd, J = 5, 8)	4.39-4.29 (m)	3.98 (s)	9.31 (d, J = 8)	7.82 (s) 7.73 (d, J = 3) 7.63 (s) 7.51 (d, J = 3)	7.80 (s) 2.74 (s)	7.79 (d, J = 1) 7.66 (d, J = 1) 4.46-4.35 (m) 4.38-4.31 (m) 3.76 (s) 2.64 (s) 2.30-2.18 (m)	chloride salt	M ⁺ = 832
20	3.45 (d, J = 17) 3.26 (d, J = 17)	4.85 (d, J = 5)	5.41 (dd, J = 5, 8)	4.42 (d, J = 14) 4.22 (d, J = 14)	obscured	9.22 (d, J = 8)	7.81 (s) 7.53 (d, J = 16) 7.49 (s) 6.83 (d, J = 16)	7.81 (s)		mono Na salt / zwitterion	M ⁺ = 712
21	3.95-3.87 (m)	4.86 (d, J = 5)	5.40 (dd, J = 5, 8)	4.48 (d, J = 13) 4.34 (d, J = 13)	3.92 (br s)	9.19 (d, J = 8)	8.10 (s) 7.52 (s) 7.46 (d, J = 16) 7.03 (d, J = 16)	7.83 (s)	4.37-4.25 (m) 3.95-3.85 (m) 3.65-3.60 (m) 3.45-3.15 (m) 2.75 (s) 2.25-2.15 (m)	bis zwitterion	M ⁺ = 837
22	3.48 (d, J = 18) 3.20 (d, J = 18)	5.12 (d, J = 5)	5.68 (dd, J = 5, 8)	4.40-4.25 (m)	4.06-3.92 (m)	9.36 (d, J = 8)	8.35 (t, J = 4) 7.87 (s) 7.60 (s) 3.70 (d, J = 4)	7.80 (s)	7.76 (d, J = 2) 7.61 (d, J = 2) 4.65-4.50 (m) 3.80-3.66 (m) 2.72 (s) 2.65 (s) 2.14-2.07 (m)	chloride salt	MH ⁺ = 847

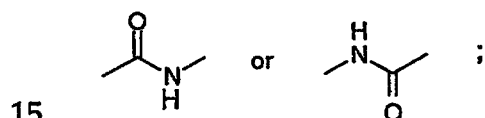
CLAIMS

We claim:

- 5 1. A compound of the formula



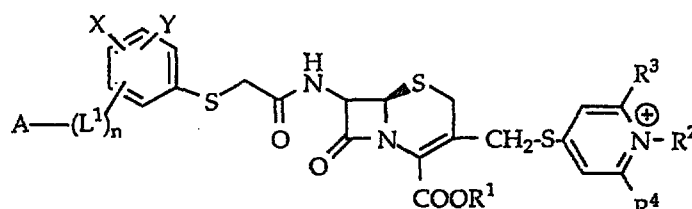
wherein Q is an optionally substituted pyridinium group connected to the
 10 sulfur atom via a ring carbon atom; X is halogen; Y is hydrogen or
 halogen; A is CO₂H, PO₃H₂, SO₃H or tetrazole; L¹ is a furan group, a
 thiophene group, a C₂-C₁₀ alkyl group, or a C₂-C₁₀ alkyl group interrupted
 by one or more groups independently selected from vinyl, S, SO, SO₂,
 SO₂NH,



n is 0 or 1; and R¹ is hydrogen or a carboxyl-protecting group; or a
 pharmaceutically acceptable salt and/or a prodrug thereof.

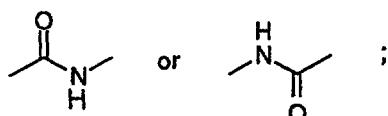
2. A compound of the formula

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IA

- wherein X is halogen; Y is hydrogen or halogen; A is CO₂H, PO₃H₂, SO₃H or tetrazole; L¹ is a furan group, a thiophene group, a C₂-C₁₀ alkyl group, or
 5 a C₂-C₁₀ alkyl group interrupted by one or more groups independently selected from vinyl, S, SO, SO₂, SO₂NH,

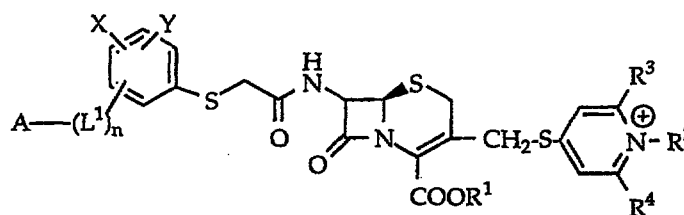


- n is 0 or 1; R³ and R⁴ are each independently selected from hydrogen or C₁-
 10 C₆ alkyl; R² is hydrogen, NH₂, pyrrolidinyl, C₃-C₆ cycloalkyl, C₁-C₆ alkyl, C₂-C₆ alkyl substituted by one or more substituents independently selected from OH, NR⁵R⁶ in which R⁵ and R⁶ are each independently hydrogen or C₁-C₆ alkyl, CO₂H, morpholinyl, morpholinyl quaternized by a C₄-C₆ alkyl group, oxo, halogen, SO₃H, PO₃H₂, imidazolyl, imidazolyl substituted by 1-
 15 2 C₁-C₆ alkyl groups, tetrazolyl, tetrazolyl substituted by 1-2 C₁-C₆ alkyl groups or N=CR⁷ in which R⁷ is a furan or thiophene ring optionally substituted by either -CO₂H or -SO₃H, phenyl or phenyl substituted by 1-3 substituents independently selected from OH, NR⁵R⁶ in which R⁵ and R⁶ are as defined above, CO₂H, morpholinyl, morpholinyl quaternized by a



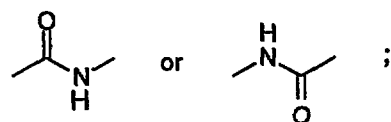
C₁-C₆ alkyl group, oxo, halogen, SO₃H, PO₃H₂, imidazolyl, imidazolyl substituted by 1-2 C₁-C₆ alkyl groups, tetrazolyl, tetrazolyl substituted by 1-2 C₁-C₆ alkyl groups or N=CR⁷ in which R⁷ is as defined above; and R¹ is hydrogen or a carboxyl-protecting group, or a pharmaceutically acceptable salt and/or a prodrug thereof.

3. A compound of the formula



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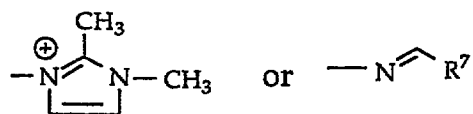
wherein X is halogen; Y is hydrogen or halogen; A is CO₂H, PO₃H₂, SO₃H or tetrazole; L¹ is a furan group, a thiophene group, a C₂-C₁₀ alkyl group or a C₂-C₁₀ alkyl group interrupted by one or two groups independently selected from vinyl, S, SO, SO₂, SO₂NH,



n is 0 or 1; R³ and R⁴ are each independently selected from hydrogen or C₁-C₆ alkyl; R² is hydrogen, NH₂, pyrrolidinyl, C₁-C₆ alkyl, C₁-C₆ alkyl substituted by one or two substituents independently selected from OH, NR⁵R⁶ in which R⁵ and R⁶ are each independently hydrogen or



C₁-C₆ alkyl, CO₂H, morpholinyl, morpholinyl quaternized by a C₁-C₆ alkyl group, oxo, halogen, SO₃H, PO₃H₂, tetrazolyl,



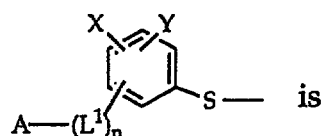
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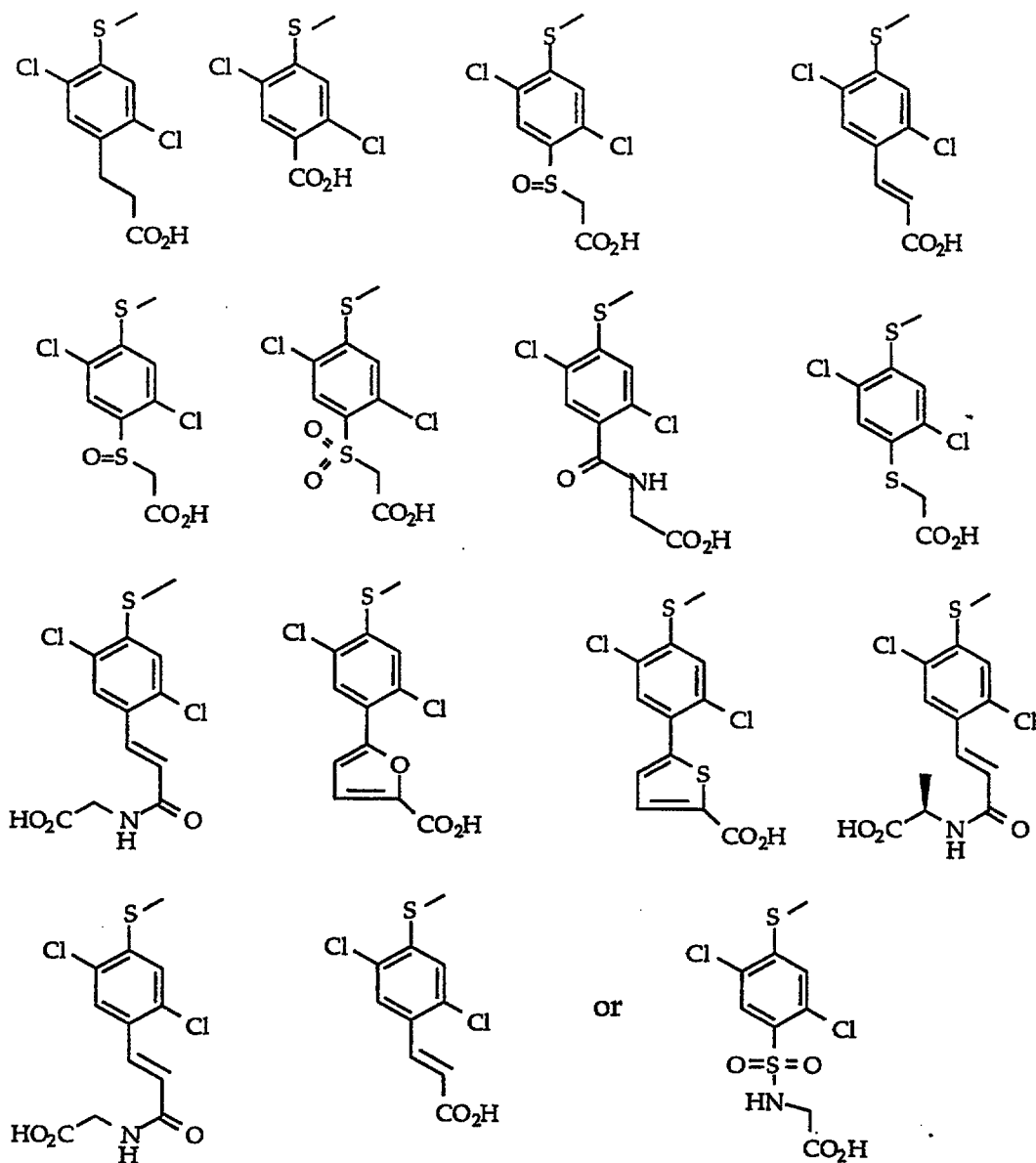
in which R⁷ is a furan or thiophene radical optionally substituted by a -CO₂H or -SO₃H group, phenyl or phenyl substituted by 1-2 substituents independently selected from OH, NR⁵R⁶ in which R⁵ and R⁶ are as defined

above, CO₂H, SO₃H, PO₃H₂, tetrazolyl, $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{N}^{\oplus}=\text{C} \\ | \\ \text{N}-\text{CH}_3 \end{array}$ or

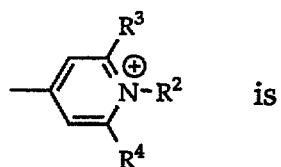
10 halogen; and R¹ is hydrogen or a carboxyl-protecting group; or a pharmaceutically acceptable salt and/or a prodrug thereof.

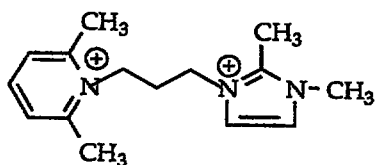
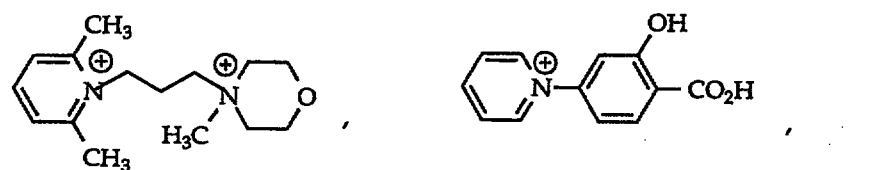
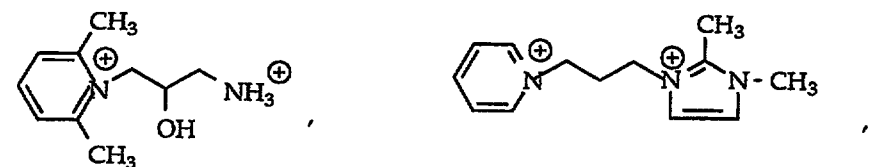
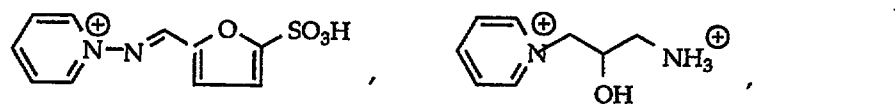
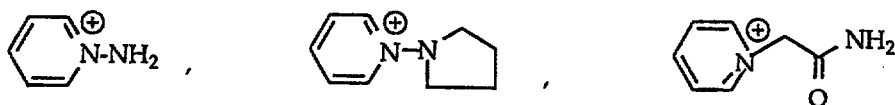
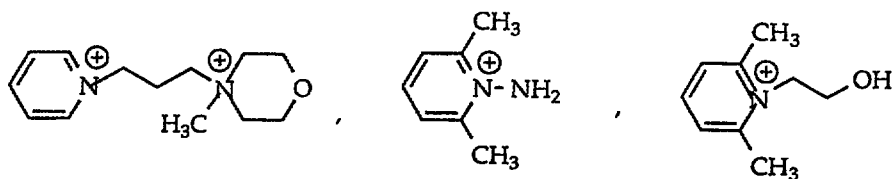
4. A compound of claim 3 wherein



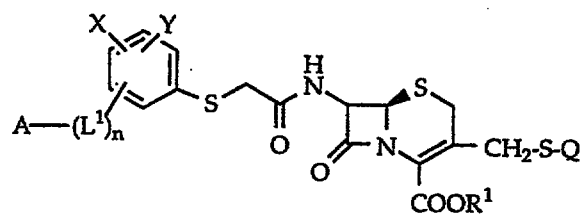


5. A compound of claim 3 or claim 4 wherein

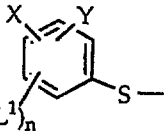


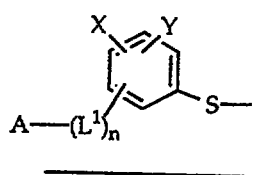


6. A compound of the formula

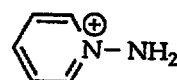
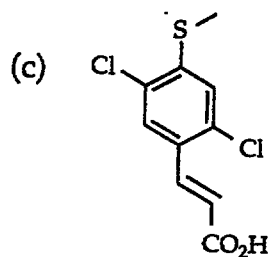
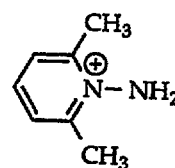
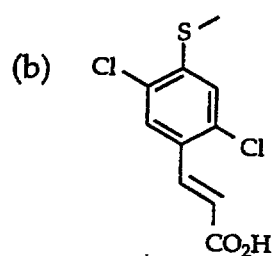
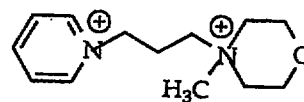
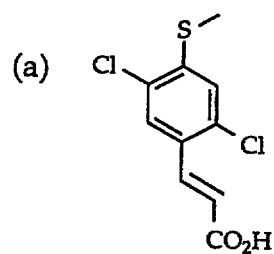




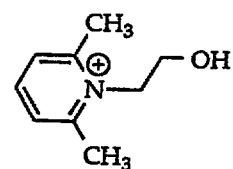
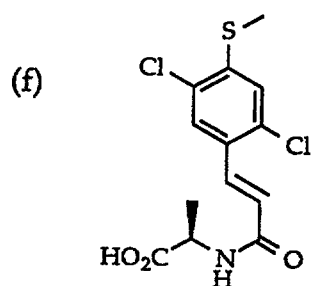
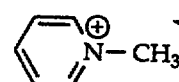
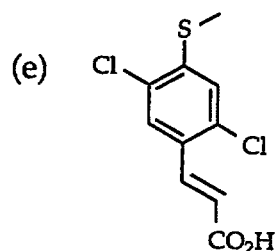
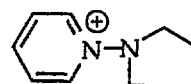
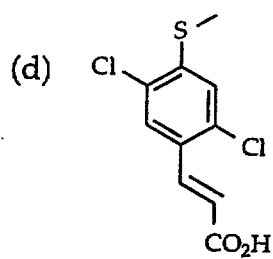
wherein $A-(L^1)_n$  and Q are as defined below:



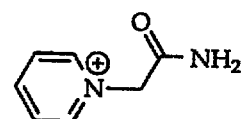
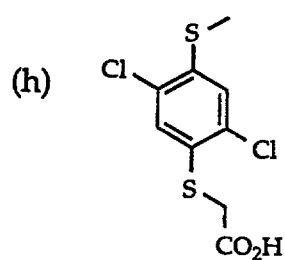
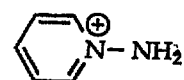
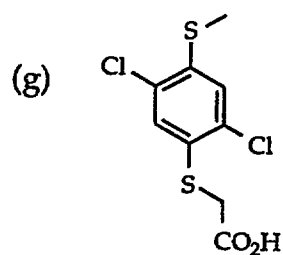
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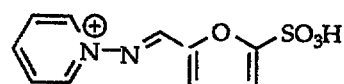
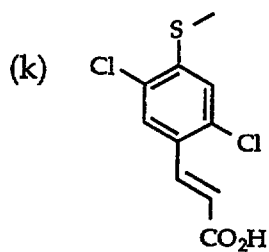
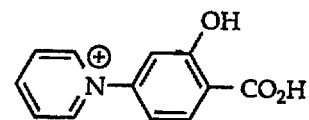
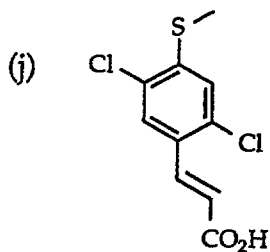
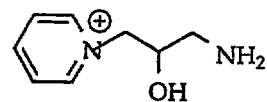
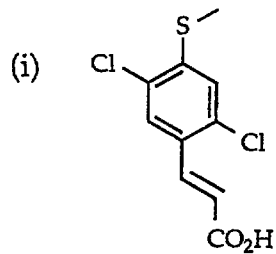
Q

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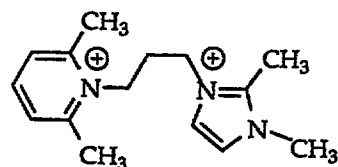
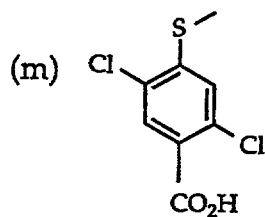
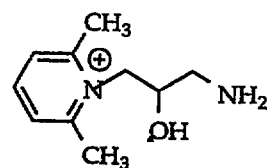
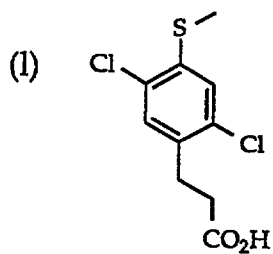


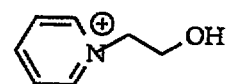
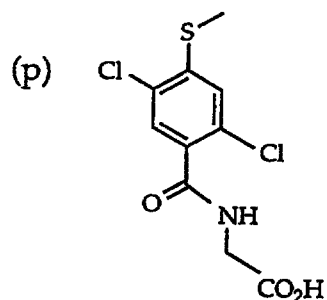
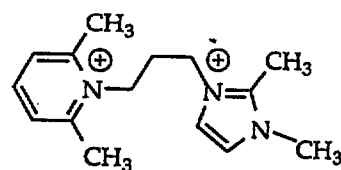
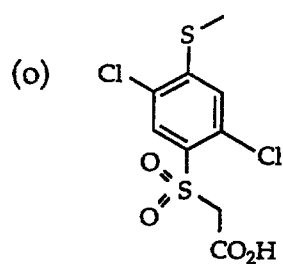
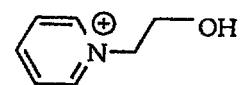
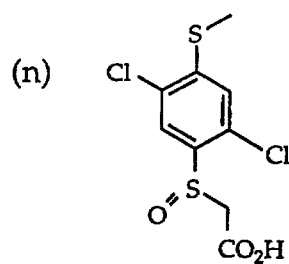
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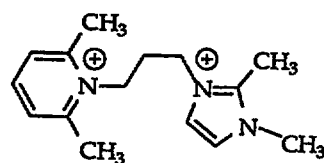
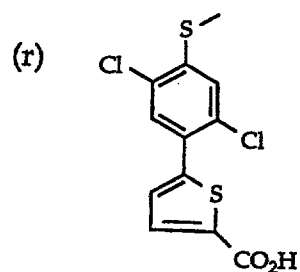
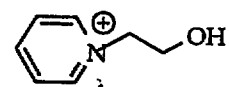
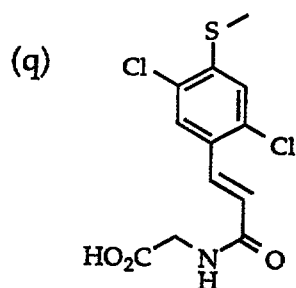


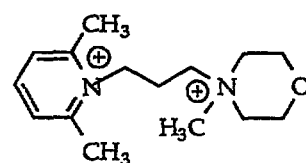
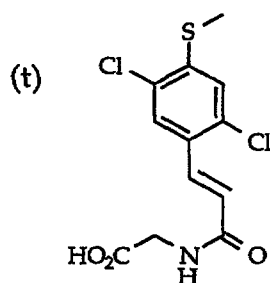
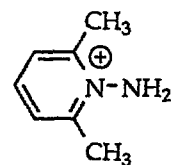
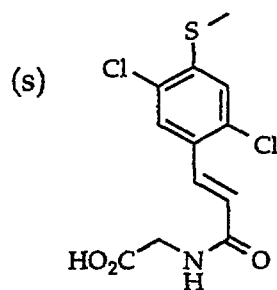
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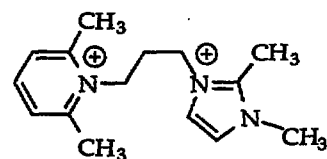
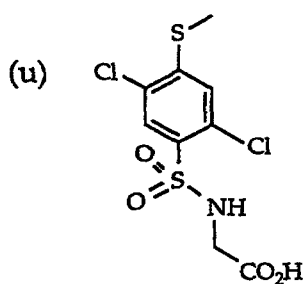


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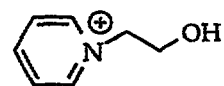
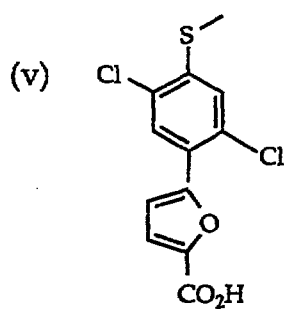




5



or

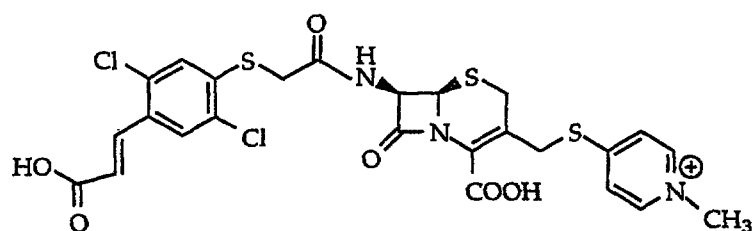




and R¹ is hydrogen or a carboxyl-protecting group;
or a pharmaceutically acceptable salt and/or a prodrug thereof.

7. The compound of the formula

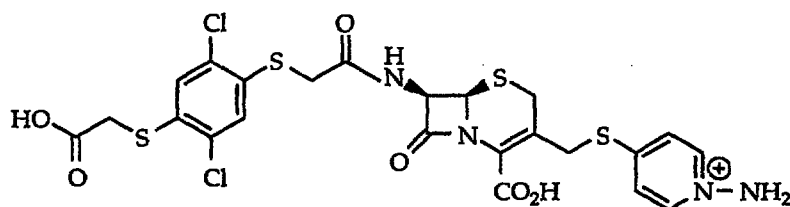
5



or a pharmaceutically acceptable salt and/or a prodrug thereof.

8. The compound of the formula

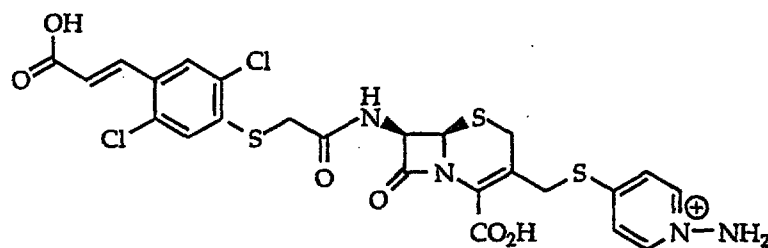
10



or a pharmaceutically acceptable salt and/or a prodrug thereof.

9. The compound of the formula

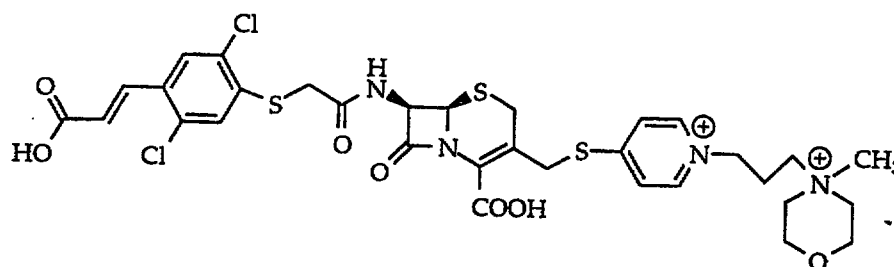
15





or a pharmaceutically acceptable salt and/or a prodrug thereof.

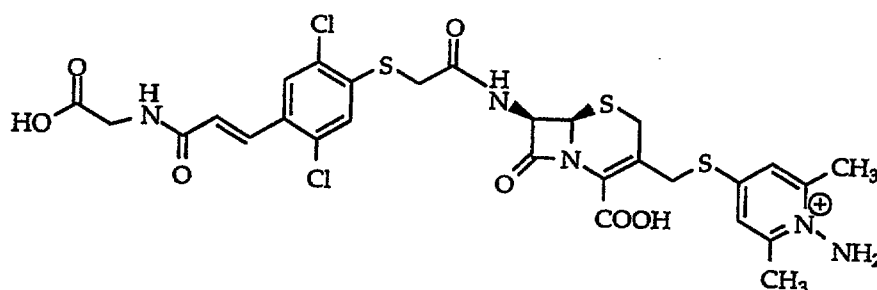
10. The compound of the formula



5

or a pharmaceutically acceptable salt and/or a prodrug thereof.

11. The compound of the formula

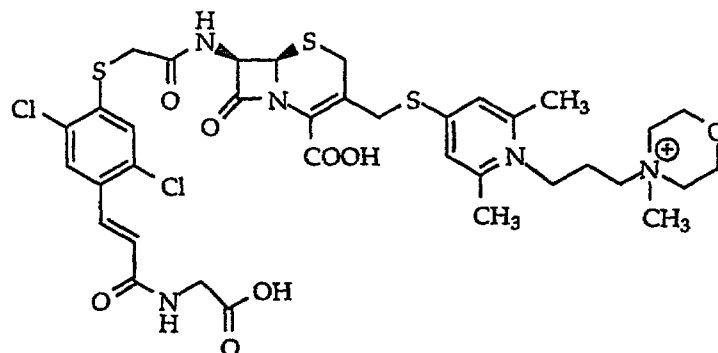


10

or a pharmaceutically acceptable salt and/or a prodrug thereof.

12. The compound of the formula

15



or a pharmaceutically acceptable salt and/or a prodrug thereof.

13. A pharmaceutical composition comprising an effective
5 antibacterial amount of a compound of Claim 1 and a pharmaceutically
acceptable carrier or excipient.
14. A method of treating a bacterial infection which comprises
administering to a host afflicted with such infection an effective
10 antibacterial amount of a compound of Claim 1.
15. A method of treating a bacterial infection caused by a strain of
methicillin-resistant *Staphylococcus aureus* which comprises
administering to a host afflicted with such infection an effective
15 antibacterial amount of a compound of Claim 1.