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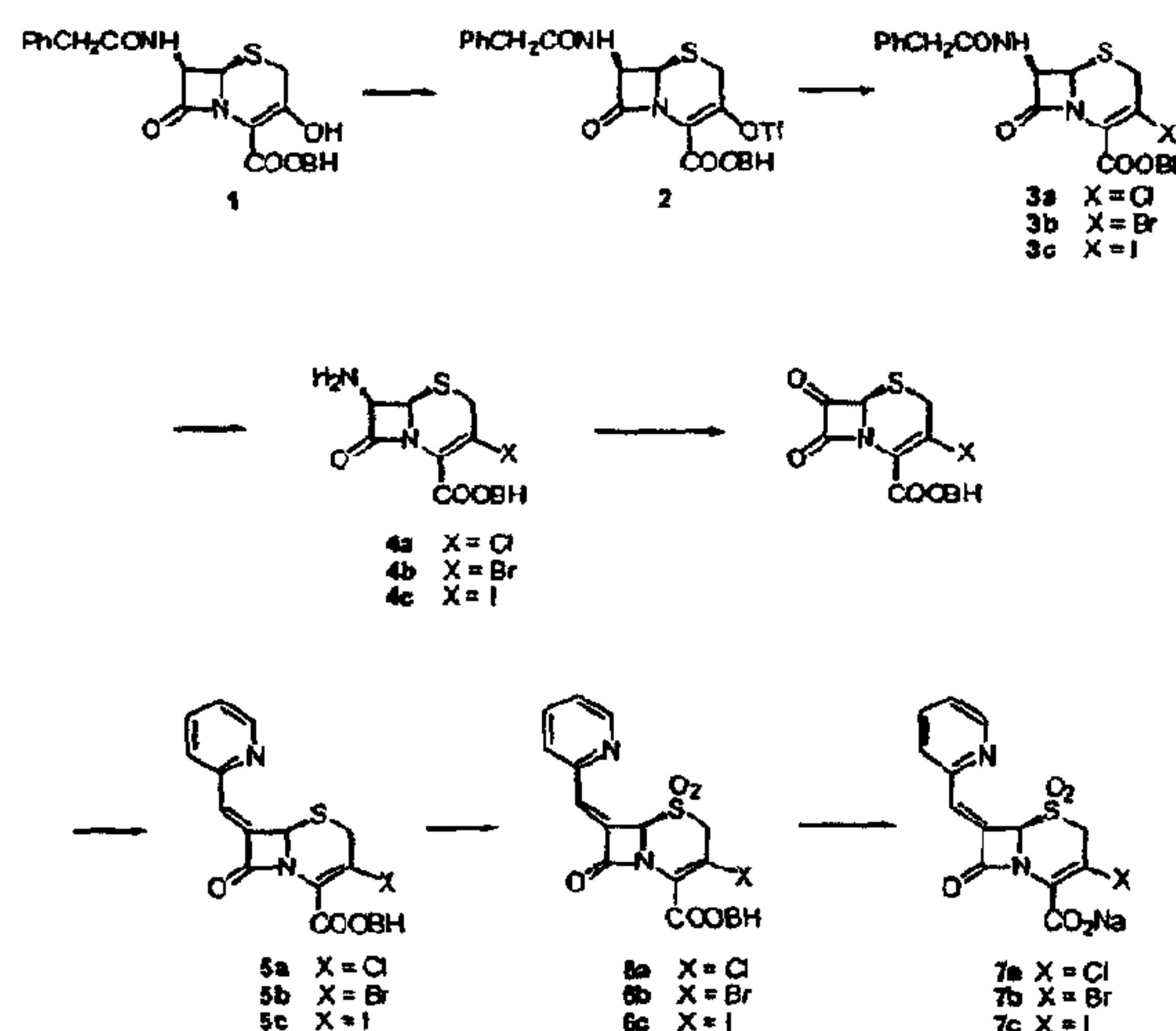
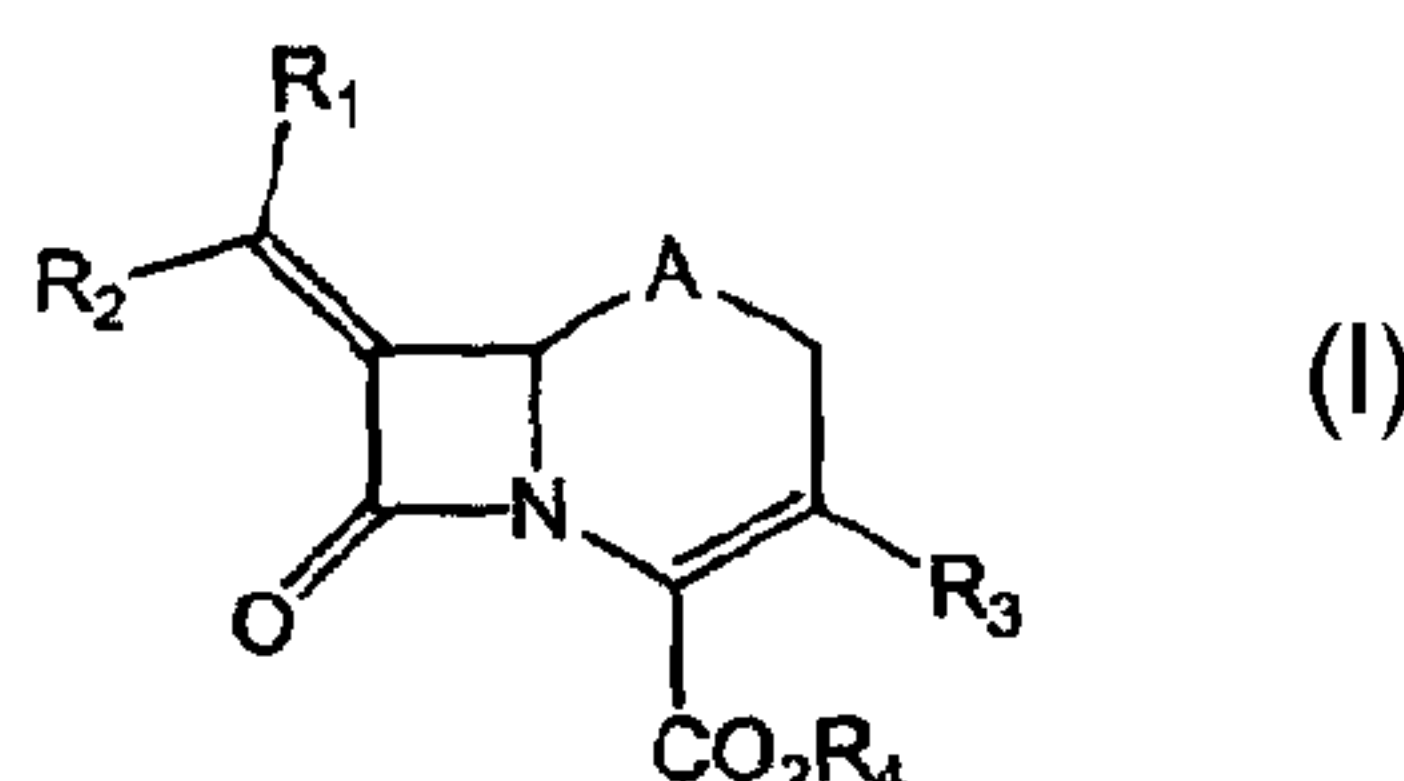
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(54) Titre : 7-ALKYLIDENE-3-SUBSTITUES-3-CEPHEM-4-CARBOXYLATES UTILISES EN TANT QU'INHIBITEURS DE  
BETA-LACTAMASE

(54) Title: 7-ALKYLIDENE-3-SUBSTITUTED-3-CEPHEM-4-CARBOXYLATES AS BETA-LACTAMASE INHIBITORS



(57) Abrégé/Abstract:

The invention provides compounds of formula (I): wherein: R<sub>1</sub>-R<sub>4</sub> and A have any of the values defined in the specification, and their pharmaceutically acceptable salts, are useful for inhibiting  $\beta$ -lactamase enzymes, for enhancing the activity of  $\beta$ -lactam antibiotics, and for treating  $\beta$ -lactam resistant bacterial infections in a mammal. The invention also provides pharmaceutical

(57) **Abrégé(suite)/Abstract(continued):**

compositions, processes for preparing compounds of formula (I), and intermediates useful for the synthesis of compounds of formula (I).

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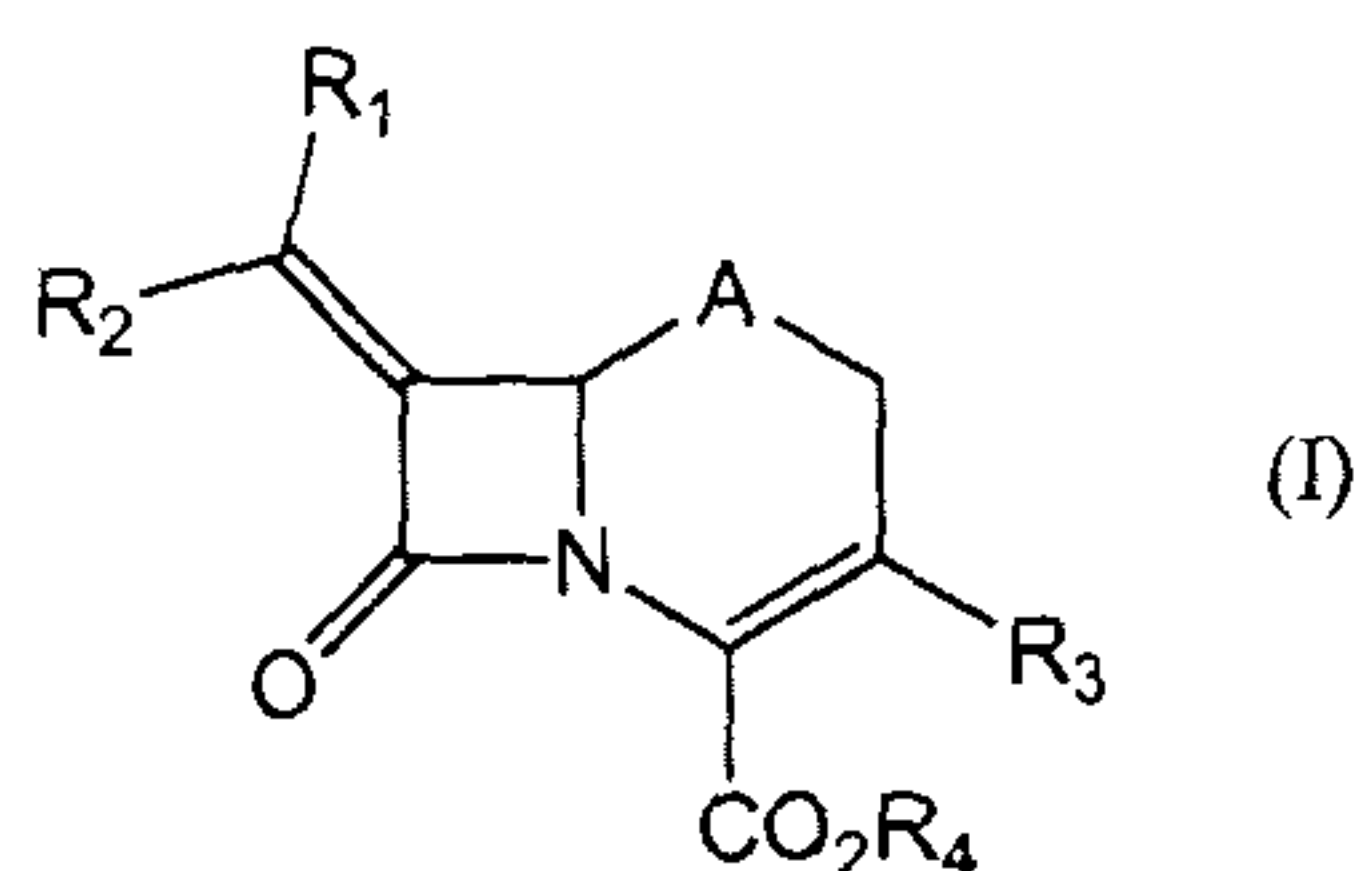
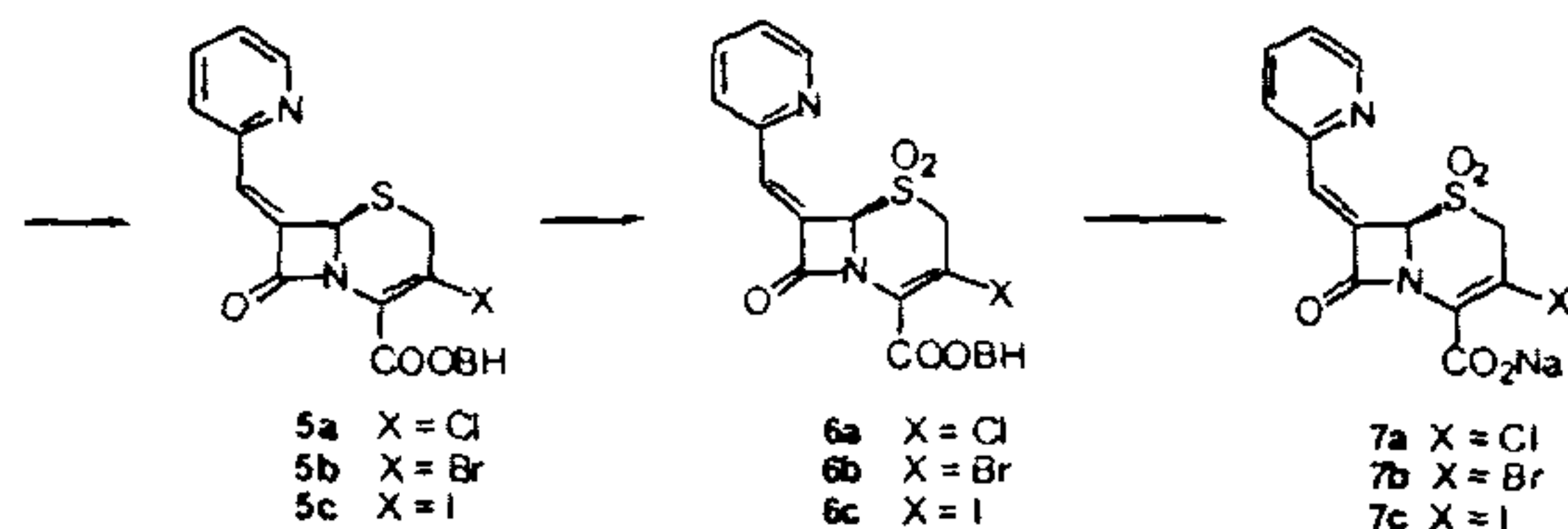
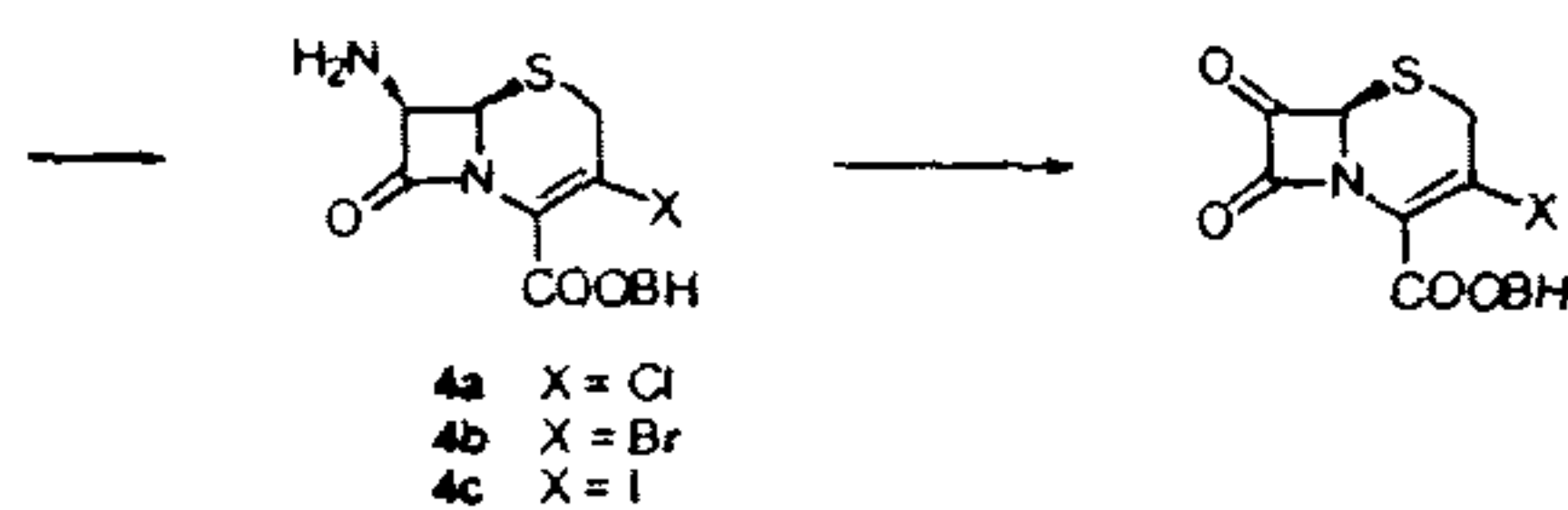
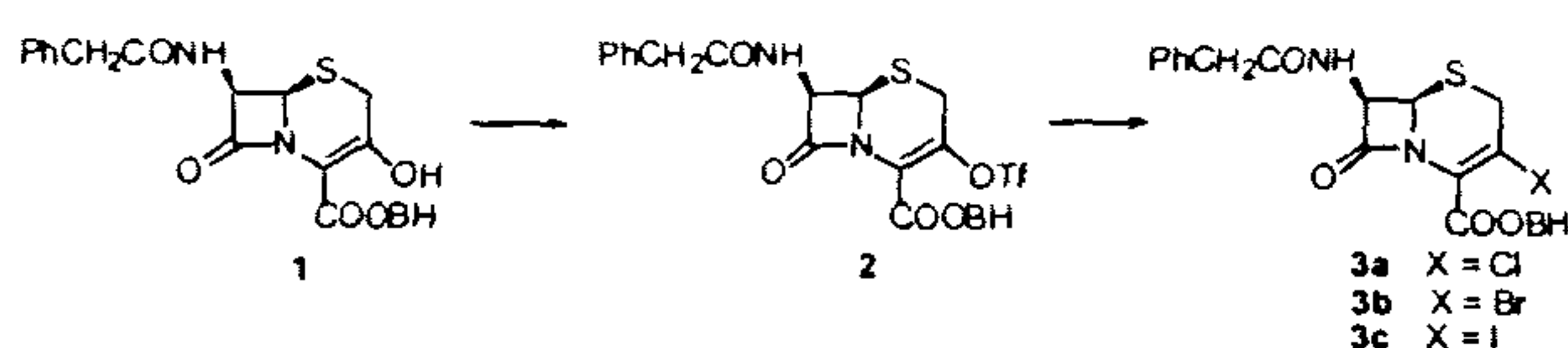
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(54) Title: 7-ALKYLIDENE-3-SUBSTITUTED-3-CEPHEM-4-CARBOXYLATES AS BETA-LACTAMASE INHIBITORS.

(57) Abstract: The invention provides compounds of formula (I): wherein: R<sub>1</sub>-R<sub>4</sub> and A have any of the values defined in the specification, and their pharmaceutically acceptable salts, are useful for inhibiting  $\beta$ -lactamase enzymes, for enhancing the activity of  $\beta$ -lactam antibiotics, and for treating  $\beta$ -lactam resistant bacterial infections in a mammal. The invention also provides pharmaceutical compositions, processes for preparing compounds of formula (I), and intermediates useful for the synthesis of compounds of formula (I).

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**7-Alkylidene-3-substituted-3-cephem-4-carboxylates as beta-Lactamase Inhibitors.**5 Priority of Invention

This application claims priority from U.S. Provisional Application Number 60/307,403, filed July 24, 2001.

Background of the Invention

10 The most important mechanism of microbial resistance to  $\beta$ -lactam antibiotics is the bacterial production of  $\beta$ -lactamases, enzymes which hydrolytically destroy  $\beta$ -lactam antibiotics, such as penicillins and cephalosporins. This type of resistance can be transferred horizontally by plasmids that are capable of rapidly spreading the resistance, not only to other members of the same strain, but even to other species. Due to such  
15 rapid gene transfer, a patient can become infected with different organisms, each possessing the same  $\beta$ -lactamase.

$\beta$ -lactamase enzymes have been organized into four molecular classes: A, B, C, and D based on amino acid sequence. Class A, which includes RTEM and the  $\beta$ -lactamase of *Staphylococcus aureus*, class C, which includes the lactamase derived from  
20 P-99 *Enterobacter cloacae*, and class D are serine hydrolases. Class A enzymes have a molecular weight of about 29 kDa and preferentially hydrolyze penicillins. The class B lactamases are metalloenzymes and have a broader substrate profile than the proteins in the other classes. Class C enzymes include the chromosomal cephalosporinases of Gram-negative bacteria and have molecular weights of approximately 39 kDa. The recently  
25 recognized class D enzymes exhibit a unique substrate profile which differs significantly from both class A and class C.

The class C cephalosporinases, in particular, are responsible for the resistance of gram negative bacteria to a variety of both traditional and newly designed antibiotics. The *Enterobacter* species, which possesses a class C enzyme, is now the third greatest  
30 cause of nosocomial infections in the United States. This class of enzymes often has poor affinities for inhibitors of the class A enzymes, such as clavulanic acid, a commonly



prescribed inhibitor, and to common in vitro inactivators, such as 6- $\beta$ -iodopenicillanate.

One strategy for overcoming this rapidly evolving bacterial resistance is the synthesis and administration of  $\beta$ -lactamase inhibitors. Frequently,  $\beta$ -lactamase inhibitors do not possess antibiotic activity themselves and are thus administered together with an  
 5 antibiotic. One example of such a synergistic mixture is the product sold under the trademark AUGMENTIN (amoxicillin, clavulanate potassium), which contains the antibiotic amoxicillin and the  $\beta$ -lactamase inhibitor, clavulanate potassium.

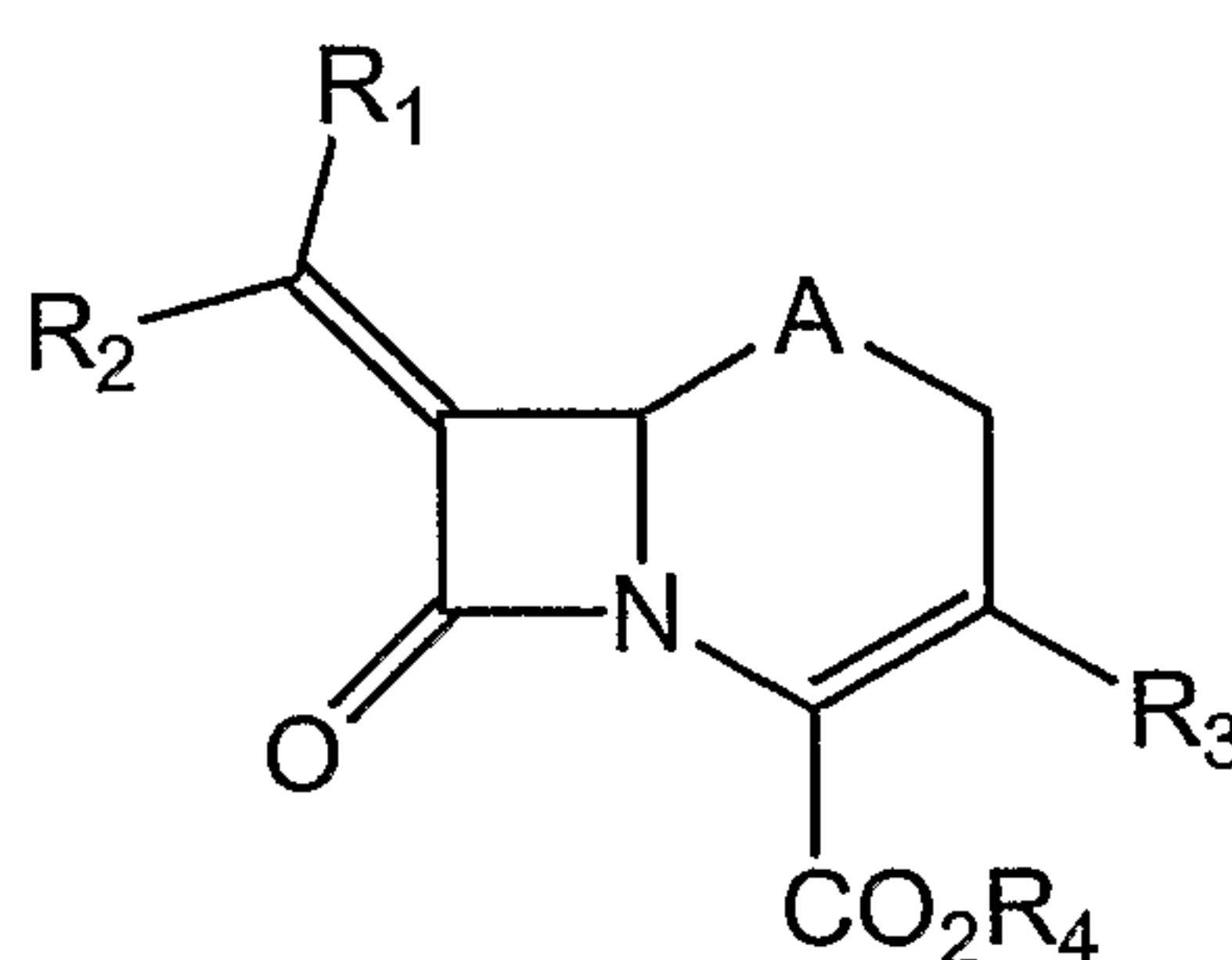
There is a continued need for novel  $\beta$ -lactamase inhibitors, and in particular, for  $\beta$ -lactamase inhibitors that can be coadministered with a  $\beta$ -lactam antibiotic.

#### Brief Description Of Drawings

Figures 1-6 illustrate the preparation of representative compounds of the invention.

#### Summary of the Invention

The invention provides a compound of formula (I):



(I)

wherein:

$R_1$  and  $R_2$  are each independently hydrogen, (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>2</sub>-C<sub>10</sub>)alkenyl, (C<sub>2</sub>-C<sub>10</sub>)alkynyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>10</sub>)alkoxy, (C<sub>1</sub>-C<sub>10</sub>)alkanoyl, (C<sub>1</sub>-C<sub>10</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>10</sub>)alkoxycarbonyl, aryl, heterocycle, halo, cyano, nitro, -COOR<sub>e</sub>, -C(=O)NR<sub>f</sub>R<sub>g</sub>, -OC(=O)NR<sub>f</sub>R<sub>g</sub>, NR<sub>f</sub>R<sub>g</sub>, or -S(O)<sub>n</sub>R<sub>h</sub>;

$R_3$  is hydrogen, halo, aryl, heteroaryl, -S(O)<sub>n</sub>R<sub>h</sub>, or

-CH=CHC(=O)NR<sub>m</sub>R<sub>p</sub>;

R<sub>4</sub> is hydrogen;

A is thio, sulfinyl, or sulfonyl;

each n is independently 0, 1, or 2;

5 each R<sub>e</sub> is independently hydrogen, or (C<sub>1</sub>-C<sub>10</sub>)alkyl;

each R<sub>f</sub> and R<sub>g</sub> is independently hydrogen, (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)alkoxy, phenyl, benzyl, phenethyl, (C<sub>1</sub>-C<sub>10</sub>)alkanoyl, or -C(=O)NR<sub>f</sub>R<sub>g</sub> wherein R<sub>f</sub> and R<sub>g</sub> form a ring optionally containing a nitrogen atom in the ring -NR<sub>e</sub>;

each R<sub>h</sub> is independently (C<sub>1</sub>-C<sub>10</sub>)alkyl, or aryl; and

10 R<sub>m</sub> is hydrogen, and R<sub>p</sub> is NH<sub>2</sub>, OH, (C<sub>2</sub>-C<sub>10</sub>)cycloalkyl, or

-(C<sub>2</sub>-C<sub>10</sub>)alkyl-NH<sub>2</sub>; or R<sub>m</sub> and R<sub>p</sub> together with the nitrogen to which they are attached form a piperidine, morpholine, thiomorpholine, pyrrolidine, or piperazine ring, wherein the piperazine is substituted at the 4-position with hydrogen or a (C<sub>1</sub>-C<sub>10</sub>)alkyl;

wherein any (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>2</sub>-C<sub>10</sub>)alkenyl, (C<sub>2</sub>-C<sub>10</sub>)alkynyl, (C<sub>3</sub>-

15 C<sub>8</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>10</sub>)alkoxy, (C<sub>1</sub>-C<sub>10</sub>)alkanoyl, (C<sub>1</sub>-C<sub>10</sub>)alkanoyloxy, or (C<sub>1</sub>-C<sub>10</sub>)alkoxycarbonyl of R<sub>1</sub> or R<sub>2</sub> is optionally substituted with one or more, substituents independently selected from halo, hydroxy, cyano, cyanato, nitro, mercapto, oxo, aryl, heterocycle, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, aryl(C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, halo(C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, heterocycle(C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, aryloxy, (heterocycle)oxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, -COOR<sub>e</sub>, -C(=O)NR<sub>f</sub>R<sub>g</sub>, -OC(=O)NR<sub>f</sub>R<sub>g</sub>, -NR<sub>h</sub>R<sub>i</sub>, or -S(O)<sub>n</sub>R<sub>k</sub>; and

wherein any aryl is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, trifluoromethyl, nitro, trifluoromethoxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, -COOR<sub>e</sub>, -C(=O)NR<sub>f</sub>R<sub>g</sub>, -OC(=O)NR<sub>f</sub>R<sub>g</sub>, NR<sub>h</sub>R<sub>i</sub>, or -S(O)<sub>n</sub>R<sub>k</sub>; or a pharmaceutically acceptable salt thereof.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier, as well as such a pharmaceutical composition that further comprises a β-lactam antibiotic.



The invention also provides a method comprising inhibiting a  $\beta$ -lactamase by contacting (*in vitro* or *in vivo*) the  $\beta$ -lactamase with an effective amount of a compound of formula (I); or a pharmaceutically acceptable salt thereof.

5 The invention also provides a therapeutic method comprising inhibiting a  $\beta$ -lactamase in a mammal in need of such therapy, by administering an effective inhibitory amount of a compound of formula (I); or a pharmaceutically acceptable salt thereof.

The invention also provides a method comprising enhancing the activity of a  $\beta$ -lactam antibiotic, by administering the  $\beta$ -lactam antibiotic to a mammal in need thereof, in combination with an effective  $\beta$ -lactamase inhibiting amount of a compound of  
10 formula (I); or a pharmaceutically acceptable salt thereof.

The invention also provides a method comprising treating a  $\beta$ -lactam resistant bacterial infection in a mammal, by administering an effective amount of a  $\beta$ -lactam antibiotic in combination with an effective  $\beta$ -lactamase inhibiting amount of a compound of formula (I); or a pharmaceutically acceptable salt thereof.

15 The invention also provides a compound of formula (I) for use in medical therapy (preferably for use in inhibiting a  $\beta$ -lactamase in a mammal, or for treating a  $\beta$ -lactam resistant bacterial infection in a mammal), as well as the use of a compound of formula (I) for the manufacture of a medicament useful for inhibiting a  $\beta$ -lactamase in a human.

The invention also provides processes and intermediates disclosed herein that are  
20 useful for preparing  $\beta$ -lactamase inhibitors of formula (I).

Compounds of formula (I) are useful as  $\beta$ -lactamase inhibitors for therapeutic applications. They are also useful as pharmacological tools for *in vitro* or *in vivo* studies to investigate the mechanisms of antibiotic resistance, to help identify other therapeutic antibiotic agents or  $\beta$ -lactamase inhibitors, to identify which  $\beta$ -lactamases are being  
25 expressed by a given microorganism, or to selectively inhibit one or more  $\beta$ -lactamases in a microorganism.

#### Detailed Description

The following definitions are used, unless otherwise described: halo is fluoro,  
30 chloro, bromo, or iodo. Alkyl, alkoxy, alkenyl, and the like, denote both straight and



branched groups. Aryl denote a phenyl radical, or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic.

Heterocycle denotes a 6-10 membered unsaturated or saturated mono- bi- or tri-cyclic ring system comprising carbon and 1, 2, 3, or 4 heteroatoms selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein each X is absent or is H, O, (C<sub>1</sub>-C<sub>4</sub>)alkyl, phenyl or benzyl. The term "heterocycle" includes "Heteroaryl," which denotes a radical attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein each X is absent or is H, O, (C<sub>1</sub>-C<sub>4</sub>)alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto. A preferred heteroaryl is, for example, a pyridyl radical.

The term "enhancing" the activity of a  $\beta$ -lactam antibiotic means improving or increasing the antibiotic activity of the compared in a statistically measurable and significant manner with respect to the activity demonstrated by the compound in the absence of a compound of the invention.

The letters "BH" or "bhl" represent a benzhydryl ester.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine  $\beta$ -lactamase inhibitory activity using the standard tests described herein, or using other similar tests which are well known in the art.

Specific values listed below for radicals, substituents and ranges, are for

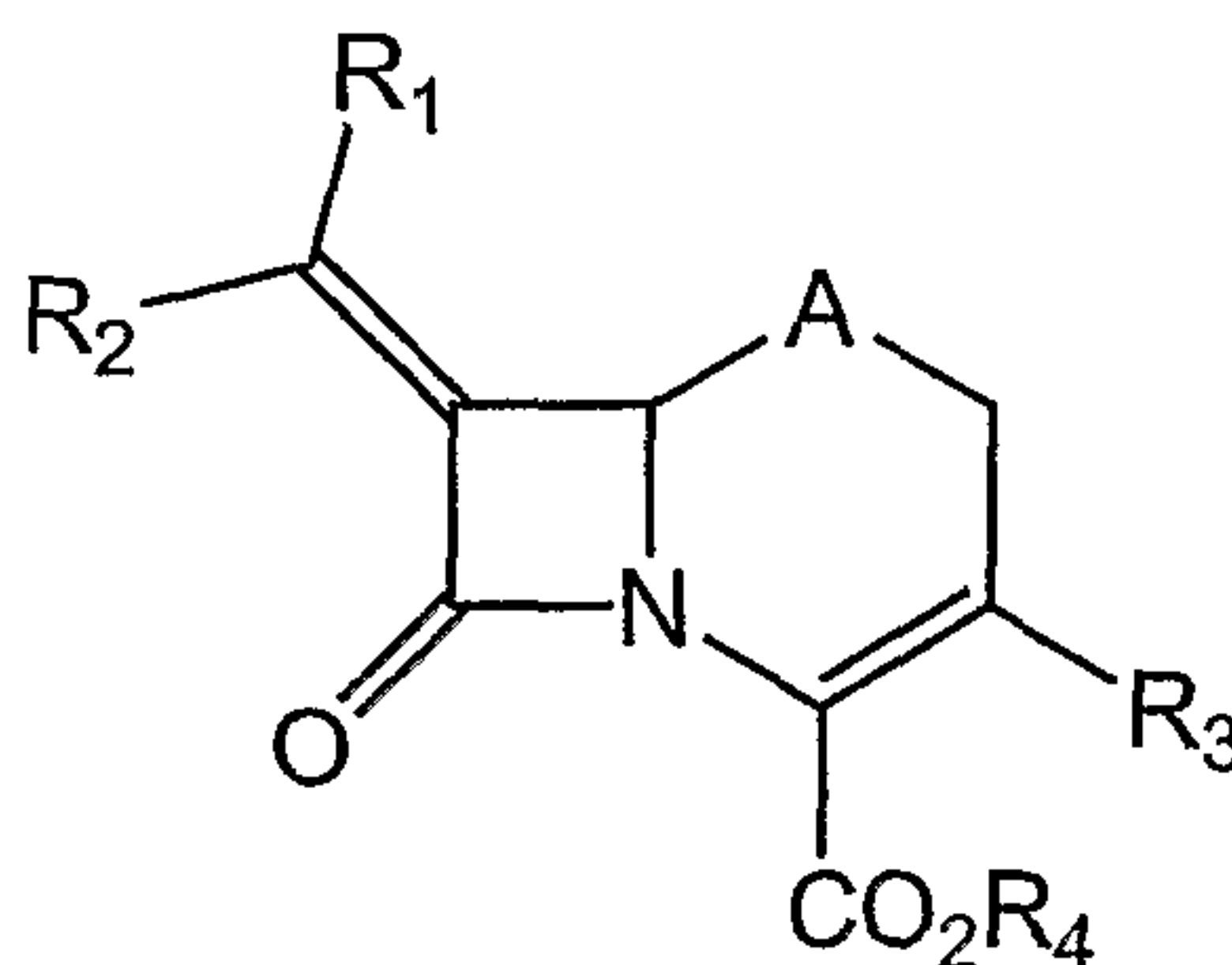


illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, (C<sub>1</sub>-C<sub>6</sub>)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, hexyl, heptyl, octyl, nonyl, or decyl; (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; (C<sub>1</sub>-C<sub>10</sub>)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentoxy, 3-pentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy or decyloxy; (C<sub>1</sub>-C<sub>6</sub>)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy; (C<sub>2</sub>-C<sub>10</sub>)alkenyl can be vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl, 5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, 4-decenyl, 5-decenyl, 6-decenyl, 7-decenyl, 8-decenyl, or 9-decenyl; (C<sub>2</sub>-C<sub>10</sub>)alkynyl can be ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 6-heptynyl, 1-octynyl, 2-octynyl, 3-octynyl, 4-octynyl, 5-octynyl, 6-octynyl, 7-octynyl, 1-nonylnyl, 2-nonylnyl, 3-nonylnyl, 4-nonylnyl, 5-nonylnyl, 6-nonylnyl, 7-nonylnyl, 8-nonylnyl, 1-decynyl, 2-decynyl, 3-decynyl, 4-decynyl, 5-decynyl, 6-decynyl, 7-decynyl, 8-decynyl, or 9-decynyl; (C<sub>1</sub>-C<sub>10</sub>)alkanoyl can be acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, or decanoyl; (C<sub>1</sub>-C<sub>10</sub>)alkoxycarbonyl can be methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, heptyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl or decyloxycarbonyl; (C<sub>1</sub>-C<sub>10</sub>)alkanoyloxy can be formyloxy, acetoxyl, propanoyloxy, butanoyloxy, isobutanoyloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy, octanoyloxy, nonanoyloxy, or decanoyloxy; aryl can be phenyl, indenyl, or naphthyl; heterocycle can benztriazolyl, triazinyl, oxazolyl, isoxazolyl, oxazolidinoyl, isoxazolidinoyl, thiazolyl, isothiazoyl, pyrazolyl, imidazolyl,

pyrrolyl, pyrazinyl, pyridinyl, morpholinyl, quinolinyl, isoquinolinyl, indolyl, pyrimidinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, or piperazinyl; and heteroaryl can be, for example, furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, 1-methyl-1H-tetrazol-5-yl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

In one embodiment, the invention provides a compound of formula (I):



(I)

wherein:

$R_1$  and  $R_2$  are each independently hydrogen,  $(C_1-C_{10})$ alkyl,  $(C_2-C_{10})$ alkenyl,  $(C_2-C_{10})$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_1-C_{10})$ alkoxy,  $(C_1-C_{10})$ alkanoyl,  $(C_1-C_{10})$ alkanoyloxy,  $(C_1-C_{10})$ alkoxycarbonyl, aryl, heteroaryl, heterocycle, halo, cyano, nitro,  $-COOR_e$ ,  $-C(=O)NR_fR_g$ ,  $-OC(=O)NR_fR_g$ ,  $NR_fR_g$ , or  $-S(O)_nR_h$ ;

$R_3$  is hydrogen, halo, aryl, heteroaryl, heterocycle,  $-Sn(R_5)_3$ ,  $-SAr$ ,  $-S(O)_nAr$ ,  $-S(O)_nR_h$ ,  $-S(O)_nNH_2$ ,  $-S(O)_nNHR_f$ ,  $-S(O)_nNR_fR_g$ ,  $-COOR_m$ ,  $-C(=O)-R_h$ ,  $-C(=O)NR_fR_g$ ,  $-CH=NOR_i$ ,  $-CH=CR_jR_k$ , or cyano;

$R_4$  is hydrogen, aryl, heterocycle,  $(C_1-C_{10})$ alkyl, benzyl, phenethyl, -diaryl substituted  $(C_1-C_{10})$ alkyl, such as  $-CHAr_2$  or  $-CHPh_2$ ;

each  $R_5$  is independently  $-(C_1-C_{10})$ alkyl,  $(C_1-C_{10})$ alkoxy, phenyl, benzyl, phenethyl;

A is thio, sulfinyl, or sulfonyl;

each n is independently 0, 1, or 2;

each  $R_e$  is independently hydrogen, or  $(C_1-C_{10})$ alkyl;



each  $R_f$  and  $R_g$  is independently hydrogen,  $(C_1-C_{10})$ alkyl,  $(C_1-C_{10})$ alkoxy, phenyl, benzyl, phenethyl,  $(C_1-C_{10})$ alkanoyl, or  $-C(=O)NR_fR_g$  wherein  $R_f$  and  $R_g$  form a ring optionally containing a nitrogen atom in the ring  $-NR_e$ ;

each  $R_h$  is independently  $(C_1-C_{10})$ alkyl, phenyl, aryl( $C_1-C_6$ )alkyl, heteroaryl, heterocycle, or heterocycle( $C_1-C_6$ )alkyl;

$R_i$  is hydrogen or  $(C_1-C_6)$ alkyl; and

$R_j$  and  $R_k$  are each independently hydrogen, halo, cyano, nitro, aryl, heterocycle,  $(C_2-C_6)$ alkenyl,  $-COOR_e$ ,  $-C(=O)NR_fR_g$ ,  $-OC(=O)NR_fR_g$ ,  $NR_fR_g$ , or  $-S(O)_nR_h$ ;

$R_m$  is  $-H$ ,  $-Na$ ,  $-K$ ,  $-Li$ , and like pharmaceutically acceptable salts,  $-(C_1-C_{10})$ alkyl,  $-(C_1-C_{10})$ cycloalkyl, benzyl, phenethyl,  $-diaryl$  substituted  $(C_1-C_{10})$ alkyl, such as  $-CHAr_2$  or  $-CHPh_2$ ;

wherein any  $(C_1-C_{10})$ alkyl,  $(C_2-C_{10})$ alkenyl,  $(C_2-C_{10})$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_1-C_{10})$ alkoxy,  $(C_1-C_{10})$ alkanoyl,  $(C_1-C_{10})$ alkanoyloxy, or  $(C_1-C_{10})$ alkoxycarbonyl of  $R_1$ ,  $R_2$ ,  $R_5$ ,  $R_j$  and  $R_k$  is optionally substituted with one or more, substituents independently selected from halo, hydroxy, cyano, cyanato, nitro, mercapto, oxo, aryl, heterocycle,  $(C_2-C_6)$ alkenyl,  $(C_2-C_6)$ alkynyl,  $(C_1-C_6)$ alkoxy,  $(C_1-C_6)$ alkanoyl,  $(C_1-C_6)$ alkanoyloxy, aryl( $C_1-C_6$ )alkanoyloxy, halo( $C_1-C_6$ )alkanoyloxy, heterocycle( $C_1-C_6$ )alkanoyloxy, aryloxy, (heterocycle)oxy,  $(C_3-C_8)$ cycloalkyl,  $-COOR_e$ ,  $-C(=O)NR_fR_g$ ,  $-OC(=O)NR_fR_g$ ,  $-NR_hR_i$ , or  $-S(O)_nR_k$ ; and

wherein any aryl is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, trifluoromethyl, nitro, trifluoromethoxy,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkanoyl,  $(C_1-C_6)$ alkanoyloxy,  $(C_1-C_6)$ alkoxycarbonyl,  $-COOR_e$ ,  $-C(=O)NR_fR_g$ ,  $-OC(=O)NR_fR_g$ ,  $NR_hR_i$ , or  $-S(O)_nR_k$ ; or a pharmaceutically acceptable salt thereof.

Specifically, A is sulfonyl  $(-SO_2-)$ .

Specifically,  $R_1$  is aryl, heterocycle, or  $-COOR_e$ .

Specifically,  $R_1$  is 2-pyridyl, or  $-COOR_e$ .

Specifically,  $R_2$  is hydrogen.

Specifically,  $R_3$  is hydrogen, halo, aryl, heterocycle,  $-Sn(R_5)_3$ ,  $-SAr$ ,  $-S(O)_nAr$ ,

$-\text{S}(\text{O})_n\text{R}_h$ ,  $-\text{S}(\text{O})_n\text{NH}_2$ ,  $-\text{S}(\text{O})_n\text{NHR}_f$ ,  $-\text{S}(\text{O})_n\text{NR}_f\text{R}_g$ ,  $-\text{COOR}_m$ ,  $-\text{C}(=\text{O})-\text{R}_h$ , or  $-\text{C}(=\text{O})\text{NR}_f\text{R}_g$ .

Specifically,  $\text{R}_3$  is hydrogen, aryl, heterocycle,  $-\text{Sn}(\text{R}_5)_3$ ,  $-\text{SAr}$ ,  $-\text{S}(\text{O})_n\text{Ar}$ ,  $-\text{S}(\text{O})_n\text{R}_h$ ,  $-\text{S}(\text{O})_n\text{NH}_2$ ,  $-\text{S}(\text{O})_n\text{NHR}_f$ , or  $-\text{S}(\text{O})_n\text{NR}_f\text{R}_g$ .

Specifically,  $\text{R}_3$  is hydrogen.

5 Specifically,  $\text{R}_3$  is halo.

Specifically,  $\text{R}_3$  is fluoro.

Specifically,  $\text{R}_3$  is chloro.

Specifically,  $\text{R}_3$  is bromo.

Specifically,  $\text{R}_3$  is iodo.

10 Specifically,  $\text{R}_3$  is aryl.

Specifically,  $\text{R}_3$  is phenyl

Specifically,  $\text{R}_3$  is heteroaryl.

Specifically,  $\text{R}_3$  is 2-thienyl.

Specifically,  $\text{R}_3$  is  $\text{S}(\text{O})_n\text{R}_h$ .

15 Specifically,  $\text{R}_3$  is  $\text{S}(\text{O})_2\text{R}_h$ .

Specifically,  $\text{R}_3$  is  $\text{S}(\text{O})_2\text{R}_h$ ; wherein  $\text{R}_h$  is methyl or phenyl.

Specifically,  $\text{R}_3$  is  $\text{SR}_h$ .

Specifically,  $\text{R}_3$  is  $\text{SR}_h$ ; wherein  $\text{R}_h$  is methyl or phenyl.

Specifically,  $\text{R}_3$  is hydrogen, halo, aryl, heteroaryl, or  $-\text{S}(\text{O})_n\text{R}_h$ .

20 Specifically,  $\text{R}_j$  and  $\text{R}_k$  are each independently hydrogen, cyano,  $-\text{COOR}_e$ ,  $(\text{C}_2-\text{C}_{10})$ alkenyl, or heteroaryl.

A specific compound of formula (I) is a compound of wherein:  $\text{R}_1$  and  $\text{R}_2$  are each independently hydrogen,  $(\text{C}_1-\text{C}_{10})$ alkyl,  $(\text{C}_2-\text{C}_{10})$ alkenyl,  $(\text{C}_2-\text{C}_{10})$ alkynyl,  $(\text{C}_3-\text{C}_8)$ cycloalkyl,  $(\text{C}_1-\text{C}_{10})$ alkoxy,  $(\text{C}_1-\text{C}_{10})$ alkanoyl,  $(\text{C}_1-\text{C}_{10})$ alkanoyloxy,  $(\text{C}_1-$

25  $\text{C}_{10})$ alkoxycarbonyl, aryl, heteroaryl, heterocycle, halo, cyano, nitro,  $-\text{COOR}_e$ ,  $-\text{C}(=\text{O})\text{NR}_f\text{R}_g$ ,  $-\text{OC}(=\text{O})\text{NR}_f\text{R}_g$ ,  $\text{NR}_f\text{R}_g$ , or  $-\text{S}(\text{O})_n\text{R}_h$ ;  $\text{R}_3$  is independently hydrogen,

fluoro,  $-\text{SPh}$ ,  $-\text{SO}_2\text{Ar}$ ,  $-\text{Sn}(\text{CH}_3)_3$ , or  $-\text{CH}=\text{CH}-\text{CO}_2\text{H}$ ;  $\text{R}_4$  is independently hydrogen,

phenyl, heterocycle,  $(\text{C}_1-\text{C}_{10})$ alkyl, benzyl, phenethyl, or  $-\text{CHPh}_2$ ;  $\text{A}$  is thio, sulfinyl, or

sulfonyl; each  $n$  is independently 0, 1, or 2; each  $\text{R}_e$  is independently hydrogen, or  $(\text{C}_1-$

30  $\text{C}_{10})$ alkyl; each  $\text{R}_f$  and  $\text{R}_g$  is independently hydrogen,  $(\text{C}_1-\text{C}_{10})$ alkyl,  $(\text{C}_1-\text{C}_{10})$ alkoxy,



phenyl, benzyl, phenethyl, (C<sub>1</sub>-C<sub>10</sub>)alkanoyl, or -C(=O)NR<sub>f</sub>R<sub>g</sub> wherein R<sub>f</sub> and R<sub>g</sub> form a ring optionally containing a nitrogen atom in the ring -NR<sub>e</sub>-; each R<sub>h</sub> is independently (C<sub>1</sub>-C<sub>10</sub>)alkyl, phenyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, heterocycle, or heterocycle(C<sub>1</sub>-C<sub>6</sub>)alkyl; R<sub>i</sub> is hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl; and R<sub>j</sub> and R<sub>k</sub> are each independently hydrogen, halo, cyano, nitro, aryl, heterocycle, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, -COOR<sub>e</sub>, -C(=O)NR<sub>f</sub>R<sub>g</sub>, -OC(=O)NR<sub>f</sub>R<sub>g</sub>, NR<sub>f</sub>R<sub>g</sub>, or -S(O)<sub>n</sub>R<sub>h</sub>; wherein any (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>2</sub>-C<sub>10</sub>)alkenyl, (C<sub>2</sub>-C<sub>10</sub>)alkynyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>10</sub>)alkoxy, (C<sub>1</sub>-C<sub>10</sub>)alkanoyl, (C<sub>1</sub>-C<sub>10</sub>)alkanoyloxy, or (C<sub>1</sub>-C<sub>10</sub>)alkoxycarbonyl of R<sub>1</sub>, R<sub>2</sub>, R<sub>j</sub> and R<sub>k</sub> is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, cyanato, nitro, mercapto, oxo, aryl, heterocycle, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, aryl(C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, halo(C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, heterocycle(C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, aryloxy, (heterocycle)oxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, -COOR<sub>e</sub>, -C(=O)NR<sub>f</sub>R<sub>g</sub>, -OC(=O)NR<sub>f</sub>R<sub>g</sub>, NR<sub>h</sub>R<sub>i</sub>, or -S(O)<sub>n</sub>R<sub>k</sub>; and wherein any aryl is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, trifluoromethyl, nitro, trifluoromethoxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, -COOR<sub>e</sub>, -C(=O)NR<sub>f</sub>R<sub>g</sub>, -OC(=O)NR<sub>f</sub>R<sub>g</sub>, NR<sub>h</sub>R<sub>i</sub>, or -S(O)<sub>n</sub>R<sub>k</sub>; or a pharmaceutically acceptable salt thereof.

Another specific compound is a compound wherein one of R<sub>j</sub> and R<sub>k</sub> is hydrogen and the other is cyano, -COOR<sub>e</sub>, (C<sub>2</sub>-C<sub>10</sub>)alkenyl, or heteroaryl.

Another specific compound is a compound wherein R<sub>j</sub> is hydrogen or halo, and R<sub>k</sub> is cyano, methoxycarbonyl, aminocarbonyl, *tert*-butoxycarbonyl, 2-pyridyl-N-oxide, nitro, or vinyl.

Another specific compound is a compound wherein A is sulfonyl; R<sub>1</sub> is 2-pyridyl, carboxy or *tert*-butoxy carbonyl; R<sub>2</sub> is hydrogen; R<sub>3</sub> is hydrogen, fluoro, -SPh, -SO<sub>2</sub>Ph, -Sn(R<sub>5</sub>)<sub>3</sub>, or -CH=CH-CO<sub>2</sub>H; and R<sub>4</sub> is hydrogen, -CHAr<sub>2</sub>, or a pharmaceutically acceptable salt.

More specifically, R<sub>j</sub> and R<sub>k</sub> are each independently hydrogen, cyano, 2-(methoxycarbonyl), 2-pyridyl-N-oxide, or vinyl.

Another specific compound is a compound of formula (I) wherein A is sulfonyl (-SO<sub>2</sub>-); R<sub>1</sub> is 2-pyridyl, carboxy or *tert*-butoxycarbonyl; R<sub>2</sub> is hydrogen; and R<sub>3</sub> is



hydrogen, halo such as fluoro, -SAr such as -SPh, -Sn(R<sub>5</sub>)<sub>3</sub>, cyano, -S(O)<sub>n</sub>Ar; -CH=NOR<sub>i</sub>, or -CH=CR<sub>j</sub>R<sub>k</sub>; or a pharmaceutically acceptable salt thereof.

A more specific compound of formula (I) is a pharmaceutically acceptable salt formed from a carboxylic acid of formula (I) wherein R<sub>4</sub> is hydrogen. Most preferred is a salt wherein R<sub>4</sub> been replaced with a sodium or potassium ion. The term pharmaceutically acceptable salts also includes poly salts (e.g. di- or tri-salts) of a compound of formula (I).

Processes and novel intermediates useful for preparing compounds of formula (I) are provided as further embodiments of the invention and are illustrated by the following procedures in which the meanings of the generic radicals are as given above unless otherwise qualified.

Representative compounds were prepared as indicated in Figures 1 to 6. Commercially available 3-hydroxy-3-cephem **1** was converted to halides **3a**, **3b**, and **3c** by employing the method of Farina (Farina et. al., J. Org. Chem. 54, 4962-4966 (1989)). The phenylacetyl group was removed upon treatment with PCl<sub>5</sub> to produce free amines **4a**, **4b**, and **4c** respectively. These were converted to the corresponding 7-oxo-3-cephems and subsequently to the 7-(2'-pyridylmethylidene)-3-cephems **5a**, **5b**, and **5c**. These were readily oxidized to the corresponding sulfones upon treatment with excess mCPBA and the 4-position carboxylate deprotected by treatment with TFA (followed by neutralization with bicarbonate) to produce the corresponding sodium salts **7a**, **7b**, and **7c**.

Iodide **6c** was also useful in producing other C3 substituted analogs through Stille Coupling reactions with selected organostannanes as shown in Figure 2. Such reactions resulted in the production of representative C3-sulfides, aryl, and heteroaryl compounds which were also deprotected as shown in Figure 2. The C3 sulfides **8a** and **8b** could also be oxidized to the corresponding C3 sulfonyl compounds and deprotected to produce the corresponding sodium salts as shown in Figure 3.

Additionally, compound **6c** was converted to the C3 stannylated analog as shown in Figure 4. This compound was utilized to generate the C3 fluorinated (**14a**) and C3 unsubstituted (**14b**) compounds as shown.

Using procedures similar to those described herein, as well as standard synthetic

techniques, the compounds of formula (I) can be prepared.

Pharmaceutically acceptable salts of compounds of formula (I) wherein  $R_4$  has been replaced with a pharmaceutically acceptable cation (e.g. a sodium or potassium ion) can conveniently be prepared from a corresponding compound of formula (I) wherein  $R_4$  is hydrogen, by reaction with a suitable base.

A useful intermediate for preparing a compound of formula (I), wherein  $R_4$  is hydrogen, is a corresponding compound wherein  $R_4$  has been replaced with a suitable removable carboxy protecting group. Such protecting groups are well known in the art, for example, see Greene, T.W.; Wutz, P.G.M. "Protecting Groups In Organic Synthesis" second edition, 1991, New York, John Wiley & Sons, Inc. Preferred protecting groups include  $(C_1-C_{10})$ alkyl,  $(C_2-C_{10})$ alkenyl,  $(C_3-C_8)$ cycloalkyl,  $(C_2-C_{10})$ alkynyl, aryl, benzyl, or benzhydryl. Thus the invention provides compounds of formula (I) wherein  $R_1$ ,  $R_2$ , and  $R_3$  have any of the values, specific values, or preferred values defined herein, and wherein  $R_4$  is  $(C_1-C_{10})$ alkyl,  $(C_2-C_{10})$ alkenyl,  $(C_3-C_8)$ cycloalkyl,  $(C_2-C_{10})$ alkynyl, aryl, benzyl, and benzhydryl.

Another useful intermediate for preparing a compound of formula (I), is a compound of formula (I) wherein  $R_3$  is a tin containing group, e.g., a group of formula  $-\text{Sn}(\text{R})_3$  wherein each R is  $(C_1-C_6)$ alkyl. Accordingly, the invention also provides a compound of formula (I) wherein  $R_1$ ,  $R_2$ , and  $R_4$  have any of the values described herein, and wherein  $R_3$  is  $-\text{Sn}(\text{R})_3$  wherein each R is  $(C_1-C_6)$ alkyl.

A compound of formula (I) wherein A is sulfonyl ( $-\text{SO}_2-$ ) can be prepared by oxidation of a corresponding compound of formula (I) wherein A is thio ( $-\text{S}-$ ), for example, by using *meta*-chloroperbenzoic acid (mCPBA).

A compound of formula (I) wherein A is sulfinyl ( $-\text{SO}-$ ) can be prepared by oxidation of a corresponding compound of formula (I) wherein A is thio ( $-\text{S}-$ ), using one equivalent of an acceptable oxidizing agent, for example, mCPBA.

A compound of formula (I) wherein  $R_3$  is hydrogen, aryl, heteroaryl, or  $-\text{SR}_h$ , can be prepared by combining a corresponding compound of formula (I) wherein  $R_3$  is halo, with an organostannane of formula  $(\text{R}_a)_3\text{Sn}-\text{R}_3$  and a catalyst, to provide the compound of formula (I). Accordingly, the invention also provides a method of preparing a compound



of formula (I) wherein  $R_3$  is hydrogen, aryl, heteroaryl, or  $-SR_h$ , and  $R_4$  is hydrogen; comprising: combining a corresponding compound of formula (I) wherein  $R_3$  is halo and  $R_4$  is a protecting group, with an organostannane of formula  $(R_a)_3Sn-R_3$  and a catalyst, to provide a compound of formula (I) wherein  $R_3$  is hydrogen, aryl, heteroaryl, or  $-SR_h$ ; and  
 5  $R_4$  is a protecting group, and removing the protecting group  $R_4$  to provide the compound of formula (I) wherein  $R_3$  is hydrogen, aryl, heteroaryl, or  $-SR_h$ , and  $R_4$  is hydrogen. In one embodiment, the catalyst comprises palladium (e.g.  $Pd_2(dba)_2$ ). In another embodiment  $R_a$  is methyl, ethyl, propyl, or butyl.

The invention also provides a method of preparing a compound of formula (I)  
 10 wherein  $R_3$  is aryl, heteroaryl, or  $-CH=CHC(=O)NR_mR_p$ , and  $R_4$  is hydrogen; comprising: combining a corresponding compound of formula (I) wherein  $R_3$  is  $-Sn(R)_3$ , each  $R$  is  $(C_1-C_6)$ alkyl, and  $R_4$  is a protecting group, with the requisite organohalide or organotriflate (e.g. a compound of formula  $R_3-X$  wherein  $X$  is a halogen or triflate) and a catalyst, to provide a compound of formula (I) wherein  $R_3$  is aryl, heteroaryl, or  
 15  $-CH=CHC(=O)NR_mR_p$ ; and  $R_4$  is a protecting group, and removing the protecting group  $R_4$  to provide the compound of formula (I) wherein  $R_3$  is aryl, heteroaryl, or  $-CH=CHC(=O)NR_mR_p$ , and  $R_4$  is hydrogen. In one embodiment, each  $R$  is methyl, ethyl, propyl, or butyl.

The invention also provides a method of preparing a compound of formula (I)  
 20 wherein  $R_3$  is H or F, and  $R_4$  is hydrogen; comprising: combining a corresponding compound of formula (I) wherein  $R_3$  is  $-Sn(R)_3$ , each  $R$  is  $(C_1-C_6)$ alkyl, and  $R_4$  is a protecting group, with  $AgOTf$  and  $XeF_2$  to provide a compound of formula (I) wherein  $R_3$  is H or F; and  $R_4$  is a protecting group, and removing the protecting group  $R_4$  to provide the compound of formula (I) wherein  $R_3$  is H or F, and  $R_4$  is hydrogen. In one  
 25 embodiment, each  $R$  is methyl, ethyl, propyl, or butyl.

Many of the starting materials employed in the synthetic methods described above are commercially available or are reported in the scientific literature. It may be desirable to optionally use a protecting group during all or portions of the above described synthetic procedures. Such protecting groups and methods for their introduction and removal are  
 30 well known in the art. See Greene, T.W.; Wutz, P.G.M. "Protecting Groups In Organic



Synthesis" second edition, 1991, New York, John Wiley & Sons, Inc.

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate,  $\alpha$ -ketoglutarate, and  $\alpha$ -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example, by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example, calcium) salts of carboxylic acids can also be made.

The compounds of formula (I) can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to a selected route of administration, i.e., by oral, parenteral, intravenous, intramuscular, topical, or subcutaneous routes.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following:



binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like.

A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be



maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

10 Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously  
15 sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

20 Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents  
25 can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with  
30 liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for



application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of the invention to the skin are disclosed in Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and  
5 Wortzman (U.S. Pat. No. 4,820,508).

The present compositions may also be prepared in suitable forms for absorption through the mucous membranes of the nose and throat or bronchial tissues and may conveniently take the form of powder or liquid sprays or inhalants, lozenges, throat paints, etc. For medication of the eyes or ears, the preparations may be presented as  
10 individual capsules, in liquid or semi-solid form, or may be used as drops, etc. Topical applications may be formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints, powders, etc.

For veterinary medicine, the composition may, for example, be formulated as an intramammary preparation in either long acting or quick-release bases.

15 Useful dosages of the compounds of the invention can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Generally, the concentration of the compound(s) of the invention in a liquid  
20 composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The compositions per unit dosage, whether liquid or solid may contain from 0.1% to 99% of active material (the present 7-vinylidene cephalosporins and optional  
25 antibiotic), the preferred range being from about 10-60%. The composition will generally contain from about 15 mg to about 1500 mg by weight of active ingredient based upon the total weight of the composition; however, in general, it is preferable to employ a dosage amount in the range of from about 250 mg to 1000 mg. In parenteral administration the unit dosage is usually the pure compound in a slightly acidified sterile  
30 water solution or in the form of a soluble powder intended for solution.

Single dosages for injection, infusion or ingestion may be administered, i.e., 1-3 times daily, to yield levels of about 0.5-50 mg/kg, for adults.

The invention provides a pharmaceutical composition, comprising an effective amount of a compound of formula (I) as described hereinabove; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier. The invention also provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) as described hereinabove; or a pharmaceutically acceptable salt thereof; a  $\beta$ -lactam antibiotic; and a pharmaceutically acceptable carrier. The present compositions are preferably presented in a form suitable for absorption by the gastro-intestinal tract.

Any  $\beta$ -lactam antibiotic is suitable for use in the pharmaceutical composition of the invention.  $\beta$ -lactam antibiotics which are well known in the art include those disclosed by R.B. Morin and M. Gorin, M.Eds.; Academic Press, New York, 1982; vol. 1-3. Preferred  $\beta$ -lactam antibiotics, suitable for use in the pharmaceutical composition of the invention, include  $\beta$ -lactam antibiotics which are preferentially deactivated by Class A and Class C  $\beta$ -lactamase enzymes, for example, amoxicillin, piperacillin, ampicillin, ceftizoxime, cefotaxime, cefuroxime, cephalixin, cefaclor, cephaloridine, and ceftazidime.

The ability of a compound of the invention to function as a  $\beta$ -lactamase inhibitor can be demonstrated using the test described below, or using other tests which are well known in the art. Representative compounds of formula (I) were evaluated as inhibitors of the Class C  $\beta$ -lactamase of *Enterobacter cloacae* P-99, a cephalosporinase, and TEM-1, a Class A penicillinase, by relative  $IC_{50}$  analysis. The  $IC_{50}$  value represents the concentration of inhibitor required to effect a 50% loss of activity of free enzyme. The  $IC_{50}$  value of each compound was determined as follows. Following a 10 minute incubation of a dilute solution of enzyme (2.56 nM) and inhibitor (<0.64 mM), a 50 mL aliquot of this incubation mixture was then further diluted into 1 mL nitrocefin solution, and the rate of hydrolysis was measured during a 1 minute period by monitoring the absorbance of nitrocefin as a function of time. In addition, the  $IC_{50}$  values of tazobactam were determined as relative controls. The data is presented in Table 1 below for representative compounds of the formulae I.



Table 1

beta-Lactamase inhibitory activity against representative  
class A (TEM-1) and class C (P99) enzymes

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Compound	TEM-1 (IC <sub>50</sub> , $\mu$ m)	P99 (IC <sub>50</sub> , $\mu$ m)
<b>7a</b>	1.82	0.003
<b>7b</b>	0.791	0.0029
<b>7c</b>	1.28	0.0047
<b>9a</b>	1.065	0.059
<b>9b</b>	0.012	0.0217
<b>9c</b>	3.54	0.043
<b>9d</b>	9.14	0.038
<b>11a</b>	0.0076	0.0907
<b>11b</b>	0.0094	0.174
<b>14a</b>	1.84	0.011
<b>14b</b>	18.52	0.116
<b>18a</b>	0.240	0.824
<b>18b</b>	7.69	0.128
<b>21a</b>	0.39	1.1
<b>21b</b>	1.59	4.2
<b>21c</b>	0.053	6.34
<b>tazobactam</b>	0.25	101.6

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The present  $\beta$ -lactamase inhibitors of formula (I) are particularly useful in the treatment of infections associated with Enterobacter, Citrobacter, and Serratia. These bacteria have the ability to attach to the epithelial cells of the bladder or kidney (causing urinary tract infections) and are resistant to multiple antibiotics including amoxicillin and ampicillin.

The present  $\beta$ -lactamase inhibitors of formula (I) are also be useful in the

treatment of infections associated with highly resistant Pneumococci. Such diseases include otitis media, sinusitis, meningitis (both in children and adults), bacteremia, and septic arthritis. Resistant pneumococcal strains have surfaced in many parts of the world. For example, in Hungary, 58% of *S. pneumoniae* are resistant to penicillin, and 70% of children who are colonized with *S. pneumoniae* carry resistant strains that are also resistant to tetracycline, erythromycin, trimethoprin/sulfamethoxazole (TMP/SMX), and 30% resistant to chloramphenicol. *Klebsiella pneumoniae* (resistant via the production of  $\beta$ -lactamase) have caused hospital outbreaks of wound infection and septicemia.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

### **EXAMPLES 1-3 (Figure 1)**

#### **Preparation of Compound 2**

Diphenylmethyl 7-phenylacetamido-3-(trifluorosulfonyloxy)-3-cephem-4-carboxylate (**2**). This compound and the subsequent halides were prepared according to the method of Farina (Farina et. al. J. Org. Chem. 54, 4962-4966 (1989)). A solution of benzhydryl 3-hydroxy-7-(phenylacetamido)ceph-3-em (**1**, 41 g, 84 mmol, commercially available from Otsuka Chemical Corp.) in anhydrous  $\text{CH}_2\text{Cl}_2$  (600 mL) was cooled to  $-78^\circ\text{C}$  and treated with dry diisopropylethylamine (15.6 mL, 90 mmol) and trifluoromethanesulfonic anhydride (14.3 mL, 85 mmol). The mixture was then stirred at  $-78^\circ\text{C}$  for 20 min. The solution was then diluted with an addition 1 L of dry  $\text{CH}_2\text{Cl}_2$  and the cooling bath was removed. The organic phase was washed with water (2 x 1L) and brine (1 x 500 mL). Then it was dried over  $\text{Na}_2\text{SO}_4$  and concentrated to afford the desired triflate (**2**) as an off-white amorphous powder. Yield = 43.5 g (85%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  = 3.42 (d,  $J$  = 18 Hz, 1H), 3.70 – 3.63 (m, 2H), 3.75 (d,  $J$  = 18 Hz, 1H), 5.03 (d,  $J$  = 5 Hz, 1H), 5.91 – 5.87 (m, 1H), 6.02 (d,  $J$  = 8.7 Hz, 1H), 6.98 (s, 1H), 7.51 – 7.24 (m, 15H).

**Preparation of Compounds 3a-3c** General Procedure for the synthesis of diphenylmethyl



3-halo-7-(phenylacetamido)-3-cephem-4-carboxylates (**3a**, **3b**, and **3c**).

To a solution of triflate **2** (10 mmol) in anhydrous THF (100 mL) was added fresh anhydrous LiX (25 mmol) and the reaction was allowed to stir under argon for 24 to 36 h while monitoring the progress by <sup>1</sup>H NMR. When the reaction was complete, water (200 mL) and EtOAc (200 mL) were added and the organic phase was washed with water (2 x 100 mL), followed by brine (1 x 100 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent produced the crude 3-halo-3-cephem-4-carboxylate ester which was further purified by column chromatography on silica gel.

Diphenylmethyl 3-chloro-7-(phenylacetamido)-3-cephem-4-carboxylate (**3a**). Yield = 90%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 3.43 (d, J = 18.5 Hz, 1H), 3.64 – 3.57 (m, 2H), 3.74 (d, J = 18.5 Hz, 1H), 4.99 (d, J = 5 Hz, 1H), 5.84 – 5.81 (m, 1H), 6.24 (d, J = 9 Hz, 1H), 6.97 (s, 1H), 7.39 – 7.24 (m, 15H).

Diphenylmethyl 3-bromo-7-(phenylacetamido)-3-cephem-4-carboxylate (**3b**). Yield = 88%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 3.64 – 3.56 (m, 3H), 3.83 (d, J = 18 Hz, 1H), 5.02 (d, J = 5 Hz, 1H), 5.81 – 5.78 (m, 1H), 6.21 (d, J = 9 Hz, 1H), 6.97 (s, 1H), 7.41 – 7.25 (m, 15H).

Diphenylmethyl 3-iodo-7-(phenylacetamido)-3-cephem-4-carboxylate (**3c**). Yield = 72%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 3.67 – 3.56 (m, 2H), 3.70 (d, J = 18.5 Hz, 1H), 3.84 (d, J = 18.5 Hz, 1H), 5.04 (d, J = 5 Hz, 1H), 5.85 – 5.81 (m, 1H), 6.16 (d, J = 9 Hz, 1H), 6.96 (s, 1H), 7.41 – 7.24 (m, 15H).

Preparation of Compounds 4a-4c General procedure for the synthesis of diphenylmethyl 3-halo-7-amino-3-cephem-4-carboxylates (**4a**, **4b**, and **4c**).

To a cooled (0 °C) solution of PCl<sub>5</sub> (25 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> was added dry pyridine (25 mmol) slowly while cooling the reaction with an ice bath. The reaction was

allowed to stir at this temperature for 1 h. The appropriate phenylacetamido-3-cephem-4-carboxylate (**3a**, **3b**, or **3c**) was then added in one portion and the reaction allowed to continue stirring for 1.5 h at the same temperature. The reaction mixture was then cooled to  $-78^{\circ}\text{C}$  and MeOH (30 mL) was added slowly and the reaction stirred for an additional 1 h. The reaction mixture was then allowed to slowly warm to reach a temperature between  $-10$  and  $0^{\circ}\text{C}$ . Water (30 mL) was then added and the solution was concentrated under vacuum to remove  $\text{CH}_2\text{Cl}_2$  and most of the MeOH. To the remaining residue, EtOAc (150 mL) and water (100 mL) were added and the water layer was basified by the addition of  $\text{NaHCO}_3$ . The organic layer was then separated and the aqueous layer was further extracted with EtOAc (1 x 50 mL). The combined organic layer was washed with water (1 x 100 mL) followed by brine (1 x 100 mL). The organic layer was then dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The crude product was further purified by column chromatography using a mixture of EtOAc and  $\text{CH}_2\text{Cl}_2$  as eluent.

Diphenylmethyl 3-chloro-7-amino-3-cephem-4-carboxylate (**4a**). Yield = 74%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  = 1.74 (br s, 2H), 3.48 (d,  $J$  = 18.5 Hz, 1H), 3.8 (d,  $J$  = 18.5 Hz, 1H), 4.75 (d,  $J$  = 5.0 Hz, 1H), 4.98 (d,  $J$  = 5.0 Hz, 1H), 7.00 (s, 1H), 7.57 – 7.26 (m, 10H).

Diphenylmethyl 3-bromo-7-amino-3-cephem-4-carboxylate (**4b**). Yield = 72%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  = 1.74 (br s, 2H), 3.62 (d,  $J$  = 18 Hz, 1H), 3.88 (d,  $J$  = 18 Hz, 1H), 4.75 (d,  $J$  = 5.0 Hz, 1H), 5.00 (d,  $J$  = 5.0 Hz, 1H), 7.00 (s, 1H), 7.44 – 7.25 (m, 10H).

Diphenylmethyl 3-iodo-7-amino-3-cephem-4-carboxylate (**4c**). Yield = 76%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  = 1.75 (br s, 2H), 3.76 (d,  $J$  = 18.5 Hz, 1H), 3.90 (d,  $J$  = 18.5 Hz, 1H), 4.75 (d,  $J$  = 5 Hz, 1H), 5.04 (d,  $J$  = 5.0 Hz, 1H), 7.00 (s, 1H), 7.46 – 7.26 (m, 10H).

Preparation of Compounds **5a-5c** General procedure for synthesis of diphenylmethyl 3-halo-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylates (**5a**, **5b**, and **5c**) from amines



(4a, 4b, and 4c).

To a solution of triphenyl(2-pyridylmethyl)phosphonium chloride hydrochloride (20 mmol, Aldrich Chemical Co.) in anhydrous THF (150 mL) was added potassium tert-butoxide (15 mmol). This slurry was then stirred at room temperature for 2 h to generate the Wittig Reagent.

Separately, to a solution of amine (4, 20 mmol) in EtOAc (200 mL) were added catalytic trifluoroacetic acid (200  $\mu$ L) and isopropylnitrite (a solution 30 to 50% in CH<sub>2</sub>Cl<sub>2</sub>, prepared by the method of Blacklock et. al., J. Org. Chem., 54, 3907-3913 (1989)). After completion of the reaction (approx. 5 min, monitored by TLC), EtOAc was removed under vacuum and the resultant 7-diazo-3-cephem-4-carboxylates was dried completely under high vacuum. This diazo compound was then immediately dissolved in anhydrous benzene (200 mL) and propylene oxide (25 mL), and treated with a catalytic amount of rhodium octanoate (0.5 g). The reaction was observed to evolve gas. After the completion of such gas evolution, the benzene solvent was removed under vacuum and the remaining solid (7-oxo-3-cephem-4-carboxylate) dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (200 mL). This solution was then cooled to -78 °C.

The solution of the aforementioned Wittig Reagent was then slowly added (via cannula) to this cold (-78 °C) solution of ketone and the reaction stirred at this temperature for 30 min. Then a saturated aqueous solution of NH<sub>4</sub>Cl was added and the reaction mixture slowly warmed to room temperature with stirring. The layers were separated and the aqueous layer extracted with an additional portion of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with water (1 x 100 mL), brine (1 x 100 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was purified by column chromatography (silica gel) using a mixture of EtOAc and CH<sub>2</sub>Cl<sub>2</sub> as eluent.

Diphenylmethyl 3-chloro-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (5a).

Overall yield (three steps from 4a) = 35%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 3.54 (d, J = 18.5 Hz, 1H), 3.96 (d, J = 18.5 Hz, 1H), 5.71 (s, 1H), 7.03 (s, 1H), 7.41 – 7.28 (m, 13H), 7.76 (t of d, J = 1.6 Hz and 7.7 Hz, 1H), 8.76 (d, J = 4 Hz, 1H).

Diphenylmethyl 3-bromo-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (**5b**).

Overall yield (three steps from **4b**) = 35%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 3.59 (d, J = 18.5 Hz, 1H), 3.95 (d, J = 18.5 Hz, 1H), 5.73 (d, J = 1 Hz, 1H), 7.05 (s, 1H), 7.47 – 7.26 (m, 13H), 7.77 (t of d, J = 1.6 Hz and 7.7 Hz, 1H), 8.76 (d, J = 4 Hz, 1H).

Diphenylmethyl 3-iodo-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (**5c**). Overall yield (three steps from **4a**) = 33%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 3.70 (d, J = 18.5 Hz, 1H), 3.94 (d, J = 18.5 Hz, 1H), 5.76 (s, 1H), 7.06 (s, 1H), 7.42 – 7.26 (m, 13H), 7.73 (t of d, J = 1.6 and 7.7 Hz, 1H), 8.71 (d, J = 4.0 Hz, 1H).

Preparation of Compounds 6a-6c General procedure for formation of diphenylmethyl 1,1-dioxo-3-halo-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylates (**6a**, **6b**, and **6c**) using oxidation with mCPBA.

To a solution of sulfide (**5**) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added mCPBA (2.5 mmol) and the reaction was stirred for 20 min at rt. A saturated aqueous solution of Na<sub>2</sub>SO<sub>3</sub> was then added and the layers were separated. The organic layer was washed with aqueous NaHCO<sub>3</sub> (1 x 25 mL), water (1 x 25 mL), and brine (1 x 25 mL). The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and the crude product further purified by flash column chromatography (silica gel) using a mixture of EtOAc and CH<sub>2</sub>Cl<sub>2</sub> as eluent.

Diphenylmethyl 3-chloro-1,1-dioxo-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (**6a**). Yield = 72%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 4.04 (d, J = 18 Hz, 1H), 4.23 (d, J = 18 Hz, 1H), 5.93 (s, 1H), 7.03 (s, 1H), 7.39 – 7.31 (m, 13H), 7.73 (t of d, J = 1.6 Hz and 7.7 Hz, 1H), 8.66 (d, J = 4 Hz, 1H).

Diphenylmethyl 3-bromo-1,1-dioxo-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (**6b**). Yield = 75%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 4.10 (d, J = 18 Hz, 1H), 4.34 (d of t, J = 18 Hz, 1H), 5.95 (s, 1H), 7.04 (s, 1H), 7.47 – 7.3 (m, 13H), 7.73 (t of d, J = 1.6 Hz



and 7.7 Hz, 1H), 8.67 (d,  $J = 4$  Hz, 1H).

Diphenylmethyl 3-iodo-1,1-dioxo-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (6c). Yield = 78%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta = 8.66$  (d,  $J = 4.0$  Hz, 1H), 7.71 (t of d,  $J = 1.6$  and 7.7 Hz, 1H), 7.49 – 7.25 (m, 13H), 7.03 (s, 1H), 5.96 (s, 1H), 4.38 (d,  $J = 18$  Hz, 1H), 4.18 (d,  $J = 18$  Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta = 160.3, 160.2, 150.4, 150.2, 138.9, 138.6, 137.0, 132.7, 130.9, 128.6, 128.5, 128.4, 128.2, 128.0, 127.5, 127.2, 126.6, 126.4, 125.3, 80.5, 74.1, 64.2$ . HRMS calcd for  $\text{C}_{26}\text{H}_{19}\text{IN}_2\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$  599.0138, obsd 599.0135.

Preparation of Compounds 7a-7c General Procedure for the deprotection of benzhydryl esters.

A solution of the appropriate benzhydryl ester (0.1 mmol) in dry anisole (3.0 mmol) was cooled in an ice-salt bath and trifluoroacetic acid (12.0 mmol) was added slowly via syringe under argon atmosphere. After 20 minutes, the volatile components were removed under vacuum and the residue was dissolved in EtOAc (5 mL). The EtOAc layer was extracted with aqueous  $\text{NaHCO}_3$  (2 x 0.15 mmol in 4 mL  $\text{H}_2\text{O}$ ). The combined water layers were directly loaded onto a chromatography column (high porous polymer, MCI gel, CHP20P Mitsubishi Chemical Corp., White Plains NY, approx. 75 to 150 mL of resin) and the product eluted with 5% EtOH in deionized water. The yield was typically between 60 to 80%.

**Example 1:** Sodium 3-chloro-1,1-dioxo-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (7a). Prepared from ester 7a according to the general procedure described above for the deprotection of benzhydryl esters.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta = 6.28$  (s, 1H), 7.44-7.34 (m, 1H), 7.48 (s, 1H), 7.62-7.59 (m, 1H), 7.84 (t of d,  $J = 1.6$  Hz and 7.7 Hz, 1H), 8.55 (d,  $J = 4.0$  Hz, 1H).

**Example 2:** Sodium 3-bromo-1,1-dioxo-7-(2'-pyridylmethylidene)-3-cephem-4-

carboxylate (**7b**). Prepared from ester **7b** according to the general procedure described above for the deprotection of benzhydryl esters. <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ = 6.29 (s, 1H), 7.45 – 7.35 (m, 1H), 7.49 (s, 1H), 7.6 – 7.57 (m, 1H), 7.85 (t of d, J = 1.6 and 7.7 Hz, 1H), 8.56 (d, J = 4.0 Hz, 1H).

5

**Example 3:** Sodium 1,1-dioxo-3-iodo-7-(2'-pyridylmethyldine)-3-cephem-4-carboxylate (**7c**). Prepared from ester **7c** according to the general procedure described above for the deprotection of benzhydryl esters. <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ = 6.29 (d, J = 1Hz, 1H), 7.33 – 7.30 (m, 1H), 7.45 (d, J = 1Hz, 1H), 7.65 – 7.61 (m, 1H), 7.83 (t of d, J = 1.6 Hz and 7.7 Hz, 1H), 8.54 (d, J = 4.0 Hz, 1H).

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### EXAMPLES 4-7 (Figure 2)

Preparation of Compounds 8a-8d General procedure for the Stille Couplings of iodide **6c** with organostannanes to produce compounds **8a – 8d**.

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To a solution of **6c** (72 mg, 0.12 mmol) in anhydrous THF were added the appropriate organostannane (0.11 mmol, e.g., Bu<sub>3</sub>Sn-R<sub>3</sub>) and Pd<sub>2</sub>(dba)<sub>3</sub> (5 mg, 0.011 mmol) under an Ar atmosphere. The reaction mixture was stirred at 65 °C for 2.5 h and was monitored by <sup>1</sup>H NMR. After completion of the reaction, solvent was removed under reduced pressure and the product dissolved in CH<sub>2</sub>Cl<sub>2</sub>. The solution was then washed with water (10 mL) and brine (10 mL). The organic layer was concentrated and purified by column chromatography (silica gel).

20

Diphenylmethyl 1,1-dioxo-3-methylsulfanyl-7-(2'-pyridylmethyldine)-3-cephem-4-carboxylate (**8a**). Yield = 67%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 2.35 (s, 3H), 3.98 (d, J = 15.5 Hz, 1H), 4.18 (d, J = 15.5 Hz, 1H), 5.72 (d, J = 1 Hz, 1H), 6.97 (s, 1H), 7.4 – 7.26 (m, 13H), 7.71 (t of d, J = 1.6 and 7.7 Hz, 1H), 8.66 (d, J = 4 Hz, 1H).

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Diphenylmethyl 1,1-dioxo-3-phenylsulfanyl-7-(2'-pyridylmethyldine)-3-cephem-4-

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carboxylate (**8b**). Yield = 72%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 8.63 (d, J = 3.9 Hz, 1H), 7.71 (t of d, J = 1.6 and 7.7 Hz, 1H), 7.53 – 7.26 (m, 19H), 7.02 (s, 1H), 5.75 (s, 1H), 3.75 (d, J = 15.6 Hz, 1H), 3.59 (d, J = 15.6 Hz, 1H).

5 Diphenylmethyl 1,1-dioxo-7-(2'-pyridylmethyldine)-3-(thiophen-2'-yl)-3-cephem-4-carboxylate (**8c**). Yield = 78%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 8.69 (d, J = 4.0 Hz, 1H), 7.72 (t of d, J = 1.6 and 7.7 Hz, 1H), 7.4 – 7.21 (m, 12H), 7.07 – 7.05 (m, 2H), 6.96 (s, 1H), 6.84 (dd, J = 1 and 4 Hz, 1H), 6.75 (t, J = 4 Hz, 1H), 5.96 (s, 1H), 4.17 (d, J = 18 Hz, 1H), 4.08 (d, J = 18 Hz, 1H).

10 Diphenylmethyl 1,1-dioxo-3-phenyl-7-(2'-pyridylmethyldine)-3-cephem-4-carboxylate (**8d**). Yield = 56%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 8.65 (d, J = 3.9 Hz, 1H), 7.7 (t of d, J = 1.6 and 7.7 Hz, 1H), 7.34 – 7.13 (m, 16H), 6.92 (d, J = 6.7 Hz, 2H), 6.85 (s, 1H), 5.98 (s, 1H), 4.08 (s, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) δ = 160.8, 159.2, 150.2, 150.0, 138.6, 15 138.1, 136.5, 134.9, 132.8, 129.9, 128.9, 128.5, 128.09, 127.9, 127.7, 127.5, 127.2, 127.0, 126.9, 125.9, 124.7, 79.0, 73.0, 56.7.

Preparation of Compounds 9a-9d Compounds **9a-9d** were prepared from Compounds **8a-8d** using the General Procedure for the Deprotection of benzhydryl esters described  
20 above.

**Example 4:** Sodium 1,1-dioxo-3-methylsulfanyl-7-(2'-pyridylmethyldine)-3-cephem-4-carboxylate (**9a**). Prepared from ester **8a** according to the general procedure described above for the deprotection of benzhydryl esters. <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ = 2.2 (s, 3H), 6.17 (s, 1H), 7.42 – 7.36 (m, 2H), 7.43 (s, 1H), 7.61 – 7.58 (m, 1H), 7.81 (t of d, J = 1.6 Hz and 7.7 Hz, 1H), 8.52 (d, J = 4.0 Hz, 1H).  
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**Example 5:** Sodium 1,1-dioxo-3-phenylsulfanyl-7-(2'-pyridylmethyldine)-3-cephem-4-carboxylate (**9b**). Prepared from ester **8b** according to the general procedure described  
30 above for the deprotection of benzhydryl esters. <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ = 6.32 (d, J

= 1 Hz, 1H), 7.42 – 7.33 (m, 6H), 7.46 (s, 1H), 7.6 – 7.58 (m, 1H), 7.81 (t of d, J = 1.6 Hz and 7.7 Hz, 1H), 8.51 (d, J = 4.0 Hz, 1H).

**Example 6:** Sodium 1,1-dioxo-7-(2'-pyridylmethylidene)-3-(thiophen-2'-yl)-3-cephem-4-carboxylate (**9c**). Prepared from ester **8c** according to the general procedure described above for the deprotection of benzhydryl esters. <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ = 6.23 (s, 1H), 7.03 – 7.00 (m, 1H), 7.1 (d, J = 4 Hz, 1H), 7.42 – 7.4 (m, 2H), 7.45 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.83 (t of d, J = 1.6 Hz and 7.7 Hz, 1H), 8.54 (d, J = 4.0 Hz, 1H).

**Example 7:** Sodium 1,1-dioxo-3-phenyl-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (**9d**). Prepared from ester **8d** according to the general procedure described above for the deprotection of benzhydryl esters. <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ = 6.24 (s, 1H), 7.39 – 7.28 (m, 6H), 7.45 (s, 1H), 7.62 – 7.60 (m, 1H), 7.82 (t of d, J = 1.6 Hz and 7.6 Hz, 1H), 8.54 (d, J = 4.0 Hz, 1H).

### EXAMPLES 8 and 9 (Figure 3)

Preparation of Compounds 10a and 10b General procedure for oxidation of the 3-position sulfur of compounds **8a** and **8b** to produce the corresponding 3-position sulfones (**10a** and **10b**).

To a solution of sulfide (**8a** or **8b**, 0.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added mCPBA (0.4 mmol) and the reaction mixture stirred at room temperature until the reaction was complete (monitored by TLC, approx. 8 h). The reaction was then quenched by the addition of a saturated solution of NaHSO<sub>3</sub>. The layers were separated and the aqueous layer extracted with an addition portion of CH<sub>2</sub>Cl<sub>2</sub> (1 x 20 mL). The combined organic layers were washed with NaHCO<sub>3</sub> (1 x 20 mL), water (1 x 20 mL), and brine (1 x 20 mL). The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under vacuum, and purified by flash chromatography (silica gel).



Diphenylmethyl 1,1-dioxo-3-methylsulfonyl-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (**10a**). Yield = 81%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 2.81 (s, 3H), 3.84 (d, J = 18.5 Hz, 1H), 4.34 (d, J = 18.5 Hz, 1H), 6.08 (s, 1H), 7.03 (s, 1H), 7.43 – 7.3 (m, 13H), 7.74 (t of d, J = 1.6 Hz and 7.7 Hz, 1H), 8.69 (d, J = 4 Hz, 1H).

Diphenylmethyl 1,1-dioxo-3-phenylsulfonyl-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (**10b**). Yield = 75%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 3.48 (d, J = 18 Hz, 1H), 4.16 (d, J = 18 Hz, 1H), 5.94 (s, 1H), 7.05 (s, 1H), 7.44 – 7.19 (m, 17H), 7.75 – 7.71 (m, 2H), 8.61 (d, J = 4 Hz, 1H).

Preparation of Compounds 11a and 11b Compounds **11a** and **11b** were prepared from Compounds **10a** and **10b** using the General Procedure for the Deprotection of benzhydryl esters described above.

**Example 8:** Sodium 1,1-dioxo-3-methylsulfonyl-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (**11a**). Prepared from ester **10a** according to the general procedure described above for the deprotection of benzhydryl esters. <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ = 3.2 (s, 3H), 4.53 (d, J = 17.6 Hz, 1H), 4.32 (d, J = 17.6 Hz, 1H), 6.41 (s, 1H), 7.49 – 7.40 (m, 1H), 7.66 – 7.58 (m, 2H), 7.86 (t of d, J = 1.6 and 7.6 Hz, 1H), 8.60 (d, J = 4.0 Hz, 1H).

**Example 9:** Sodium 1,1-dioxo-3-phenylsulfonyl-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (**11b**). Prepared from ester **10b** according to the general procedure described above for the deprotection of benzhydryl esters. <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ = 6.33 (s, 1H), 7.40 – 7.39 (m, 1H), 7.62 – 7.54 (m, 6H), 7.71 (m, 1H), 7.83 (t of d, J = 1.6 and 7.6 Hz, 1H), 8.55 (d, J = 4.0 Hz, 1H).

#### EXAMPLES 10 and 11 (Figure 4)

Preparation of Compounds 12 Diphenylmethyl 1,1-dioxo-7-(2'-pyridylmethylidene)-3-

(trimethylstannyl)-3-cephem-4-carboxylate (**12**).

To a solution of **6c** (1.0 g, 1.71 mmol) in dry THF was added hexamethylditin (0.67 g, 2.0 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (175 mg, 0.2 mmol) under an Ar atmosphere. The reaction mixture was stirred at 60 °C for 1.5 h, while monitoring by <sup>1</sup>H NMR. After completion of the reaction, solvent was removed under reduced pressure. The product was then dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with water (50 mL) and brine (30 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated under reduced pressure, and purified by flash chromatography using EtOAc/ CH<sub>2</sub>Cl<sub>2</sub> as eluent to obtain a 60% yield of **13**. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 8.66 (d, J = 3.9 Hz, 1H), 7.72 (t of d, J = 1.6 and 7.7 Hz, 1H), 7.54 (d, J = 7.5 Hz, 2H), 7.43 to 7.26 (m, 11H), 6.92 (s, 1H), 5.88 (s, 1H), 4.07 (d, J = 18.5 Hz, 1H), 3.93 (d, J = 18.5 Hz, 1H), 0.15 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) δ = 162.6, 158.4, 150.8, 150.3, 142.1, 139.6, 139.2, 136.8, 133.9, 130.6, 129.8, 128.6, 128.4, 128.2, 127.9, 127.5, 127.1, 126.0, 124.9, 80.3, 73.1, 57.6, -6.6. HRMS calcd for C<sub>29</sub>H<sub>29</sub>N<sub>2</sub>O<sub>5</sub>SSn [M+H]<sup>+</sup> 637.0819, obsd 637.0823.

Preparation of Compounds **13a** and **13b** Reaction of **12** with XeF<sub>2</sub>: Synthesis of diphenylmethyl 1,1-dioxo-3-fluoro-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (**13a**) and diphenylmethyl 1,1-dioxo-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylate (**13b**).

To a solution of stannane **12** (0.1 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> was added AgOTf (0.11 mmol) and the reaction mixture was cooled in an ice-salt bath under argon. XeF<sub>2</sub> (0.11 mmol) was then added in one portion and the reaction stirred for 10 min. At this time, water was added, the layers separated. The aqueous layer was extracted with an additional portion of CH<sub>2</sub>Cl<sub>2</sub> (1 x 25 mL), and the combined organic layers were washed with water (1 x 25 mL) and brine (1 x 25 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After the solvent was removed under vacuum, the products were purified by flash chromatography on silica gel.



Diphenylmethyl 1,1-dioxo-3-fluoro-7-(2'-pyridylmethyldine)-3-cephem-4-carboxylate (13a). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 8.65 (d, J = 4.0 Hz, 1H), 7.71 (t of d, J = 1.5 and 7.7 Hz, 1H), 7.47 – 7.27 (m, 13H), 7.04 (s, 1H), 5.84 (s, 1H), 4.23 (d of d, J = 5.4 and 20 Hz, 1H), 4.08 (d of d, J = 5.4 and 20 Hz, 1H).

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Diphenylmethyl 1,1-dioxo-7-(2'-pyridylmethyldine)-3-cephem-4-carboxylate (13b). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 8.66 (d, J = 4.0 Hz, 1H), 7.76 (t of d, J = 1.5 and 7.7 Hz, 1H), 7.48 – 7.25 (m, 13H), 6.99 (s, 1H), 6.34 (d of d, J = 3.5 and 2.0 Hz), 5.94 (s, 1H), 4.04 (d of d, 1.5 and 17.5 Hz, 1H), 3.83 (d of d, J = 5.6 and 17.5 Hz, 1H). HRMS calcd for C<sub>26</sub>H<sub>21</sub>N<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup> 473.1171, obsd 473.1148.

10

Preparation of Compounds 14a and 14b Compounds 14a and 14b were prepared from Compounds 13a and 13b using the General Procedure for the Deprotection of benzhydryl esters described above.

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**Example 10:** Sodium 1,1-dioxo-3-fluoro-7-(2'-pyridylmethyldine)-3-cephem-4-carboxylate (14a). Prepared from ester 13a according to the general procedure described above for the deprotection of benzhydryl esters. <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ = 6.19 (s, 1H), 7.46 – 7.35 (m, 2H), 7.58 – 7.55 (m, 1H), 7.8 (t of d, J = 1.6 Hz and 7.6 Hz, 1H), 8.52 (d, J = 4.0 Hz, 1H).

20

**Example 11:** Sodium 1,1-dioxo-7-(2'-pyridylmethyldine)-3-cephem-4-carboxylate (14b). Prepared from ester 13b according to the general procedure described above for the deprotection of benzhydryl esters. <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ = 6.21 (s, 1H), 7.38 – 7.35 (m, 1H), 7.43 (s, 1H), 7.61 – 7.59 (m, 1H), 7.81 (t of d, J = 1.6 Hz and 7.6 Hz, 1H), 8.51 (d, J = 4.0 Hz, 1H).

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### EXAMPLES 12-16 (Figures 5 and 6)

Preparation of Compounds 16a, 16b, and 20a-20c General procedure for the formation

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of amides from carboxylic acids (Schemes 5 and 6). The following procedure was used to prepare compound **16a** and **16b** from compound **15** and was also used to prepare compounds **20a**, **20b** and **20c** from compound **19**.

5 To a solution of the carboxylic acid (0.3 mmol) in dry CH<sub>3</sub>CN (10 mL) was added Et<sub>3</sub>N (0.6 mmol), the appropriate amine, RNH<sub>2</sub> (0.45 mmol), and BOP reagent (0.3 mmol) at room temperature. The reaction was monitored by TLC and was usually complete in 30 min. CH<sub>3</sub>CN was then removed under vacuum. To the residue was added CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and water (25 mL). After separation of the layers, the aqueous layer was  
10 extracted a second time with CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and the combined organic layers were washed with water (10 mL) followed by brine (25 mL). These organic layers were then dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under vacuum, and purified by column chromatography. The yields of these coupling reactions were typically 50 to 70%.

15 Preparation of Compounds **17a**, **17b**, and **19** General procedure used for the oxidation of sulfides **16a** and **16b** to the corresponding sulfones **17a** and **17b** as well as for the oxidation of sulfide **15** to sulfone **19**.

This procedure is identical to the general procedure for formation of  
20 diphenylmethyl 1,1-dioxo-3-halo-7-(2'-pyridylmethylidene)-3-cephem-4-carboxylates (**6a**, **6b**, and **6c**) using oxidation with mCPBA which is described above.

Preparation of Compounds **18a**, **18b**, and **21a-21c** General procedure for the deprotection of the benzhydryl esters (**17a**, **17b**, **20a**, **20b**, and **20c**) to produce the  
25 corresponding carboxylic acid salts (**18a**, **18b**, **21a**, **21b**, and **21c**, respectively).

This procedure is identical to the General Procedure for the deprotection of benzhydryl esters described above.

30 **Example 12:** Sodium 3-(*N*-cyclopropyl-2'-carbamoylvinyl)-1,1-dioxo-7-(2''-



pyridylmethyldine)-3-cephem-4-carboxylate (**18a**)  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  = 0.56 – 0.52 (m, 2H), 0.8 – 0.75 (m, 2H), 2.68 – 2.65 (m, 1H), 4.26 (d,  $J$  = 17.5 Hz, 1H), 4.39 (d,  $J$  = 17.5 Hz, 1H), 5.95 (d,  $J$  = 15.5 Hz, 1H), 6.38 (s, 1H), 7.5 – 7.45 (m, 2H), 7.57 (s, 1H), 7.69 (d,  $J$  = 8 Hz, 1H), 7.9 (t of d,  $J$  = 1.6 Hz and 7.7 Hz, 1H), 8.63 (d,  $J$  = 4 Hz, 1H).

5

**Example 13:** Sodium 3-(*N*-hydroxy-2'-carbamoylvinyl)-1,1-dioxo-7-(2''-

pyridylmethyldine)-3-cephem-4-carboxylate (**18b**)  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  = 5.88 (d,  $J$  = 16 Hz, 1H), 6.33 (s, 1H), 7.33 (d,  $J$  = 16 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.49 (s, 1H), 7.65 (d,  $J$  = 8 Hz, 1H), 7.86 (t of d,  $J$  = 1.6 Hz and 7.7 Hz, 1H), 8.6 (d,  $J$  = 4 Hz, 1H).

10

**Example 14:** Sodium 3-[2'-(hydrazinocarbonyl)vinyl]-1,1-dioxo-7-(2''-

pyridylmethyldine)-3-cephem-4-carboxylate (**21a**)  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  = 5.92 (d,  $J$  = 16 Hz, 1H), 6.25 (s, 1H), 7.68 – 7.43 (m, 3H), 7.67 (d,  $J$  = 8 Hz, 1H), 7.88 (t of d,  $J$  = 1.6 Hz and 7.7 Hz, 1H), 8.61 (d,  $J$  = 4 Hz, 1H).

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**Example 15:** Sodium 3-{[*N*-(3''-aminopropyl)-2'-carbamoyl]vinyl}-1,1-dioxo-7-(2'''-

pyridylmethyldine)-3-cephem-4-carboxylate (**21b**)  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  = 1.87 (q,  $J$  = 7 Hz, 2H), 2.96 (t,  $J$  = 7.5 Hz, 1H), 3.31 (t,  $J$  = 6.5 Hz, 1H), 5.98 (d,  $J$  = 16 Hz, 1H), 6.33 (s, 1H), 7.48 – 7.40 (m, 2H), 7.52 (s, 1H), 7.64 (d,  $J$  = 8 Hz, 1H), 7.85 (t of d,  $J$  = 1.6 Hz and 7.7 Hz, 1H), 8.58 (d,  $J$  = 4 Hz, 1H).

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**Example 16:** Sodium 3-[3'-(4''-methylpiperazin-1''-yl)-3'-oxopropenyl]-1,1-dioxo-7-

(2'''-pyridylmethyldine)-3-cephem-4-carboxylate (**21c**)  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  = 2.19 (s, 3H), 2.46 – 2.42 (m, 4H), 3.8 – 3.76 (m, 4H), 6.37 (d,  $J$  = 16 Hz, 1H), 6.43 (s, 1H), 7.51 – 7.4 (m, 3H), 7.53 (s, 1H), 7.66 (d,  $J$  = 16 Hz, 1H), 7.86 (t of d,  $J$  = 1.6 Hz and 7.7 Hz, 1H), 8.59 (d,  $J$  = 4 Hz, 1H).

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**Example 17:** The following illustrate representative pharmaceutical dosage forms,

containing a compound of Formula (I) ('Compound X'), for therapeutic or prophylactic

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use in humans.

	<u>(i) Tablet 1</u>	<u>mg/tablet</u>
	'Compound X'	100.0
5	Lactose	77.5
	Povidone	15.0
	Croscarmellose sodium	12.0
	Microcrystalline cellulose	92.5
	Magnesium stearate	<u>3.0</u>
10		300.0
	<u>(ii) Tablet 2</u>	<u>mg/tablet</u>
	'Compound X'	20.0
	Microcrystalline cellulose	410.0
15	Starch	50.0
	Sodium starch glycolate	15.0
	Magnesium stearate	<u>5.0</u>
		500.0
20	<u>(iii) Capsule</u>	<u>mg/capsule</u>
	'Compound X'	10.0
	Colloidal silicon dioxide	1.5
	Lactose	465.5
	Pregelatinized starch	120.0
25	Magnesium stearate	<u>3.0</u>
		600.0
	<u>(iv) Injection 1 (1 mg/ml)</u>	<u>mg/ml</u>
	'Compound X' (free acid form)	1.0
30	Dibasic sodium phosphate	12.0
	Monobasic sodium phosphate	0.7
	Sodium chloride	4.5
	1.0 N Sodium hydroxide solution	
	(pH adjustment to 7.0-7.5)	q.s.
35	Water for injection	q.s. ad 1 mL



	<u>(v) Injection 2 (10 mg/ml)</u>	<u>mg/ml</u>
	'Compound X' (free acid form)	10.0
	Monobasic sodium phosphate	0.3
	Dibasic sodium phosphate	1.1
5	Polyethylene glycol 400	200.0
	01 N Sodium hydroxide solution	
	(pH adjustment to 7.0-7.5)	q.s.
	Water for injection	q.s. ad 1 mL
10	<u>(vi) Aerosol</u>	<u>mg/can</u>
	'Compound X'	20.0
	Oleic acid	10.0
	Trichloromonofluoromethane	5,000.0
	Dichlorodifluoromethane	10,000.0
15	Dichlorotetrafluoroethane	5,000.0
	<u>(vii) Tablet 1</u>	<u>mg/tablet</u>
	'Compound X'	100.0
	$\beta$ -lactam antibiotic	100.0
20	Lactose	77.5
	Povidone	15.0
	Croscarmellose sodium	12.0
	Microcrystalline cellulose	92.5
	Magnesium stearate	<u>3.0</u>
25		400.0
	<u>(viii) Tablet 2</u>	<u>mg/tablet</u>
	'Compound X'	20.0
	$\beta$ -lactam antibiotic	20.0
30	Microcrystalline cellulose	410.0
	Starch	50.0
	Sodium starch glycolate	15.0
	Magnesium stearate	<u>5.0</u>
		520.0
35	<u>(ix) Capsule</u>	<u>mg/capsule</u>
	'Compound X'	10.0
	$\beta$ -lactam antibiotic	10.0
	Colloidal silicon dioxide	1.5
40	Lactose	465.5
	Pregelatinized starch	120.0
	Magnesium stearate	<u>3.0</u>
		610.0

	<u>(x) Injection 1</u>	<u>mg/ml</u>
	'Compound X' (free acid form)	1.0
	$\beta$ -lactam antibiotic	2.0
	Dibasic sodium phosphate	12.0
5	Monobasic sodium phosphate	0.7
	Sodium chloride	4.5
	1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
	Water for injection	q.s. ad 1 mL
10	<u>(xi) Injection 2</u>	<u>mg/ml</u>
	'Compound X' (free acid form)	10.0
	$\beta$ -lactam antibiotic	5.0
	Monobasic sodium phosphate	0.3
15	Dibasic sodium phosphate	1.1
	Polyethylene glycol 400	200.0
	0.1 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
	Water for injection	q.s. ad 1 mL
20	<u>(xii) Aerosol</u>	<u>mg/can</u>
	'Compound X'	20.0
	$\beta$ -lactam antibiotic	20.0
	Oleic acid	10.0
25	Trichloromonofluoromethane	5,000.0
	Dichlorodifluoromethane	10,000.0
	Dichlorotetrafluoroethane	5,000.0

30           The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. " $\beta$ -lactam antibiotic" can be any compound possessing antibiotic properties (e.g. amoxicillin, piperacillin, ampicillin, ceftizoxime, cefotaxime, cefuroxime, cephalixin, cefaclor, cephaloridine, or ceftazidime). Although specific quantities of "Compound X" and " $\beta$ -lactam antibiotic" are shown in the above illustrative  
35 examples, it is to be understood that the compounds can be present in any ratio provided the final formulation possesses the desired antibiotic properties.

          All publications, patents, and patent documents are incorporated by reference herein in their entirety. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood  
40 that many variations and modifications may be made while remaining within the spirit



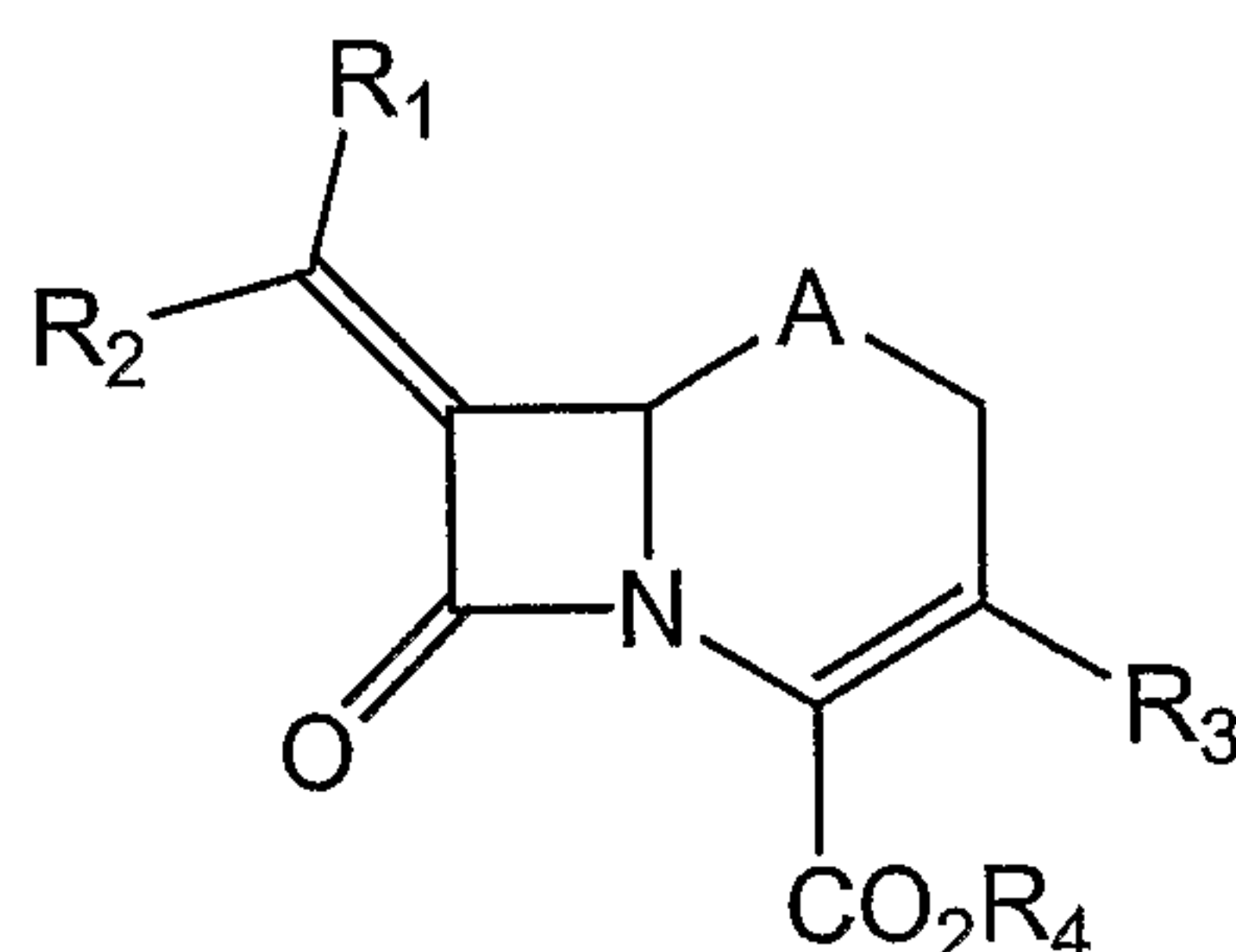
and scope of the invention.

## CLAIMS

What is claimed is:

1. A compound of formula (I):

5



(I)

wherein:

- 10  $R_1$  and  $R_2$  are each independently hydrogen,  $(C_1-C_{10})$ alkyl,  $(C_2-C_{10})$ alkenyl,  $(C_2-C_{10})$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_1-C_{10})$ alkoxy,  $(C_1-C_{10})$ alkanoyl,  $(C_1-C_{10})$ alkanoyloxy,  $(C_1-C_{10})$ alkoxycarbonyl, aryl, heterocycle, halo, cyano, nitro,  $-COOR_e$ ,  $-C(=O)NR_fR_g$ ,  $-OC(=O)NR_fR_g$ ,  $NR_fR_g$ , or  $-S(O)_nR_h$ ;

$R_3$  is hydrogen, halo, aryl, heteroaryl,  $-S(O)_nR_h$ , or  $-CH=CHC(=O)NR_mR_p$ ;

- 15  $R_4$  is hydrogen;

A is thio, sulfinyl, or sulfonyl;

each n is independently 0, 1, or 2;

each  $R_e$  is independently hydrogen, or  $(C_1-C_{10})$ alkyl;

- 20 each  $R_f$  and  $R_g$  is independently hydrogen,  $(C_1-C_{10})$ alkyl,  $(C_1-C_{10})$ alkoxy, phenyl, benzyl, phenethyl,  $(C_1-C_{10})$ alkanoyl, or  $-C(=O)NR_fR_g$  wherein  $R_f$  and  $R_g$  form a ring optionally containing a nitrogen atom in the ring  $-NR_e$ ;

each  $R_h$  is independently  $(C_1-C_{10})$ alkyl, or aryl; and

- 25  $R_m$  is hydrogen, and  $R_p$  is  $NH_2$ , OH,  $(C_2-C_{10})$ cycloalkyl, or  $-(C_2-C_{10})$ alkyl- $NH_2$ ; or  $R_m$  and  $R_p$  together with the nitrogen to which they are attached form a piperidine, morpholine, thiomorpholine, pyrrolidine, or piperazine ring, wherein



the piperazine is substituted at the 4-position with hydrogen or a (C<sub>1</sub>-C<sub>10</sub>)alkyl;

wherein any (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>2</sub>-C<sub>10</sub>)alkenyl, (C<sub>2</sub>-C<sub>10</sub>)alkynyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>10</sub>)alkoxy, (C<sub>1</sub>-C<sub>10</sub>)alkanoyl, (C<sub>1</sub>-C<sub>10</sub>)alkanoyloxy, or (C<sub>1</sub>-C<sub>10</sub>)alkoxycarbonyl of R<sub>1</sub> or R<sub>2</sub> is optionally substituted with one or more, substituents independently selected from halo, hydroxy, cyano, cyanato, nitro, mercapto, oxo, aryl, heterocycle, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, aryl(C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, halo(C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, heterocycle(C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, aryloxy, (heterocycle)oxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, -COOR<sub>e</sub>, -C(=O)NR<sub>f</sub>R<sub>g</sub>, -OC(=O)NR<sub>f</sub>R<sub>g</sub>, -NR<sub>h</sub>R<sub>i</sub>, or -S(O)<sub>n</sub>R<sub>k</sub>; and

wherein any aryl is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, trifluoromethyl, nitro, trifluoromethoxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, -COOR<sub>e</sub>, -C(=O)NR<sub>f</sub>R<sub>g</sub>, -OC(=O)NR<sub>f</sub>R<sub>g</sub>, NR<sub>h</sub>R<sub>i</sub>, or -S(O)<sub>n</sub>R<sub>k</sub>; or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein R<sub>1</sub> is aryl, heterocycle, or -COOR<sub>e</sub>.

3. The compound of claim 1 wherein R<sub>1</sub> is 2-pyridyl, or -COOR<sub>e</sub>.

4. The compound of claim 1 wherein R<sub>2</sub> is hydrogen.

5. The compound of claim 1 wherein R<sub>3</sub> is hydrogen.

6. The compound of claim 1 wherein R<sub>3</sub> is halo.

7. The compound of claim 1 wherein R<sub>3</sub> is fluoro.

8. The compound of claim 1 wherein R<sub>3</sub> is chloro.

9. The compound of claim 1 wherein R<sub>3</sub> is bromo.

10. The compound of claim 1 wherein  $R_3$  is iodo.

11. The compound of claim 1 wherein  $R_3$  is aryl.

12. The compound of claim 1 wherein  $R_3$  is phenyl

13. The compound of claim 1 wherein  $R_3$  is heteroaryl.

14. The compound of claim 1 wherein  $R_3$  is 2-thienyl.

15. The compound of claim 1 wherein  $R_3$  is  $S(O)_nR_h$ .

16. The compound of claim 1 wherein  $R_3$  is  $S(O)_2R_h$ .

17. The compound of claim 16 wherein  $R_h$  is methyl or phenyl.

18. The compound of claim 1 wherein  $R_3$  is  $SR_h$ .

19. The compound of claim 18 wherein  $R_h$  is methyl or phenyl.

20. The compound of claim 1 wherein  $R_3$  is hydrogen, halo, aryl, heteroaryl, or  $-S(O)_nR_h$ .

21. The compound of claim 1 wherein A is sulfonyl.

22. The compound of claim 1 wherein A is sulfonyl;  $R_1$  is 2-pyridyl, carboxy or *tert*-butoxy carbonyl;  $R_2$  is hydrogen; and  $R_3$  is hydrogen, fluoro, chloro, bromo, iodo, -SPh, -SO<sub>2</sub>Ph, -SMe, -SO<sub>2</sub>Me, or thiophene-2-yl; or a pharmaceutically acceptable salt.



23. A pharmaceutical composition comprising a compound of claim 1; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

24. The composition of claim 23 further comprising a  $\beta$ -lactam antibiotic.

5

25. The use of a compound of claim 1 for the manufacture of a medicament useful for inhibiting a  $\beta$ -lactamase in a mammal.

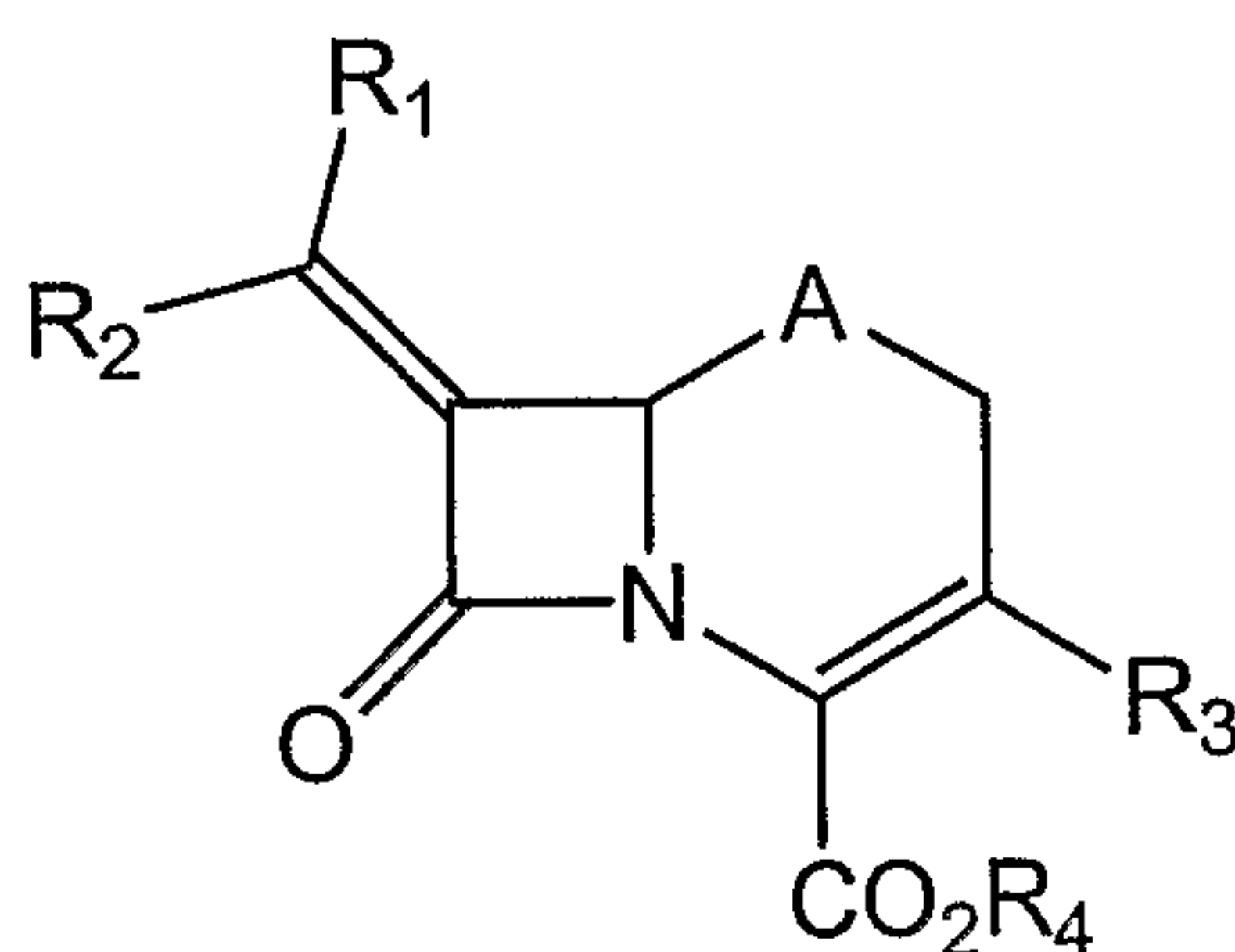
26. The use of a compound of claim 1 for the manufacture of a medicament useful for enhancing the activity of a  $\beta$ -lactam antibiotic in a mammal.

10

27. The use of a compound of claim 1 for the manufacture of a medicament useful for treating a  $\beta$ -lactam resistant bacterial infection in a mammal.

15 28. A compound of claim 1 for use in medical therapy.

29. A compound of formula (I):



(I)

20

wherein:

$R_1$  and  $R_2$  are each independently hydrogen,  $(C_1-C_{10})$ alkyl,  $(C_2-C_{10})$ alkenyl,  $(C_2-C_{10})$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_1-C_{10})$ alkoxy,  $(C_1-C_{10})$ alkanoyl,  $(C_1-C_{10})$ alkanoyloxy,  $(C_1-C_{10})$ alkoxycarbonyl, aryl, heteroaryl, heterocycle, halo, cyano, nitro,  $-COOR_e$ ,  $-C(=O)NR_fR_g$ ,  $-OC(=O)NR_fR_g$ ,  $NR_fR_g$ , or  $-S(O)_nR_h$ ;

5  $R_3$  is  $-Sn(R)_3$  wherein each  $R$  is  $(C_1-C_6)$ alkyl;

$R_4$  is hydrogen or a protecting group;

$A$  is thio, sulfinyl, or sulfonyl;

each  $n$  is independently 0, 1, or 2;

each  $R_e$  is independently hydrogen, or  $(C_1-C_{10})$ alkyl;

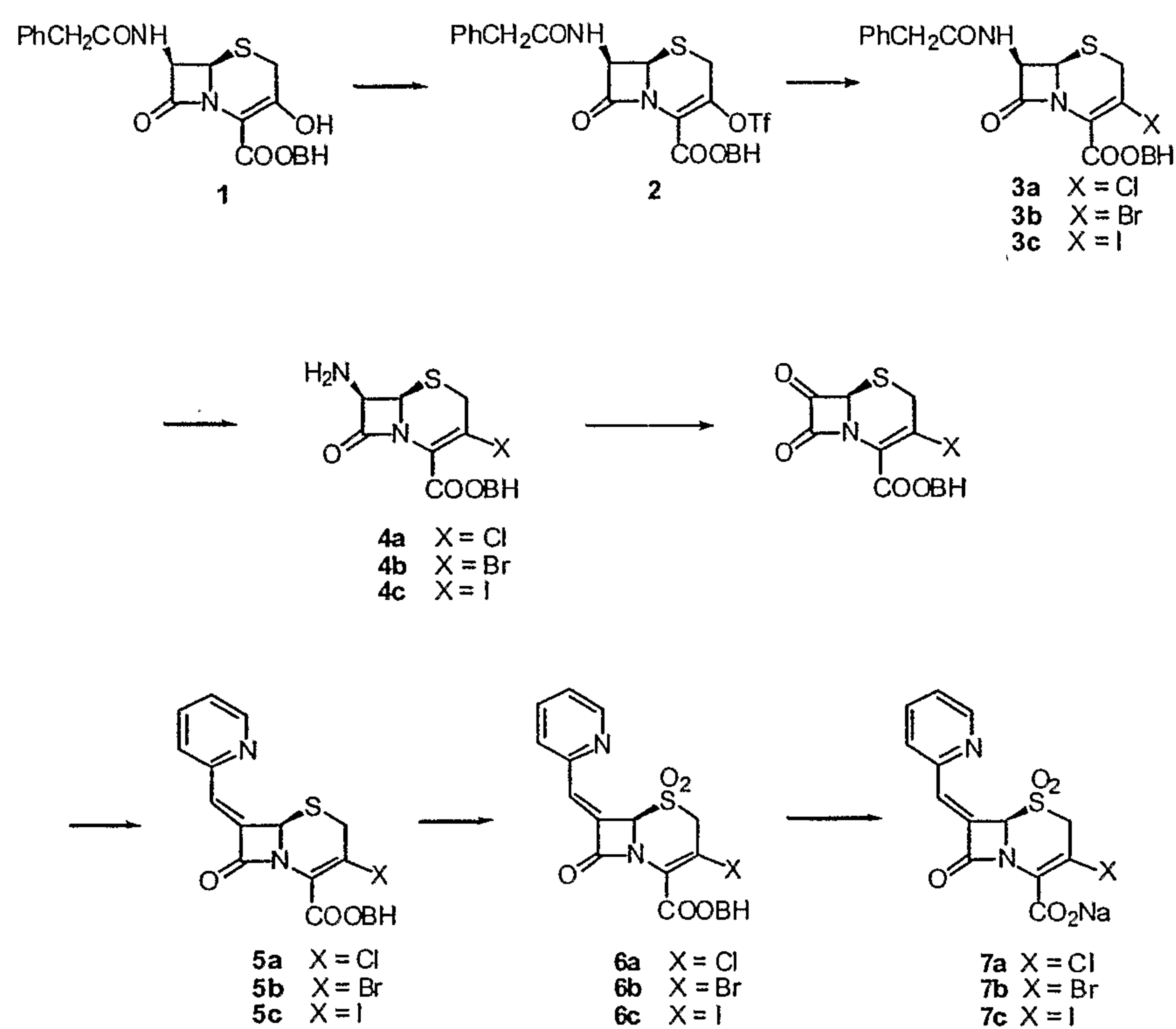
10 each  $R_f$  and  $R_g$  is independently hydrogen,  $(C_1-C_{10})$ alkyl,  $(C_1-C_{10})$ alkoxy, phenyl, benzyl, phenethyl,  $(C_1-C_{10})$ alkanoyl, or  $-C(=O)NR_fR_g$  wherein  $R_f$  and  $R_g$  form a ring optionally containing a nitrogen atom in the ring  $-NR_e$ ;

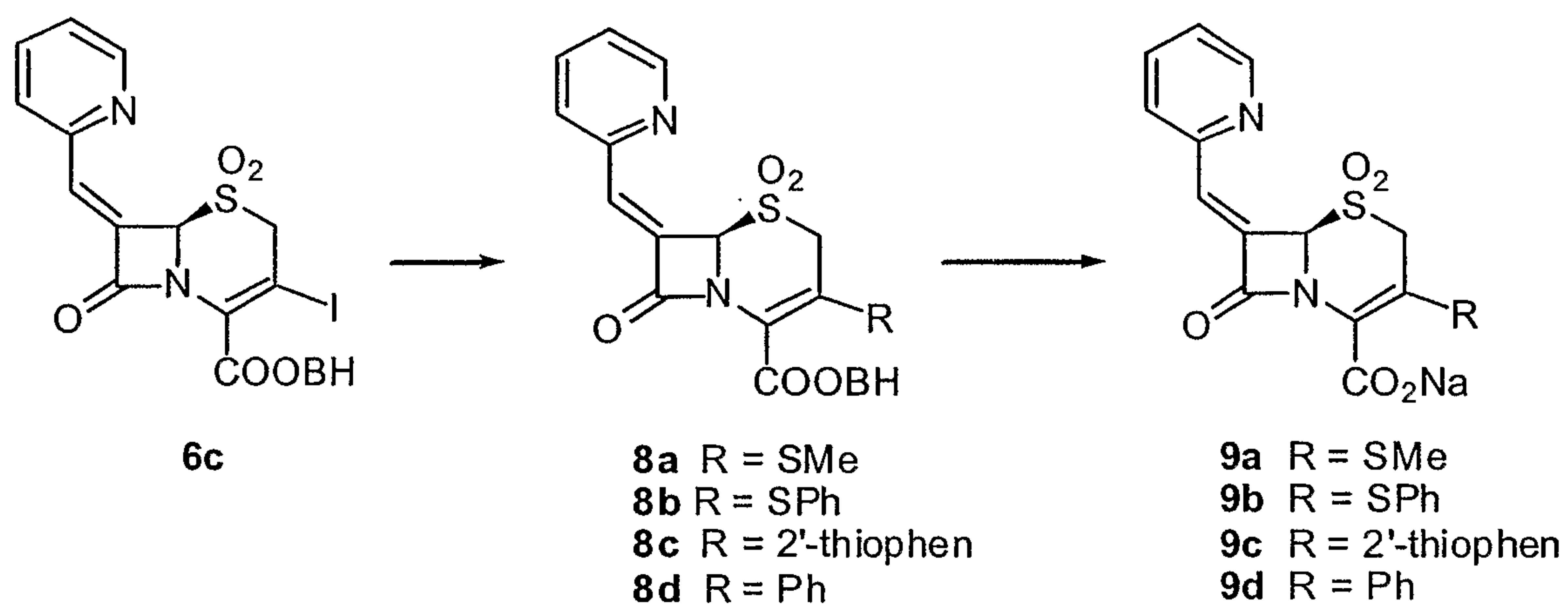
each  $R_h$  is independently  $(C_1-C_{10})$ alkyl, or aryl;

15 wherein any  $(C_1-C_{10})$ alkyl,  $(C_2-C_{10})$ alkenyl,  $(C_2-C_{10})$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_1-C_{10})$ alkoxy,  $(C_1-C_{10})$ alkanoyl,  $(C_1-C_{10})$ alkanoyloxy, or  $(C_1-C_{10})$ alkoxycarbonyl of  $R_1$  or  $R_2$  is optionally substituted with one or more, substituents independently selected from halo, hydroxy, cyano, cyanato, nitro, mercapto, oxo, aryl, heterocycle,  $(C_2-C_6)$ alkenyl,  $(C_2-C_6)$ alkynyl,  $(C_1-C_6)$ alkoxy,  $(C_1-C_6)$ alkanoyl,  $(C_1-C_6)$ alkanoyloxy, aryl $(C_1-C_6)$ alkanoyloxy, halo $(C_1-C_6)$ alkanoyloxy, heterocycle $(C_1-C_6)$ alkanoyloxy, aryloxy, (heterocycle)oxy,  $(C_3-C_8)$ cycloalkyl,  $-COOR_e$ ,  $-C(=O)NR_fR_g$ ,  $-OC(=O)NR_fR_g$ ,  $-NR_hR_i$ , or  $-S(O)_nR_k$ ; and

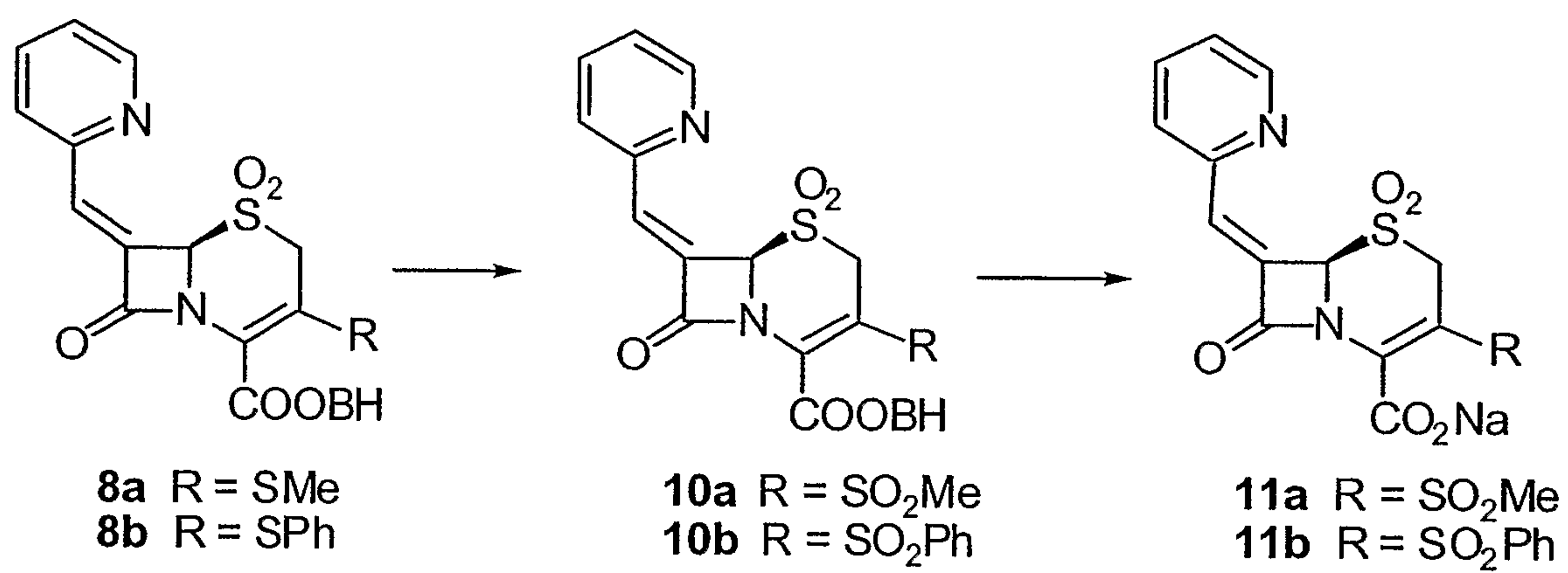
20 wherein any aryl is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, trifluoromethyl, nitro, trifluoromethoxy,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkanoyl,  $(C_1-C_6)$ alkanoyloxy,  $(C_1-C_6)$ alkoxycarbonyl,  $-COOR_e$ ,  $-C(=O)NR_fR_g$ ,  $-OC(=O)NR_fR_g$ ,  $NR_hR_i$ , or  $-S(O)_nR_k$ ;



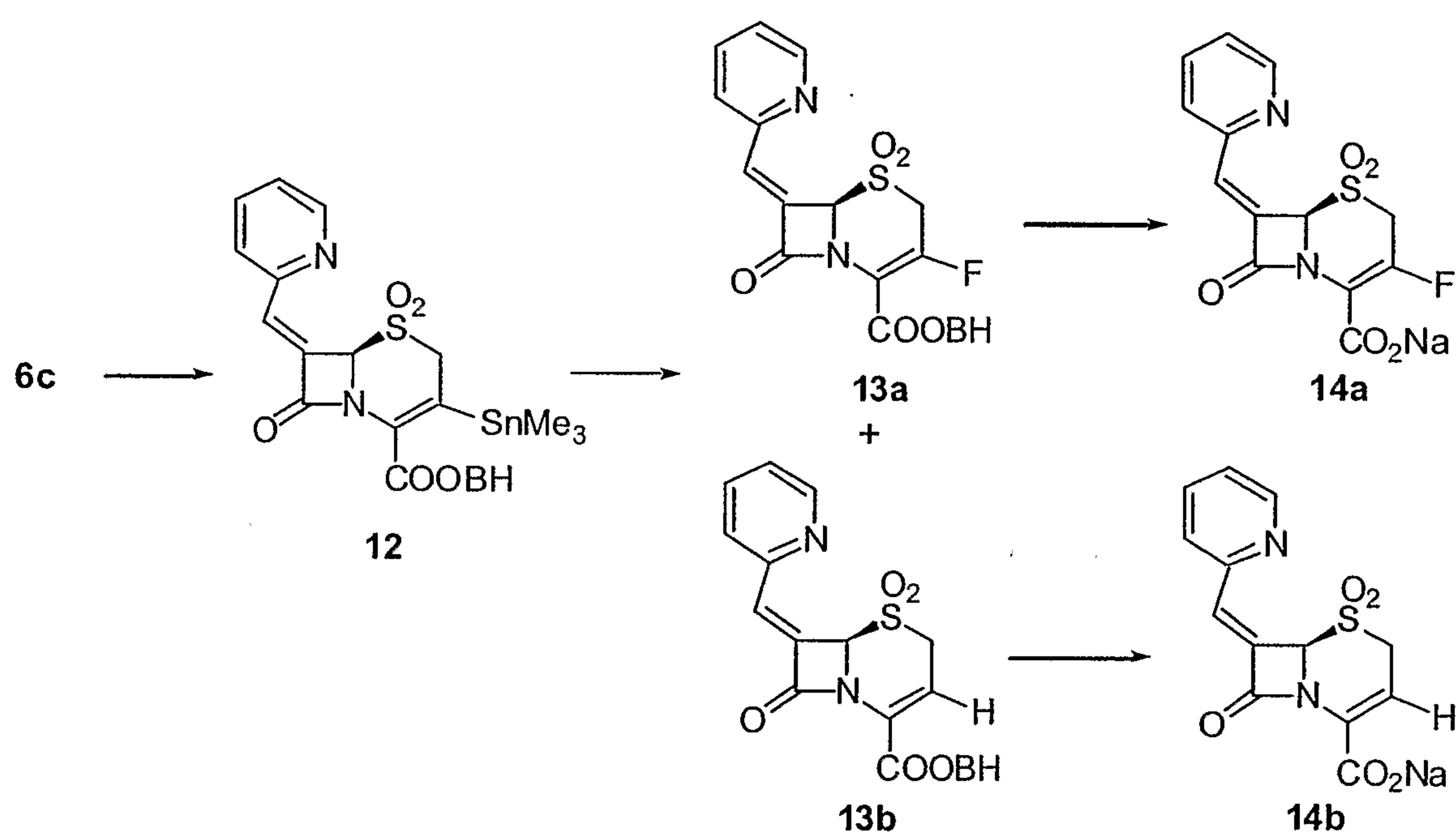
**Figure 1**

**Figure 2**



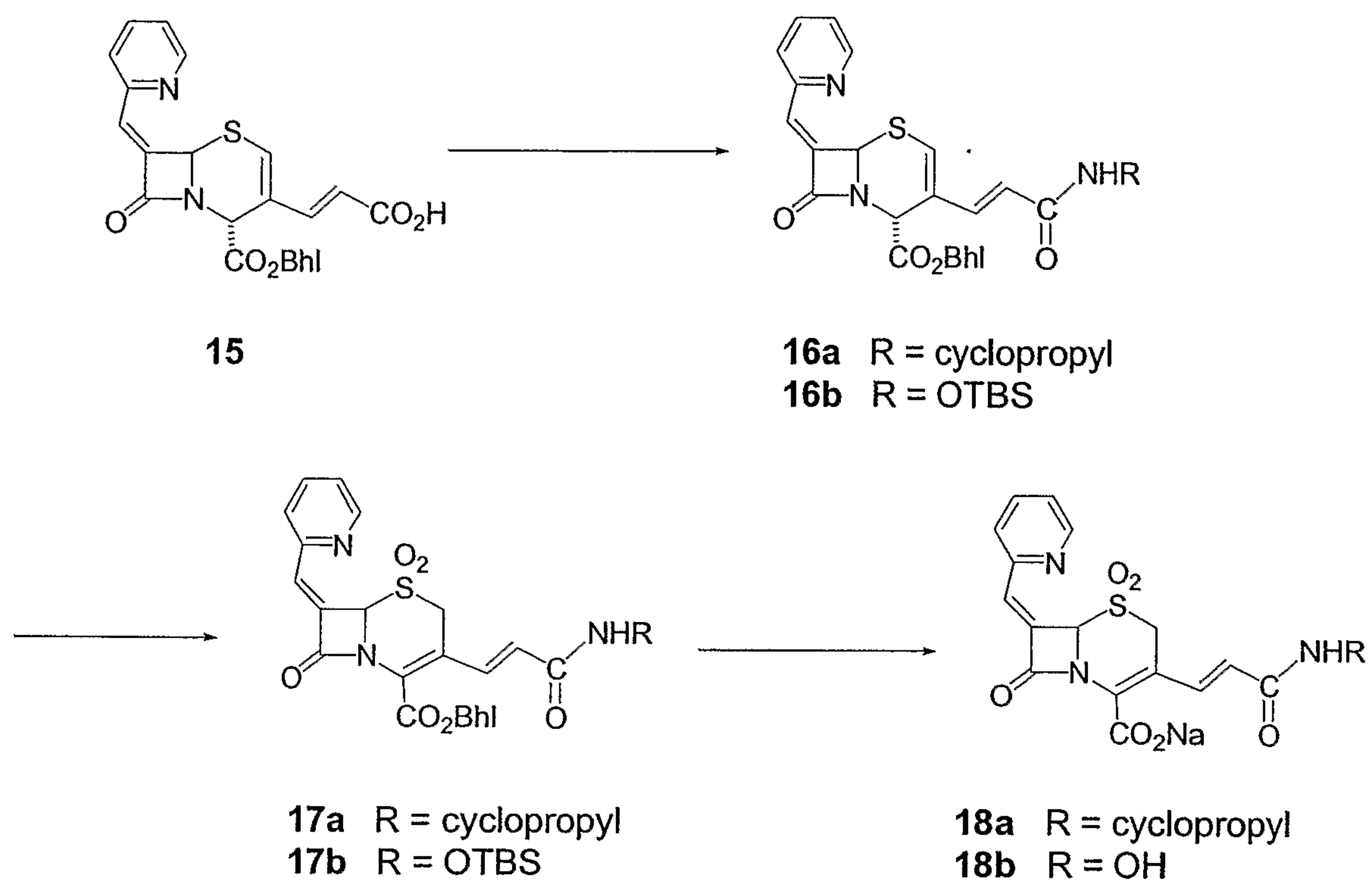
**Figure 3**

## Figure 4





## Figure 5



**Figure 6**