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(72) DININNO, FRANK P., US

(72) DYKSTRA, KEVIN D., US

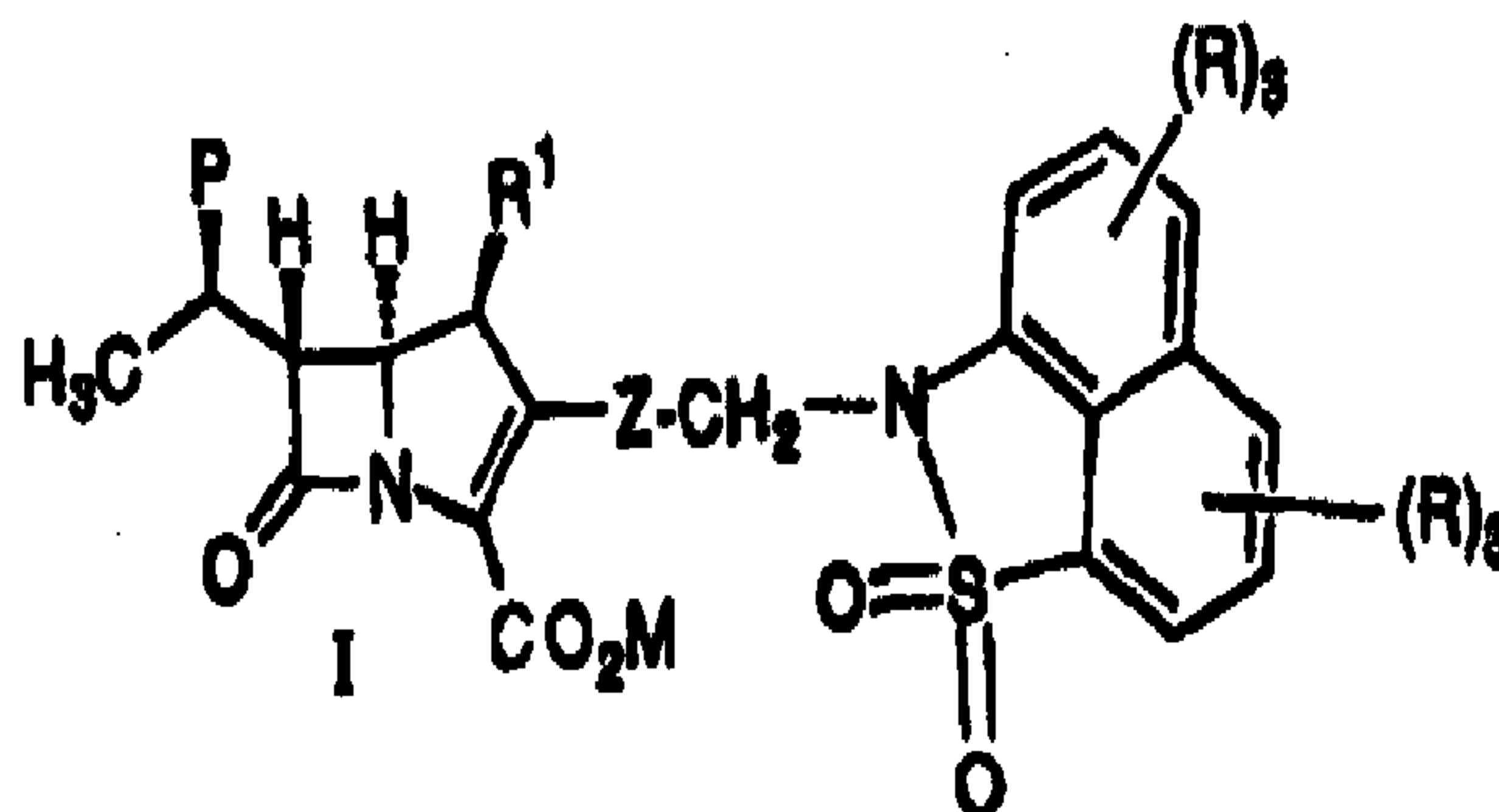
(71) MERCK & CO., INC., US

(51) Int.Cl.⁷ C07D 487/04, A61K 31/395

(30) 1997/10/02 (60/060,867) US

(54) **COMPOSES ANTIBACTERIENS DE CARBAPENEM,
COMPOSITIONS CONTENANT CES COMPOSES ET
PROCEDES DE TRAITEMENT**

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



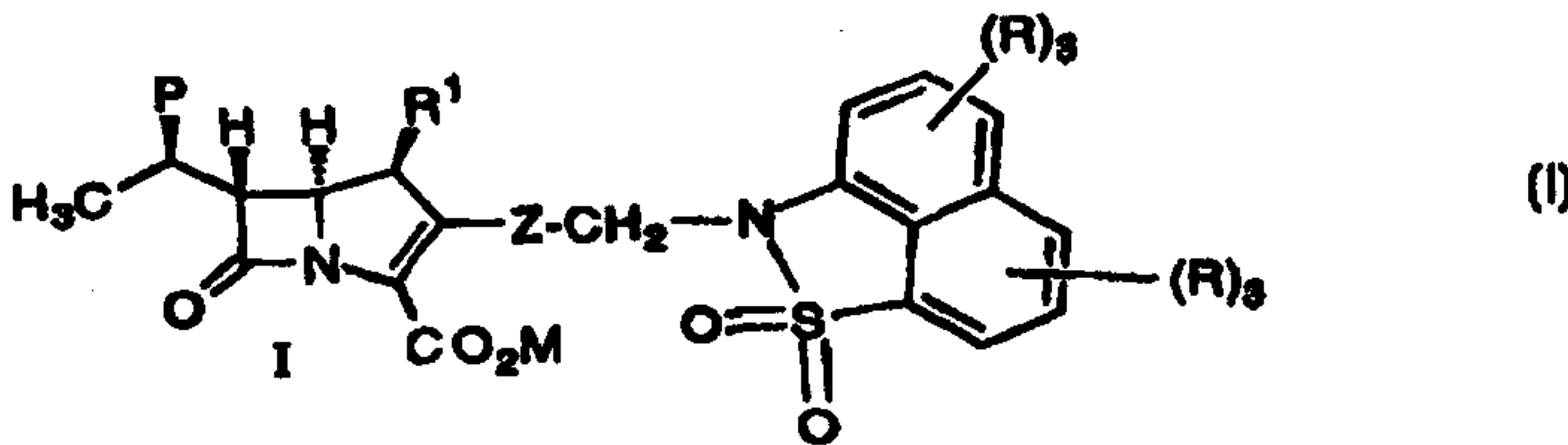
(I)

(57) La présente invention porte sur des agents antibactériens de carbapenem dans lesquels le noyau de carbapenem est substitué en position 2 par un naphtosultan lié par un groupe $-Z-CH_2$. Le naphtosultan est également substitué par divers groupes substituants comprenant des groupes cationiques. Les composés de cette invention sont représentés par la formule (I). L'invention porte également sur des compositions pharmaceutiques et sur leurs procédés d'utilisation.

(57) The present invention relates to carbapenem antibacterial agents in which the carbapenem nucleus is substituted at the 2-position with a naphthosultam linked through a $-Z-CH_2$ group. The naphthosultam is further substituted with various substituent groups including cationic groups. The compounds are represented by formula (I). Pharmaceutical compositions and methods of use are also included.

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(21) International Application Number: PCT/US98/20259 (22) International Filing Date: 28 September 1998 (28.09.98) (30) Priority Data: 60/060,867 2 October 1997 (02.10.97) US (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DININNO, Frank, P. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). DYKSTRA, Kevin, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: CARBAPENEM ANTIBACTERIAL COMPOUNDS, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT 		
(57) Abstract The present invention relates to carbapenem antibacterial agents in which the carbapenem nucleus is substituted at the 2-position with a naphthosultam linked through a -Z-CH₂ group. The naphthosultam is further substituted with various substituent groups including cationic groups. The compounds are represented by formula (I). Pharmaceutical compositions and methods of use are also included.		

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TITLE OF THE INVENTION

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

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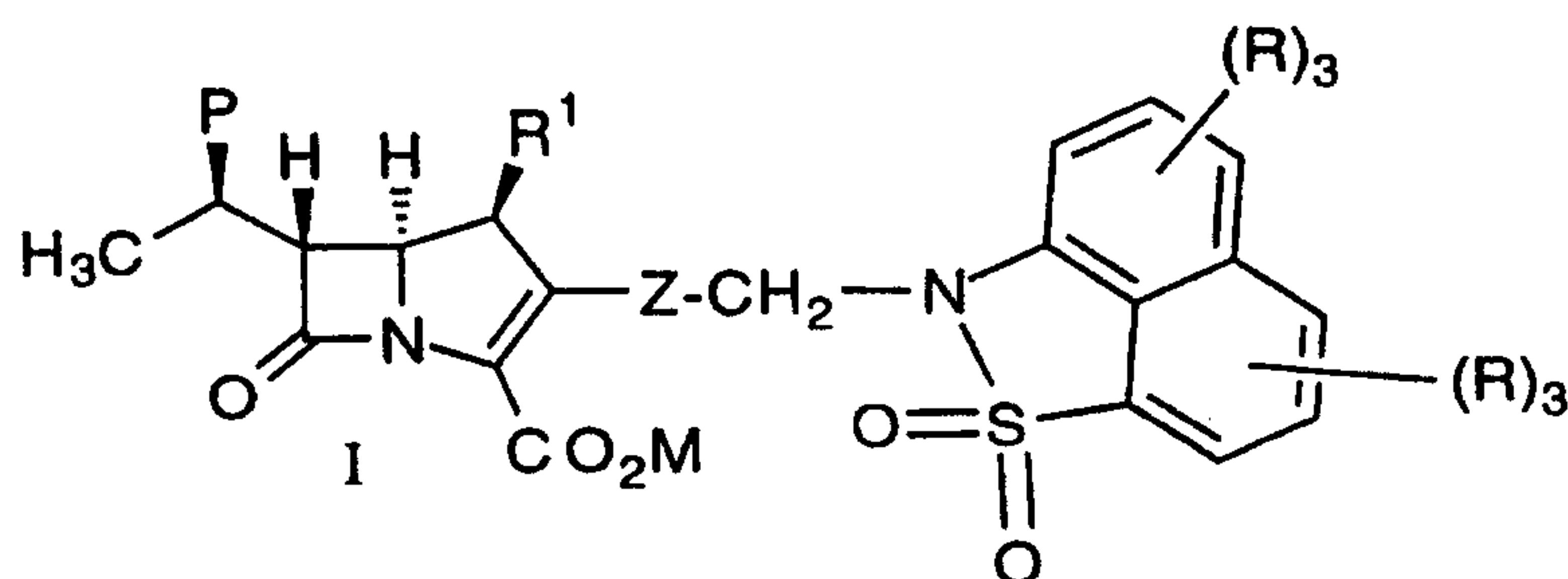
BACKGROUND OF THE INVENTION

The present invention relates to carbapenem
antibacterial agents in which the carbapenem nucleus is substituted
at the 2-position with a naphthosultam linked through a group
10 -Z-CH₂-. Z represents an *trans*-ethenediyl or ethynediyl group. The
naphthosultam is further substituted with various substituent groups
including at least one cationic group.

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

SUMMARY OF THE INVENTION

25 The invention includes a compound represented by
formula I:



30 as well as pharmaceutically acceptable salts thereof, wherein:

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R^1 represents H or methyl;

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

Z represents *trans*-ethenediyl or ethynediyl;

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

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

20

each R^a , R^b and R^c independently represents hydrogen, $-C_{1-6}$ straight- or branched-chain alkyl, unsubstituted or substituted with one to four R^d groups, or $-C_{3-7}$ cycloalkyl, unsubstituted or substituted with one to four R^d groups;

25

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

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

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each R^d independently represents halo; -CN; -NO₂; -NR^eR^f; -OR^g; -SR^g; -CONR^eR^f; -COOR^g; -SOR^g; -SO₂R^g; -SO₂NR^eR^f; -NR^eSO₂R^f; -COR^e; -NR^eCOR^f; -OCOR^e; -OCONR^eR^f; -NR^eCONR^fR^g; -NR^eCO₂R^h; -OCO₂R^h; -C(NR^e)NR^fR^g; -NR^eC(NH)NR^fR^g; -NR^eC(NR^f)R^g or -Q;

R^e , R^f and R^g represent hydrogen or -C₁₋₆ straight- or branched-chain alkyl unsubstituted or substituted with one to four R^i groups;

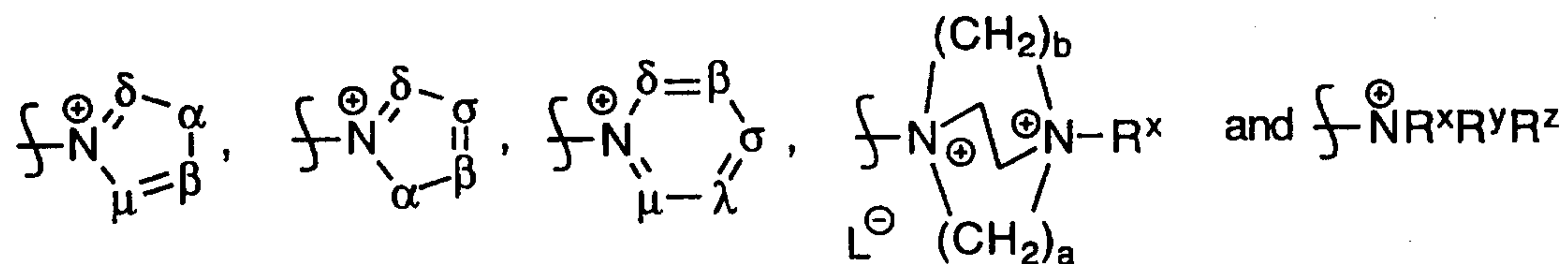
or R^e and R^f taken together with any intervening atoms represent a 4-6 membered saturated ring optionally interrupted by one to three of O, S, -C(O)- or NR^g with R^g as defined above, said ring being unsubstituted or substituted with one to four R^i groups;

each R^i independently represents halo; -CN; -NO₂; phenyl; -NHSO₂R^h; -OR^h; -SR^h; -N(R^h)₂; -N⁺(R^h)₃; -C(O)N(R^h)₂; -SO₂N(R^h)₂; heteroaryl; heteroarylium; -CO₂R^h; -C(O)R^h; -OCOR^h; -NHCOR^h; guanidiny; carbamimidoyl or ureido;

each R^h independently represents hydrogen, a -C₁₋₆ straight or branched-chain alkyl group, a -C₃₋₆ cycloalkyl group or phenyl, or when two R^h groups are present, said R^h groups may be taken in combination and represent a 4-6 membered saturated ring, optionally interrupted by one or two of O, S, SO₂, -C(O)-, NH and NCH₃;

25

Q is selected from the group consisting of:



wherein:

a and b are 1, 2 or 3;

L⁻ is a pharmaceutically acceptable counterion;

α represents O, S or NR^s;

30

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β , δ , λ , μ and σ represent CR^t , N or N^+R^s , provided that no more than one of β , δ , λ , μ and σ is N^+R^s which is balanced by L^- as defined above;

5 each R^s independently represents hydrogen; phenyl or $-\text{C}_{1-6}$ straight- or branched-chain alkyl, unsubstituted or substituted with one to four R^i groups;

10 each R^t independently represents hydrogen; halo; phenyl; $-\text{CN}$; $-\text{NO}_2$; $-\text{NR}^u\text{R}^v$; $-\text{OR}^u$; $-\text{SR}^u$; $-\text{CONR}^u\text{R}^v$; $-\text{COOR}^h$; $-\text{SOR}^u$; $-\text{SO}_2\text{R}^u$; $-\text{SO}_2\text{NR}^u\text{R}^v$; $-\text{NR}^u\text{SO}_2\text{R}^v$; $-\text{COR}^u$; $-\text{NR}^u\text{COR}^v$; $-\text{OCOR}^u$; $-\text{OCONR}^u\text{R}^v$; $-\text{NR}^u\text{CO}_2\text{R}^v$; $-\text{NR}^u\text{CONR}^v\text{R}^w$; $-\text{OCO}_2\text{R}^v$; $-\text{C}_{1-6}$ straight- or branched-chain alkyl, unsubstituted or substituted with one to four R^i groups;

15 R^u and R^v represent hydrogen or $-\text{C}_{1-6}$ straight- or branched-chain alkyl, unsubstituted or substituted with one to four R^i groups;

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

25 each R^w independently represents hydrogen; $-\text{C}_{1-6}$ straight- or branched-chain alkyl, unsubstituted or substituted with one to four R^i groups; C_{3-6} cycloalkyl optionally substituted with one to four R^i groups; phenyl optionally substituted with one to four R^i groups, or heteroaryl optionally substituted with 1-4 R^i groups;

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

R^x represents hydrogen or a C_{1-8} straight- or branched-chain alkyl, optionally interrupted by one or two of O, S, SO, SO_2 , NR^w , $\text{N}^+\text{R}^h\text{R}^w$, or $-\text{C}(\text{O})-$, said chain being unsubstituted or substituted

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

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

or R^x and R^y together with any intervening atoms represent a 4-6 membered saturated ring optionally interrupted by O, S, SO₂,
 15 NR^w, N⁺R^hR^w or -C(O)-, unsubstituted or substituted with 1 - 4 Rⁱ groups,

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

Pharmaceutical compositions and methods of treatment are also included herein.

25

DETAILED DESCRIPTION OF THE INVENTION

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

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

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 10 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred alkyl groups include methyl, ethyl, propyl,

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isopropyl, butyl, t-butyl, cyclopentyl and cyclohexyl. When substituted, alkyl groups may be substituted with up to four substituent groups, selected from R^d and R^i , as defined, at any available point of attachment. When the alkyl group is said to be substituted with an alkyl group, this is interchangeable with

5 "branched alkyl group".
Cycloalkyl is a specie of alkyl containing from 3 to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings which are
10 fused.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl.
15 Ethenediyl refers to the moiety $-\text{CH}_2=\text{CH}_2-$, in the cis or trans configuration, as well as mixtures thereof.

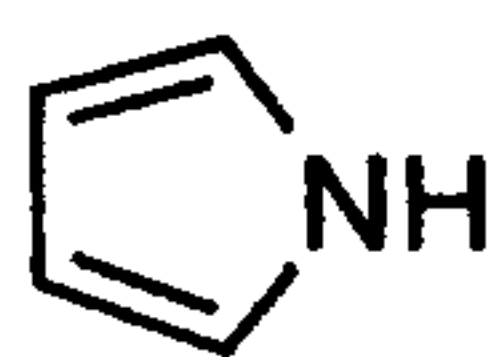
The term "alkynyl" refers to a hydrocarbon radical straight or branched, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Preferred alkynyl groups
20 include ethynyl, propynyl and butynyl. Ethynediyl refers to $-\text{C}\equiv\text{C}-$.

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

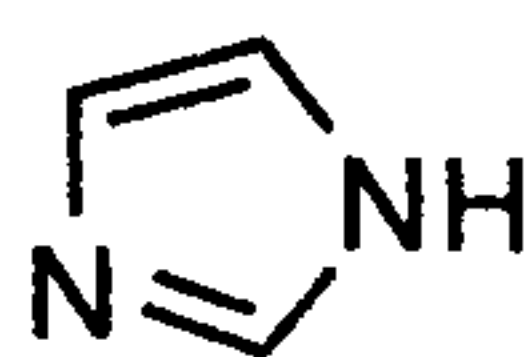
30 The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment,

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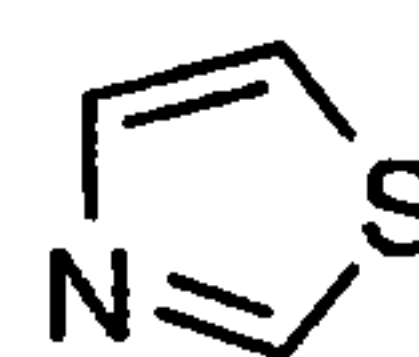
and in which one or two additional carbon atoms is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms, said heteroaryl group being optionally substituted as described herein. Examples of this type are pyrrole, pyridine, oxazole, thiazole and oxazine. Additional nitrogen atoms may be present together with the first nitrogen and oxygen or sulfur, giving, e.g., thiadiazole. Examples include the following:



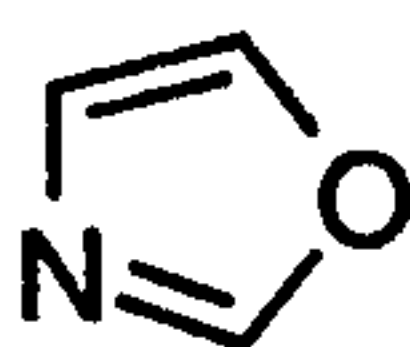
pyrrole (pyrrolyl)



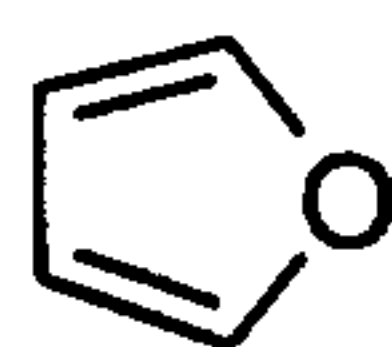
imidazole (imidazolyl)



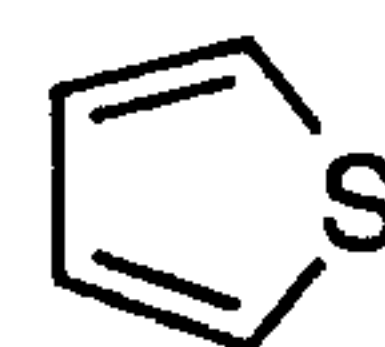
thiazole (thiazolyl)



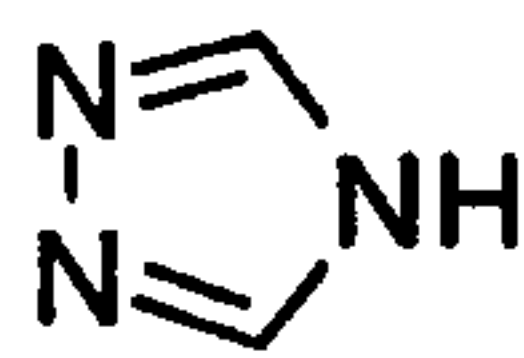
oxazole (oxazolyl)



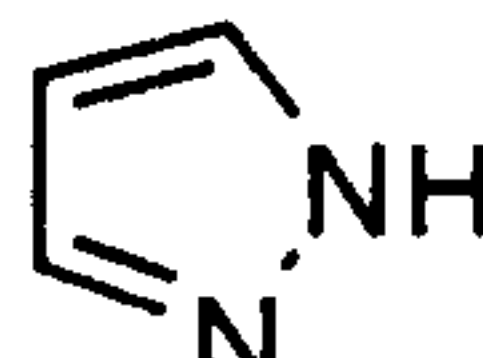
furan (furyl)



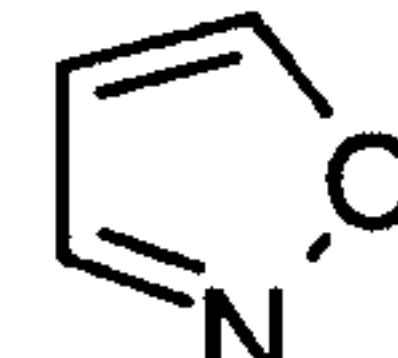
thiophene (thienyl)



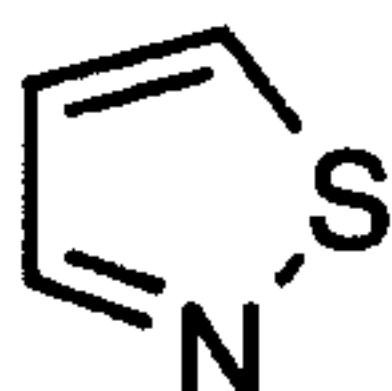
triazole (triazolyl)



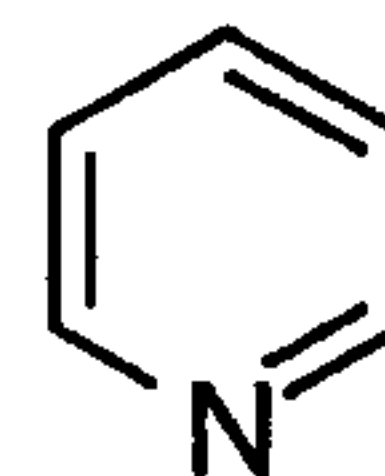
pyrazole (pyrazolyl)



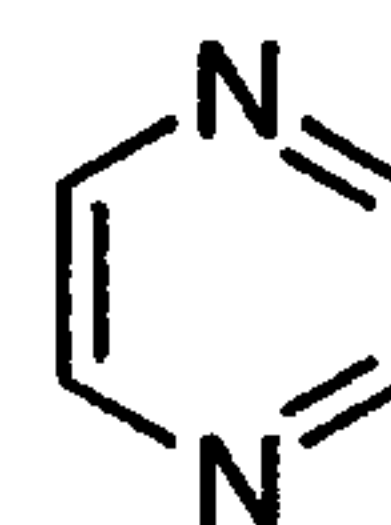
isoxazole (isoxazolyl)



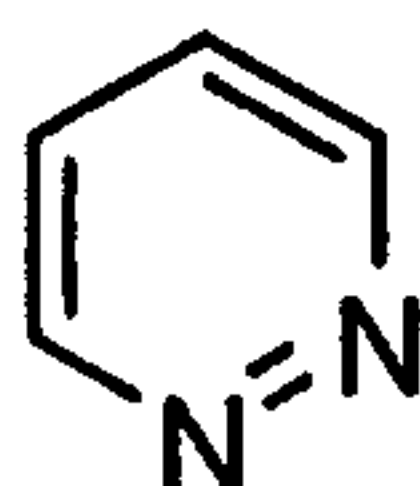
isothiazole (isothiazolyl)



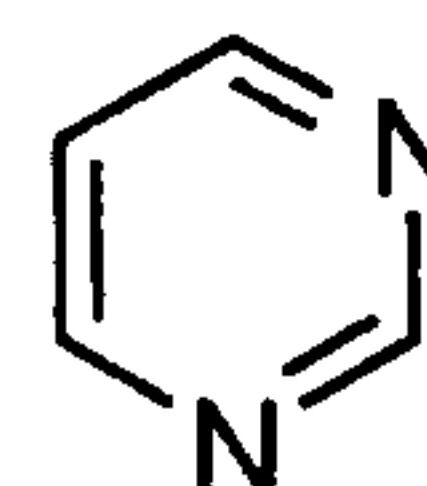
pyridine (pyridinyl)



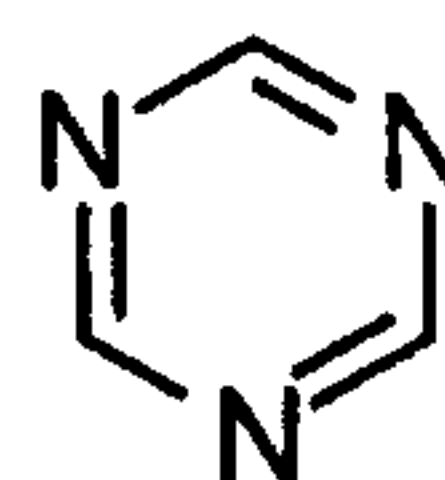
pyrazine (pyrazinyl)



pyridazine (pyridazinyl)



pyrimidine (pyrimidinyl)

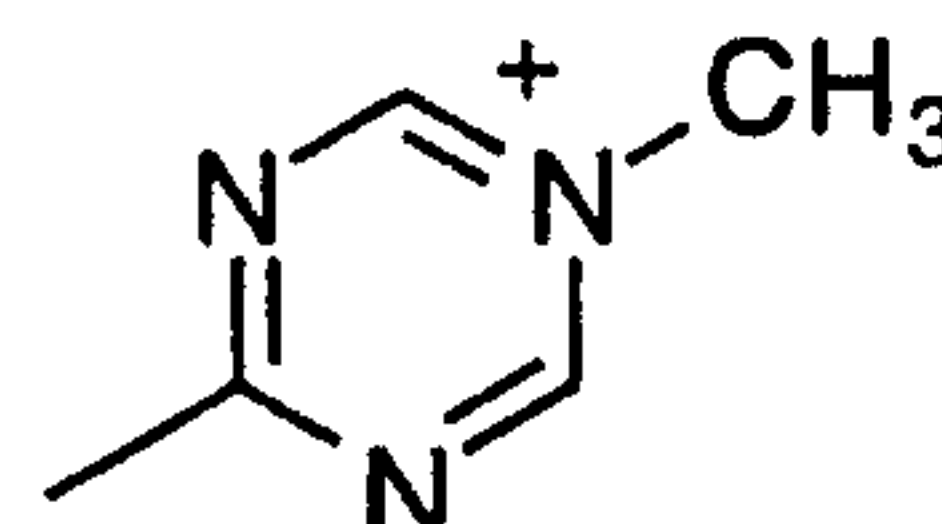
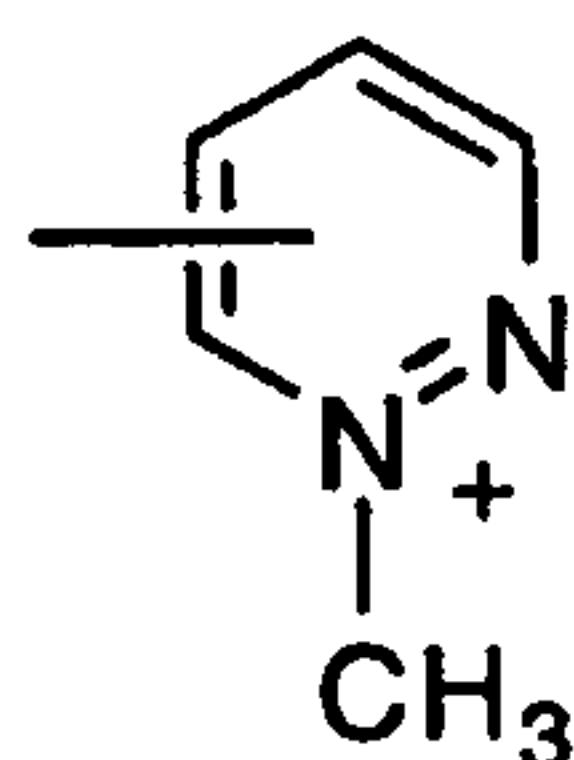
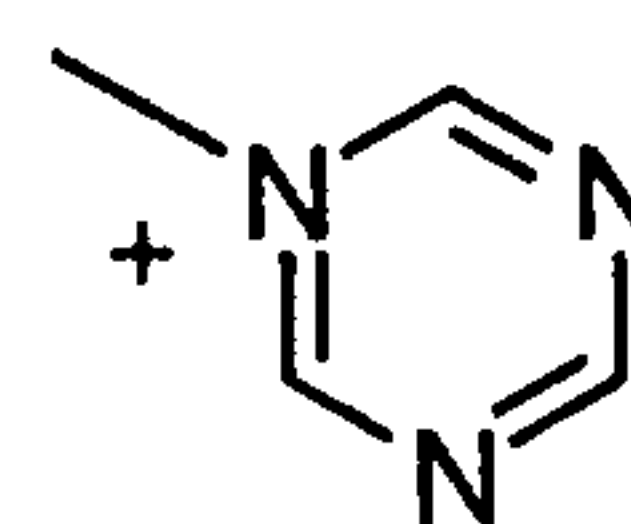
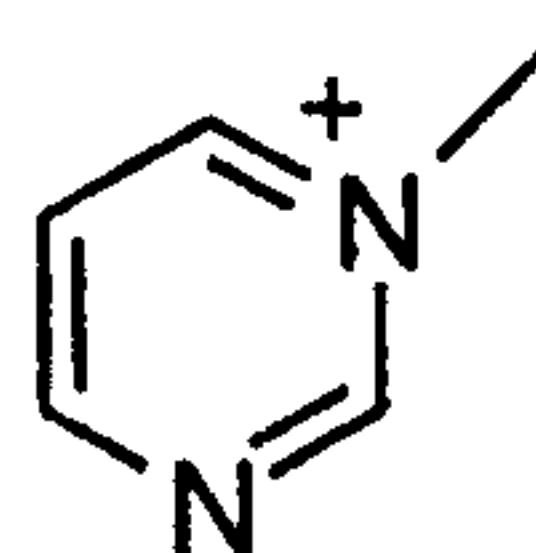
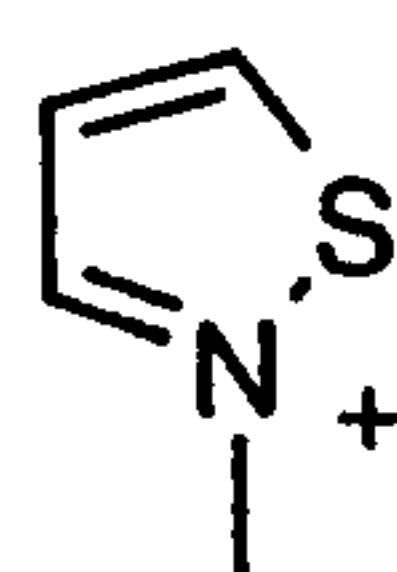
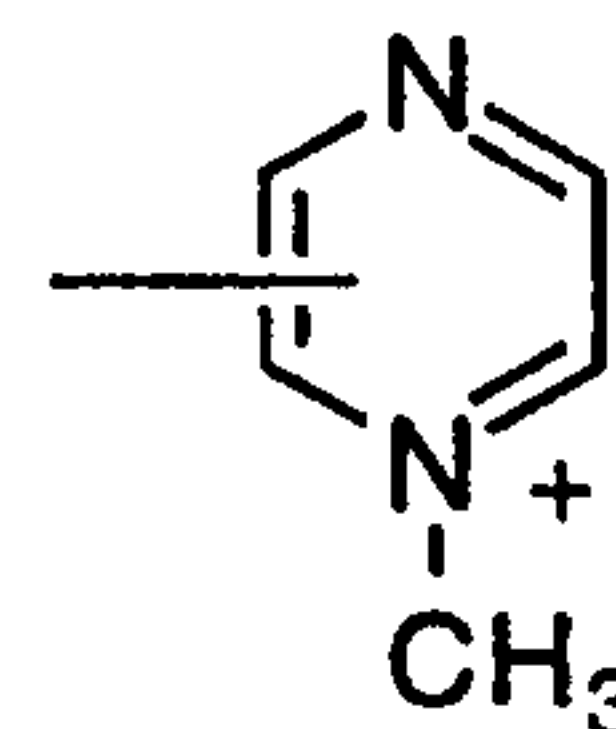
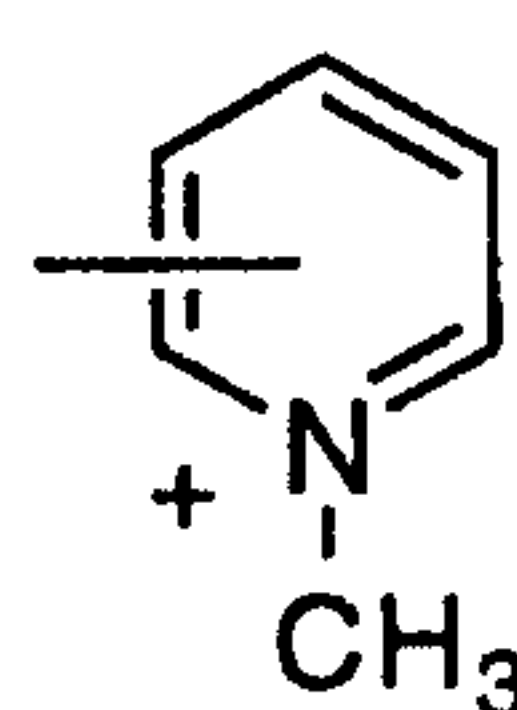
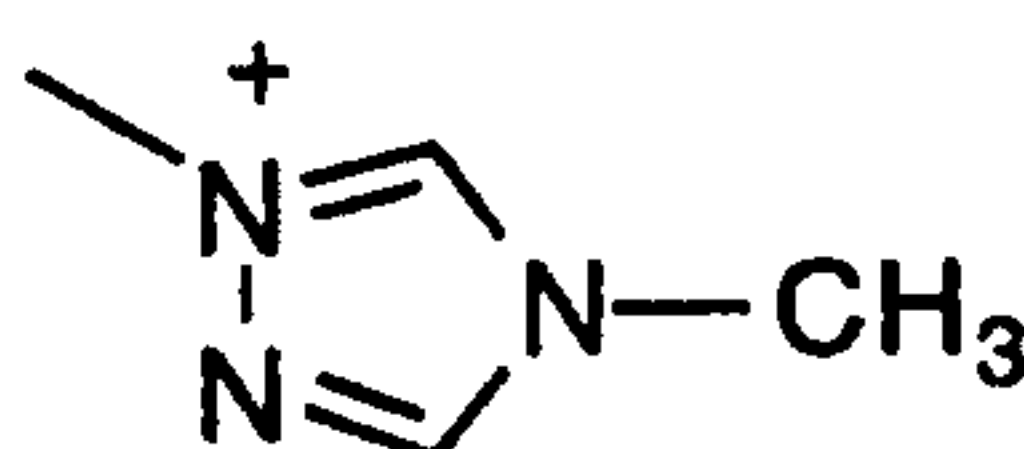
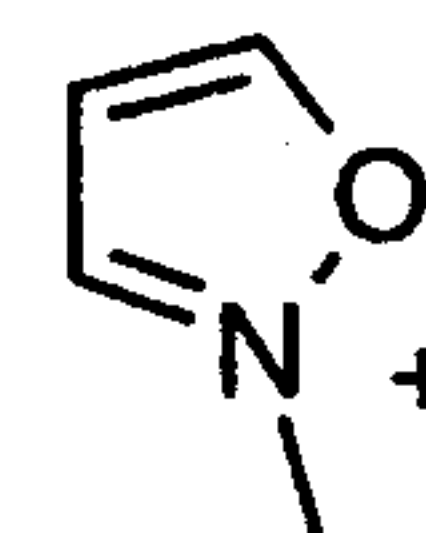
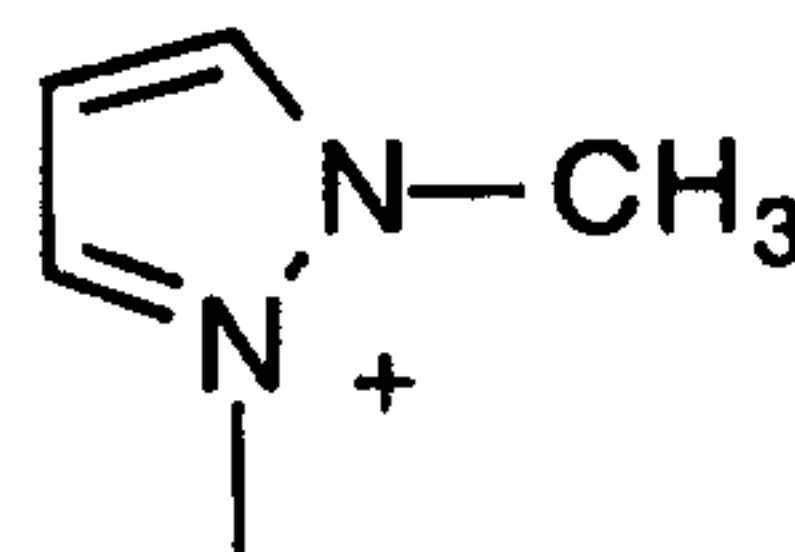
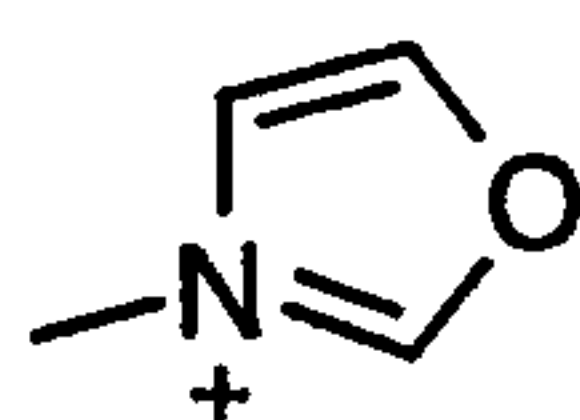
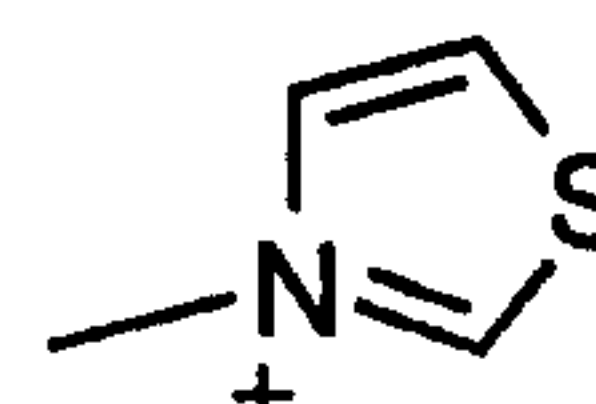
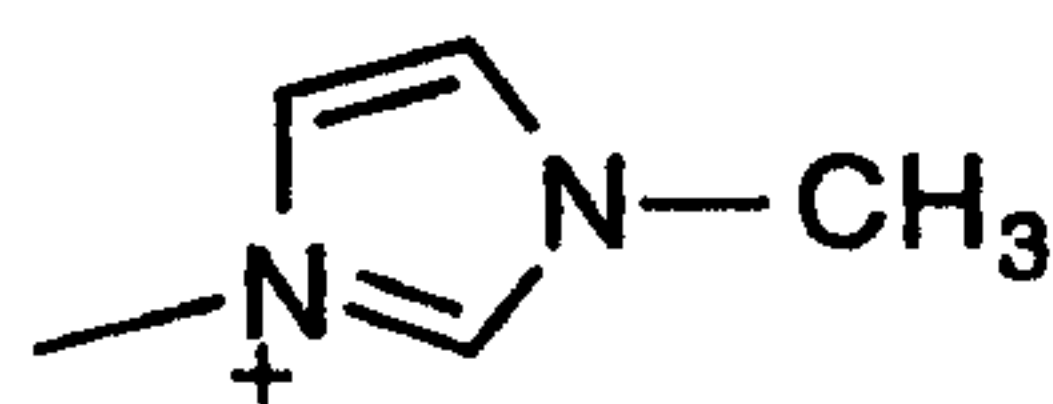
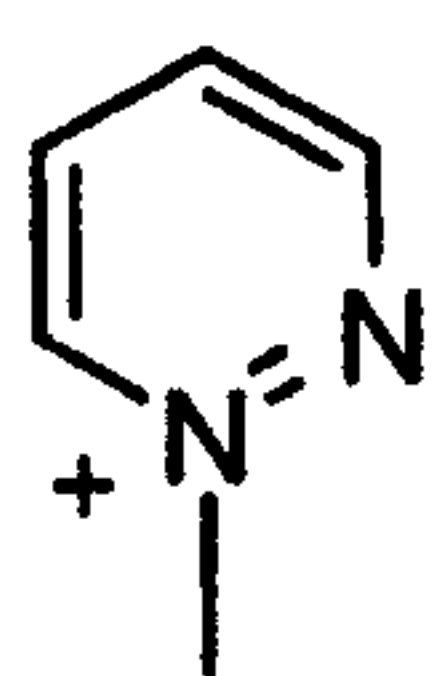


triazine (triazinyl)

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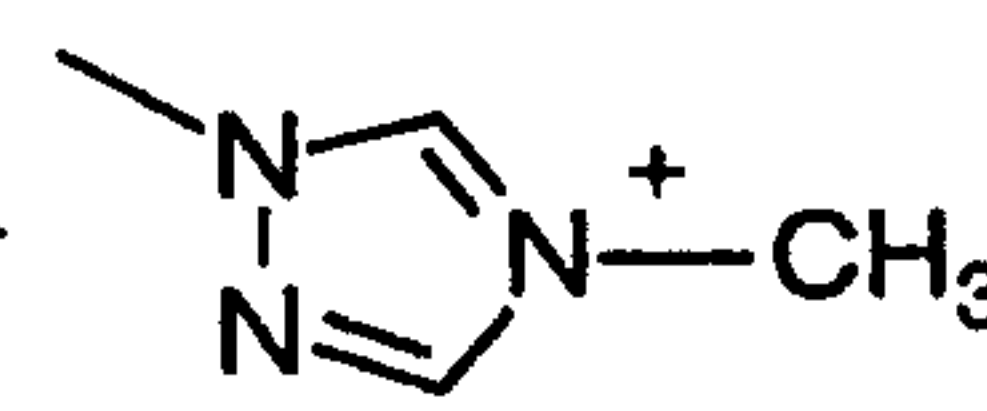
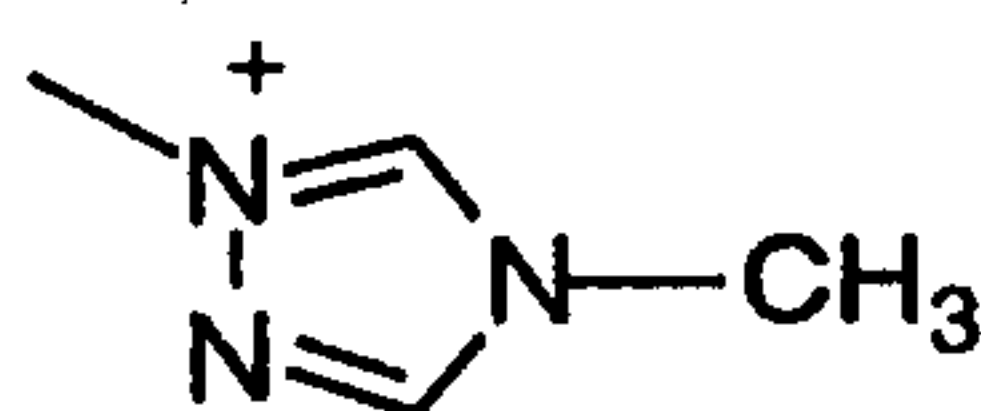
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Heteroarylium refers to heteroaryl groups bearing a quaternary nitrogen atom and thus a positive charge. Examples include the following:



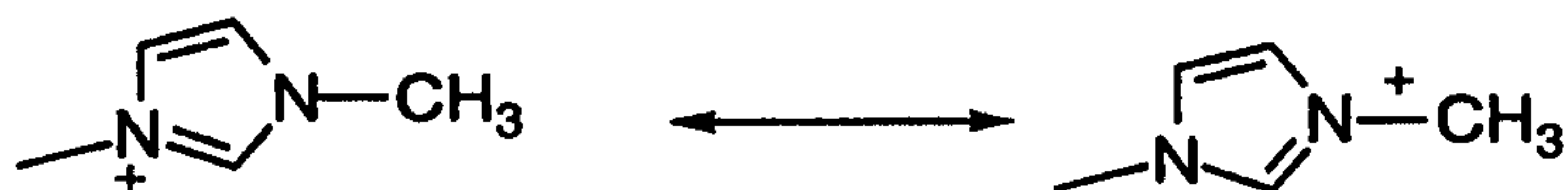
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When a charge is shown on a particular nitrogen atom in a ring which contains one or more additional nitrogen atoms, it is understood that the charge may reside on a different nitrogen atom in the ring by virtue of charge resonance that occurs.



and

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

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

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

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

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

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

When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art,

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and with reference to standard textbooks, such as Greene, T. W. et al. Protective Groups in Organic Synthesis Wiley, New York (1991). Examples of suitable protecting groups are contained throughout the specification.

5 When an alkyl group is "interrupted by" 1 or more moieties, such as O, S, N, -C(O)- and the like, this includes alkyl groups which are terminated by the moiety or moieties, as well as alkyl groups that are interrupted or terminated by combinations of such groups. Thus for example, -C(O)O-, -OC(O)-, -C(O)NR⁸- and
10 similar such moieties are included. Examples of alkyl groups terminated by the moiety or moieties are as follows: -O-C₁₋₆ alkyl, -C₁₋₆ alkyl-O-, -C₁₋₆ alkyl-OC(O)-, -O-C₁₋₆ alkyl-S- and the like. Obviously other moieties are included in accordance with the general description contained herein.

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

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

 Examples of suitable C-6 hydroxyethyl protecting groups include triethylsilyl, t-butyldimethylsilyl, o-nitrobenzyloxycarbonyl,

- 11 -

p-nitrobenzyloxycarbonyl, benzyloxycarbonyl, allyloxycarbonyl, t-butyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl and the like.

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

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

- 12 -

triethylhydroammonium, meglumine, triethanolhydroammonium, etc.

The pharmaceutically acceptable salts referred to above also include acid addition salts. Thus, the Formula I compounds can be used in the form of salts derived from inorganic or organic acids. Included among such salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate.

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

Biolabile esters are biologically hydrolyzable, and may be suitable for oral administration, due to good absorption through the stomach or intestinal mucosa, resistance to gastric acid degradation and other factors. Examples of biolabile esters include compounds in which M represents an alkoxyalkyl, alkylcarbonyloxyalkyl, alkoxycarbonyloxyalkyl, cycloalkoxyalkyl, alkenyloxyalkyl, aryloxyalkyl, alkoxyaryl, alkylthioalkyl, cycloalkylthioalkyl, alkenylthioalkyl, arylthioalkyl or alkylthioaryl group. These groups can be substituted in the alkyl or aryl portions thereof with acyl or halo groups. The following M species are examples of biolabile ester forming moieties.: acetoxymethyl,

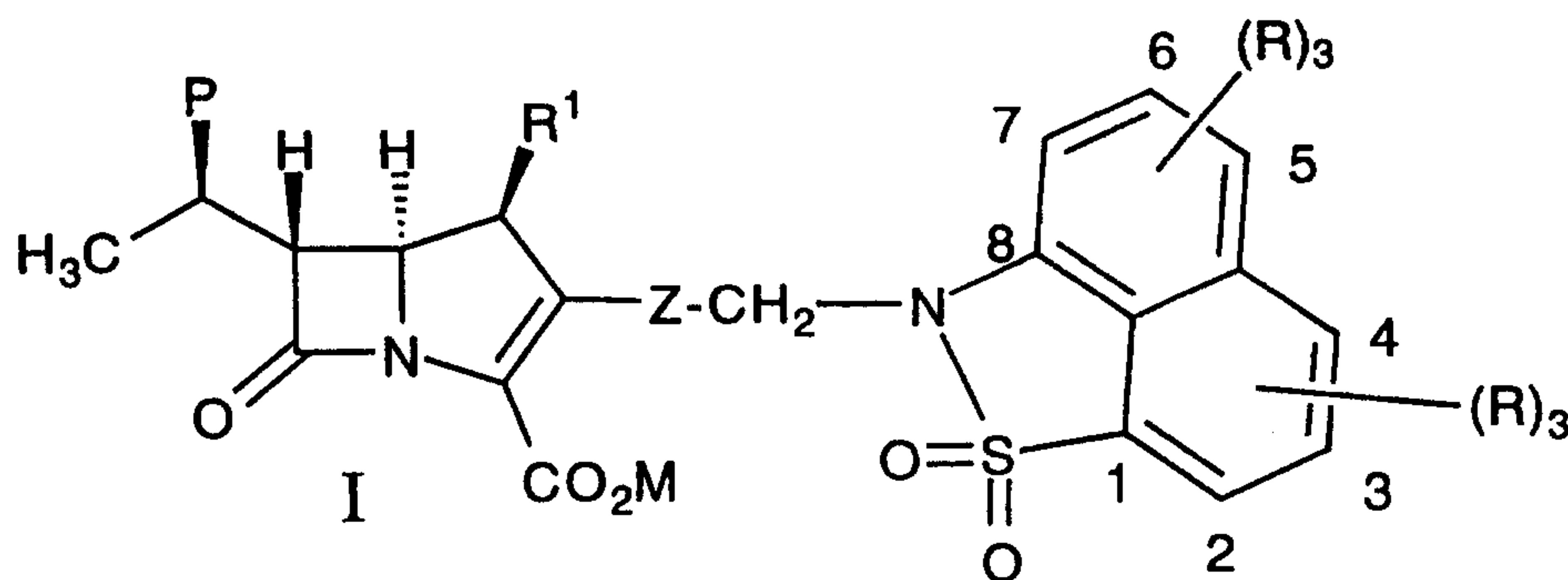
- 13 -

1-acetoxyethyl, 1-acetoxypropyl, pivaloyloxymethyl, 1-isopropylloxycarbonyloxyethyl, 1-cyclohexylloxycarbonyloxyethyl, phthalidyl and (2-oxo-5-methyl-1,3-dioxolen-4-yl)methyl.

L⁻ can be present or absent as necessary to maintain the appropriate charge balance. When present, L⁻ represents a pharmaceutically acceptable counterion. Most anions derived from inorganic or organic acids are suitable. Representative examples of such counterions are the following: acetate, adipate, aminosalicylate, anhydromethylenecitrate, ascorbate, aspartate, benzoate, benzenesulfonate, bromide, citrate, camphorate, camphorsulfonate, chloride, estolate, ethanesulfonate, fumarate, glucoheptanoate, gluconate, glutamate, lactobionate, malate, maleate, mandelate, methanesulfonate, pantothenate, pectinate, phosphate/diphosphate, polygalacturonate, propionate, salicylate, stearate, succinate, sulfate, tartrate and tosylate. Other suitable anionic species will be apparent to the ordinarily skilled chemist.

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

Numbering of the naphthosultam platform is as follows:



25

In a subset of the compounds of the invention, at least one of the R groups attached to the naphthosultam platform contains a positively charged moiety. Thus, it includes Q, or a moiety which in turn contains a positively charged group.

- 14 -

Z represents *trans*-ethenediyl or ethynediyl. When Z represents ethenediyl, only the *trans* configuration across the double bond is contemplated.

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

Another subset of compounds of formula I which is of interest relates to compounds of formula I wherein one R represents a group which contains a positively charged moiety,
15 and the remaining R groups are selected from hydrogen and C₁₋₆ straight or branched chain alkyl, unsubstituted or substituted with one to four R^d groups. More particularly, this subset of interest includes compounds of formula I wherein one R represents a group containing a positively charged moiety and the remaining R groups
20 are hydrogen.

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

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

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

$$\begin{array}{c} \delta \\ \text{N}^{\oplus} \\ \mu = \beta \\ \alpha \end{array}, \quad \begin{array}{c} \delta \\ \text{N}^{\oplus} \\ \alpha - \beta \\ \alpha \end{array} \quad \text{and} \quad \begin{array}{c} (\text{CH}_2)_b \\ \text{N}^{\oplus} \\ \text{L}^{\ominus} \\ (\text{CH}_2)_a \\ \text{N}^{\oplus} - \text{R}^x \end{array}$$
$$\begin{array}{c} \text{(CH}_2\text{)}_b \\ \diagup \quad \diagdown \\ \text{N}^{\oplus} \quad \text{N}^{\oplus} - \text{R}^x \\ \diagdown \quad \diagup \\ \text{L}^{\ominus} \quad \text{(CH}_2\text{)}_a \end{array}$$

one R group which is attached to the naphthosultam platform contains at least one positively charged moiety, and the

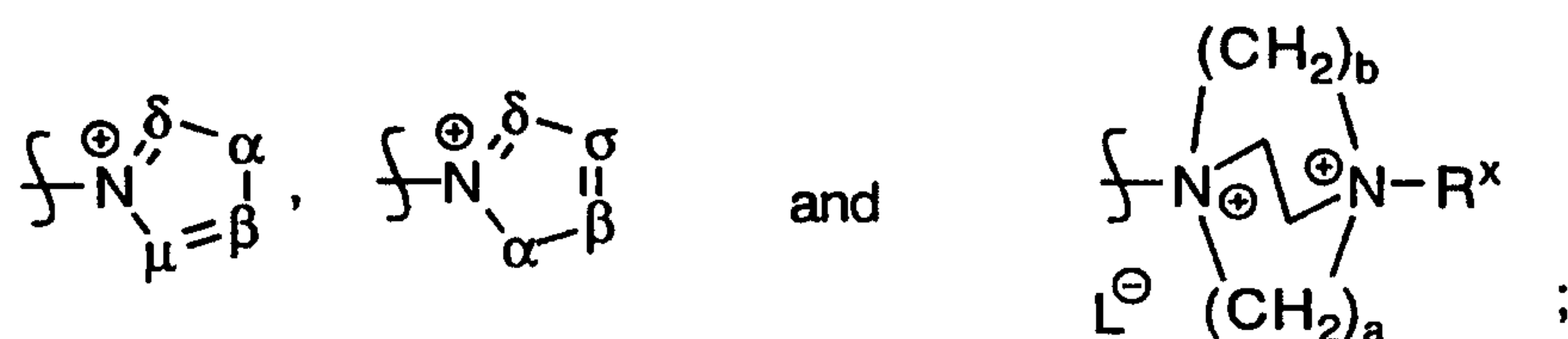
- 16 -

remaining R groups are selected from hydrogen and C₁₋₆ straight or branched chain alkyl, unsubstituted or substituted with one to four R^d groups;

R^d is as originally defined;

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

Q is selected from the group consisting of:



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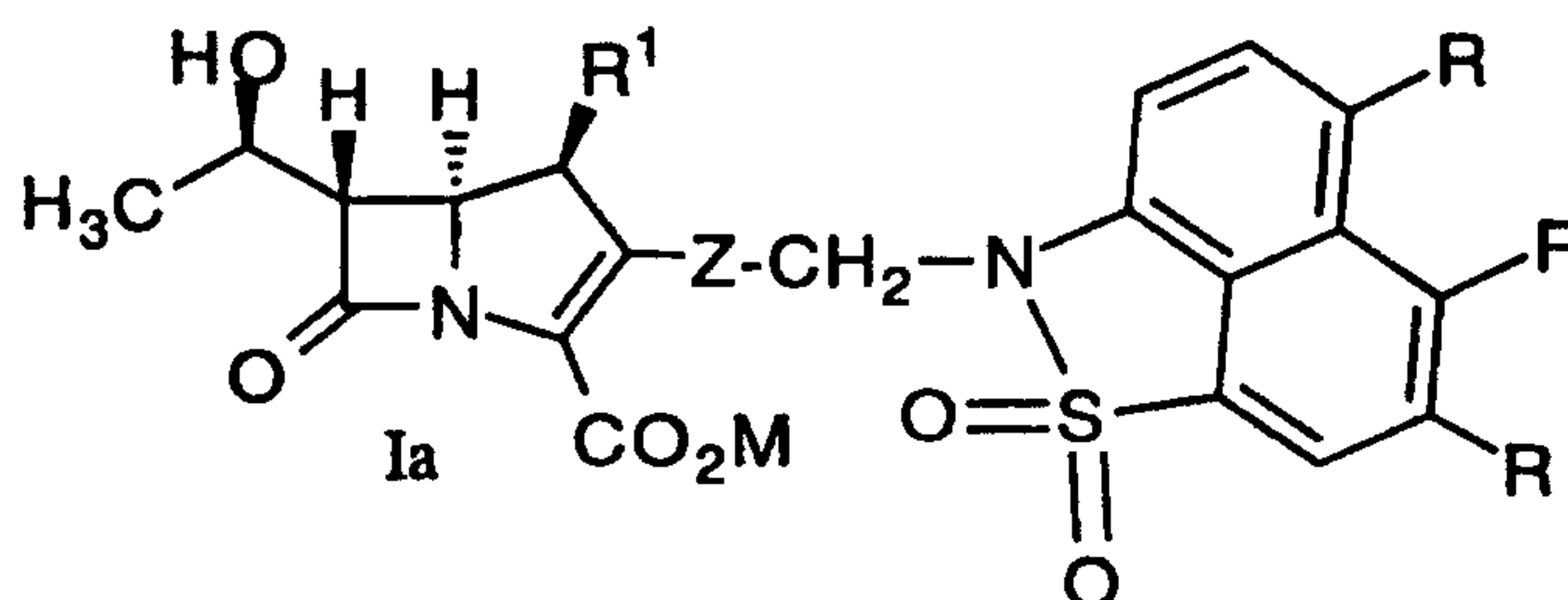
wherein L⁻, a and b are as originally defined, and R^x represents a member selected from the group consisting of: hydrogen or a C₁₋₈ straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO₂, NR^w, N⁺R^hR^w,

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

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

25 A more preferred subset of compounds of the invention is represented by formula Ia:

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or a pharmaceutically acceptable salt thereof, wherein:

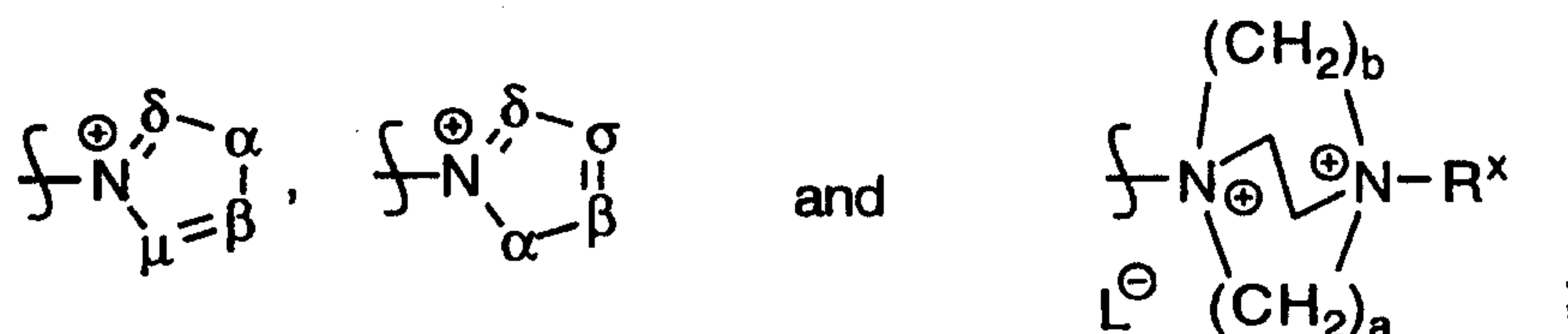
CO₂M represents a carboxylate anion;

- 5 one R group is attached to the naphthosultam platform which contains a positively charged moiety, and the other R groups are selected from hydrogen and C₁₋₆ straight or branched chain alkyl, unsubstituted or substituted with one to four R^d groups;

Z represents trans -CH₂=CH₂- or ethynediyl;

- 10 R^d is as originally defined;

Q is selected from the group consisting of:



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

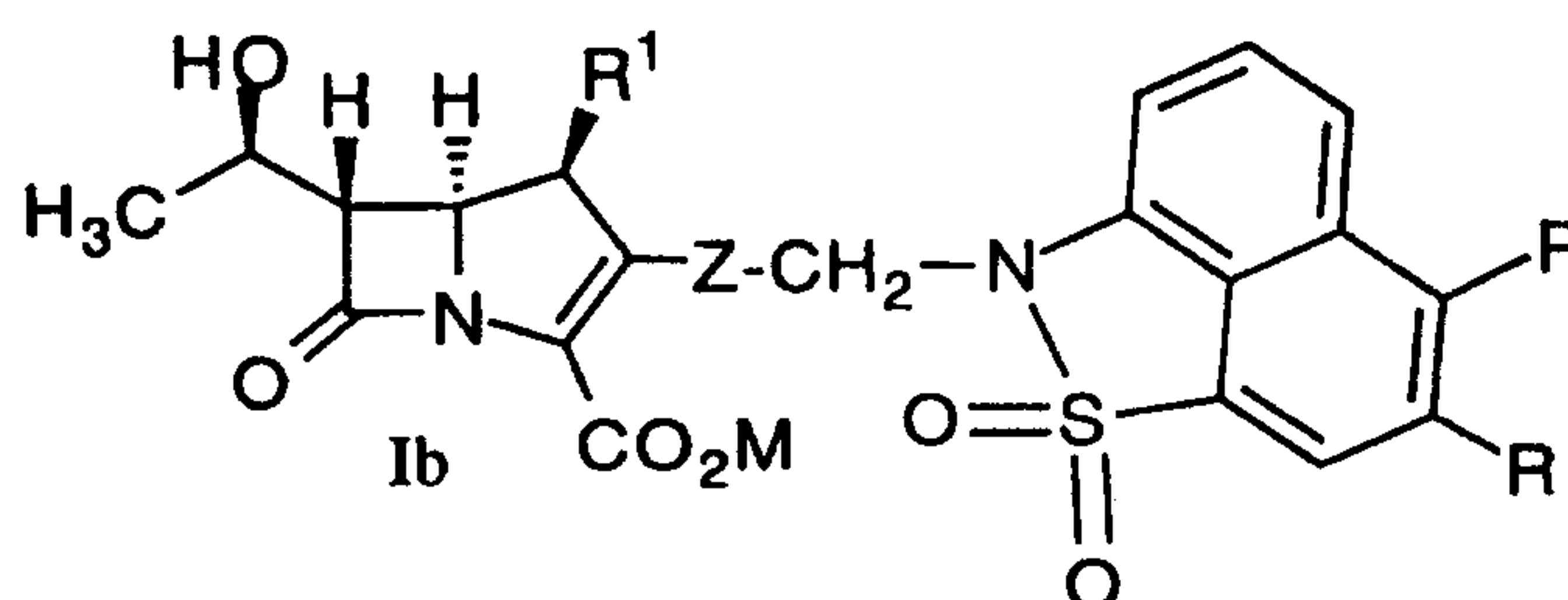
- 18 -

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

and R^w is as originally defined.

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

Another more preferred subset of compounds is represented by formula Ib:



10

or a pharmaceutically acceptable salt thereof, wherein:

CO_2M represents a carboxylate anion;

one R group is attached to the naphthosultam platform which contains a positively charged moiety, and the other R group is selected from hydrogen and C_{1-6} straight or branched chain alkyl, unsubstituted or substituted with one to four R^d groups;

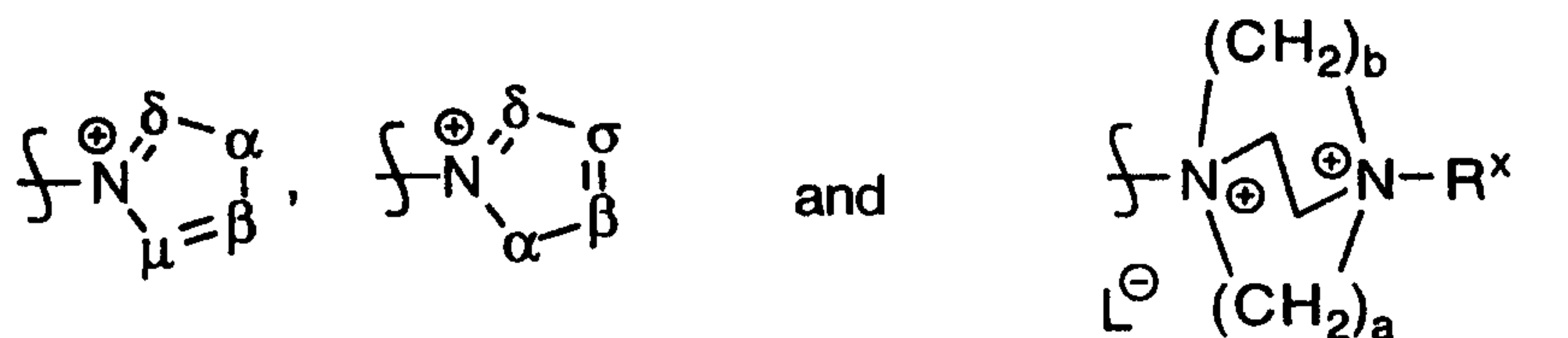
15

Z represents *trans* $-CH_2=CH_2-$ or ethynediyl;

R^d is as originally defined;

Q is selected from the group consisting of:

20



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

R^x represents a member selected from the group consisting of: hydrogen or a C_{1-8} straight- or branched- chain alkyl, optionally interrupted by one or two of O , S , SO , SO_2 , NR^w , $N^+R^hR^w$, or $-C(O)-$, said chain being unsubstituted or substituted with one to

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

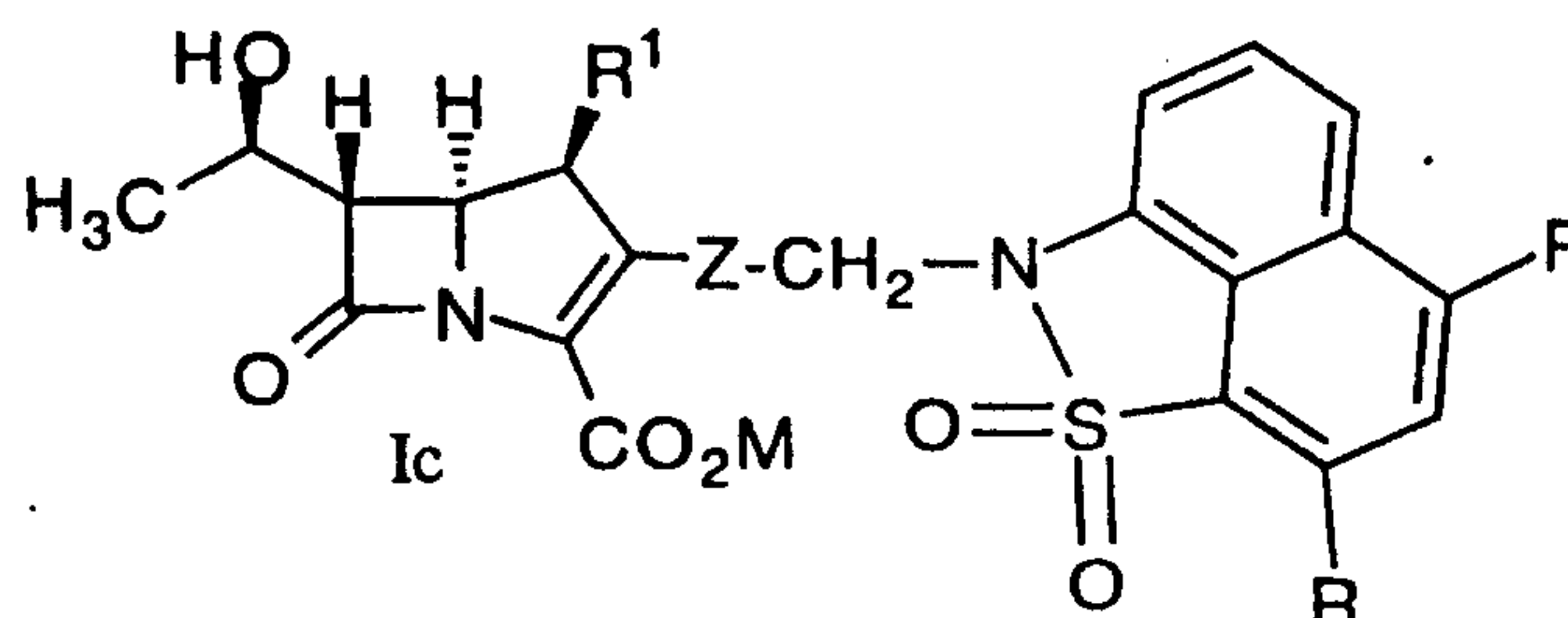
R^h represents hydrogen or a C₁-6 straight or branched chain alkyl group;

and R^w is as originally defined.

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

Another more preferred subset of compounds is represented by formula Ic:

15



or a pharmaceutically acceptable salt thereof, wherein:

CO₂M represents a carboxylate anion;

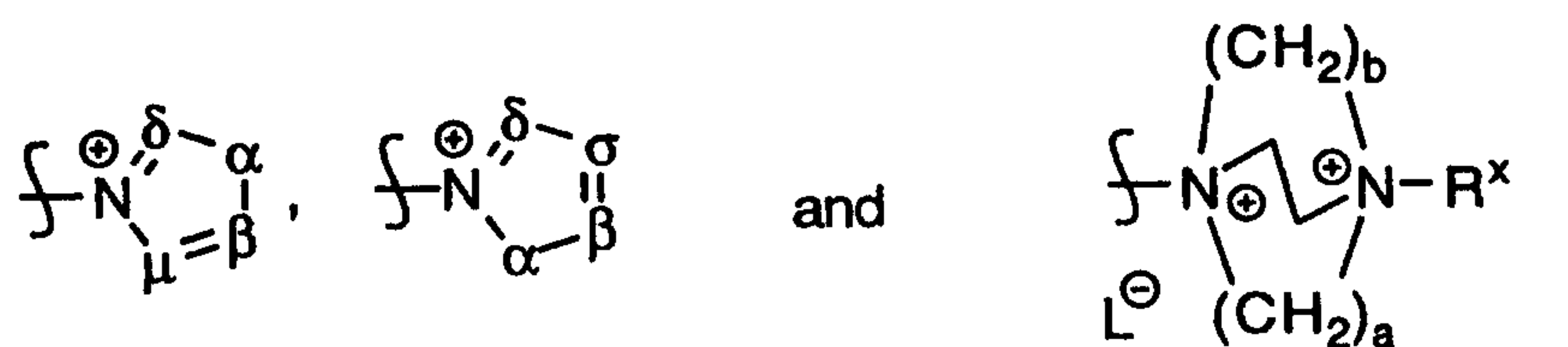
one R group is attached to the naphthosultam platform which contains a positively charged moiety, and the other R group is selected from hydrogen, halo and C₁-6 straight or branched chain alkyl, unsubstituted or substituted with one to four R^d groups;

Z represents *trans* -CH₂=CH₂- or ethynediyl;

R^d is as originally defined;

Q is selected from the group consisting of:

- 20 -



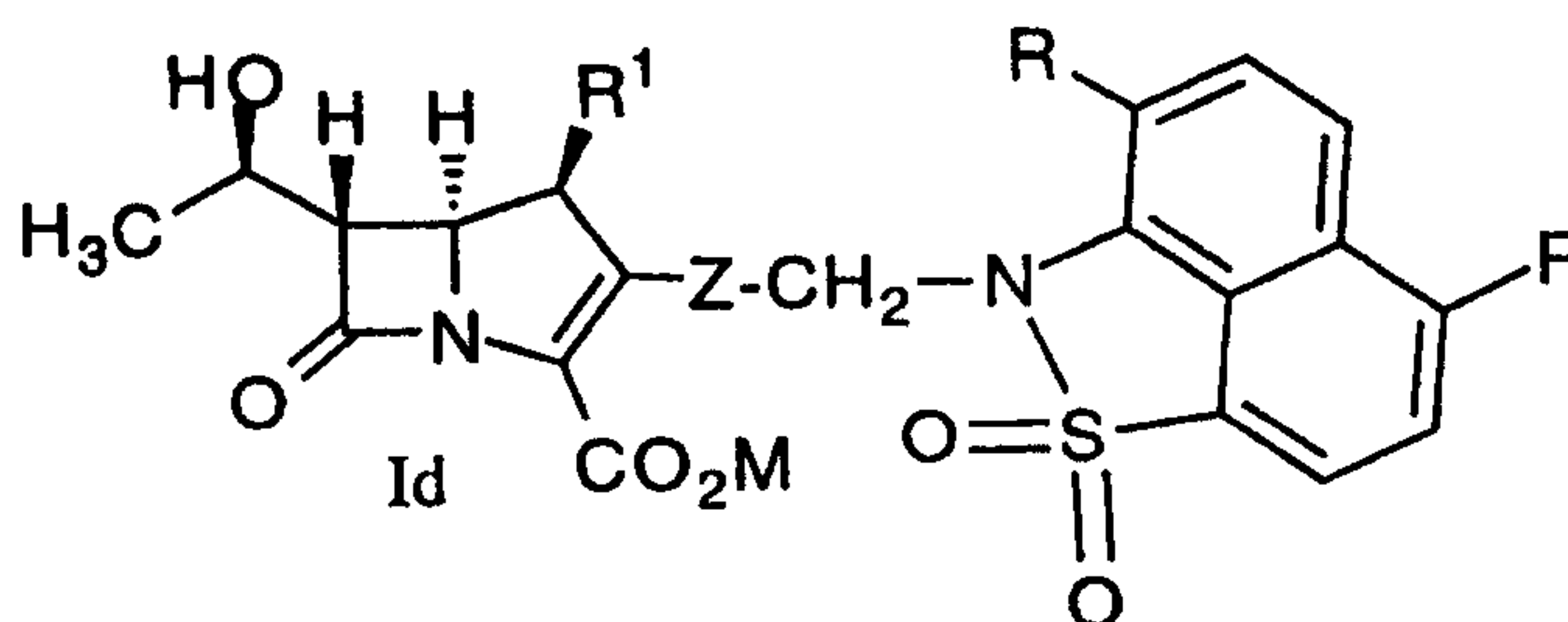
wherein L⁻, a and b are as originally defined, and R^x represents a member selected from the group consisting of:
 5 hydrogen or a C₁-8 straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO₂, NR^w, N⁺R^hR^w, or -C(O)-, said chain being unsubstituted or substituted with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

15 R^h represents hydrogen or a C₁-6 straight or branched chain alkyl group;

and R^w is as originally defined.

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

20 Another more preferred subset of compounds is represented by formula Id:



or a pharmaceutically acceptable salt thereof, wherein:

25 CO₂M represents a carboxylate anion;

one R group is attached to the naphthosultam platform which contains a positively charged moiety, and the other R group is

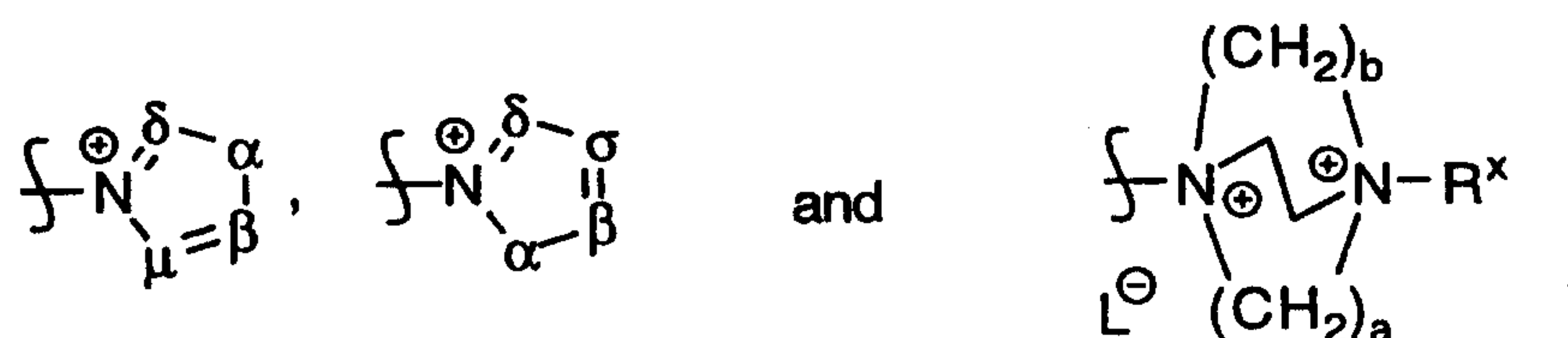
- 21 -

selected from hydrogen, halo and C₁₋₆ straight or branched chain alkyl, unsubstituted or substituted with one to four R^d groups;

Z represents *trans* -CH₂=CH₂- or ethynediyl;

R^d is as originally defined;

5 Q is selected from the group consisting of:



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

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

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

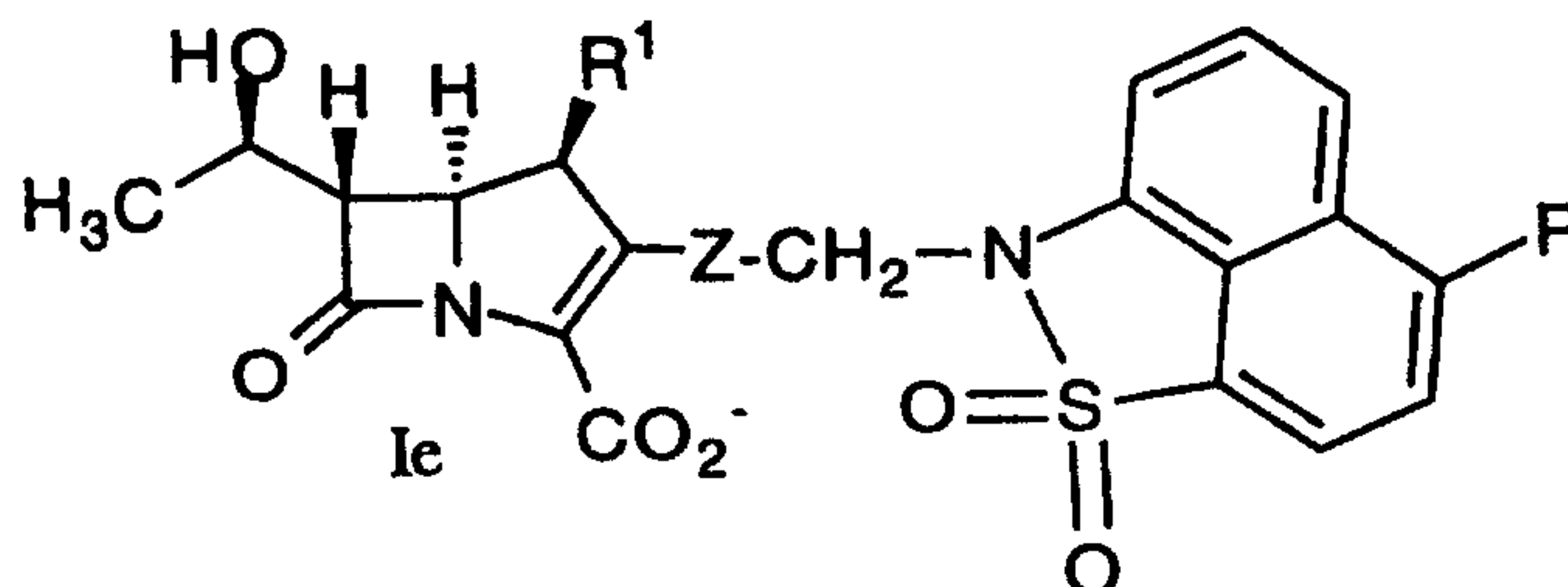
and R^w is as originally defined.

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

Still more preferably, the present invention relates to a compound represented by formula Ia wherein the R group at position 4 represents a positively charged moiety, and the R groups at position 3 and 5 represent hydrogen.

30 In particular, such compounds can be represented by formula Ie:

- 22 -



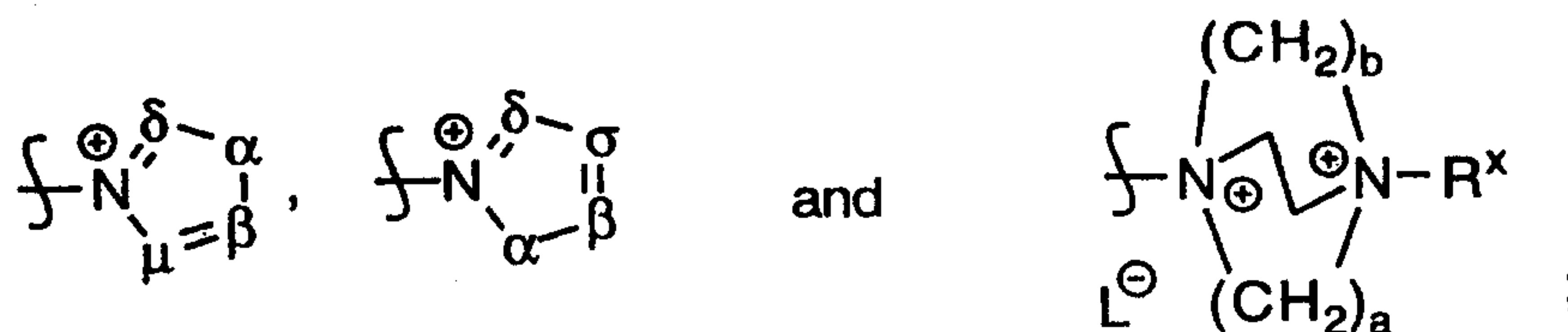
or a pharmaceutically acceptable salt thereof, wherein:

- 5 R contains a positively charged moiety selected from the group consisting of: Q and a C₁₋₆ straight or branched alkyl chain substituted with one R^d group which is Q;

Z represents *trans* -CH₂=CH₂- or ethynediyl;

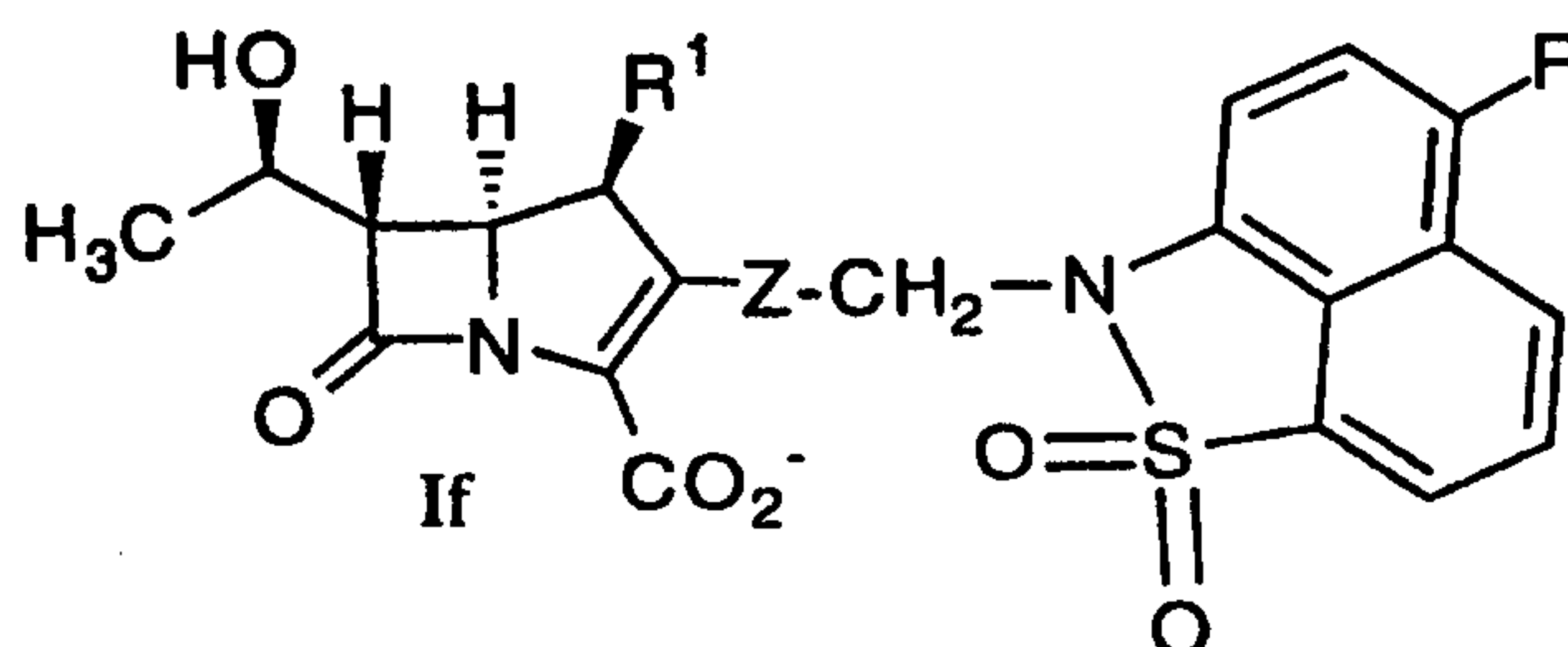
Q is selected from the group consisting of:

10



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

- 23 -

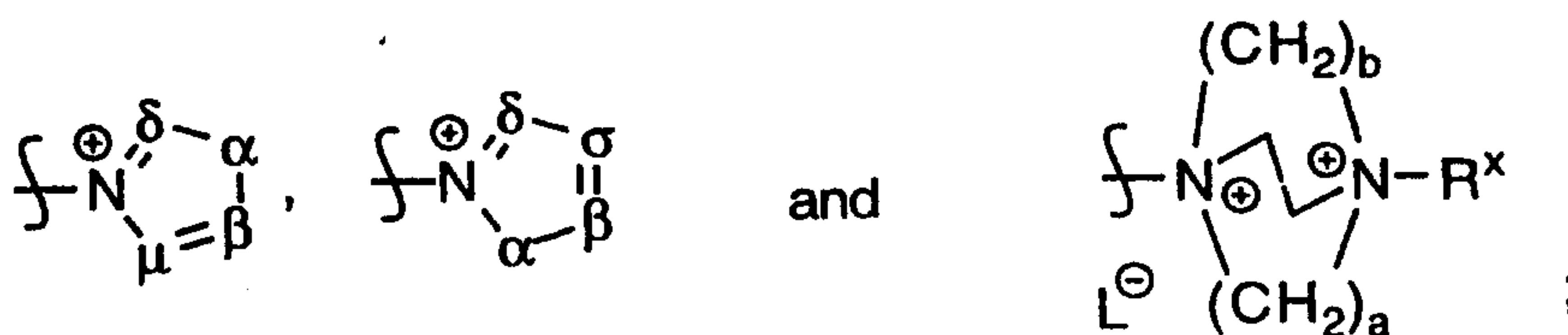


or a pharmaceutically acceptable salt thereof, wherein:

5 R contains a positively charged moiety selected from the group consisting of: Q and a C₁₋₆ straight or branched alkyl chain substituted with one R^d group which is Q;

Z represents *trans* -CH₂=CH₂- or ethynediyl;

Q is selected from the group consisting of:



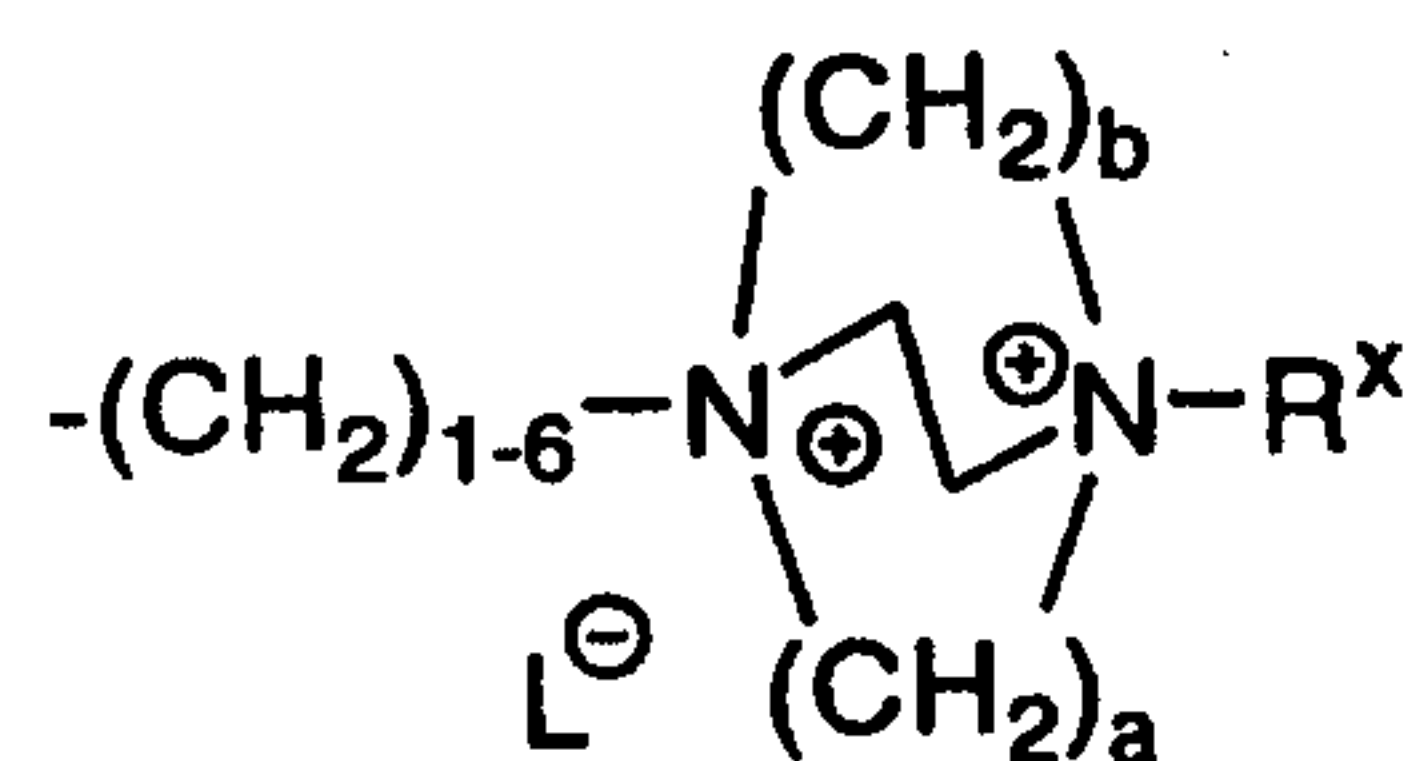
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wherein L⁻, a and b are as originally defined, and R^x represents a member selected from the group consisting of: hydrogen or a C₁₋₈ straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO₂, NR^w, N⁺R^hR^w, or -C(O)-,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

20 A still more preferred subset of compounds of the invention is represented by formula Ie wherein:

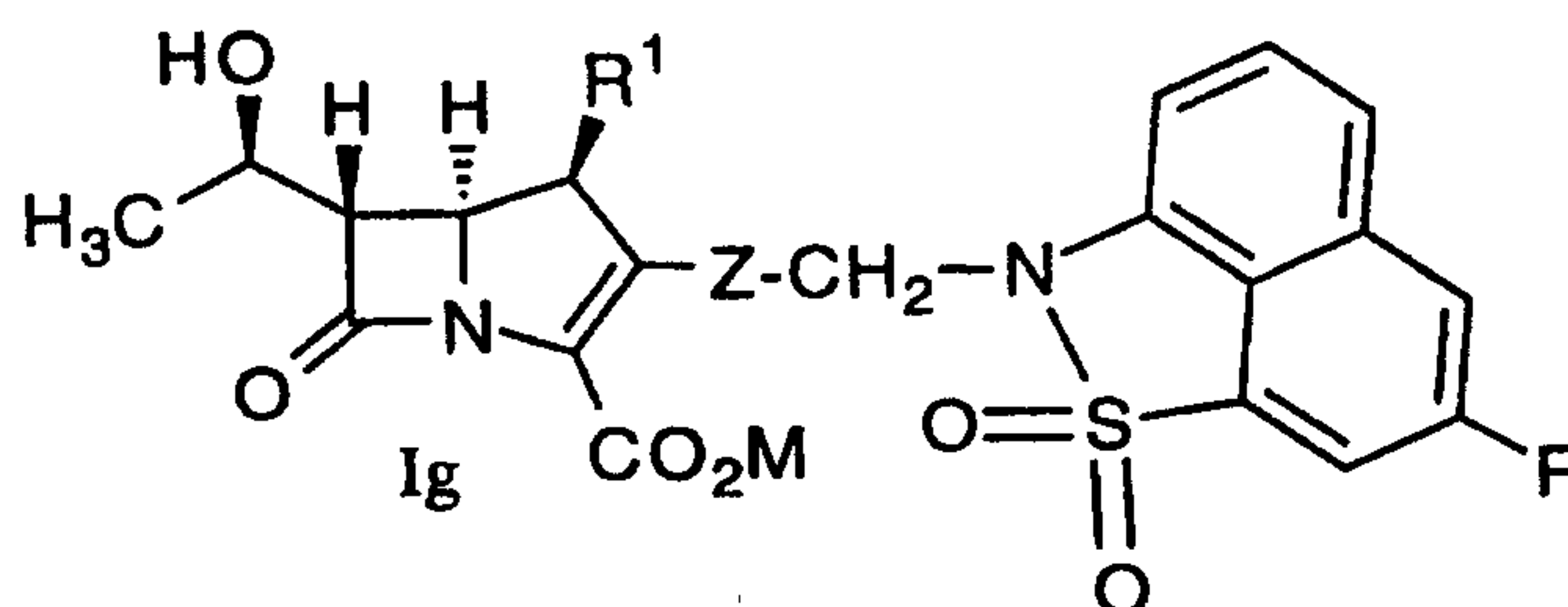
R represents

- 24 -



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

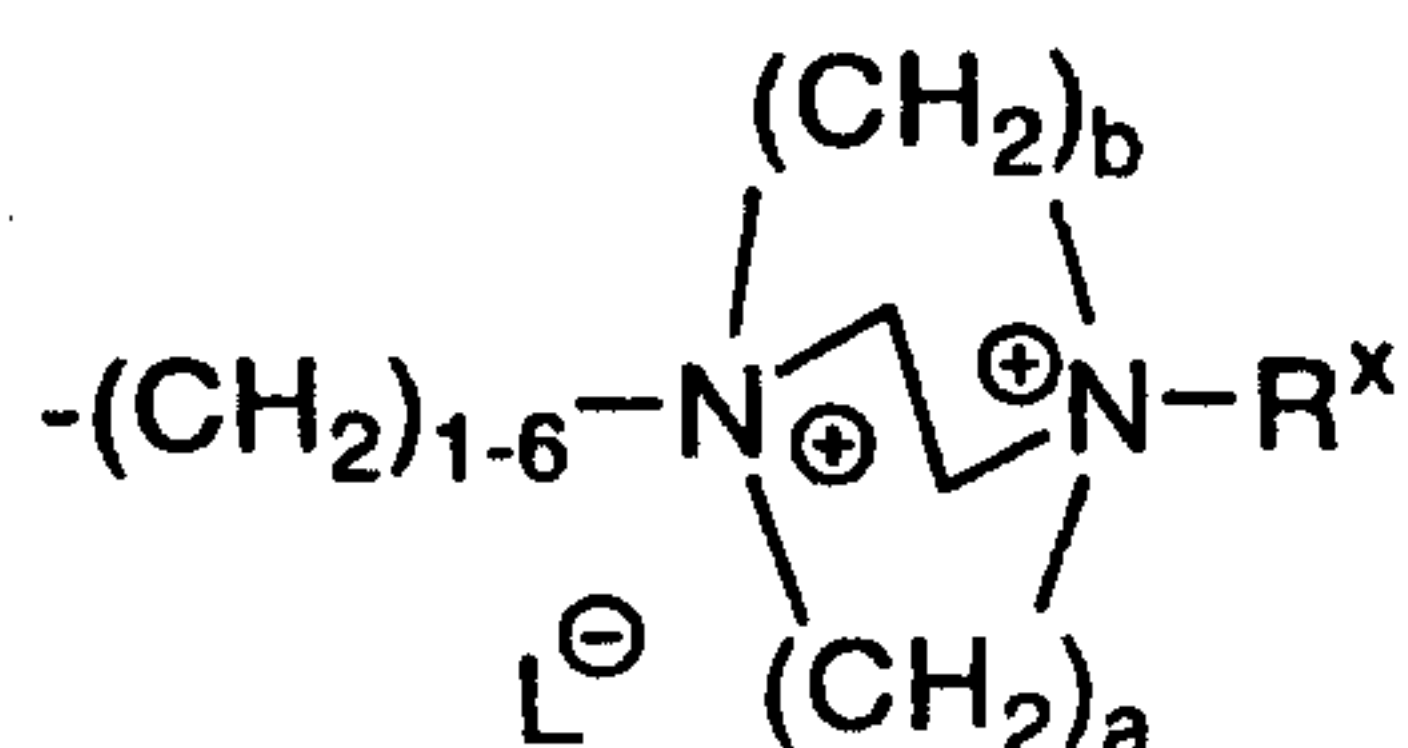
Another more preferred subset of compounds of the
 5 invention is represented by formula Ig:



wherein:

R represents

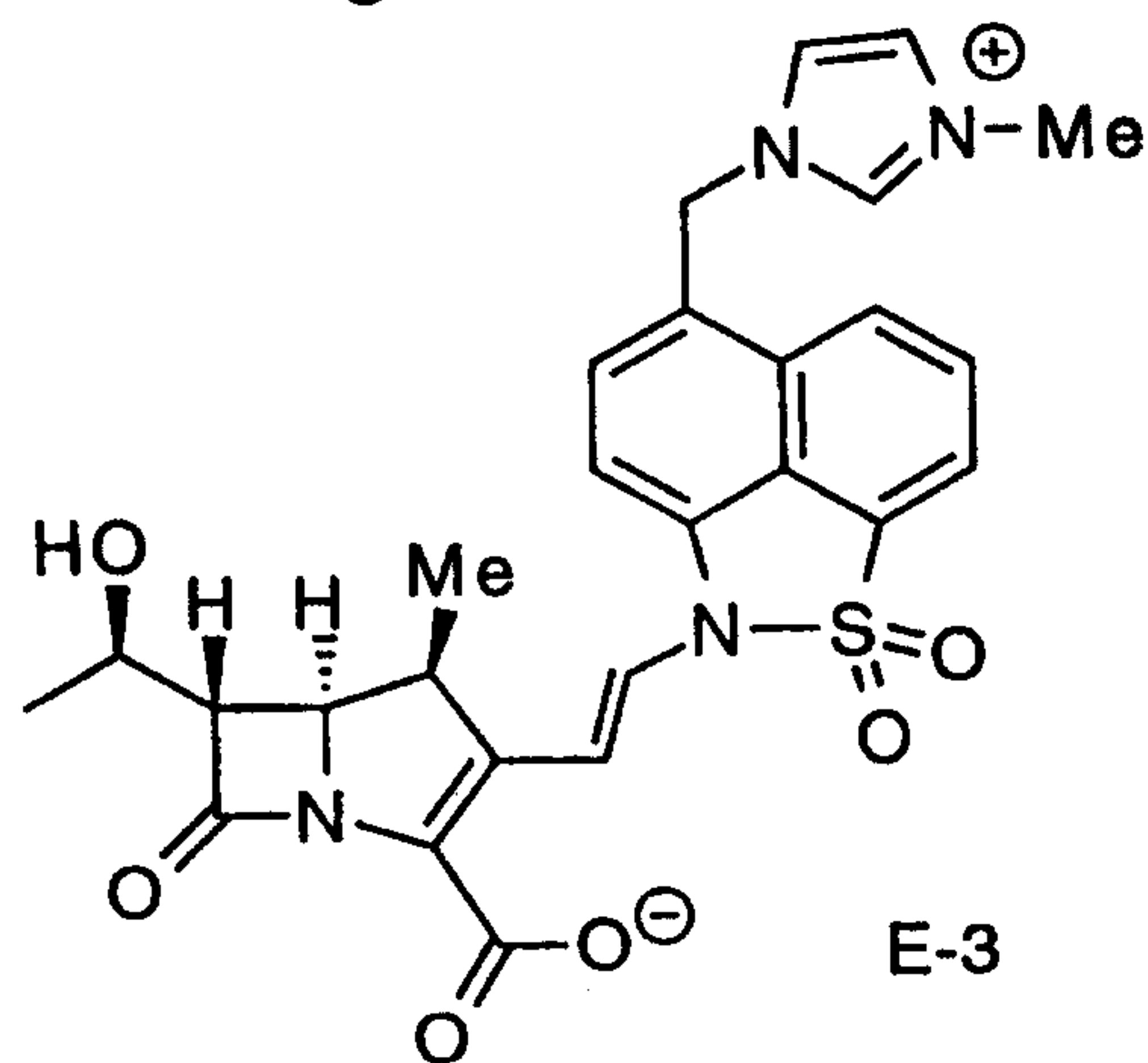
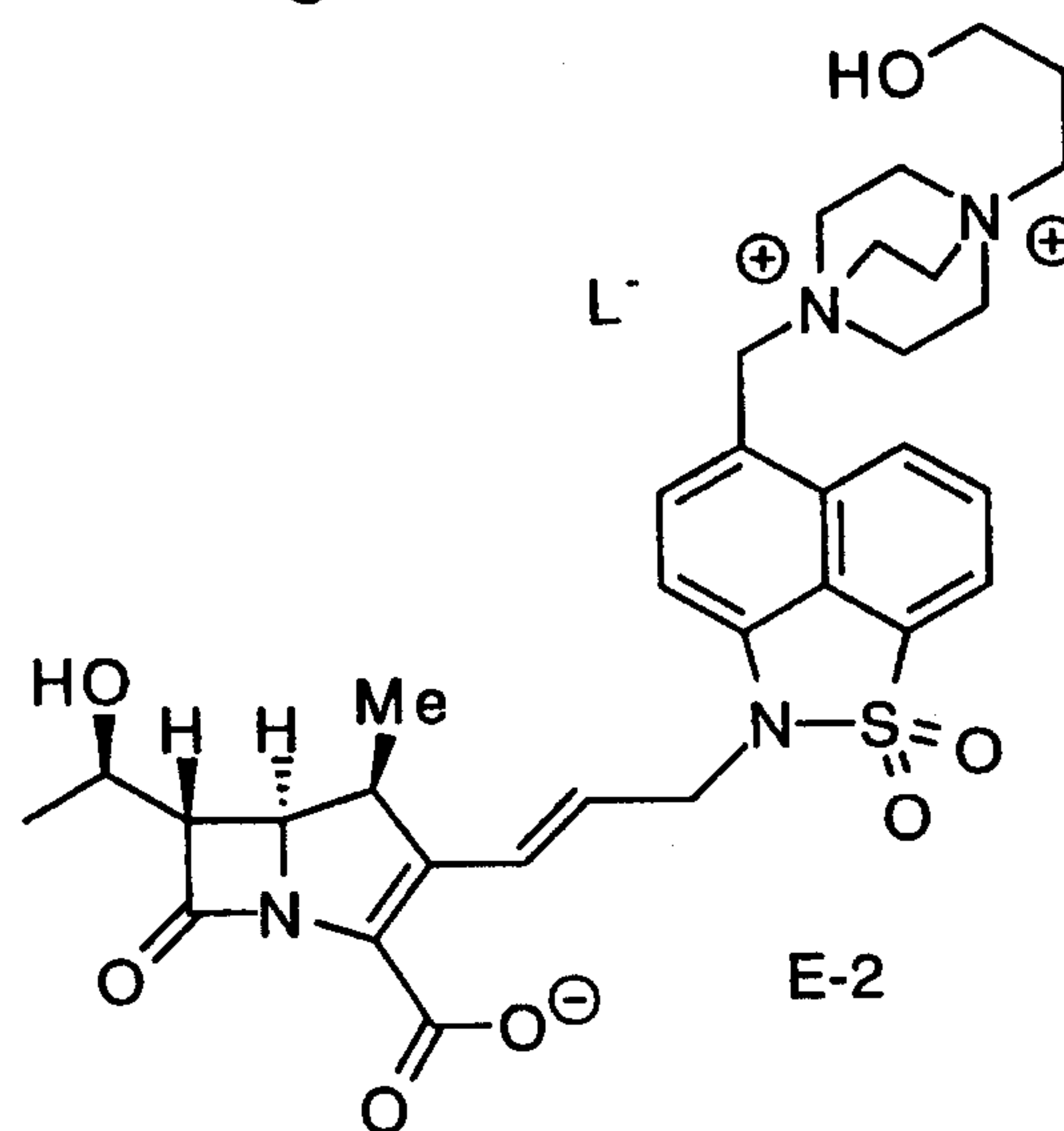
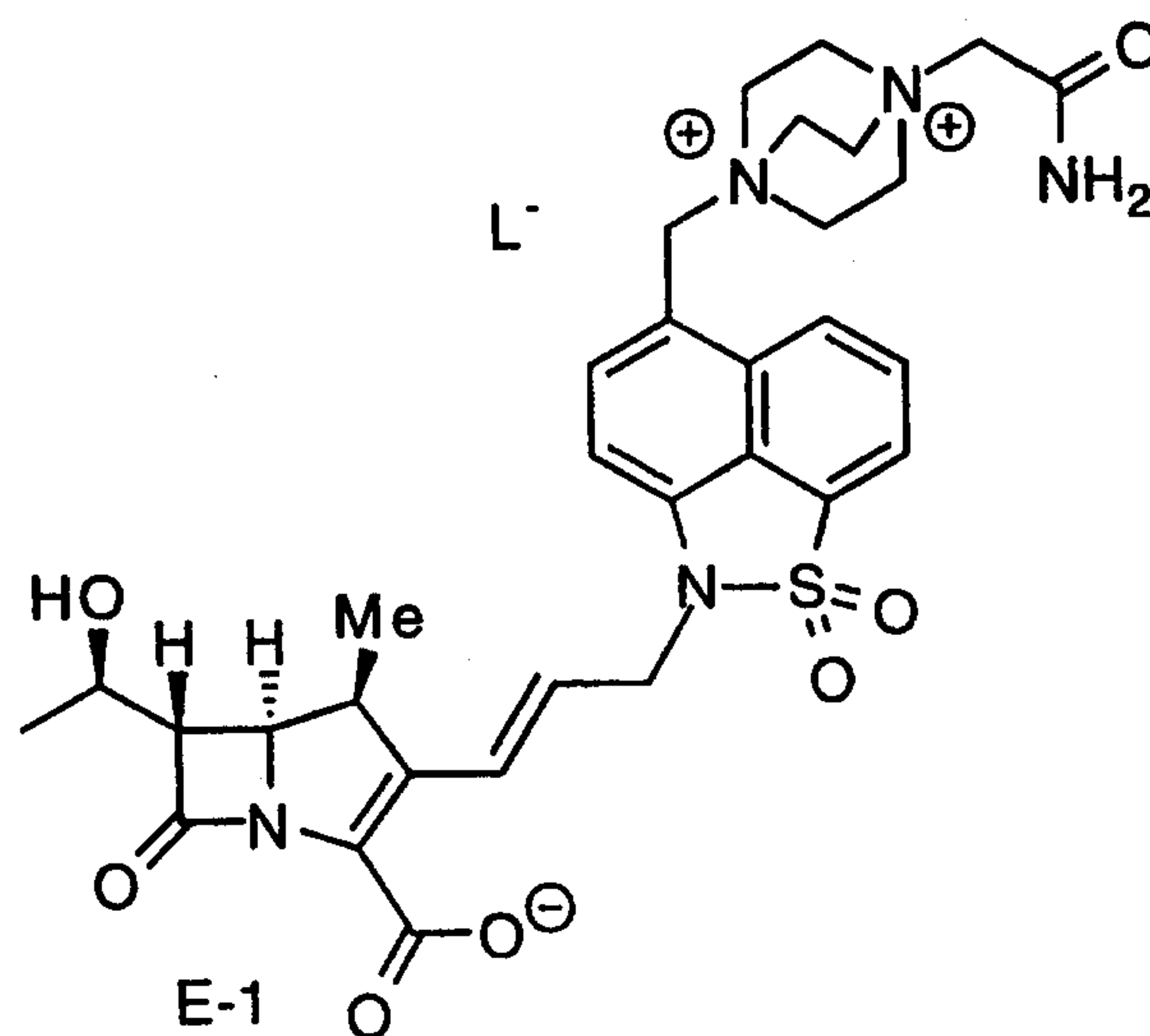
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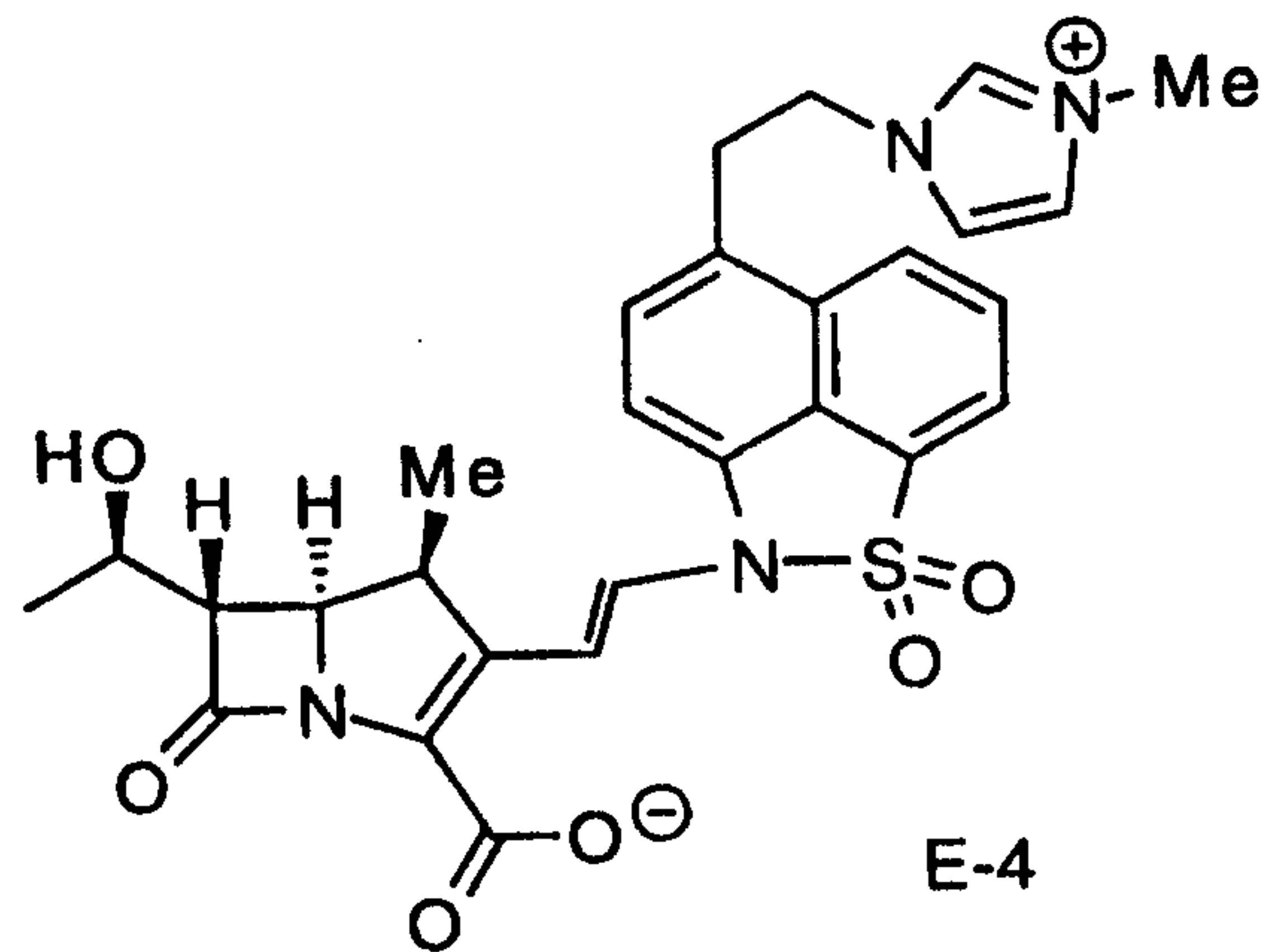
and R^x , a , b and L^- are as originally defined.

Representative examples of compounds of the invention
 15 are as follows:

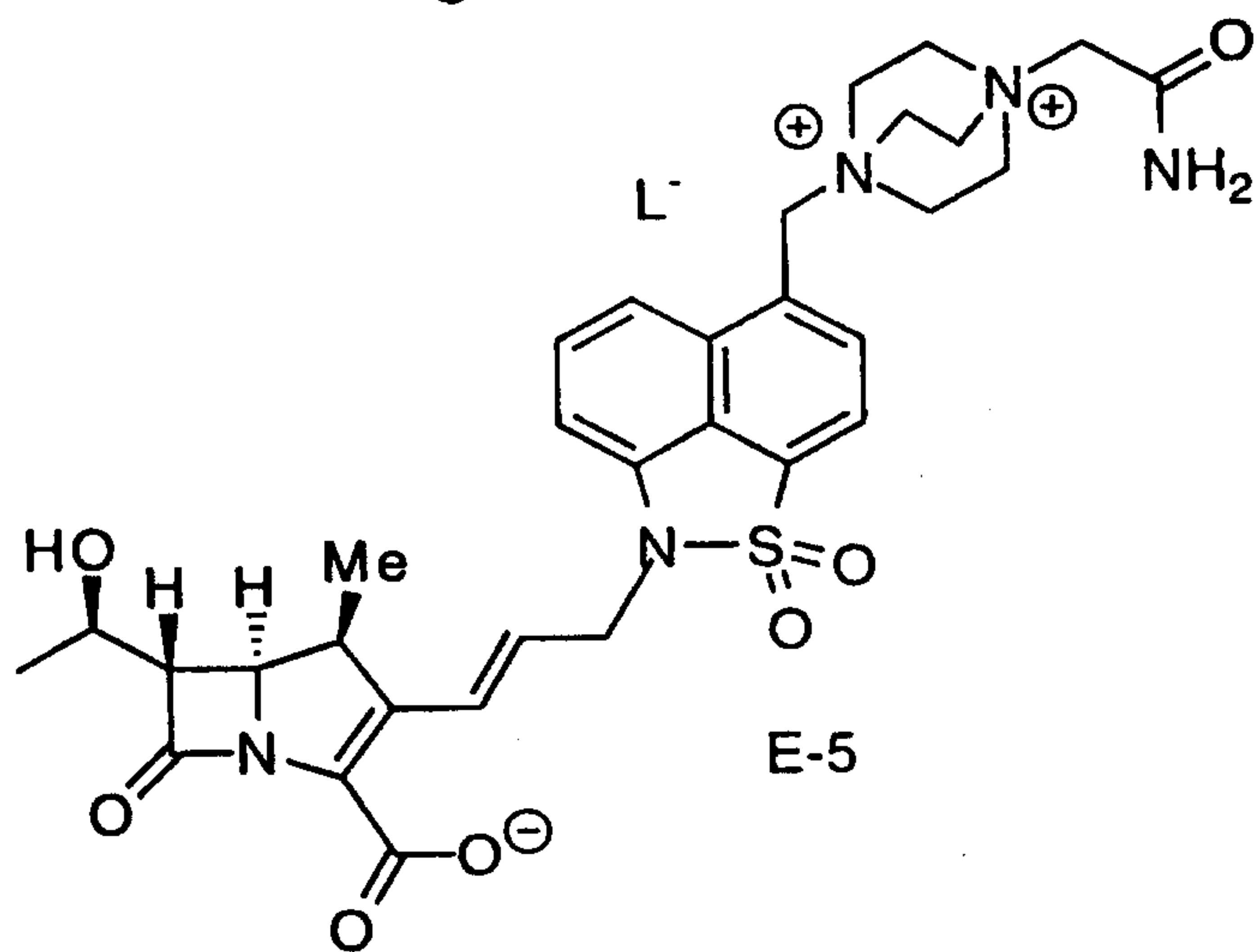
- 25 -



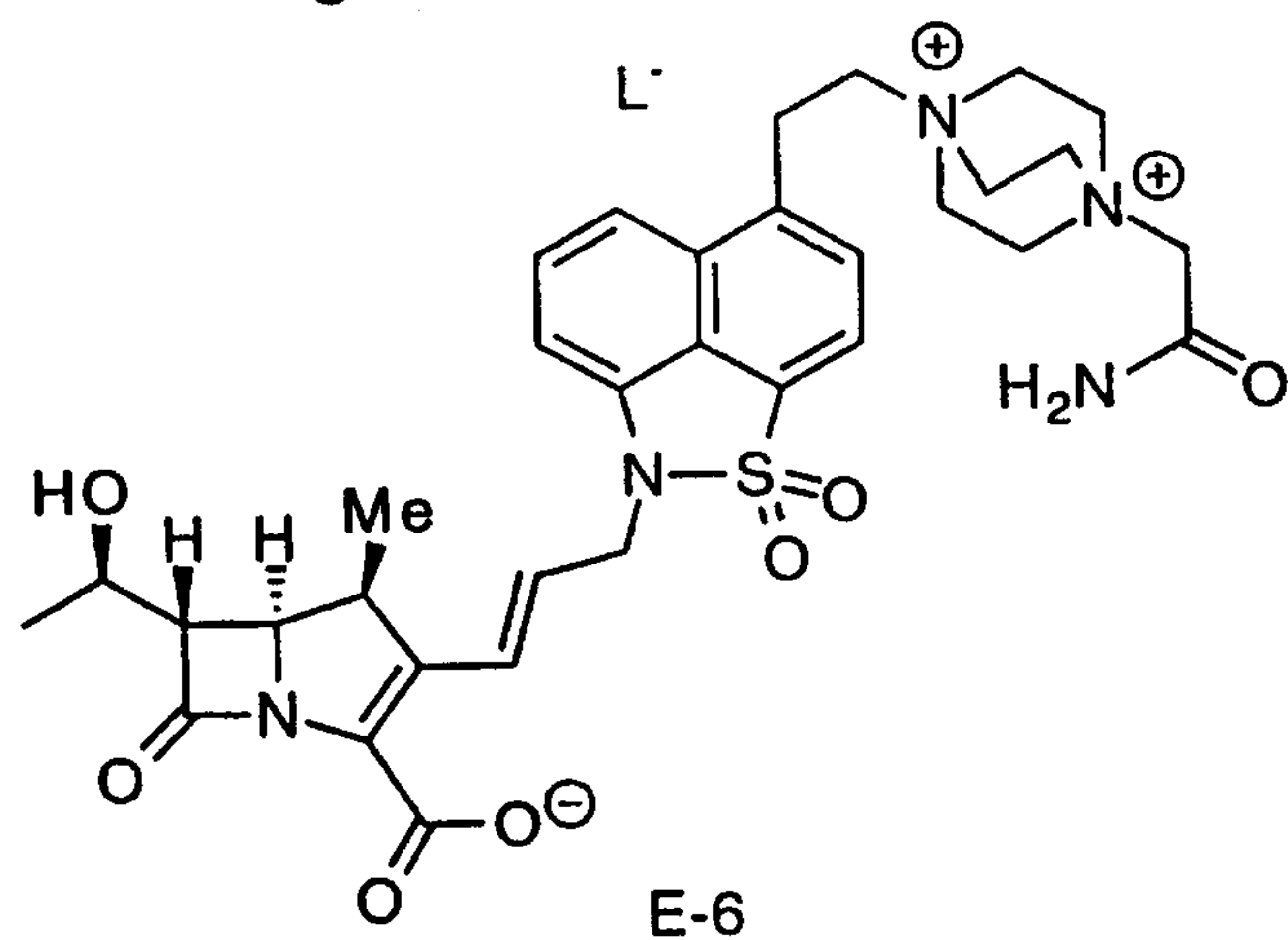
- 26 -



E-4

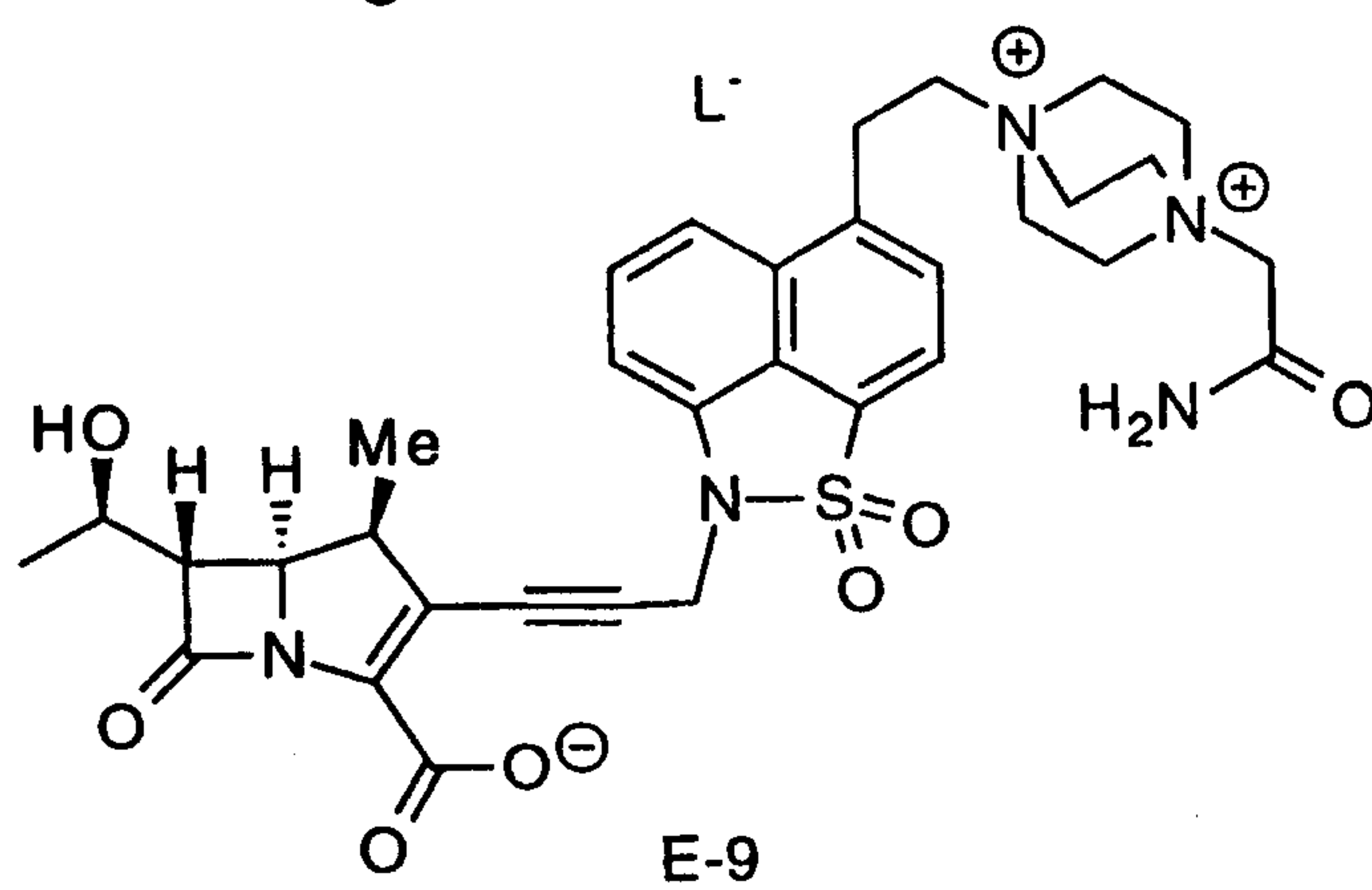
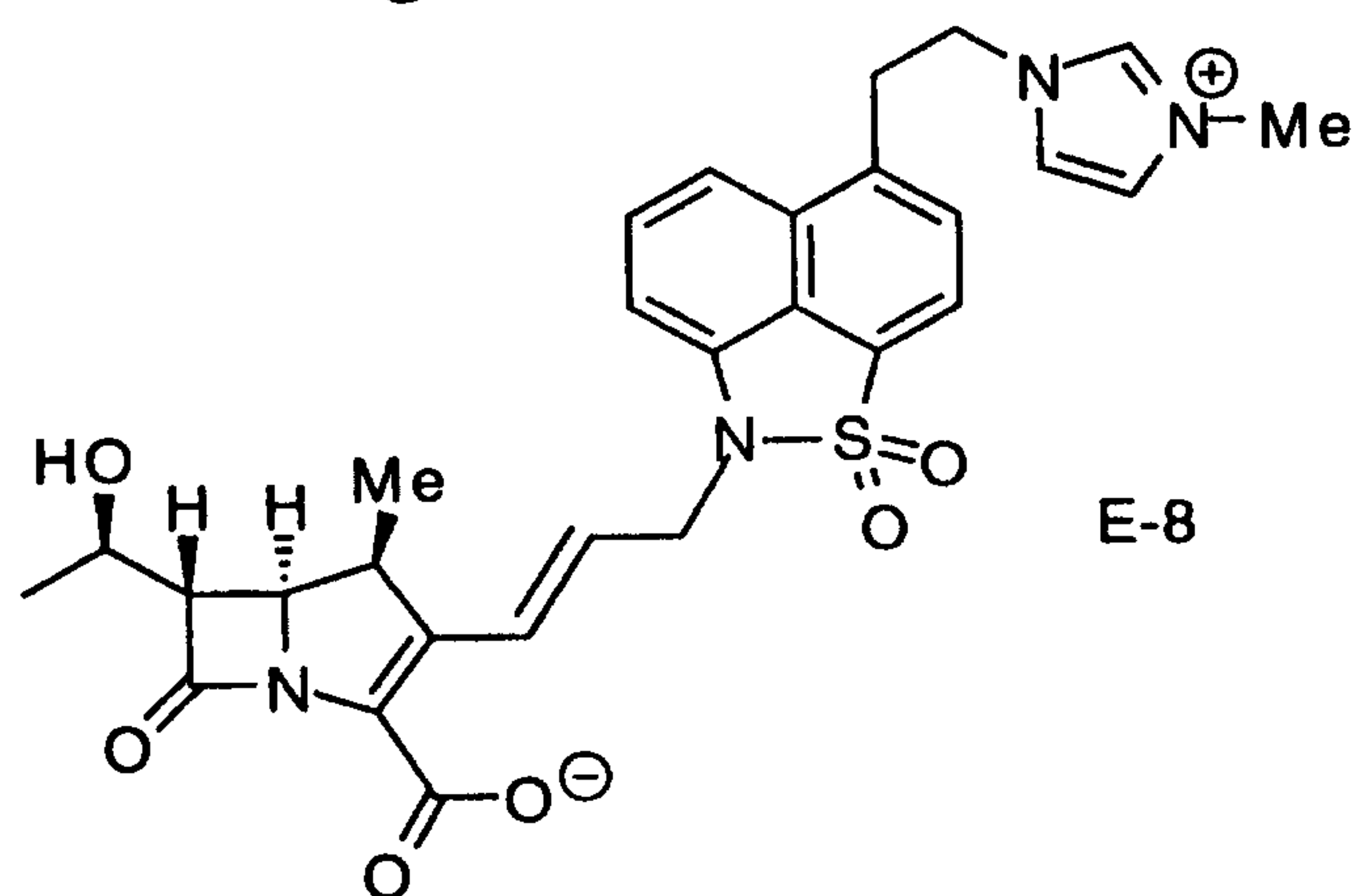
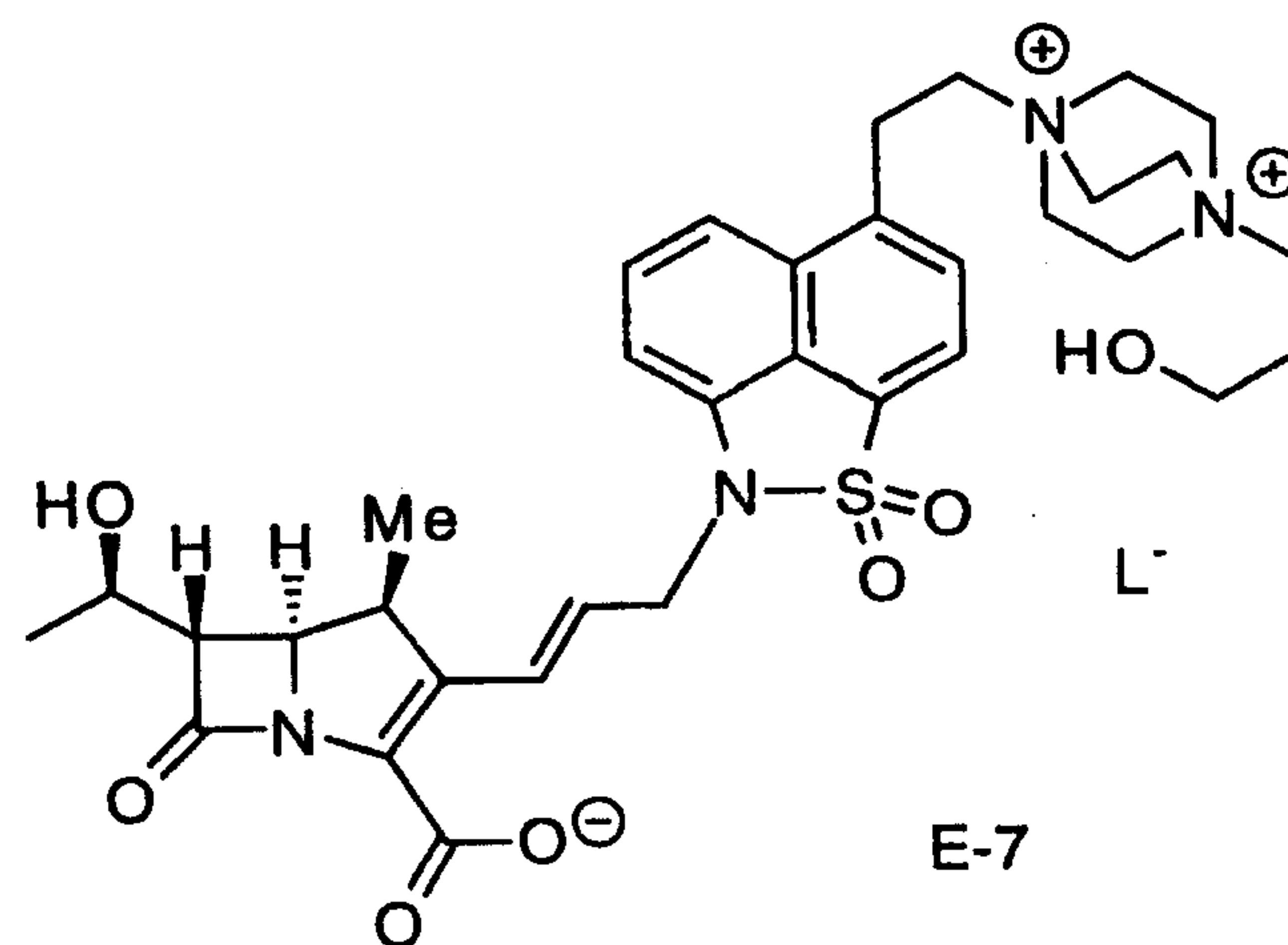


E-5

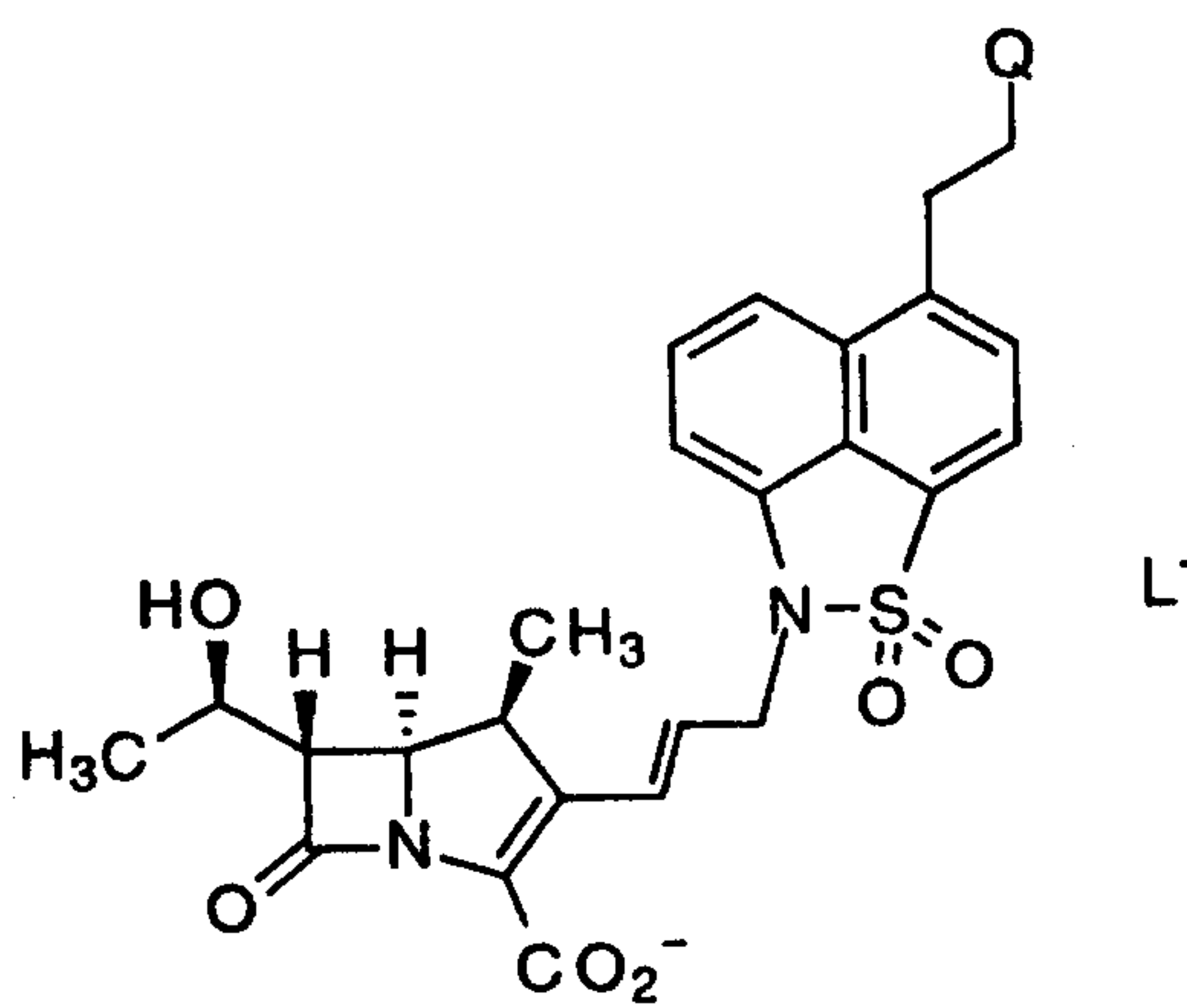
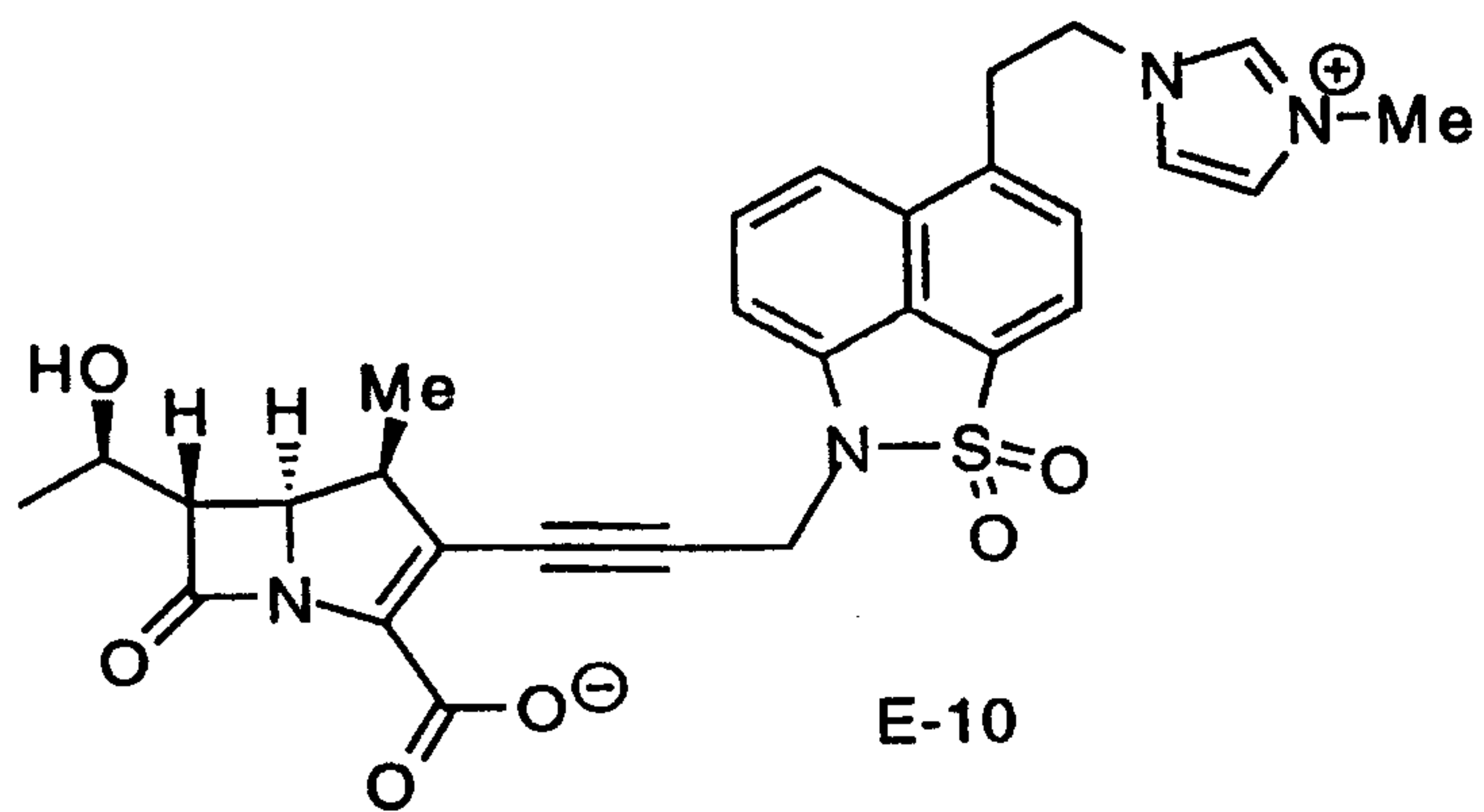


E-6

- 27 -



- 28 -

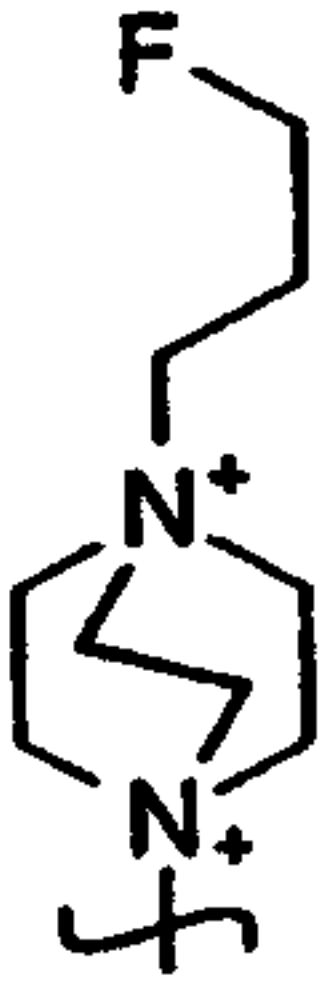
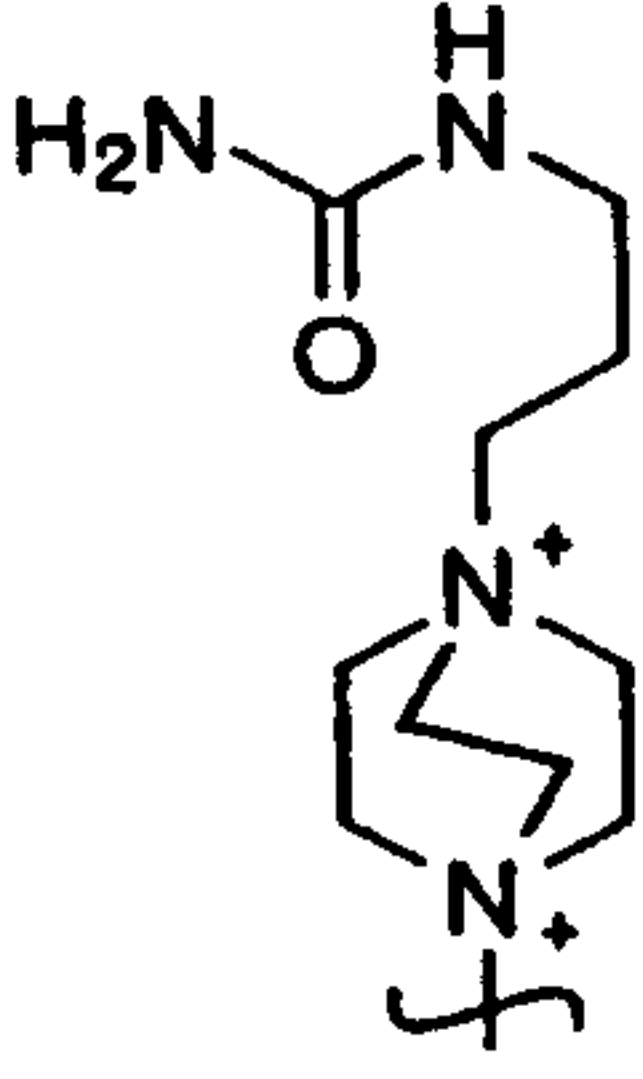
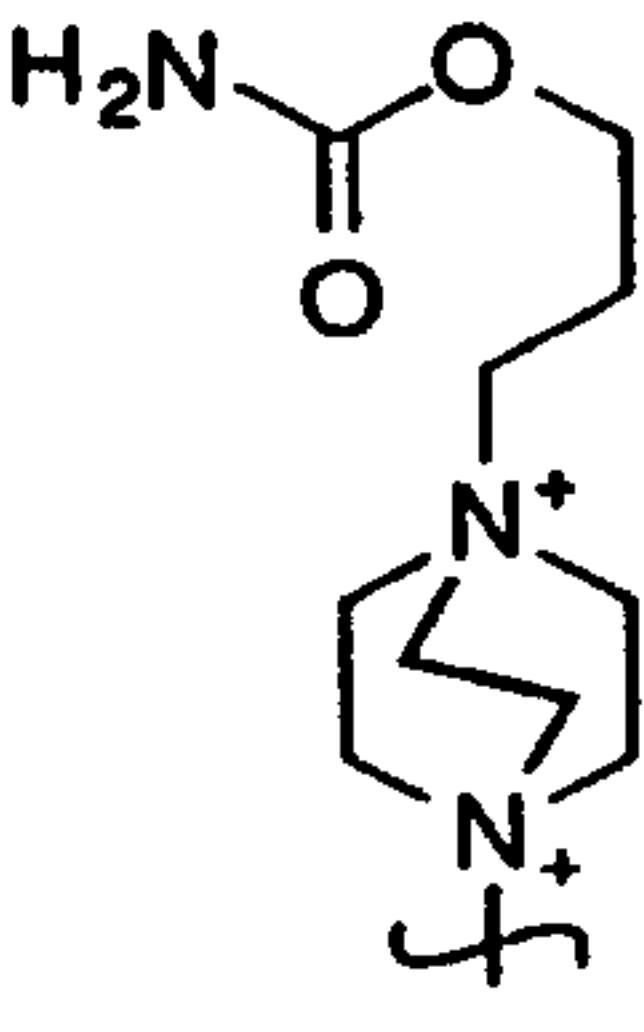
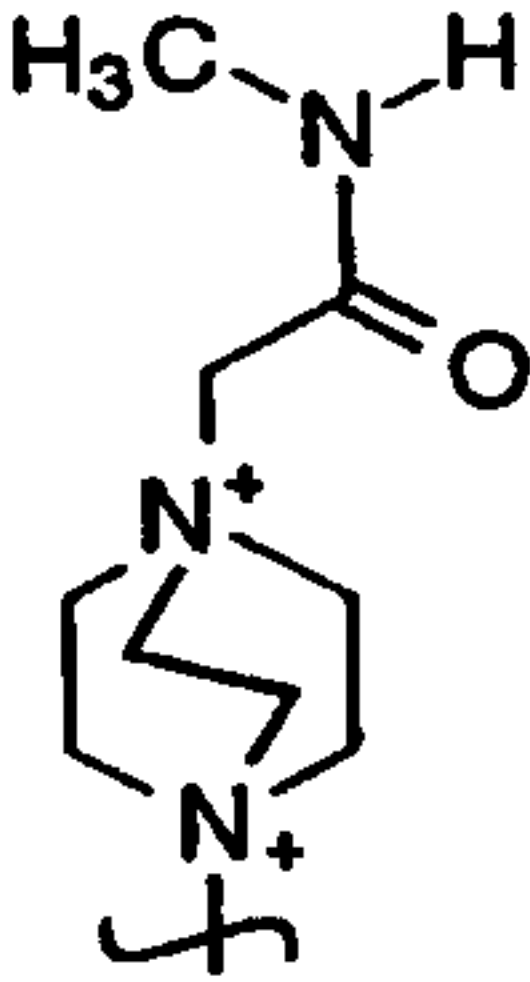
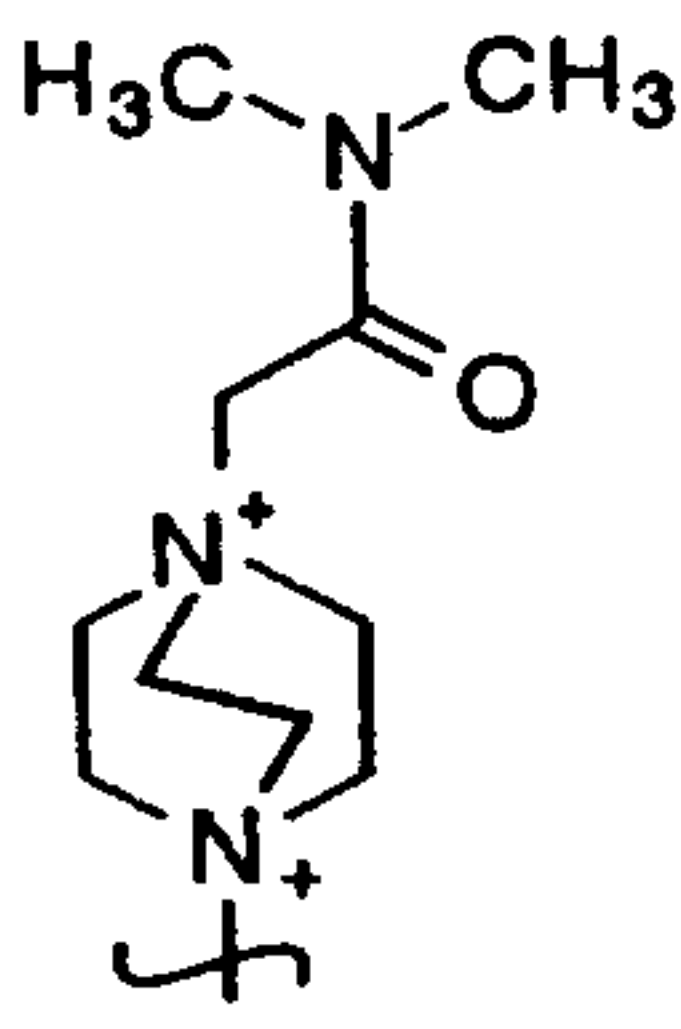
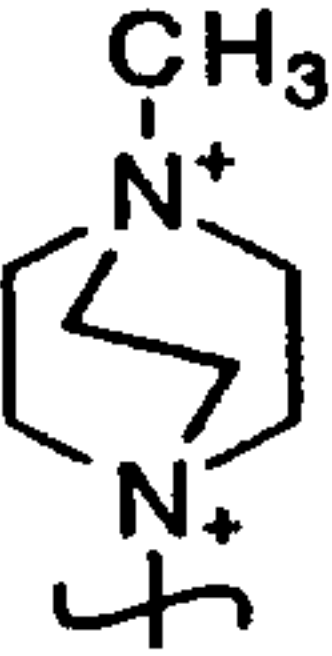
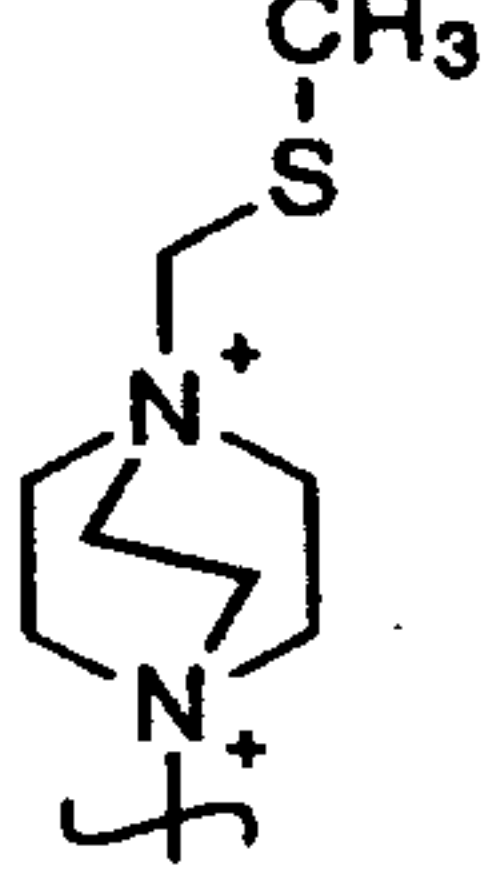
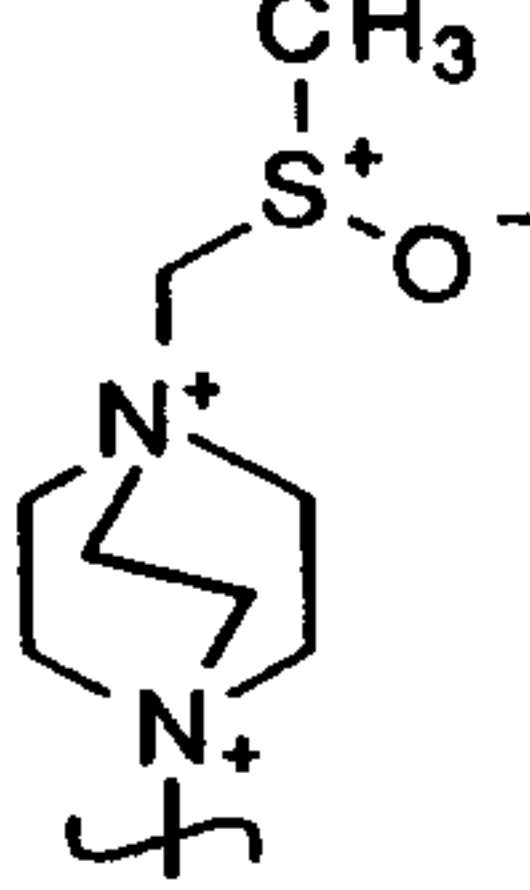
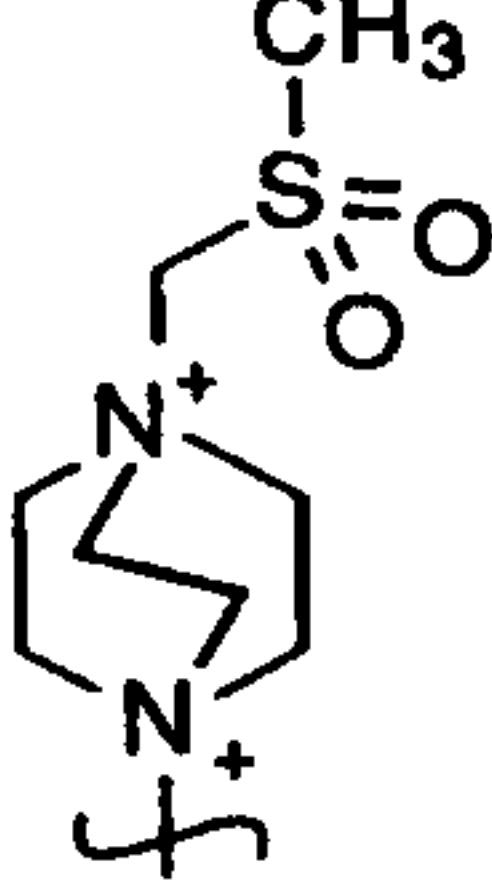


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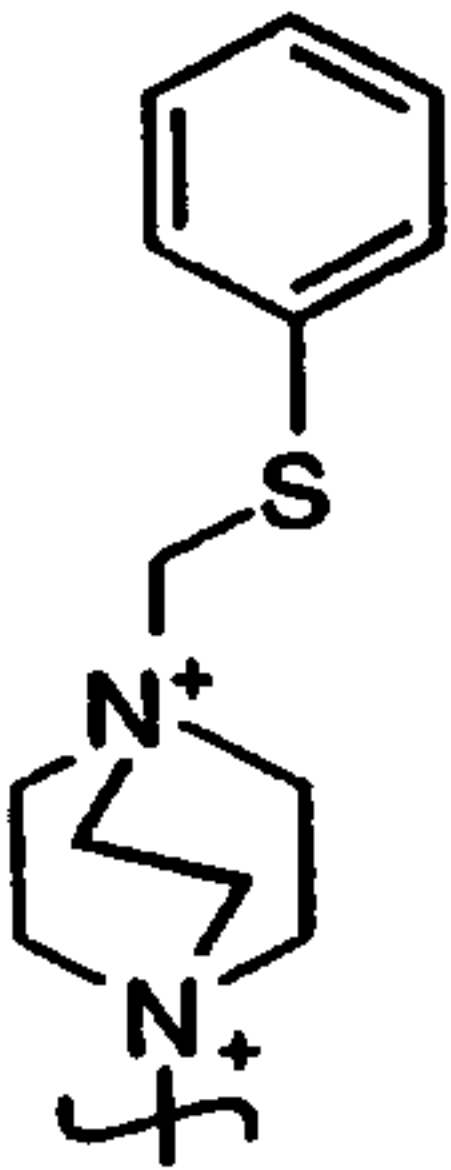
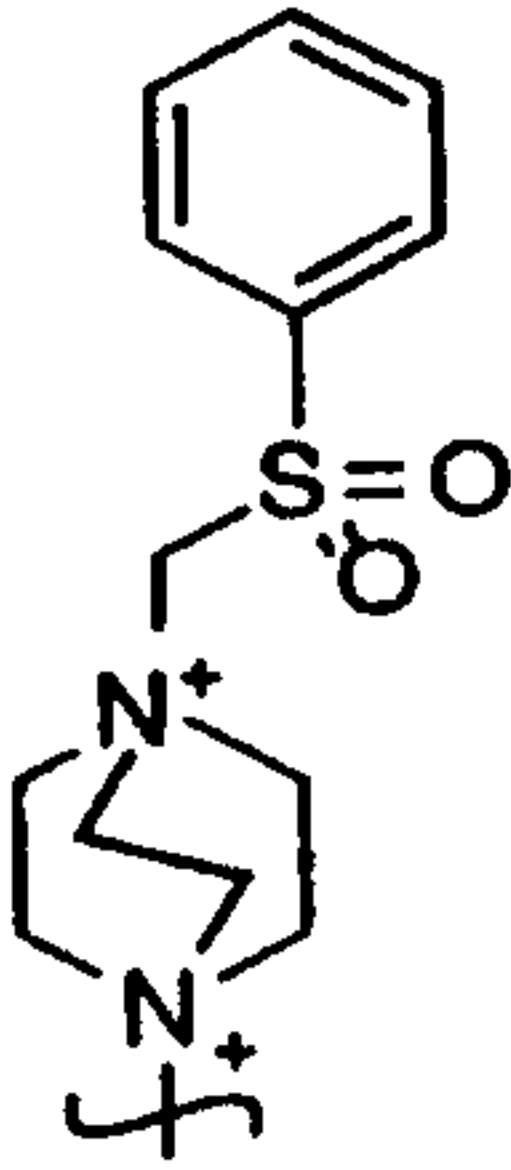
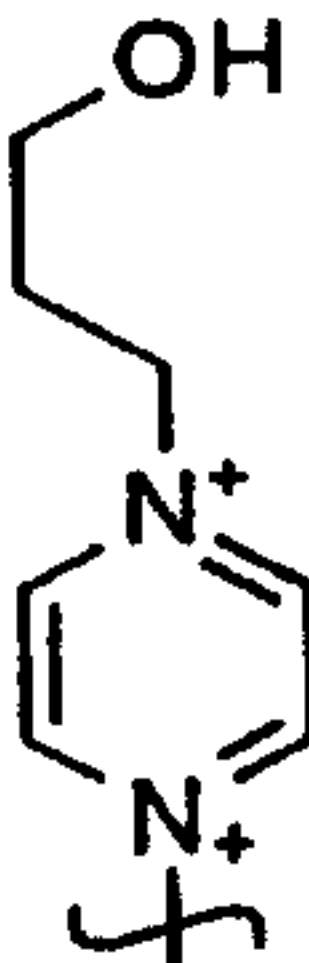
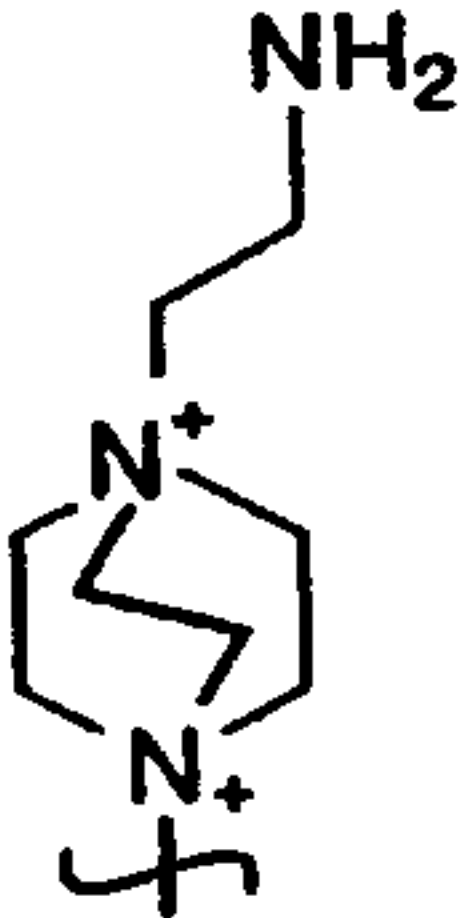
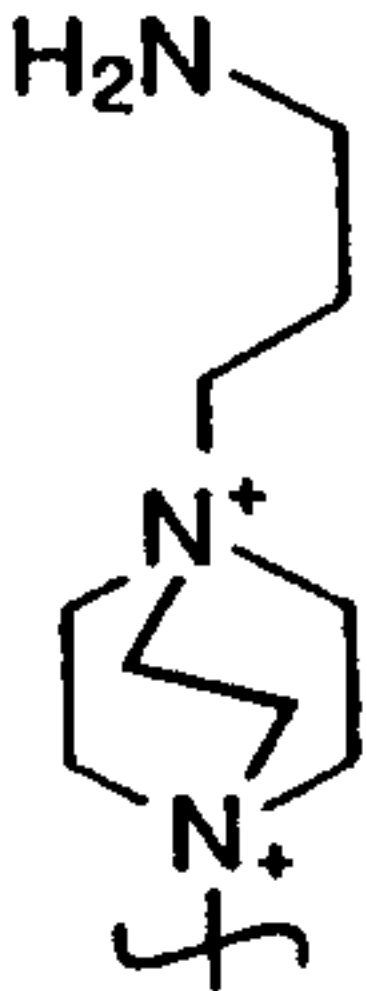
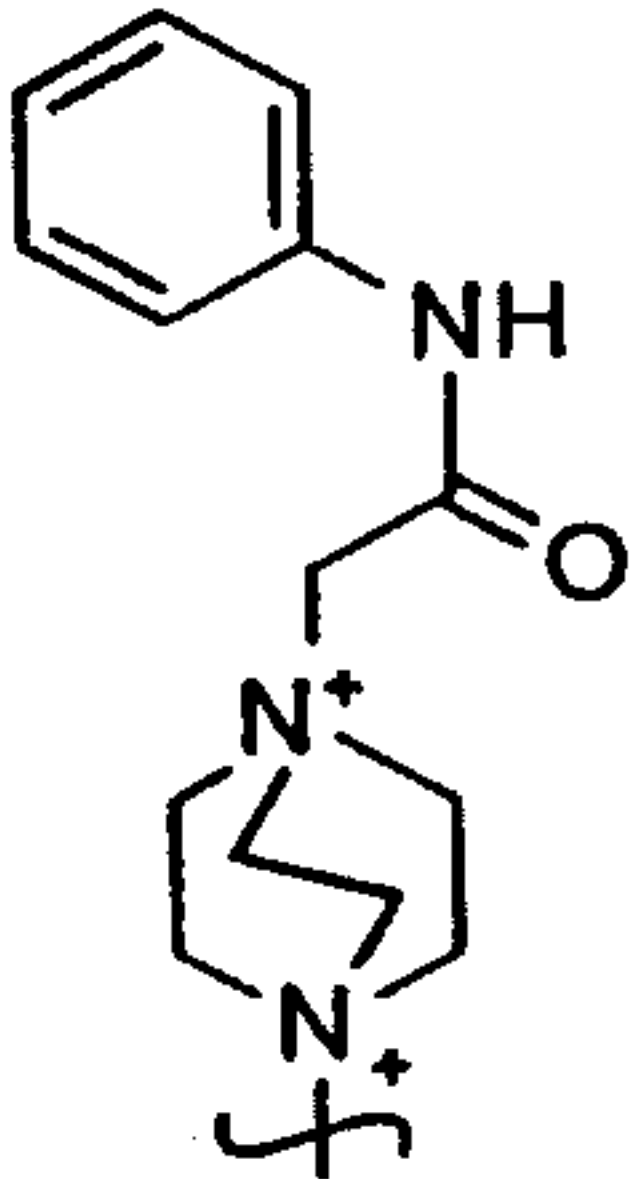
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9		10		11	

Ph = phenyl

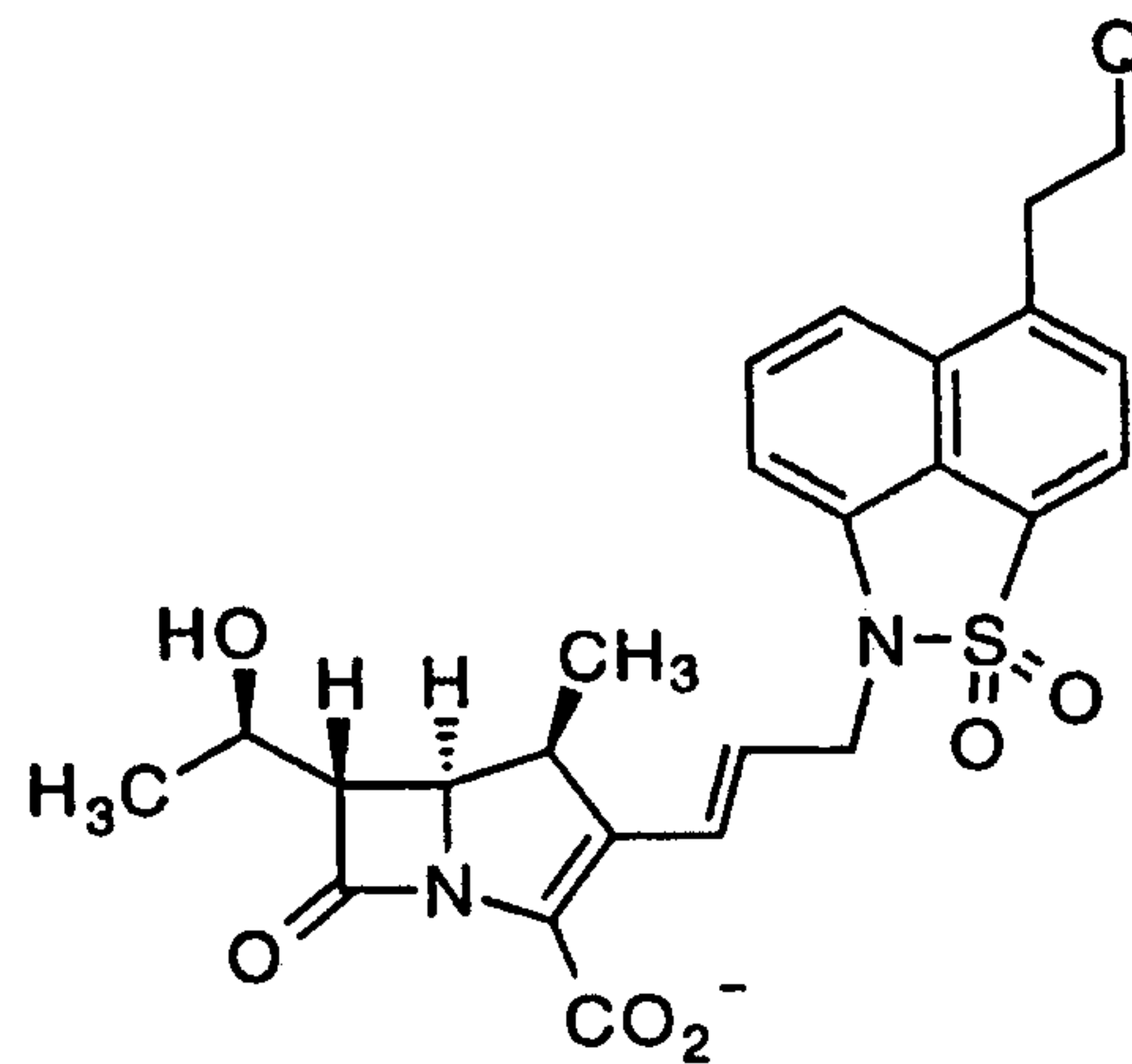
- 29 -

#		#		#	
12		13		14	
15		16		17	
18		19		20	

- 30 -

21	 <chem>c1ccc(cc1)S[C+]23C4CCN(C4)CC23</chem>	22	 <chem>O=S(=O)(c1ccccc1)[C+]23C4CCN(C4)CC23</chem>	23	 <chem>OCC[C+]23C4CCN(C4)CC23</chem>
24	 <chem>NCC[C+]23C4CCN(C4)CC23</chem>	25	 <chem>NCC[C+]23C4CCN(C4)CC23</chem>	26	 <chem>Nc1ccccc1C(=O)C[C+]23C4CCN(C4)CC23</chem>

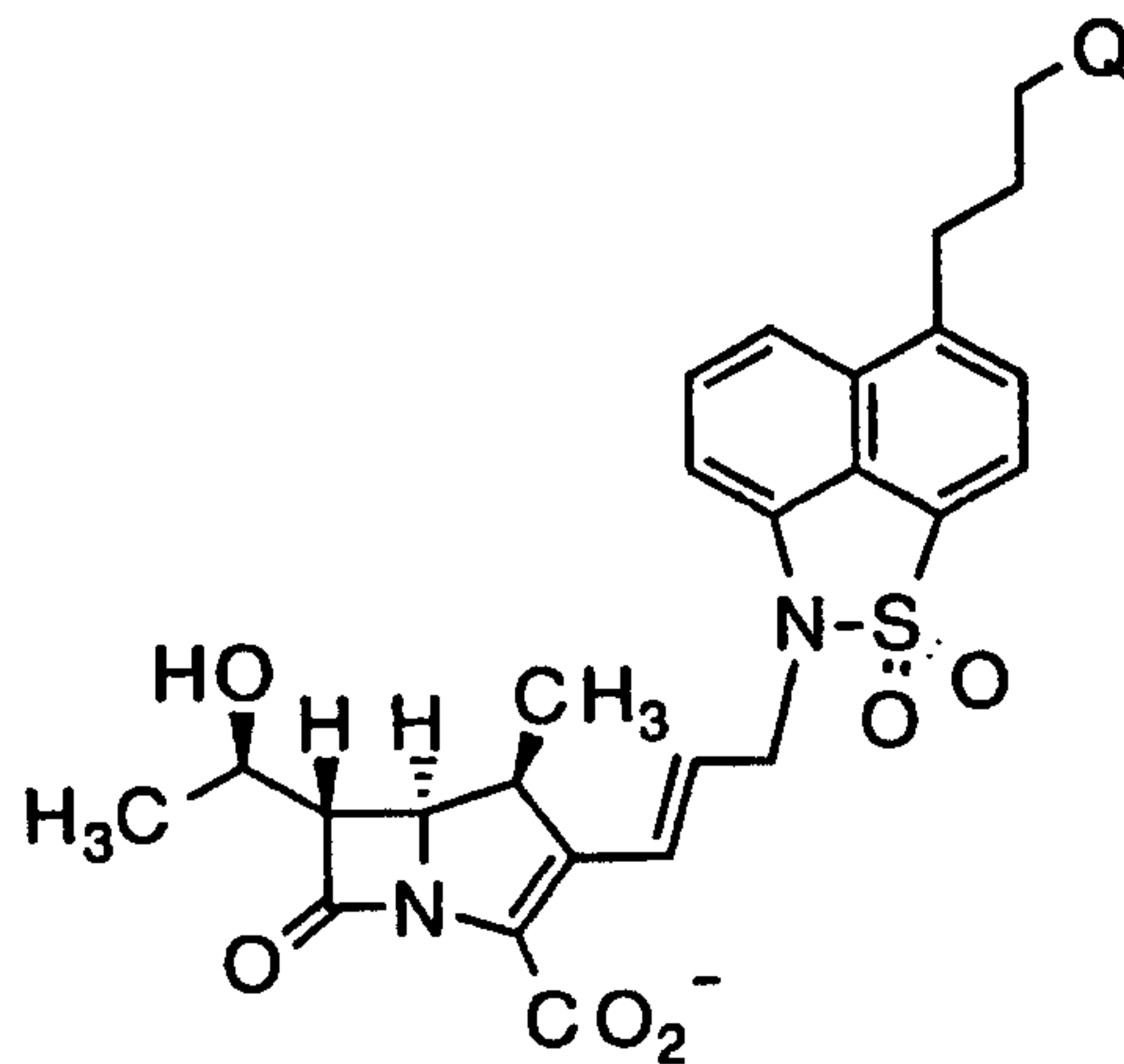
- 31 -



Table

#	Q	#	Q	#	Q
27		28		29	
30		31		32	

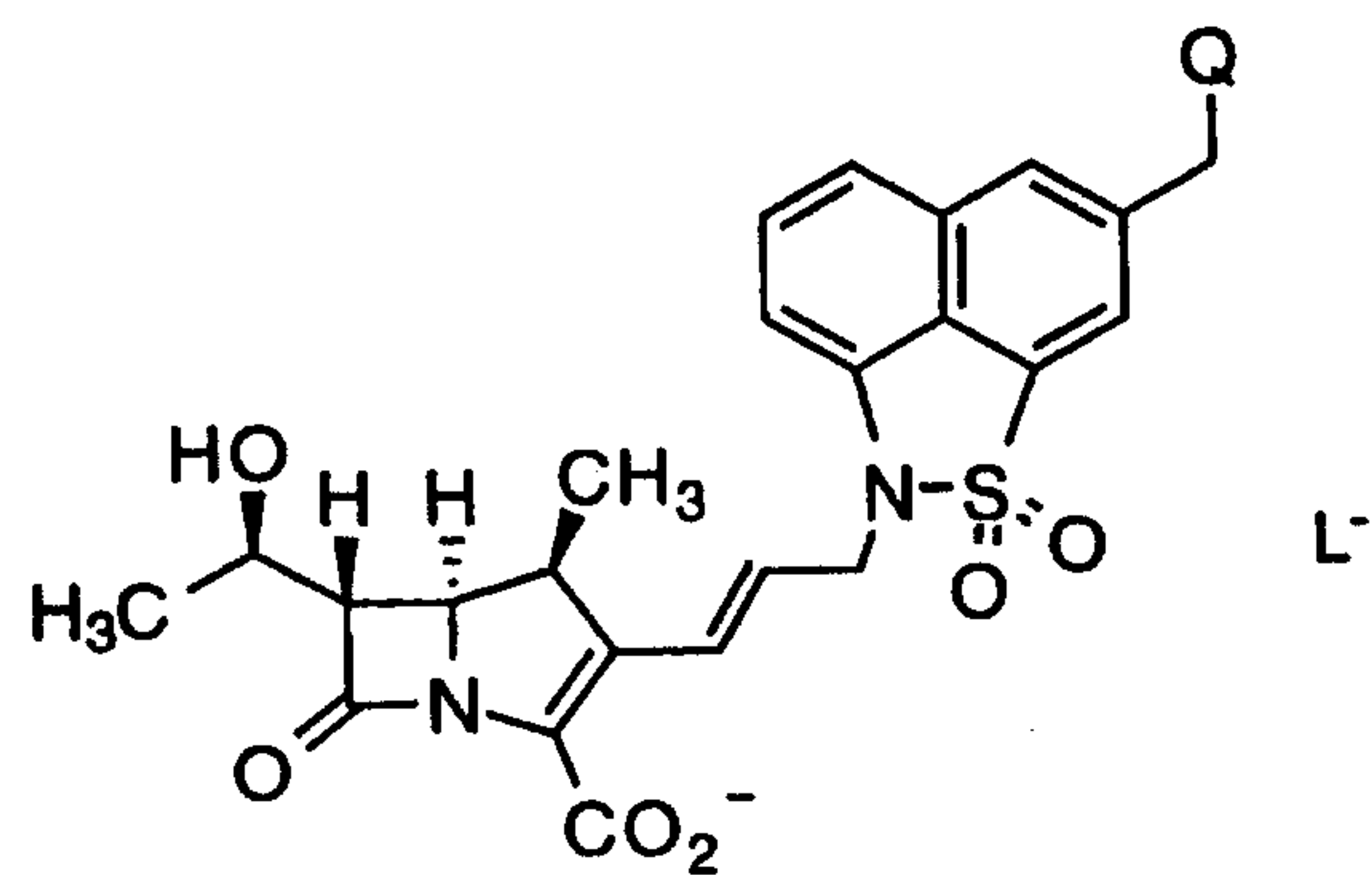
- 32 -



Table

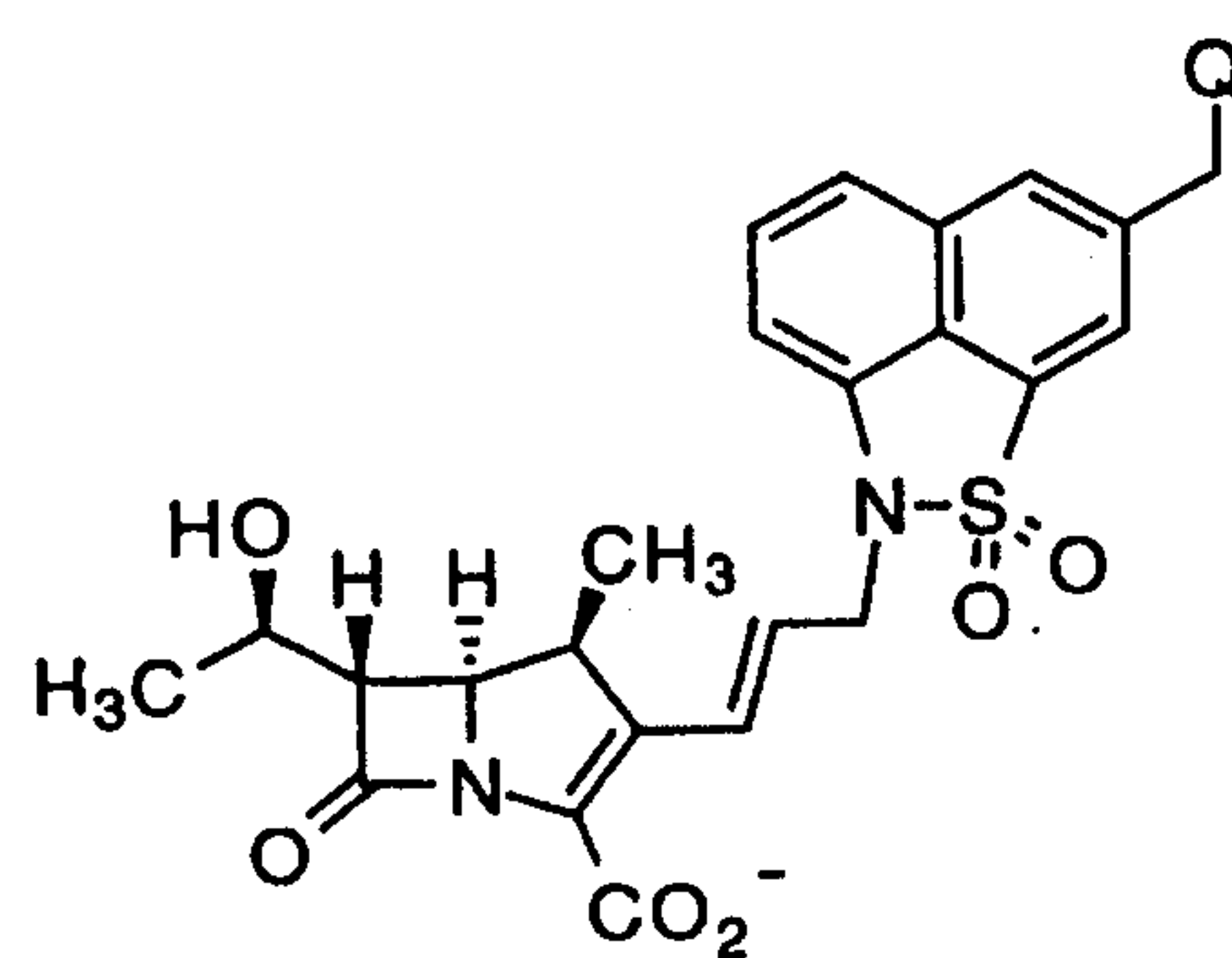
#	Q	#	Q	#	Q
34	NH_2 C=O L^-	35	HO-CH_2 L^-	36	CH_3 Q

- 33 -



Table

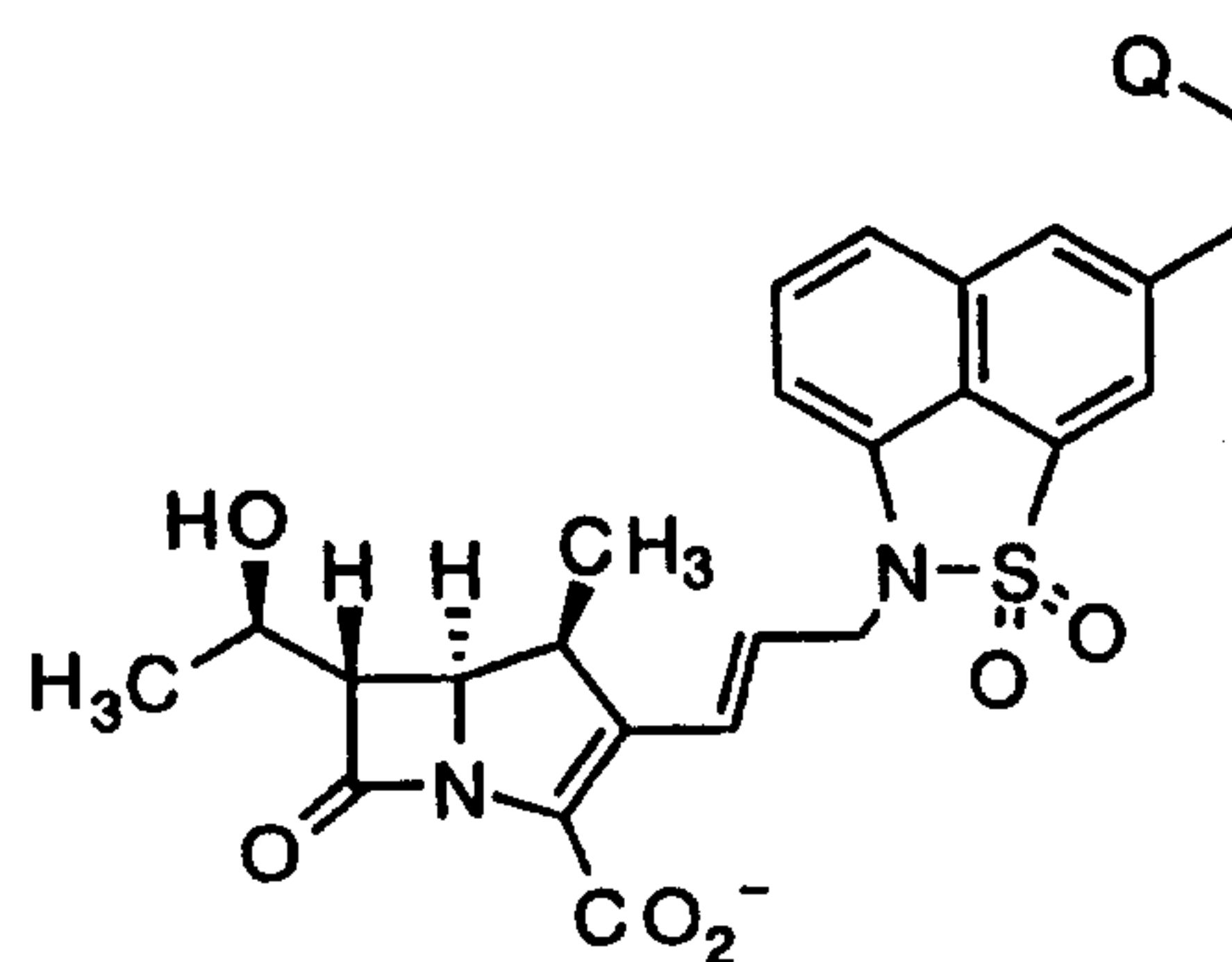
#	Q	#	Q	#	Q
38		39		40	



Table

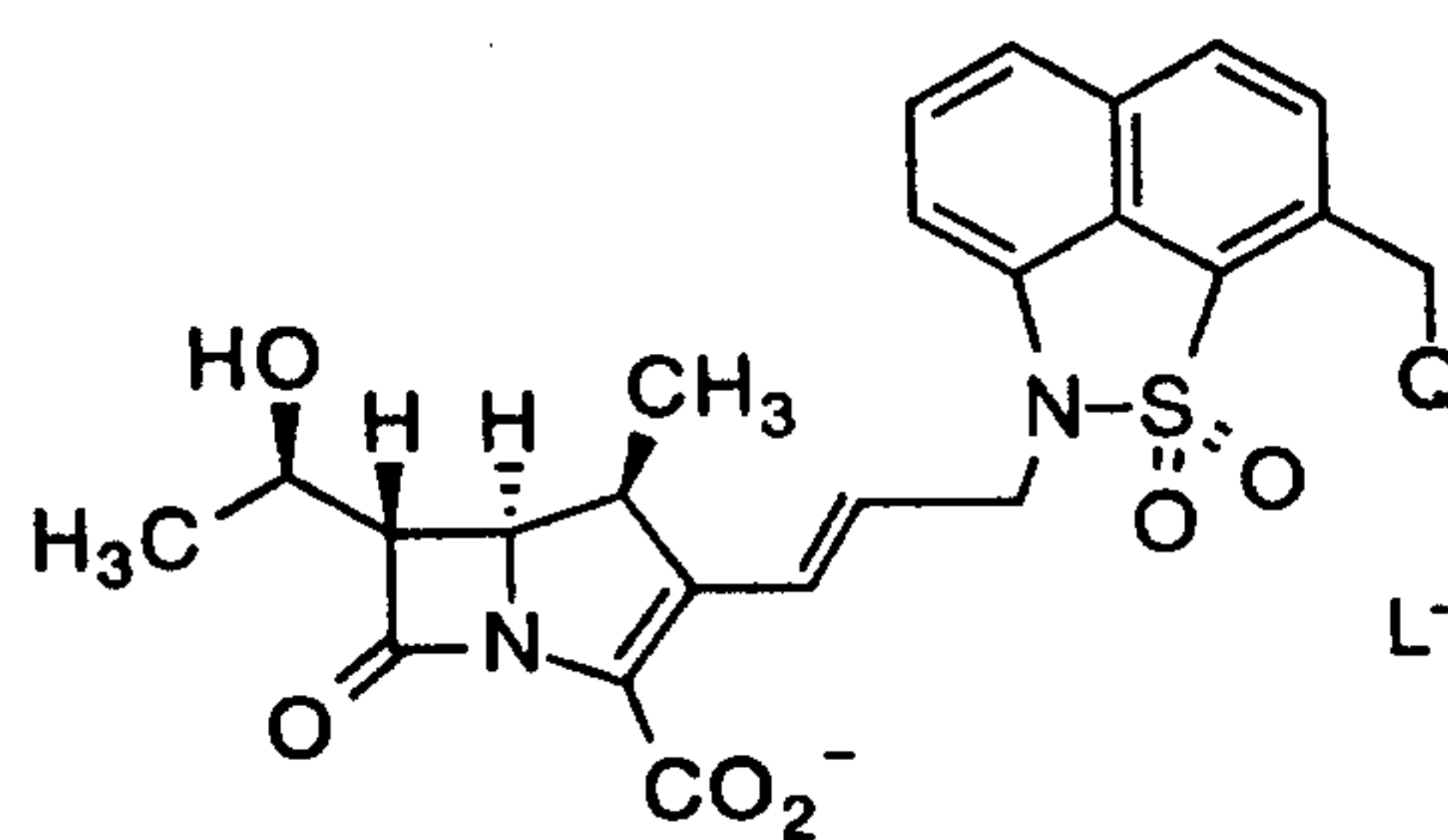
#	Q	#	Q	#	Q
41		42		43	

- 34 -



TABLE

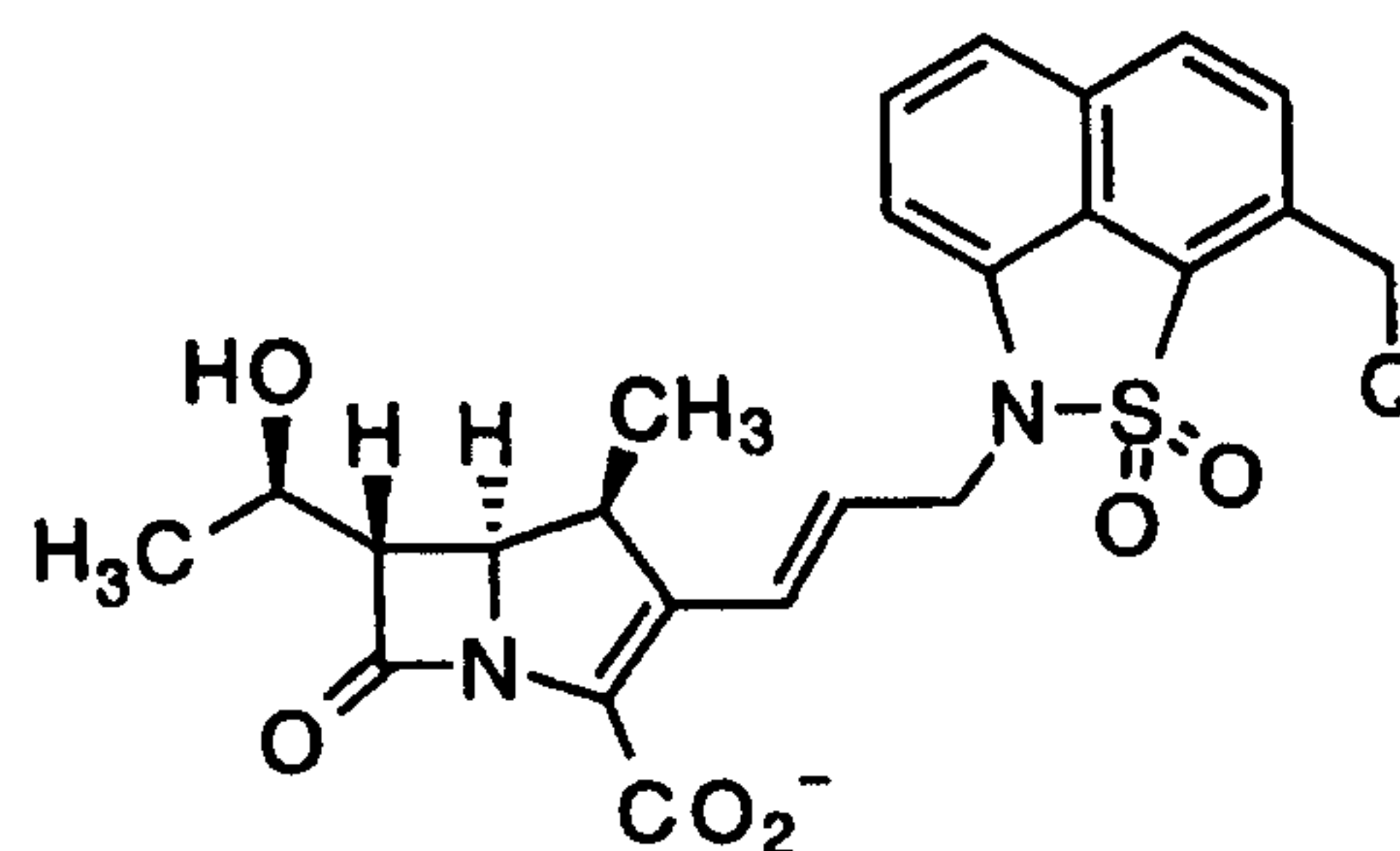
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45		46		47	



Table

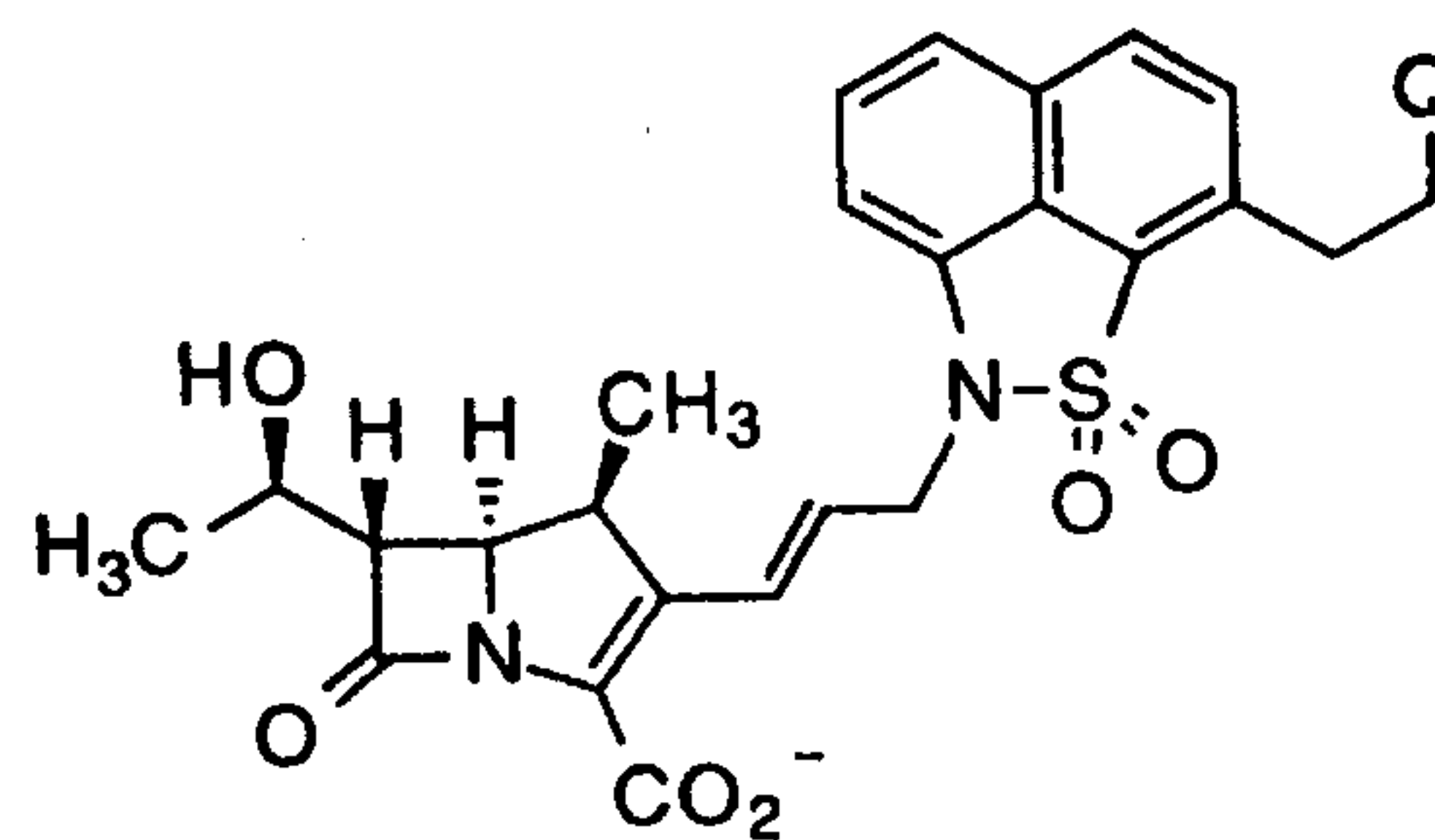
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49		50		51	

- 35 -



Table

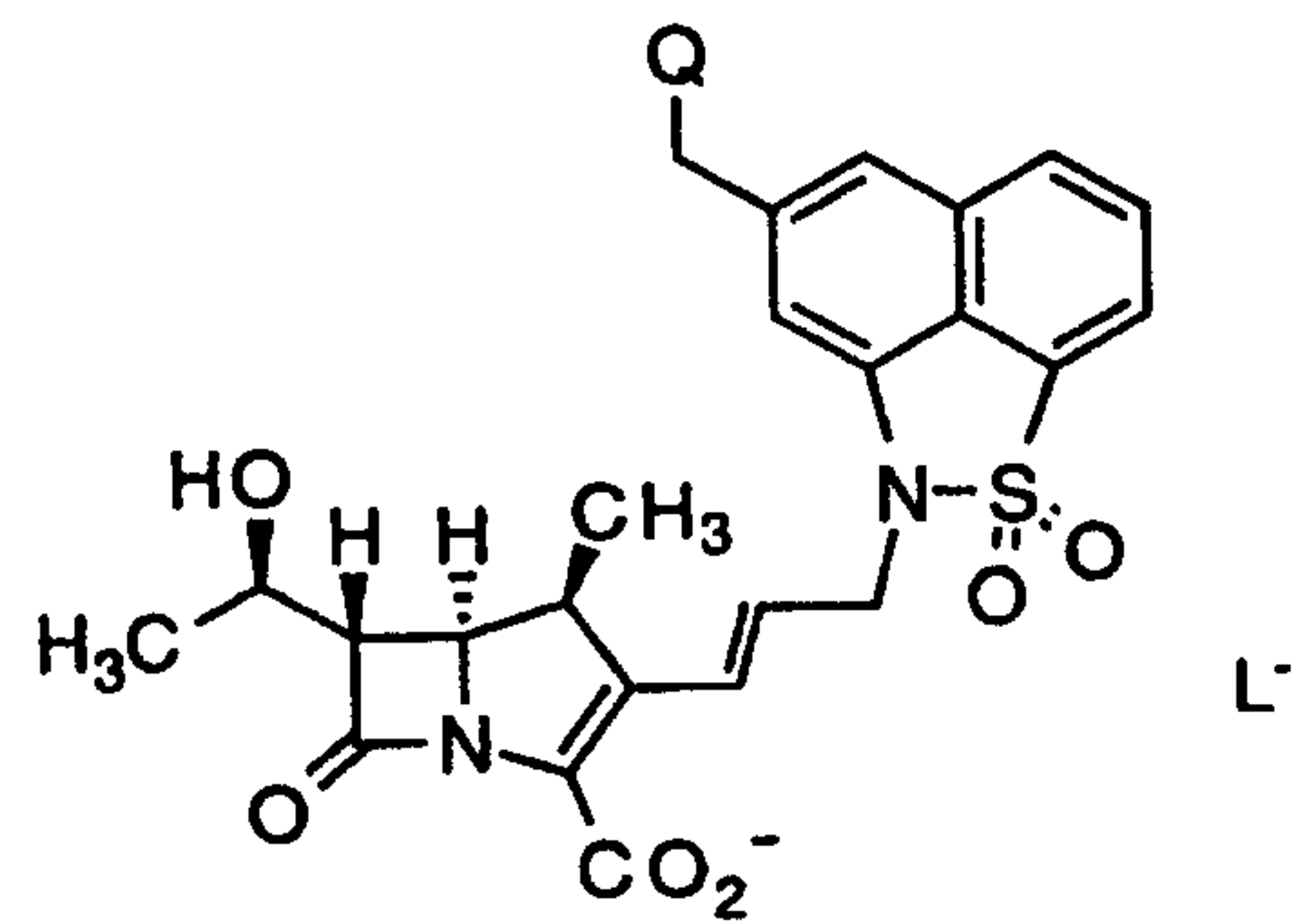
#	Q	#	Q	#	Q
52		53		54	



TABLE

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56		57		58	

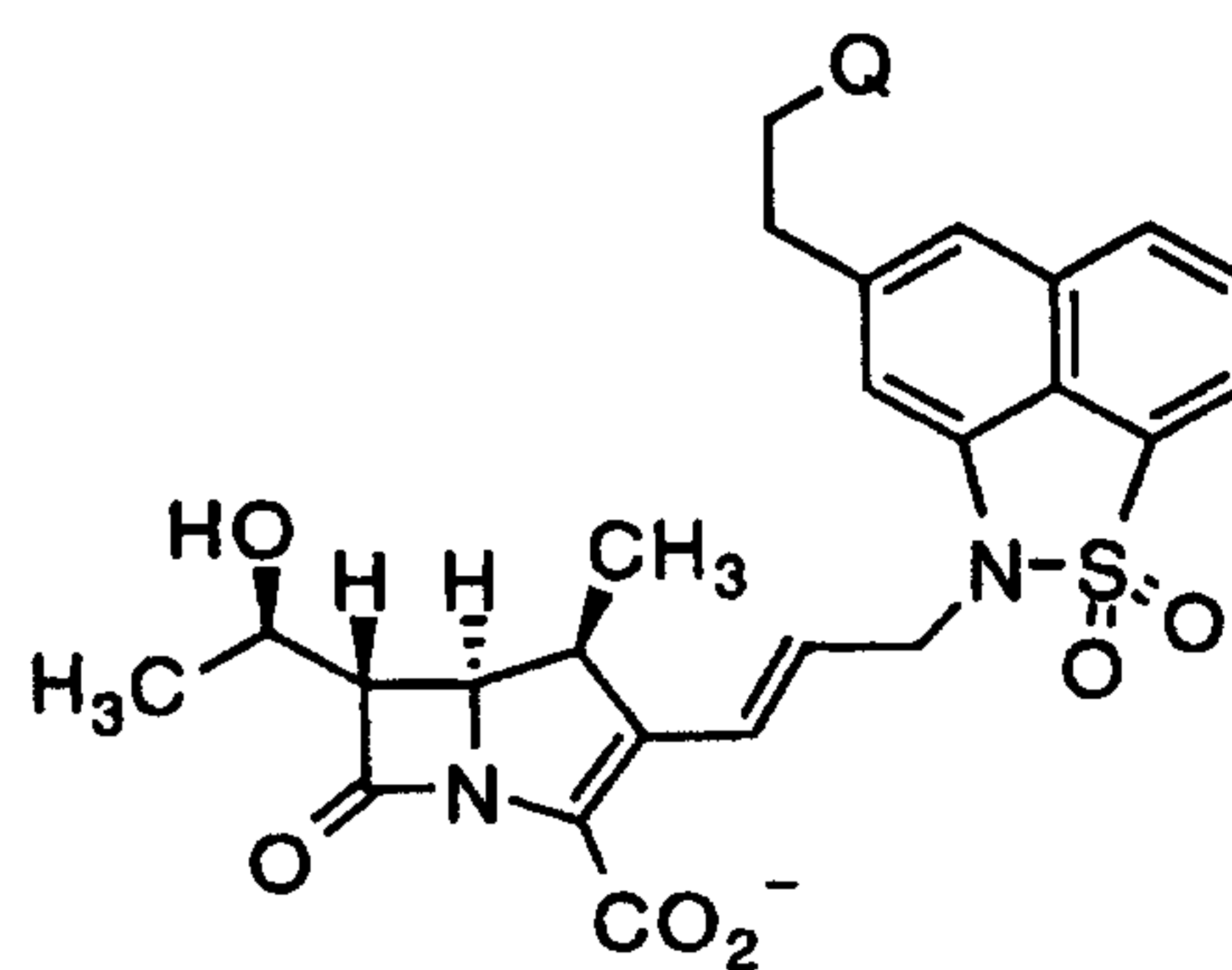
- 36 -



Table

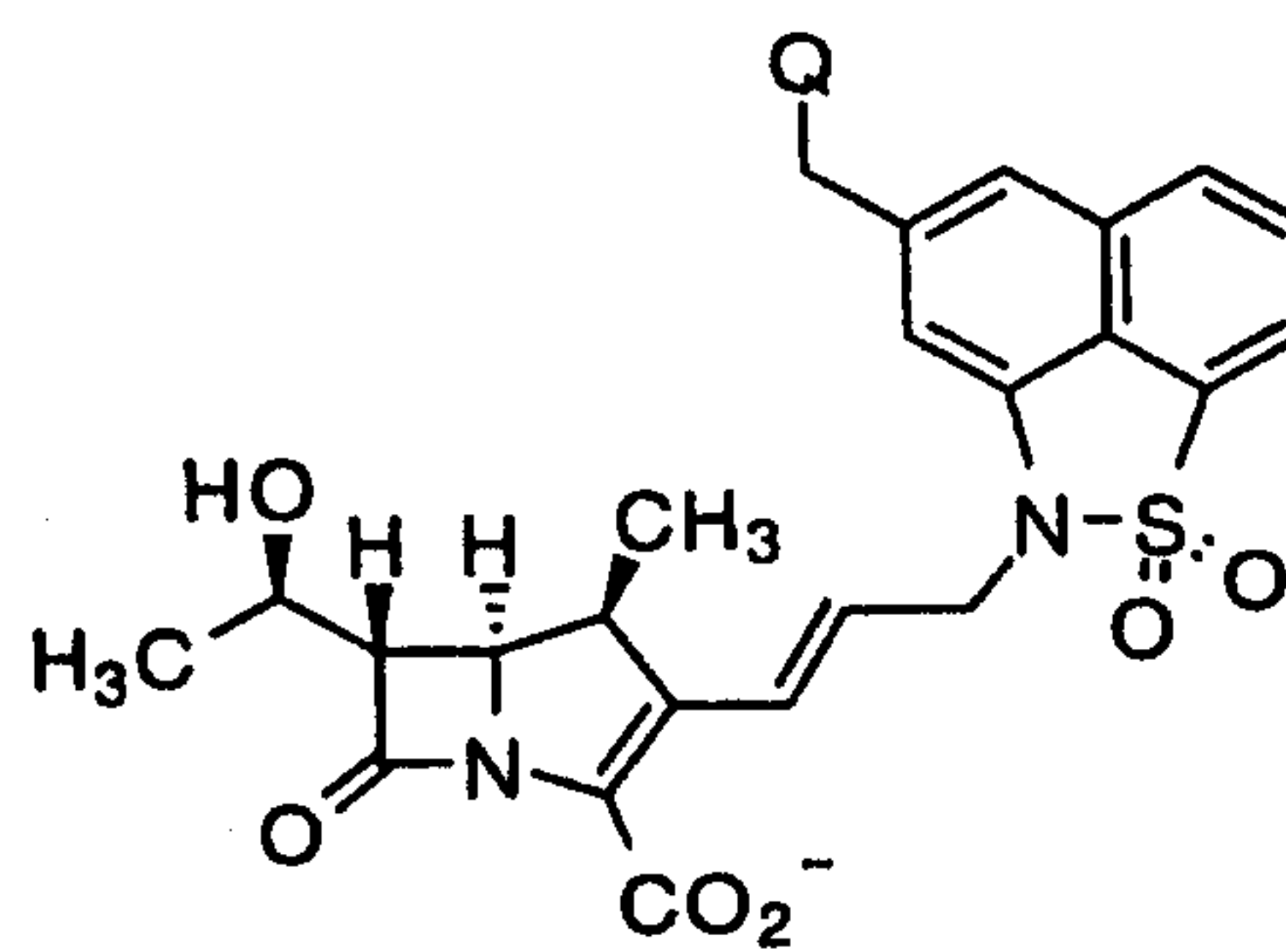
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60		61		62	

- 37 -



Table

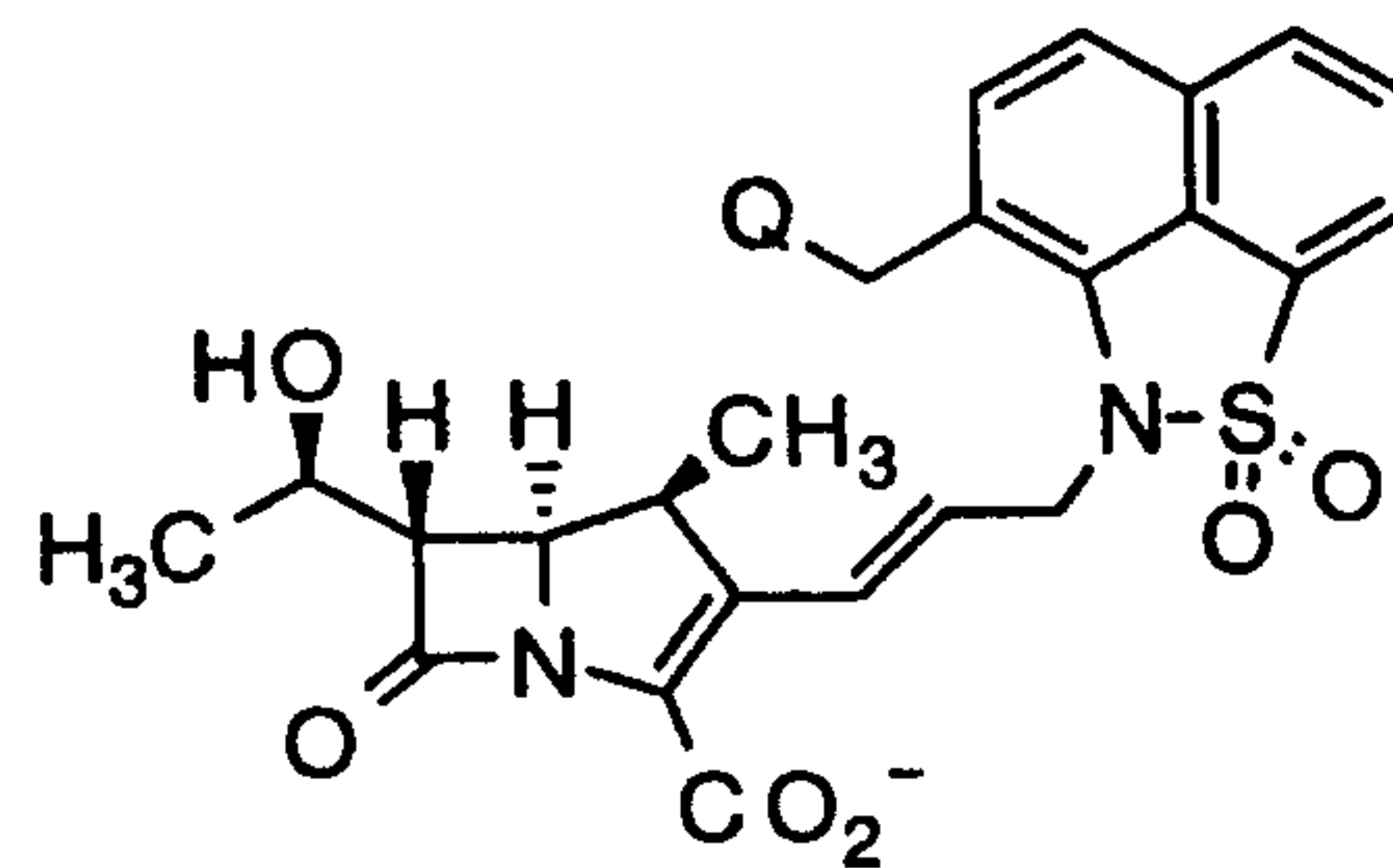
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67		68		69	



TABLE

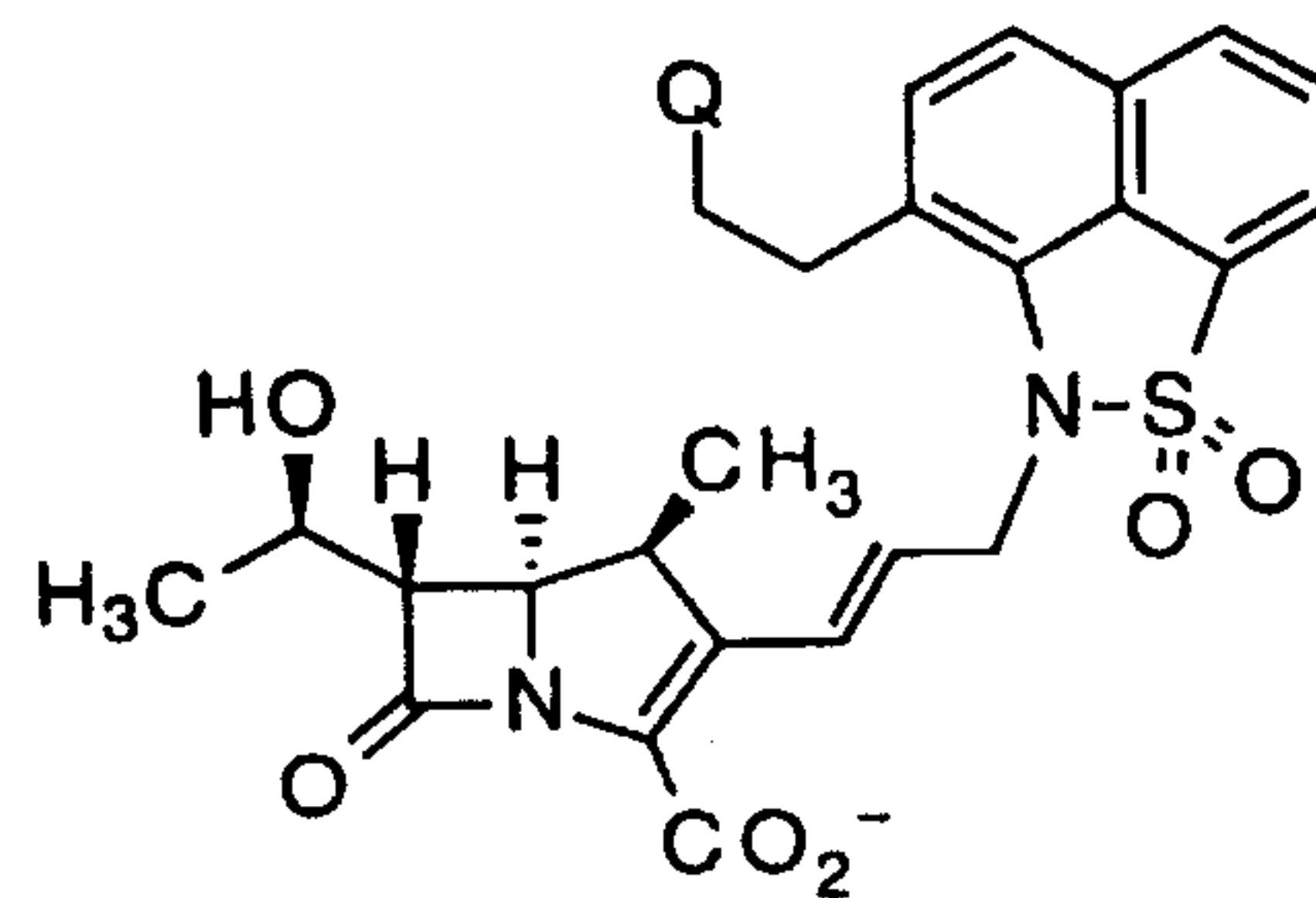
63		64		65	
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- 38 -



TABLE

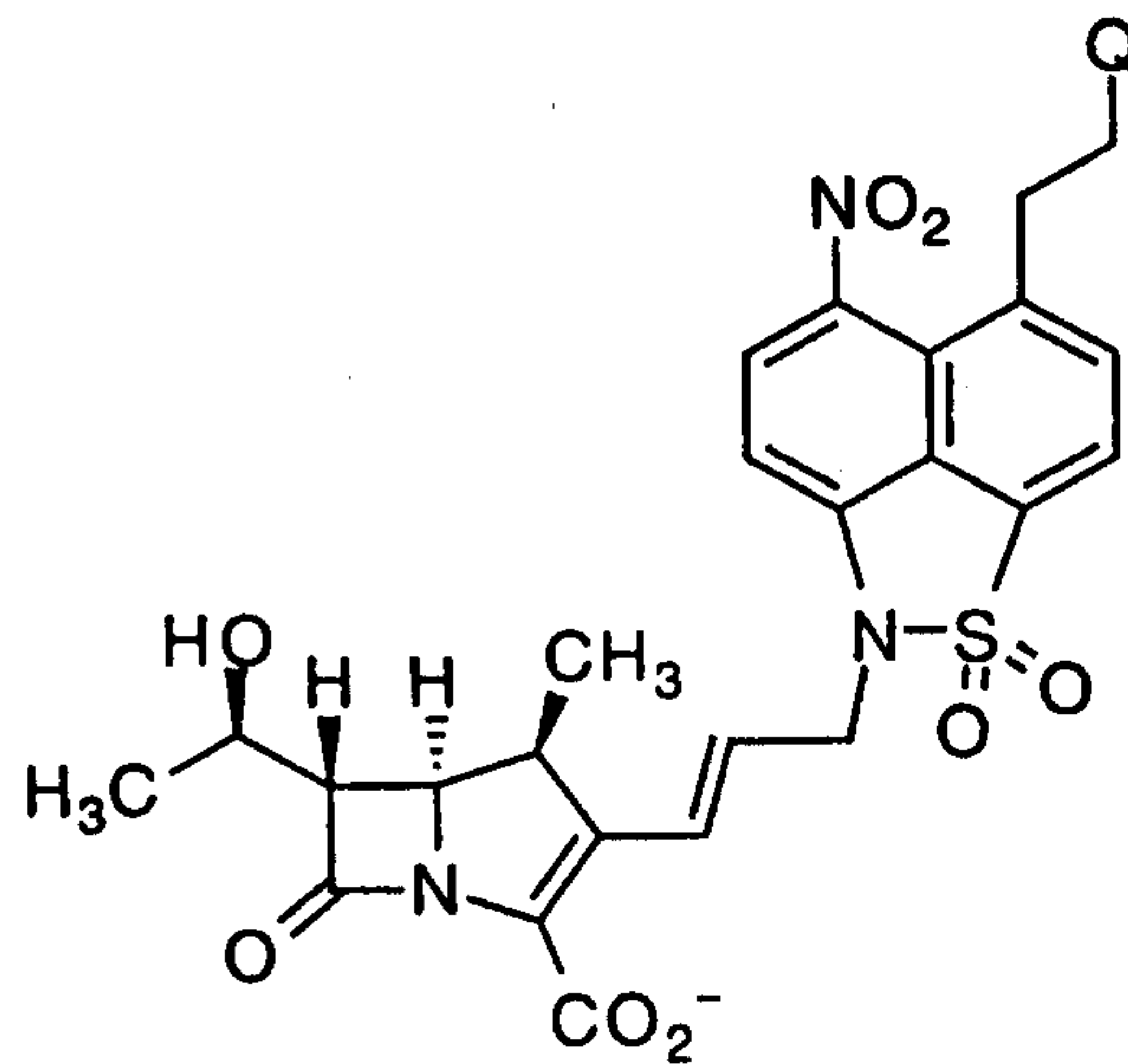
#	Q	#	Q	#	Q
74		75		76	



Table

#	Q	#	Q	#	Q
78		79		80	

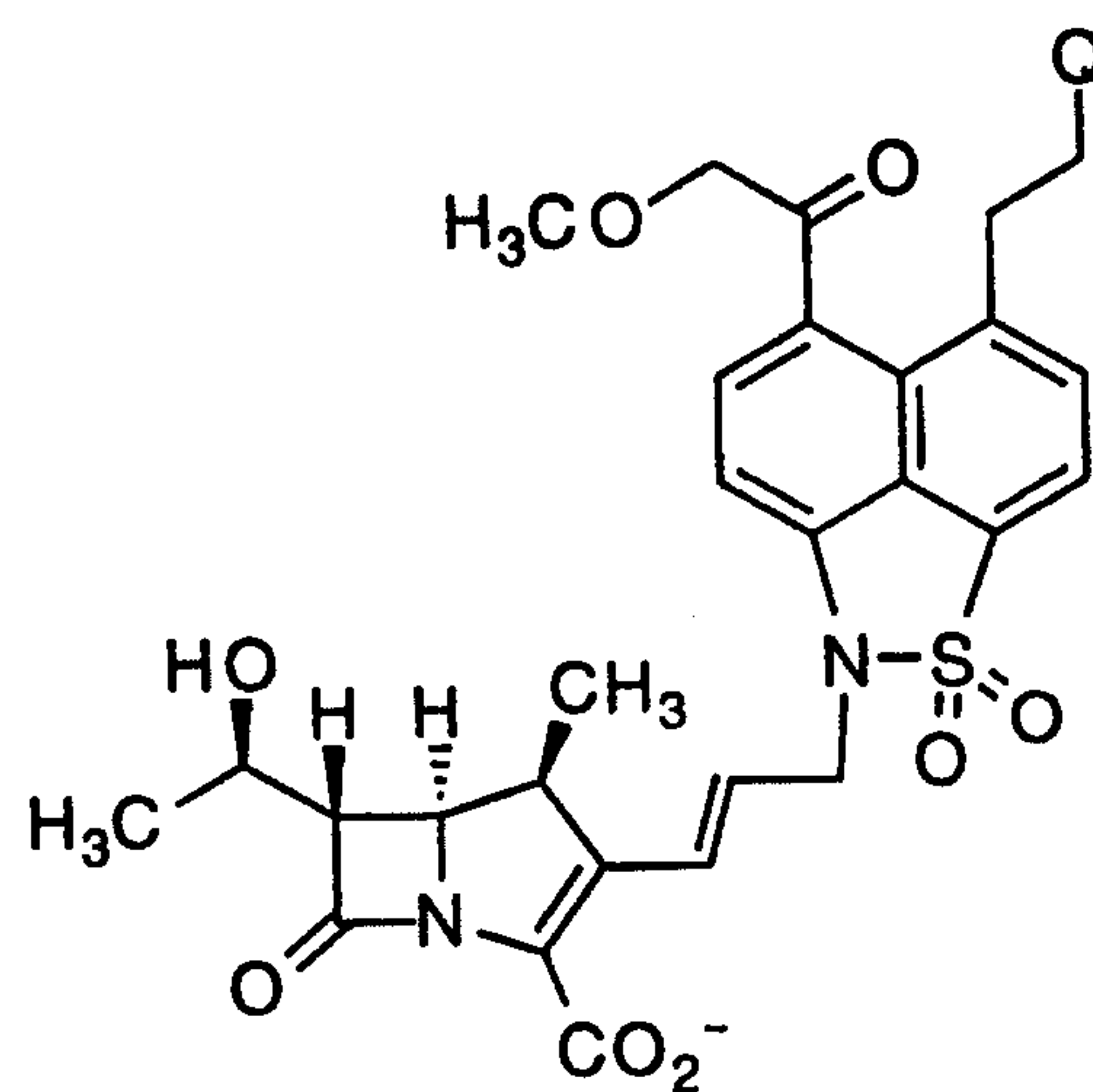
- 39 -



TABLE

#	Q	#	Q	#	Q
82		83		84	

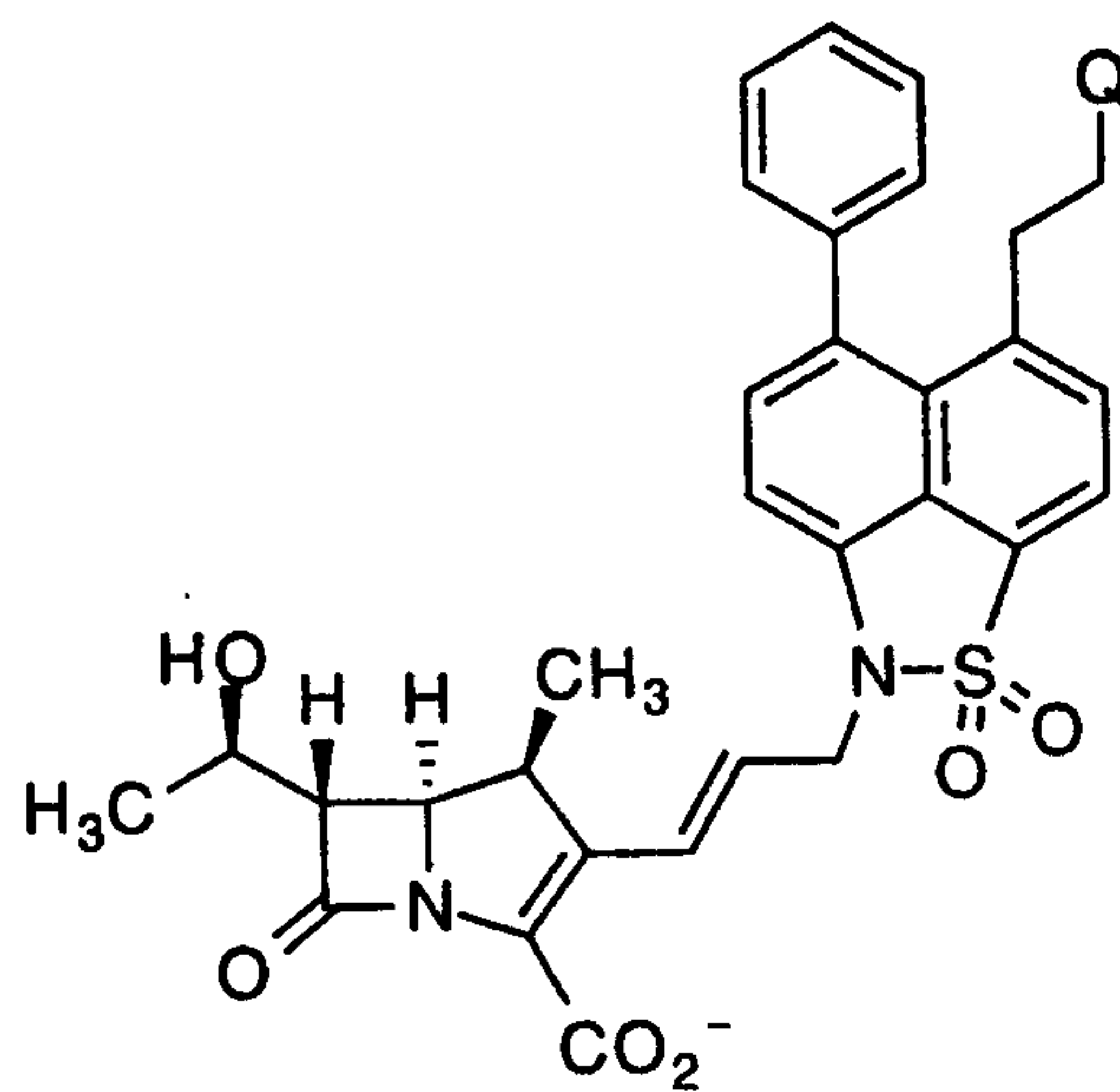
- 40 -



Table

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86		87		88	

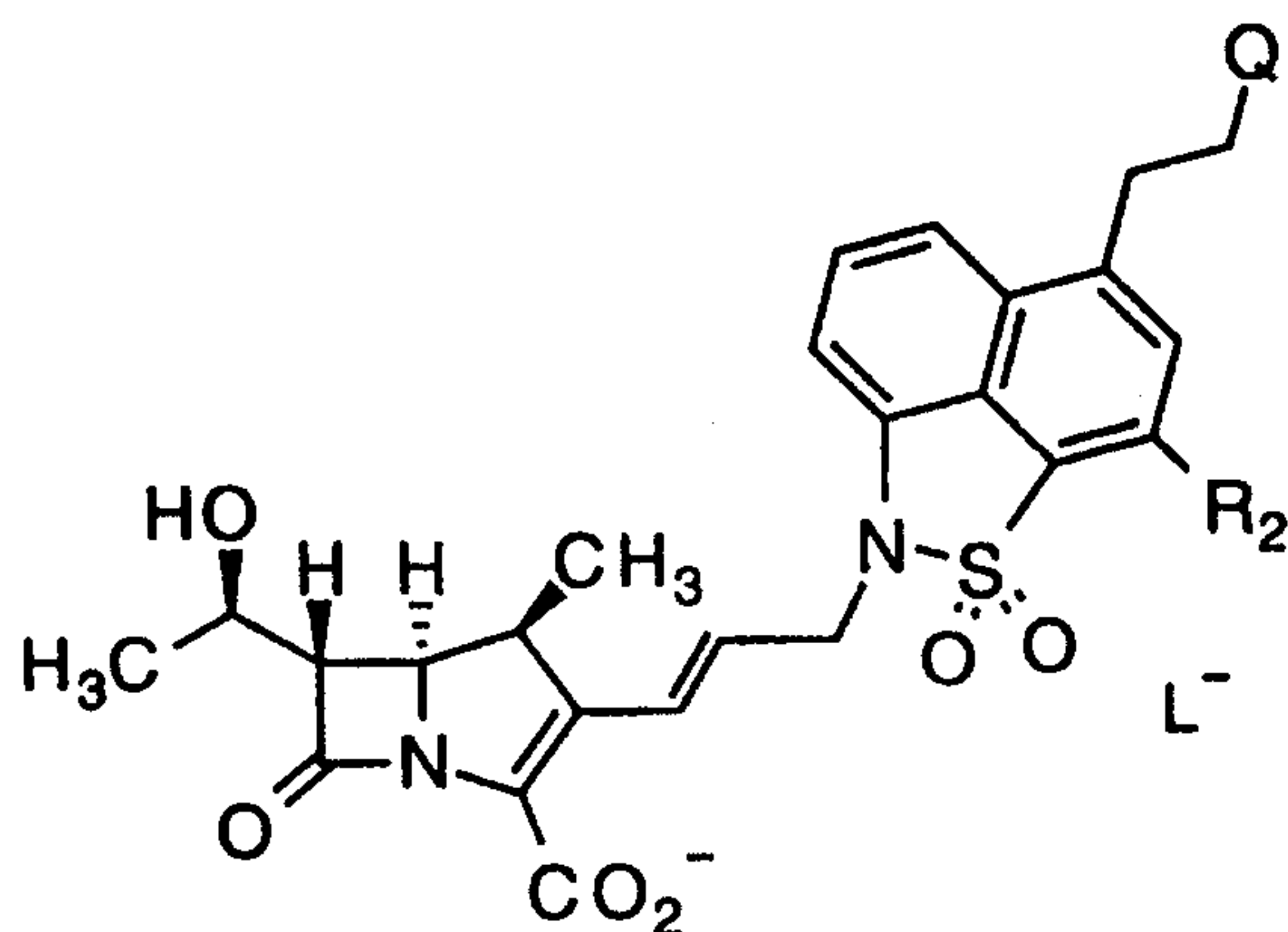
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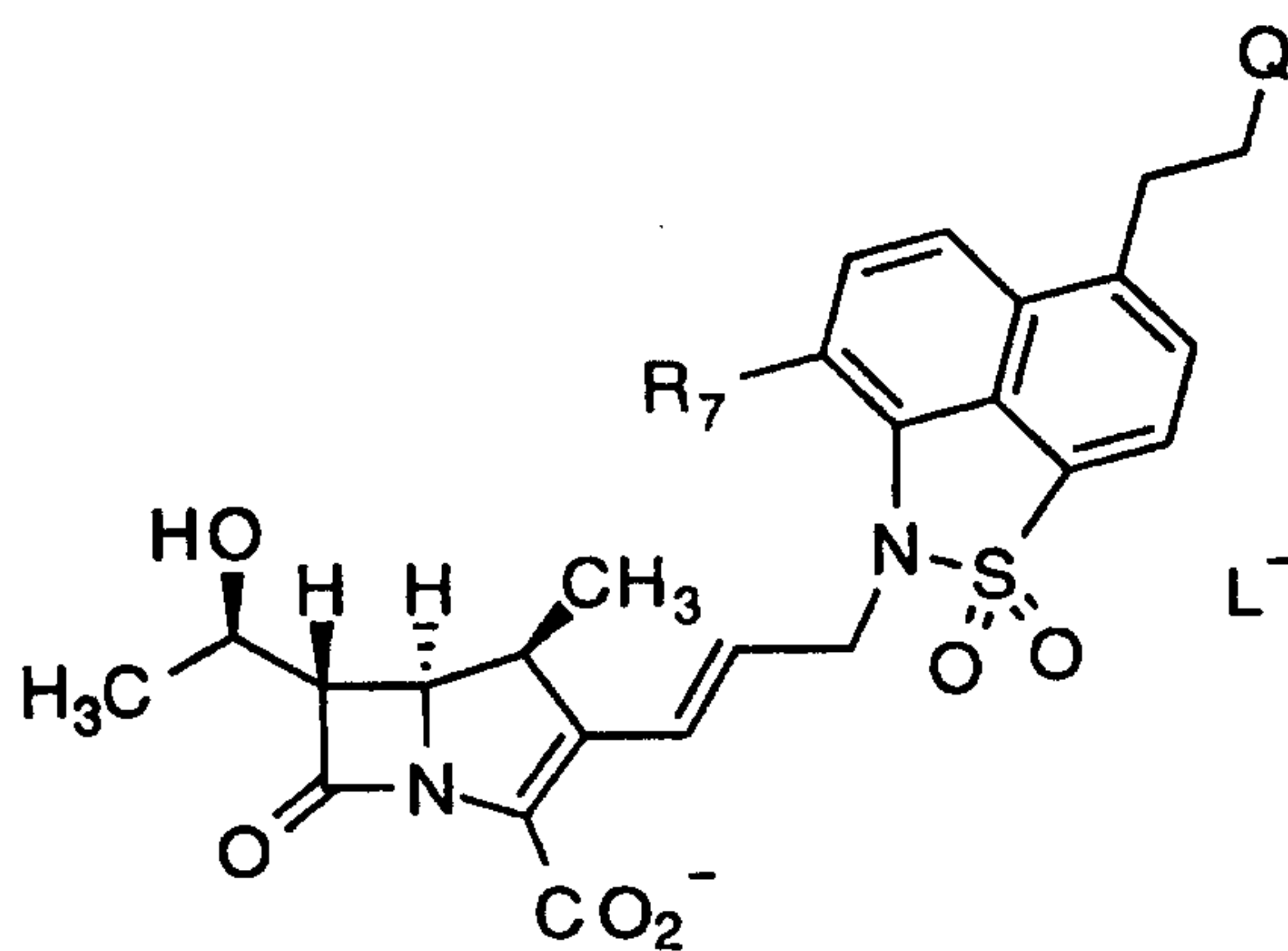
TABLE

#	Q	#	Q	#	Q
90		91		92	

- 42 -



R_2	Q	R_2	Q	R_2	Q	R_2	Q
Cl		CH_3		Cl		CH_3	



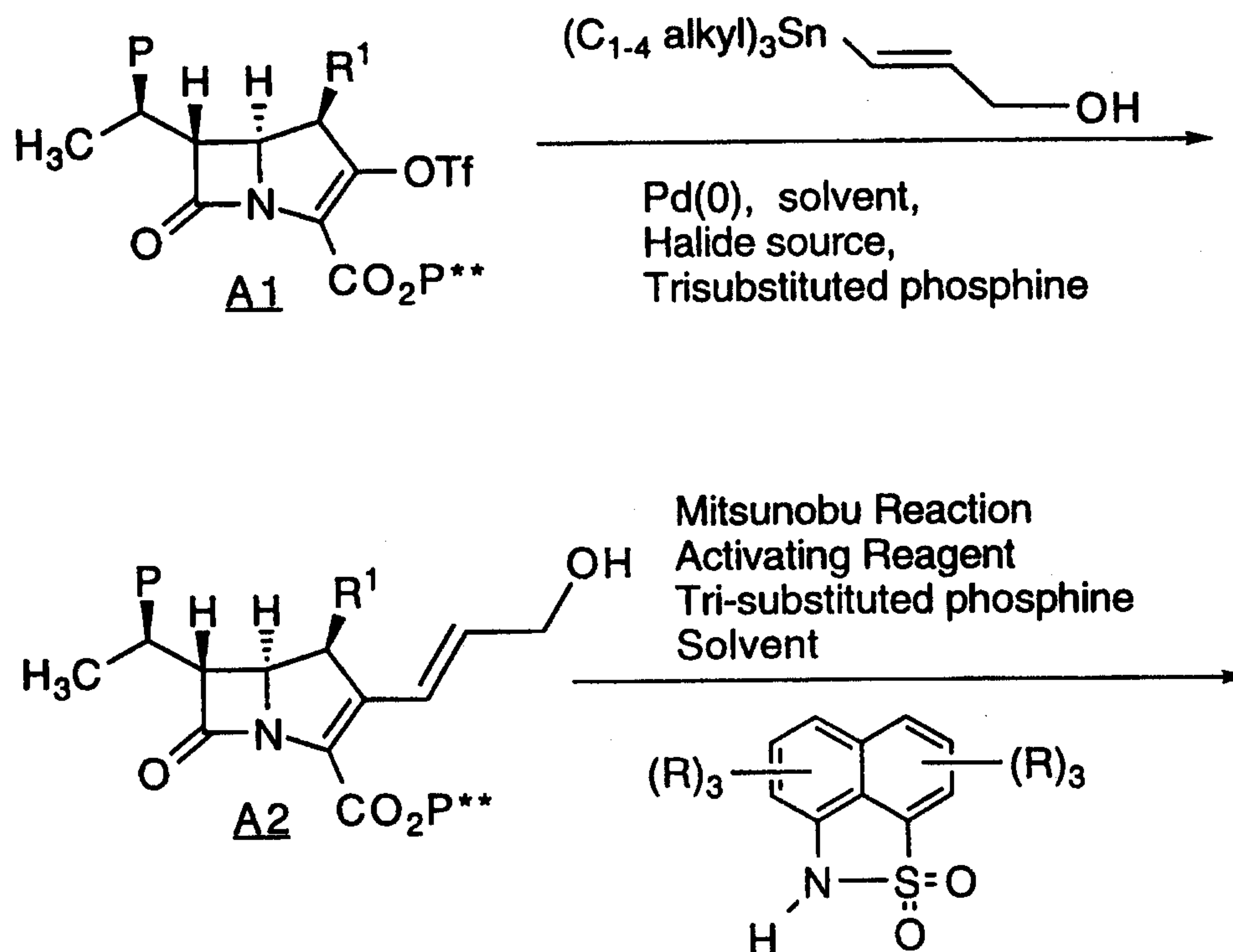
R_7	Q	R_7	Q	R_7	Q	R_7	Q
Cl		CH_3		Cl		CH_3	

- 43 -

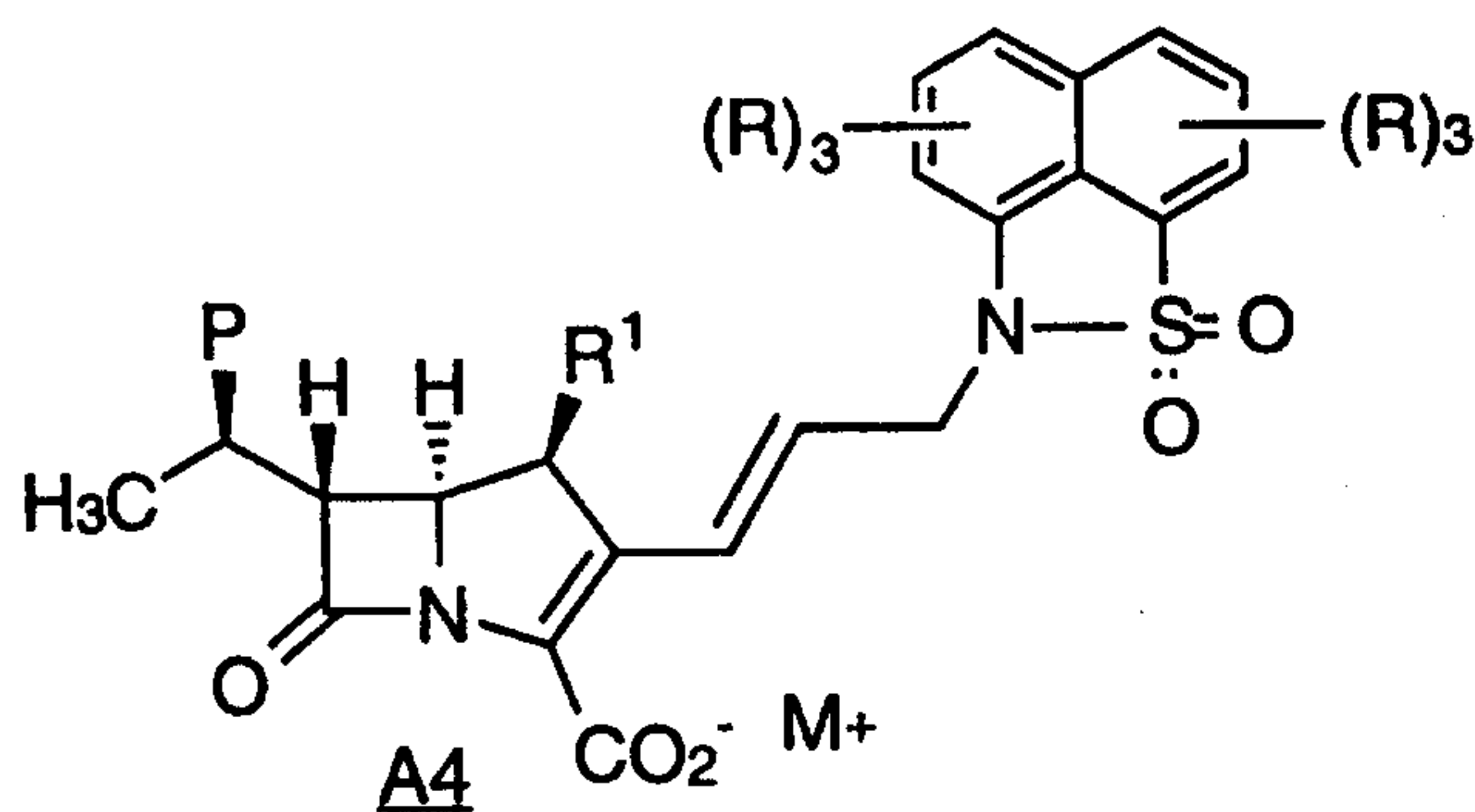
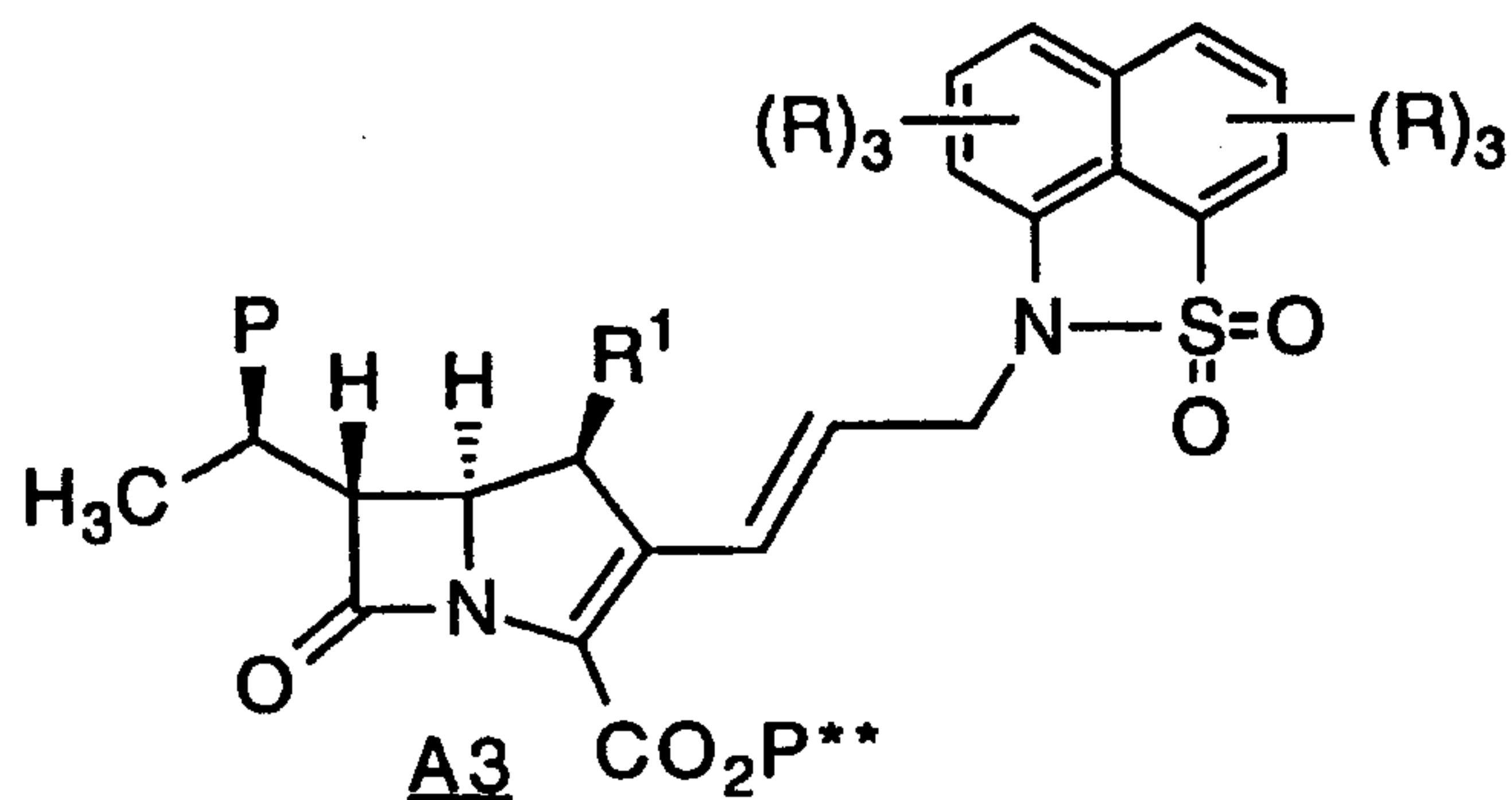
wherein Q is as defined in the tables and L⁻ represents a pharmaceutically acceptable counterion.

- The compounds of the present invention are prepared as depicted in Flow sheets A and B. The vinyl linked carbapenems are prepared, as shown in Flow sheet A, by reacting a suitably protected, activated 2-triflyl-carbapen-2-em-3-carboxylate A1 with a hydroxy allylic trialkyl stannane, to produce A2, and then reacting the naphthosultam under Mitsunobu conditions to produce A3. Removing any protecting groups which are present affords the desired final vinyllic product A4.

FLOW SHEET A



- 44 -

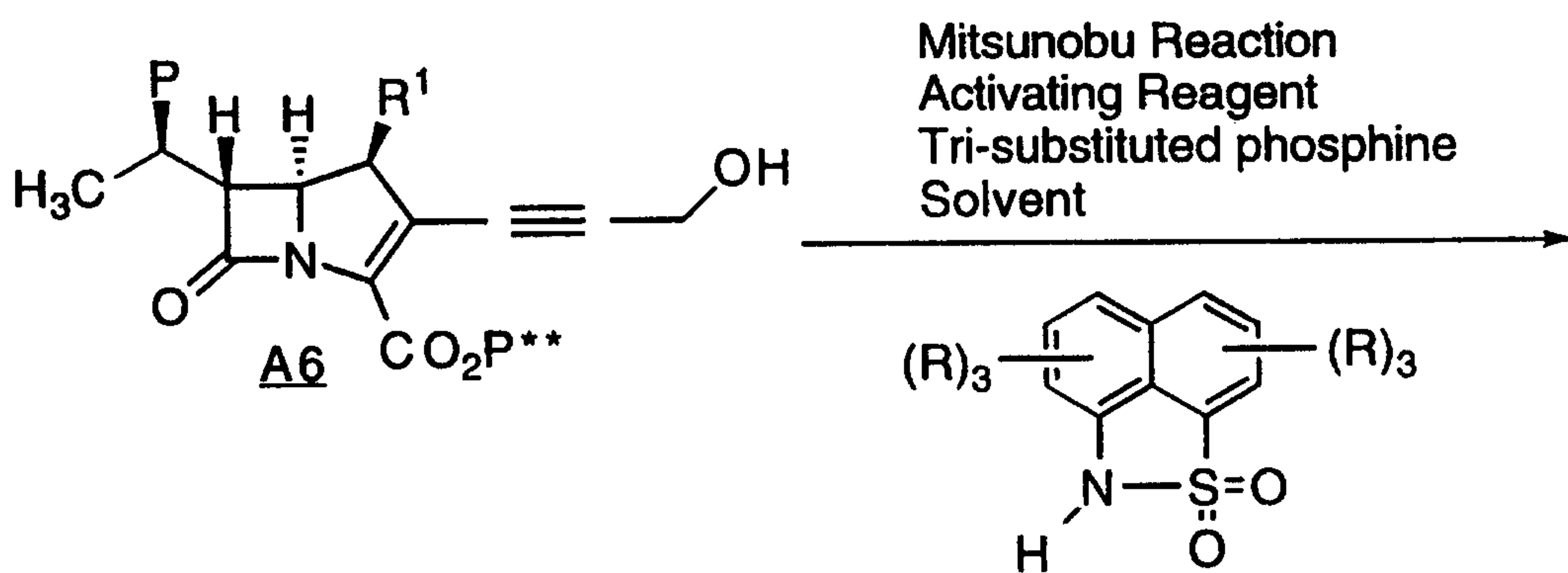
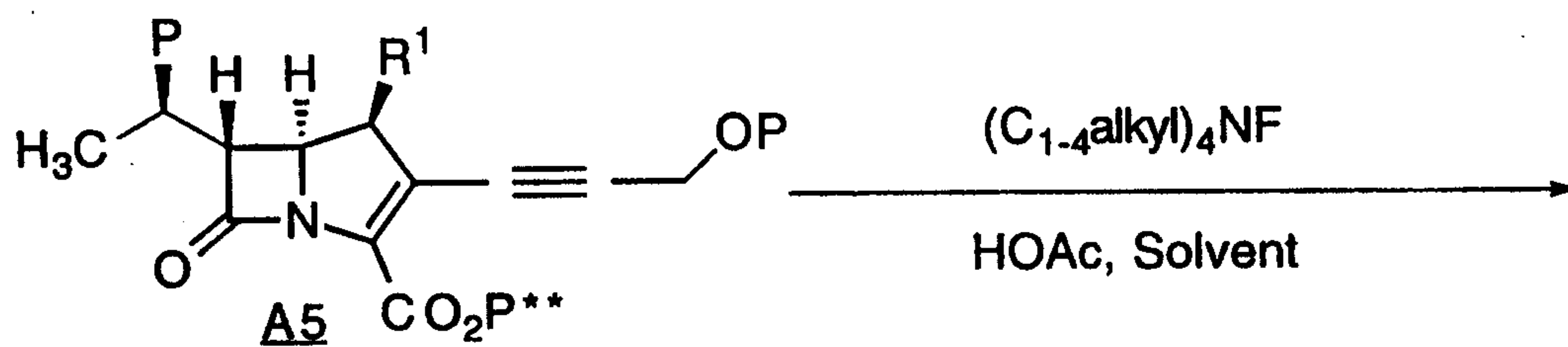
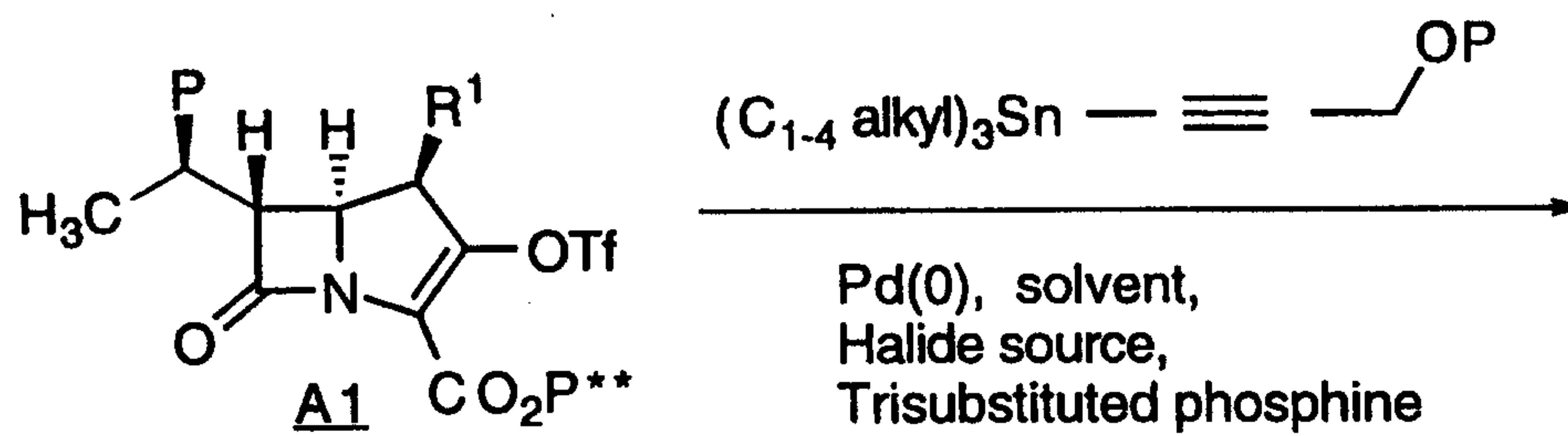


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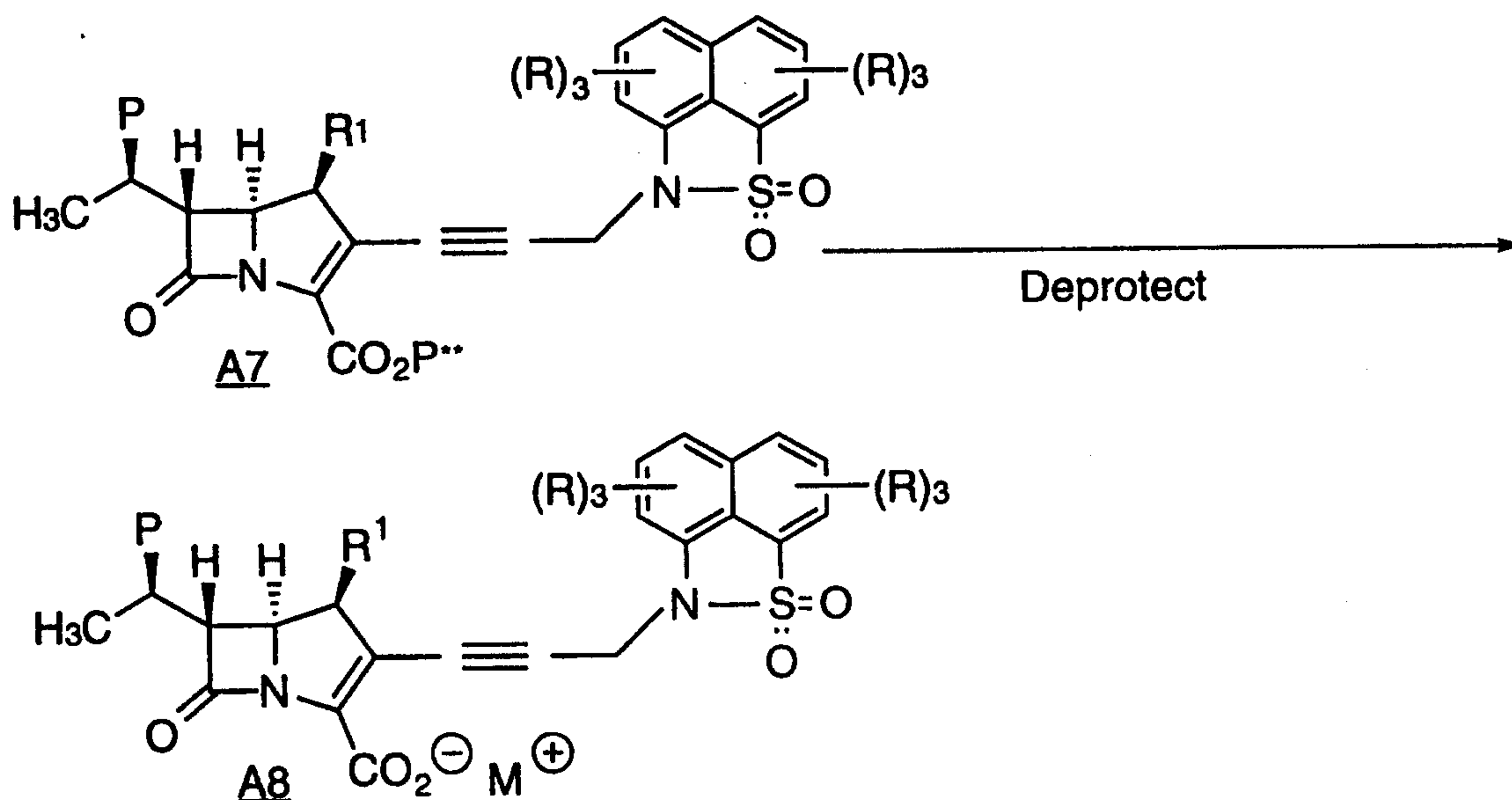
The acetylenic linked carbapenems are prepared as shown in Flow sheet B in which intermediate A1 is reacted with a protected hydroxy propargylic trialkyl stannane to produce A5, deprotecting the propargylic hydroxy group to produce A6, and then reacting the

10 naphthosultam under Mitsunobu conditions to produce A7. Removing any protecting groups which are present affords the desired final

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acetylenic product A8.FLOW SHEET B

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With reference to the flow sheets above, P, R¹, R, and M, are as defined with respect to the compounds of formula I, except that

5 M⁺ may be a metal cation, e.g., Na⁺.

P** represents a carboxyl protecting group.

The naphthosultam side chain group used in the syntheses of the compounds of the present invention have, in some cases, been described in the chemical literature. In other cases, precursor

10 compounds which may be readily converted to the requisite naphthosultam have been described in the literature. In cases where the requisite naphthosultam is not known in the literature it is necessary to synthesize the naphthosultam by a newly developed synthesis. One skilled in the art can adapt a previously published synthesis of an

15 analogous naphthosultam to prepare the requisite compound in a straightforward manner without undue experimentation. Numerous examples of naphthosultam synthesis are described herein (see below).

The naphthosultam side chain group is initially reacted with a suitably protected carbapen-2-em-3-carboxylate A2 or A3 substituted

20 with an allylic or propargyl group respectively at position 2.

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The carbapenem activated at position 2 A1 can be obtained in accordance with U. S. Pat. No. 4,994,568 granted on February 19, 1991, the teachings of which are incorporated herein by reference.

The carboxylic acid group at C-3 of the carbapenem is
5 generally protected as a carboxyl protecting group such as p-nitrobenzyl (PNB), allyl, p-methoxybenzyl, trichloroethyl, 2-trimethylsilylethyl, and the like. Furthermore, the hydroxyl group of the 6-(hydroxyethyl) side-chain is optionally protected with a hydroxyl protecting group such as trimethylsilyl (TMS), triethylsilyl (TES), tert-butyldimethylsilyl
10 (TBDMS), tert-butyldiphenylsilyl (TBDPS), acetyl, allyloxycarbonyl, 2-trimethylsilylethoxy carbonyl, 2-trichloroethoxycarbonyl and the like.

Attachment of the naphthosultam side chain group to the carbapenem is accomplished by treating a solution of the allyl or propargyl substituted carbapenem A2 or A3 respectively and the
15 naphthosultam side chain group in a suitable solvent such as tetrahydrofuran (THF), ether, acetonitrile, dimethylformamide (DMF), benzene, dimethylsulfoxide (DMSO), and the like with a combination of reagents that comprise the Mitsunobu reaction (for a review see: Hughes, D.L. *Organic Reactions*, Paquette, L. ed., Vol. 42, John Wiley
20 & Sons, USA, 1992.) such as an azodicarboxylate like diethylazodicarboxylate (DEAD), diisopropyldiazodicarboxylate (DIAD), and tetramethyldiazodicarboxamide (TMAD), or the like, and a tri-substituted phosphine, such as triphenylphosphine, tri-n-butylphosphine,
25 and the like, at a temperature between about -20 °C and 35 °C for about 5 to 90 minutes.

Alternatively, the naphthosultam and carbapenem can be simultaneously added to a preformed complex of the diazocarboxylate and phosphine. Once the naphthosultam, carbapenem, and activating
30 reagent(s) have been mixed, the reaction is allowed to proceed at a temperature between about -20 °C and 35 °C for about 5 to 90 minutes.

The resulting mixture is then subjected to a standard work-up procedure familiar to those skilled in the art to afford a crude 2-naphthosultam-methyl substituted carbapenem which is purified, if

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necessary, by recrystallization or by chromatography on silica gel, eluting with a suitable solvent or mixture of two or more solvents, such as hexane, ethyl acetate, ether, benzene, dichloromethane, chloroform, acetone, methanol and the like.

- 5 Modification of the naphthosultam side chain is best accomplished before removal of the protecting groups. For compounds which contain a hydroxyl group in the side chain, a positively charged substituent may be introduced into the side chain by first activating the hydroxyl group, such as by converting it to a suitable leaving group,
10 e.g., triflate, mesylate, tosylate, iodide, chloride, bromide and the like, and then displacing the resulting leaving group with a compound Q, such as N-methyl-imidazole, N-(2-hydroxyethyl)-imidazole, N-methyl-diazabicyclooctane, 1-(carbamoylmethyl)-4-aza-1-azoniabicyclo-[2.2.2.]-octane, 1-(3-hydroxyprop-1-yl)-4-aza-1-azoniabicyclo-[2.2.2.]-octane,
15 pyridine, morpholine and the like which contains a nitrogen atom that can act as a nucleophile.

- Alternatively, in some cases, the charged substituent may be incorporated in the naphthosultam side chain before addition of the naphthosultam to the carbapenem or may be introduced after
20 deprotection. However, introduction of the charged substituent before deprotection is greatly preferred.

- In some cases, activation of the hydroxyl group and displacement by the charged moiety may be accomplished in a single step by taking advantage of the basic character of compound Q and
25 using it as a base in the activation reaction.

- The conversion of the hydroxyl group to a suitable leaving group is accomplished by treating the hydroxyl substituted compound in a suitable solvent such as dichloromethane, tetrahydrofuran, ether, benzene and the like with the activating reagent,
30 such as trifluoromethanesulfonic anhydride, methanesulfonic anhydride, toluenesulfonic anhydride, methanesulfonyl chloride, benzenesulfonyl chloride, toluenesulfonyl chloride, and the like in the presence of a suitable base, such as triethylamine, tributylamine, diisopropylethyl-

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amine, and the like, at a temperature between about -100°C and 0°C for about 5 to 120 minutes. The intermediate thus obtained contains a leaving group, which may be converted to a more suitable leaving group, e.g., iodide, by treating a solution of the intermediate in a
5 suitable solvent such as acetone, methyl ethyl ketone, and the like at about -10°C to 50°C with an excess of sodium iodide or potassium iodide for about 0.25 to 24 hours.

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

The activated hydroxyl group or iodide is displaced by reacting the activated intermediate with reagent Q. In some cases, activation and displacement of the hydroxyl group may be accomplished
15 in a single step. The activating reagent is added to a solution of the hydroxyl substituted compound in the presence of a suitable base in a suitable solvent such as dichloromethane, tetrahydrofuran, ether, DMF, benzene, acetonitrile, DMSO, and the like as described in the preceding paragraphs. The resulting activated intermediate is treated with 1-3
20 molar equivalents of compound Q at a temperature between about -78°C and 50°C for about 15 to 120 minutes. In some cases, it is desirable to form the activated intermediate in one solvent, isolate the activated intermediate and conduct the displacement reaction in a different solvent. In other cases, the displacement may be conducted without
25 isolation of the intermediate and, in cases where Q is also used as a base, may even be concurrent with the formation of the activated intermediate.

In cases where the displacement reaction is best accomplished by using the iodide, a solution of the iodide is combined
30 with an approximately equivalent amount (0.9 - 1.05 molar equivalents) of compound Q. A silver salt of a non-nucleophilic acid, such as silver trifluoromethanesulfonate, silver tetrafluoroborate and the like is then added. Although the reaction will proceed in the absence of the silver salt, the reaction proceeds more rapidly in the presence of the silver

- 50 -

salt. In addition, the silver salt assists in the removal of the displaced iodide from the reaction mixture which can improve the efficiency of subsequent steps. The resulting mixture is then subjected to a standard work-up procedure familiar to those skilled in the art to afford a crude
5 product which is purified, if necessary, by recrystallization or chromatography.

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

15 The synthesis of the target compound can be completed by removing any protecting groups which are present in the penultimate intermediate using standard techniques. The deprotected final product is then purified, as necessary, using techniques such as ion exchange chromatography, HPLC on reverse phase silica gel, MPLC on reverse
20 phase polystyrene gel, and the like or by recrystallization.

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

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

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

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

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

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

Compositions for injection, a preferred route of delivery, may be prepared in unit dosage form in ampules, or in multidose containers. The injectable compositions may take such
15 forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain various formulating agents. Alternatively, the active ingredient may be in powder (lyophilized or non-lyophilized) form for reconstitution at the time of delivery with a suitable vehicle, such as sterile water. In injectable compositions,
20 the carrier is typically comprised of sterile water, saline or another injectable liquid, e.g., peanut oil for intramuscular injections. Also, various buffering agents, preservatives and the like can be included.

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

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

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated, the route and frequency of administration, the sensitivity of the pathogen to the

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particular compound selected, the virulence of the infection and other factors. Such matters, however, are left to the routine discretion of the physician according to principles of treatment well known in the antibacterial arts. Another factor influencing the
5 precise dosage regimen, apart from the nature of the infection and peculiar identity of the individual being treated, is the molecular weight of the compound.

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

The invention described herein also includes a method of treating a bacterial infection in a mammal in need of such treatment
20 comprising administering to said mammal a compound of formula I in an amount effective to treat said infection.

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

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

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

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

The compounds of the present invention may, where DHP inhibition is desired or necessary, be combined or used with the appropriate DHP inhibitor as described in the aforesaid patents and published application. The cited European Patent Applications define the procedure for determining DHP susceptibility of the present carbapenems and disclose suitable inhibitors, combination compositions and methods of treatment. A preferred weight ratio of Formula I compound: DHP inhibitor in the combination compositions is about 1:1.

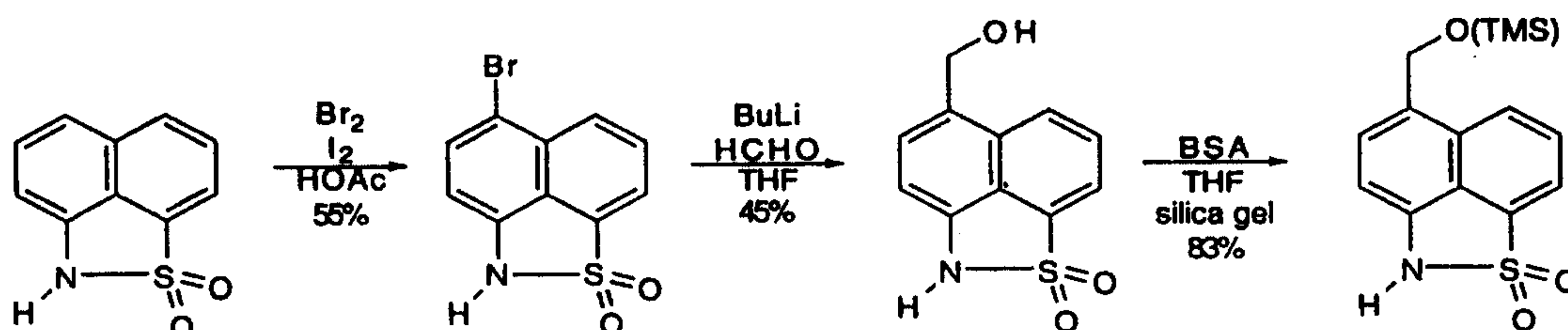
A preferred DHP inhibitor is 7-(L-2-amino-2-carboxy-ethylthio)-2-(2,2-dimethylcyclopropanecarboxamide)-2-heptenoic acid or a useful salt thereof.

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

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PREPARATIVE EXAMPLE 1
SYNTHESIS OF 5-(TRIMETHYLSILYLOXYMETHYL)-1,8-NAPHTHOSULTAM



Step 1: 5-Bromo-1,8-naphthosultam

A suspension of 1,8-naphthosultam (5 g, 24.4 mmol) in acetic acid (20 mL) was treated with a dark solution of iodine (6.5 g, 25.6 mmol) and bromine (1.3 mL, 25.2 mmol) in acetic acid (20 mL) over 10 minutes. The suspension was stirred an additional 95 minutes then placed in a 60°C oil bath for 30 minutes. After cooling to room temperature, the mixture was added to a 1% aqueous NaHSO₃ solution (300 mL). The dark precipitate was filtered and dried overnight under a stream of nitrogen. The resulting solid (6 g) was dissolved in ethyl acetate then silica gel (ca. 6 g) was added and the mixture was evaporated under vacuum. The silica-adsorbed mixture was loaded onto a 4.5 x 30 cm silica column (silica gel 60) and was eluted with 5% ethyl acetate/ methylene chloride, collecting 25 mL fractions. Fractions 24-60 were combined and evaporated to give a green solid which was recrystallized from toluene to give the title compound as a light green solid (3.8 g).
¹H NMR (CDCl₃, 500 MHz) δ 6.82 (d, ArH), 6.83 (br.s, NH), 7.80 (d, ArH), 7.93 (t, ArH), 8.05 (d, ArH) and 8.38 (d, ArH).

Step 2: 5-(hydroxymethyl)-1,8-naphthosultam

A solution of 5-bromo-1,8-naphthosultam (0.5 g, 1.76 mmol) in anhydrous tetrahydrofuran (10 mL) under nitrogen was cooled in a dry ice / acetone bath in a three neck flask. N-butyllithium (2.75 mL of a 1.6 M solution in hexanes, 4.4 mmol) was added over

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2 minutes and the suspension was stirred an additional 7 minutes. Paraformaldehyde (0.317 g, 10.6 mmol), placed in the bulb of a drying tube which was attached to the flask, was heated with a heat gun while a slow stream of nitrogen was blown over the solid. The generated
5 formaldehyde was carried into the flask and the carrier gas vented through a line connected to a Firestone valve over a period of 13 minutes. After an additional 5 minutes, the mixture was removed from the bath and stirred for 10 minutes. Aqueous hydrochloric acid (3 mL of a 2 N solution) was added and the clear suspension was stirred an
10 additional 10 minutes. The mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The ethyl acetate layer was washed with saturated aqueous sodium chloride (20 mL), dried over magnesium sulfate, filtered, and evaporated. The solid residue (0.5 g) was dissolved in 5% methanol/ methylene chloride and was loaded onto a 24 x 4.5 cm
15 silica gel column (silica gel 60, packed/ loaded/ eluted with 5% methanol/ methylene chloride), collecting 8 mL fractions. Fractions 12-42 were combined and evaporated to give the title compound as a white solid (0.185 g).
¹H NMR (DMSO-d₆, 500 MHz) δ 4.85 (d, CH₂OH), 5.22 (t, CH₂OH),
20 6.82 (d, ArH), 7.52 (d, ArH), 7.83 (t, ArH), 8.13 (d, ArH) and 8.38 (d, ArH).

Step 3: 5-(trimethylsilyloxymethyl)-1,8-naphthosultam

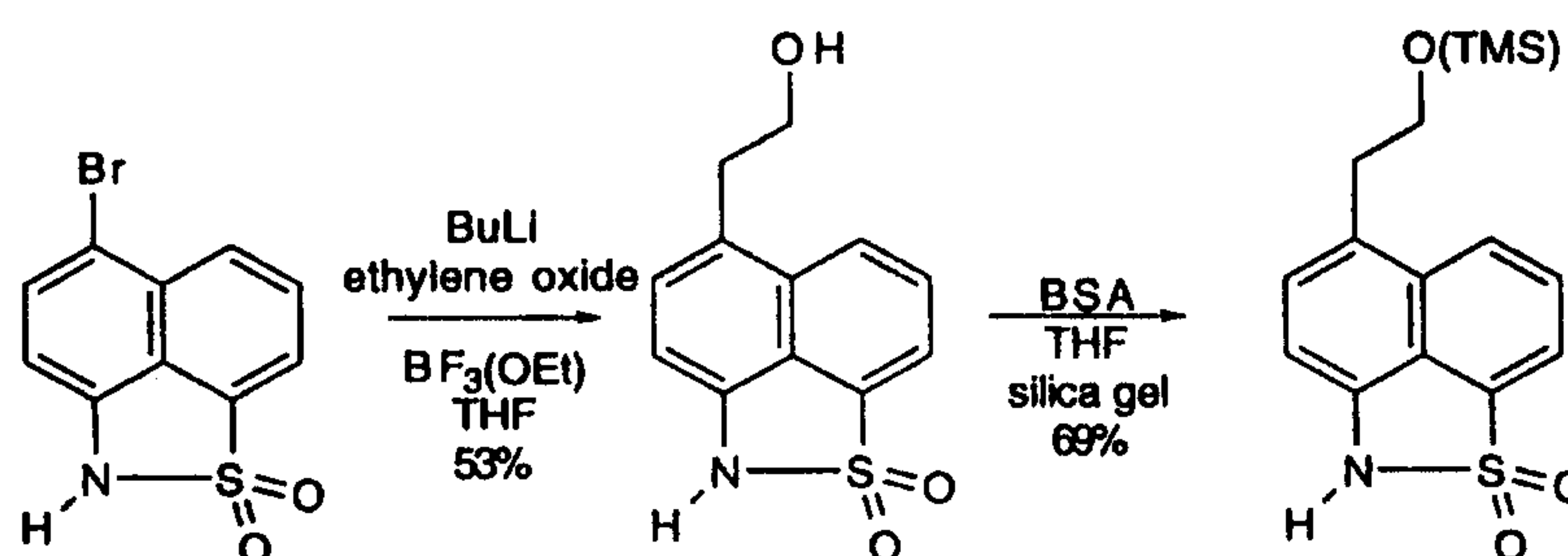
A solution of 5-(hydroxymethyl)-1,8-naphthosultam (0.185 g, 0.79 mmol) in tetrahydrofuran (1 mL) was treated with N,O-Bis(trimethylsilyl)acetamide ((BSA), 0.49 mL, 1.98 mmol). The
25 mixture was stirred at room temperature for 1 hour then evaporated. The residual oil was dissolved in methylene chloride (1 mL) and was filtered through silica gel 60 (2.5 g), eluting the silica with additional methylene chloride (50 mL). The solvent was evaporated under vacuum
30 and the residue was lyophilized from benzene (3 mL) to give the title compound as a white solid (0.20 g).

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^1H NMR (CDCl_3 , 500 MHz) δ 0.19 (s, SiMe_3), 5.07 (s, CH_2), 6.83 (d, ArH), 6.87 (br.s, NH), 7.50 (d, ArH), 7.78 (t, ArH), 7.95 (d, ArH) and 8.26 (d, ArH).

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PREPARATIVE EXAMPLE 2
SYNTHESIS OF 5-(2-(TRIMETHYLSILYLOXY)-ETHYL)-1,8-NAPHTHOSULTAM



Step 1: 5-(2-(hydroxy)-ethyl)-1,8-naphthosultam

- 10 A solution of 5-bromo-1,8-naphthosultam (0.6 g, 2.11 mmol) in anhydrous tetrahydrofuran (10mL) under nitrogen was cooled in a dry ice/ acetone bath. N-butyllithium (3.3 mL of a 1.6 M solution in hexanes, 5.28 mmol) was added over 7 minutes and the suspension was stirred an additional 8 minutes. An excess of ethylene oxide was slowly
- 15 bubbled into the mixture over 5 minutes. Boron trifluoride etherate (0.26 mL, 2.11 mmol) was then added over 5 minutes. After an additional 20 minutes, the reaction was quenched with the addition of acetic acid (0.35 mL, 6 mmol). The mixture was partitioned between ethyl acetate (100 mL) and water (100 mL). The ethyl acetate layer was
- 20 washed with saturated aqueous sodium chloride (50 mL), dried over magnesium sulfate, filtered, and evaporated. The residual oil (0.7 g) was dissolved in 5% methanol/ methylene chloride and was loaded onto a 24 x 2.75cm silica gel column (silica gel 60, packed/ loaded/ eluted with 5% methanol/ methylene chloride), collecting 8 mL fractions.
- 25 Fractions 26-39 were combined and evaporated to give the title compound as an oil (0.28 g).

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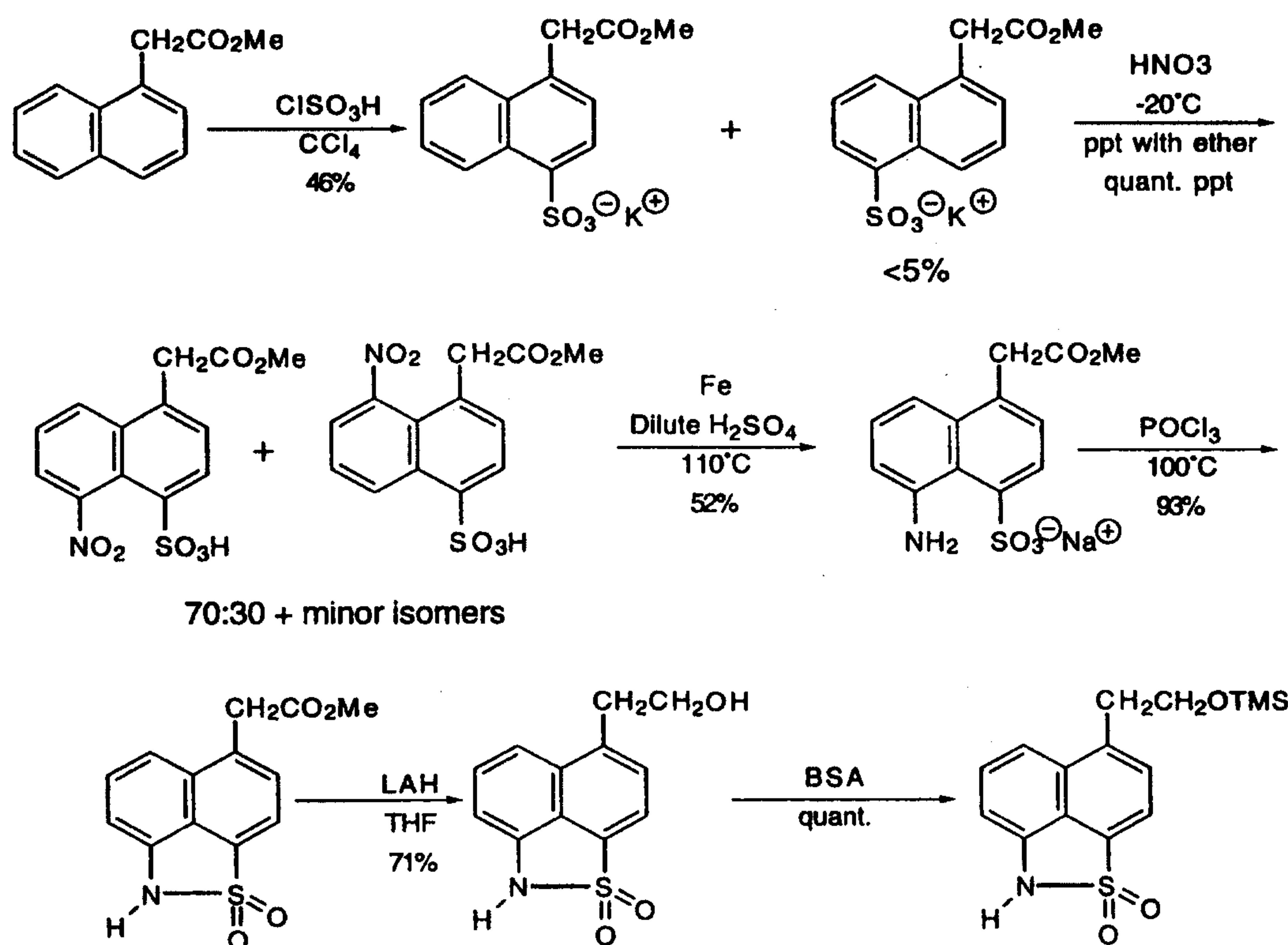
^1H NMR (DMSO- d_6 , 500 MHz) δ 3.22 (t, CH_2Ar), 3.87 (t, CH_2OH), 6.79 (d, ArH), 7.35 (d, ArH), 7.74 (t, ArH), 7.91 (d, ArH) and 8.21 (d, ArH).

Step 2: 5-(2-(trimethylsilyloxy)-ethyl)-1,8-naphthosultam

- 5 A solution of 5-(2-(hydroxy)-ethyl)-1,8-naphthosultam (0.09 g, 0.36 mmol) in tetrahydrofuran (1 mL) was treated with N,O-Bis(trimethylsilyl)acetamide (0.223 mL, 0.90 mmol). The mixture was stirred at room temperature for 20 minutes and was evaporated. The residual oil was dissolved in methylene chloride (3 mL) and was filtered
- 10 through silica gel 60 (2.7 g), eluting the silica with additional methylene chloride (50 mL). The solvent was evaporated under vacuum and the residue was lyophilized from benzene (3 mL) to give the title compound as a white solid (0.08 g).

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PREPARATIVE EXAMPLE 3
SYNTHESIS OF 4-(2-(TRIMETHYLSILOXY)-ETHYL)-1,8-NAPHTHOSULTAM



5 Step 1: potassium 1-(methoxycarbonylmethyl)-4-naphthalene sulfonate

A solution of methyl 1-naphthaleneacetate (1 mL, 5.77 mmol) in carbon tetrachloride (1 mL) was cooled under nitrogen in an ice bath. Chlorosulfonic acid (0.38 mL, 5.7 mmol) was added dropwise over 8 minutes. After an additional 30 minutes, the viscous mixture was removed from the bath and was stirred at room temperature for 17 hours to give a white solid. The solid was partitioned between methylene chloride (5 mL) and water (5 mL). After filtering through solka-floc, the methylene chloride layer was extracted with more water (2 x 5 mL), and the combined aqueous extracts were basified with potassium carbonate to give a precipitate. The suspension was concentrated to approximately 5 mL and was cooled in an ice bath. The suspension was then filtered and the collected solid was washed with cold water (2 mL). The solid was dried under a stream of

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nitrogen to give the title compound as a white solid (0.84 g).

¹H NMR (DMSO-d₆, 500 MHz) δ 3.73 (s, OMe), 4.27 (s, CH₂Ar), 7.53 (d, ArH), 7.71 (t, ArH), 7.76 (t, ArH), 8.06 (d, ArH), 8.10 (d, ArH) and 8.73 (d, ArH).

5 Step 2: 1-(methoxycarbonylmethyl)-5-nitro-4-naphthalene sulfonic acid

Potassium 1-(methoxycarbonylmethyl)-4-naphthalene sulfonate (10 g, 31.4 mmol) was added portionwise over 30 minutes to 90% nitric acid, which was cooled in a methanol / ice bath to approximately -15°C. After 2 hours, the bath temperature had reached -10°C
10 and diethyl ether (200 mL) was added to the mixture. The precipitated solid was filtered, washed with ether (100 mL) and isopropanol (20 mL), and dried under a stream of nitrogen to give the title compound as an approximately 70:30 mixture of the 5- and 8-nitro isomers (approximately 12 g).

15 ¹H NMR (D₂O, 500 MHz) δ 3.69 (s, OMe), 4.30 (s, CH₂Ar), 7.67 (t, ArH), 7.71 (d, ArH), 8.18 (d, ArH), 8.29 (d, ArH) and 8.33 (d, ArH).

Step 3: sodium 1-(methoxycarbonylmethyl)-5-amino-4-naphthalene sulfonate

1-(methoxycarbonylmethyl)-5-nitro-4-naphthalene sulfonic
20 acid (2 g, 6.15 mmol) was dissolved in water (20 mL), containing 0.5 mL concentrated sulfuric acid, and was added dropwise over 5 minutes to a refluxing suspension of iron (4 g, 71.6 mmol) in water (100 mL). After refluxing for one hour, the dark mixture was cooled to room temperature, made basic with sodium carbonate, and concentrated to
25 approximately 30mL. The residual mixture was placed on a CG-161 amberchrom resin column (2.5 x 30 cm). The column was washed with water (200 mL), 10% MeCN/ H₂O(200 mL), and 25% MeCN/ H₂O (400 mL), collecting 25 mL fractions. Fractions 21-28 were combined and evaporated to give the title compound as a dark solid (0.675 g).

30 ¹H NMR (D₂O, 500 MHz) δ 3.64 (s, OMe), 4.18 (s, CH₂Ar), 7.04 (d, ArH), 7.38 (d, ArH), 7.41 (d, ArH), 7.45 (t, ArH) and 8.22 (d, ArH).

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Step 4: 4-(methoxycarbonylmethyl)-1,8-naphthosultam

Sodium 1-(methoxycarbonylmethyl)-5-amino-4-naphthalene sulfonate (0.675 g, 2.13 mmol) was suspended in phosphorous oxychloride (10 g, 65.2 mmol) and was refluxed for 1 hour to give a thin suspension. The mixture was cooled to room temperature and was partitioned between ethyl acetate (100 mL) and water (100 mL). The water layer was extracted with ethyl acetate (50 mL) and the combined ethyl acetate layers were washed with saturated aqueous sodium chloride (100 mL), dried over magnesium sulfate, filtered and evaporated to give the title compound as a solid (0.55 g).

¹H NMR (CDCl₃, 500 MHz) δ 3.72 (s, OMe), 4.15 (s, CH₂Ar), 6.86 (br s, NH), 6.97 (d, ArH), 7.60 (t, ArH), 7.67 (d, ArH), 7.71 (d, ArH) and 7.95 (d, ArH).

Step 5: 4-(2-(hydroxy)-ethyl)-1,8-naphthosultam

A solution of 4-(methoxycarbonylmethyl)-1,8-naphthosultam (0.2 g, 0.72 mmol) in tetrahydrofuran (2 mL) was cooled under nitrogen in an ice bath. Lithium aluminum hydride (1.44 mL of a 1.0 M solution in THF, 1.44 mmol) was added over 1 minute to give a light yellow suspension. After 30 minutes, water was carefully added and the mixture was partitioned between ethyl acetate (30 mL) and 1N hydrochloric acid (10 mL). The aqueous layer was extracted with ethyl acetate (50 mL) and the combined ethyl acetate layers were washed with saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate, filtered and evaporated. The residual solid (0.16g) was purified by preparative thin layer chromatography (2 x 1000 micron silica gel plates, developed/ eluted with 5% MeOH/CH₂Cl₂) to give the title compound as a solid (0.127 g).

¹H NMR (0.14 mL CDCl₃ and 0.01 mL CD₃OD, 500 MHz) δ 3.33 (t, CH₂Ar), 3.91 (t, CH₂OH), 6.84 (d, ArH), 7.49 (dd, ArH), 7.59 (d, ArH), 7.59 (d, ArH) and 7.83 (d, ArH).

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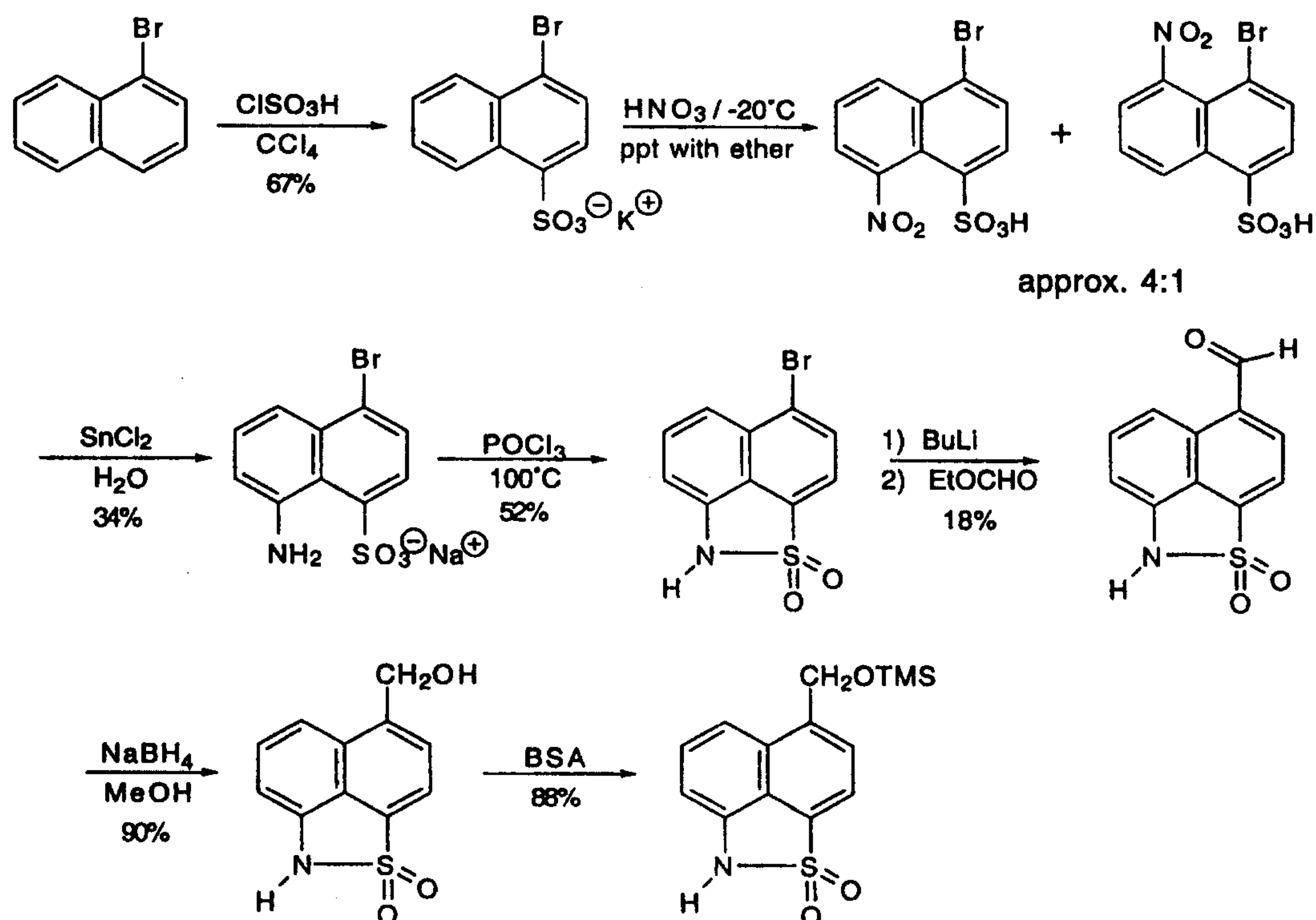
Step 6: 4-(2-(trimethylsilyloxy)-ethyl)-1,8-naphthosultam

N,O-Bistrimethylsilylacetamide (0.31 mL, 1.25 mmol) was added to a solution of 4-(2-(hydroxy)-ethyl)-1,8-naphthosultam (0.125 g, 0.50 mmol) in tetrahydrofuran (1 mL). After one hour the mixture was evaporated and the residue was dissolved in methylene chloride (2 mL) and filtered through silica gel (2.5 g). The silica gel was eluted with methylene chloride (50 mL), the solvent was evaporated and the residue was lyophilized from benzene (3 mL) to give the title compound as an oil (0.16 g, quant.).

¹H NMR (CDCl₃, 500 MHz) δ 0.035 (s, TMS), 3.37 (t, CH₂Ar), 3.94 (t, CH₂O(TMS)), 6.95 (d, ArH), 7.56 (dd, ArH), 7.64 (d, ArH), 7.71 (d, ArH) and 7.92 (d, ArH).

PREPARATIVE EXAMPLE 4

15 SYNTHESIS OF 4-(TRIMETHYLSILYLOXYMETHYL)-1,8-NAPHTHOSULTAM



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Step 1: potassium 1-bromo-4-naphthalenesulfonate

A solution of 1-bromonaphthalene (19 mL, 137 mmol) in carbon tetrachloride (24 mL) was cooled in an ice bath under nitrogen. Chlorosulfonic acid (9.1 mL, 137 mmol) was added dropwise over 20 minutes. After an additional 5 minutes, the heavy grey suspension was removed from the ice bath and was stirred at room temperature for 16 hours to give a grey paste. The mixture was partitioned between methylene chloride (100 mL) and water (300 mL). The aqueous layer was made basic with potassium carbonate and the resulting suspension was filtered. The collected solid was washed with methylene chloride (50 mL) and water (50 mL), and dried under vacuum to give the title compound as a white solid (30 g).

¹H NMR (DMSO-d₆, 500 MHz) δ 7.61 (m, ArH), 7.65 (m, ArH), 7.82 (m, 2ArH), 8.14 (dd, ArH), and 8.90 (dd, ArH).

Step 2: 1-bromo-5-nitro-4-naphthalene sulfonic acid

Potassium 1-bromo-4-naphthalenesulfonate (1.38 g, 4.24 mmol) was added portionwise over 20 minutes to 90% nitric acid (2 mL), which was cooled in a methanol/ ice bath to approximately -15°C. After 1.5 hours, the mixture was placed in a refrigerator for 20 hours. Diethyl ether (20 mL) was added and the precipitated solid was filtered, washed with ether (100 mL) and isopropanol (20 mL), and dried under a stream of nitrogen to give the title compound as an approximately 4:1 mixture of the 5- and 8-nitro isomers (1.25 g).

¹H NMR (D₂O, 500 MHz) δ 7.70 (dd, ArH), 8.09 (d, ArH), 8.20 (d, ArH), 8.21 (dd, ArH), and 8.63 (d, ArH).

Step 3: sodium 1-bromo-5-amino-4-naphthalenesulfonate

1-Bromo-5-nitro-4-naphthalenesulfonate (1 g, 3.01 mmol) and tin chloride dihydrate (1.83 g, 8.1 mmol) were suspended in a mixture of water (10 mL) and ethanol (10 mL). The resulting mixture was heated for 3 hours in a 100 °C oil bath. The mixture was cooled to room temperature and filtered. The collected solid was suspended in water (20 mL) and the mixture was made basic with sodium carbonate

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then placed on a CG-161 amberchrom resin column (3 x 9 cm). The column was washed with water (300 mL) and was eluted with 25% MeCN/ H₂O, collecting 12 mL fractions. Fractions 17-19 were combined and evaporated to give the title compound as a solid (0.33 g).

- 5 ¹H NMR (D₂O, 500 MHz) δ 7.07 (dd, ArH), 7.49 (t, ArH), 7.83 (d, ArH), 7.85 (dd ArH) and 8.08 (d, ArH).

Step 4: 4-bromo-1,8-naphthosultam

- Sodium 1-bromo-5-amino-4-naphthalenesulfonate (1.2 g, 3.70 mmol) was suspended in phosphorous oxychloride (10 mL, 107 mmol) and the mixture was refluxed for 1 hour to give a thin suspension. The mixture was cooled to room temperature and was added to ice (100 mL). The precipitate was collected and washed with water (20 mL) then dried under vacuum (0.675 g). A second crop was obtained from the filtrate (0.186 g). The combined solids were dissolved in 5% methanol in methylene chloride and were placed on a silica gel column (29 x 3.5cm, packed and eluted with 5% methanol in methylene chloride), collecting 8 mL fractions. Fractions 27-39 were combined and evaporated to give the title compound as a solid (0.55 g).

- 15 ¹H NMR (0.14mLCDCl₃ and 0.01mL CD₃OD, 500 MHz) δ 6.89 (d, ArH), 7.58(dd ArH), 7.68 (d, ArH), 7.73 (d, ArH) and 7.95 (d, ArH).

Step 5: 4-formyl-1,8-naphthosultam

- A solution of 4-bromo-1,8-naphthosultam (0.24 g, 0.845 mmol) in anhydrous tetrahydrofuran (5 mL) was cooled in a dry ice/ acetone bath under nitrogen. n-Butyllithium (1.32 mL of a 1.6 M solution in hexanes, 2.11 mmol) was added and the mixture was stirred for 5 minutes. Ethyl formate (1 mL, 12.4 mmol) was then added, and after an additional 5 minutes, 2N aqueous hydrochloric acid (3 mL) was added. The flask was removed from the bath and the yellow solution was partitioned between ethyl acetate (30 mL) and water (30 mL). The ethyl acetate layer was washed with saturated aqueous sodium chloride (20 mL), dried over magnesium sulfate, filtered, and evaporated. The residual oil was purified on preparative silica gel

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plates (3 x 1000 micron/ developed and eluted with 5% methanol/ methylene chloride) to give the title compound as a red solid (0.035 g).

¹H NMR (CDCl₃, 500 MHz) δ 7.09 (d, ArH), 7.78 (dd, ArH), 8.12 (d, ArH), 8.30(d, ArH), 8.70 (d, ArH) and 10.5 (s, CHO).

5 Step 6: 4-(hydroxymethyl)-1,8-naphthosultam

A solution of 4-formyl-1,8-naphthosultam (0.035 g, 0.15 mmol) in anhydrous methanol (1 mL) was cooled in an ice bath under nitrogen. Sodium borohydride (0.011 g, 0.3 mmol) was added and the solution was stirred for 30 minutes. The mixture was partitioned
10 between methylene chloride (10 mL) and 0.2N aqueous hydrochloric acid (10 mL). The aqueous layer was extracted with 5% methanol in methylene chloride (2 x 10 mL), and the combined organic layers were evaporated to give the title compound as a yellow solid (0.032 g).

¹H NMR (0.14mLCDCl₃and 0.01mL CD₃OD, 500 MHz) δ 5.13 (s, CH₂OH), 6.85 (d, ArH), 7.50 (dd, ArH), 7.57 (d, ArH), 7.82 (d, ArH)
15 and 7.88 (d, ArH).

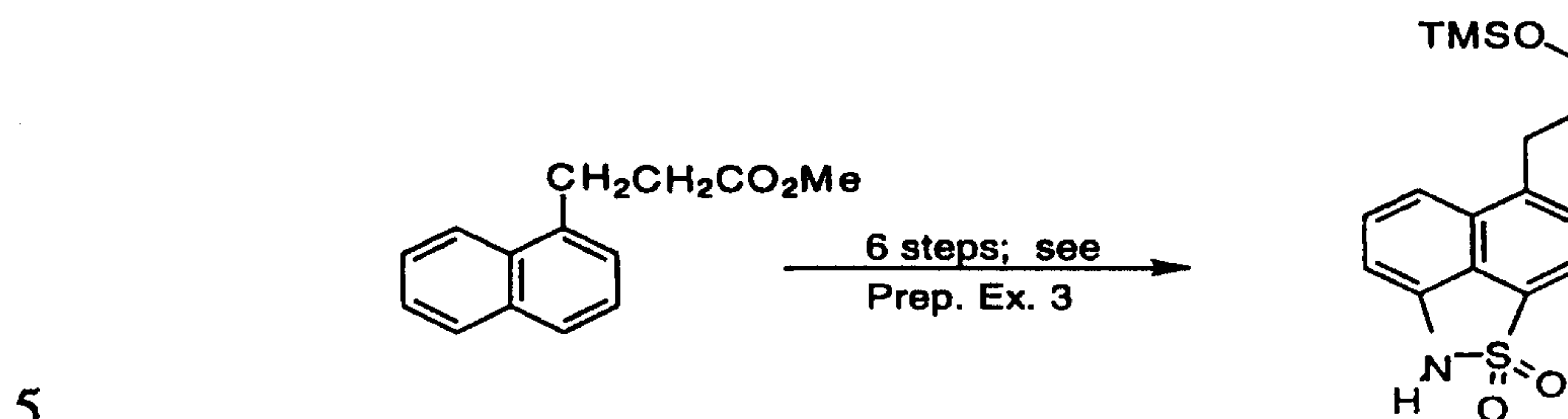
Step 7: 4-(trimethylsilyloxymethyl)-1,8-naphthosultam

A solution of 4-(hydroxymethyl)-1,8-naphthosultam (0.032 g, 0.136 mmol) in tetrahydrofuran (0.5 mL) was treated with
20 N,O-Bis(trimethylsilyl)acetamide (0.084 mL, 0.34 mmol). The mixture was stirred at room temperature for 45 minutes and was evaporated. The residual oil was dissolved in methylene chloride (1 mL) and was filtered through silica gel 60 (1 g), eluting the silica with additional methylene chloride (50 mL). The solvent was evaporated under vacuum
25 and the residue was lyophilized from benzene (3 mL) to give the title compound as a white solid (0.037 g).

¹H NMR (CDCl₃, 500 MHz) δ 0.23 (s, SiMe₃), 6.78 (brs, NH), 5.23 (s, CH₂), 6.97 (d, ArH), 7.58 (dd, ArH), 7.64 (d, ArH), 7.90 (d, ArH) and 7.97 (d, ArH).

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PREPARATIVE EXAMPLE 5
SYNTHESIS OF 4-(3-TRIMETHYLSILYLOXYPROP-1-YL)-1,8-NAPHTHOSULTAM

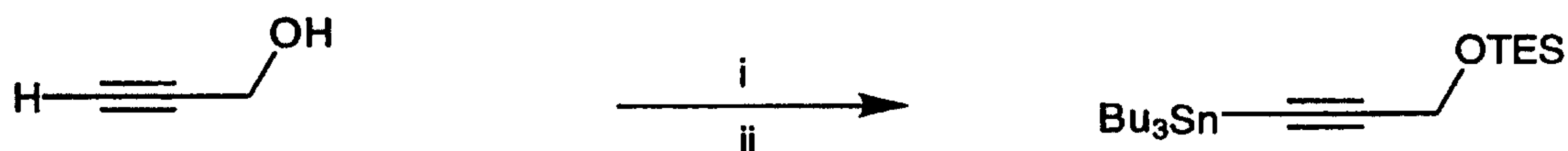


Steps 1-6 Synthesis of 4-(3-trimethylsilyloxyprop-1-yl)-1,8-naphthosultam

10 By substitution of methyl 1-naphthalenepropionate for methyl 1-naphthaleneacetate in the procedure of Preparative Example 3, 4-(3-trimethylsilyloxyprop-1-yl)-1,8-naphthosultam is prepared.

EXAMPLE 6

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20 i) To a stirred solution of commercially available propargyl alcohol (5.0g, 35.72 mmoles,) in 50 mL of N,N-dimethyl formamide chilled to 0° C in an N₂ atmosphere was added imidazole (668mg, 9.83 mmoles) and the reaction was stirred for 5 min. Neat triethylsilyl chloride (16.2 ml, 96.21 mmoles) was then added to the above solution

25 in a dropwise manner over 5 min. The colorless solution was stirred for 10 minutes at ambient temperature and was partitioned between a biphasic mixture of ethyl acetate, dilute aqueous sodium bicarbonate and ice. The ethyl acetate extract was washed with water and saturated brine

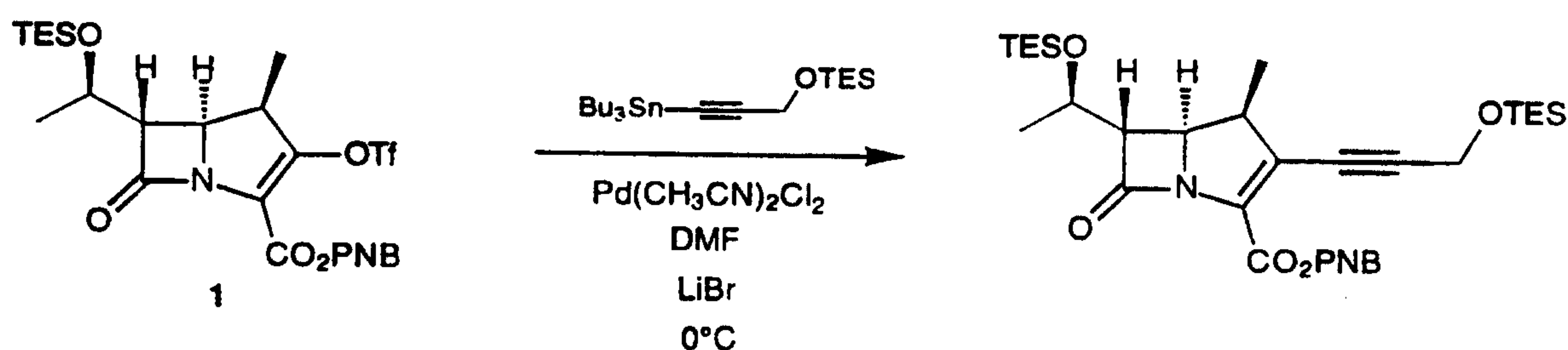
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and was dried with anhydrous sodium sulfate. The resulting extract was conc. in vacuo providing a viscous oil, which was subsequently placed under a partial pressure (3.7 mm) and was fractionally distilled (57-61° C) to give 3.03 g of pure triethylsilyloxypropynylether, as a colorless oil.

ii) To a stirred solution of triethylsilyloxypropynylether (3.03g, 18.15 mmol) in 33 mL tetrahydrofuran in an N₂ atmosphere at -78° C was added dropwise n-butyllithium (8.0ml, 19.96 mmol) over 30 min. The reaction was warmed to -20° C, stirred for 1 hr., and t-butylin chloride (5.89ml, 21.78 mmol) was then added dropwise over 30 min., and the reaction was again stirred for 1 hr. The dark solution was partitioned between a biphasic mixture of ethyl acetate, water and ice. The ethyl acetate extract was washed with water and saturated brine and dried with anhydrous sodium sulfate. The extract was concentrated in vacuo providing a dark viscous oil. The crude stannane was purified using flash chromatography (florisil 200-400 mesh) and was eluted with 9:1 hexanes: dichloromethane to give, 6.12 g of pure product, as a colorless oil.

¹H NMR (CDCl₃) δ: 0.64 (q, 6H), 0.91 (t, 6H), 1.02 (t, 18H), 1.31 (m, 6H), 1.72 (m, 6H), 4.34 (s, 2H).

EXAMPLE 7



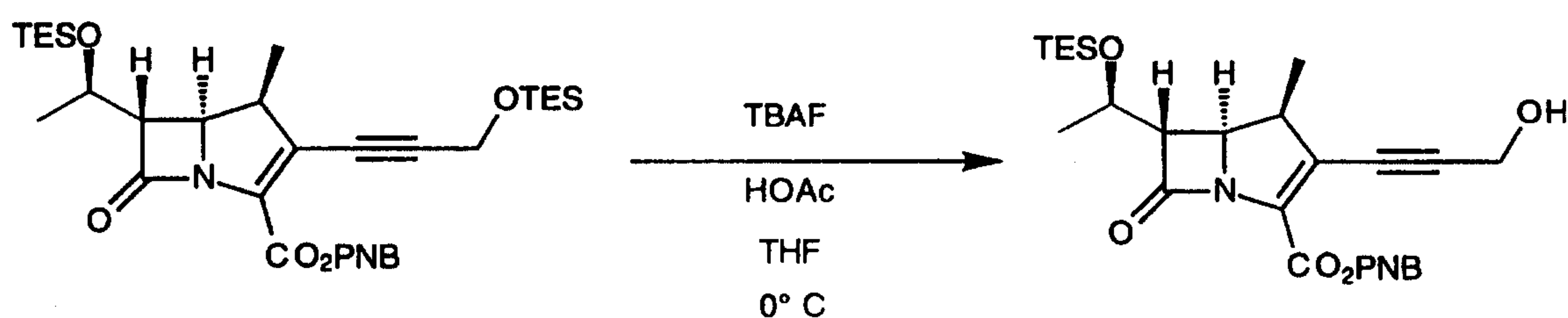
To a stirred solution of carbapenem 2-yl-triflate 1 (100mg, 0.164 mmol) and triethylsilyloxypropynylstannane (112mg, 0.246 mmol) in 2mL of N,N-dimethyl formamide in an N₂ atmosphere and at 0° C was added lithium bromide (28mg, 0.328 mmol) and bis-acetonitrilepalladium(II) chloride (2.1mg, 0.0082 mmol). The reaction was stirred for 1 hr. and was partitioned between a biphasic

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mixture of ethyl acetate, water and ice. The resulting ethyl acetate extract was washed with water and saturated brine and was dried with anhydrous sodium sulfate. The extract was concentrated in vacuo and the resulting crude residue was purified using silica gel plate layer chromatography (2 x 1000 microns) and was eluted with 4:1 hexane ethyl acetate to give 70mg of the desired product, as a pale yellow oil.

^1H NMR (CDCl_3) δ : 0.59 (m, 12H), 0.73 (m, 18H), 1.24 (d, 3H), 1.26 (d, 3H), 3.18 (m, 1H), 3.20 (dd, 1H), 4.12 (p, 1H), 4.25 (dd, 1H), 4.53 (s, 2H), 5.28-5.49 (q, 2H), 7.65 (d, 2H), 8.21 (d, 2H).

EXAMPLE 8

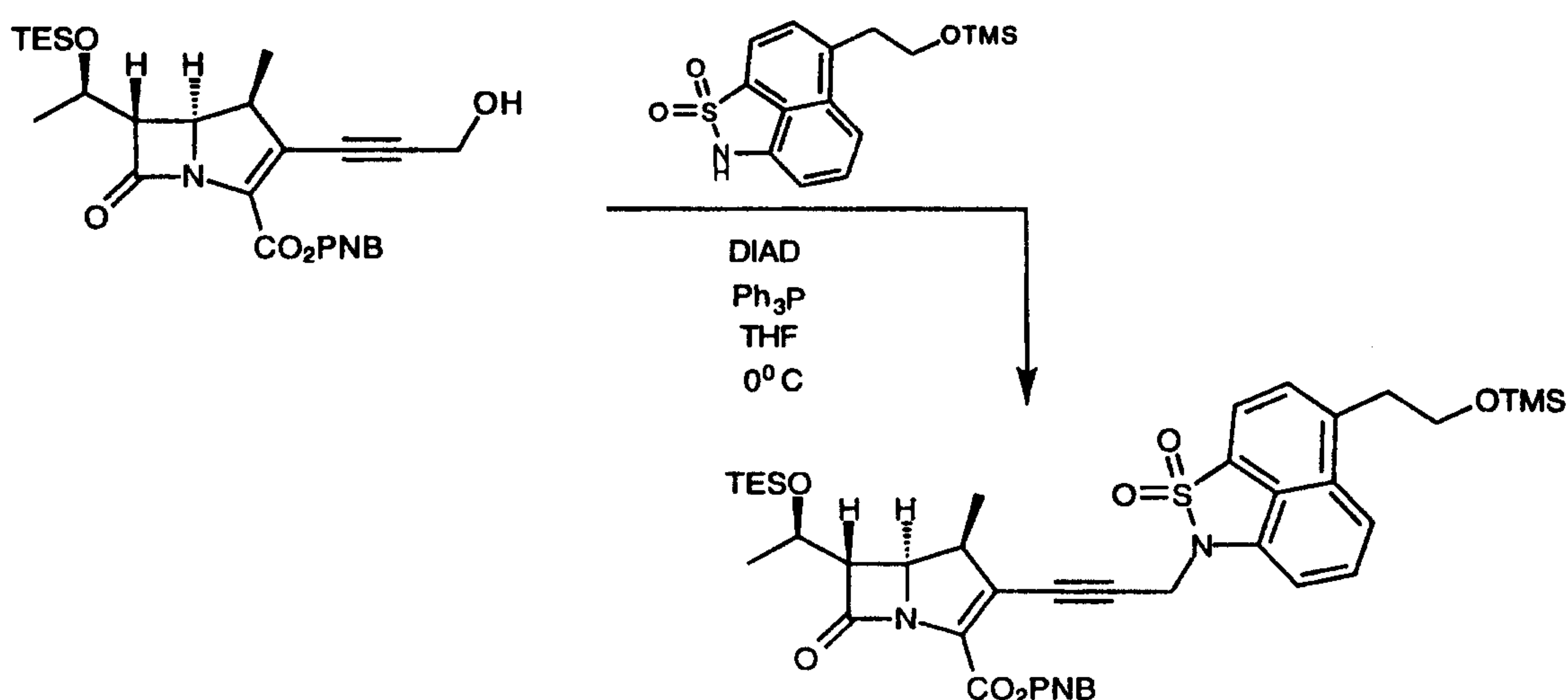


To a stirred solution of (1S,5R,6S)-6-((1R)-triethylsilyloxyethyl)-3-(4-nitrobenzylcarboxyl)-2-(1-triethylsilyloxy-1-propynyl)-1-(methyl)-carbapenem (77mg, 0.122 mmoles) in 2 mL THF in an N_2 atmosphere at 0° C was added acetic acid (11 μl , 0.183 mmoles) and a 1.0 M tetrahydrofuran solution of tetra-butylammonium fluoride (122 μl 0.122 mmoles). The reaction was stirred for 1 hr. and was partitioned between a biphasic mixture of ethyl acetate, aq. sodium bicarbonate and ice. The resulting ethyl acetate extract was washed with water and saturated brine. The extract was dried with sodium sulfate and was conc. in vacuo providing a pale yellow solid. The resulting crude product was purified on silica gel plate layer chromatography (1 x 1000 microns) and was eluted with 1:1 hexanes: ethyl acetate to afford 33 mg of the desired product, as a semi-crystalline solid.

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^1H NMR (CDCl_3) δ : 0.57 (q, 6H), 0.90 (t, 9H), 1.22 (t, 6H), 1.74 (t, 1H), 3.16 (m, 1H), 3.23 (dd, 1H), 4.23-4.32 (m, 2H), 4.48 (d, 2H), 5.26-5.48 (q, 2H), 7.64 (d, 2H), 8.21 (d, 2H)

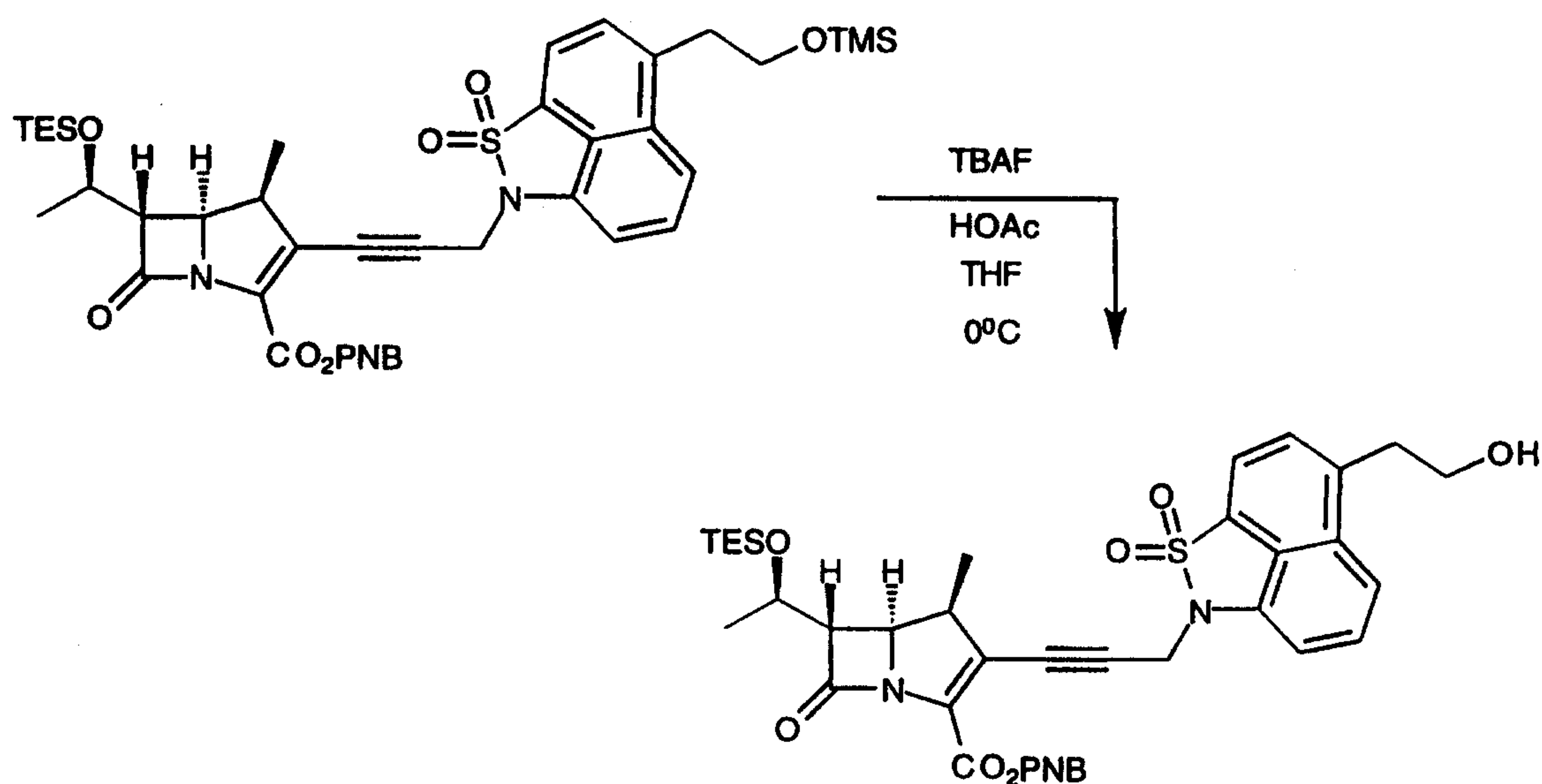
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EXAMPLE 9

To a stirred solution of (1S,5R,6S)-6-((1R)-triethylsilyloxyethyl)-3-(4-nitrobenzylcarboxyl)-2-(1-hydroxypropynyl)-1-(methyl)-carbapenem (84mg, 0.164 mmoles), 4-(2-(trimethylsilyloxy)-ethyl)-1,8-naphthosultam (43mg, 0.137 mmoles) and triphenyl phosphine (43mg, 0.164 mmoles) in 2mL of THF at 0°C in an N_2 atmosphere was added diisopropylazodicarboxylate and the reaction was stirred for 20 min. The reaction mixture was concentrated in vacuo to ca 1.0 ml and was purified using silica gel plate layer chromatography (1 x 1000 micron) and eluted with 1:1 hexanes: ethyl acetate to afford 57 mg of the desired product, as a colorless oil.

^1H NMR (CDCl_3) δ : 0.05 (s, 9H), 0.52 (q, 6H), 0.88 (t, 9H), 1.11 (d, 3H), 1.19 (d, 3H), 3.10 (m, 1H), 3.25 (dd, 1H), 3.31 (t, 2H), 3.86 (t, 2H), 4.18 (m, 2H), 4.77 (s, 2H), 5.16-5.38 (q, 2H), 6.91 (dd, 1H), 7.45 (d, 2H), 7.50-7.62 (M, 3H), 7.85 (dd, 1H), 8.00 (d, 2H).

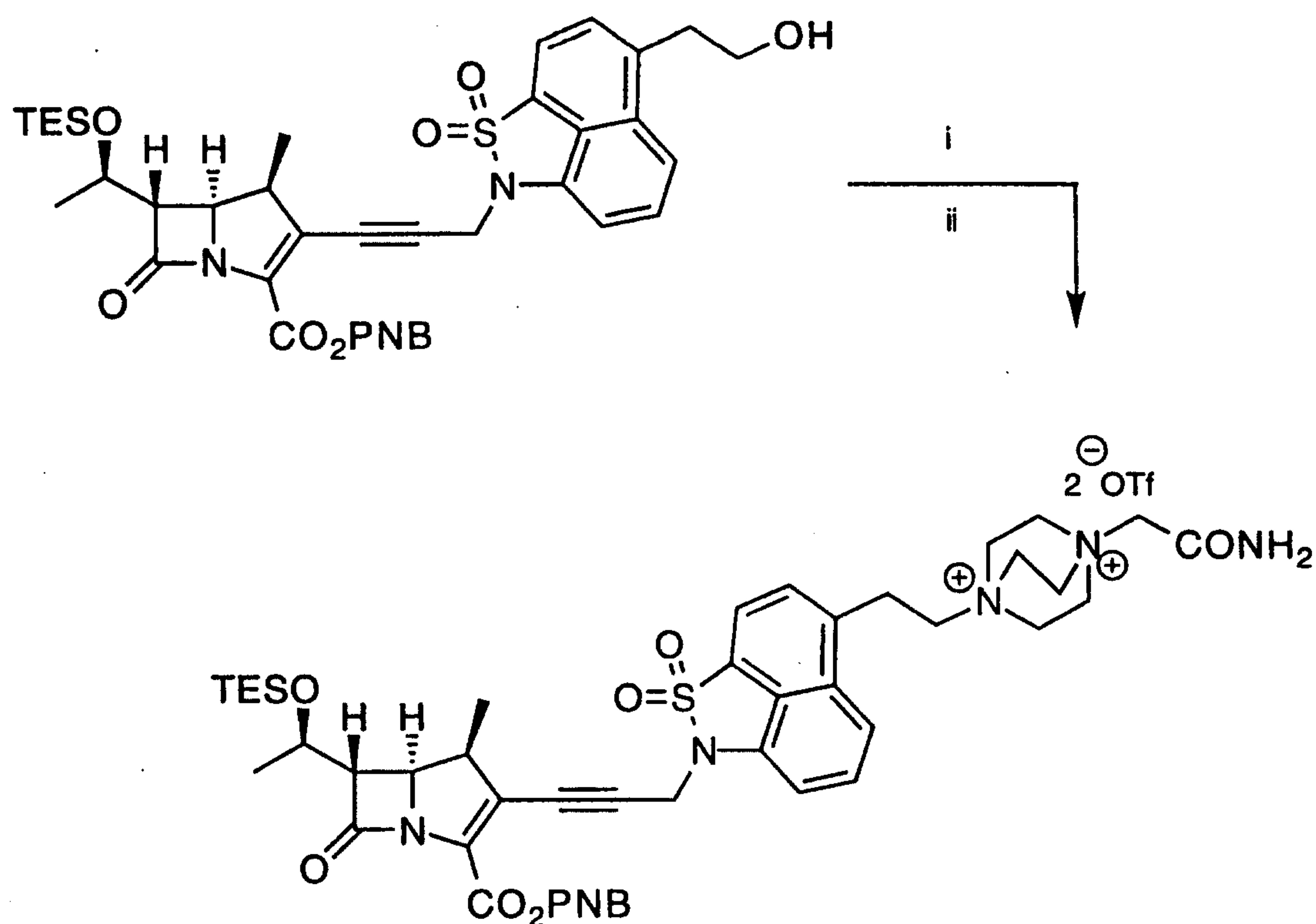
- 69 -

EXAMPLE 10

To a stirred solution of (1S,5R,6S)-6-((1R)-triethylsilyloxyethyl)-3-(4-nitrobenzylcarboxyl)-2-(4-(2-(trimethylsilyloxy)-ethyl)-1,8-naphthosultam-1-propynyl)-1-(methyl)-carbapenem (48mg, 0.0563 mmoles) in 1mL of THF at 0°C in an N₂ atmosphere was added acetic acid (4.8μl, 0.0845 mmoles) and a 1.0 M tetrahydrofuran solution of tetra-butylammonium fluoride (59μl, 0.059 mmoles). The reaction was stirred for 10 min. and was partitioned between a biphasic mixture of ethyl acetate, aq. sodium bicarbonate and ice. The ethyl acetate extract was washed with water and saturated brine and dried with sodium sulfate. The resulting extract was concentrated in vacuo providing a viscous residue. The resulting residue was purified on silica gel plate layer chromatography (2 x 1000 micron plates) and was eluted with 3:2 hexanes: ethyl acetate to provide 34 mg of the desired product, as a tan solid.

¹H NMR (CDCl₃) δ: ¹H NMR (CDCl₃) d: 0.52 (q, 6H), 0.88 (t, 9H), 1.13 (d, 3H), 1.24 (d, 3H), 1.55 (t, 1H), 3.14 (m, 1H), 3.28 (dd, 1H), 3.35 (t, 2H), 3.91 (bt, 2H), 4.21 (m, 2H), 4.76 (s, 2H), 5.20-5.33 (q, 2H), 6.91 (d, 1H), 7.45 (d, 2H), 7.52 (t, 1H), 7.58-7.60 (M, 2H), 7.88 (dd, 1H), 8.02 (d, 2H).

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EXAMPLE 11

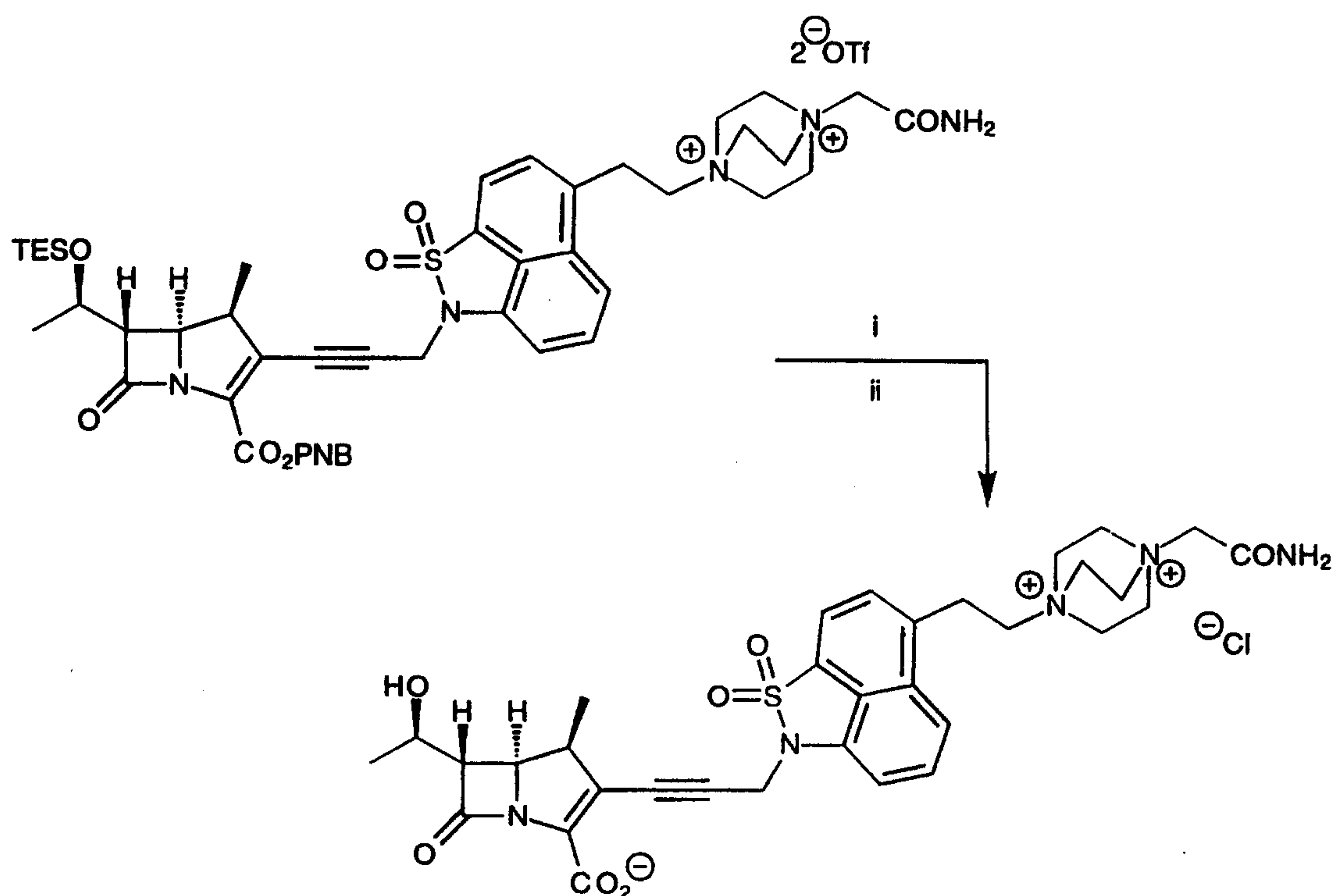
- 5 i) To a stirred solution of (1S,5R,6S)-6-((1R)-triethylsilyloxyethyl)-3-(4-nitrobenzylcarboxyl)-2-(4-(2-(hydroxy)-ethyl)-1,8-naphthosultam-1-propynyl)-1-(methyl)-carbapenem (51mg, 0.0684 mmoles) in 1mL of methylene chloride at -20°C in an N₂ atmosphere was added 2,6-lutidine (8.4μl, 0.0761 mmoles) and the
- 10 reaction was stirred for 5 min. Triflic anhydride (12.7 μl 0.0798 mmoles) was then added and the reaction was stirred for an additional 20 min. The reaction mixture was partitioned between a biphasic mixture of ethyl acetate, water, ice and 50 μl of aqueous 2N hydrochloric acid. The ethyl acetate extract was washed with water,
- 15 saturated brine, dried with sodium sulfate. The extract was concentrated in vacuo, to give the crude alkyl triflate in quantitative yield.

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ii) The resulting crude alkyl triflate, obtained above, was dissolved in acetonitrile (2.0 ml) and was placed in an N₂ atmosphere. To the stirred solution, dabcoacetamide triflate salt (33 mg 0.103 mmoles) was added and the reaction was stirred for 3 hrs. at ambient temperature. The reaction was then diluted with diethyl ether (10 ml) forming an oilish suspension. The suspension was centrifuged and the ethereal supernatant was discarded. The resulting oil was pumped in vacuo to give a semi-crystalline solid. The crude product was purified on a amberchrom CG-161 resin packed column (2.5 x 10 cm) and eluted with a water-acetonitrile gradient. The combined fractions containing product were concentrated in vacuo to ca 10 ml, and lyophilized to give 35 mg of the desired product, as a white lyophilizate.

¹H NMR (d₆-(CH₃)₂CO) δ: 0.57 (q, 6H), 0.91 (t, 9H), 1.16 (t, 6H), 3.22 (m, 1H), 3.49 (dd, 1H), 4.02 (m, 2H), 4.30-4.35 (m, 4H), 4.64 (s, 12 H), 4.72 (s, 2H), 4.79 (s, 2H), 5.24-5.38 (q, 2H), 7.18 (d, 1H), 7.21 (bs, 1H), 7.58 (d, 2H), 7.71 (m, 2H), 7.82 (dd, 1H), 7.92 (d, 1H), 8.05 (d, 2H), 8.09 (dd, 1H).

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EXAMPLE 12

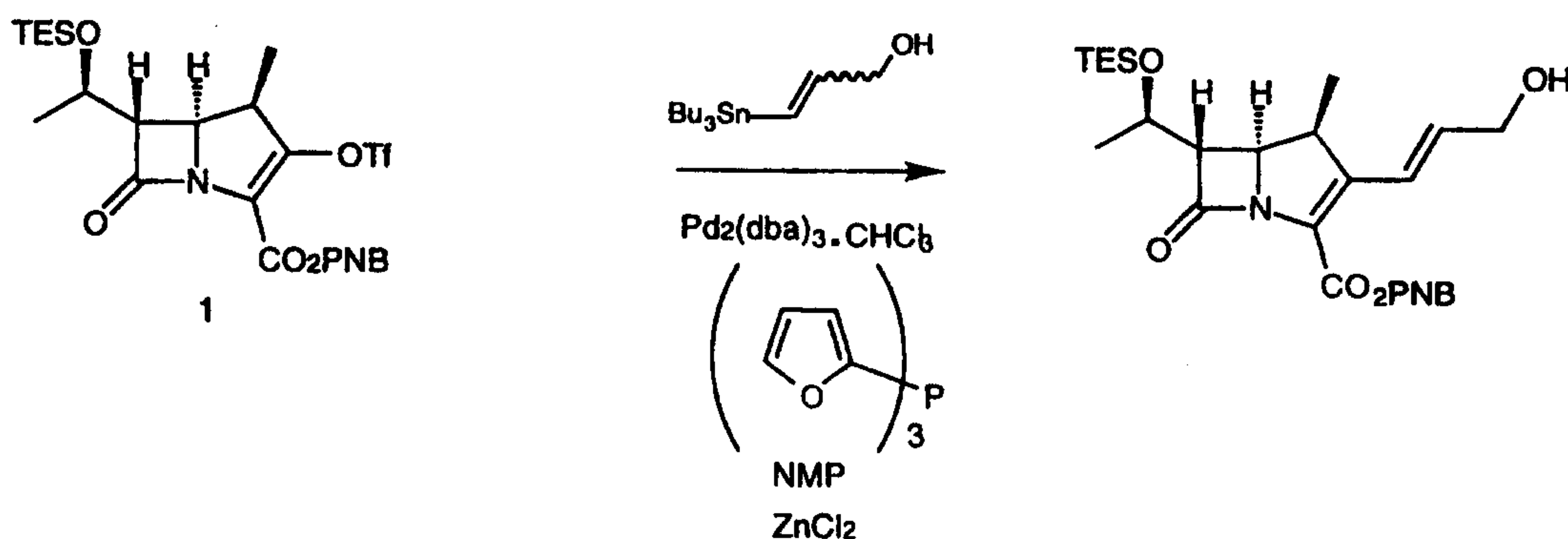
- i) To a stirred solution of (1S,5R,6S)-6-((1R)-triethylsilyloxyethyl)-3-(4-nitrobenzylcarboxyl)-2-(4-(2-(4-carbamoylmethyl-1,4-diazoniabicyclo-{2.2.2}-oct-1-yl-methyl)-1,8-naphthosultam-1-propynyl)-1-(methyl)-carbapenem triflate (35mg, 0.0292 mmoles) in 1mL of THF-water(2:1) at 0°C in an N₂ atmosphere was added aqueous 2N hydrochloric acid (14.6ml, 0.0292 mmoles) and the reaction was stirred for 1 hr.
- ii) The reaction mixture was adjusted to neutral pH with aqueous sodium bicarbonate (29μl, 0.0292 mmoles). Then 5% platinum on carbon catalyst (3.5mg, 10 wt.%) was added and the black suspension was placed in a hydrogen atmosphere. The reaction was stirred vigorously for 22 min., at atmospheric pressure and ambient temperature. The black suspension was filtered through celite plug to provide a colorless solution which was then treated with macro prep ion exchange resin (2.0 ml's packed in a 1.0 x 10 cm column) and eluted with 5 % aq. brine. The saline solution containing the crude product

- 73 -

was subsequently desalted using Amberchrom CG-161 resin (10 ml packed in a 1.0 x 10 cm column) and was eluted with an acetonitrile-water gradient. Fractions containing purified product were combined, concentrated in vacuo to ca 20 ml and lyophilized to afford 15.8 mg of the desired product as a white lyophilizate.

¹H NMR (2:1 D₂O: CD₃CN) δ: 1.24 (d, 3H), 1.52 (d, 3H), 3.20 (m, 1H), 3.62 (dd, 1H), 4.04 (bt, 2H), 4.24 (bt, 2H), 4.38 (dd, 1H), 4.44-4.54 (m, 7H), 4.62 (s, 6H), 4.78 (s, 2H), 5.28 (s, 2H), 7.58 (d, 1H), 8.18 (d, 1H), 8.36 (t, 1H), 8.38 (dd, 1H), 8.46 (d, 1H).

EXAMPLE 13

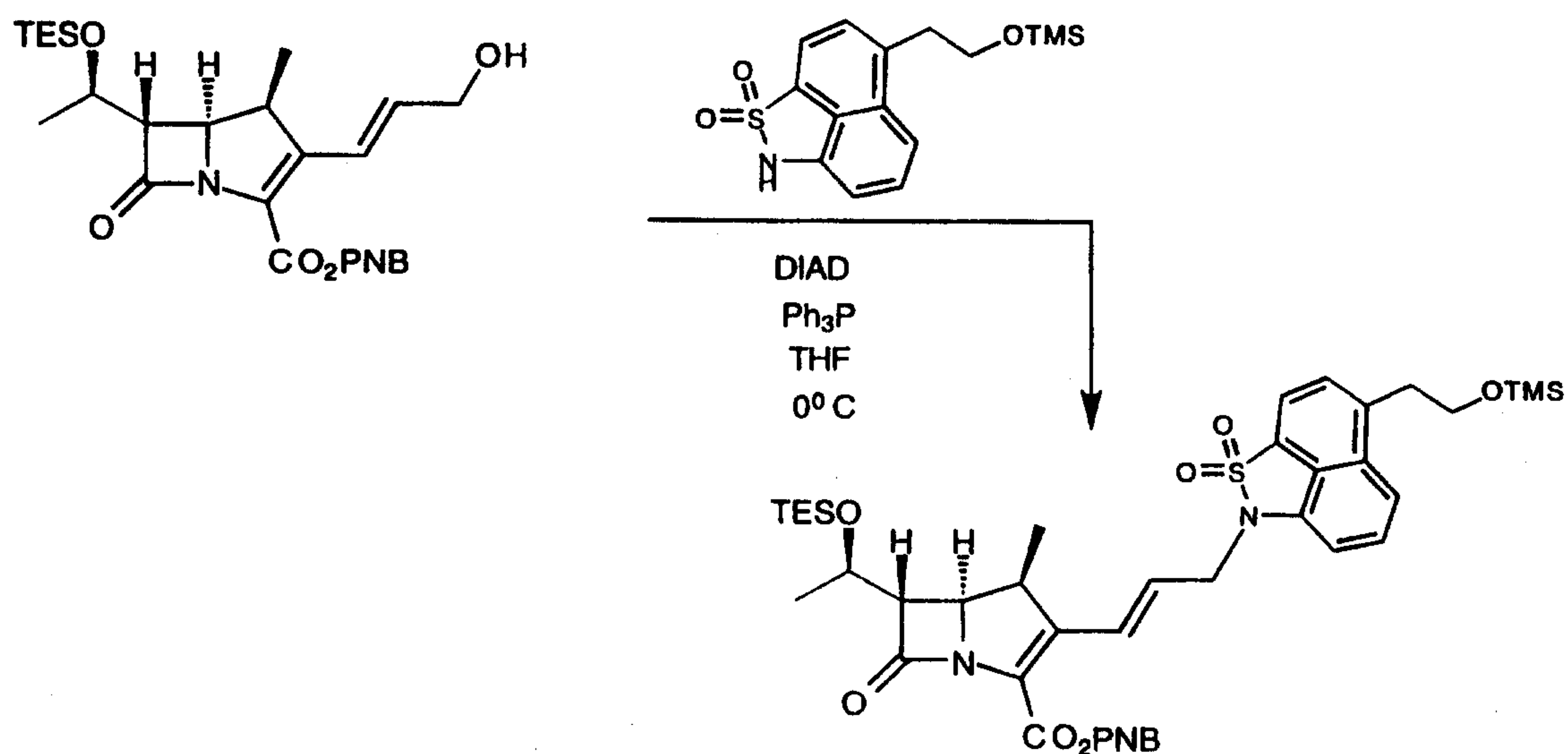


To a stirred solution of carbapenem-2-yl-triflate **1** (200mg, 0.329 mmoles) and a 2:1 mixture of (*E*)-:(*Z*)-vinylstannanes (144μl, 0.493 mmoles) [prepared according to Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, 23, 3851] in 4mL of NMP in an N₂ atmosphere was added palladium dibenzylideneacetone-chloroform catalyst (17mg, 0.0165 mmoles) and tris-trifuryl phosphine (7.6mg, 0.0329 mmoles). A 1.0 M ethereal solution of zinc chloride (362μl, 0.0329 mmoles) was then added and the reaction was stirred for 6 hrs. forming a black suspension. The reaction mixture was partitioned between a biphasic mixture of ethyl acetate, water and ice. The ethyl acetate extract was washed with water and saturated brine and dried with sodium sulfate. The extract was concentrated in vacuo, providing a brown viscous oil, which was purified using silica gel plate layer

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chromatography and was eluted with 1:1 ethyl acetate: hexanes to provide 103 mg of the title compound, as a colorless oil.

^1H NMR (CDCl_3) δ : 0.58 (m, 6H), 0.94 (t, 9H), 1.22 (d, 3H), 1.29 (d, 3H), 3.23 (dd, 1H), 3.37 p, 1H), 4.19 (dd, 1H), 4.21 (m, 1H), 4.32 (dd, 2H), 5.26-5.48 (q, 2H), 6.18 (dt, 1H), 7.27 (d, 1H), 7.68 (d, 2H), 8.22 (d, 2H).

EXAMPLE 14

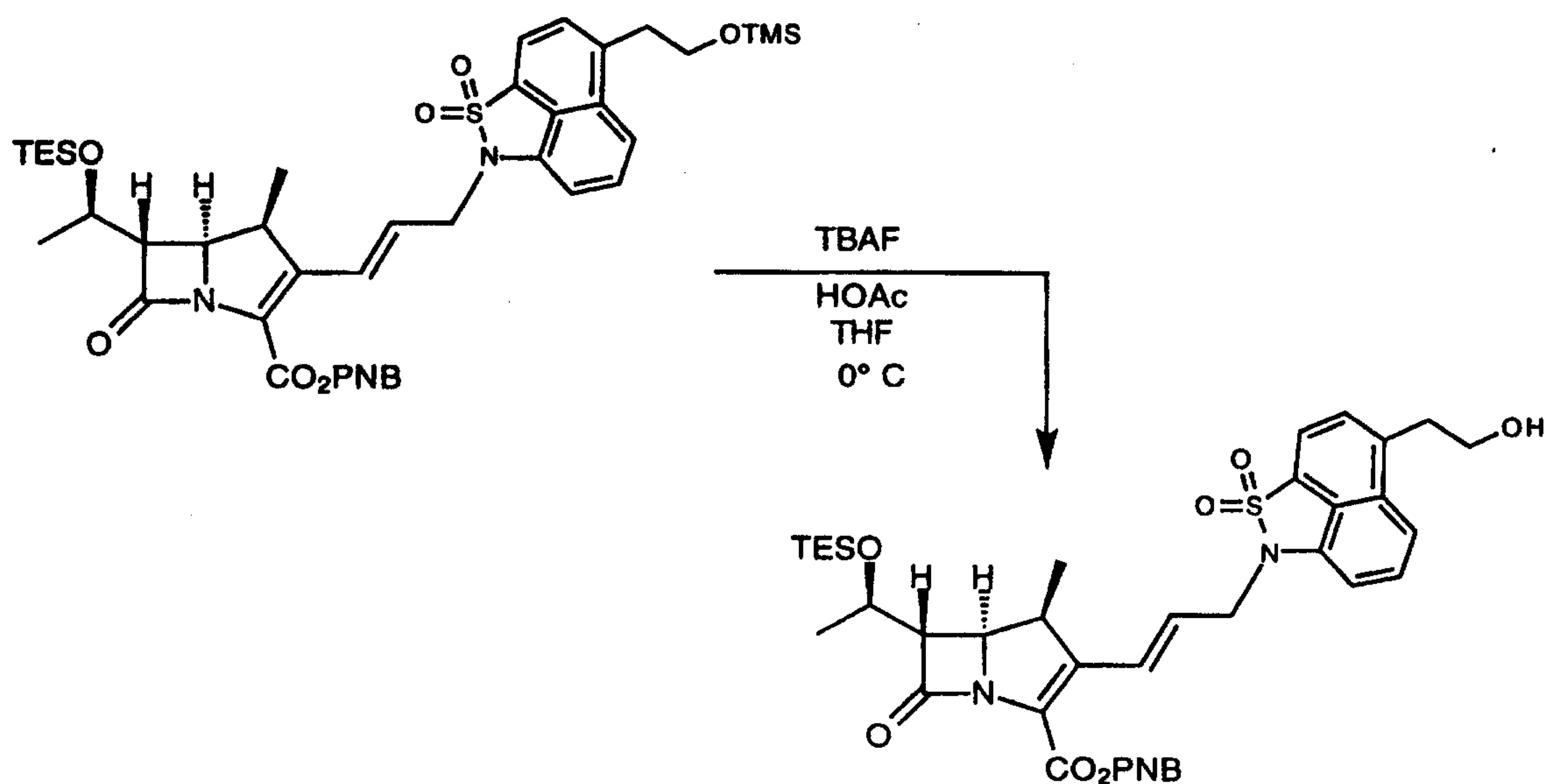
10

Using the procedure outlined in example 9, the compound depicted above is prepared.

EXAMPLE 15

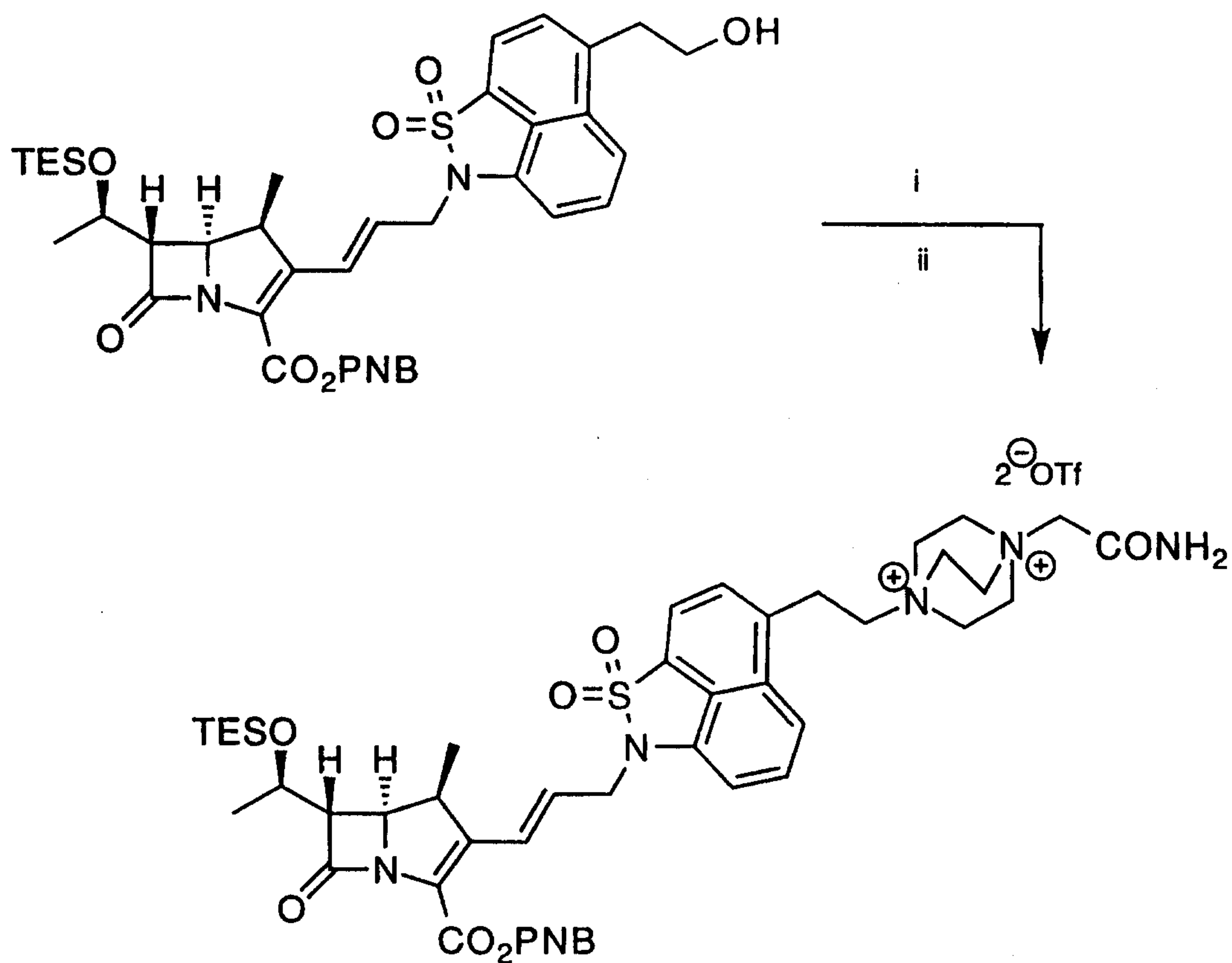
15

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Using the procedure outlined in example 10, the compound depicted above is prepared.

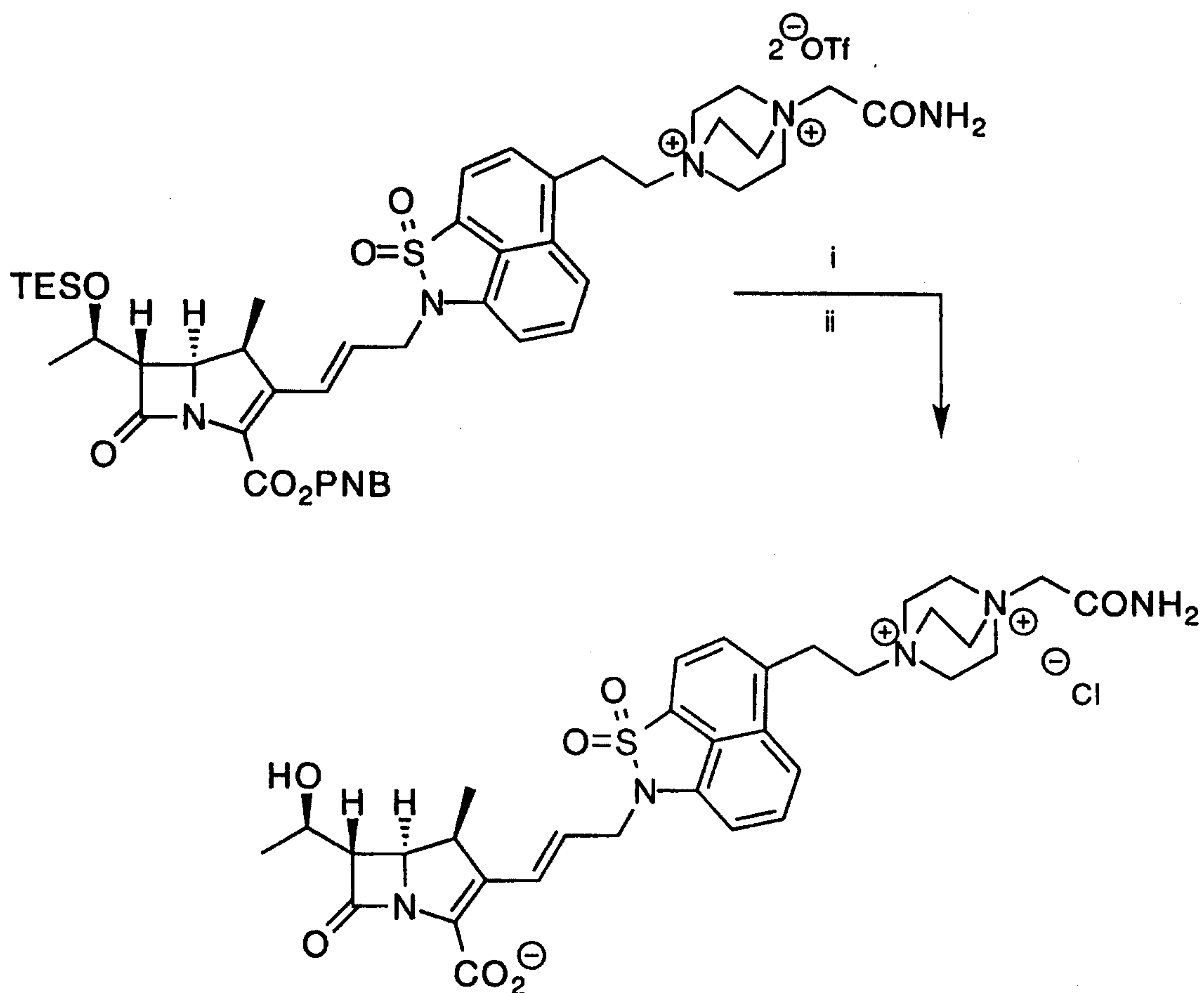
5

EXAMPLE 16

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Using the procedure outlined in example 11, the compound depicted above is prepared.

EXAMPLE 17

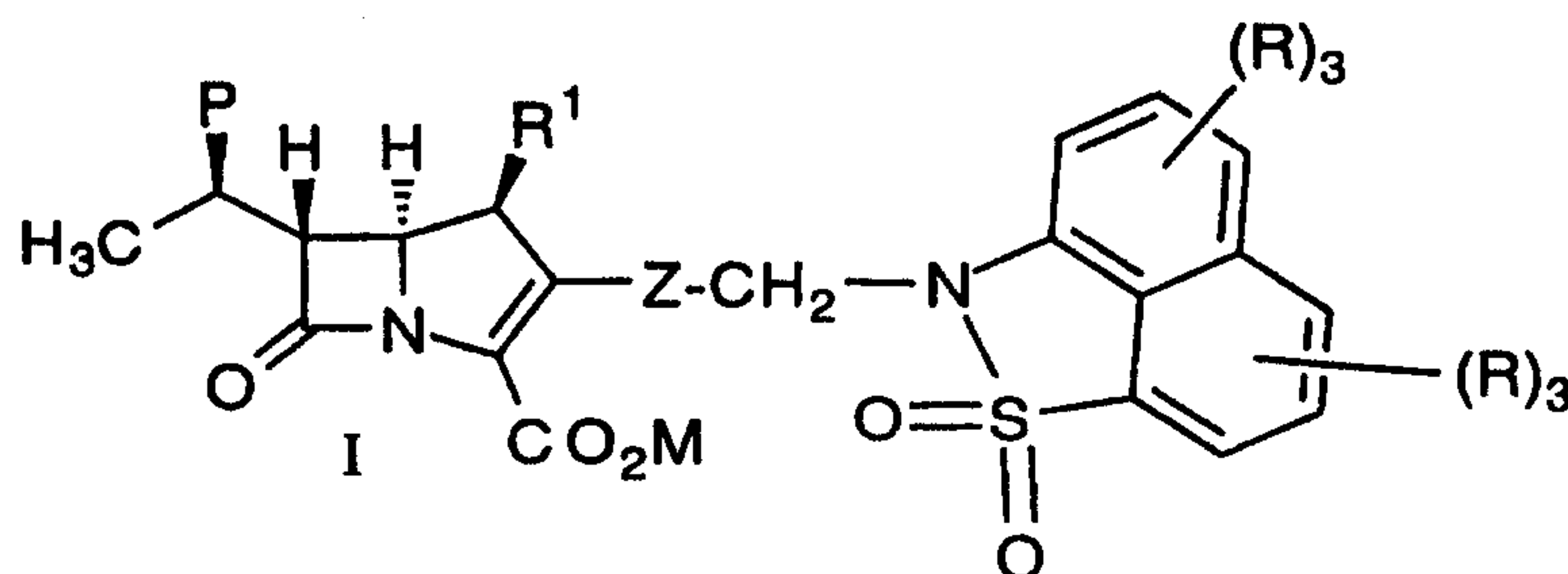


5 Using the procedure outlined in example 12, the compound depicted above is prepared.

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WHAT IS CLAIMED IS:

1. A compound represented by formula I:



5

or a pharmaceutically acceptable salt thereof, wherein:

R¹ represents H or methyl;

10

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

15

Z represents *trans*-ethenediyl or ethynediyl;

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

20

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

25

each R^a, R^b and R^c independently represents hydrogen,

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-C₁₋₆ straight- or branched-chain alkyl, unsubstituted or substituted with one to four R^d groups, or -C₃₋₇ cycloalkyl, unsubstituted or substituted with one to four R^d groups;

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

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

15 each R^d independently represents halo; -CN; -NO₂; -NR^eR^f; -OR^g; -SR^g; -CONR^eR^f; -COOR^g; -SOR^g; -SO₂R^g; -SO₂NR^eR^f; -NR^eSO₂R^f; -COR^e; -NR^eCOR^f; -OCOR^e; -OCONR^eR^f; -NR^eCONR^fR^g; -NR^eCO₂R^h; -OCO₂R^h; -C(NR^e)NR^fR^g; -NR^eC(NH)NR^fR^g; -NR^eC(NR^f)R^g or -Q;

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

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

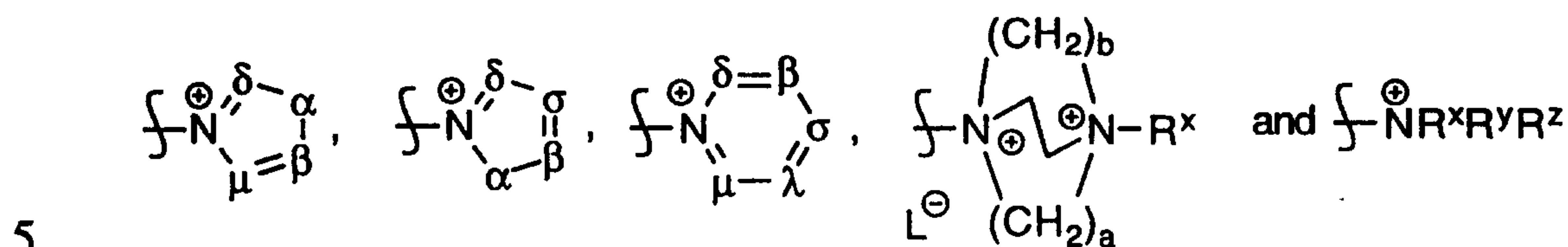
30 each Rⁱ independently represents halo; -CN; -NO₂; phenyl; -NHSO₂R^h; -OR^h; -SR^h; -N(R^h)₂; -N⁺(R^h)₃; -C(O)N(R^h)₂; -SO₂N(R^h)₂; heteroaryl; heteroarylium; -CO₂R^h; -C(O)R^h; -OCOR^h; -NHCOR^h; guanidiny; carbamimidoyl or ureido;

each R^h independently represents hydrogen, a -C₁₋₆ straight or branched-chain alkyl group, a -C₃₋₆ cycloalkyl group or phenyl, or when two R^h groups are present, said R^h groups may be taken in

- 79 -

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

Q is selected from the group consisting of:



wherein:

a and b are 1, 2 or 3;

L⁻ is a pharmaceutically acceptable counterion;

α represents O, S or NR^s;

10 β, δ, λ, μ and σ represent CR^t, N or N⁺R^s, provided that no more than one of β, δ, λ, μ and σ is N⁺R^s which is balanced by L⁻ as defined above;

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

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

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

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

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

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

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

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

25 or R^x and R^y together with any intervening atoms represent a 4-6 membered saturated ring optionally interrupted by O, S, SO₂, NR^w, N⁺R^hR^w or -C(O)-, unsubstituted or substituted with 1 - 4 R^i groups,

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

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

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

10

4. A compound in accordance with claim 3 wherein one R represents a group containing a positively charged moiety and the remaining R groups are hydrogen.

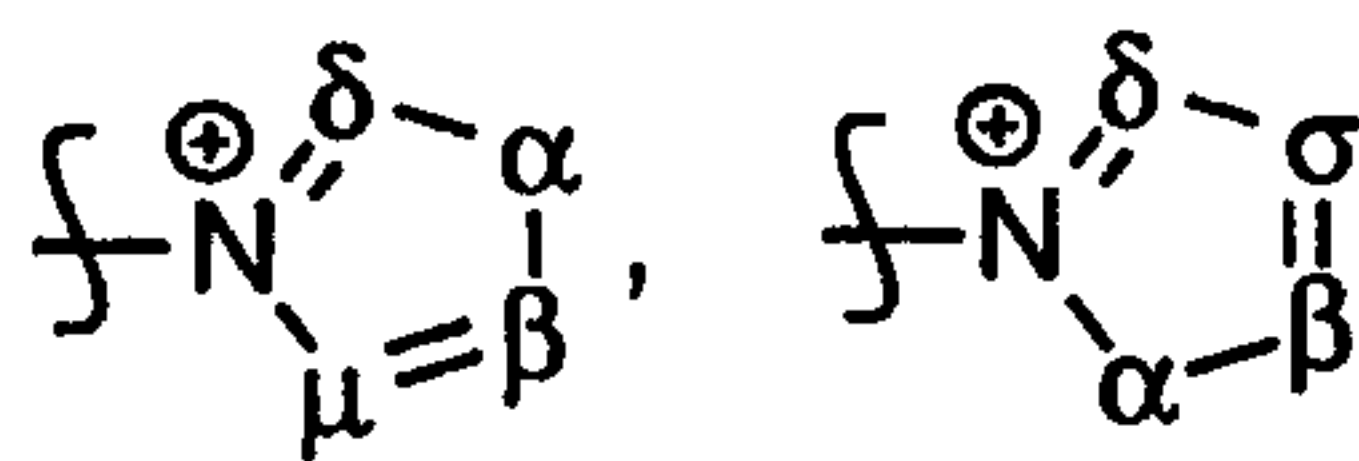
15

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

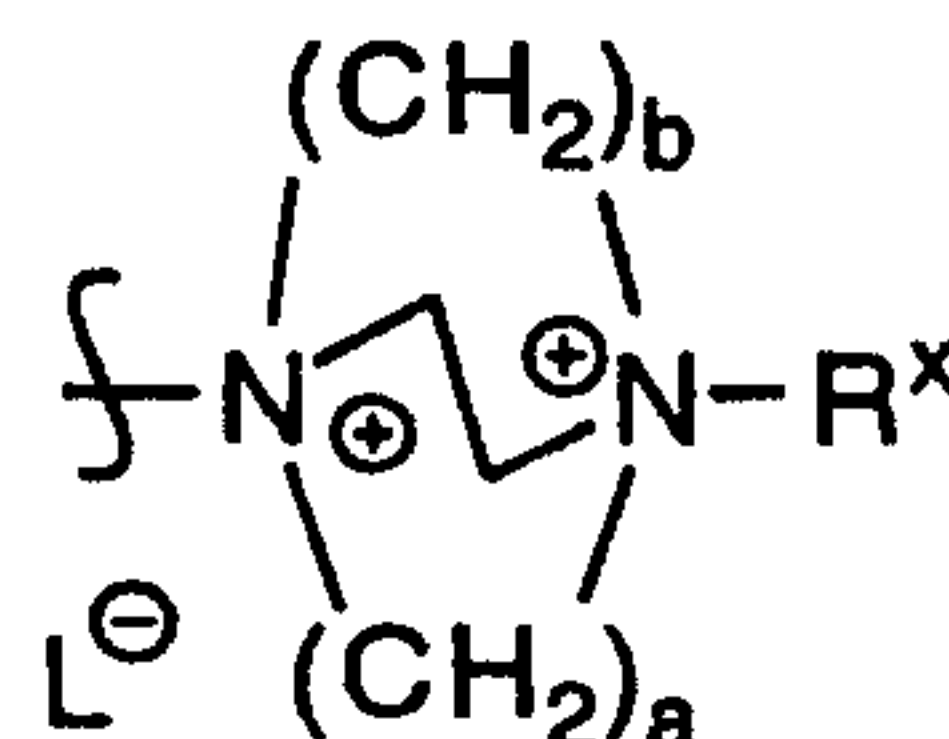
20 6. A compound in accordance with claim 5 wherein the R groups contain two positive charges, balanced by a carboxylate anion and a negatively charged counterion.

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

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



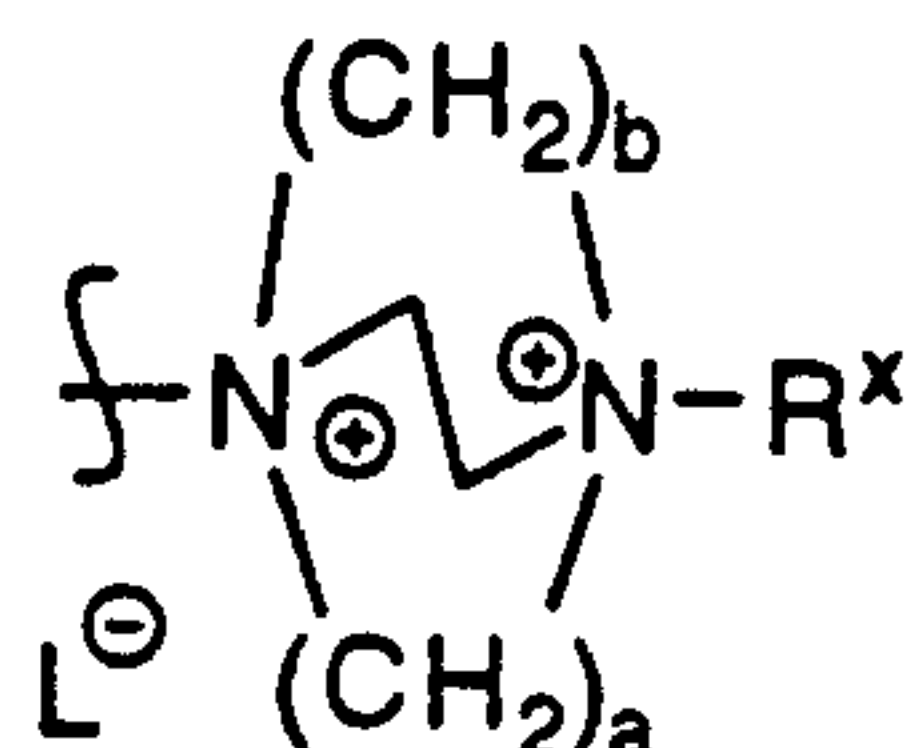
and



30

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9. A compound in accordance with claim 8 wherein wherein Q represents:



5

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

10

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

15

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

20

11. A compound in accordance with claim 1 wherein: CO₂M represents a carboxylate anion;

one R group which is attached to the naphthosultam platform contains at least one positively charged moiety, and the remaining R groups are selected from hydrogen and C₁-6 straight or branched chain alkyl, unsubstituted or substituted with one to four R^d groups.

25

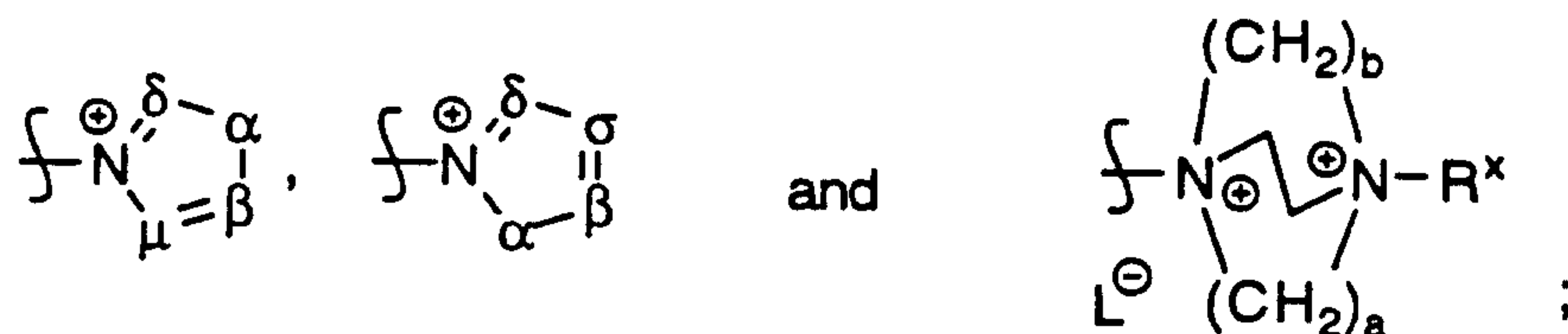
R^d is as originally defined;

- 83 -

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

Q is selected from the group consisting of:

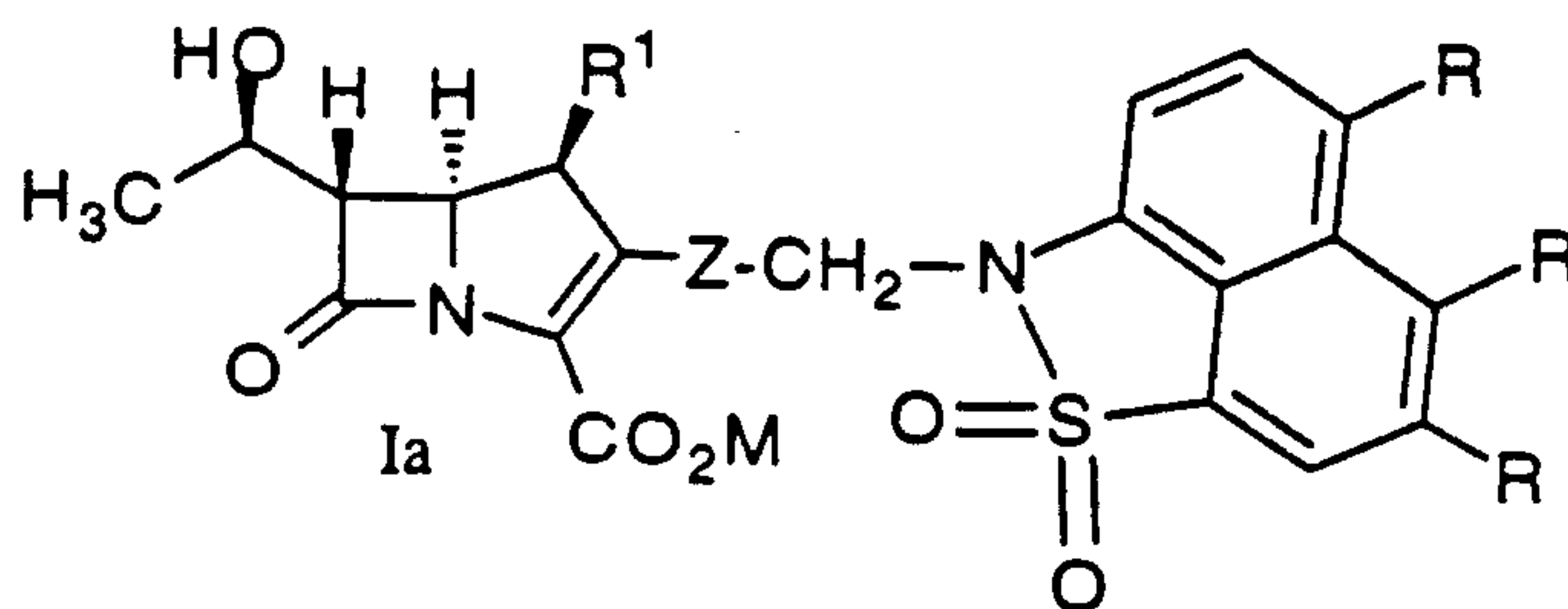
5



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

20

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



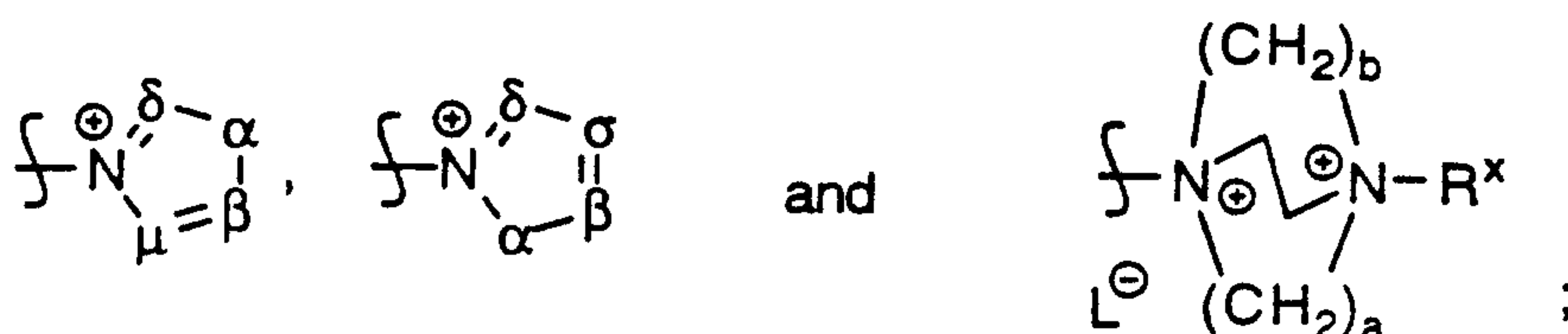
25 or a pharmaceutically acceptable salt thereof, wherein:
CO₂M represents a carboxylate anion;

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one R contains a positively charged moiety, and the other R groups are selected from hydrogen and C1-6 straight or branched chain alkyl, unsubstituted or substituted with one to four
5 R^d groups;

R^d is as originally defined;

Q is selected from the group consisting of:



10

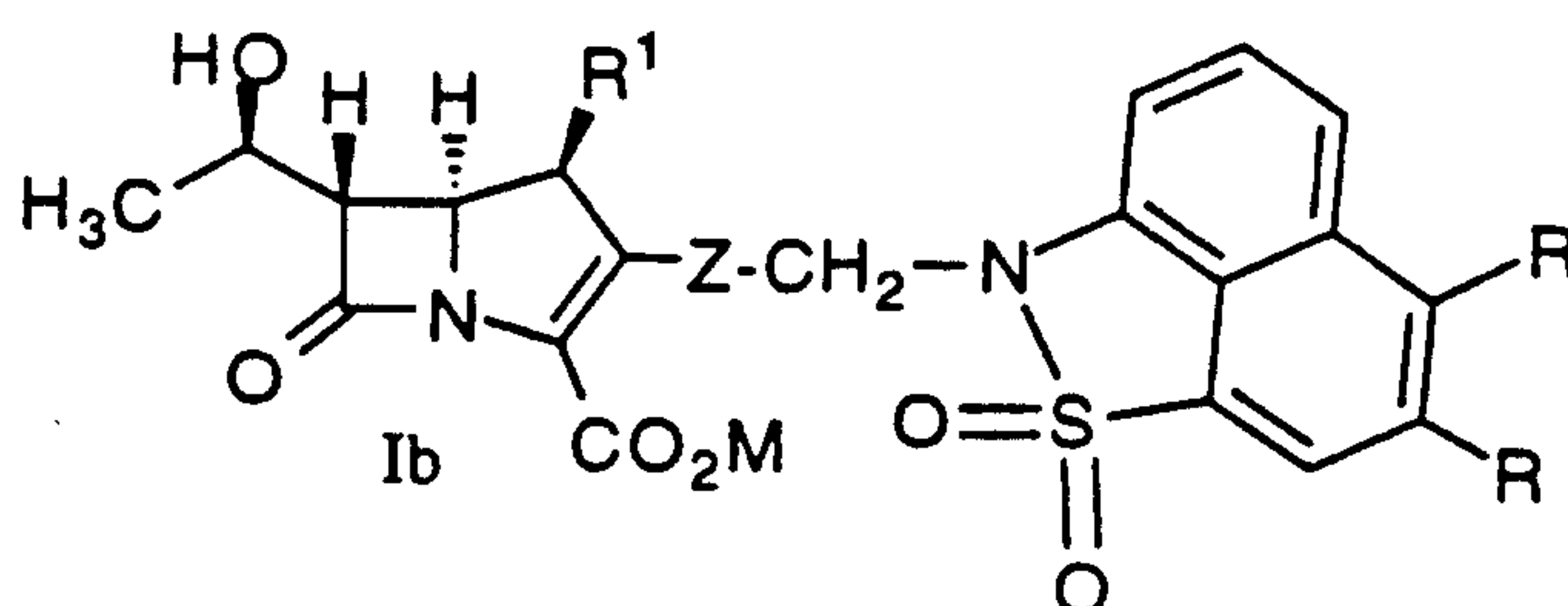
wherein L^- , a and b are as originally defined, and R^x represents a member selected from the group consisting of: hydrogen or a C1-8 straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO₂, NR^w, N⁺R^hR^w, or -
15 C(O)-, said chain being unsubstituted or substituted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

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

25 R^w is as originally defined.

13. A compound in accordance with claim 1 represented by formula Ib:

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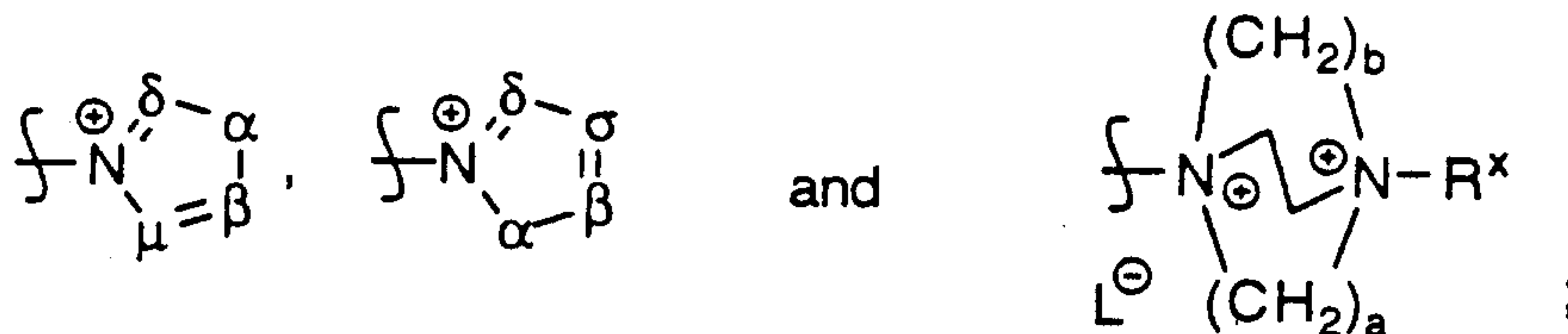
or a pharmaceutically acceptable salt thereof, wherein:

CO₂M represents a carboxylate anion;

- 5 one R group is attached to the naphthosultam platform which contains a positively charged moiety, and the other R group is selected from hydrogen and C₁-6 straight or branched chain alkyl, unsubstituted or substituted with one to four R^d groups;

R^d is as originally defined;

- 10 Q is selected from the group consisting of:

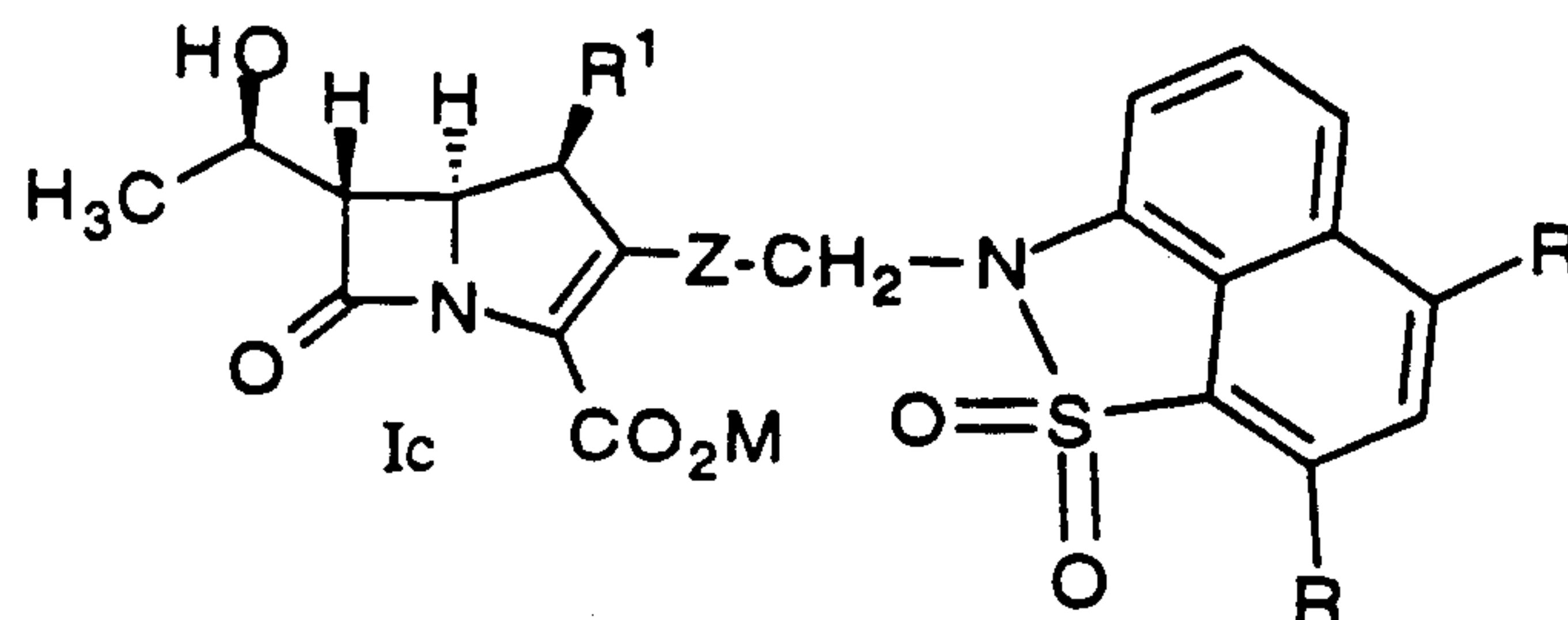


- wherein L⁻, a and b are as originally defined, and R^x represents a member selected from the group consisting of:
- 15 hydrogen or a C₁-8 straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO₂, NR^w, N⁺R^hR^w, or -C(O)-, said chain being unsubstituted or substituted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

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R^W is as originally defined.

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



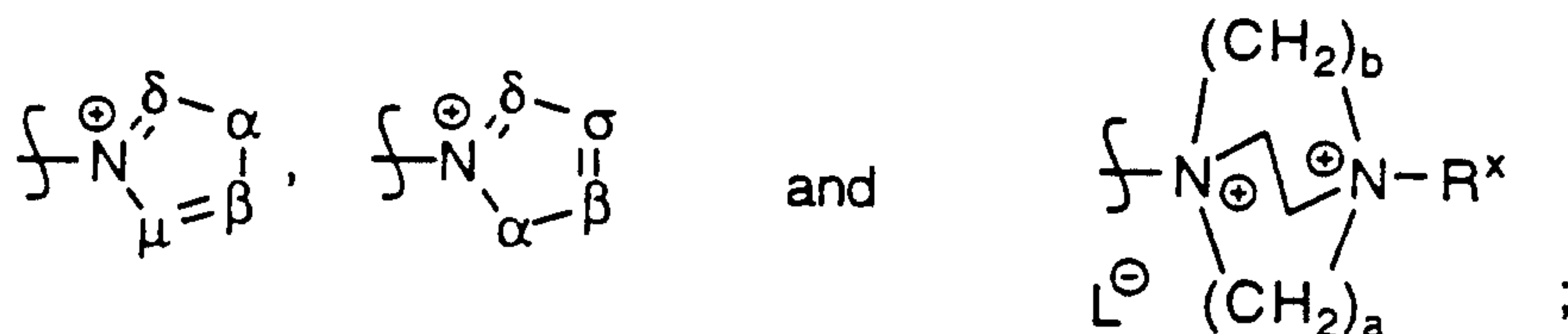
or a pharmaceutically acceptable salt thereof, wherein:

CO₂M represents a carboxylate anion;

- 10 one R group is attached to the naphthosultam platform
which contains a positively charged moiety, and the other R group is
selected from hydrogen, halo and C₁-6 straight or branched chain
alkyl, unsubstituted or substituted with one to four R^d groups;

R^d is as originally defined;

- 15 Q is selected from the group consisting of:



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

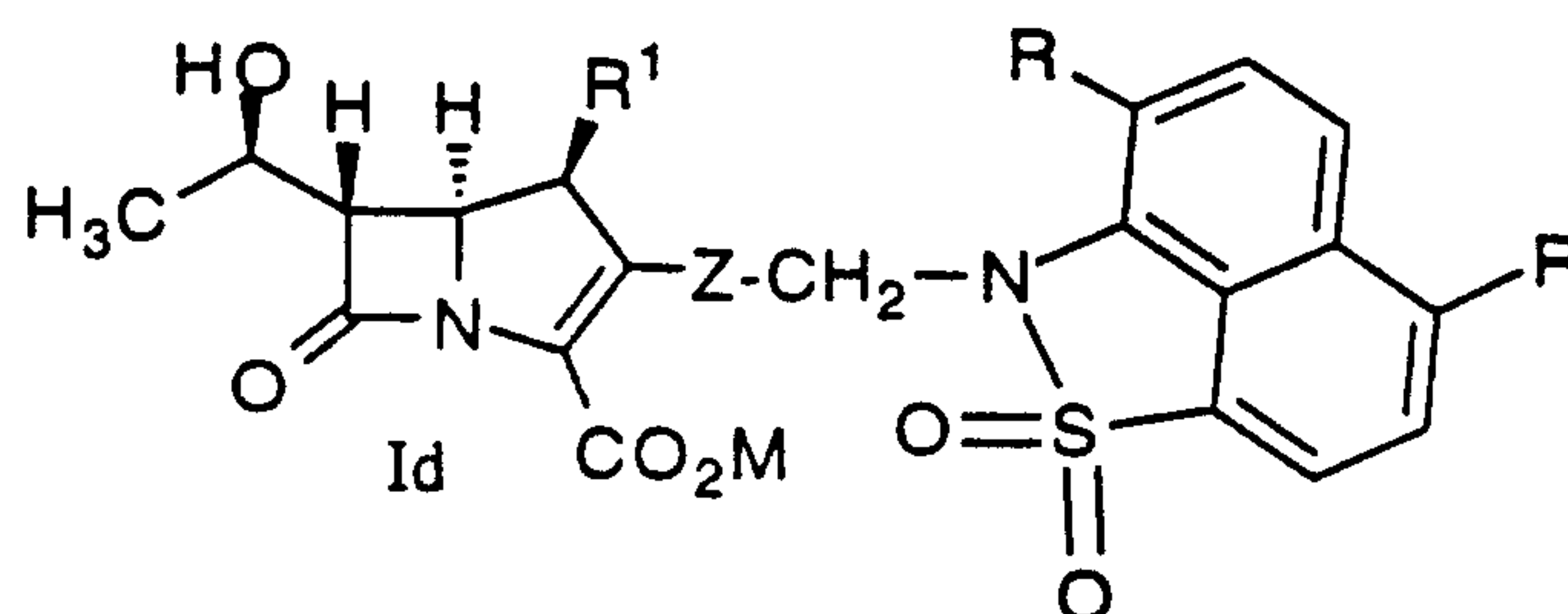
- 87 -

with from one to four R^i groups or with one to two C1-3 straight- or branched- chain alkyl groups, said alkyl groups being unsubstituted or substituted with one to four R^i groups;

5 R^h represents hydrogen or a C1-6 straight or branched chain alkyl group;

R^w is as originally defined.

15 15. A compound in accordance with claim 1 represented by formula Id:



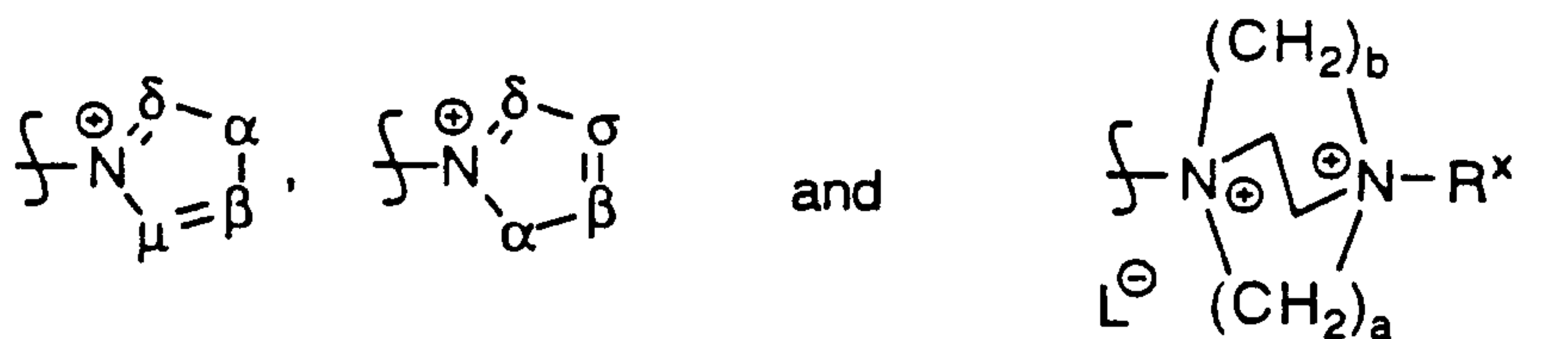
or a pharmaceutically acceptable salt thereof, wherein:

CO_2M represents a carboxylate anion;

15 one R group is attached to the naphthosultam platform which contains a positively charged moiety, and the other R group is selected from hydrogen, halo and C1-6 straight or branched chain alkyl, unsubstituted or substituted with one to four R^d groups;

R^d is as originally defined;

20 Q is selected from the group consisting of:



25 wherein L^- , a and b are as originally defined, and R^x represents a member selected from the group consisting of: hydrogen or a C1-8 straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO_2 , NR^w , $N^+R^hR^w$, or -

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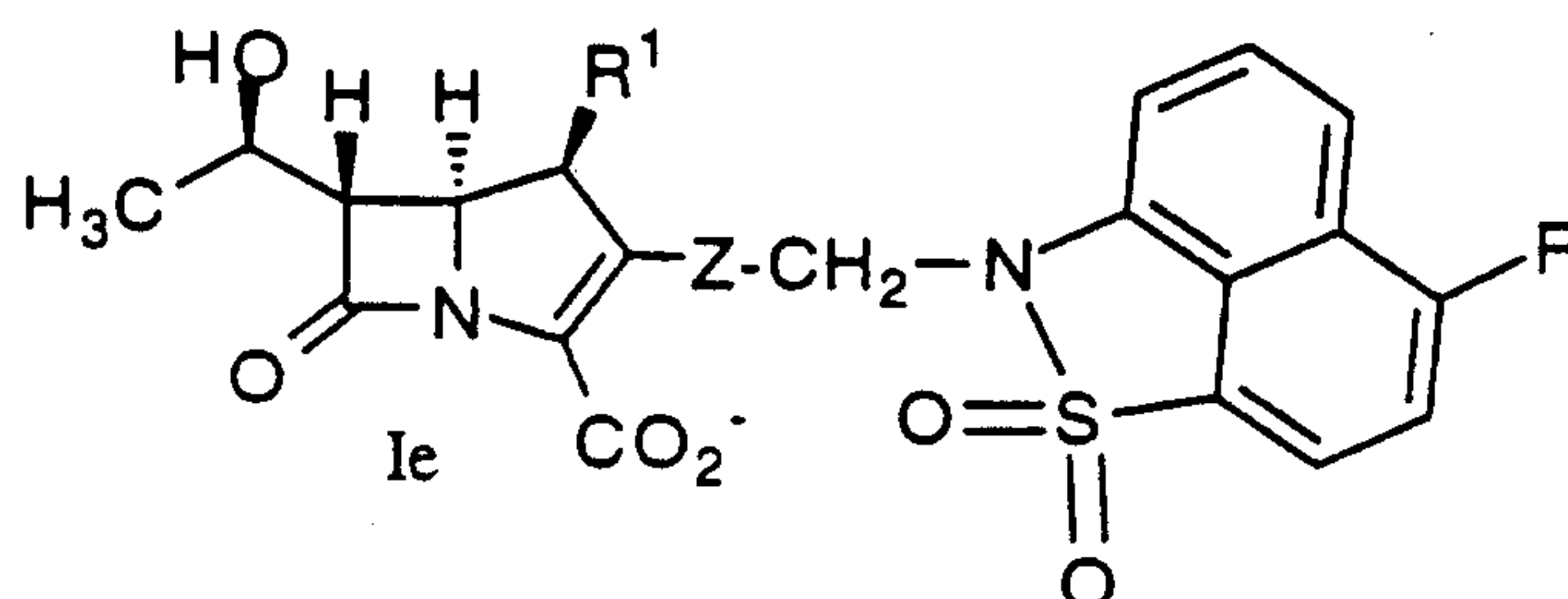
- 88 -

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

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

and R^W is as originally defined.

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

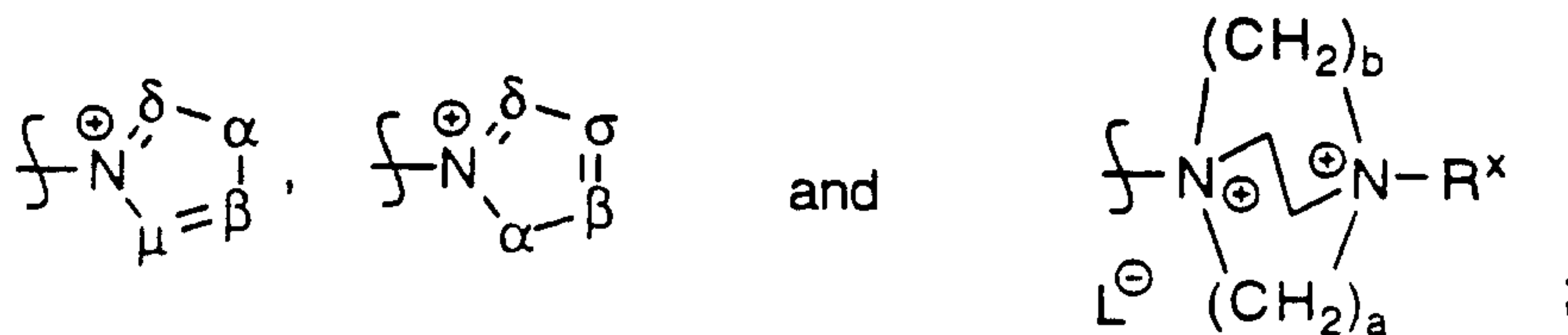


or a pharmaceutically acceptable salt thereof, wherein:

20 R contains a positively charged moiety selected from the group consisting of: -R*, Q, and a C₁₋₆ straight or branched alkyl chain substituted with one R^d group;

R^d is independently selected -R* or Q;

25 Q is selected from the group consisting of:



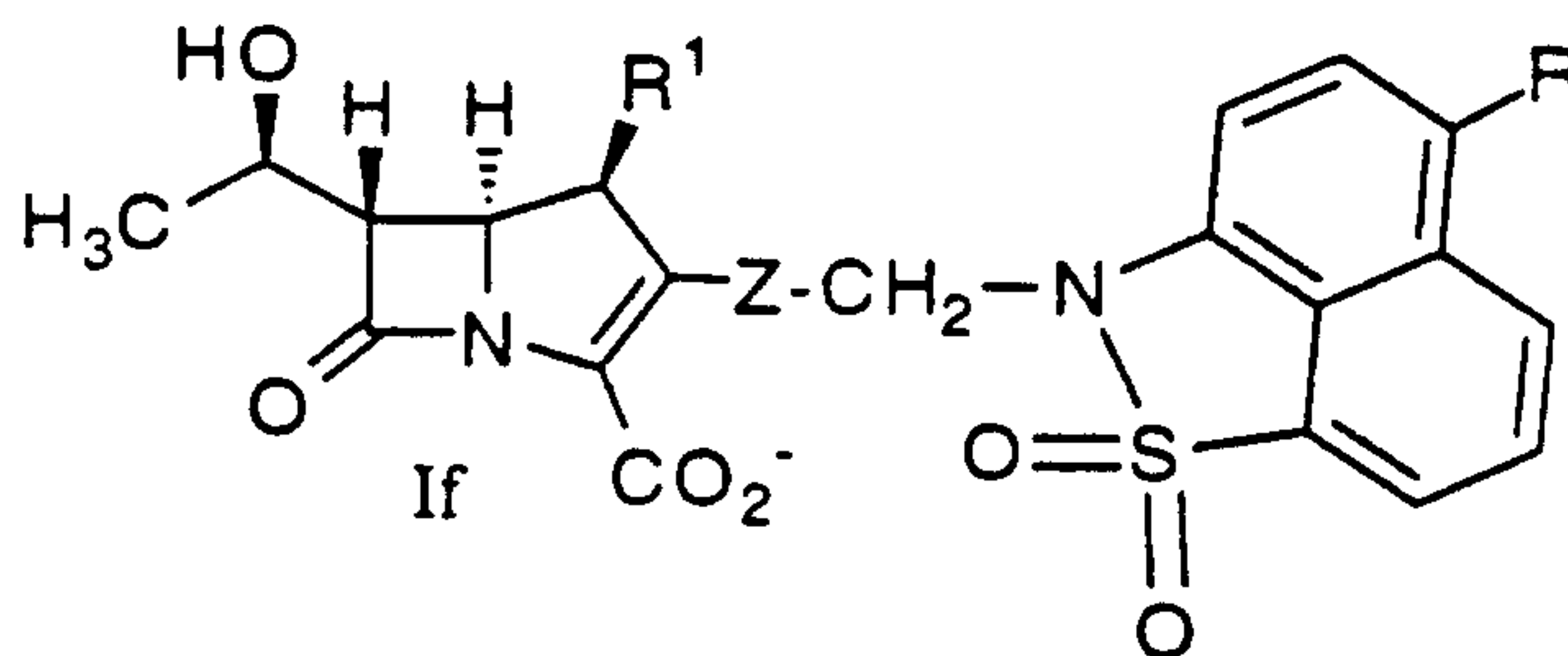
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wherein L⁻, a and b are as originally defined, and R^x represents a member selected from the group consisting of:
 5 hydrogen or a C₁-8 straight- or branched- chain alkyl, optionally interrupted by one or two of O, S, SO, SO₂, NR^w, N⁺R^hR^w, or -C(O)-,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

15

17. A compound in accordance with claim 1 represented by formula If:

20



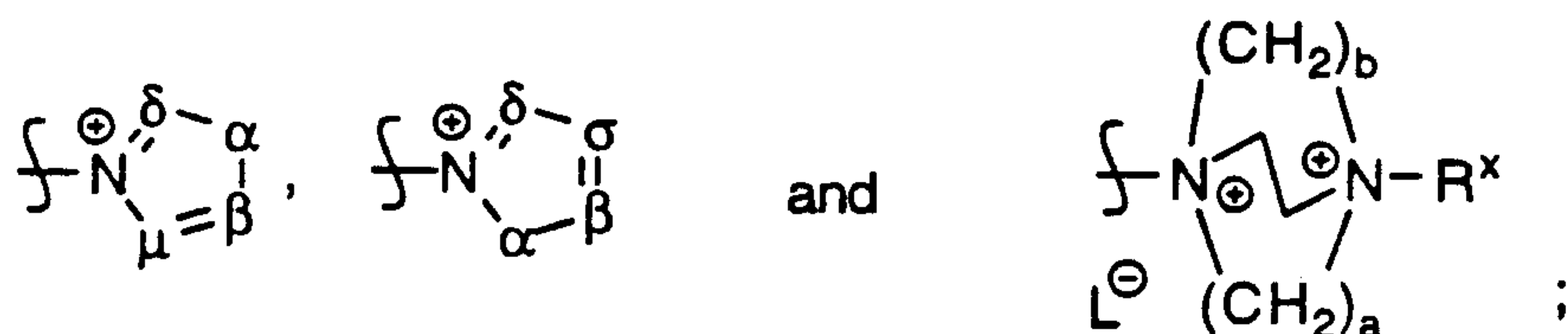
or a pharmaceutically acceptable salt thereof, wherein:

25 R contains a positively charged moiety selected from the group consisting of: -R^{*}, Q, and a C₁-6 straight or branched alkyl chain substituted with one R^d group;

R^d is independently selected -R^{*} or Q;

Q is selected from the group consisting of:

- 90 -

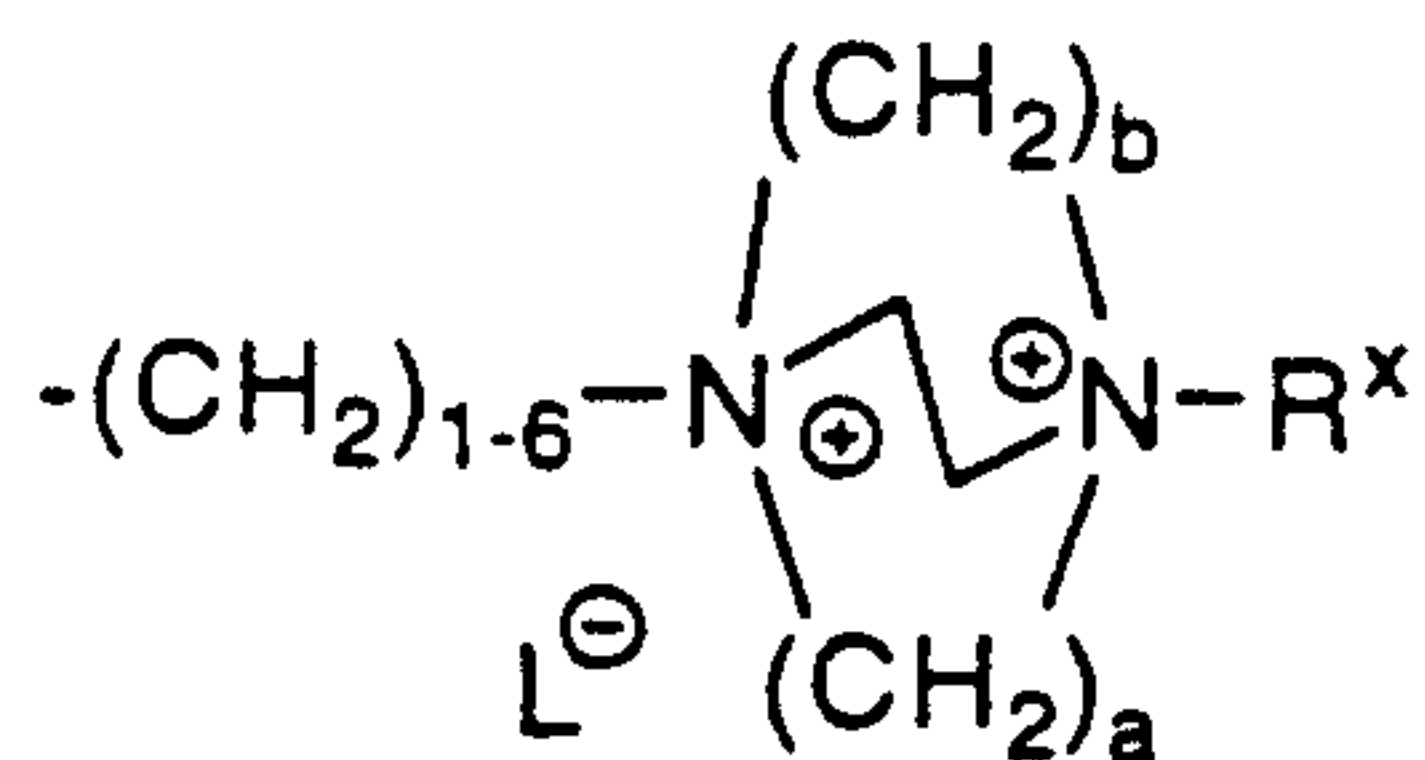


- wherein L^- , a and b are as originally defined, and R^x
- 5 represents a member selected from the group consisting of:
hydrogen or a C₁₋₈ straight- or branched- chain alkyl, optionally
interrupted by one or two of O, S, SO, SO₂, NR^W, N⁺R^hR^W, or -
C(O)-, said chain being unsubstituted or substituted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

18. A compound in accordance with claim 16
wherein:

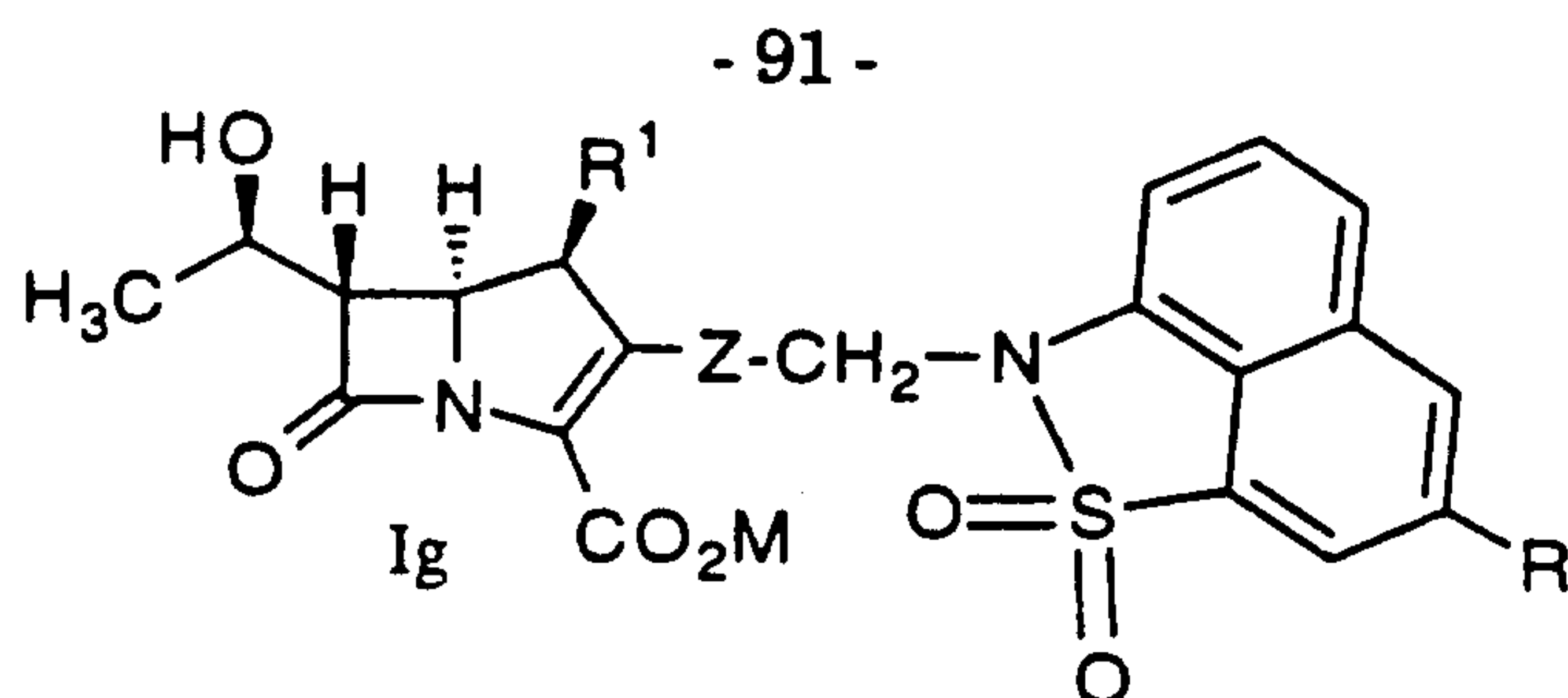
R represents

20



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

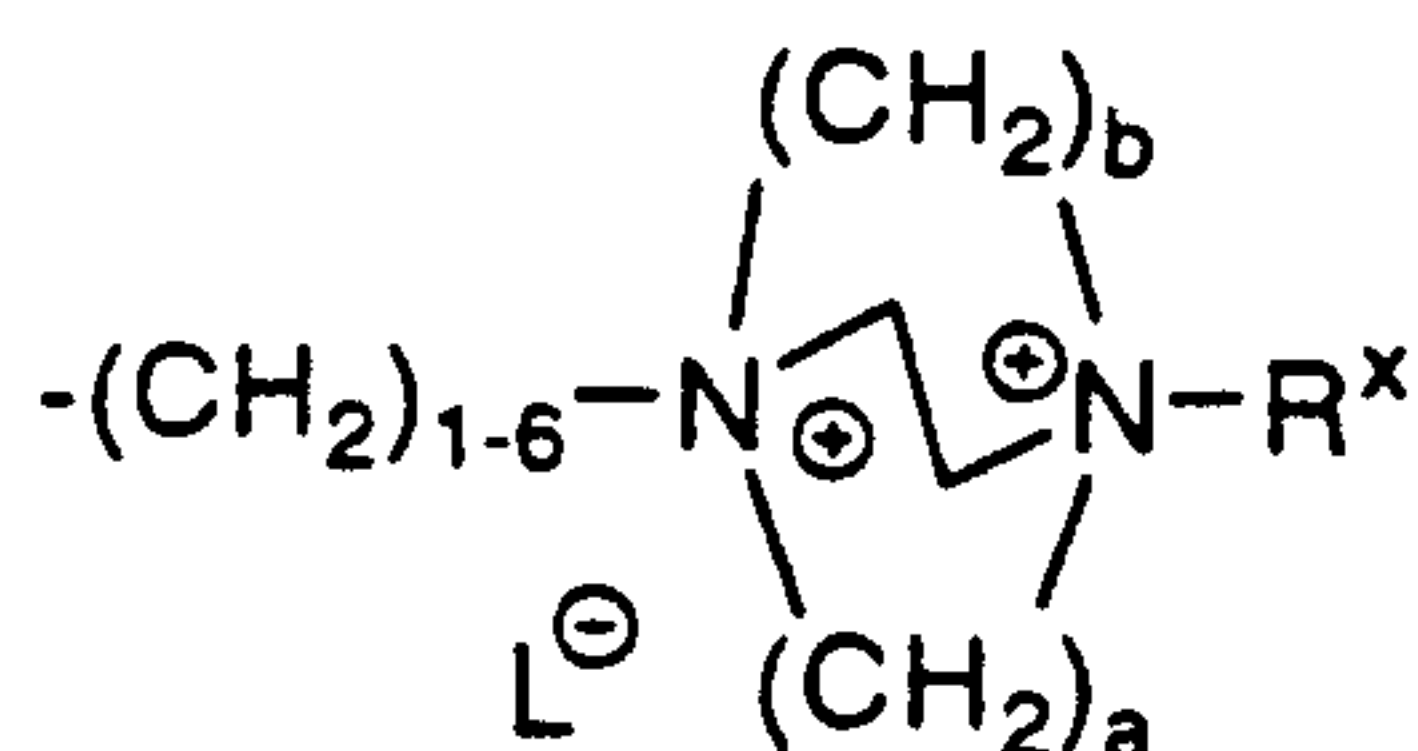
- 25 19. A compound in accordance with claim 1
represented by formula Ig:



wherein:

5

R represents



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

10

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

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

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

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

25