

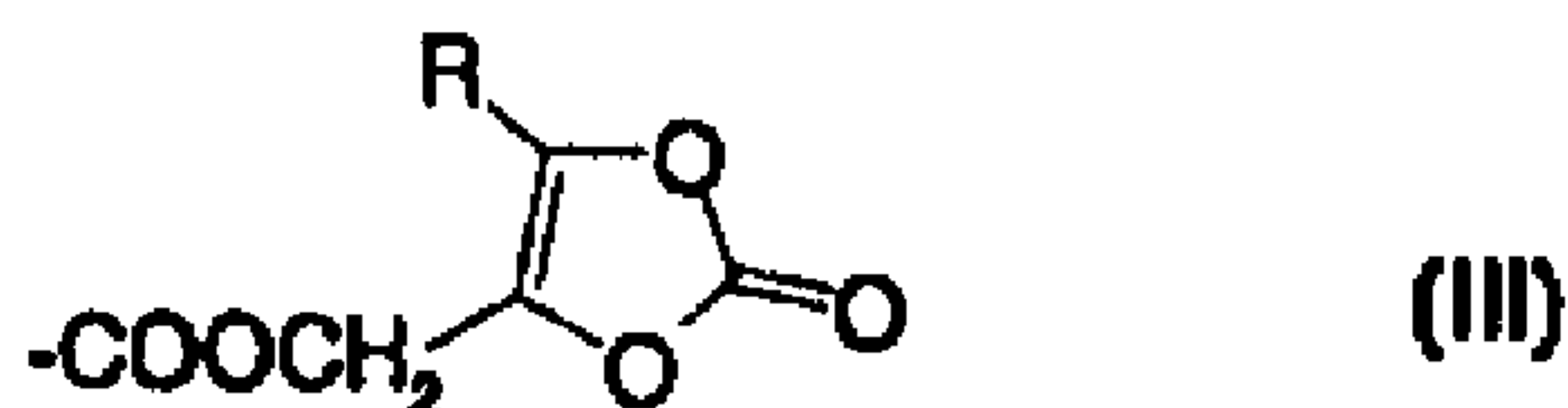
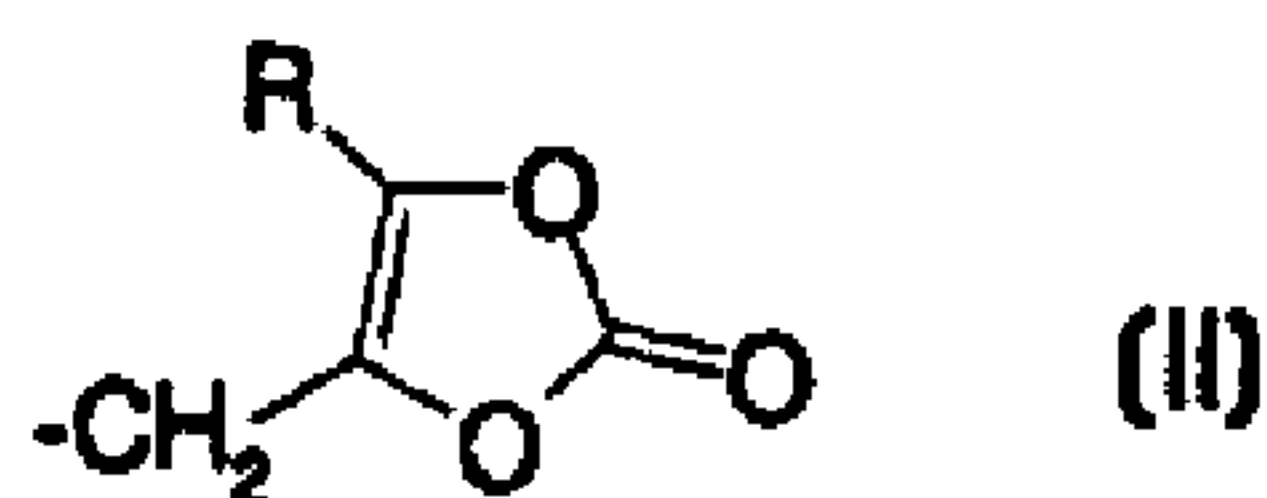
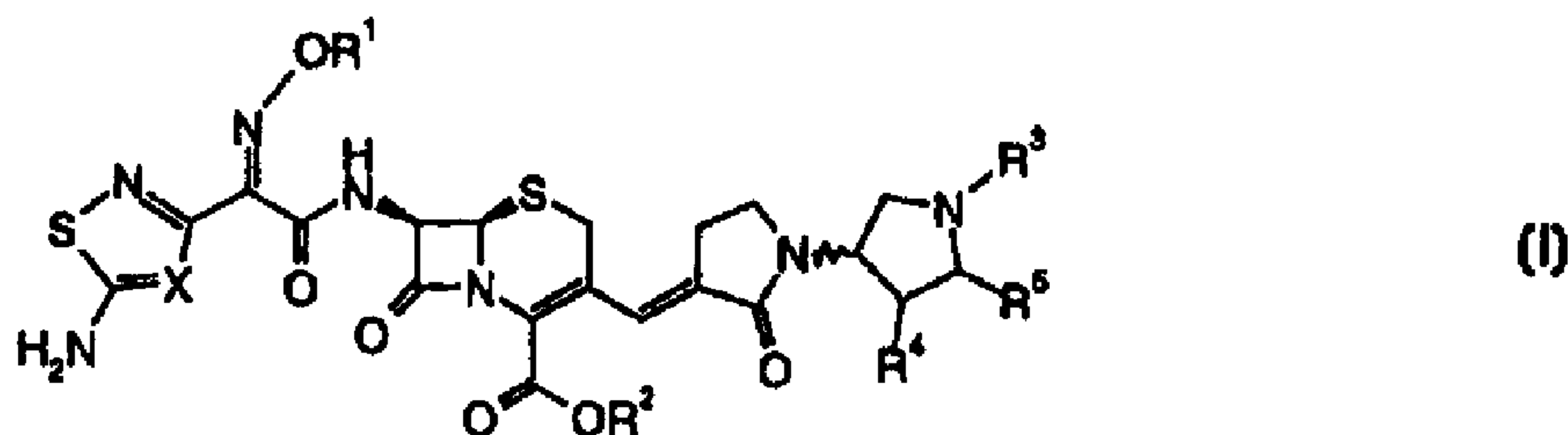


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(54) **DERIVES DE 3-(2-OXO-[1,3']BIPYRROLIDINYL-3-
YLIDENEMETHYL)-CEPHEMES**

(54) **DERIVATIVES OF 3-(2-OXO-[1,3']BIPYRROLIDINYL-3-
YLIDENEMETHYL)-CEPHEMS**



(57) La présente invention concerne des composés représentés par la formule générale (I). Dans cette formule, R¹ est hydrogène, C₁₋₆-alkyle, éventuellement substitué par un fluoro, ou C₃₋₆-cycloalkyle. R² est hydrogène ou un groupe appartenant aux -CH₂C(=CHR)-COOR, -CH₂OCOR, -CH(R)OCOR, -CH(R)OCOOR, -CH(OCOR)OCOR et -CH₂OCOR et (II). R³ est hydrogène ou un groupe appartenant aux -CH₂C(=CH₂)-COOR, -COOCH₂C(=CHR)-COOR, -COOCH₂OCOR, -COOCH(R)OCOR,

(57) The present invention is concerned with new compounds of formula (I) wherein R¹ is hydrogen, C₁₋₆-alkyl, optionally substituted by fluoro, or C₃₋₆-cycloalkyl; R² is hydrogen or a group selected from -CH₂C(=CHR)-COOR, -CH₂OCOR, -CH(R)OCOR, -CH(R)OCOOR, -CH(OCOR)OCOR, -CH₂COCH₂OCOR and (II); R³ is hydrogen or group selected from -CH₂C(=CH₂)-COOR, -COOCH₂C(=CHR)-COOR, -COOCH₂OCOR,





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$-\text{COOCH}(\text{R})\text{OCOR}$, $-\text{COOCH}(\text{OCOR})\text{OCOR}$ et $-\text{COOCH}_2\text{COCH}_2\text{OCOR}$ et (III). En outre dans la mesure où l'un de R^2 et R^3 est hydrogène et que l'autre de R^2 et R^3 n'est pas hydrogène, R est hydrogène ou C_{1-6} -alkyle. R^4 est hydrogène ou hydroxy. R^5 est hydrogène ou ω -hydroxyalkyle. Enfin, X est CH ou N. L'invention concerne également des sels pharmaceutiquement acceptables de ces composés, ainsi que des hydrates de ces composés et de leurs sels. L'invention concerne enfin l'utilisation des composés représentés par la formule générale (I) et des sels pharmaceutiquement acceptables de ces composés ainsi que l'utilisation des hydrates de ces composés et de leurs sels pour la fabrication de préparations pharmaceutiques renfermant de tels composés.

$-\text{COOCH}(\text{OCOR})\text{OCOR}$, $-\text{COOCH}_2\text{COCH}_2\text{OCOR}$, and (III); with the proviso that one of R^2 and R^3 is $-\text{COOCH}(\text{R})\text{OCOR}$, $-\text{CO}$ CH(R)OCOR, hydrogen and the other of R^2 and R^3 is different from hydrogen, R is hydrogen or C_{1-6} -alkyl; R^4 is hydrogen or hydroxy, R^5 is hydrogen or ω -hydroxyalkyl; and X is CH or N, as well as pharmaceutically acceptable salts of said compounds and hydrates of said compounds and of their salts, and with the use of compounds of formula (I) and of pharmaceutically acceptable salts of said compounds and hydrates of said compounds and of their salts for the manufacture of pharmaceutical preparations containing such compounds.



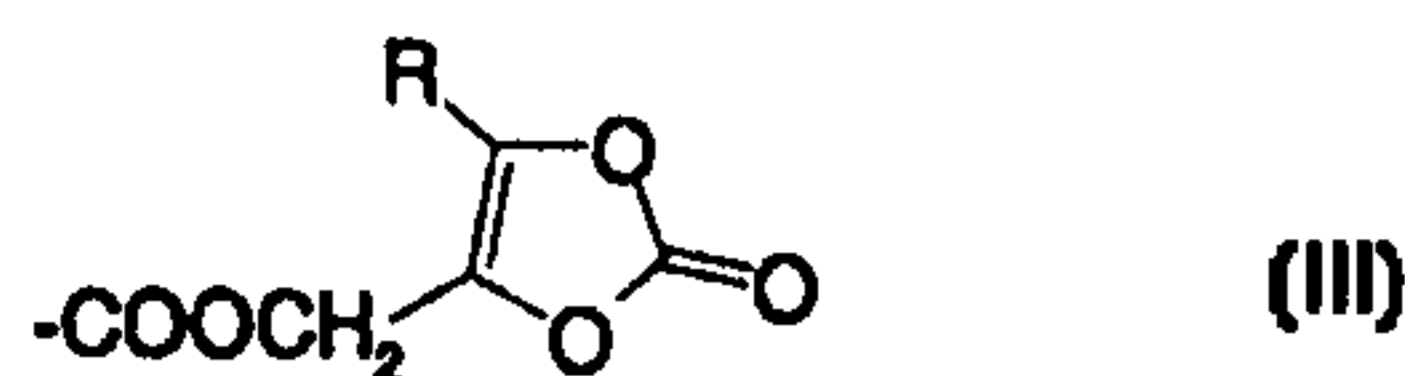
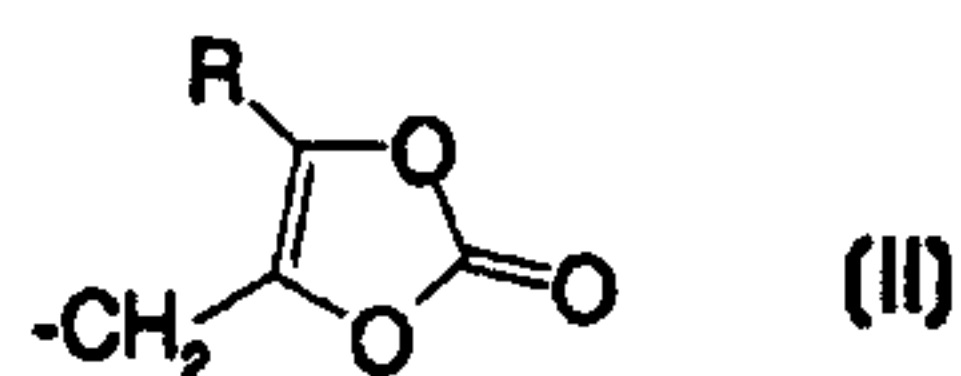
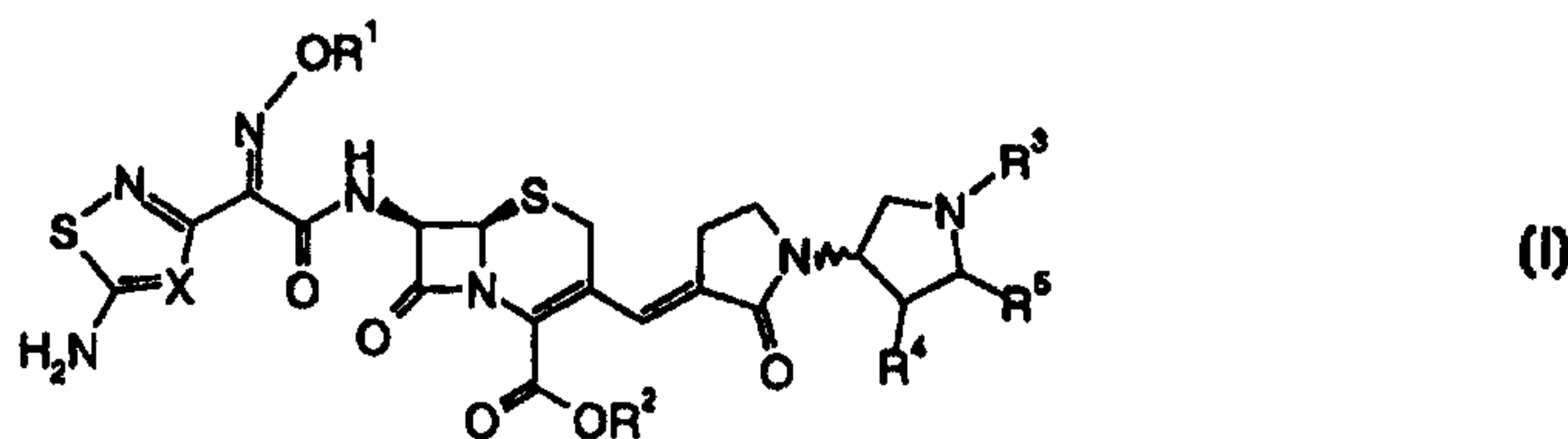
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<p>(21) International Application Number: PCT/EP99/03907</p> <p>(22) International Filing Date: 7 June 1999 (07.06.99)</p> <p>(30) Priority Data: 98110888.9 15 June 1998 (15.06.98) EP 98117099.6 10 September 1998 (10.09.98) EP</p> <p>(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basle (CH).</p> <p>(72) Inventors: HEBEISEN, Paul; St. Alban-Ring 184, CH-4052 Basle (CH). HUBSCHWERLEN, Christian; Rue de la Gendarmerie, F-68200 Durmenach (FR). SPECKLIN, Jean-Luc; 2, rue des Faisans, F-68680 Kembs-Schaferhof (FR).</p> <p>(74) Agent: KJELLSAA-BERGER, Hanny; Grenzacherstrasse 124, CH-4070 Basle (CH).</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, 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).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	

(54) Title: DERIVATIVES OF 3-(2-OXO-[1,3']BIPYRROLIDINYL-3-YLIDENEMETHYL)-CEPHEMS

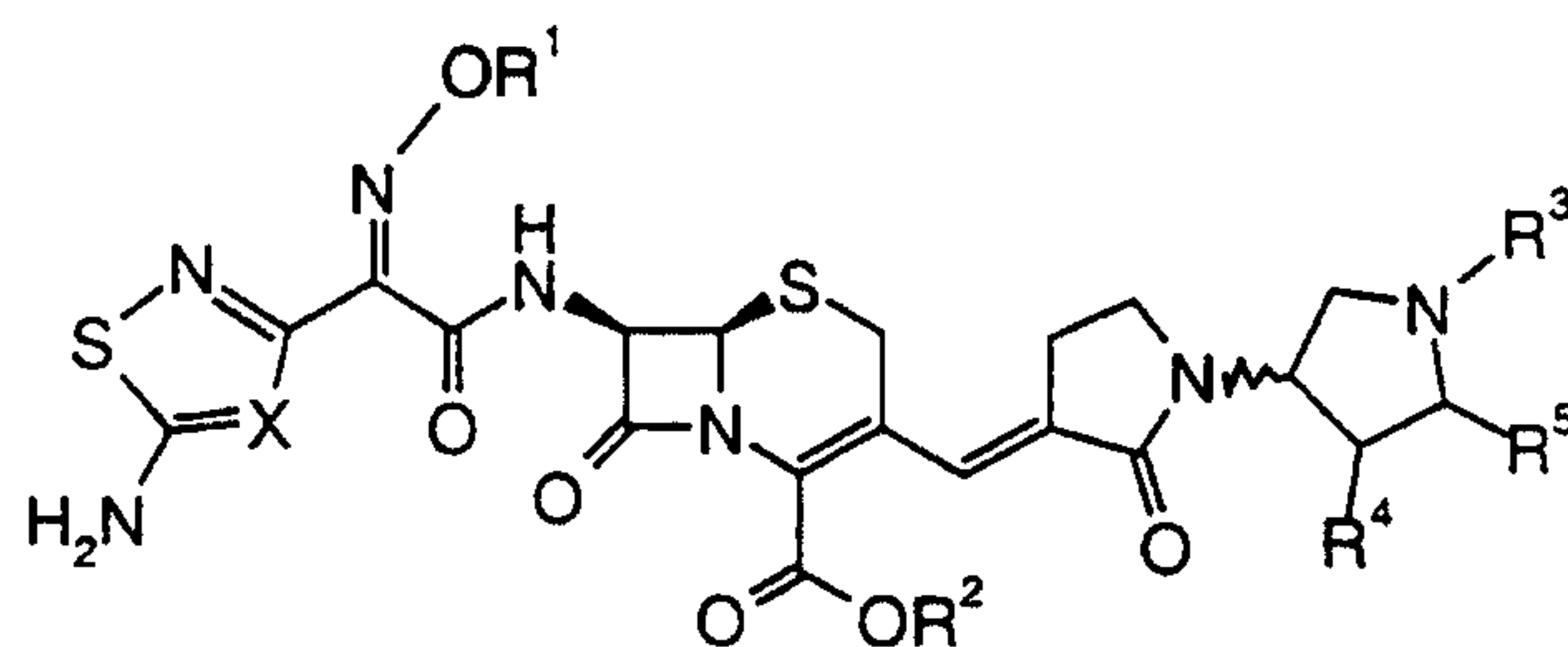


(57) Abstract

The present invention is concerned with new compounds of formula (I) wherein R¹ is hydrogen, C₁₋₆-alkyl, optionally substituted by fluoro, or C₃₋₆-cycloalkyl; R² is hydrogen or a group selected from -CH₂C(=CHR)-COOR, -CH₂OCOR, -CH(R)OCOR, -CH(R)OCOOR, -CH(OCOR)OCOR, -CH₂COCH₂OCOR and (II); R³ is hydrogen or group selected from -CH₂C(=CH₂)-COOR, -COOCH₂C(=CHR)-COOR, -COOCH₂OCOR, -COOCH(R)OCOR, -CO CH(R)OCOOR, -COOCH(OCOR)OCOR, -COOCH₂COCH₂OCOR, and (III); with the proviso that one of R² and R³ is hydrogen and the other of R² and R³ is different from hydrogen, R is hydrogen or C₁₋₆-alkyl; R⁴ is hydrogen or hydroxy, R⁵ is hydrogen or ω-hydroxyalkyl; and X is CH or N, as well as pharmaceutically acceptable salts of said compounds and hydrates of said compounds and of their salts, and with the use of compounds of formula (I) and of pharmaceutically acceptable salts of said compounds and hydrates of said compounds and of their salts for the manufacture of pharmaceutical preparations containing such compounds.

Derivatives of 3-(2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl)-cephems

The present invention is concerned with new compounds of formula I

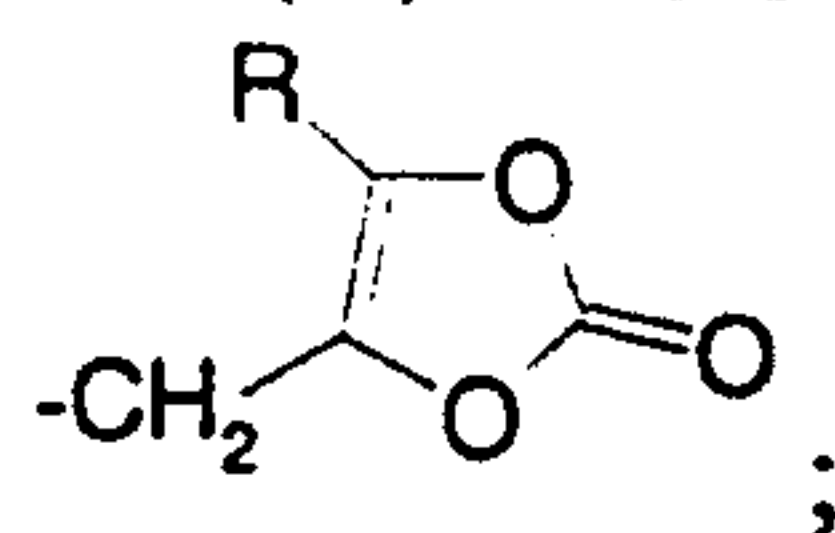


I

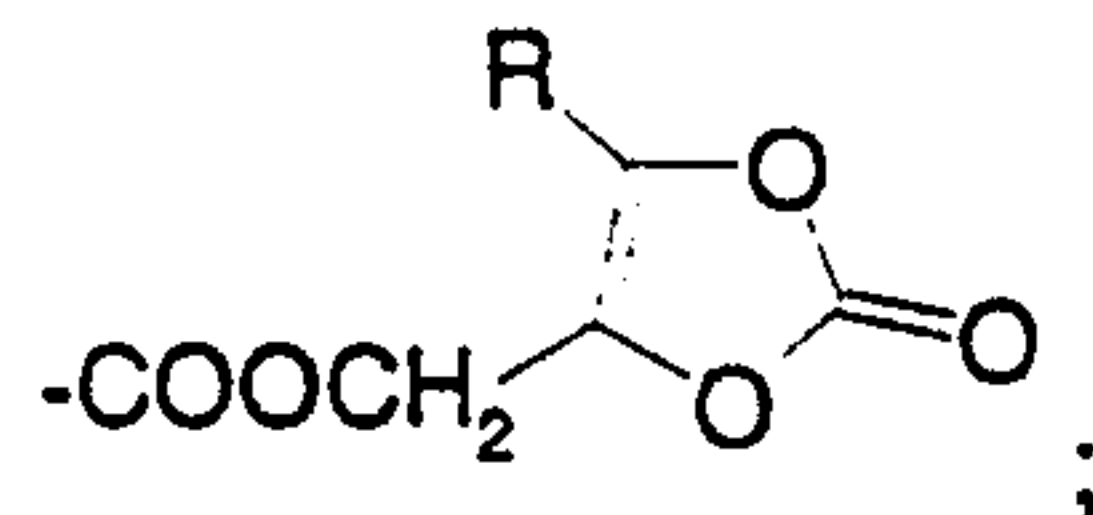
5 wherein

R¹ is hydrogen, C₁₋₆-alkyl, optionally substituted by fluoro, or C₃₋₆-cycloalkyl;

R² is hydrogen or a group selected from
 -CH₂C(=CHR)-COOR, -CH₂OCOR, -CH(R)OCOR,
 10 -CH(R)OCOOR, -CH(OCOR)OCOR, -CH₂COCH₂OCOR and



R³ is hydrogen or group selected from -CH₂C(=CH₂)-COOR,
 -COOCH₂C(=CHR)-COOR, -COOCH₂OCOR,
 -COOCH(R)OCOR, -COOCH(R)OCOOR,
 15 -COOCH(OCOR)OCOR, -COOCH₂COCH₂OCOR, and



with the proviso that one of R² and R³ is hydrogen and the other of R² and R³ is different from hydrogen,

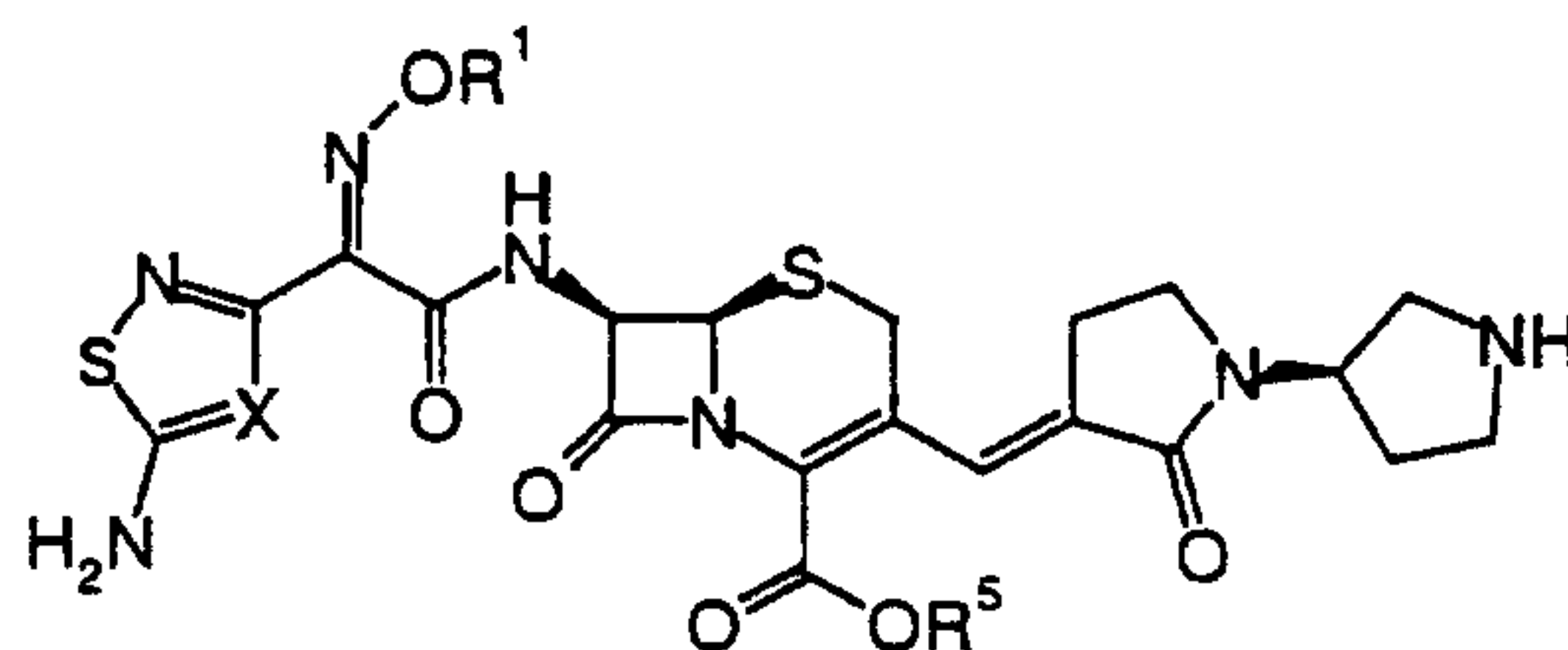
R is hydrogen or C₁₋₆-alkyl;

- 2 -

- R⁴ is hydrogen or hydroxy,
 R⁵ is hydrogen or ω-hydroxyalkyl; and
 X is CH or N,

as well as pharmaceutically acceptable salts of said compounds and hydrates
 5 of the compounds of formula I and of their salts.

Vinylpyrrolidinon cephaslosporin derivatives are known to be useful
 antibiotic compounds as described in EP A-0 841 339, furthermore compounds
 of formula A



A

10 wherein

R¹ and X are as defined above and R⁵ is hydrogen, and pharmaceutically
 acceptable salts thereof,

especially (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxy-
 imino-acetylamino]-8-oxo-3-[(E)-(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidene-
 15 methyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid are potent
 antibacterial agents with activity against methicillin resistant staphylococci,
 both *in vitro* and *in vivo*. However, these compounds have limited solubility,
 not allowing bolus injections. It is therefore necessary to find derivatives of the
 compounds A to render these compounds suitable for parenteral and
 20 intramuscular application.

From J. Med. Chem. (1996), 39(2), 480-6; US patent no. 5 466 811;
 Bioorganic and Medicinal Chem. Lett. 1997,7,2909-2912; US patent no.
 5 610 314 (oxodioxolenyl)methyl carbamates are known to form derivatives of
 amines e.g. for fibrinogen receptor antagonists, ampicillin, norfloxacin and
 25 other pharmaceuticals. Furthermore, 2-(alkyloxycarbonyl)-2-alkylideneethyl
 esters have been described as prodrugs of carboxylic acids for cephalosporins,
 J. Antibiot. (1992), 45(8), 1358-64. Both types of derivatives have been used to
 improve the oral bioavailability of the corresponding drugs.

It has now been found that the compounds of formula I exhibit better
 30 solubility in water and buffers at physiological pH. *In vitro* and *in vivo* they
 were readily converted to compounds of formula A and can therefore be used
 for parenteral and intramuscular application forms. The invention is thus also
 concerned with pharmaceutical preparations containing a compound of
 formula I and a therapeutically inert carrier.

As used herein "pharmaceutically acceptable salts" useful in this invention include salts derived from metals, salts from amino acids and salts of mineral or organic acids. Examples of preferred metal salts are those derived from the alkali metals, for example, lithium (Li⁺), sodium (Na⁺) and potassium (K⁺). Especially preferred is sodium. Other salts are derived from amino acids such as, for example, salts with arginine or lysine. Examples of salts of mineral acids are for example hydrochlorides, sulphates or phosphates, and examples of salts of organic acids are mesylates (methylsulfonic acid salts), napsylates (naphthene-2-sulfonic acid salts), besylates (benzenesulfonic acid salts), maleates, salicylates, tartrates, lactates, citrates, benzoates, succinates, acetates and the like. Especially preferred are chlorides, sulfates, phosphates, lactates and mesylates.

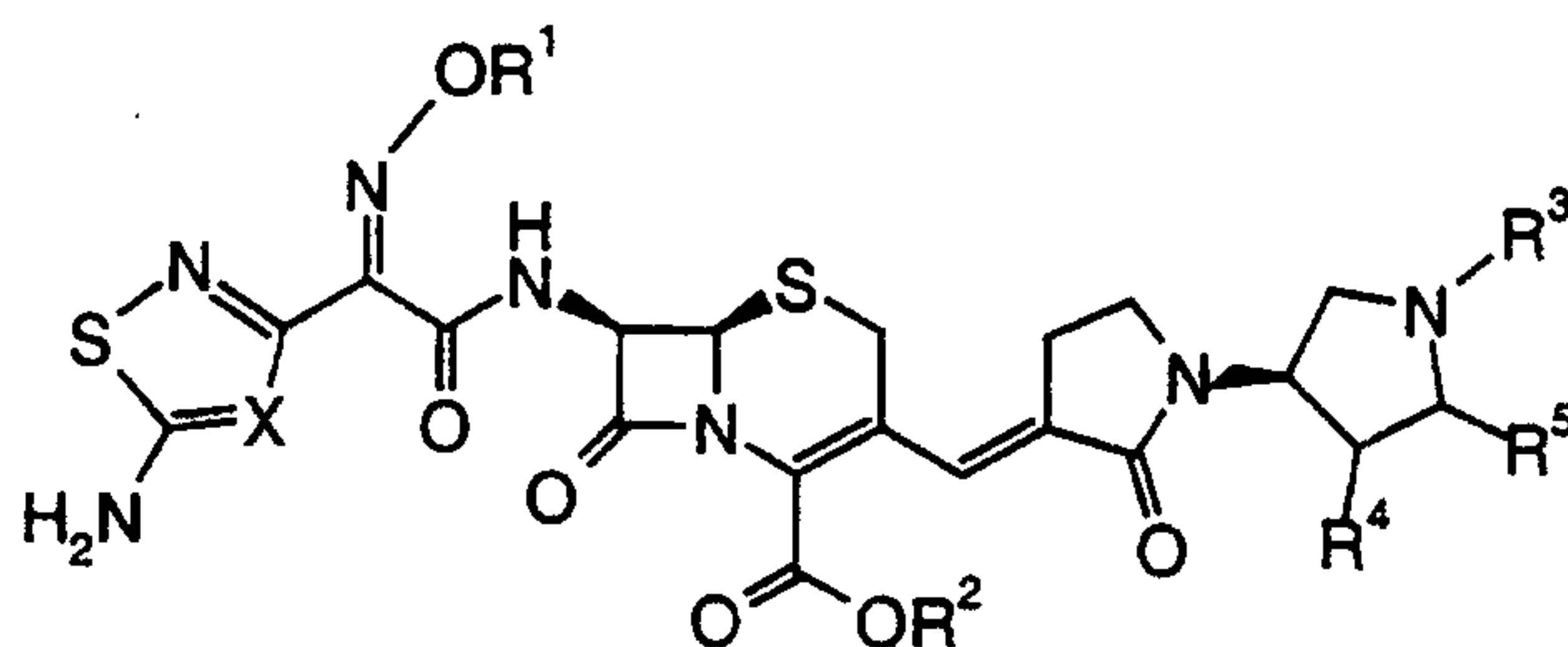
In the formulas represented herein, when substituents are illustrated as joined to the nucleus a solid line (—), indicates that the substituent is in the β -orientation, that is, above the plane of the molecule, a broken line (- - - -), indicates that the substituent is in the α -orientation, that is, below the plane of the molecule whereas the line (~~~~~) indicates that the bond is either in α - or in β -orientation.

The term "C₁₋₆-alkyl, optionally substituted by fluoro" refers to both straight and branched chain saturated hydrocarbon groups having 1 to 6 and preferably 1 to 4 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, tertiary butyl and the like, these group may be substituted by one or more fluorine atoms as e.g. in fluoromethyl or trifluoromethyl.

As used herein, the term " ω -hydroxyalkyl" refers to both straight and branched chain saturated hydrocarbon groups as defined above bearing a hydroxy group in the terminal position, e.g. hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, preferably hydroxymethyl.

By the term "C₃₋₆-cycloalkyl" is meant a 3-6 membered saturated carbocyclic moiety, e.g., cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, in particular cyclopentyl.

Especially preferred compounds of formula I are the compounds of formula



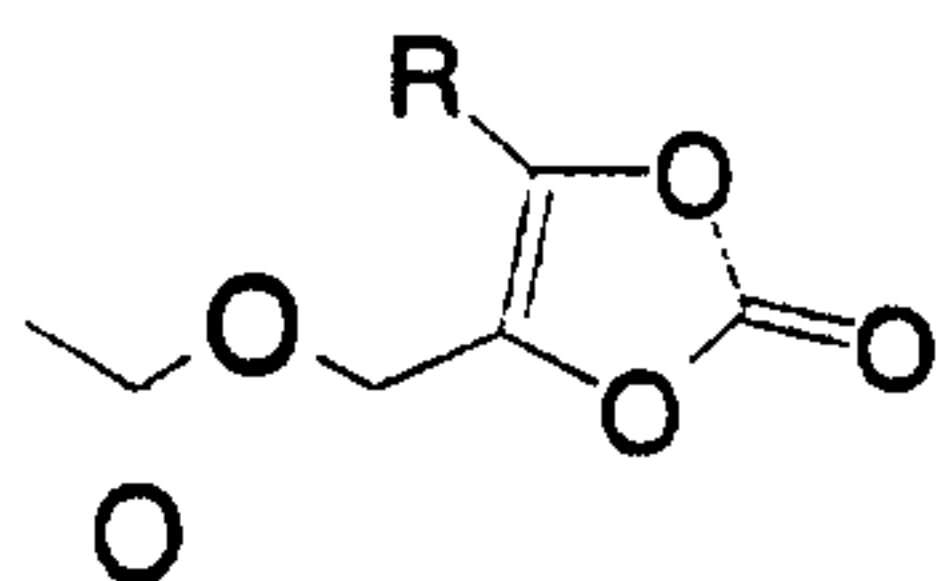
I-a

wherein, R^1 , R^2 , R^3 , and X are as defined above and R^4 and R^5 are hydrogen, as well as pharmaceutically acceptable salts of said compounds and hydrates of the compounds of formula I-a and of their salts.

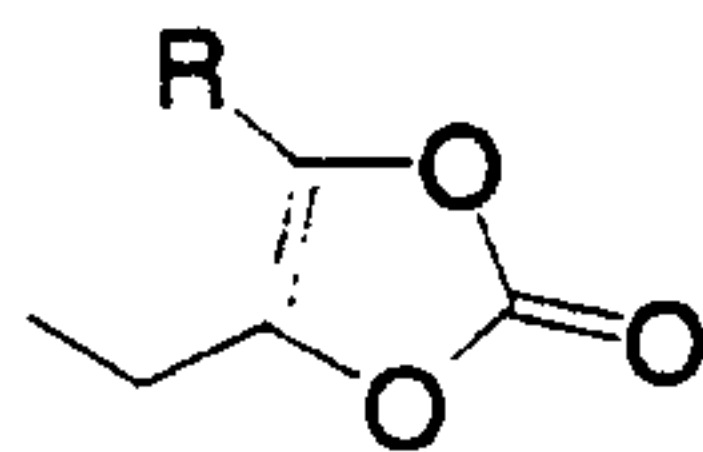
- 5 Further preferred compounds are epimers and diastereoisomers of formula I-a.

Preferred compounds of formula I and formula I-a are compounds wherein R^1 is hydrogen, X is N and R^2 is hydrogen and R^3 is a group chosen from

- 10 $-\text{CH}_2\text{C}(=\text{CH}_2)\text{-COOCH}_2\text{CH}_3$,
 $-\text{COO-CH}_2\text{C}(=\text{CHCH}_2\text{CH}_3)\text{-COOCH}_2\text{CH}(\text{CH}_3)_2$,
 and particularly



- 15 Further preferred compounds of formula I are compounds wherein R^1 and R^3 are hydrogen, X is N and R^2 is a group chosen from
 $-\text{CH}_2\text{C}(=\text{CHCH}_2\text{CH}_3)\text{-COOCH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{C}(=\text{CH}_2)\text{-COOCH}_2\text{CH}_3$,
 $-\text{CH}_2\text{OCOC}(\text{CH}_3)_3$, $-\text{CH}(\text{CH}_3)\text{OCOCH}_3$, $-\text{CH}(\text{CH}_3)\text{OCOOCH}_2\text{CH}_3$,
 $-\text{CH}(\text{OCOCH}_3)\text{OCOCH}_3$, $-\text{CH}_2\text{COCH}_2\text{OCOCH}_3$, and



- 20 Especially preferred compounds of formula I and I-a are

(6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-(R)-1'-(5-methyl-2-oxo-[1,3]dioxol-4-ylmethoxycarbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

- 25 (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-(R)-1'-(5-ethyl-2-oxo-[1,3]dioxol-4-ylmethoxycarbonyl)-2-

oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

(6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(R)-1'-(2-oxo-5-propyl-[1,3]dioxol-4-ylmethoxycarbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

(6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(R)-1'-(5-isopropyl-2-oxo-[1,3]dioxol-4-ylmethoxycarbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

(6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(R)-1'-(5-tert-butyl-2-oxo-[1,3]dioxol-4-ylmethoxycarbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

(6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(R)-1'-(E-2-isobutoxycarbonyl-pent-2-enyloxycarbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

(6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(R)-1'-(2-ethoxycarbonyl-allyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)

(6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-5'-hydroxymethyl-1'-(5-methyl-2-oxo-[1,3]dioxol-4-ylmethoxycarbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt

(6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(3'S,4'S)- and -(3'R,4'R)-4'-hydroxy-1'-(5-methyl-2-oxo-[1,3]dioxol-4-ylmethoxycarbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt

The compounds of formula I and I-a as well as their salts can be hydrated. The hydration can be effected in the course of the manufacturing process or can occur gradually as a result of hygroscopic properties of an initially anhydrous product.

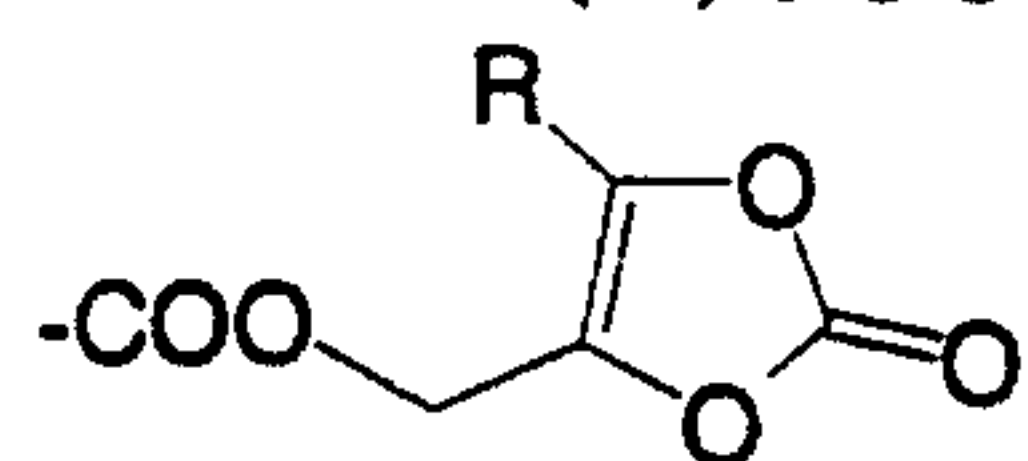
The compounds of the present invention are useful as antibiotics having potent and broad antibacterial activity; especially against methicillin resistant Staphylococci (MRSA) and *Pseudomonas aeruginosa*.

The products in accordance with the invention can be used as medicaments, for example, in the form of pharmaceutical preparations for parenteral administration, and for this purpose are preferably made into preparations as lyophilisates or dry powders for dilution with customary agents, such as water or isotonic common salt or carbohydrate (e.g. glucose) solution.

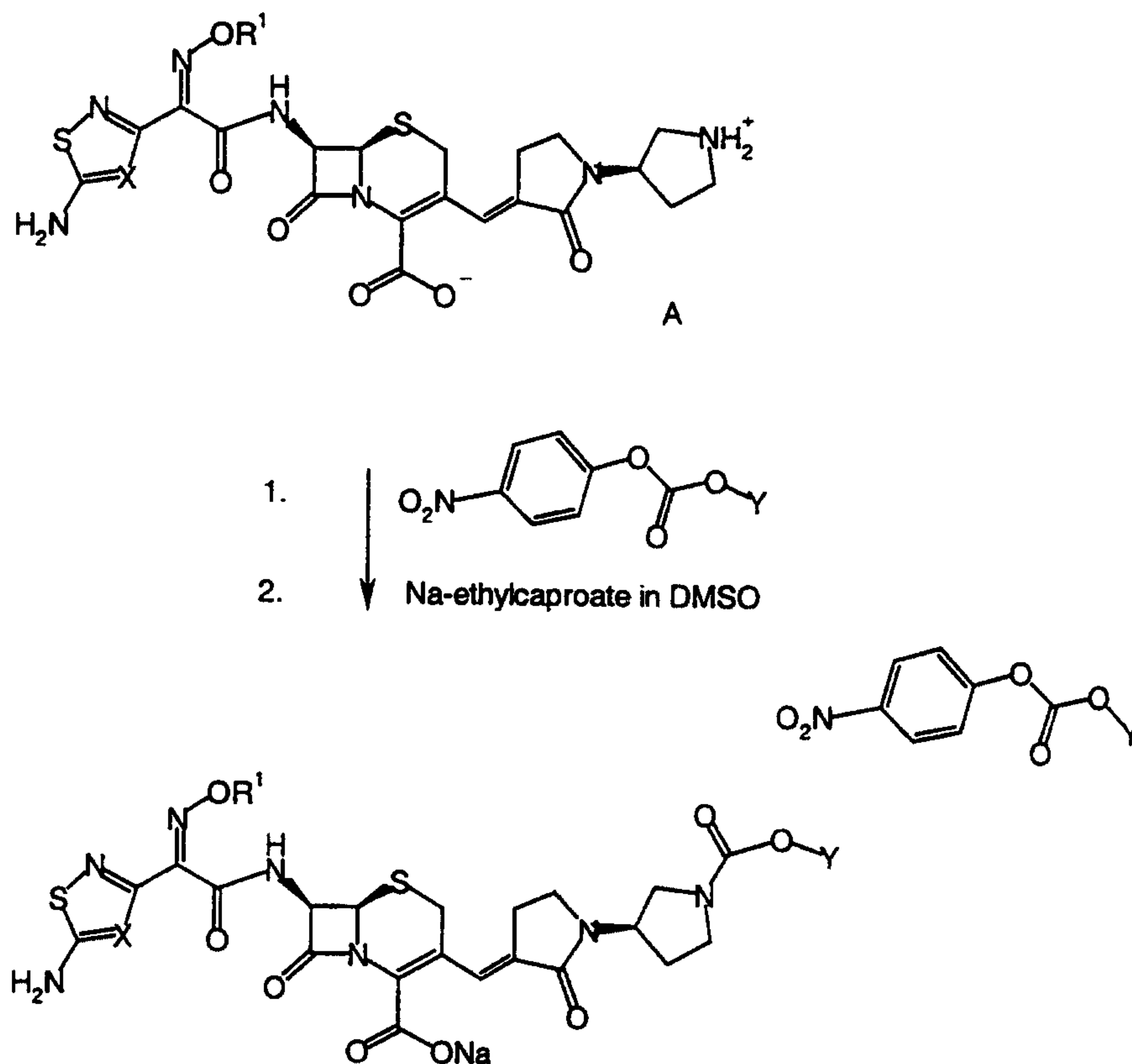
Depending on the nature of the pharmacologically active compound the pharmaceutical preparations can contain the compound for the prevention and treatment of infectious diseases in mammals, humans and non-humans. A daily dosage of about 10 mg to about 4000 mg, especially about 50 mg to about 3000 mg, is usual, with those of ordinary skill in the art appreciating that the dosage will depend also upon the age, conditions of the mammals, and the kind of diseases being prevented or treated. The daily dosage can be administered in a single dose or can be divided over several doses. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg, and 2000 mg can be contemplated.

The compounds of the formula I and I-a in accordance with the invention as well as their pharmaceutically acceptable salts, hydrates, or readily hydrolyzable esters can for example be prepared in accordance to procedures given below:

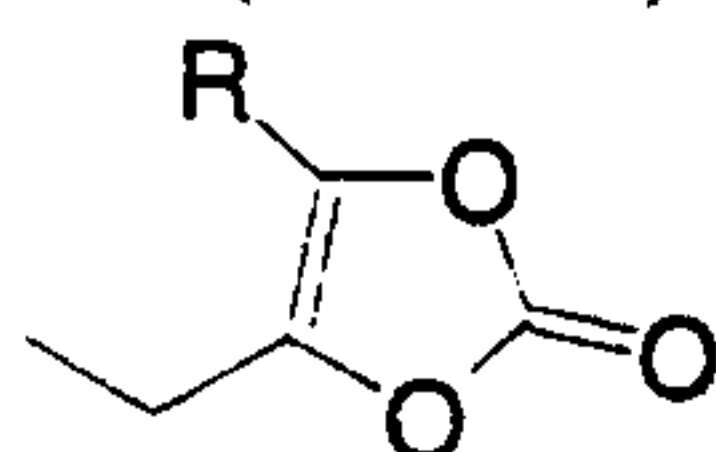
Compounds of formula I and I-a wherein R^2 is hydrogen and R^3 is a group $-\text{COOCH}_2\text{C}(=\text{CHR})-\text{COOR}$, $-\text{COOCH}_2\text{OCOR}$, $-\text{COOCH}(\text{R})\text{OCOR}$, $-\text{COOCH}(\text{R})\text{OCOR}$, $-\text{COOCH}(\text{OCOR})\text{OCOR}$, $-\text{COOCH}_2\text{COCH}_2\text{OCOR}$ or



can be prepared according to Scheme 1 by acylation of compounds of formula A with the corresponding carbonic acid 4-nitrophenyl ester.

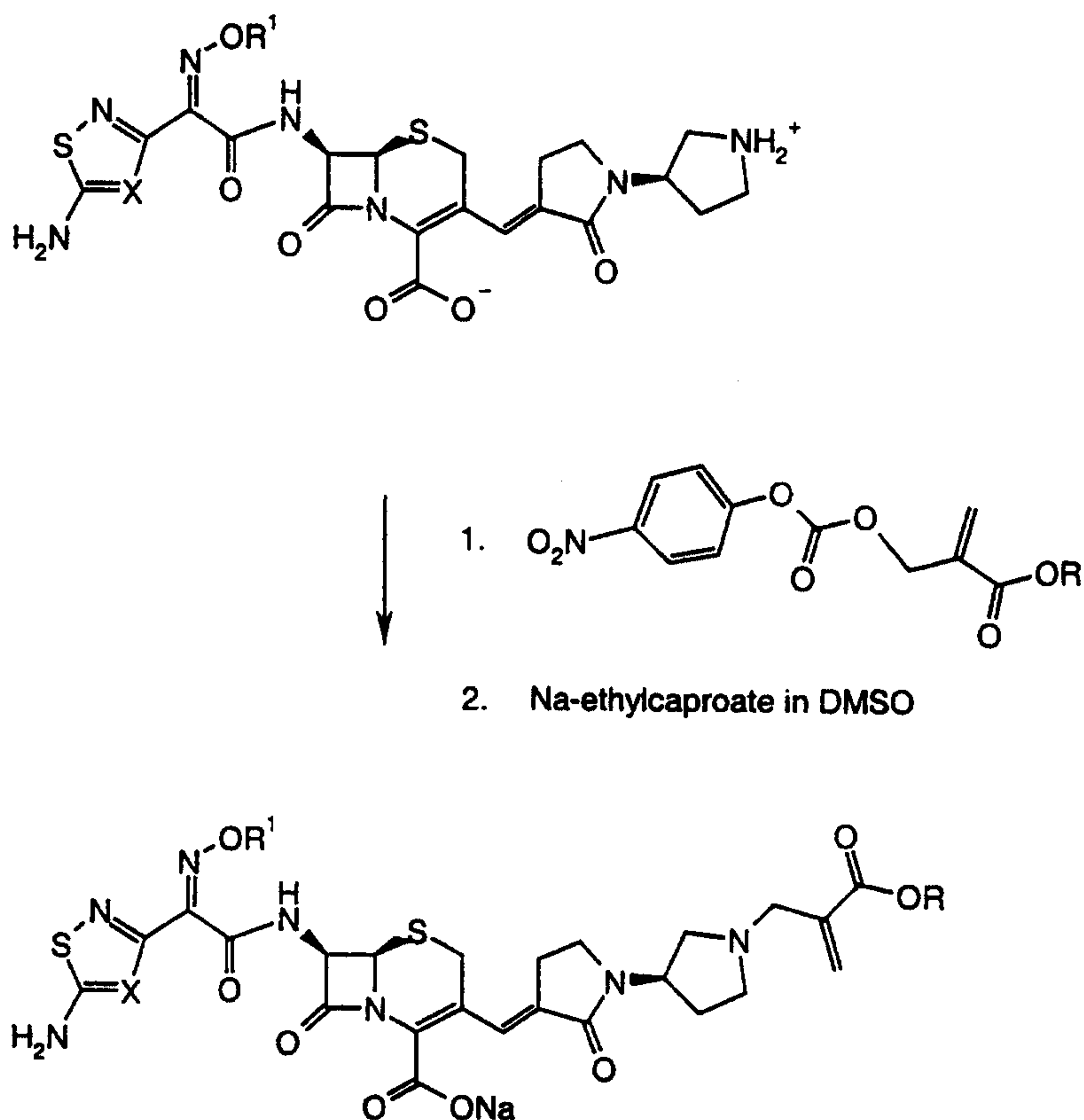
Scheme 1

wherein R^1 and R are as defined above and Y is a group
 $-\text{CH}_2\text{C}(=\text{CHR})-\text{COOR}$, $-\text{CH}_2\text{OCOR}$, $-\text{CH}(\text{R})\text{OCOR}$, $-\text{CH}(\text{R})\text{OCOO}$,
 5 $-\text{CH}(\text{OCOR})\text{OCOR}$, $-\text{CH}_2\text{COCH}_2\text{OCOR}$, or



For the preparation of compounds of formula I and I-a wherein R^3 is
 $-\text{CH}_2\text{C}(=\text{CH}_2)-\text{COOR}$ a compound of formula A is reacted with 2-(4-nitro-
 10 phenoxycarbonyloxymethyl)-acrylic acid ethyl ester. This reaction proceeds
 with loss of carbon dioxide, cf. scheme 2:

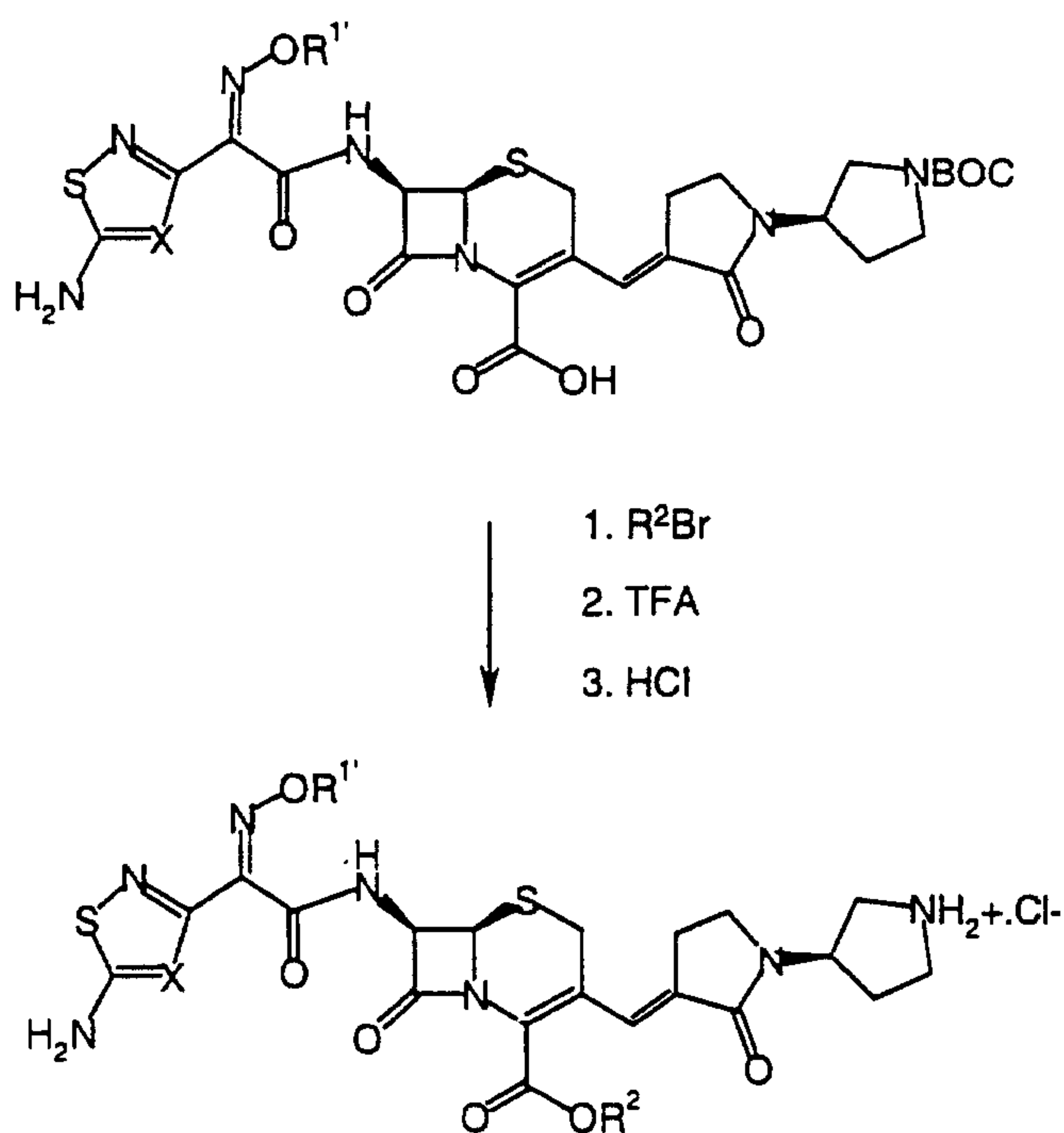
Scheme 2



The synthesis of the compounds of formula I and I-a, wherein R³ is
 5 hydrogen, (Scheme 3) is accomplished via alkylation of the carboxylate,
 preferably at the stage of the fully protected compound of formula A.
 Protecting groups for R¹ are preferably, the trityl and in position R³ tert.-
 butyloxycarbonyl (BOC). Removal of the tert.-butyloxycarbonyl and trityl-
 protecting groups is accomplished by conventional methods and the desired
 10 compounds of formula I and I-a are isolated as the hydrochloride salts by
 precipitation from dioxane.

- 9 -

Scheme 3



5 wherein R¹ is C₁₋₆-alkyl, optionally substituted by fluoro, or C₃₋₆-cycloalkyl or a protecting group, preferably trityl, and BOC is tert.-butyloxycarbonyl

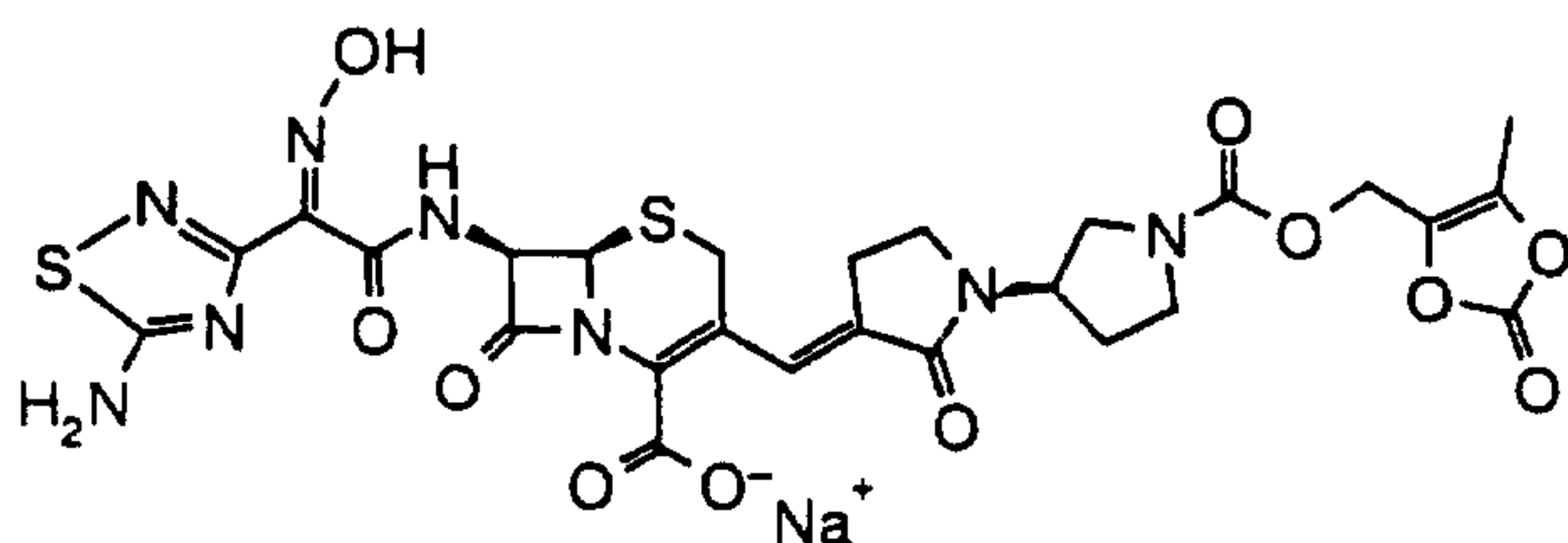
Compounds of formula A are known compounds and can be prepared according to the methods described in EP A-0 849 269 ~~appl. no. 97119528.4.~~

The alkylating agents, i.e. the compounds R²Br or R²Cl are known compounds, some are commercially available.

10 The following examples further illustrate the invention, however, without limiting its scope.

Examples

15 **1.1. Synthesis of (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(R)-1'-(5-methyl-2-oxo-[1,3]dioxol-4-ylmethoxycarbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid**



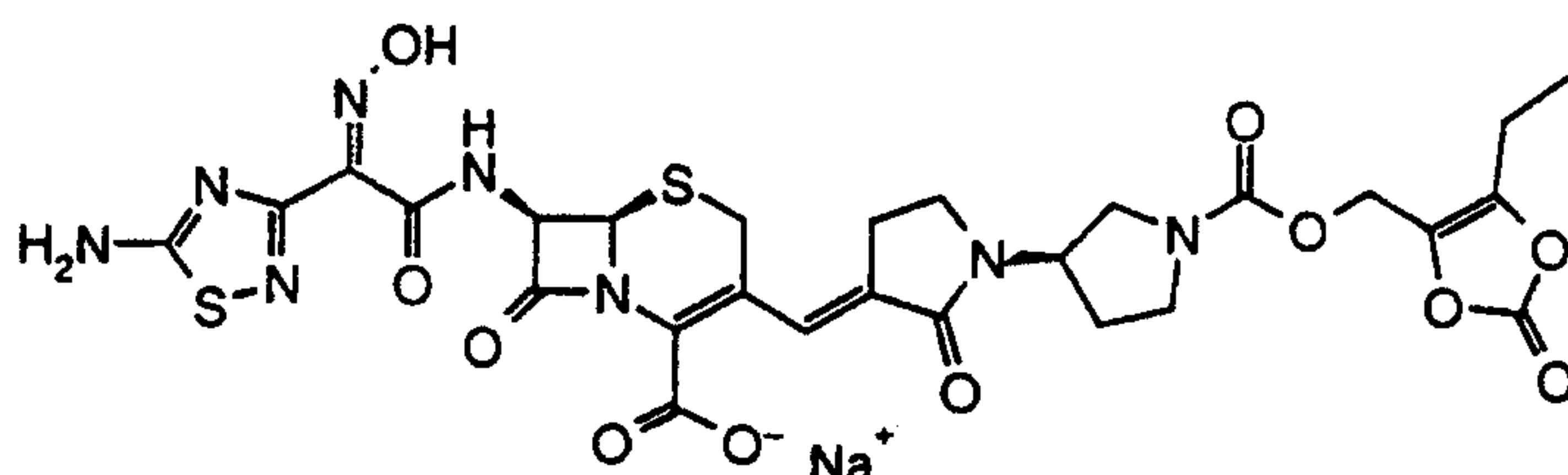
To a solution of 13.2 g (44.72 mmol) of carbonic acid 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester 4-nitro-phenyl ester in 200 ml of

dimethylsulfoxide are added 20.0 g of (6R,7R)-7-[(Z)-2-(5-amino-
 [1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-8-oxo-3-[(E)-(R)-2-oxo-
 [1,3']bipyrrolidinyl-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-
 5 carboxylic acid. The mixture is stirred under argon at room temperature for 4
 hours and 1000 ml of acetone are added. The slightly turbid solution is
 clarified by filtration over a fluted filter. To the clear motherliquour are added
 34.0 ml (34 mmol) of a 1N solution of sodium-2-ethylcaproate in acetone at
 room temperature during 20 minutes. The slightly yellow suspension is stirred
 for 10 minutes at room temperature, the solid is collected by filtration,
 10 washed with 1000 ml of acetone and 1000 ml of n-pentane and dried under
 high vacuum. The product is suspended in 600 ml of acetone and stirred at
 room temperature for 2 hours. The product is collected by filtration and dried
 under high vacuum to yield 23.94 g of the title compound as an off-white
 powder.

15 MS(ISP): $M+H^+=691.3$; $M+NH_4^+=708.2$; $M+Na^+=713.1$

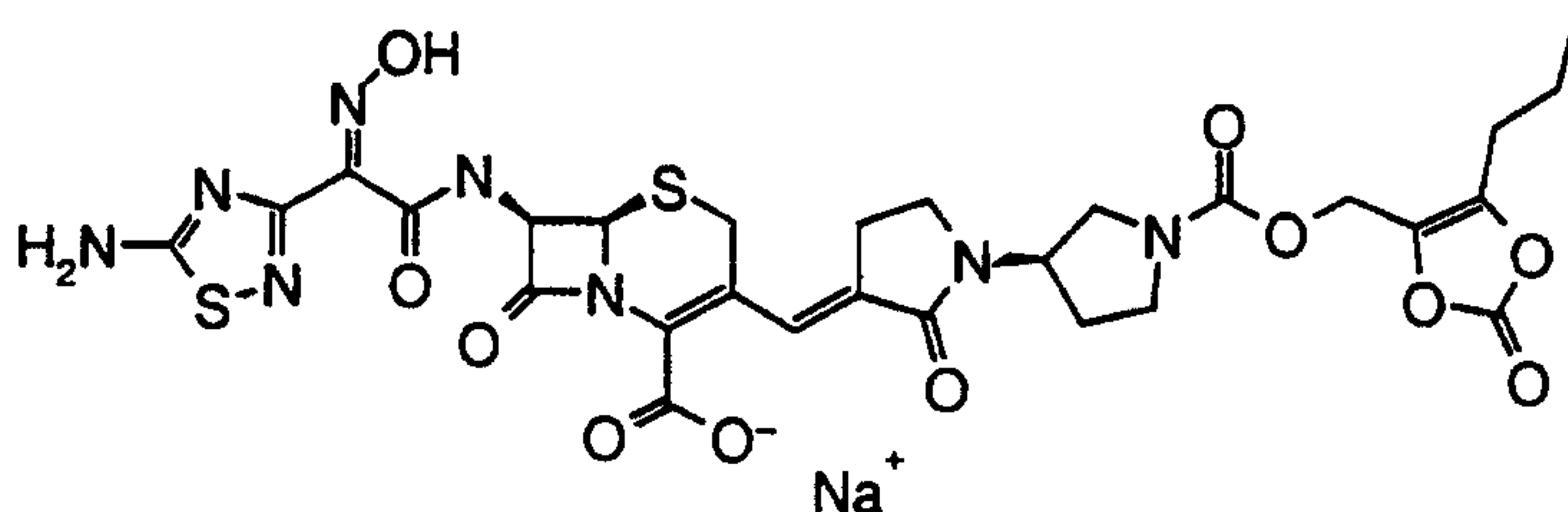
In a similar manner, the following carbamates are prepared from the
 corresponding mixed carbonates:

1.2. (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-
 acetylamino]-3-[(E)-(R)-1'-(5-ethyl-2-oxo-[1,3]dioxol-4-ylmethoxy-
 20 carbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-
 aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)



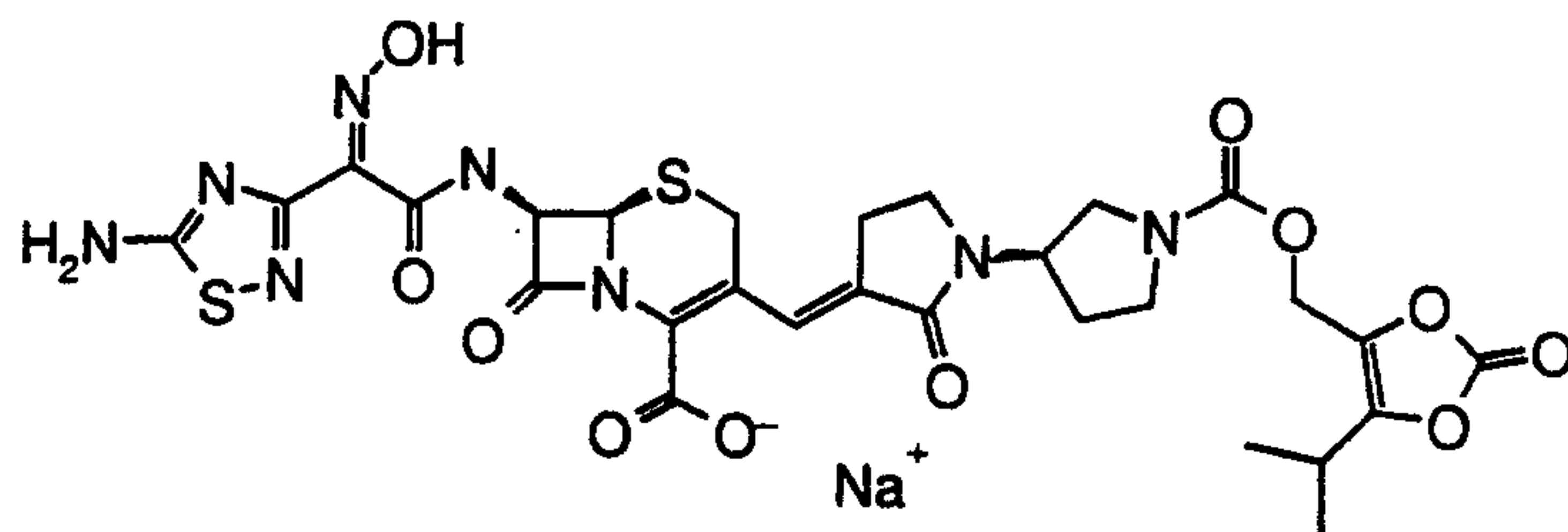
MS (ISP): $M+H^+=705.2$, $M+NH_4^+=722.3$, $M+Na^+=727.2$

1.3. (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-
 25 acetylamino]-3-[(E)-(R)-1'-(2-oxo-5-propyl-[1,3]dioxol-4-ylmethoxy-
 carbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-
 aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)



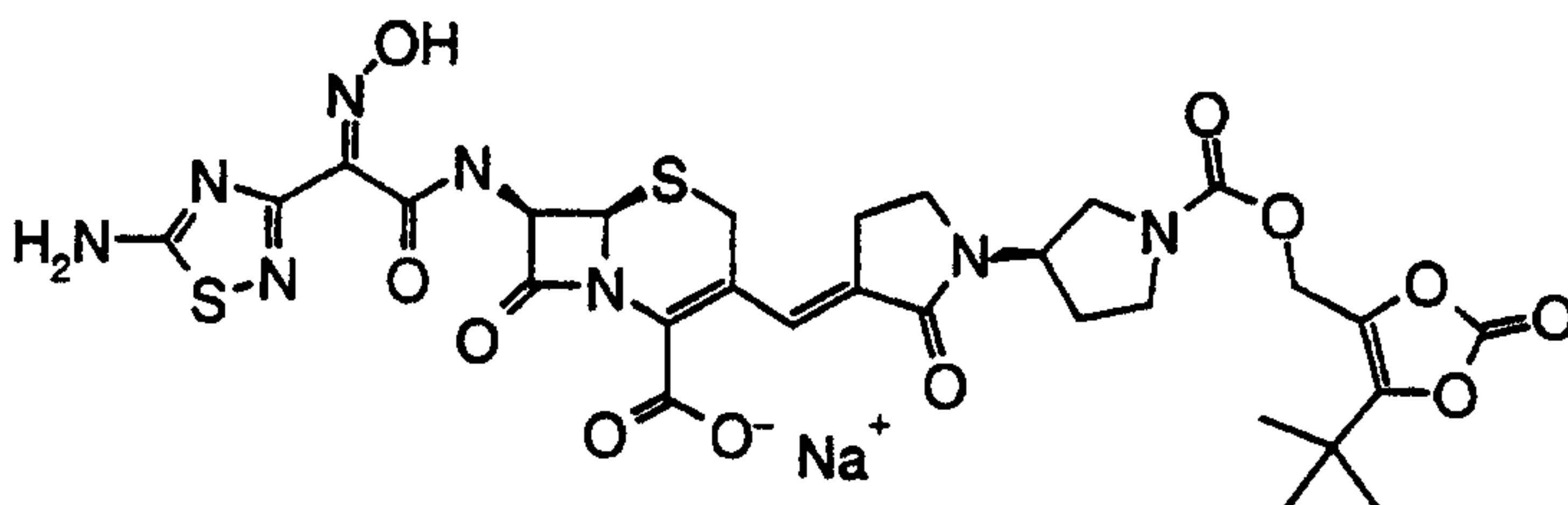
MS (ISP): $M+H^+=719.3, M+NH_4^+=736.2, M+Na^+=741.2$

- 1.4. (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(R)-1'-(5-isopropyl-2-oxo-[1,3]dioxol-4-ylmethoxy-carbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-
5 aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)



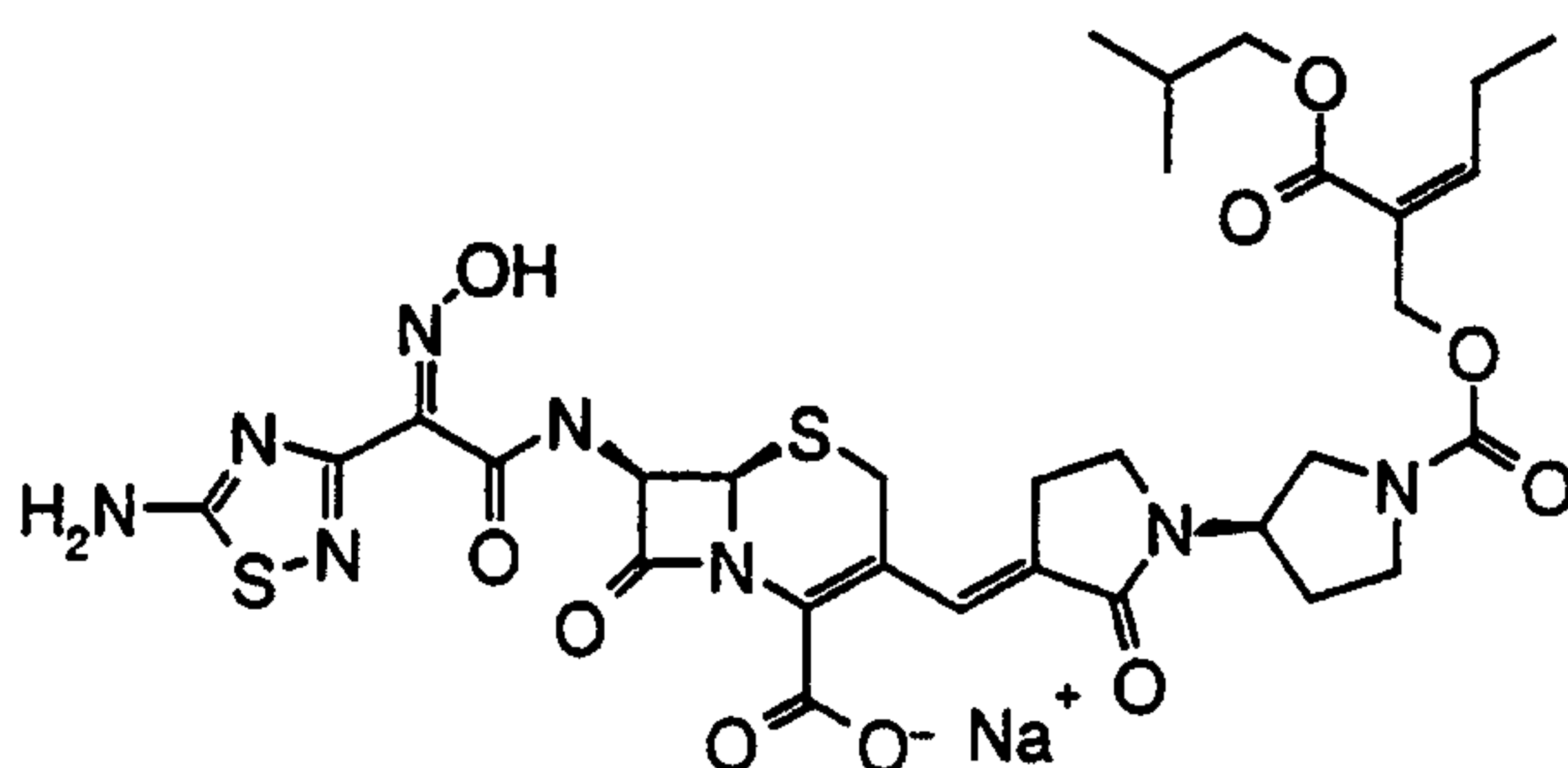
MS (ISP): $M+H^+=719.3, M+NH_4^+=736.2, M+Na^+=741.2$

- 1.5. (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(R)-1'-(5-tert-butyl-2-oxo-[1,3]dioxol-4-ylmethoxy-carbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-
10 aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)



MS (ISP): $M+H^+=733.2, M+NH_4^+=750.4$

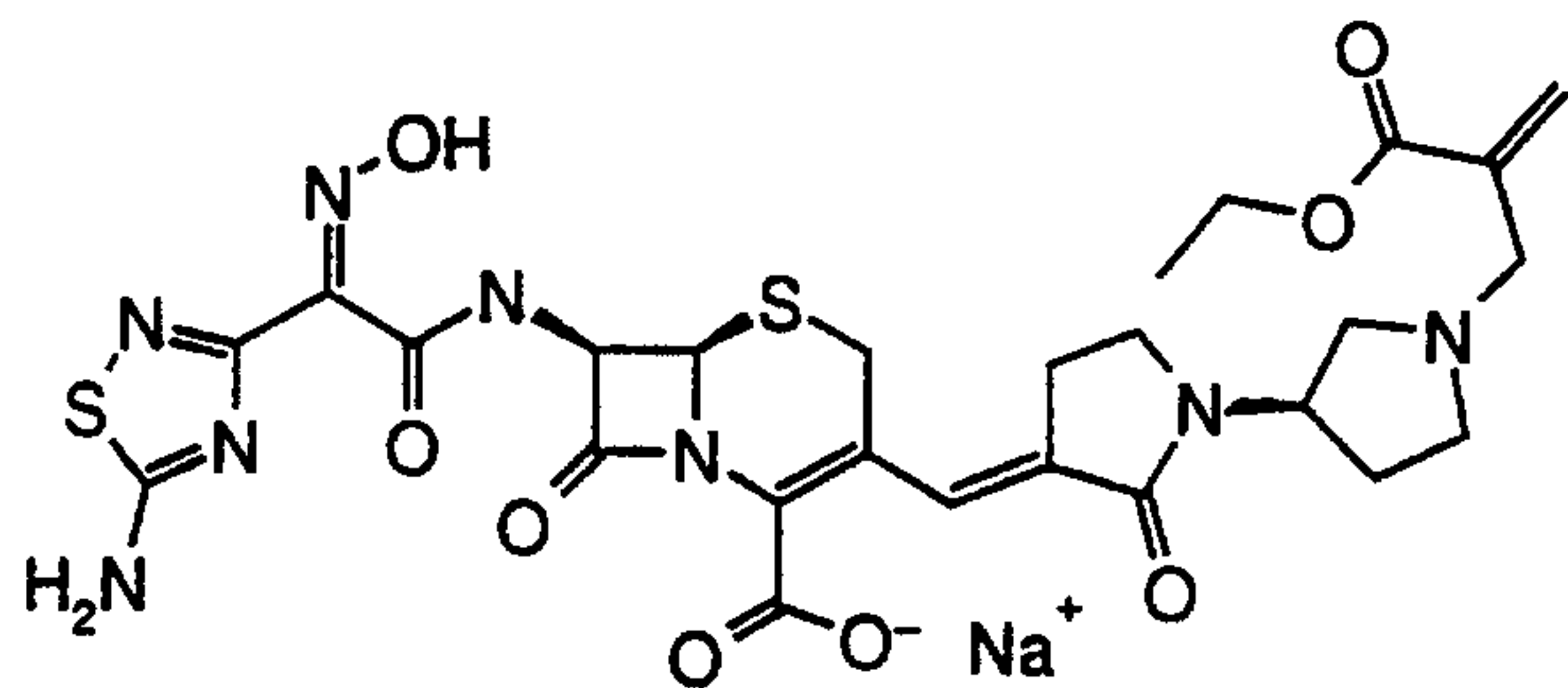
- 1.6. (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(R)-1'-(E-2-isobutoxycarbonyl-pent-2-
15 enyloxycarbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)



MS (ISP): $M+H^+=747.4, M+NH_4^+=764.3, M+Na^+=769.3$

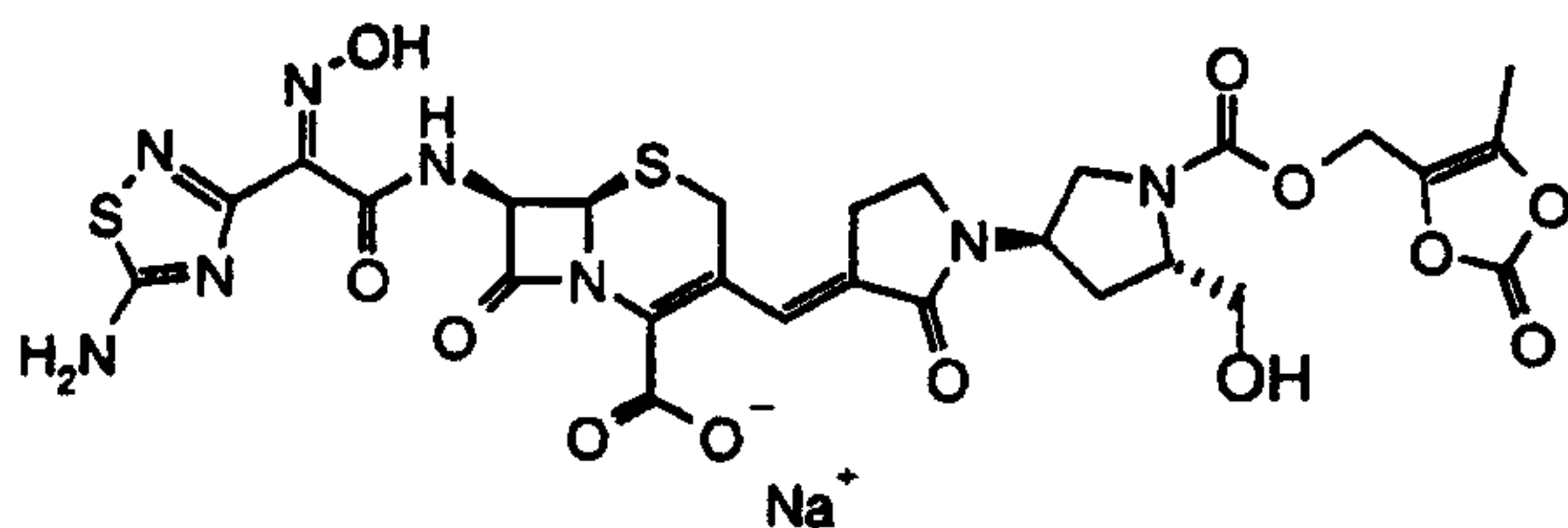
- 20 1.7. (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(R)-1'-(2-ethoxycarbonyl-allyl)-2-oxo-

[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)



MS (ISP): $M+H^+=647.4$

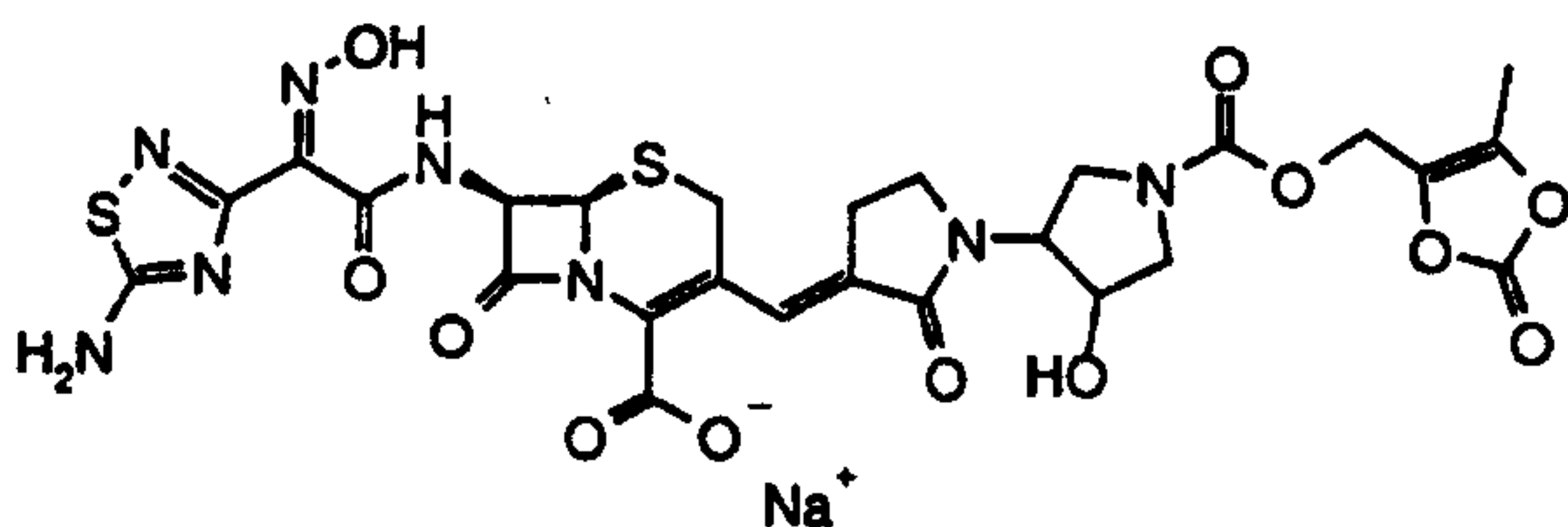
- 5 **1.8. (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(3'R,5'S)-5'-hydroxymethyl-1'-(5-methyl-2-oxo-[1,3]dioxol-4-ylmethoxycarbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt**



10

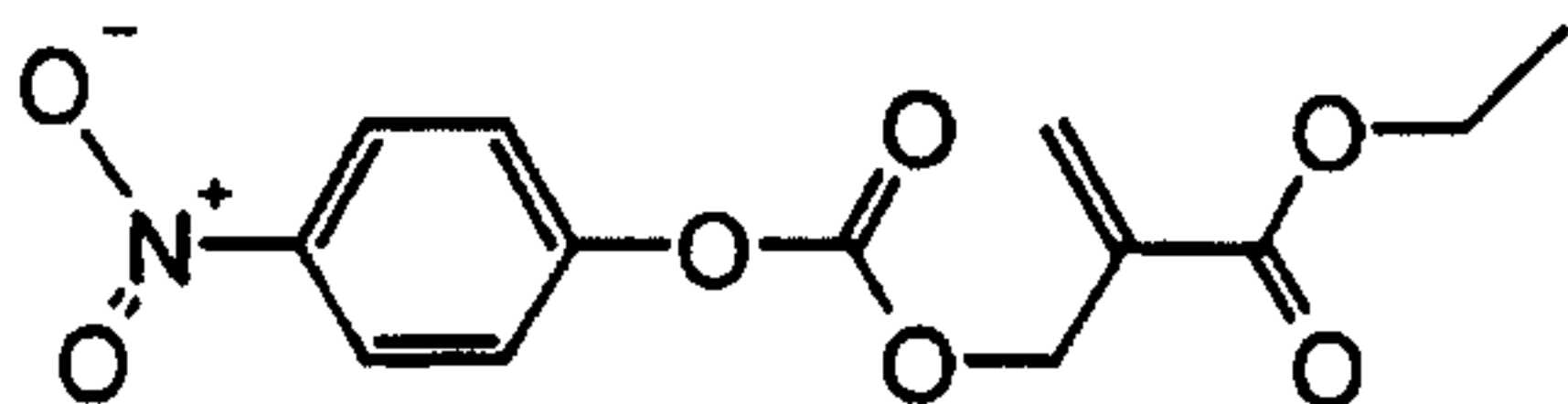
MS(ISP): $M+H^+=721.3$; $M+NH_4^+=738.2$; $M+Na^+=743.2$

- 15 **1.9 1:1 Mixture of (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-3-[(E)-(3'S,4'S)- and -(3'R,4'R)-4'-hydroxy-1'-(5-methyl-2-oxo-[1,3]dioxol-4-ylmethoxycarbonyl)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1)**



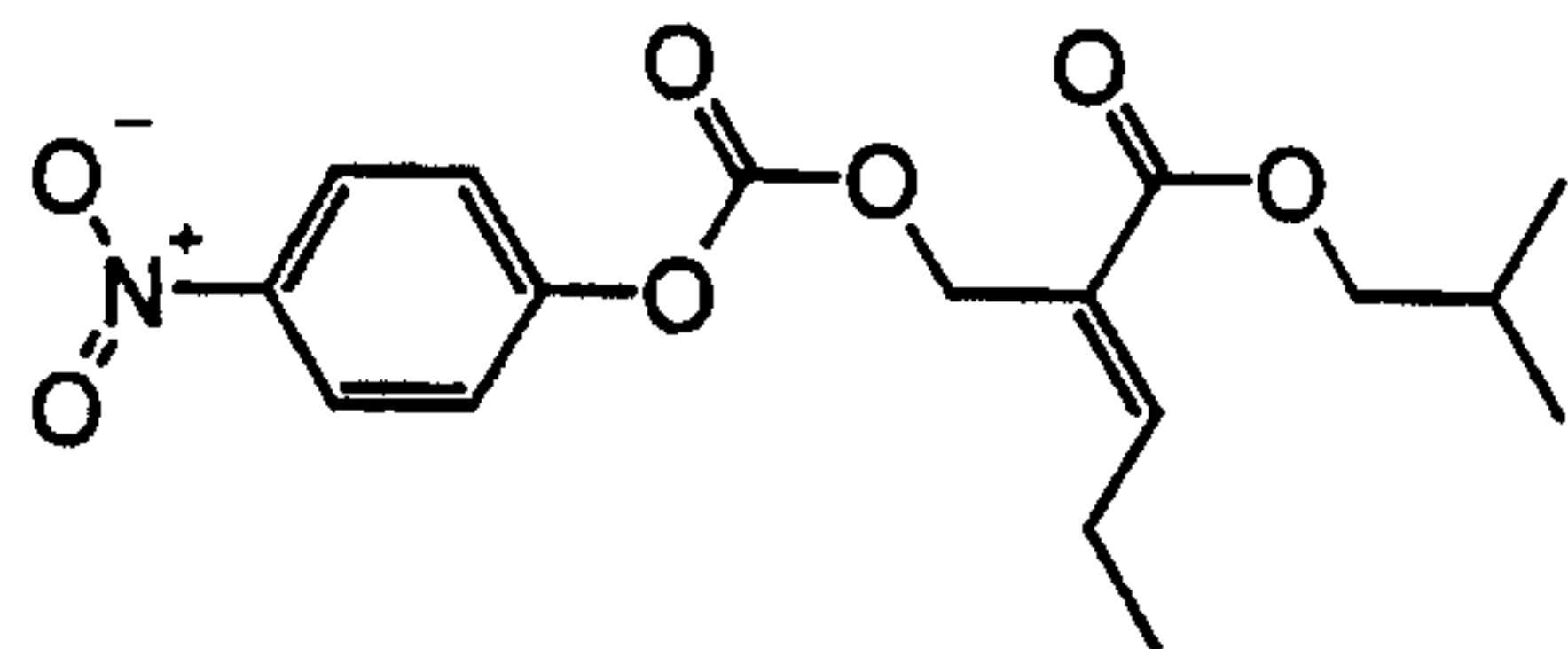
MS(ISN): $M-H^+=705.3$

- 20 **Preparation of the starting materials for examples 1.7. and 1.6.:**
a) 2-(4-Nitro-phenoxy-carbonyloxymethyl)-acrylic acid ethyl ester



A mixture of 2.60 g of 2-hydroxymethyl-acrylic acid ethyl ester (0.020 mol) and 4.0 g of 4-nitrophenyl-chloroformate (0.020 mol) in 70 ml dichloromethane is treated with a solution of 5.5 ml (0.030 mol) of ethyl-diisopropylamine in 55 ml of dichloromethane at 0°C for two hours. The mixture is hydrolyzed with 10% potassium bicarbonate, the phases are separated and the product contained in the organic phase is purified by chromatography on silica gel using a 4:1 mixture of n-hexane and ethyl acetate as eluent. The product fractions are collected and evaporated yielding 3.5g (60%) of the title compound as a white crystalline solid with melting point 42-43°C after crystallisation from t-butylmethyl ether and n-hexane.

b) 2-(4-Nitro-phenoxy-carbonyloxymethyl)-pent-2-enoic acid isobutyl ester

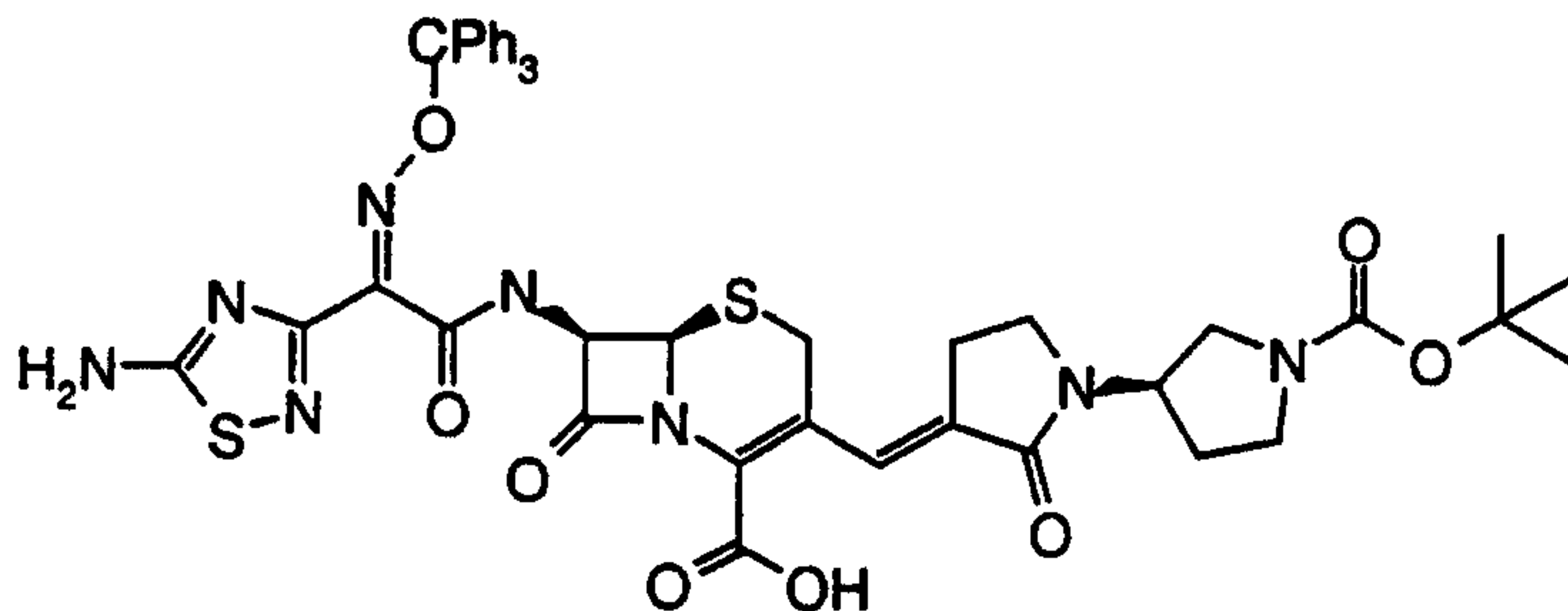


is prepared according to the procedure described above. A yellowish oil is obtained.

MS (EI): $M+H^+=352$ $M-C_4H_7O = 278$

Example 2

2.1. a) Synthesis of (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-trityloxyimino-acetylamino]-3-[(E)-(R)-1'-tert-butoxycarbonyl-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid



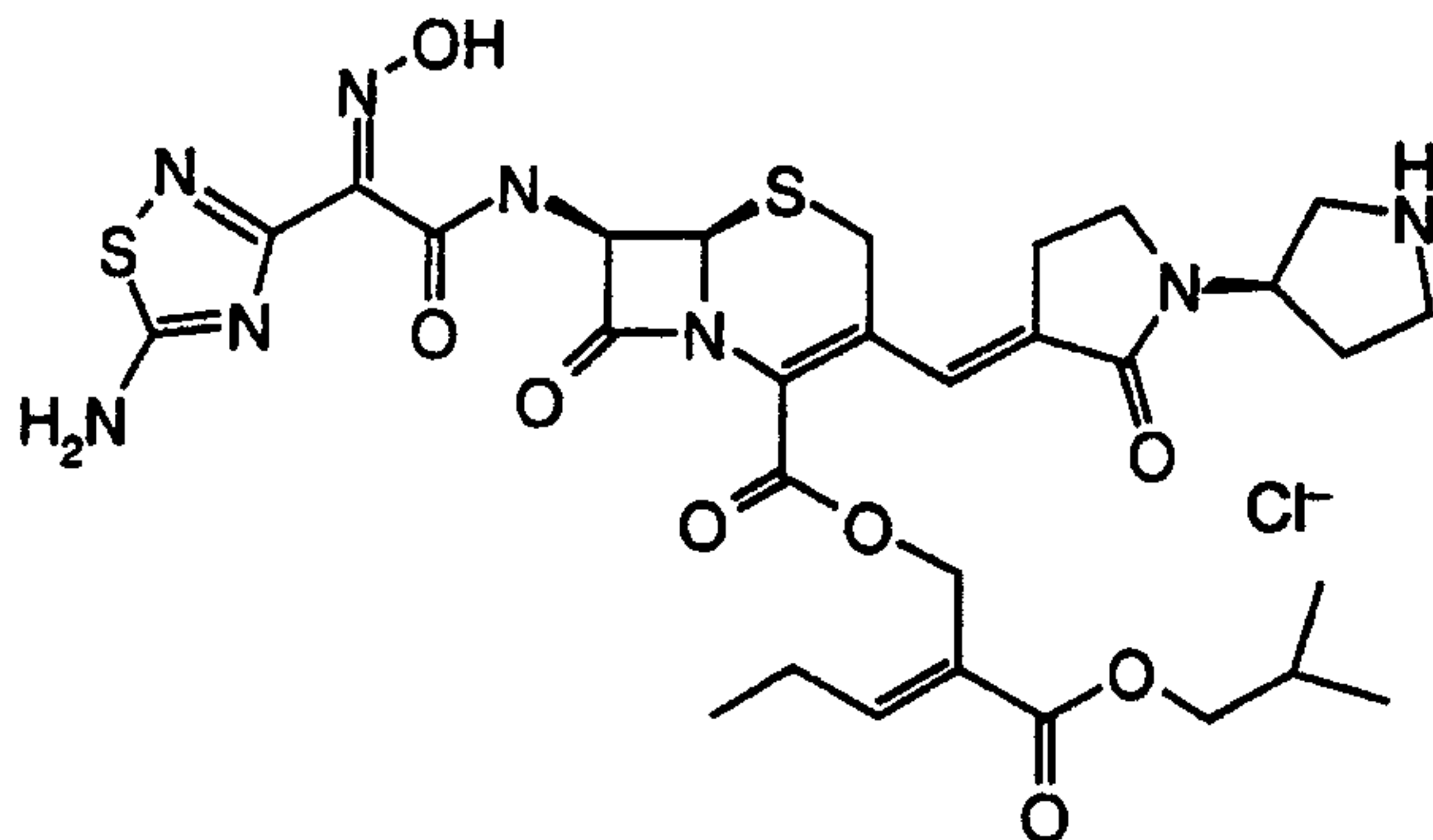
To a solution of 1.67g (1.965 mmol) of (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-trityloxyimino-acetylamino]-8-oxo-3-[(E)-(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid hydrochloride salt (1:2) in 20.0 ml of dimethylformamide are added 0.56 ml (4.00 mmol) of triethylamine and 0.554 g di-tert-butyl dicarbonate and the

mixture is stirred at room temperature for 1.5 hours. The mixture is diluted with 500 ml of ethyl acetate and 100 ml water. The pH is adjusted to 2 by the addition of 1N hydrochloric acid. The phases are separated and the organic phase is washed twice with 100 ml of water, clarified by filtration over a fluted
 5 filter and concentrated. 100 ml of diethyl ether are added and the resulting suspension is stirred at room temperature for 1 hour. The solid is collected by filtration, washed with diethyl ether and dried, yielding 1.31g (76%) of the title compound as a beige powder.

MS (ISP): (M+H)⁺=877.4 (M+NH₄)⁺=894.4 (M+Na)⁺=899.4

10

b) Synthesis of (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-8-oxo-3-[(E)-(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid (E)-2-isobutoxycarbonyl-pent-2-enyl ester hydrochloride (1:1.6)



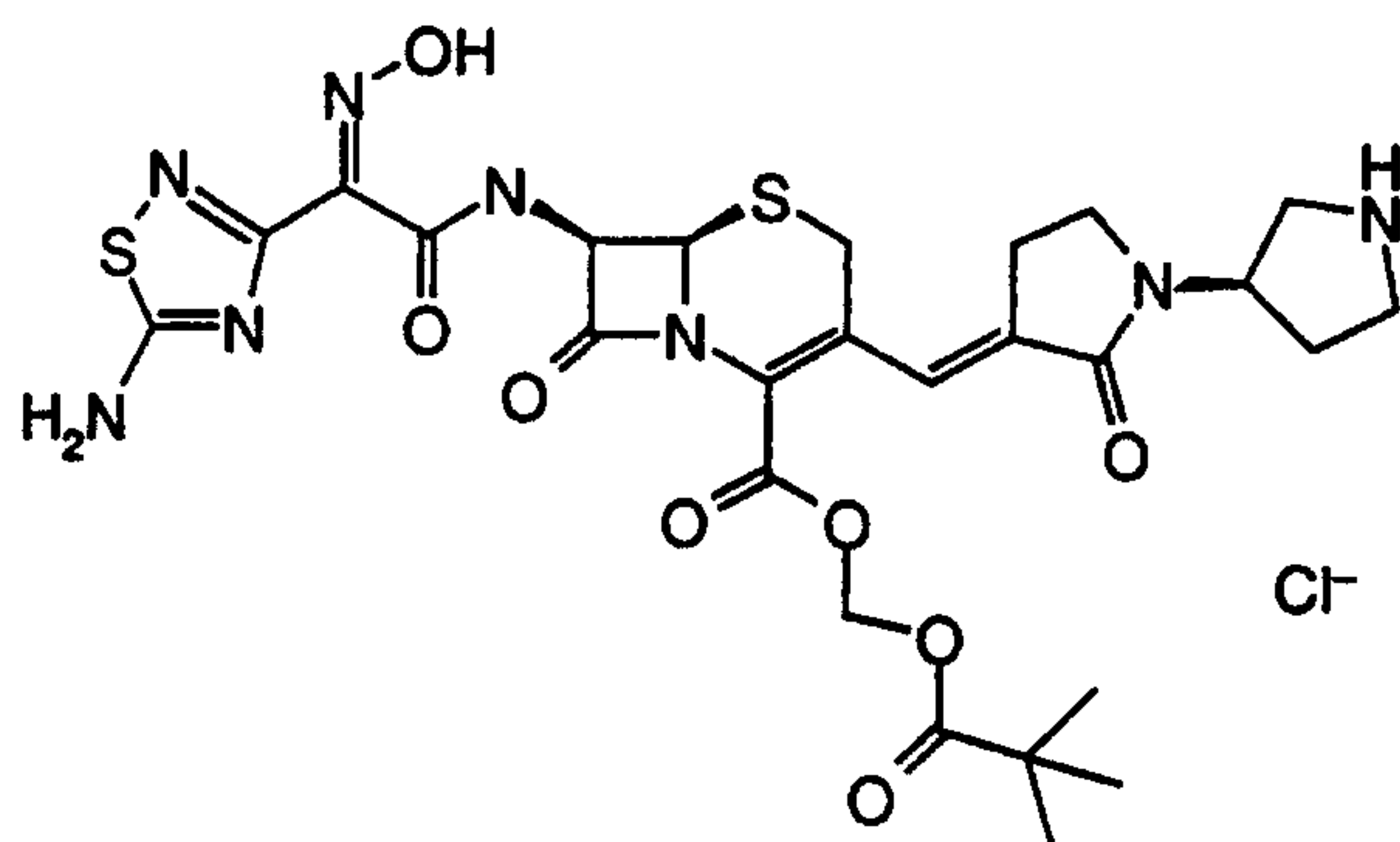
15

To a solution of 0.150 g (0.171 mmol) of (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-trityloxyimino-acetylamino]-3-[(E)-(R)-1'-tert-butoxycarbonyl-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid in 1 ml of dimethylsulfoxide are added 18.7 mg of (0.163
 20 mmol) 1,1-3,3-tetramethyl guanidine and 64 mg (0.257 mmol) of isobutyl (Z)-2-(bromomethyl)-2-pentenoate, and the mixture is stirred at room temperature for 20 minutes. The solvent is evaporated under high vacuum and the residue purified by chromatography on MCI-gel using a gradient of 40 to 100% of acetonitrile in water as eluent. The product fractions are collected and the
 25 organic solvent is removed by evaporation. The product is extracted from the remaining aqueous phase with dichloromethane. The combined organic phases are dried over magnesium sulfate, evaporated to dryness and triturated with tert-butylmethyl ether to yield 130 mg (0.125 mmol) beige crystals with melting point 158-159°C which are dissolved in 1.2 ml of dichloromethane. To
 30 this solution are added 0.0366 ml (0.23 mmol) of triethylsilane and 0.38 ml of trifluoroacetic acid at 0°C and the mixture is stirred for 1 hour. To the

resulting clear solution 2.0 ml of dioxane are added and the mixture is concentrated under vacuum. The residue is dissolved in 2.0 ml of dioxane and 0.182 ml of a 1.9 N solution of hydrochloric acid in dioxane are added with stirring at room temperature. The precipitate is collected by filtration washed
5 with dioxane and acetone and dried yielding 85 mg of the title compound as beige crystals melting at 139-140°C (dec). HPLC: 99.%(area) MS: M+H⁺=703.3

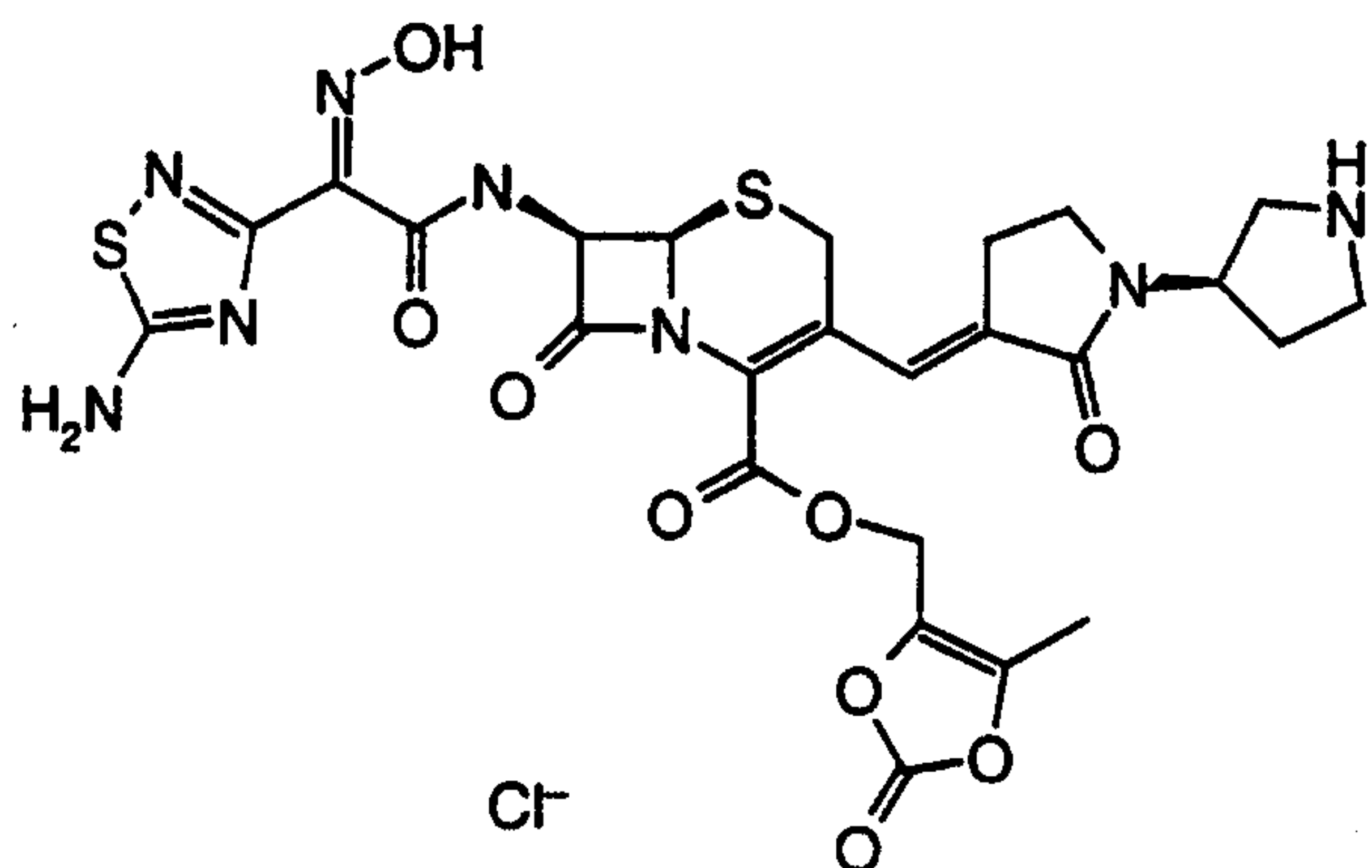
In a similar manner the following prodrug-ester compounds are prepared starting from the corresponding alkyl halides:

2.2. (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-
10 acetylamino]-8-oxo-3-[(E)-(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidene-
methyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 2,2-
dimethyl-propionyloxymethyl ester hydrochloride



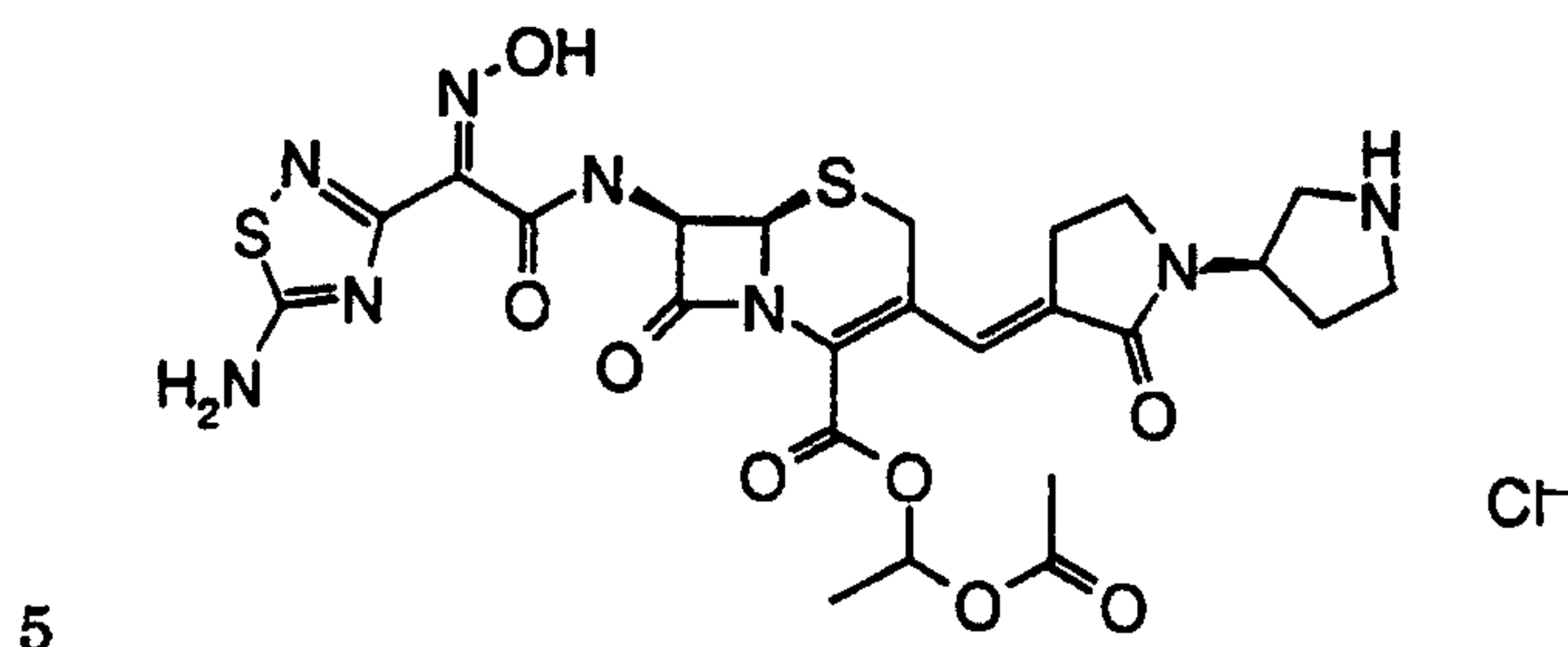
MS (ISP): M+H⁺=649.3

2.3. (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-
15 acetylamino]-8-oxo-3-[(E)-(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidene-
methyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 5-methyl-
2-oxo-[1,3]dioxol-4-ylmethyl ester hydrochloride (1:1.5)



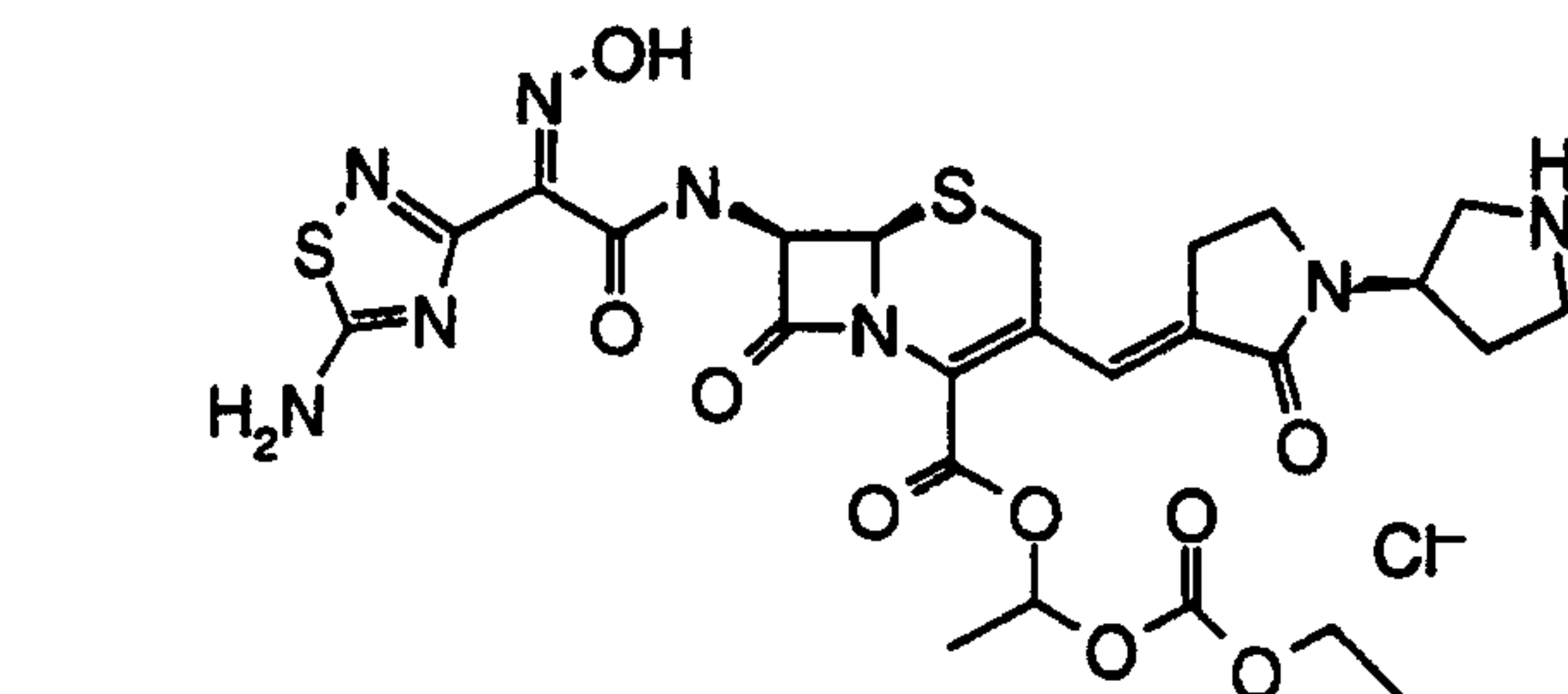
20 MS (ISP): M+H⁺=647.3

2.4. 1:1 Mixture of (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-8-oxo-3-[(E)-(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid (R)- and (S)-1-acetoxy-ethyl ester hydrochloride (1:1.2)



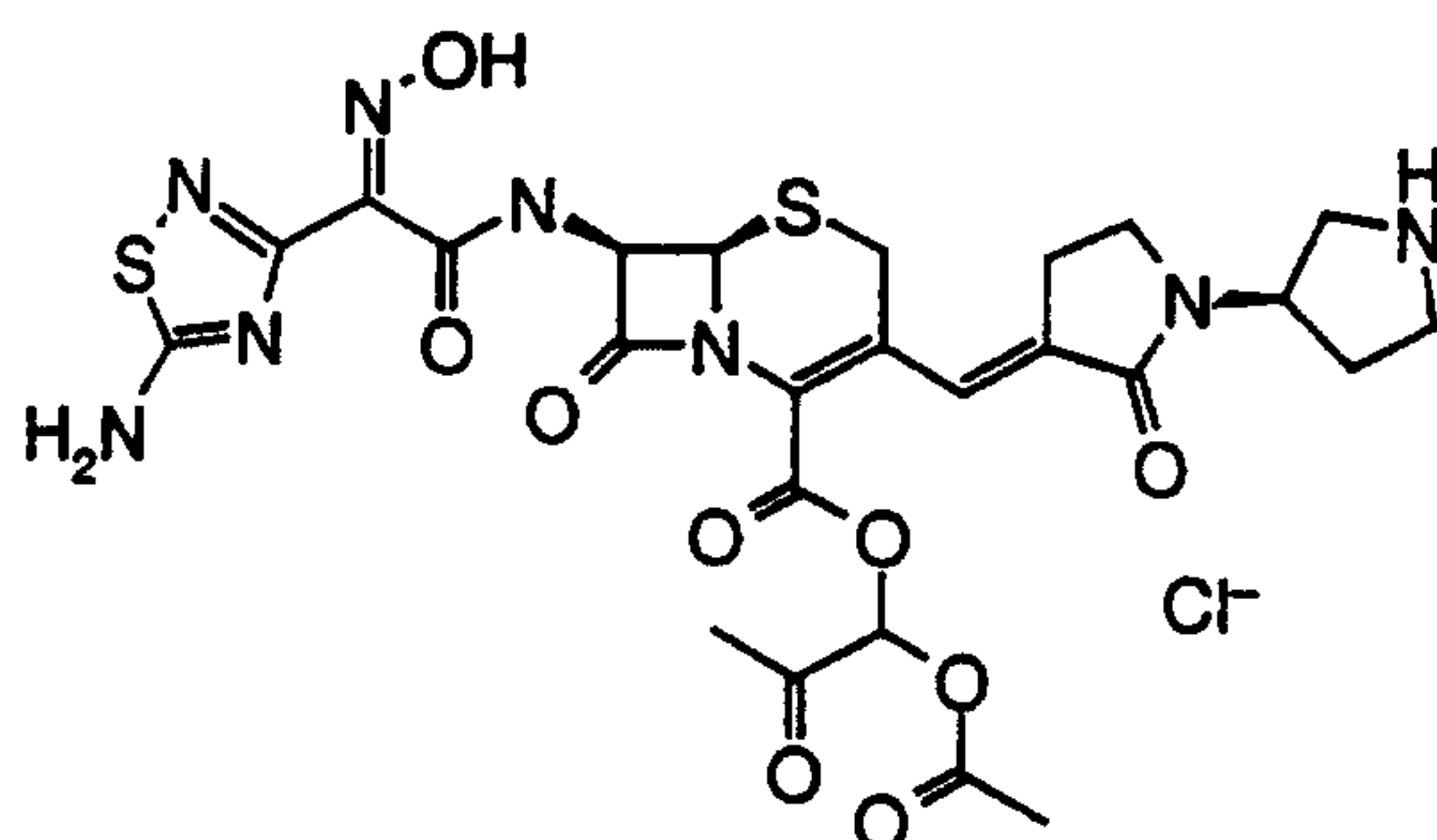
MS (ISP): $M+H^+=621.3$

2.5. 1:1 Mixture of (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-8-oxo-3-[(E)-(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid (R)- and (S)-1-ethoxycarbonyloxy-ethyl ester hydrochloride (1:1.4)



MS (ISP): $M+H^+=651.2$

2.6. 1:1 Mixture of (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-8-oxo-3-[(E)-(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid (R)- and (S)-1-acetoxy-2-oxo-propyl ester hydrochloride (1:1.4)

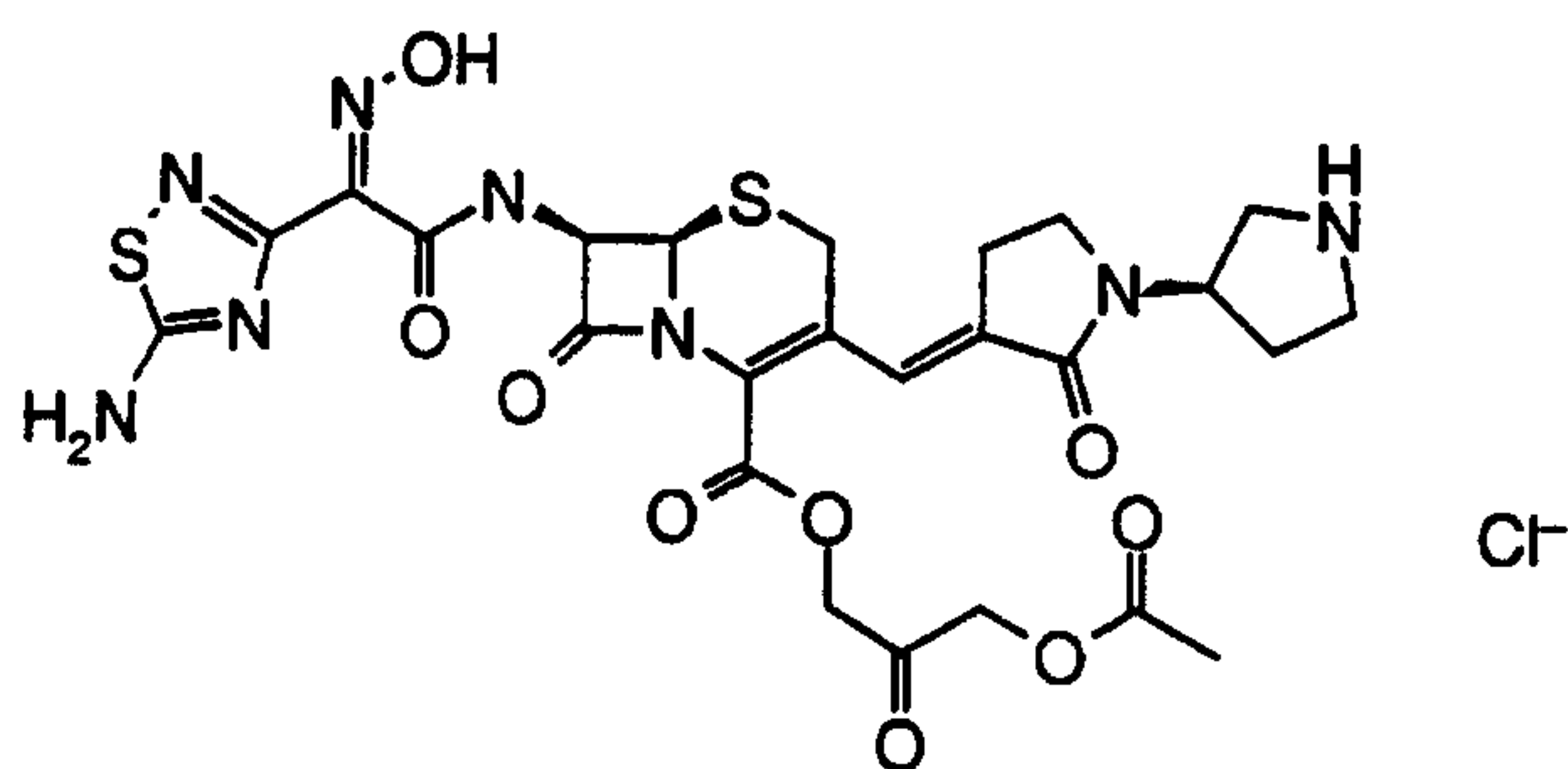


MS (ISP): $M+H^+=649$

2.7. (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-8-oxo-3-[(E)-(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidene-

20

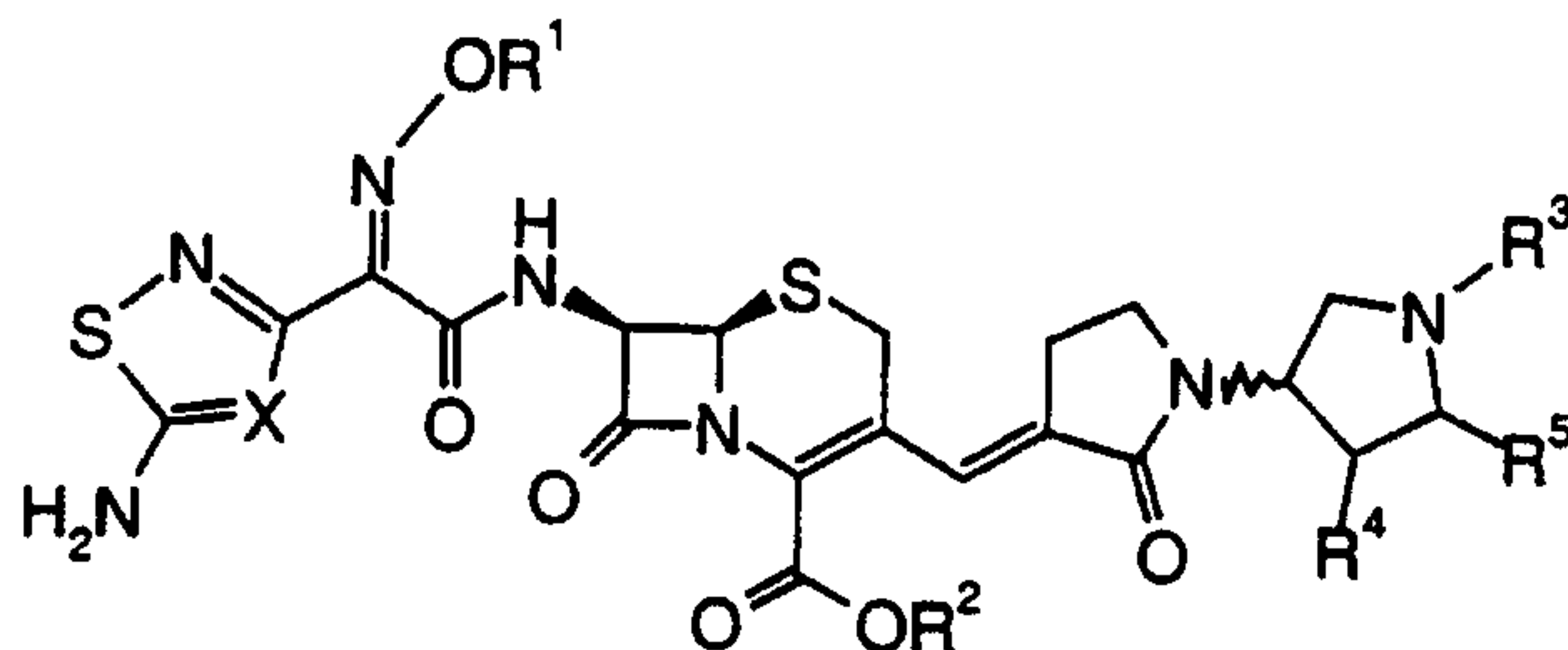
methyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 3-acetoxy-2-oxo-propyl ester hydrochloride (1:1.65)



MS (ISP): $M+H^+=649.2$

Claims

1. Compounds of formula I



I

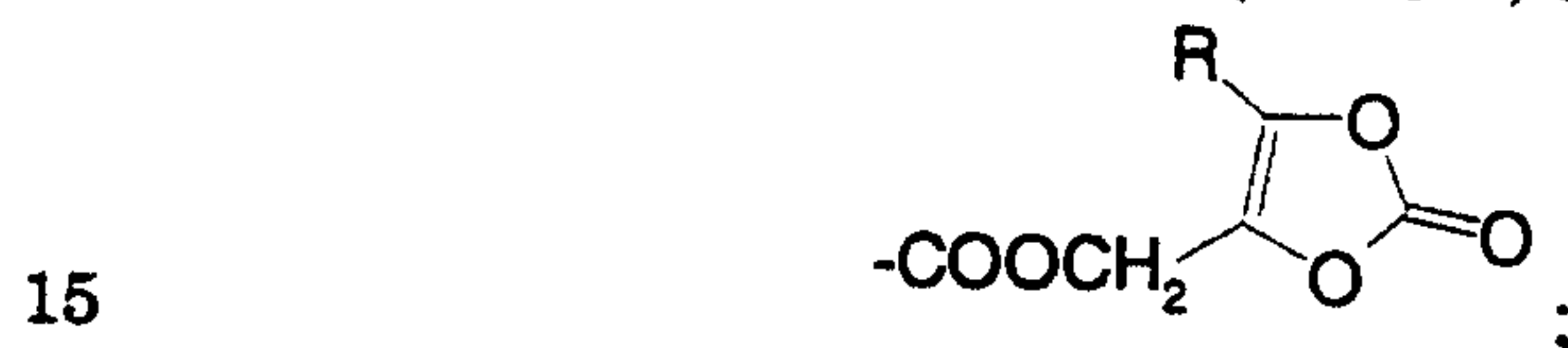
wherein

5 R^1 is hydrogen, C_{1-6} -alkyl, optionally substituted by fluoro, or C_{3-6} -cycloalkyl;

R^2 is hydrogen or a group selected from
 $-CH_2C(=CHR)-COOR$, $-CH_2OCOR$, $-CH(R)OCOR$,
 $-CH(R)OCOOR$, $-CH(OCOR)OCOR$, $-CH_2COCH_2OCOR$ and



R^3 is hydrogen or group selected from $-CH_2C(=CH_2)-COOR$,
 $-COOCH_2C(=CHR)-COOR$, $-COOCH_2OCOR$,
 $-COOCH(R)OCOR$, $-COOCH(R)OCOOR$,
 $-COOCH(OCOR)OCOR$, $-COOCH_2COCH_2OCOR$, and



with the proviso that one of R^2 and R^3 is hydrogen and the other of R^2 and R^3 is different from hydrogen,

R is hydrogen or C_{1-6} -alkyl;

R^4 is hydrogen or hydroxy,

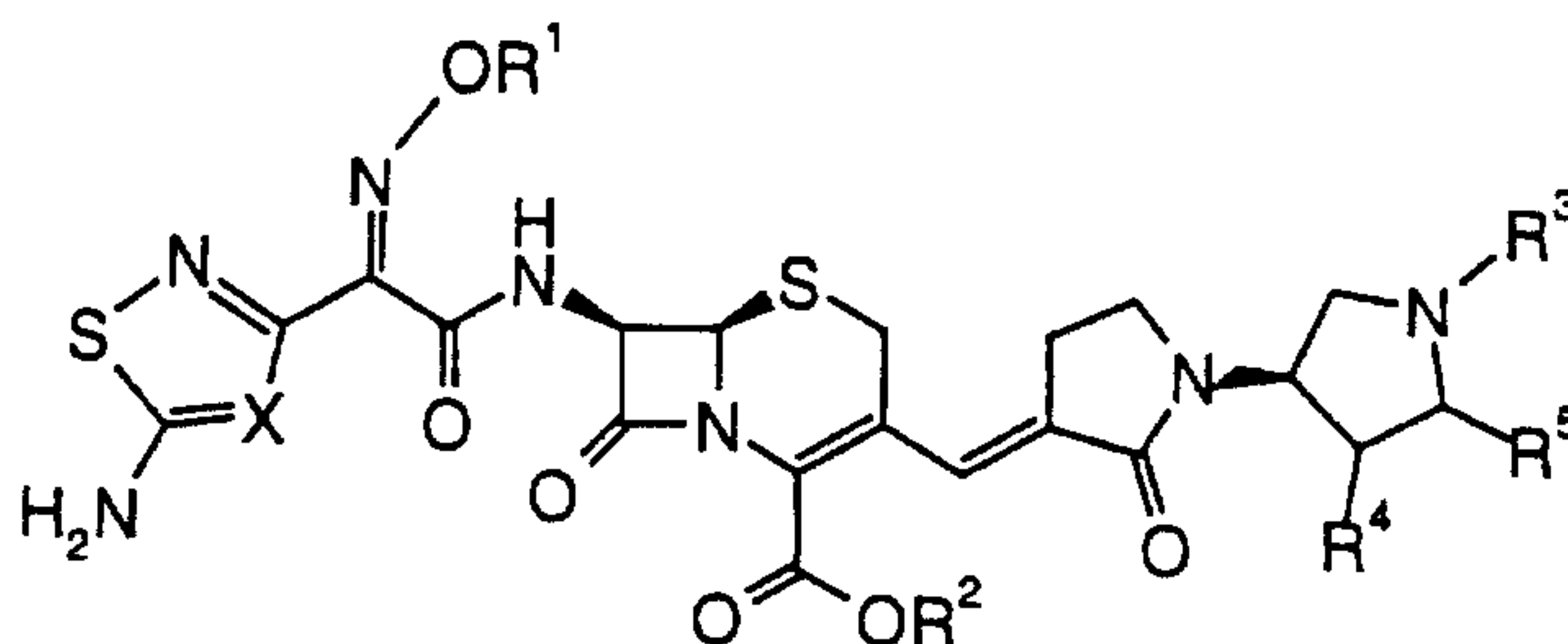
20 R^5 is hydrogen or ω -hydroxyalkyl; and

X is CH or N,

as well as pharmaceutically acceptable salts of said compounds and hydrates of the compounds of formula I and of their salts.

- 19 -

2.. Compounds according to claim 1 of formula I-a



I-a

wherein R^1 , R^2 , R^3 and X are as defined in claim 1 and R^4 and R^5 are hydrogen,

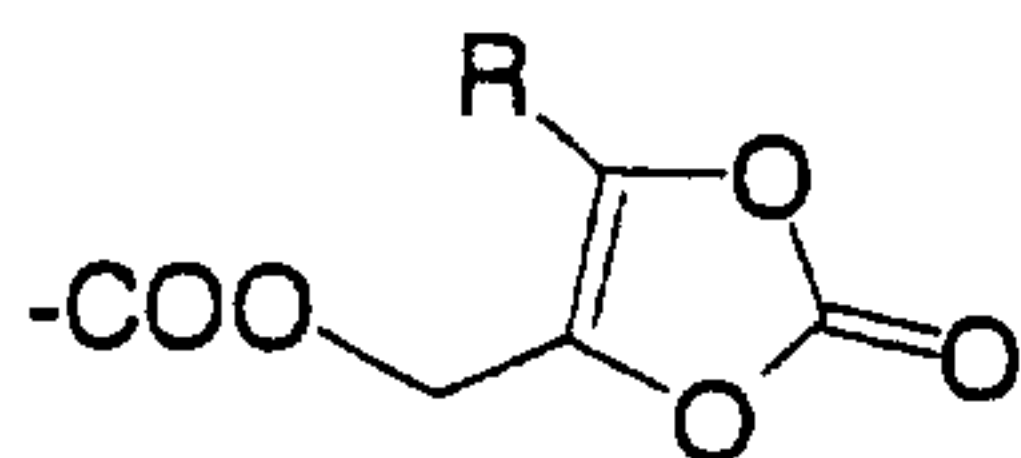
5 as well as pharmaceutically acceptable salts of said compounds and hydrates of the compounds of formula I-a and of their salts.

3. Compounds according to claim 1 or 2, wherein R^1 is hydrogen, X is N, R^2 is hydrogen and R^3 is a group

-COO-CH₂C(=CHCH₂CH₃)-COOCH₂CH(CH₃)₂,

10 -CH₂C(=CH₂)-COOCH₂CH₃,

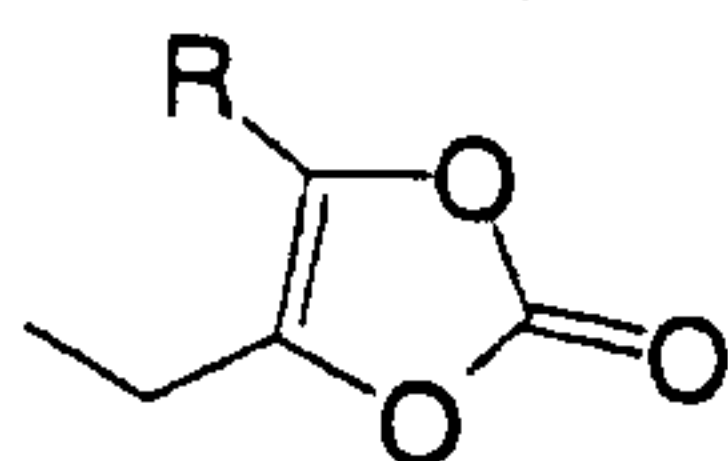
or



4.. Compounds according to claim 1 or 2 wherein R^1 and R^3 are hydrogen, X is N and R^2 is -CH₂C(=CHCH₂CH₃)-COOCH₂CH(CH₃)₂,

15 -CH₂C(=CH₂)-COOCH₂CH₃, -CH₂OCOC(CH₃)₃, -CH(CH₃)OCOCH₃,

-CH(CH₃)OCOOCH₂CH₃, -CH(OCOCH₃)OCOCH₃, -CH₂COCH₂OCOCH₃, or



5.. The compound according to claims 1 and 2

(6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-
 20 3-[(E)-(R)-1'-(5-methyl-2-oxo-[1,3]dioxol-4-ylmethoxycarbonyl)-2-oxo-[1,3']-
 bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-
 carboxylic acid

6. The compound according to claims 1 and 2

(6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetylamino]-
 25 3-[(E)-(R)-1'-(5-ethyl-2-oxo-[1,3]dioxol-4-ylmethoxycarbonyl)-2-oxo-[1,3']-
 bipyrrolidinyl-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-
 carboxylic acid sodium salt (1:1)

7. Compounds as in any one of claims 1 to 6 for use as pharmaceutically active substances, particularly for the treatment and prophylaxis of infectious diseases.

8. A pharmaceutical preparation containing a compound according to any
5 one of claims 1 to 6 and a therapeutically inert carrier, particularly for the treatment and prophylaxis of infectious diseases.

9. The use of the compounds according to any one of claims 1 to 6 in the treatment and prophylaxis of infectious diseases or for the manufacture of medicaments for the treatment and prophylaxis of infectious diseases.

10
