PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 501/46, A61K 31/545 — A1

(11) International Publication Number: WO 92/18508

(43) International Publication Date: 29 October 1992 (29.10.92)

(21) International Application Number: PCT/JP92/00472

(22) International Filing Date: 14 April 1992 (14.04.92)

(30) Priority data:
9107973.1 15 April 1991 (15.04.91) GB

(71) Applicant *(for all designated States except US):* FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* SAKANE, Kazuo [JP/JP]; 15, Azayamagata, Mino, Kawanishi-shi, Hyogo 666-01 (JP). YAMANAKA, Hideaki [JP/JP]; 77-10, Kuzuhanakanoshiba 2-chome, Hirakata-shi, Osaka 573 (JP). SAKURAI, Minoru [JP/JP]; 2-2-10, Midorigaoka, Ikeda-shi, Osaka 563 (JP).

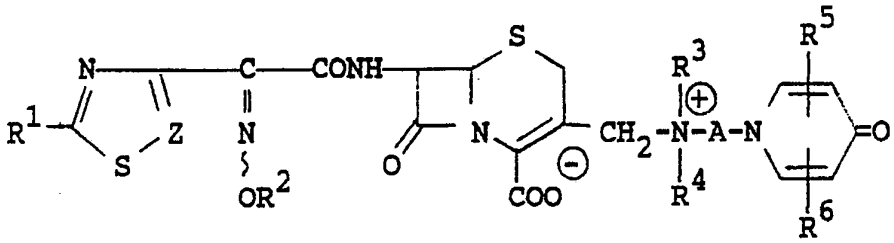
(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: NEW CEPHEM COMPOUNDS

(I)



(57) Abstract

New cephem compounds of formula (I) wherein R^1 is amino or protected amino, Z is N or CH, R^2 is hydrogen or an organic group, R^3 is lower alkyl, R^4 is lower alkyl, A is lower alkylene, R^5 is hydroxy or protected hydroxy, and R^6 is carboxy, protected carboxy, etc., and pharmaceutically acceptable salts thereof which are useful as a medicament.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CS	Czechoslovakia
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GN	Guinea
GR	Greece
HU	Hungary
IT	Italy
JP	Japan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
MC	Monaco
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NL	Netherlands
NO	Norway
PL	Poland
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SN	Senegal
SU	Soviet Union
TD	Chad
TG	Togo
US	United States of America

DESCRIPTION

NEW CEPHEM COMPOUNDS

TECHNICAL FIELD

This invention relates to new cephem compounds and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

Some cephem compounds have been known as described, for example, in U.S. Patent 4,457,929 and European Patent Application Publication No. 0345671 A2.

DISCLOSURE OF INVENTION

The present invention relates to new cephem compounds and pharmaceutically acceptable salts thereof. More particularly, it relates to new cephem compounds and pharmaceutically acceptable salts thereof, which have antimicrobial activities, to processes for preparation thereof, to pharmaceutical composition comprising the same, and to a method for treating infectious diseases in human being and animals.

Accordingly, one object of the present invention is to provide the cephem compounds and pharmaceutically acceptable salts thereof, which are highly active against a number of pathogenic microorganisms.

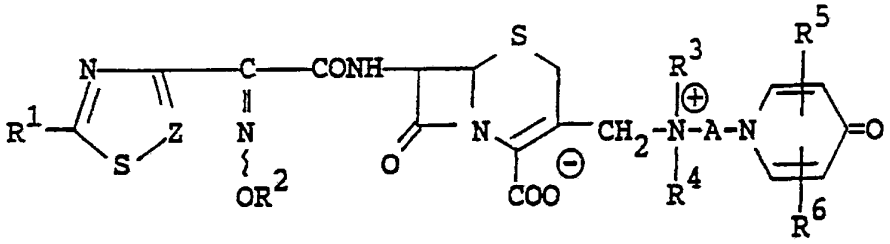
Another object of the present invention is to provide processes for the preparation of the cephem compounds and salts thereof.

A further object of the present invention is to provide pharmaceutical composition comprising, as an active ingredient, said cephem compounds or their

pharmaceutically acceptable salts.

Still further object of the present invention is to provide a method for treating infectious diseases caused by pathogenic microorganisms, which comprises administering said cephem compounds to infected human being or animals.

The object cephem compounds of the present invention are novel and can be represented by the following general formula (I) :

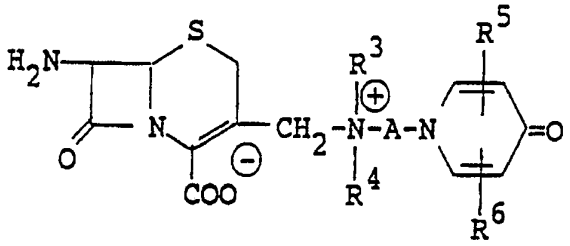


(I)

wherein R^1 is amino or protected amino,
Z is N or CH,
R^2 is hydrogen or an organic group,
R^3 is lower alkyl,
R^4 is lower alkyl,
A is lower alkylene,
R^5 is hydroxy or protected hydroxy, and
R^6 is carboxy, protected carboxy, carbamoyl, or mono or di substituted carbamoyl.

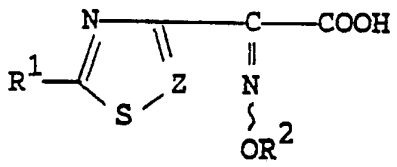
The object compound (I) of the present invention can be prepared by the following processes.

Process (1)



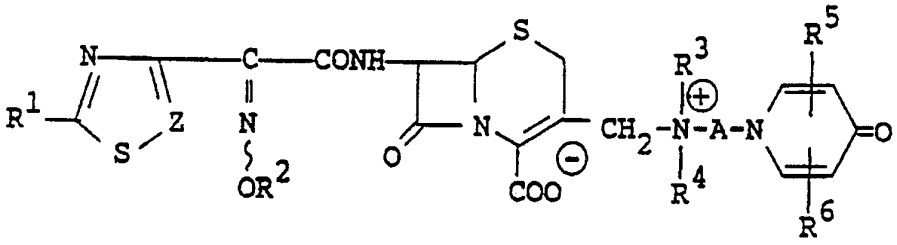
(II)

or its reactive derivative at the amino group or a salt thereof



(III)

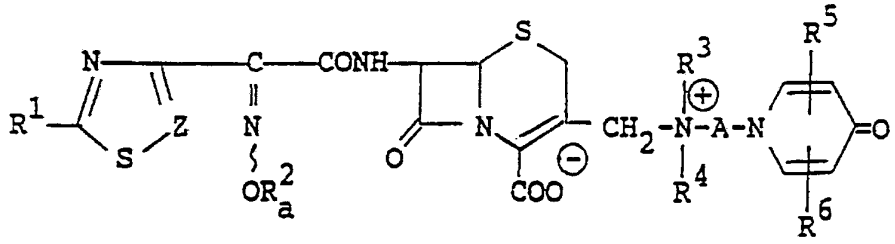
or its reactive derivative at the carboxy group or a salt thereof



(I)

or a salt thereof

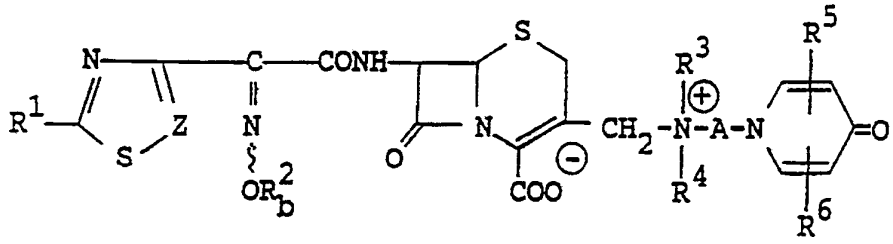
Process (2)



(Ia)

or a salt thereof

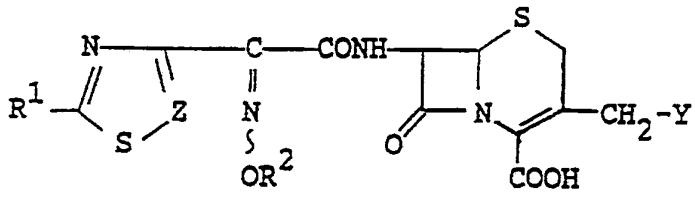
↓ Elimination reaction of the carboxy protective group in R_a^2



(Ib)

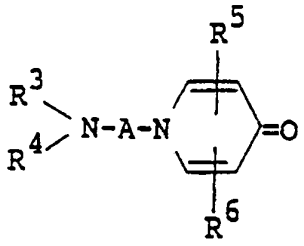
or a salt thereof

Process (3)



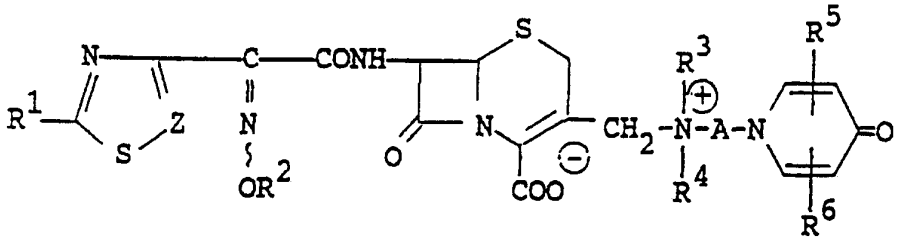
(IV)

or a salt thereof



(V)

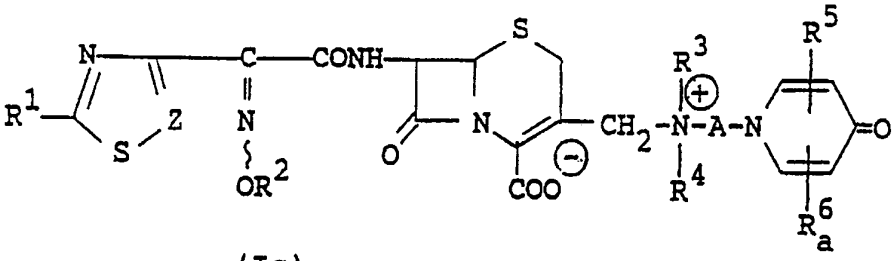
or a salt thereof



(I)

or a salt thereof

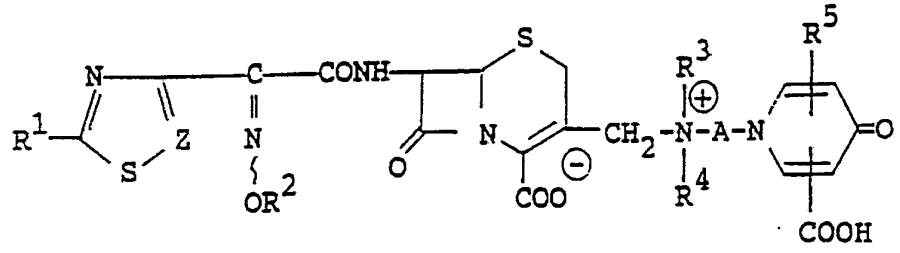
Process (4)



(Ic)

or a salt thereof

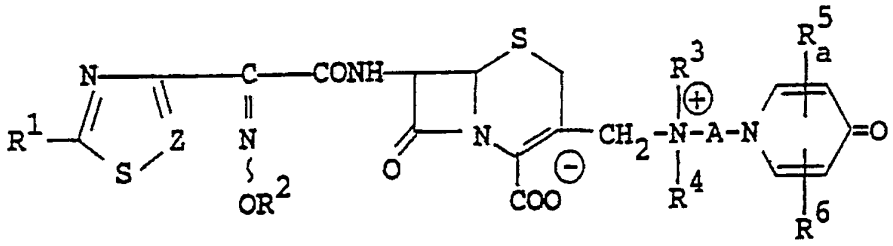
Elimination reaction of the carboxy protective group in R_a^6



(Id)

or a salt thereof

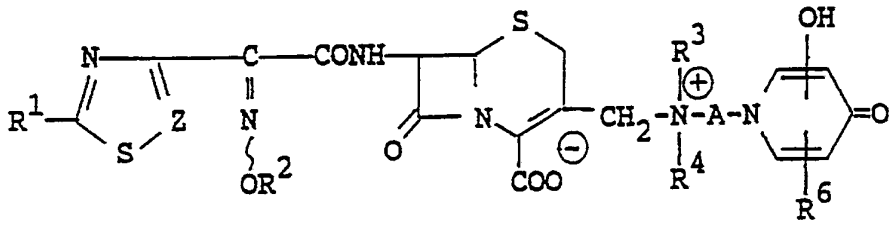
Process (5)



(Ie)

or a salt thereof

Elimination reaction of the hydroxy protective group in R_a^5



(If)

or a salt thereof

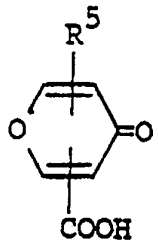
wherein R^1, R^2, R^3, R^4, R^5, R^6, Z and A are each as defined above,

R_a^2 is protected carboxy(lower)alkyl,

$R^2_{b_5}$ is carboxy(lower)alkyl,
R^5_a is protected hydroxy,
R^6_a is protected carboxy and
Y is a leaving group.

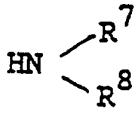
The starting compounds (II) and (V) or salts thereof can be prepared by the following Processes.

Process (A)



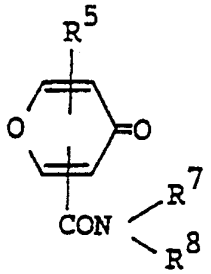
(VI)

or its reactive derivative
at the carboxy group or a salt thereof



(VII)

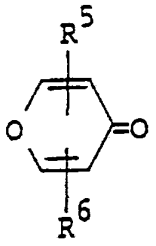
or its reactive derivative
or a salt thereof



(VIIIa)

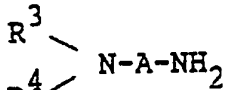
or a salt thereof

Process (B)



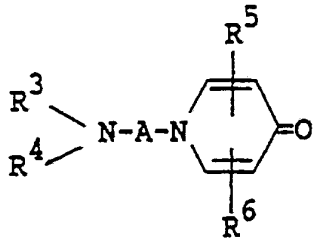
(VIII)

or a salt thereof



(IX)

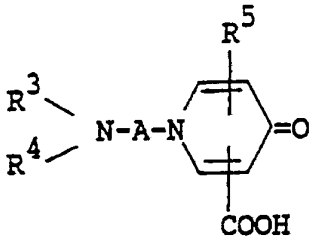
or a salt thereof



(V)

or a salt thereof

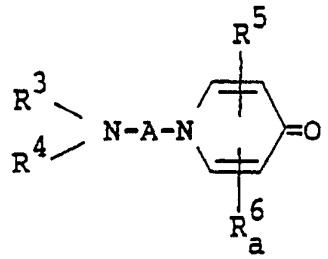
Process (C)



(V_a)

or a salt thereof

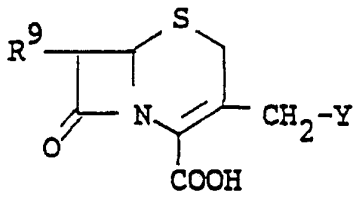
introduction reaction of the carboxy protective group



(Vb)

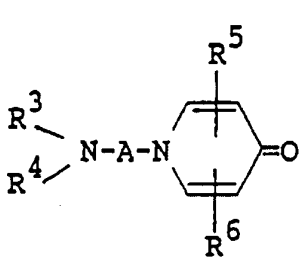
or a salt thereof

Process (D)



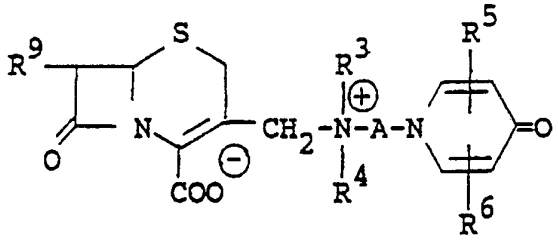
(X)

or a salt thereof



(V)

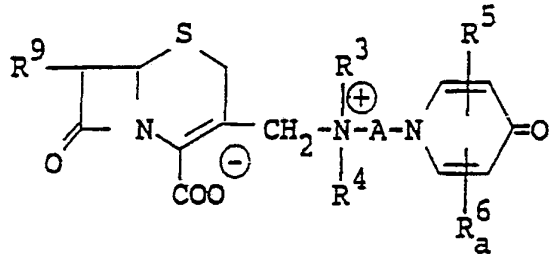
or a salt thereof



(IIa)

or a salt thereof

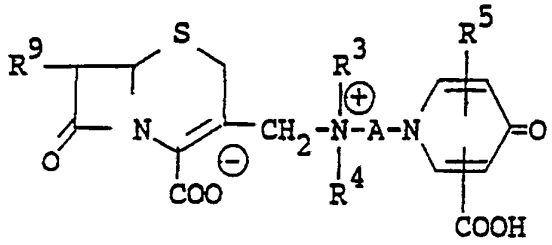
Process (E)



(IIb)

or a salt thereof

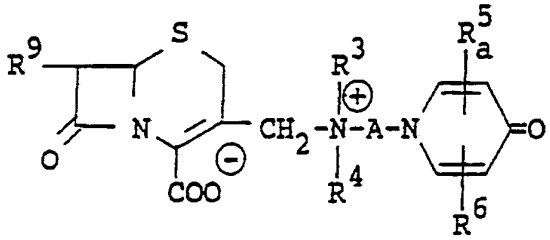
Elimination reaction of the carboxy protective group in R_a^6



(IIc)

or a salt thereof

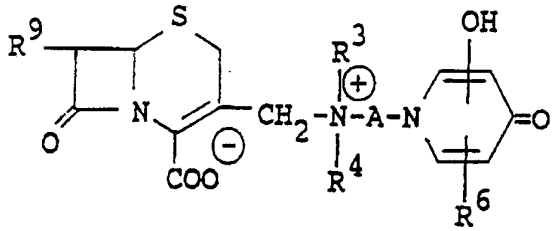
Process (F)



(IId)

or a salt thereof

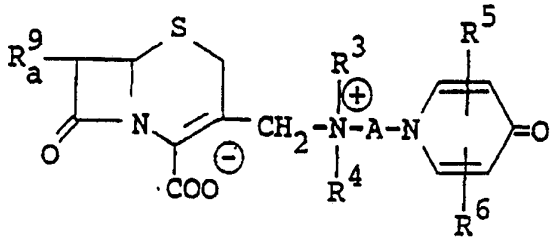
Elimination reaction of the hydroxy protective group in R_a^5



(IIe)

or a salt thereof

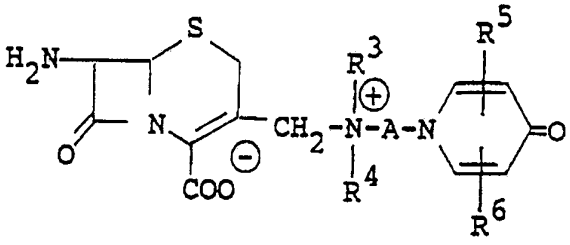
Process (G)



(IIf)

or a salt thereof

Elimination reaction of the amino protective group in R_a^9



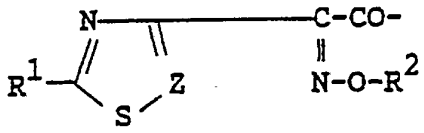
(II)

or a salt thereof

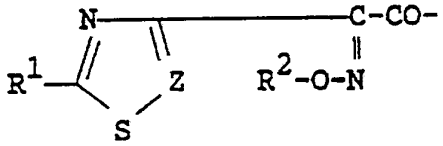
wherein R^3, R^4, R^5, R^5_a, R^6, R^6_a, A and Y are each as defined above,
R^7 is hydrogen or lower alkyl,
R^8 is hydrogen or lower alkyl,
R^9 is amino or protected amino and
R^9_a is protected amino.

Regarding the compounds (I), (Ia)~(If), (III) and (IV), it is to be understood that said compounds include syn isomer, anti isomer and a mixture thereof.

For example, with regard to the object compound (I), syn isomer means one geometrical isomer having the partial structure represented by the following formula :

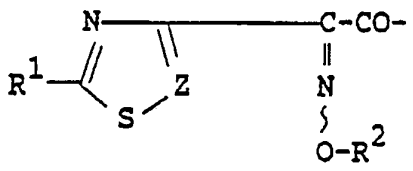


(wherein R^1, R^2 and Z are each as defined above) and anti isomer means the other geometrical isomer having the partial structure represented by the following formula :



(wherein R^1, R^2 and Z are each as defined above), and all of such geometrical isomers and mixture thereof are included within the scope of this invention.

In the present specification and claim, the partial structure of these geometrical isomers and mixture thereof are represented for convenient sake by the following formula :



(wherein R^1, R^2 and Z are each as defined above).

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s) unless otherwise indicated.

Suitable "lower alkyl" may include straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and the like.

Suitable "protected amino" may include an acylamino or an amino group substituted by a conventional protecting group such as ar(lower)alkyl which may have suitable substituent(s) (e.g. benzyl, trityl, etc.) or the like.

Suitable "acyl moiety" in the term "acylamino" may include carbamoyl, aliphatic acyl group and acyl group containing an aromatic or heterocyclic ring. And, suitable examples of the said acyl may be lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl, etc.); lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tertiarybutoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.); lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, etc.); arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.); aroyl (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl, indancarbonyl, etc.); ar(lower)alkanoyl (e.g. phenylacetyl,

phenylpropionyl, etc.); ar(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), and the like. The acyl moiety as stated above may have suitable substituent(s) such as halogen (e.g. chlorine, bromine, iodine or fluorine) or the like.

Suitable "organic group" may include lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, tert-pentyl, hexyl, etc.),

mono(or di or tri)halo(lower)alkyl (e.g. chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, chloroethyl, dichloroethyl, trichloroethyl, fluoroethyl, trifluoroethyl, etc.),

lower alkenyl (e.g., vinyl, 1-propenyl, allyl, 1-methylallyl, 1 or 2 or 3-butenyl, 1 or 2 or 3 or 4-pentenyl, 1 or 2 or 3 or 4 or 5-hexenyl, etc.),

lower alkynyl (e.g., ethynyl, 1-propynyl, propargyl, 1-methylpropargyl, 1 or 2 or 3-butynyl, 1 or 2 or 3 or 4-pentynyl, 1 or 2 or 3 or 4 or 5-hexynyl, etc.),

aryl (e.g., phenyl, naphthyl, etc.),

ar(lower)alkyl such as phenyl(lower)alkyl (e.g., benzyl, phenethyl, phenylpropyl, etc.),

carboxy(lower)alkyl wherein lower alkyl moiety can be referred to the ones as exemplified above, protected carboxy(lower)alkyl wherein lower alkyl moiety can be referred to the ones as exemplified above and protected carboxy moiety can be referred to the ones as exemplified below, and the like.

Suitable "protected carboxy" and "protected carboxy moiety" in the term "protected carboxy(lower)alkyl" may include esterified carboxy and the like. And suitable examples of said ester may be the ones such as lower alkyl ester (e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, t-pentyl ester, hexyl ester, etc.); lower alkenyl ester (e.g., vinyl ester, allyl ester,

etc.); lower alkynyl ester (e.g., ethynyl ester, propynyl ester, etc.); lower alkoxyalkyl ester (e.g., methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.); lower alkylthioalkyl ester (e.g., methylthiomethyl ester, ethylthiomethyl ester, ethylthioethyl ester, isopropylthiomethyl ester, etc.); mono(or di or tri)halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.); lower alkanoyloxy(lower)alkyl ester (e.g., acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 2-acetoxyethyl ester, 2-propionyloxyethyl ester, etc.); lower alkanesulfonyl(lower)alkyl ester (e.g. mesylmethyl ester, 2-mesylethyl ester etc.); ar(lower)alkyl ester, for example, phenyl(lower)alkyl ester which may have one or more suitable substituent(s) (e.g., benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.); aryl ester which may have one or more suitable substituent(s) such as substituted or unsubstituted phenyl ester (e.g., phenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, 4-chlorophenyl ester, 4-methoxyphenyl ester, etc.); tri(lower)alkyl silyl ester; lower alkylthioester (e.g. methylthioester, ethylthioester, etc.) and the like.

Suitable "lower alkylene" may include methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and the like.

Suitable "protective group" in the "protected hydroxy group" may include acyl as mentioned above, phenyl(lower)alkyl which may have one or more suitable

substituent(s) (e.g. benzyl, 4-methoxybenzyl, etc.), tetrahydropyranyl and the like.

Suitable mono or di substituted carbamoyl may be mono or di(lower)alkylcarbamoyl (e.g. methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, propylcarbamoyl, dipropylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl, etc.), and the like.

Suitable "leaving group" may be halogen [e.g. chlorine, bromine, iodine, etc.], acyloxy such as sulfonyloxy [e.g. benzenesulfonyloxy, tosyloxy, mesyloxy, etc.], lower alkanoyloxy [e.g. acetyloxy, propionyloxy, etc.] or the like.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and include a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.], an organic acid salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic acid salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], a salt with an amino acid [e.g. arginine salt, aspartic acid salt, glutamic acid salt, etc.], and the like.

The processes for preparing the object and starting compounds of the present invention are explained in detail in the following.

Process (1)

The compound (I) or a salt thereof can be prepared by

reacting the compound (II) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the amino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide [e.g. N-(trimethylsilyl)acetamide], bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (II) with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative at the carboxy group of the compound (III) may include a conventional one used in a β-lactam chemistry, an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl

ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, benzothiazolyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (III) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonyl-bis(2-methylimidazole); pentamethylene-ketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus

oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process (2)

The compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to elimination reaction of the carboxy protective group in R_a^2. Suitable method of this elimination reaction may include conventional one such as hydrolysis, reduction and the like.

(i) For Hydrolysis :

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]-

non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

(ii) For reduction :

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium,

palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.) copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the like. The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process (3)

The compound (I) or a salt thereof can be prepared by reaction the compound (IV) or a salt thereof with the compound (V) or a salt thereof.

The present reaction may be carried out in a solvent such as acetone, chloroform, acetonitrile, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, methanol, ethanol, diethyl ether, tetrahydrofuran, dimethyl sulfoxide, or any other organic solvent which does not adversely affect the reaction. The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming. The reaction may also be carried out in the presence of an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an

alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, tri(lower)alkylamine [e.g. trimethylamine, triethylamine, diisopropylethylamine etc.], picoline, alkali metal alkanoate [e.g. sodium 2-ethylhexanoate, etc.], N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

Process (4)

The compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or a salt thereof to elimination reaction of the carboxy protective group in R_a^6. This reaction can be carried out in a similar manner to that of the aforementioned Process (2), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (2). The present invention includes, within the scope of the invention, the case that the protected hydroxy group in R^5 is transformed into a hydroxy group during the reaction.

Process (5)

The compound (If) or a salt thereof can be prepared by subjecting the compound (Ie) or a salt thereof to elimination reaction of the hydroxy protective group in R_a^5. This reaction can be carried out in a similar manner to that of the aforementioned Process (2), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (2).

Process (A)

The compound (VIIIa) or a salt thereof can be prepared by reacting the compound (VI) or its reactive derivative at the carboxy group or a salt thereof with the

compound (VII) or its reactive derivative or a salt thereof.

The reaction is usually carried out in a conventional solvent such as water, alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process (B)

The compound (V) or a salt thereof can be prepared by reacting the compound (VIII) or a salt thereof with the compound (IX) or a salt thereof.

The reaction is usually carried out in a conventional solvent such as water, alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (C)

The compound (Vb) or a salt thereof can be prepared by subjecting the compound (Va) or a salt thereof to introduction reaction of the carboxy protective group.

The introducing agent of a carboxy protective group to be used in this reaction may include a conventional esterifying agent such as an alcohol or its reactive derivative (e.g. halide, sulfonate, sulfate, diazo compound, etc.), and the like.

This reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, tri(lower)alkylamine, pyridine, or the like.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as N,N-dimethylformamide, tetrahydrofuran, dioxane, methanol, ethanol, etc., or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

In case that the alcohol is used as the introducing agent of a carboxy protective group, the reaction can be carried out in the presence of a condensing agent as illustrated in Process (1).

Process (D)

The compound (IIa) or a salt thereof can be prepared by reacting the compound (X) or a salt thereof with the compound (V) or a salt thereof.

The reaction is usually carried out in a conventional solvent such as alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

This reaction may also be carried out in the presence of an inorganic or an organic base as defined in Process (3).

Process (E)

The compound (IIc) or a salt thereof can be prepared by subjecting the compound (IIb) or a salt thereof to elimination reaction of the carboxy protective group in R_a^6. This reaction can be carried out in a similar manner

to that of the aforementioned Process (2), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (2).

The present invention includes, within the scope of the invention, the case that the protected hydroxy group in R^5 is transformed into a hydroxy group during the reaction.

Process (F)

The compound (IIe) or a salt thereof can be prepared by subjecting the compound (IId) or a salt thereof to elimination reaction of the hydroxy protective group in R_a^5. This reaction can be carried out in a similar manner to that of the aforementioned Process (2), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (2).

Process (G)

The compound (II) or a salt thereof can be prepared by subjecting the compound (IIf) or a salt thereof to elimination reaction of the amino protective group in R_a^9. This reaction can be carried out in a similar manner to that of the aforementioned Process (2), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (2).

Suitable salts of the object and starting compounds and their reactive derivatives in Process (1)~(5) and (A)~(G) can be referred to the ones as exemplified for the compound (I).

The object compound (I) and pharmaceutically acceptable salts thereof are novel and exhibit high antimicrobial activity, inhibiting the growth of a wide variety of pathogenic microorganisms including Gram-

positive and Gram-negative microorganisms and are useful as antimicrobial agents.

Now in order to show the utility of the object compound (I), the test data on MIC (minimal inhibitory concentration) of representative compound of this invention are shown in the following.

Test method :

In vitro antibacterial activity was determined by the two-fold agar-plate dilution method as described below.

One loopful of an overnight culture of each test strain in Trypticase-soy broth (10^8 viable cells per ml) was streaked on heart infusion agar (HI-agar)containing graded concentrations of representative test compound, and the minimal inhibitory concentration (MIC) was expressed in terms of μg/ml after incubation at 37°C for 20 hours.

Test compound :

(1) 7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)ethyl}-ammoniomethyl]-3-cephem-4-carboxylate (syn isomer)

Test result :

MIC (μg/ml)

Test strain	Test compound (1)
P. aeruginosa	≤ 0.025

For therapeutic administration, the object compound (I) and pharmaceutically acceptable salts thereof of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically

acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration.

The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

In needed, there may be included in the above preparations, auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compound (I) to be applied, etc. In general, amounts between 1 mg and about 4,000 mg or even more per day may be administered to a patient. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg of the object compound (I) of the present invention may be used in treating diseases infected by pathogenic microorganisms.

Preferred embodiments of the object compound (I) are as follows.

R^1 is amino or acylamino,
Z is N or CH,
R^2 is hydrogen, lower alkyl,
carboxy(lower)alkyl, or
protected carboxy(lower)alkyl [more preferably esterified carboxy(lower)alkyl; most preferably lower alkoxycarbonyl(lower)alkyl],
R^3 is lower alkyl,

R^4 is lower alkyl,
A is lower alkylene,
R^5 is hydroxy, acyloxy, or phenyl(lower)alkoxy which may have one or more suitable substituent(s) [more preferably lower alkoxyphenyl(lower)alkoxy], and
R^6 is carboxy, esterified carboxy [more preferably phenyl(lower)alkyloxycarbonyl which may have one or more suitable substituent(s); most preferably benzhydryloxycarbonyl], carbamoyl, or mono or di(lower)alkylcarbamoyl.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To a stirred suspension of 2-carboxy-4-oxo-5-(4-methoxybenzyloxy)-4H-pyran (20 g) in N,N-dimethylformamide (400 ml) were added 1-hydroxybenzotriazole (10.8 g) and N,N'-dicyclohexylcarbodiimide (16.4 g) at 5°C, and the mixture was stirred at the same temperature for 15 minutes. Then to the mixture was added 28% ammonia in water (5.5 ml) at the same temperature. The mixture was stirred at the same temperature for 4 hours, and at room temperature for 4 hours. The mixture was poured into water, and adjusted to pH 9 with 1N sodium hydroxide to give the precipitate. The precipitate was collected by filtration, and washed with water. The precipitate was added to ethyl acetate at room temperature, and the suspension was stirred at the same temperature for 15 minutes. The insoluble material was collected by filtration and washed with ethyl acetate. The insoluble material was dried under reduced pressure to give crude 2-carbamoyl-4-oxo-5-(4-methoxybenzyloxy)-4H-pyran (32.7 g).

IR (Nujol) : 1645, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 4.91 (2H, s), 6.87 (1H, s), 6.96 (2H, d, J=8.7Hz), 7.36 (d, J=8.7Hz), 8.04 (1H, br s), 8.20 (1H, s), 8.31 (1H, br s)

Preparation 2

To a stirred suspension of 2-carboxy-4-oxo-5-(4-methoxybenzyloxy)-4H-pyran (10 g) in N,N-dimethylformamide (200 ml) were added 1-hydroxybenzotriazole (5.4 g) and N,N'-dicyclohexylcarbodiimide (8.2 g) at 5°C, and the mixture was stirred at the same temperature for 30 minutes. Then to the mixture was added 50% dimethylamine in water (3.59 g) at the same temperature. The mixture was stirred at the same temperature for 3 hours, and at room temperature for 6 hours. The mixture was poured into water, and adjusted to pH 8 with 1N sodium hydroxide. After extracted with chloroform, the organic layer was washed with water, dried with magnesium sulfate, filtered and evaporated under reduced pressure. To the residue was added isopropyl alcohol, and the mixture was stirred at room temperature for 1 hour. The insoluble material was collected by filtration, washed with isopropyl alcohol and dried under reduced pressure to give 2-(N,N-dimethylcarbamoyl)-4-oxo-5-(4-methoxybenzyloxy)-4H-pyran (7.60 g).

NMR (DMSO-d_6, δ) : 2.96 (3H, s), 2.99 (3H, s), 3.77 (3H, s), 4.88 (2H, s), 6.59 (1H, s), 6.95 (2H, d, J=8.7Hz), 7.36 (2H, d, J=8.7Hz), 8.28 (1H, s)

Preparation 3

To a stirred suspension of 2-carboxy-4-oxo-5-(4-methoxybenzyloxy)-4H-pyran (268 g) in ethanol (2.7 ℓ) was added N,N-dimethylethylenediamine (400 ml) at room

temperature, and the solution was refluxed for 2 hours. After removal of ethanol under reduced pressure, the residue was purified by column chromatography on silica gel (acetone/water as eluent) to give 1-[2-(N,N-dimethylamino)ethyl]-2-carboxy-4-oxo-5-(4-methoxybenzyloxy)-1,4-dihydropyridine. To a stirred solution of the product in N,N-dimethylformamide (1 ℓ) was added diphenyldiazomethane (565 g) at room temperature, and the solution was warmed to 60°C and then stirred at the same temperature for 12 hours. The solution was poured into water, and extracted with ethyl acetate. The organic layer was washed with water, and then to the organic layer was added acetic acid (110 ml) to decompose excess diphenyldiazomethane, and the mixture was stirred at room temperature for 2 hours. Then the solution was adjusted to pH 10 with an aqueous solution of N-sodium hydroxide. After separation, the organic layer was washed with brine and concentrated under reduced pressure. To the residue was added hexane to give a precipitate. After filtration, the precipitate was washed with hexane and dried in vacuo to give 1-[2-(N,N-dimethylamino)ethyl]-2-benzhydryloxycarbonyl-4-oxo-5-(4-methoxybenzyloxy)-1,4-dihydropyridine (199 g).

NMR (DMSO-d_6, δ) : 1.85 (6H, s), 2.28 (2H, m), 3.74 (3H, s), 4.20 (2H, m), 4.97 (2H, s), 6.75 (1H, s), 6.91-7.54 (15H, m), 7.69 (1H, s)

Preparation 4

(1) To a stirred suspension of 2-carbamoyl-4-oxo-5-(4-methoxybenzyloxy)-4H-pyran (32.7 g) in ethanol (33 ml) was added N,N-dimethylethylenediamine (19.5 ml) at room temperature, and the mixture was refluxed for 4 hours. After removal of ethanol under reduced pressure, the residue was purified by column chromatography on silica gel (acetone/water as eluent) to give 2-carbamoyl-1-[2-(N,N-dimethylamino)ethyl]-4-oxo-5-(4-methoxybenzyloxy)-

1,4-dihydropyridine (12.95 g).

NMR (DMSO-d_6, δ) : 2.10 (6H, s), 2.46 (2H, t, J=6.3Hz), 3.75 (3H, s), 4.09 (2H, t, J=6.3Hz), 4.95 (2H, s), 6.25 (1H, s), 6.93 (2H, d, J=8.7Hz), 7.33 (2H, d, J=8.7Hz), 7.56 (1H, s), 7.90 (1H, br s), 8.30 (1H, br s)

The following compound was obtained according to a similar manner to that of Preparation 4-(1).

(2) 1-[2-(N,N-Dimethylamino)ethyl]-2-(N,N-dimethylcarbamoyl)-4-oxo-5-(4-methoxybenzyloxy)-1,4-dihydropyridine

NMR (DMSO-d_6, δ) : 2.08 (6H, s), 2.38-2.52 (2H, m), 2.93 (3H, s), 2.97 (3H, s), 3.75 (3H, s), 3.80-4.18 (2H, m), 4.93 (2H, s), 6.10 (1H, s), 6.94 (2H, d, J=8.7Hz), 7.34 (2H, d, J=8.7Hz), 7.62 (1H, s)

Preparation 5

To an ice-cooled solution of 1-[2-(N,N-dimethylamino)ethyl]-2-benzhydryloxycarbonyl-4-oxo-5-(4-methoxybenzyloxy)-1,4-dihydropyridine (2.0 g) and sodium 2-ethylhexanoate (0.65 g) in N,N-dimethylformamide (10 ml) was added 7β-formamido-3-chloromethyl-3-cephem-4-carboxylic acid (1.07 g). After stirred at the same temperature for 1.5 hours, the reaction mixture was poured into a mixture of isopropyl ether (50 ml) and ethyl acetate (50 ml). The resulting precipitate was collected by filtration, washed with isopropyl ether and dried in vacuo. The dried precipitate (2.0 g) was suspended in dichloromethane (4 ml) and anisole (4 ml). Trifluoroacetic acid (10 ml) was dropwise added to the above suspension under ice-cooling. The mixture was stirred at 5°C for an hour and poured into isopropyl ether

(100 ml). The resulting precipitate was collected by filtration, washed with ethyl acetate and dried in vacuo to give 7β-formamido-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)ethyl}-ammoniomethyl]-3-cephem-4-carboxylate trifluoroacetate (1.44 g).

IR (Nujol) : 1780, 1665, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 3.11 (3H, s), 3.20 (3H, s), 3.43, 3.91 (2H, ABq, J=16.8Hz), 3.75 (2H, m), 4.38, 4.83 (2H, ABq, J=13.5Hz), 4.80 (2H, m), 5.28 (1H, d, J=5Hz), 5.85 (1H, dd, J=8Hz), 6.96 (1H, s), 7.94 (1H, s), 8.15 (1H, s), 9.20 (1H, d, J=8Hz)

Preparation 6

To a mixture of 7β-formamido-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)ethyl}-ammoniomethyl]-3-cephem-4-carboxylate trifluoroacetate (1.40 g) and methanol (28 ml) was added conc. hydrochloric acid (1.32 ml) with stirring. After stirred at 25°C for 5 hours, the reaction mixture was poured into acetone (140 ml). The resulting precipitate was collected by filtration and dried in vacuo. The dried powder (0.75 g) was dissolved into water (7.5 ml) and subjected to column chromatography on Diaion HP-20 (30 ml) (trademark : Mitsubishi Kasei Corporation). The elution was carried out with water and the fractions containing the object compound (23 ml) were collected. To the ice-cooled solution obtained above was added isopropyl alcohol (69 ml) slowly. The resulting precipitate was collected by filtration and dried in vacuo to give 7β-amino-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)ethyl}ammoniomethyl]-3-cephem-4-carboxylate dihydrochloride (0.22 g).

IR (Nujol) : 3330, 1775, 1607 cm^{-1}

NMR (D_2O, δ) : 3.19 (3H, s), 3.25 (3H, s), 3.60, 4.05 (2H, ABq, J=16.8Hz), 3.95 (2H, m), 4.23, 4.83 (2H, ABq, J=13.5Hz), 4.98 (2H, m), 5.22 (1H, d, J=5Hz), 5.44 (1H, d, J=5Hz), 7.32 (1H, s), 8.05 (1H, s)

Example 1

To a solution of 7β-amino-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)ethyl}-ammoniomethyl]-3-cephem-4-carboxylate dihydrochloride (0.20 g) in a mixture of tetrahydrofuran (10 ml) and water (10 ml) was dropwise added a solution of 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetyl chloride hydrochloride (syn isomer) (0.16 g) in tetrahydrofuran (2 ml) at 15-20°C. During the reaction, the pH of reaction mixture was kept between 5.0 and 5.5 with an aqueous solution saturated with sodium bicarbonate. After 30 minutes, the mixture was adjusted to pH 6.0 with an aqueous solution saturated with sodium bicarbonate and stirred at 20°C for 6 hours. After evaporation of organic solvent under reduced pressure, the aqueous solution was diluted with water (30 ml) and adjusted to pH 1.0 with 6N hydrochloric acid. The resulting aqueous solution (40 ml) was subjected to column chromatography on Diaion HP-20 (20 ml). After the column was washed with water, the elution was carried out with 30% aqueous methanol. The fraction containing the object compound was freeze-dried to give 7β-{2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido}-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)-ethyl}ammoniomethyl]-3-cephem-4-carboxylate (syn isomer) (0.13 g).

IR (Nujol) : 1760, 1640 (sh), 1602 cm^{-1}

NMR (D_2O-$NaHCO_3$, δ) : 3.13 (3H, s), 3.17 (3H, s), 3.46, 3.94 (2H, ABq, J=17Hz), 3.80 (2H, m),

4.08 (2H, m), 4.12, 4.76 (2H, ABq, J=13.5Hz), 4.80 (2H, m), 5.37 (1H, d, J=5Hz), 5.90 (1H, d, J=5Hz), 6.68 (1H, s), 7.28 (1H, s)

Example 2

To a solution of 7β-amino-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)ethyl}-ammoniomethyl]-3-cephem-4-carboxylate dihydrochloride (0.50 g) in a mixture of tetrahydrofuran (15 ml) and water (15 ml) was dropwise added a solution of S-2-benzothiazolyl-2-(2-aminothiazol-4-yl)-2-(1-tert-butoxycarbonyl-1-methylethoxyimino)ethanethioate (syn isomer) (0.70 g) in tetrahydrofuran (10 ml) at 20°C. After stirred for 6 hours at the same temperature, the reaction mixture was diluted with water (30 ml) and ethyl acetate (30 ml) and adjusted to pH 7.0 with an aqueous solution saturated with sodium bicarbonate. The separated aqueous layer was washed with ethyl acetate (30 ml) three times. After adjusted to pH 1.0 with 6N hydrochloric acid, the aqueous layer was subjected to column chromatography on Diaion HP-20 (50 ml). The object compound was eluted with 50% aqueous methanol, and the fractions containing the object compound were freeze-dried to give 7β-[2-(2-aminothiazol-4-yl)-2-(1-tert-butoxy-carbonyl-1-methylethoxyiminoacetamido]-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)-ethyl}ammoniomethyl]-3-cephem-4-carboxylate (syn isomer) (0.33 g). The compound (0.30 g) obtained above was suspended in anisole (2 ml) and trifluoroacetic acid (6 ml) was added under ice-cooling with stirring. After stirred for 3 hours at ambient temperature, the mixture was poured into diisopropyl ether (100 ml). The resulting precipitate was collected by filtration, washed with diisopropyl ether and dried under reduced pressure. The dried precipitate was dissolved in water (60 ml) at pH

1.0. The aqueous solution was subjected to column chromatography on Diaion HP-20 (20 ml). After the column was washed with water, the object compound was eluted with 30% aqueous methanol and freeze-dried to give 7β-[2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)-acetamido]-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)ethyl}ammoniomethyl]-3-cephem-4-carboxylate (syn isomer) (0.19 g).

IR (Nujol) : 3220, 1772, 1650 (sh.), 1609 cm^{-1}

NMR (D_2O-$NaHCO_3$, δ) : 1.49 (3H, s), 1.50 (3H, s), 3.13 (3H, s), 3.18 (3H, s), 3.48, 3.94 (2H, ABq, J=16.8Hz), 4.14, 4.74 (2H, ABq, J=13.5Hz), 4.70 (2H, m), 5.39 (1H, d, J=5Hz), 5.87 (1H, d, J=5Hz), 6.71 (1H, s), 6.97 (1H, s), 7.39 (1H, s)

Example 3

(1) To a stirred solution of 1-[2-(N,N-dimethylamino)-ethyl]-2-benzhydryloxycarbonyl-4-oxo-5-(4-methoxybenzyloxy)-1,4-dihydropyridine (30 g) and diisopropylethylamine (25.3 ml) in N,N-dimethylformamide (150 ml) was added 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-chloromethyl-3-cephem-4-carboxylic acid trifluoroacetate (syn isomer) (30 g) at 3°C, and the solution was stirred at the same temperature for 2 hours. The solution was poured into ethyl acetate (1.5 ℓ) to give a precipitate. After filtration, the precipitate was washed with ethyl acetate followed by diethyl ether, and dried in vacuo to give 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[N,N-dimethyl-N-[2-{2-benzhydryloxycarbonyl-4-oxo-5-(4-methoxybenzyloxy)-1,4-dihydropyridin-1-yl}ethyl]ammoniomethyl]-3-cephem-4-carboxylate (syn isomer). To a stirred suspension of this compound in anisole (230 ml) was added trifluoroacetic

acid (306 ml) dropwise over 30 minutes under ice-cooling, and the solution was stirred at 3°C for 1 hour. The solution was poured into diisopropyl ether (3 ℓ) to give a precipitate and the precipitate was collected by filtration. The precipitate was washed with diisopropyl ether followed by diethyl ether. After dried in vacuo, the powder was dissolved into water at pH 6.5. The aqueous solution was subjected to column chromatography on Diaion HP-20 (100 ml). The desired product was eluted with water. The eluate was adjusted to pH 1 with 6N hydrochloric acid, and the resulting precipitate was removed by filtration. The filtrate was subjected to column chromatography on Diaion HP-20 (1.7 ℓ) and eluted with 30% aqueous methyl alcohol. The fractions containing the desired product were combined and evaporated under reduced pressure to remove methyl alcohol. The residue was lyophilized to give 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)ethyl}ammoniomethyl]-3-cephem-4-carboxylate (syn isomer) (9.39 g).

IR (Nujol) : 1760, 1645 (sh.), 1600 cm^{-1}

NMR (D_2O-$NaHCO_3$, δ) : 1.52 (3H, s), 1.53 (3H, s), 3.13 (3H, s), 3.19 (3H, s), 3.47, 3.93 (2H, ABq, J=16.8Hz), 3.83 (2H, m), 4.13, 4.75 (2H, ABq, J=13.5Hz), 4.8 (2H, m), 5.39 (1H, d, J=5.0Hz), 5.90 (1H, d, J=5.0Hz), 6.74 (1H, s), 7.58 (1H, s)

The following compounds were obtained according to a similar manner to that of Example 3-(1).

(2) 7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[N,N-dimethyl-N-{2-(2-carbamoyl-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)ethyl}-

ammoniomethyl]-3-cephem-4-carboxylate (syn isomer).

IR (Nujol) : 1765, 1665 cm^{-1}

NMR (D_2O-$NaHCO_3$, δ) : 1.53 (6H, s), 3.16 (6H, d, J=12.2Hz), 3.44-4.80 (8H, m), 5.39 (1H, d, J=5.0Hz), 5.85 (1H, d, J=5.0Hz), 6.81 (1H, s), 7.68 (1H, s)

(3) 7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[N,N-dimethyl-N-[2-{2-(N,N-dimethylcarbamoyl)-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl}ethyl]ammoniomethyl]-3-cephem-4-carboxylate (syn isomer).

IR (Nujol) : 1770, 1655, 1625 cm^{-1}

NMR (D_2O-$NaHCO_3$, δ) : 1.53 (6H, s), 3.05-3.18 (12H, m), 3.34-4.91 (8H, m), 5.39 (1H, d, J=5.0Hz), 5.88 (1H, d, J=5.0Hz), 6.60 (1H, s), 7.73 (1H, s)

Example 4

To a mixture of ethanol (1 ml) and 1N hydrochloric acid (2.52 ml) was added 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)ethyl}ammoniomethyl]-3-cephem-4-carboxylate (syn isomer) (0.50 g) at 20°C. The clear solution of the mixture was cooled with ice, and ethanol (6.5 ml) was added thereto. After the mixture was stirred for 2 hours, the resulting precipitate was collected by filtration, washed with ethanol and dried in vacuo to give 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)ethyl}ammoniomethyl]-3-cephem-4-carboxylate hydrochloride (syn isomer).

IR (Nujol) : 3300, 2700-2500 (br), 1770, 1715, 1665, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.46 (6H, s), 3.12 (3H, s), 3.22 (3H, s), 3.70, 4.06 (2H, ABq, J=17.4Hz), 3.8-4.1 (2H, m), 4.45, 4.65 (2H, ABq, J=13.3Hz), 5.0 (2H, m), 5.35 (1H, d, J=5Hz), 5.95 (1H, dd, J=5Hz, 8Hz), 7.61 (1H, s), 8.3 (2H, br s), 8.39 (1H, s), 9.59 (1H, d, J=8Hz)

Example 5

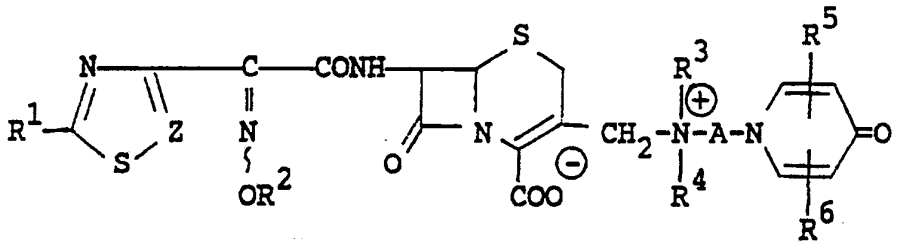
To a mixture of 1M aqueous sulfuric acid (30.2 ml) and ethanol (20 ml) was added 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)-acetamido]-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)ethyl}ammoniomethyl]-3-cephem-4-carboxylate (syn isomer) (6 g) at 20-25°C. Ethanol (70 ml) was dropwise added to the above solution for 80 minutes. After the mixture was stirred at the same temperature for 2 hours, the resulting precipitate was collected by filtration, washed with ethanol and dried in vacuo to give 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)-ethyl}ammoniomethyl]-3-cephem-4-carboxylate sulfate (syn isomer) (4.6 g).

IR (Nujol) : 3300, 2800-2500 (br), 1773, 1715, 1670, 1600, 1160 cm^{-1}

NMR (DMSO-d_6, δ) : 1.46 (6H, s), 3.07 (3H, s), 3.16 (3H, s), 3.68, 3.98 (2H, ABq, J=17.3Hz), 3.7-3.9 (2H, m), 4.33, 4.69 (2H, ABq, J=13.2Hz), 4.8 (2H, m), 5.30 (1H, d, J=5Hz), 5.97 (1H, dd, J=5Hz, 8Hz), 7.02 (1H, s), 7.88 (1H, s), 8.22 (2H, br s), 9.58 (1H, dd, J=5Hz, 8Hz)

C L A I M S

1. A compound of the formula :



wherein R^1 is amino or protected amino,
Z is N or CH,
R^2 is hydrogen or an organic group,
R^3 is lower alkyl,
R^4 is lower alkyl,
A is lower alkylene,
R^5 is hydroxy or protected hydroxy, and
R^6 is carboxy, protected carboxy, carbamoyl, or mono or di substituted carbamoyl,
or pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein
R^1 is amino or acylamino,
R^2 is hydrogen,lower alkyl, carboxy(lower)alkyl, or protected carboxy(lower)alkyl,
R^5 is hydroxy, acyloxy, or phenyl(lower)alkyloxy which may have one or more suitable substituent(s), and
R^6 is carboxy, esterified carboxy, carbamoyl, or mono or di(lower)alkylcarbamoyl.

3. A compound of claim 2, wherein
R^2 is lower alkyl, carboxy(lower)alkyl, or esterified carboxy(lower)alkyl,
R^5 is hydroxy, acyloxy, or lower

alkoxyphenyl(lower)alkoxy, and

R^6 is carboxy, phenyl(lower)alkyloxycarbonyl which may have one or more suitable substituent(s), carbamoyl, or di(lower)alkylcarbamoyl.

4. A compound of claim 3, wherein

R^2 is lower alkyl, carboxy(lower)alkyl, or lower alkoxycarbonyl(lower)alkyl, and

R^6 is carboxy, benzhydryloxycarbonyl, carbamoyl, or di(lower)alkylcarbamoyl.

5. A compound of claim 4, wherein

R^1 is amino,

Z is N,

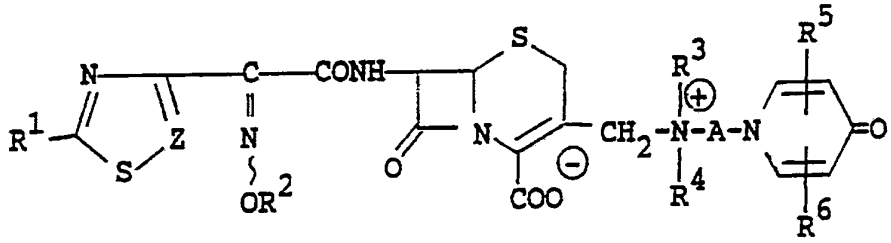
R^2 is carboxy(lower)alkyl,

R^5 is hydroxy, and

R^6 is carboxy.

6. A compound of claim 5, which is 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[N,N-dimethyl-N-{2-(2-carboxy-4-oxo-5-hydroxy-1,4-dihydropyridin-1-yl)-ethyl}ammoniomethyl]-3-cephem-4-carboxylate (syn isomer).

7. A process for preparing a compound of the formula :



wherein R^1 is amino or protected amino,

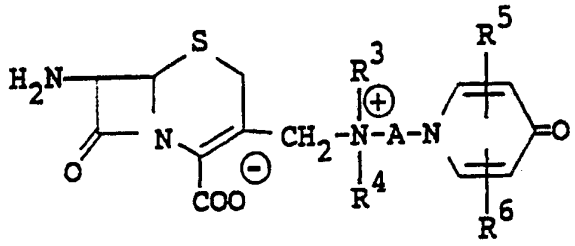
Z is N or CH,

R^2 is hydrogen or an organic group,
R^3 is lower alkyl,
R^4 is lower alkyl,
A is lower alkylene,
R^5 is hydroxy or protected hydroxy, and
R^6 is carboxy, protected carboxy, carbamoyl, or mono or di substituted carbamoyl,

or a salt thereof,

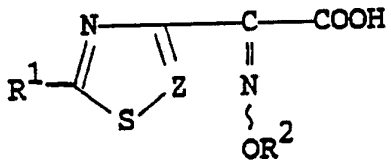
which comprises,

(1) reacting a compound of the formula :



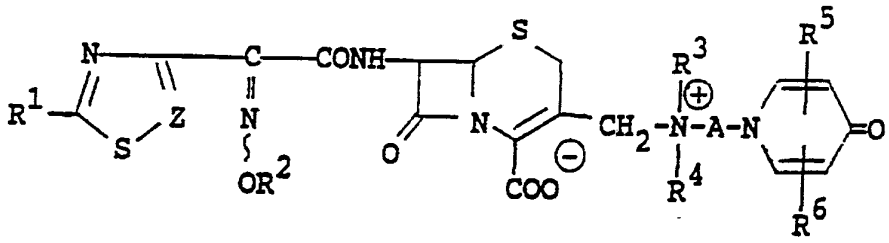
wherein R^3, R^4, R^5, R^6 and A are each as defined above,

or its reactive derivative at the amino group or a salt thereof with a compound of the formula :



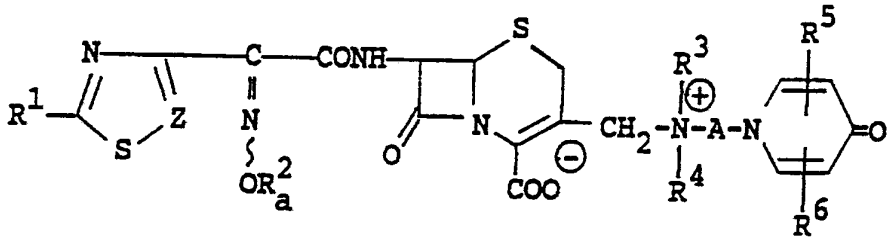
wherein R^1, R^2 and Z are each as defined above,

or its reactive derivative at the carboxy group or a salt thereof to give a compound of the formula :

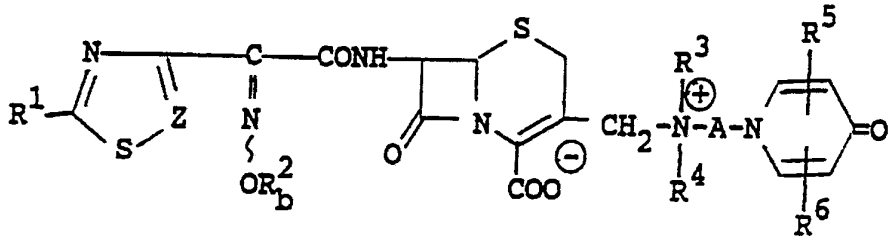


wherein R^1, R^2, R^3, R^4, R^5, R^6, Z and A are each as defined above,
or a salt thereof, or

(2) subjecting a compound of the formula :

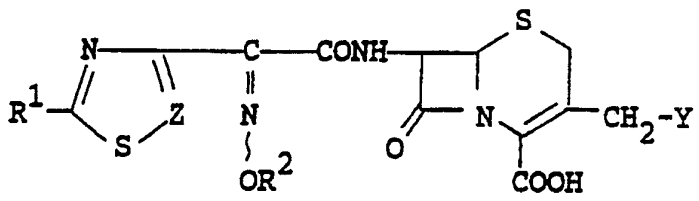


wherein R^1, R^3, R^4, R^5, R^6, Z and A are each as defined above,
R_a^2 is protected carboxy(lower)alkyl,
or a salt thereof to elimination reaction of the carboxy protective group in R_a^2 to give a compound of the formula :

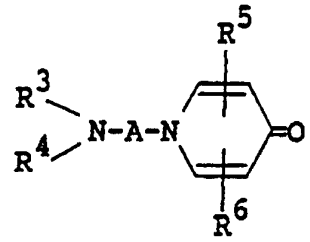


wherein R^1, R^3, R^4, R^5, R^6, Z and A are each as defined above,
R_b^2 is carboxy(lower)alkyl,
or a salt thereof, or

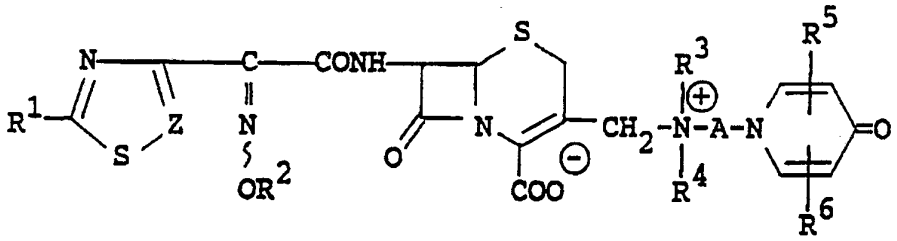
(3) reacting a compound of the formula :



wherein R^1, R^2 and Z are each as defined above,
Y is a leaving group,
or a salt thereof with a compound of the formula :

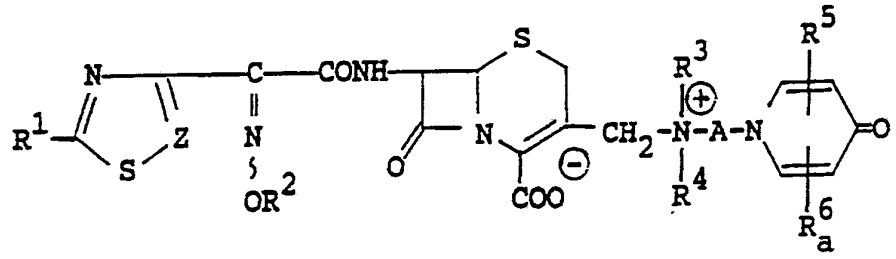


wherein R^3, R^4, R^5, R^6 and A are each as defined above,
or a salt thereof to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, R^6, Z and A are each as defined above,
or a salt thereof, or

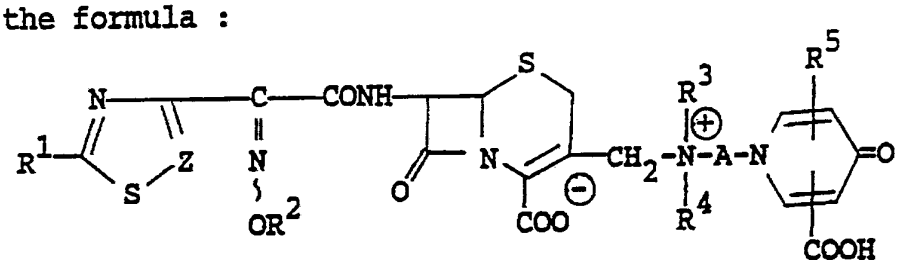
(4) subjecting a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, Z and A are each as defined above,

R_a^6 is protected carboxy,

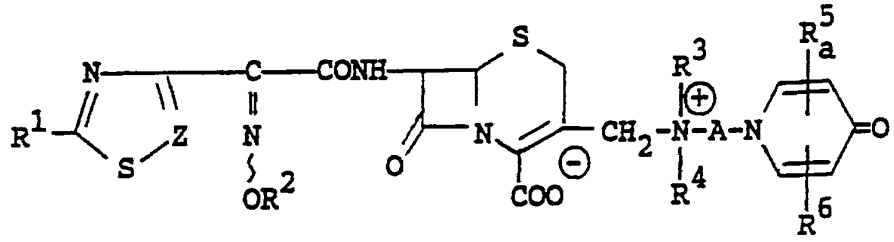
or a salt thereof to elimination reaction of the carboxy protective group in R_a^6 to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, Z and A are each as defined above,

or a salt thereof, or

(5) subjecting a compound of the formula :

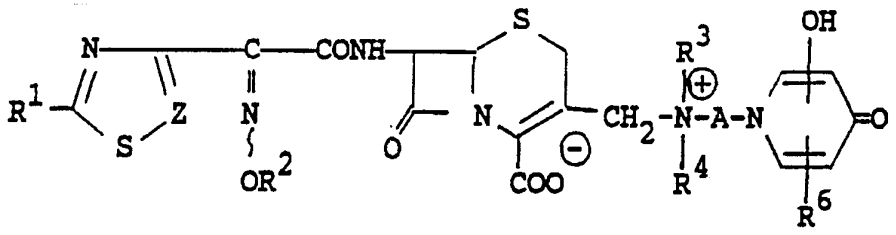


wherein R^1, R^2, R^3, R^4, R^6, Z and A are each as defined above,

R_a^5 is protected hydroxy,

or a salt thereof to elimination reaction of the hydroxy protective group in R_a^5 to give a compound of

the formula :



wherein R^1, R^2, R^3, R^4, R^6, Z and A are each as defined above,
or a salt thereof.

8. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

9. A method for the treatment of infectious diseases which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

10. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as an antimicrobial agent.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 92/00472

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 501/46 A 61 K 31/545

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 501/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	Chemical Abstracts, vol. 107, no. 13, 28 September 1987, (Columbus, Ohio, US), see page 612, column 2, abstract no. 115433p, & JP,A,6230778 (BANYU PHARMACEUTICAL) 9 February 1987 ---	1-10
A	Patent Abstracts of Japan, vol. 12, no. 213 (C-505)[3060], 17 June 1988, & JP,A,6310792 (TAKEDA) 18 January 1988 ---	1-10
A	EP,A,0345671 (FUJISAWA) 13 December 1989, see the complete specification (cited in the application) ---	1-10
A	GB,A,2117770 (BRISTOL-MYERS) 19 October 1983, & US,A,4457929 (cited in the application) -----	1-10

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03-07-1992	30. 07. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Natalie Weinberg

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

Ir ational application No.
PCT/JP 92/00472

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: ** because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 9 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition

2. [ ] Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. JP 9200472 SA 58230

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/07/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0345671	13-12-89	AU-B-	622906	30-04-92
		AU-A-	3583989	07-12-89
		JP-A-	2028187	30-01-90
GB-A- 2117770	19-10-83	US-A-	4457929	03-07-84
		AT-B-	388163	10-05-89
		AT-B-	389515	27-12-89
		AT-B-	383129	25-05-87
		AU-B-	564971	03-09-87
		CA-A-	1213883	11-11-86
		CH-A-	655118	27-03-86
		DE-A,C	3311300	29-09-83
		FR-A,B	2523973	30-09-83
		JP-A-	58198490	18-11-83
		LU-A-	84717	05-12-83
		NL-A-	8301053	17-10-83
		OA-A-	7354	31-08-84
		SE-B-	453092	11-01-88
		SE-A-	8301726	25-11-83
		SU-A-	1205772	15-01-86
		SU-A-	1373325	07-02-88
		SU-A-	1313351	23-05-87