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New cephem compounds and processes for preparation thereof.

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Description

The present invention relates to new cepham compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to new cepham 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 or animals.


Accordingly, one object of the present invention is to provide the cepham 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 cepham compounds and salts thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said cepham 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 cepham compounds to infected human being or animals.

The object cepham compounds are novel and can be represented by the following general formula [I]:

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \\
\text{S} & \quad \text{C-CONH} \\
\text{N} & \quad \text{O} \\
\text{O-R^2} & \\
\text{R^1} & \quad \text{N} \\
\text{R^2} & \quad \text{CH_2} \\
\text{R^5} & \quad \text{R^4} \cdot (X^\oplus)_n
\end{align*}
\]

wherein

\[
\begin{align*}
\text{R}^1 & \quad \text{amino or protected amino}, \\
\text{R}^2 & \quad \text{hydrogen, tetrahydropyranyl, (C_1-C_6)alkyl, dihalogenated (C_1-C_6)alkyl, cyclo(C_1-C_6)-} \\
\text{alkenyl, thietanyl, carboxy(C_1-C_6)alkyl or protected carboxy(C_1-C_6)alkyl}, \\
\text{R}^3 & \quad \text{(C_1-C_6)alkyl}, \\
\text{R}^4 \text{ and } \text{R}^5 & \quad \text{each hydrogen, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, amino or protected} \\
\text{R}^5 & \quad \text{amino,} \\
\text{X}^\oplus & \quad \text{COO^\oplus carboxy or protected carboxy}, \\
\text{n} & \quad \text{0 or 1,}
\end{align*}
\]

with proviso that

(i) when \( \text{R}^2 \) is carboxy(C_1-C_6)alkyl or protected carboxy(C_1-C_6)alkyl, then \( \text{R}^1 \) is hydrogen and

(ii) when \( \text{R}^5 \) is COO^\oplus, then \( n \) is 0, and

(iii) when \( \text{R}^5 \) is carboxy or protected carboxy, then \( n \) is 1, and

a pharmaceutically acceptable salt thereof.

As to the object compounds [I], the following points are to be noted.

That is, the object compounds [I] include syn isomer, anti isomer and a mixture thereof. Syn isomer means one geometrical isomer having the partial structure represented by the following formula:
(wherein R¹ and R² are each as defined above),

and anti isomer means the other geometrical isomer having the partial structure represented by the following formula:

![Chemical Structure Image]

(wherein R¹ and R² 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:

![Chemical Structure Image]

(wherein R¹ and R² are each as defined above).

Another point to be noted is that the pyrazolio moiety of the compounds [I] can also exist in the tautomeric form, and such tautomeric equilibrium can be represented by the following scheme:

![Chemical Structure Image]

(wherein R³, R⁴, and R⁵ are each as defined above.).

Both of the above tautomeric isomers are included within the scope of the present invention, and in the present specification and claim, however, the object compounds [I] are represented for the convenient sake by one expression of the pyrazolio group of the formula (A).

The cepham compounds [I] of the present invention can be prepared by processes as illustrated in the following reaction schemes.
Process (I)

\[
\begin{align*}
H_2N & \quad \text{asymmetric ring structure} \\
& \quad \text{with functional groups} \\
& \quad \text{R}\_6 \\
& \quad \text{N} \\
& \quad \text{O} \\
& \quad \text{R}\_5 \\
& \quad \text{CH}_2 \\
& \quad \text{R}\_4 \cdot \text{(X)}\_n \\
& + \\
& \quad \text{Zwitterion} \\
& \quad \text{R}\_1 \quad \text{N} \\
& \quad \text{O} \\
& \quad \text{R}\_2 \\
& \quad \text{C-COOH} \\
\end{align*}
\]

[II]

or its reactive derivative
at the amino group,
or its salt

\[
\begin{align*}
\rightarrow \\
& \quad \text{R}\_1 \quad \text{C-CNH} \\
& \quad \text{N} \\
& \quad \text{O} \quad \text{R}\_2 \\
& \quad \text{R}\_5 \\
& \quad \text{CH}_2 \\
& \quad \text{R}\_4 \cdot \text{(X)}\_n \\
\end{align*}
\]

[III]

or its reactive derivative at the carboxy group,
or its salt

Process 2

\[
\begin{align*}
\text{Elimination} \\
of \text{the amino} \\
\text{protective group in R}\_1 \\
\rightarrow \\
\end{align*}
\]

[Ia]

or its salt
Process 3

[Ib]
or its salt

[IV]
or its salt

[I]
or its salt
Process 4

Elimination of the carboxy protective group in \( R^6 \)

\[ \text{[Ic]} \]
or its salt

Process 5

Elimination of the hydroxy protective group of \( R^2 \)

\[ \text{[Ie]} \]
or its salt
[If]
or its salt

**Process 6**

Elimination of the amino protective group in $R^5$

[Ig]
or its salt

[Ih]
or its salt
Process 7

Elimination of the carboxy protective group in R₂

\[ \text{[Ii]} \]

or its salt

\[ \text{[Ij]} \]

or its salt

Process 8

\[ \text{[VI]} \]

or its salt
wherein

- $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $X^\circ$, and $n$ are each as defined above,
- $R_1^*$ is protected amino,
- $R_2^*$ is tetrahydropyranyl,
- $R_3^*$ is protected carboxy($C_1$-$C_6$)alkyl,
- $R_4^*$ is carboxy($C_1$-$C_6$)alkyl,
- $R_5^*$ is protected amino,
- $R_6^*$ is carboxy or protected carboxy,
- $R_7^*$ is protected carboxy,
- $R_8^*$ is COO$^\circ$ or carboxy,
- $Y$ is a leaving group,
- $Z$ is an acid residue.
In the above and subsequent descriptions of this specification, suitable examples of the various definitions are explained in detail as follows:

Suitable protective group in the protected amino group may include ar(C1-C6)alkyl such as mono or di or triphenyl(C6-C6)alkyl [e.g. benzyl, phenethyl, 1-phenylethyl, benzhydryl and trityl] and acyl as explained hereinafter.

Suitable acyl may be aliphatic acyl, aromatic acyl, arylaliphatic acyl and heterocyclic-aliphatic acyl derived from carboxylic acid, carbamic acid, carboxylic acid and sulfonic acid.

Suitable example of the acyl group thus explained may be (C1-C6)alkanoyl [e.g. formyl, acetyl, propionyl, hexanoyl and pivaloyl], mono(or di or tri)halo(C1-C6)alkanoyl [e.g. chloroacetyl and trifluoroacetyl], (C1-C6)alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, tert-pent-tyloxycarbonyl and hexyloxycarbonyl], mono(or di or tri)halo(C1-C6)alkoxycarbonyl [e.g. chloroethoxycarbonyl, dichloroethoxycarbonyl and trichloroethoxycarbonyl], acryl [e.g. benzoyl, tolouyl, xylolyl and naphthoyl], ar(C1-C6)alkanoyl such as phenyl(C1-C6)alkanoyl [e.g. phenylacetyl and phenylpropionyl], arylacarbonyl [e.g. phenoxyacarbonyl and naphthylacarbonyl], ariloxycarbonyl(C1-C6)alkanoyl such as phenoxy(C1-C6)-alkanoyl [e.g. phenoxyacetyl and phenoxypropionyl], arylethoxyl (e.g. phenylethoxyloxy) and naphthylethoxyl), ar(C1-C6)alkoxycarbonyl which may have suitable substituent(s) such as phenyl(C1-C6)-alkoxycarbonyl which may have nitro or (C1-C6)alkoxy [e.g. benzylcarbonyl, phenethylcarbonyl, p-nitrobenzylcarbonyl and p-methoxybenzylcarbonyl], thienylacetyl, imidazolylacetyl, furylacetyl, tetrazolylacetyl, thiazoylacetyl, thiazolylacetyl, thiopyrlacetyl, thiazolylpropionyl, thiazolylpropionyl, (C1-C6)alkylsulfonyl [e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, pentylsulfonyl and butylsulfonyl], arylsulfonyl [e.g. phenylsulfonyl, tolylsulfonyl, xylylsulfonyl and naphthylsulfonyl] and ar(C1-C6)alkylsulfonyl such as phenyl(C1-C6)alkylsulfonyl [e.g. benzylsulfonyl, phenethylsulfonyl and benzhydrylsulfonyl].

Preferable example of the protected amino group thus defined may be (C1-C6)alkylamino and (C1-C6)alkanoylamino, more preferable one may be triphenyl(C6-C6)alkylamino and (C1-C6)alkanoylamino, and the most preferable one may be trimethylamino and formamido.

Suitable "(C1-C6)alkyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl or hexyl, in which the preferred one may be (C1-C6)alkyl and the most preferred one may be methyl and isopropyl.

Suitable "cyclo(C2-C6)alkenyl" may be cyclopentenyl, cyclobutenyl, cyclooctenyl or cyclohexenyl, in which the preferred one may be cyclo(C2-C6)alkenyl, more preferred one may be cyclooctenyl and the most preferred one may be 2-cyclopenten-1-yl and 3-cyclopenten-1-yl.

Suitable "dihalogenated (C1-C6)alkyl" may be difluoromethyl, dichloromethyl, difluoroethyl, dichloroethyl, difluoropropyl, dichlorobutyl or difluorohexyl, in which the preferred one may be difluorocyclohexyl and the most preferred one may be difluoromethyl.

Suitable "thietanyl" may be 2- or 3-thietanyl.

Suitable "hydroxy(C1-C6)alkyl" may be hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl or hydroxyhexyl, in which the preferred one may be hydroxyethyl(C1-C6)alkyl and the most preferred one may be hydroxymethyl.

Suitable "(C1-C6)alkoxy" may be a straight or branched one such as methoxy, ethoxy, propoxy, isoproxy, butoxy, tert-butoxy, pentyloxy or hexyloxy, in which the preferred one may be (C1-C6)alkoxy and the most preferred one may be methoxy.

Suitable "protected carboxy" may be an esterified carboxy group, and concrete examples of the ester moiety in said esterified carboxy group may be the ones such as (C1-C6)alkyl ester [e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester and 1-cyclopropyl ester] which may have suitable substituent(s), for example, (C1-C6)alkanoyloxy(C1-C6)-alkyl ester [e.g. acetoxyethyl ester, propionyloxyethyl ester, butyroxyethyl ester, valeryloxyethyl ester, pivaloxyethyl ester, 1-acetoxyethyl ester, 1-propionyloxyethyl ester, 2-propionyloxyethyl ester and hexanoyloxyethyl ester], (C1-C6)alkanesulfonyl(C1-C6)alkyl ester [e.g. 2-mesyloxyethyl ester] or mono(or di or tri)halo(C1-C6)alkyl ester [e.g. 2-iodoethyl ester and 2,2,2-trichloroethyl ester]; (C1-C6)alkenyl ester [e.g. vinyl ester and allyl ester]; (C1-C6)alkynyl ester [e.g. ethynyl ester and propynyl ester]; ar(C1-C6)alkenyl ester which may have suitable substituent(s) [e.g. benzyl ester, 4-methoxyphenyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxymethyl) ester, 3,4-dimethoxybenzyl ester and 4-hydroxy-3,5-dimethylbenzyl ester]; aryl ester which may have suitable substituent(s) [e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, 4-tert-butylphenyl ester, xylol ester, mesityl ester and cumenyl ester]; in which the preferred one may be mono or di or triphenyl(C1-C6)-alkyl ester and the most preferred one may be benzhydryl ester.

Suitable "carboxy(C1-C6)alkyl" may be carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 1-carboxy-1-methylpropyl, 3-carboxypropyl, 2-carboxypropyl, 2-carboxymethylpropyl, 1-carboxybutyl, 2-carboxymethyl-2-
methylpropyl or 5-carboxyethyl, in which the preferred one may be carboxy(C1-C6)alkyl and the most preferred one may be carboxymethyl.

In the term "protected carboxy(C1-C6)alkyl!", suitable "protected carboxy" can be referred to the ones as exemplified before and the preferred "protected carboxy(C1-C6)alkyl!" may be esterified carboxy(C1-C6)-alkyl, in which more preferred one may be (C1-C6)alkoxyacarbonyl(C1-C6)alkyl such as methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-tert-butoxycarbonyl ethyl, 2-ethoxycarbonylbethylyl, 1-tert-butoxycarbonyl-1-methyl ethyl, 3-propropoxycarbonylbipropyl, 2-isopropoxycarbonylbipropyl, 2-isobutoxycarbonylbipropyl, 1-tert-butoxycarbonylbutoyl, 2-pentoylcarbonylbipropyl-2-methyl propyl or 5-hexyloxy carbonyl hexyl, and much more preferred one may be (C1-C6)alkoxy carbonyl(C1-C6)alkyl, the most preferred one may be tert-butoxycarbonylmethyl.

Suitable "a leaving group" may be halogen [e.g. chlorine, bromine and iodine], acyloxy such as sulfonlxylo [e.g. benzenesulfonyl oxy, tosylxy and mesylxy], or (C1-C6)alkanoyloxy [e.g. acetylxy and propionyloxy].

Suitable "anion" may be formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, chloride, bromide, iodide, sulfate or phosphate.

Suitable "an acid residue" may be halogen (e.g. fluorine, chlorine, bromine and iodine) or acyloxy as exemplified above.

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

In this respect, it is to be noted the compounds [ia], [ib], [ic], [id], [ie], [if], [ig], [ih], [ii], [i] and [ik] are included within the scope of the compounds [I], and accordingly the suitable salts of these compounds [ia] to [ik] are to be referred to those as exemplified for the object compounds [I] mentioned above.

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

Process 1

The object compound [I] and its salt can be prepared by reacting a compound [II] or its reactive derivative at the amino group or a salt thereof with a 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 carboxyl compound such as aldehyde or ketone; a silyl derivative formed by the reaction of the compound [II] with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide or bis(trimethylsilyl)urea; and a derivative formed by reaction of the compound [II] with phosphorus trichloride or phosgene.

Suitable salts of the compound [II] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

Suitable reactive derivative at the carboxy group of the compound [III] may include an acid halide, an acid anhydride, an activated amide and an activated ester.

Suitable examples of the reactive derivatives may be an acid chloride; an acid anhydride; a mixture of aldhyde chloride, methacryloyl chloride, benzyl cyanide and so on; an acid ester; an activated ester; a cyanomethyl ester, methoxymethyl ester, dimethylaminomethyl [(CH₃)₂N=CH-] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesitylphenyl ester, phenylaminophenyl ester, phenyl thiocarbamate, p-nitrophenyl thiocarbamate, dicyclohexylcarbodiimide, DMPU, and so on.

These methods can be used to prepare a compound [I] or a salt thereof.
yphthalimide and 1-hydroxy-1H-benzotriazole). These reactive derivatives can optionally be selected from them according to the kind of the compound [III] to be used.

Suitable salts of the compound [III] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol and ethanol], acetone, dioxane, acetoniitrile, 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-dimethylaminocyclohexyl)-carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide; N,N'-carboxybis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphénylketone-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; (C═C)alkyl haloformate [e.g. ethyl chloroformate and isopropyl chloroformate]; triphenylphosphine; 2-ethyl-7-hydroxybenzoxazolium salt; 2-ethyl-5-(m-sulfophenyl)benzoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzensulfonyloxy)-6-chloro-1H-benzotriazole; or so-called Wilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, methanesulfonyl chloride.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, alkali metal bicalcinate, tri(C═C)alkylamine, pyridine, N-(C═C)alkylmorpholine or N,N-di(C═C)alkybenzylamine.

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

Process 2

The object compound [Ib] and its salt can be prepared by subjecting a compound [Ia] or its salt to elimination reaction of the amino protective group in R₉.

This reaction is carried out in accordance with a conventional method such as hydrolysis or reduction.

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 and potassium], an alkaline earth metal [e.g. magnesium and calcium], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine and triethylamine], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane or 1,8-diazabicyclo[5.4.0]Undec-7-ene.

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

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol and ethanol], 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.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

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

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 and platinum wire], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium carbonate and palladium on barium carbonate], nickel catalysts [e.g. reduced nickel, nickel oxide and Raney nickel], cobalt catalysts [e.g. reduced cobalt and Raney cobalt], iron catalysts [e.g. reduced iron and Raney iron], or copper catalysts [e.g. reduced copper, Raney copper and Ullman copper].
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, or a mixture thereof.

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

The present invention includes within the scope of the invention the case that the group of the formula: \(-O-R^2\) (wherein \(R^2\) is tetrahydropyranyl or cyclo(C_5-C_6)alkeny1) is transformed into hydroxy during this reaction, the case that protected amino in \(R^3\) and/or \(R^2\) are transformed into amino, the case that protected carboxy in \(R^2\) is transformed into carboxy and the case that protected carboxy(C_1-C_6)alkyl in \(R^2\) is transformed into carboxy(C_1-C_6)alkyl.

Process 3

The object compound [I] and its salt can be prepared by reacting a compound [IV] or its salt with a compound [V] or its salt.

Suitable salts of the compounds [IV] can be referred to the ones as exemplified for the compound [I].

Suitable salts of the compounds [V] may be an organic acid salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate], or an inorganic acid salt [e.g. hydrochloride, hydrobromide, sulfate and phosphate].

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, 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, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound [V] is in liquid, it can also be used as a solvent. The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, or organic base such as trialkylamine. The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating. The present reaction is preferably carried out in the presence of alkali metal halide [e.g. sodium iodide and potassium iodide], alkali metal thiocyanate [e.g. sodium thiocyanate and potassium thiocyanate].

Anion \(X^-\) may be the one derived from a leaving group \(Y\) and may be the other one converted therefrom by a conventional method.

Process 4

The object compound [I] and its salt can be prepared by subjecting a compound [Ic] or its salt to elimination reaction of the carboxy protective group in \(R^2\).

This reaction can be carried out in a similar manner to that of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent and reaction temperature] of this reaction are to be referred to those as explained in Process 2.

The present invention includes within the scope of the invention the cases that protected amino in \(R^1\) and/or \(R^3\) and/or \(R^2\) and/or the group of the formula: \(-O-R^2\) (wherein \(R^2\) is tetrahydropyranyl or cyclo(C_5-C_6)alkeny1) and/or protected carboxy(C_1-C_6)alkyl in \(R^2\) are transformed into amino and/or hydroxy and/or carboxy(C_1-C_6)alkyl, respectively during this reaction.

Process 5

The object compound [I] and its salt can be prepared by subjecting a compound [Ie] or its salt to elimination reaction of tetrahydropyranyl of \(R^2\).

This reaction can be carried out in a similar manner to that of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent, reaction temperature] of this reaction are to be referred to those as explained in Process 2.

The present invention includes within the scope of the invention the cases that protected amino in \(R^1\) and/or \(R^3\) and/or \(R^5\) and/or protected carboxy(C_1-C_6)alkyl in \(R^2\), and/or protected carboxy in \(R^5\) are transformed into amino and/or carboxy(C_1-C_6)alkyl and/or carboxy, respectively during this reaction.
Process 6

The object compound [Ih] or its salt can be prepared by subjecting a compound [Ig] or its salt to elimination reaction of the amino protective group in R2.

This reaction can be carried out in a similar manner to that of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions (e.g. base, acid, catalyst, solvent and reaction temperature) of this reaction are to be referred to those as explained in Process 2.

The present invention includes within the scope of the invention the cases that protected amino in R1 and/or R4, and/or protected carboxy in R5, and/or protected carboxy(C1-C8)alkyl in R6, and/or the group of the formula: -O-R2 (wherein R2 is tetrahydropranyl or cyclo(C2-C8)alkenyl) are transformed into amino, and/or carboxy, and/or carboxy(lower)alkyl, and/or hydroxy, respectively during this reaction.

Process 7

The object compound [Ii] and its salt can be prepared by subjecting the compound [Ii] or its salt to elimination reaction of the carboxy protective group in R2.

This reaction can be carried out in a similar manner to that of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions (e.g. base, acid, catalyst, solvent and reaction temperature) of this reaction are to be referred to those as explained in Process 2.

The present invention includes within the scope of the invention the cases that protected amino in R1 is transformed into amino during this reaction.

Process 8

The compound [Ik] or its salt can be prepared by reacting the compound [VI] or its salt with the compound [VII].

Suitable salt of the compound [VI] may include the ones as exemplified for the compound [I].

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as ethyl acetate, methylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dioxane, water, acetic acid, formic acid, or a mixture thereof.

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

Process 9

The object compound [I] or its salt can be prepared by reducing a compound [VIII] or its salt.

Suitable salts of the compound [VIII] can be referred to the ones as exemplified for the compound [I].

The present reduction can be carried out by a conventional method which is applied for the transformation of

\[
\begin{align*}
O \\
\uparrow \\
-S-
\end{align*}
\]

into -S-, for example, by using phosphorus trichloride, a combination of stannous chloride and acetyl chloride, a combination of an alkali metal iodide [e.g. sodium iodide] and trihaloacetic anhydride [e.g. trifluoroacetic anhydride].

The present reduction is usually carried out in a solvent such as acetone, dioxane, acetonitrile, N,N-dimethylformamide, benzene, hexane, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling or at ambient temperature.

The anion of the compound [I] can be exchanged for another anion by a conventional method as described in Example mentioned later.

When the compound [I] obtained by the above Processes is in a form of salt, it can be transformed into its free form by a conventional method, e.g. reaction with a base or passing through a non-ionic adsorption resin.
Some of the starting compounds [II] and [III] used in Process 1, all the starting compound [VI] used in Process 8 and all the starting compound [VIII] in Process 9 are new and such new starting compounds can be represented by the following formulas.

or its salt

or its salt
or its salt

wherein
\[ R^1, R^2, R^3, R^4, R^5, X, n \text{ and } Z \] each as defined above,
\[ R^6 \text{ and } R^7 \] each hydrogen, \((C_1-C_6)\)alkyl, hydroxy\((C_1-C_6)\)alkyl, \((C_1-C_6)\)alkoxy, amino or protected amino, with proviso that
\[ R^8 \text{ and } R^9 \] not hydrogens at the same time,

with proviso that
(i) when \( R^2 \) is carboxy\((C_1-C_6)\)alkyl or protected
then \( R^8 \) is hydrogen and
\( R^9 \) is amino,
(ii) when \( R^6 \) is \( \text{COO}^\ominus \),
then \( n \) is 0, and
(iii) when \( R^5 \) is carboxy or protected carboxy,
then \( n \) is 1.

The new starting compounds [IIa], [IIla], [VI] and [VIII] can be prepared by the following methods.
Method for the preparation of Compound [IIa]

Method A

**Step 1**

![Chemical structure](image)

[X]

or its salt

[IX]

or its salt

![Chemical structure](image)

[XI]

or its salt
Step 2

\[
\text{Reduction} \quad \xrightarrow{\text{R}^7} \quad \text{[XI] or its salt}
\]

Step 3

\[
\text{Elimination of the amino protective group} \quad \xrightarrow{\text{R}^7} \quad \text{[XII] or its salt}
\]
[IIa]

or its salt
Method for the preparation of Compound [IIla]

Method B

\[
\begin{align*}
R^1 & \quad \text{or its salt} \\
\text{N} & \quad \text{or its salt}
\end{align*}
\]

Method for the preparation of Compound [VI]

Method C

Step 1

\[
\begin{align*}
\text{O} & \quad \text{or its salt} \\
\text{CH}_3\text{-C-C-R}^8 & \quad \text{or its salt}
\end{align*}
\]

[XIV]  [XV]
Step 2

\[
\text{Introduction of } R_d^2 \text{ group}
\]

[XV]

[XVI]

Step 3

\[
\text{Elimination of carbonyl protective group}
\]

[XVI']

[XVII]

Step 4

\[
\text{Elimination of carboxy protective group}
\]

[XVII']

[XVIII]
Step 5

\[
\begin{align*}
&\text{halogenation} \\
&\text{or its salt}
\end{align*}
\]

Step 6

\[
\begin{align*}
&\text{or its reactive derivative} \\
&\text{at the carboxy group, or its salt}
\end{align*}
\]

\[
\begin{align*}
&\text{or its reactive derivative} \\
&\text{at the amino group, or its salt}
\end{align*}
\]
Method for the preparation of Compound [VIII]

Method D
\((\text{C}_1-\text{C}_6)\text{alkyl}, \ \text{cyclo(C}_2-\text{C}_5)\text{alkenyl}, \ \text{thietanyl}, \ \text{carboxy(C}_1-\text{C}_6)\text{alkyl} \text{ or protected carboxy(C}_1-\text{C}_6)\text{alkyl}, \)

R\(^7\) is
protected amino,

R\(^8\) is
carboxy or protected carboxy,

R\(^9\) is
protected carboxy, and

Y\(_1\) and Y\(_2\) are
each a leaving group.

Methods A to D for the preparation of the starting compounds [IIa], [IIIa], [VI] and [VIII] are explained in detail in the following.

Method A

Step 1:

The object compound [XI] can be prepared by reacting a compound [IX] with a compound [X] or its salt.

Suitable salts of the compounds [IX] and [XI] can be referred to the ones as exemplified for the compound [I] and salt of the compound [X] can be referred to the acid addition salt for the compound [I].

This reaction can be carried out in a similar manner to that of Process 3 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. solvent and reaction temperature] of this reaction are to be referred to those as explained in Process 3.

The compound [XI] obtained by this step can be used for next step with or without isolation or purification.

Anion X\(^9\) may be the one derived from a leaving group Y\(_1\) and may be the other one converted therefrom by a conventional method.

Step 2:

The object compound [XII] can be prepared by reducing a compound [XI].

Suitable salt of the compound [XII] can be referred to the ones as exemplified for the compound [I].

The present reduction can be carried out by a conventional method which is applied for the transformation of

\[
\begin{array}{c}
\text{O} \\
\uparrow \\
-\text{S}^{-}
\end{array}
\]

into \(-\text{S}^{-}\), for example, by using phosphorus trichloride, a combination of stannous chloride and acetyl chloride, a combination of an alkali metal iodide [e.g. sodium iodide] and trihaloacetic anhydride [e.g. trifluoroacetic anhydride].

The present reduction is usually carried out in a solvent such as acetone, dioxane, acetonitrile, N,N-dimethylformamide, benzene, hexane, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling or at ambient temperature.

Step 3:

The object compound [IIa] and its salt can be prepared by subjecting a compound [XII] to elimination reaction of the amino protective group.

Suitable salts of the compounds [IIa] can be referred to the ones as exemplified for the compound [I].

This reaction can be carried out in a similar manner to that of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent and reaction temperature] of this reaction are to be referred to those as explained in Process 2.

The present invention includes within the scope of the invention the case that protected carboxy in R\(^6\) is transformed into carboxy during this reaction.
Method B

The object compound [IIIa] and its salt can be prepared by reacting a compound [XIII] or its salt with 3-cyclohexen-1-ylmethoxyamine or its salt.

Suitable salts of the compounds [IIIa] and [XIII] can be referred to the ones as exemplified for the compound [II].

Suitable salts of 3-cyclohexen-1-ylmethoxyamine can be referred to the acid addition salt as exemplified for the compound [I].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol and ethanol], dioxane, acetonitrile, tetrahydrofuran, methylene chloride, chloroform, ethyl acetate, N,N-dimethylformamide, or a mixture thereof 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 can be carried out in the presence of catalytic amount of a conventional acid or base as exemplified in Process 2.

Method C

Step 1

The object compound [XV] or its salt can be prepared by reacting the compound [XIV] or its salt with aniline or its salt.

Suitable salt of aniline can be referred to acid addition salt as exemplified for the compound [I].

This reaction is usually carried out in the presence of an acid such as acetic acid or p-toluene sulfonic acid.

This reaction is usually carried out in a solvent such as benzene, toluene or any other solvent which does not adverse the reaction.

The reaction temperature is not critical and this reaction is usually carried out under warming to heating.

Step 2

The object compound [XVI] or its salt can be prepared by subjecting the compound [XV] to introduction reaction of R₃ group.

Suitable salt of the compound [XVI] can be referred to salt with a base as exemplified for the compound [I].

Suitable introduction reaction of R₃ group may include substitution reaction with a compound of the formula : R₂-Y₂ (wherein R₂ is as defined above and Y₂ is a leaving group as exemplified before).

This substitution reaction can be carried out in a similar manner to that of Process 3 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. solvent and reaction temperature] of this reaction are to be referred to those as explained in Process 3.

In case that R₃ to be introduced is (C₁₋C₆)alkyl, di(C₁₋C₆)alkyl sulfate (e.g. dimethyl sulfate, diethyl sulfate), diazo(C₁₋C₆)alkane (e.g. diazomethane) and trihalo(C₁₋C₆)alkane (e.g. difluorochloromethane) can be used for this introduction reaction. This reaction can be carried out in a conventional manner.

Step 3

The object compound [XVII] or its salt can be prepared by subjecting the compound [XVI'] or its salt to elimination reaction of the carbonyl protective group.

Suitable salt of the compounds [XVI'] and [XVII] can be referred to salt with a base as exemplified for the compound [I].

The elimination reaction of this step may be hydrolysis and this hydrolysis can be carried out in a similar manner to that of Process 2.

The present invention includes within the scope of the invention the case that protected carboxy in R₈ is also transformed into carboxy during this reaction.
Step 4

The object compound [XVIII] or its salt can be prepared by subjecting the compound [XVII] or its salt to elimination reaction of carboxy protective group.

Suitable salt of the compound [XVII] can be referred to salt with a base as exemplified for the compound [I].

This reaction can be carried out in a similar manner to that of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent and reaction temperature] of this reaction are to be referred to those as explained in Process 2.

Sulfonyl halide [e.g. sulfonyl chloride] can be also used for this reaction. This reaction can be carried out in a conventional manner. In this case, halogenation in the next step may occur at the same time. The present invention includes this case within the scope of the invention.

Step 5

The object compound [XIX] or its salt can be prepared by subjecting the compound [XVIII] or its salt to halogenation reaction.

Suitable salt of the compound [XIX] can be referred to salt with a base as exemplified for the compound [I].

The halogenation reaction in this step may include a reaction with sulfonyl halide [e.g. sulfonyl chloride].

The reaction with sulfonyl halide is usually carried out in a solvent such as acetic acid, tetrachloromethane, methylene chloride or any other solvent which does not adverse the reaction.

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

Step 6

The object compound [VI] or its salt can be prepared by reacting the compound [II] or its reactive derivative at the amino group or its salt with the compound [XIX] or its reactive derivative at the carboxy group or its salt.

Suitable reactive derivative at the carboxy group of the compound [XIX] can be referred to the ones as exemplified for that of the compound [III] in Process 1.

This reaction can be carried out in a similar manner to that of Process 1 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent and reaction temperature] of this reaction are to be referred to those as explained in Process 1.

Method D

The object compound [VIII] or its salt can be prepared by reacting the compound [XX] or its salt with the compound [V] or its salt.

Suitable salts of the compounds [VIII] and [XX] can be referred to the ones as exemplified for the compound [I].

This reaction can be carried out in a similar manner to that of Process 3 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. solvent and reaction temperature] of this reaction are to be referred to those as explained in Process 3.

Anion X⁻ may be the one derived from a leaving group Y₂ and may be the other one converted therefrom by a conventional method.

The compounds [I], [Ilb], [Id], [II], [III], [IIIa], [IIIb], [IIIc], [IIIId], [VI], [XII], [XV], [XVI], [XVII], [XVIII], [XIX] and [VIII] obtained by the above Processes and Methods can be isolated and purified by a conventional manner such as pulverization, recrystallization, column chromatography or reprecipitation.

It is to be noted the compound [I] to [VI], [VIII] to [XIII] and [XVI] to [XX], [Ia] to [In], [IIa] and [IIia] may include one or more stereoisomers due to asymmetric carbon atoms and all of such isomers and a mixture thereof are included within the scope of this invention.

The object compounds [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.

Among the object compounds [I], the compound having the more potent antimicrobial activities can be represented by the following formula:
wherein

- $R^1$ is amino or protected amino,
- $R^2$ is hydrogen, tetrahydropyranyl, (C$_1$-C$_6$)alkyl, dihalogenated (C$_1$-C$_6$)alkyl, cyclo(C$_3$-C$_5$)-alkenyl or thietanyl,
- $R^3$ is (C$_1$-C$_6$)alkyl,
- $R^4$ and $R^5$ are each hydrogen, (C$_1$-C$_6$)alkyl, hydroxy(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxy, amino or protected amino,
- $R^6$ is COO$^-$, carboxy or protected carboxy
- $X^0$ is an anion, and
- $n$ is 0 or 1,

with proviso that

(i) when $R^6$ is COO$^-$, then $n$ is 0, and
(ii) when $R^6$ is carboxy or protected carboxy, then $n$ is 1,

and a pharmaceutically acceptable salt thereof, in which the more preferred one may be represented by the following formula:

wherein

- $R^2$ is (C$_1$-C$_6$)alkyl or dihalogenated (C$_1$-C$_6$)alkyl,
- $R^3$ is (C$_1$-C$_6$)alkyl,
- $R^4$ and $R^5$ are each hydrogen, (C$_1$-C$_6$)alkyl or amino,

and a pharmaceutically acceptable salt thereof, the much more preferred one may be the compound [Im]

wherein

- $R^2$ is dihalogenated (C$_1$-C$_6$)alkyl,
- $R^3$ is as defined above, and
- $R^4$ and $R^5$ are each hydrogen,

and a pharmaceutically acceptable salt thereof, or the compound [Im]

wherein

- $R^2$ and $R^3$ are each as defined above,
- $R^4$ is (C$_1$-C$_6$)alkyl and
- $R^5$ is amino,

and a pharmaceutically acceptable salt thereof.

Now in order to show the utility of the object compounds [I], the test data on MIC (minimal inhibitory concentration) of representative compounds [I] 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 (10^6 viable cells per ml) was streaked on heart infusion agar (H-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 compounds:

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)-acetamid]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) (hereinafter referred to as Compound A).
7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamid]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) (hereinafter referred to as Compound B).
7β-[2-(2-Aminothiazol-4-yl)-2-(methoxyiminoacetamid)-3-(3-amino-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) (hereinafter referred to as Compound C).
7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)-acetamid]-3-(3-amino-2,4-dimethyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer) (hereinafter referred to as Compound D).

Test results:

<table>
<thead>
<tr>
<th>Test strains</th>
<th>MIC (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>E. coli 31</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>P. mirabilis 1</td>
<td>0.05</td>
</tr>
<tr>
<td>P. vulgaris IAM1025</td>
<td>0.05</td>
</tr>
</tbody>
</table>

For therapeutic administration, the object compounds [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 and lemonade.

If 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 and ethylene glycol.

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. 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, 2000 mg of the object compounds [I] of the present invention may be used in treating diseases infected by pathogenic microorganisms.

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

Preparation 1

A mixture of benzhydryl 7β-tert-butoxycarbonylamino-2-(3-iodomethyl-3-cephem-4-carboxylate 1-oxide (18.5 g) and N-methylpyrazole (37 ml) was stirred at ambient temperature for 15 hours. After the reaction mixture was added to diisopropyl ether (500 ml), the precipitates were collected by filtration, and washed with diisopropyl ether to give benzhydryl 7β-tert-butoxycarbonylamino-2-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate 1-oxide iodide (20.3 g).

IR (Nujol): 3400, 1800, 1729, 1630, 1500 cm⁻¹
NMR (DMSO-d$_6$, $\delta$) : 1.45 (7H, s), 3.72, 4.05 (2H, ABq, $J$ = 18Hz), 3.87 (3H, s), 5.10 (1H, d, $J$ = 5Hz), 5.32, 5.55 (2H, ABq, $J$ = 14Hz), 5.90 (1H, dd, $J$ = 5Hz, 8Hz), 6.52 (1H, d, $J$ = 8Hz), 6.90 (1H, t, $J$ = 3Hz), 7.00 (1H, s), 7.42 (10H, m), 8.33 (1H, d, $J$ = 3Hz), 8.53 (1H, d, $J$ = 3Hz)

Preparation 2

Benzhydryl 7β-tert-butoxycarbonylamino-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate 1-oxide iodide was obtained according to a similar manner to that of Preparation 1.

IR (Nujol) : 1795, 1715, 1630 cm$^{-1}$

NMR (DMSO-d$_6$, $\delta$) : 1.43 (9H, s), 2.41 (3H, s), 3.58, 3.97 (2H, ABq, $J$ = 18Hz), 3.69 (3H, s), 5.06 (1H, d, $J$ = 5Hz), 5.38 (2H, br. s), 5.86 (1H, dd, $J$ = 8Hz, 5Hz), 6.47 (1H, d, $J$ = 8Hz), 6.71 (1H, d, $J$ = 3Hz), 6.93 (1H, s), 7.15-7.60 (10H, m), 8.15 (1H, d, $J$ = 3Hz)

Preparation 3

To a solution of benzhydryl 7β-tert-butoxycarbonylamino-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate 1-oxide iodide (20 g) and N,N-dimethylformamide (100 ml) was stirred at -35°C. Phosphorus trichloride (7.8 g) was added thereto and stirred for 10 minutes at the same temperature. The reaction mixture was added to water (600 ml). The precipitates were collected by filtration and washed with water to give benzhydryl 7β-tert-butoxycarbonylamino-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate iodide (15.4 g).

IR (Nujol) : 3300, 1780, 1710, 1500 cm$^{-1}$

NMR (DMSO-d$_6$, $\delta$) : 1.48 (9H, s), 3.60 (2H, br. s), 3.87 (3H, s), 5.20 (1H, d, $J$ = 5Hz), 5.53 (2H, br. s), 5.63 (1H, dd, $J$ = 5Hz, 8Hz), 6.87 (1H, t, $J$ = 3Hz), 6.97 (1H, s), 7.43 (10H, m), 7.92 (1H, d, $J$ = 8Hz), 8.45 (1H, d, $J$ = 3Hz), 8.55 (1H, d, $J$ = 3Hz)

Preparation 4

Benzhydryl 7β-tert-butoxycarbonylamino-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate iodide was obtained according to a similar manner to that of Preparation 3.

IR (Nujol) : 3300, 1780, 1710, 1610 cm$^{-1}$

NMR (DMSO-d$_6$, $\delta$) : 1.44 (9H, s), 2.44 (3H, s), 3.43 (2H, br. s), 3.71 (3H, s), 5.18 (1H, d, $J$ = 5Hz), 5.48 (2H, br. s), 5.63 (1H, dd, $J$ = 8Hz, 5Hz), 6.74 (1H, d, $J$ = 3Hz), 6.94 (1H, s), 7.10-7.60 (10H, m), 7.97 (1H, d, $J$ = 8Hz), 8.30 (1H, d, $J$ = 3Hz)

Preparation 5

To a solution of benzhydryl 7β-tert-butoxycarbonylamino-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate iodide (22.3 g) and anisole (22 ml) in methylene chloride (66 ml) was added trifluoroacetic acid (44 ml) under ice-cooling. After the mixture was stirred at ambient temperature for an hour, the reaction mixture was added dropwise to diisopropyl ether (600 ml). The resultant precipitates were collected by filtration to give bis(trifluoroacetic acid) salts of 7β-amino-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (16.83 g).

IR (Nujol) : 1770 cm$^{-1}$

NMR (DMSO-d$_6$, $\delta$) : 3.50 (2H, br. s), 4.11 (3H, s), 5.26 (2H, s), 5.60 (2H, br.s), 6.94 (1H, t, $J$ = 3Hz), 8.48 (1H, d, $J$ = 3Hz), 8.62 (1H, d, $J$ = 3Hz)

Preparation 6

Bis(trifluoroacetic acid) salts of 7β-amino-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate was obtained according to a similar manner to that of Preparation 5.

IR (Nujol) : 1775, 1670, 1620 cm$^{-1}$

NMR (DMSO-d$_6$, $\delta$) : 2.49 (3H, s), 3.49 (2H, br. s), 3.92 (3H, s), 5.28 (2H, br. s), 5.58 (2H, br. s), 6.79 (1H, d, $J$ = 3Hz), 8.38 (1H, d, $J$ = 3Hz)
Preparation 7

To a solution of sodium iodide (1.46 g) in acetone (5 ml) was added benzhydryl 7β-terbutoxycarbonylamino-3-chloromethyl-3-cephem-4-carboxylate (5 g) at ambient temperature. The mixture was stirred at the same temperature for 10 minutes and N-methylpyrazole (5 ml) was added thereto. The resultant mixture was stirred at the same temperature for 24 hours and poured into a mixture of tetrahydrofuran (25 ml), ethyl acetate (25 ml) and water (25 ml). The separated organic layer was washed with brine, and dried over magnesium sulfate. The solution was evaporated in vacuo to give benzhydryl 7β-terbutoxy carbonylamino-3-(2-methyl-1-pyrazol)imethyl-3-cephem-4-carboxylate iodide (6.45 g), the physical data of which were identical to those of the compound prepared in Preparation 3.

Preparation 8

Benzhydryl 7β-(2-hydroxybenzylideneamino)-3-(2-methyl-1-pyrazol)imethyl-3-cephem-4-carboxylate iodide was obtained according to a similar manner to that of Preparation 7.

IR (Nujol): 1780, 1720, 1620 cm⁻¹

NMR (DMSO-d₆, δ) : 3.45 (2H, br. s), 3.88 (3H, s), 5.12 (1H, d, J = 5Hz), 5.40 (2H, br. s), 5.85 (1H, d, J = 5Hz), 6.83 (1H, t, J = 3Hz), 6.94 (1H, s), 7.12-7.66 (14H, m), 8.37 (1H, d, J = 3Hz), 8.43 (1H, d, J = 3Hz), 8.81 (1H, s)

Preparation 9

To a solution of benzhydryl 7β-(2-hydroxybenzylideneamino)-3-(2-methyl-1-pyrazol)imethyl-3-cephem-4-carboxylate iodide (1 g) in tetrahydrofuran (20 ml) and ethanol (3 ml) was added conc. hydrochloric acid (0.14 ml) at ambient temperature. After stirring at the same temperature for 1 hour, the mixture was poured into tetrahydrofuran (20 ml). The resulting precipitates were collected by filtration to give hydrochloric acid salt of benzhydryl 7β-amino-3-(2-methyl-1-pyrazol)imethyl-3-cephem-4-carboxylate iodide (0.65 g).

IR (Nujol): 1785, 1720 cm⁻¹

NMR (DMSO-d₆, δ) : 3.47 and 3.83 (2H, ABq, J = 18Hz), 3.91 (3H, s), 5.31 (1H, d, J = 5Hz), 5.39 (1H, d, J = 5Hz), 5.66 (2H, br. s), 6.87 (1H, t, J = 3Hz), 6.96 (1H, s), 7.10-7.57 (10H, m), 8.65 (2H, d, J = 3Hz)

Preparation 10

A mixture of benzhydryl 7β-[2-(2-cyclopenten-1-yloxyiminio)-2-(2-formamidothiazol-4-yl)acetamido]-3-iodomethyl-3-cephem-4-carboxylate 1-oxide (syn isomer, 7 g) and N-methylpyrazole (17.5 ml) was stirred at ambient temperature for 4.5 hours. The reaction mixture was poured into ethyl acetate (500 ml). Precipitates were collected by filtration, washed with ethyl acetate and diisopropyl ether to give benzhydryl 7β-[2-(2-cyclopenten-1-yloxyiminio)-2-(2-formamidothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazol)imethyl-3-cephem-4-carboxylate 1-oxide iodide (syn isomer, 5.4 g).

IR (Nujol): 3300, 1800, 1720, 1670, 1540 cm⁻¹

NMR (DMSO-d₆, δ) : 2.15 (2H, m), 2.33 (2H, m), 3.53, 3.80 (2H, ABq, J = 18Hz), 3.87 (3H, s), 5.15 (1H, d, J = 5Hz), 5.40 (3H, m), 6.10 (2H, m), 6.90 (1H, t, J = 2Hz), 7.00 (1H, s), 7.10-7.60 (10H, m), 7.48 (1H, s), 8.35 (1H, d, J = 2Hz), 8.54 (1H, s), 8.54 (1H, m), 9.15 (1H, d, J = 8Hz)

Preparation 11

To a solution of 3-cyclopenten-1-ol (15.3 g), N-hydroxyphthalimide (29.7 g) and triphenylphosphine (47.7 g) in tetrahydrofuran (250 ml) was added diethyl azodicarboxylate (31.7 g) at 40 to 50 °C. After stirring at 45 °C for 2 hours, the reaction mixture was poured into ice-water and extracted with ethyl acetate. The separated organic layer was washed with 5% aqueous solution of sodium bicarbonate, brine, successively and dried over magnesium sulfate. The solvent was evaporated in vacuo, and the residual oil was subjected to column chromatography on silica gel. The desired product was eluted with 15% ethyl acetate in n-hexane to give N-(3-cyclopenten-1-yloxy)phthalimide (25.6 g).

IR (Nujol): 1790, 1730 cm⁻¹

NMR (CDCl₃, δ) : 2.8-2.9 (4H, m), 5.30 (1H, m), 5.80 (2H, s), 7.85 (4H, m)
Preparation 12

A mixture of N-(3-cyclopenten-1-yloxy)phthalimide (5.0 g) and hydrazine hydrate (1.32 g), methanol (10 ml) and methylene chloride (50 ml) was stirred at ambient temperature for 30 minutes. The precipitates were filtered off, and the filtrate was washed with water. The separated organic layer was concentrated under reduced pressure. To the residue were added 2-(2-formamidothiazol-4-yl)glyoxylic acid (3.50 g), pyridine (3.5 ml), water (35 ml) and tetrahydrofuran (15 ml). After stirring at ambient temperature for 1 hour, the mixture was poured into water (100 ml) and adjusted to pH 8.0 with 5% aqueous solution of sodium bicarbonate. The aqueous layer was washed with ethyl acetate twice, acidified to pH 2.0 with 10% hydrochloric acid and extracted with ethyl acetate. The separated organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure to give 2-(3-cyclopenten-1-yloxyimino)-2-(2-formamidothiazol-4-yl)acetic acid (syn isomer, 4.65 g).

mp : 160-161 °C
IR (Nujol) : 3200, 1710, 1545 cm⁻¹
NMR (DMSO-d₆, δ) : 2.4-2.8 (4H, m), 5.0 (1H, m), 5.77 (2H, s), 7.54 (1H, s), 8.57 (1H, s), 12.5 (br. s)

Preparation 13

A mixture of 2-(2-trityliminothiazol-4-yi)-2-difluoromethoxyiminoacetamide (syn isomer) (2.4 g) and diisopropylethylamine (1.29 g) in N,N-dimethylformamide (35 ml) was cooled to -30 °C and mesyl chloride (1.15 g) was added dropwise thereto. The mixture was stirred at -20 to -30 °C for 30 minutes to give an activated acid solution. On the other hand, a mixture of benzhydryl 7β-amino-3-chloromethyl-3-cephem-4-carboxylate (2.18 g) and N-trimethylsilylaceticamide (5.25 g) in methylene chloride (20 ml) was stirred to be a clear solution for 30 minutes at room temperature and then cooled to -20 °C. To this solution was added the activated acid solution obtained above in one portion. The mixture was stirred for 30 minutes at -15 to -10 °C, poured into water and extracted with ethyl acetate. The extract was washed with water three times, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated in diisopropyl ether to give benzhydryl 7β-[2-(2-trityliminothiazol-4-yl)-2-difluoromethoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylate (syn isomer) (4.64 g).

IR (Nujol) : 1780, 1720, 1670, 1590, 1520 cm⁻¹

Preparation 14

A mixture of acetic anhydride (38.86 ml) and formic acid (15.54 ml) was stirred at 45 °C for 45 minutes. To this mixture was added 5-amino-1-methylpyrazole (10 g) under ice-cooling, and the reaction mixture was stirred at the same temperature for 10 minutes. The resultant mixture was poured into a mixture of water and ethyl acetate, and the resultant solution was adjusted to pH 8 with potassium carbonate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate six times. The organic layers were combined, dried over magnesium sulfate, and evaporated in vacuo to give 5-formamido-1-methylpyrazole (12.88 g).

mp : 71-73 °C
IR (Nujol) : 3300, 3200, 1705, 1590 cm⁻¹
NMR (CDCl₃, δ) : 3.69 and 3.74 (3H, each s), 6.04 and 6.23 (1H, each d, J = 3Hz), 7.34 (1H, s), 8.21 (1H, s)

Preparation 15

The following compounds were obtained according to a similar manner to that of Preparation 14.

1) 4-Formamido-1-methylpyrazole

mp : 44-45 °C
IR (Nujol) : 3250, 1665, 1585 cm⁻¹
NMR (CDCl₃, δ) : 3.83 (3H, s), 7.33 (1H, s), 7.83 (1H, s), 8.17 (1H, s)

2) 5-Formamido-1,4-dimethylpyrazole

IR (Nujol) : 3200, 1665, 1585 cm⁻¹
NMR (CDCl₃, δ) : 1.90 and 1.98 (3H, each s), 3.64 and 3.72 (3H, each s), 7.29 and 7.31 (1H, each s), 8.10 (1H, broad s), 8.33 and 9.03 (1H, each s)
Preparation 16

To a mixture of benzhydryl 7β-tert-butoxycarbonylamino-3-chloromethyl-3-cephem-4-carboxylate (15 g) and sodium iodide (4.37 g) in acetone (15 ml) was added 5-formamido 1-methylpyrazole (15 g) at ambient temperature. After being stirred for 40 hours at the same temperature, the mixture was poured into a mixture of water and ethyl acetate. The organic layer was separated and washed with water, aqueous sodium chloride solution, and dried over magnesium sulfate. The solution was evaporated in vacuo to give benzhydryl 7β-tert-butoxycarbonylamino-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate iodide (20.95 g).

IR (Nujol): 1780, 1710, 1580 cm⁻¹
NMR (DMSO-d₆, δ): 1.40 (9H, s), 3.41 (2H, broad s), 3.65 (3H, s), 5.12 (1H, d, J = 5Hz), 5.36 (2H, broad s), 5.57 (1H, dd, J = 8Hz and 5Hz), 6.88 (1H, s), 6.89 (1H, m), 7.10-7.48 (10H, m), 7.83 (1H, d, J = 8Hz), 8.24 (1H, d, J = 3Hz), 8.45 (1H, s)

Preparation 17

The following compounds were obtained according to a similar manner to that of Preparation 16.

1. Benzhydryl 7β-tert-butoxycarbonylamino-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate iodide
   IR (Nujol): 1785, 1720, 1605 cm⁻¹
   NMR (DMSO-d₆, δ): 1.39 (9H, s), 3.42 (2H, broad s), 3.77 (3H, s), 5.11 (1H, d, J = 5Hz), 5.41 (2H, broad s), 5.60 (1H, dd, J = 8Hz and 5Hz), 6.89 (1H, s), 7.18-7.52 (10H, m), 7.96 (1H, d, J = 8Hz), 8.25 (1H, s), 8.51 (1H, s), 8.57 (1H, s)

2. Benzhydryl 7β-tert-butoxycarbonylamino-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate iodide
   IR (Nujol): 3300, 1780, 1705 cm⁻¹
   NMR (DMSO-d₆, δ): 1.42 (9H, s), 1.98 (3H, s), 3.45 (2H, broad s), 3.63 (3H, s), 5.19 (1H, d, J = 5Hz), 5.40 (2H, broad s), 5.61 (1H, dd, J = 5Hz and 8Hz), 6.95 (1H, s), 7.21-7.58 (10H, m), 8.00 (1H, d, J = 8Hz), 8.21 (1H, s), 8.43 (1H, s)

Preparation 18

To a solution of benzhydryl 7β-tert-butoxycarbonylamino-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate iodide (20.9 g) and anisole (20 ml) in methylene chloride (40 ml) was added dropwise trifluoroacetic acid (40 ml) under ice-cooling. After being stirred for 1.5 hours at ambient temperature, the mixture was poured into a mixture of diisopropyl ether (300 ml) and ethyl acetate (300 ml). The resultant precipitate was collected by filtration to give bis(trifluoroacetic acid) salts of 7β-amino-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-ccephem-4-carboxylate (16.20 g).

IR (Nujol): 3350, 1770, 1600 cm⁻¹
NMR (DMSO-d₆, δ): 3.45 (2H, s), 3.87 (3H, s), 5.18 (2H, s), 5.47 (2H, s), 6.95 (1H, d, J = 3Hz), 8.33 (1H, d, J = 3Hz), 8.47 (1H, s)

Preparation 19

The following compounds were obtained according to a similar manner to that of Preparation 18.

1. Bis(trifluoroacetic acid)salts of 7β-amino-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-ccephem-4-carboxylate.
   IR (Nujol): 3400, 1780, 1660, 1605 cm⁻¹
   NMR (DMSO-d₆, δ): 3.51 (2H, broad s), 4.06 (3H, s), 5.23 (2H, s), 5.55 (2H, broad s), 8.30 (1H, s), 8.61 (1H, s), 8.67 (1H, s)

2. Bis(trifluoroacetic acid)salts of 7β-amino-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-ccephem-4-carboxylate
   NMR (DMSO-d₆, δ): 2.01 (3H, s), 3.48 (2H, broad s), 3.83 (3H, s), 5.24 (2H, s), 5.50 (2H, broad s), 8.26 (1H, s), 8.41 (1H, s)

32
Preparation 20

Conc. hydrochloric acid (4.09 g) was added to a solution of benzhydryl 7β-tert-butoxycarbonylamino-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate iodide (27 g) in formic acid (108 ml), and stirred at ambient temperature for 2.5 hours. The reaction mixture was added to a mixture of acetone (720 ml) and ethyl acetate (1440 ml). The precipitates were collected by filtration and successively washed with ethyl acetate to give 7β-amino-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate hydrochloride hydroiodide (15.3 g).

IR (Nujol): 3350, 3100, 1780, 1710, 1620 cm⁻¹

NMR (D₂O-NaHCO₃, δ): 3.42 and 3.56 (2H, ABq, J = 18Hz), 4.10 (3H, s), 5.02 (1H, d, J = 5Hz), 5.22 (1H, d, J = 5Hz), 5.27 and 5.52 (2H, ABq, J = 14Hz), 6.80 (1H, t, J = 3Hz), 8.23 (2H, d, J = 3Hz)

Preparation 21

A mixture of 7β-amino-3-(2-methyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate hydrochloride hydroiodide (10 g) in water (70 ml) and acetone (130 ml) was stirred at 0-5 °C for 1.5 hours. The precipitates crystallized out of the solution were collected by filtration, washed with a mixture of acetone (24 ml) and water (6 ml) and then acetone to give 7β-amino-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate hydrochloride tetrahydrate (6.6 g).

IR (Nujol): 3350, 3100, 1800, 1780 (s), 1600, 1510 cm⁻¹

NMR (D₂O, δ): 3.33 and 3.60 (2H ABq, J = 18Hz), 4.11 (3H, s), 5.18 (1H, d, J = 5Hz), 5.32 (1H, d, J = 5Hz), 5.32 and 5.53 (2H, ABq, J = 14Hz), 6.80 (1H, t, J = 3Hz), 8.23 (2H, d, J = 3Hz)

Preparation 22

Concentrated hydrochloric acid (0.353 ml) was added to a mixture of bis(trifluoroacetic acid) salt of 7β-amino-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (0.565 g) in tetrahydrofuran (3 ml) and methanol (3 ml) at ambient temperature. After being stirred at the same temperature for 12 hours, the mixture was added dropwise to ethyl acetate (100 ml). The resulting precipitate was collected by filtration to give 7β-amino-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trihydrochloride (292 mg).

NMR (DMSO-d₆, δ): 3.31 and 3.56 (2H, ABq, J = 18Hz), 3.67 (3H, s), 5.20 (2H, broad s), 5.29 (2H, broad s), 5.87 (1H, d, J = 3Hz), 8.12 (1H, d, J = 3Hz)

Preparation 23

A solution of tert-butyl 2-hydroxyimino-3-oxobutyrate (130 g), aniline (76 ml) and acetic acid (14 ml) in benzene (1.2 l) was refluxed with Dean Stark water separator for 5 hours. The resulting solution was cooled and washed with 5% aqueous sodium bicarbonate solution and water. After being dried over magnesium sulfate, the organic solvent was evaporated in vacuo. The residue was triturated with a mixture of n-hexane (300 ml) and disopropyl ether (100 ml). The precipitate was collected by filtration, washed with n-hexane to give tert-butyl 2-hydroxyimino-3-phenylaminobutyrate (71.2 g).

IR (Nujol): 3380, 1722, 1625 cm⁻¹

NMR (CDCl₃, δ): 1.50 (9H, s), 2.12 (3H, s), 6.5-7.3 (5H, m)

Preparation 24

Ethyl 2-hydroxyimino-3-phenylaminobutyrate was prepared according to a similar manner to that of Preparation 23.

IR (film): 3550, 1735, 1639, 1598 cm⁻¹

Preparation 25

Into a solution of tert-butyl 2-hydroxyimino-3-phenylaminobutyrate (2.0 g) in a mixture of 1,4-dioxane (50 ml) and ethanol (10 ml) was bubbled difluorochloromethane under ice-cooling with stirring until the solution was saturated with the gas. To the mixture was added dropwise 4N sodium hydroxide solution (19 ml) at 15 °C with gentle bubbling of difluorochloromethane. After the addition, the mixture was stirred under the same condition for 2 hours. The resulting mixture was neutralized to pH 7.0 with 6N hydrochloric acid and
extracted with ethyl acetate. The separated organic layer was washed with 5% aqueous sodium chloride solution three times, dried over magnesium sulfate and concentrated under reduced pressure to give an oil (2.03 g). The residual oil was subjected to column chromatography on silica gel (20 g) and eluted with a mixture of n-hexane and diethyl ether (15:1) to give tert-butyl 2-difluoromethoxyimino-3-phenyliminobutyrate (0.80 g).

IR (Film) : 1740, 1639, 1598 cm⁻¹
NMR (CDCl₃, δ) : 1.50 (9H, s), 2.10 (3H, s), 6.60 (1H, t, J = 7Hz), 6.7-7.3 (5H, m)

Preparation 26

Ethyl 2-difluoromethoxyimino-3-phenyliminobutyrate was prepared according to a similar manner to that of Preparation 25.
IR (Nujol) : 1755, 1640, 1598 cm⁻¹
NMR (CDCl₃, δ) : 1.35 (3H, t, J = 7Hz), 2.08 (3H, s), 4.33 (2H, q, J = 7Hz), 6.62 (1H, t, J = 7Hz), 6.6-7.5 (5H, m)

Preparation 27

(1) To a solution of tert-butyl 2-difluoromethoxyimino-3-phenyliminobutyrate (0.76 g) in tetrahydrofuran (3.8 ml) was added 1N hydrochloric acid (3.64 ml) under ice-cooling. After being stirred at 20 °C for 1.5 hours, the mixture was extracted with ethyl acetate. The separated organic layer was washed with water three times, dried over magnesium sulfate and concentrated under reduced pressure to give tert-butyl 2-difluoromethoxyimino-3-oxobutyrate (0.55 g).
IR (film) : 1750, 1715 cm⁻¹
NMR (CDCl₃, δ) : 1.40 (9H, s), 2.39 (3H, s), 6.57 (1H, t, J = 7Hz)

(2) To a solution of tert-butyl 2-difluoromethoxyimino-3-oxobutyrate (5.0 g) in acetic acid (5 ml) was added sulfuryl chloride (8.5 ml). The mixture was stirred at 60-63 °C for 7 hours. The solvent was evaporated in vacuo to give 4-chloro-2-difluoromethoxyimino-3-oxobutyric acid (4.5 g) as a glassy mass.
IR (film) : 1710-1750 (broad) cm⁻¹
NMR (CDCl₃, δ) : 4.63 (2H, s), 6.73 (1H, t, J = 7Hz)

Preparation 28

Ethyl 2-difluoromethoxyimino-3-oxobutyrate was prepared according to a similar manner to that of Preparation 27 (1).
IR (film) : 1755, 1715 cm⁻¹
NMR (CDCl₃, δ) : 1.38 (3H, t, J = 7Hz), 2.43 (3H, s), 4.36 (2H, q, J = 7Hz), 6.65 (1H, t, J = 7Hz)

Preparation 29

To a solution of tert-butyl 2-difluoromethoxyimino-3-oxobutyrate (9.4 g) in acetic acid (9.4 ml) was added sulfuryl chloride (2.55 ml) under ice-cooling. After stirred at ambient temperature for an hour, the reaction mixture was concentrated under reduced pressure. The residual oil was dissolved in ethyl acetate. The ethyl acetate solution was washed with water, dried over magnesium sulfate, and evaporated in vacuo. The residue was crystallized with diisopropyl ether to give (Z)-2-difluoromethoxyimino-3-oxobutyric acid (4.73 g).
mp : 118-120 °C
IR (Nujol) : 2860, 1730, 1710 cm⁻¹
NMR (CDCl₃ + DMSO-d₆, δ) : 2.45 (3H, s), 6.42 (1H, t, J = 70.4Hz)

Preparation 30

To a solution of tert-butyl 2-hydroxyimino-3-phenyliminobutyrate (1.0 g) in acetone (10 ml) was added potassium carbonate (0.63 g) and dimethyl sulfate (0.43 ml) under ice-cooling. The mixture was stirred at the same temperature for 30 minutes and stirred at ambient temperature for 4 hours. The resulting suspension was poured into ice-water and extracted with diisopropyl ether. The organic layer was washed with water, dried over magnesium sulfate, and evaporated in vacuo. The residual oil was subjected to column chromatography on silica gel to give tert-butyl 2-methoxyimino-3-phenyliminobutyrate (0.88 g).
Example 1

Vilsmeier reagent was prepared from N,N-dimethylformamide (0.36 ml) and phosphoryl chloride (0.42 ml) in a usual manner. Vilsmeier reagent was suspended in ethyl acetate (7.5 ml), and 2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetic acid (syn isomer, 0.88 g) was added thereto under ice-cooling. The mixture was stirred at the same temperature for 30 minutes to produce an activated acid solution. A solution of bis(trifluoroacetic acid) salts of 7β-amino-3-(2-methyl-1-pyrazolio)methyl-3-cephe-4-carboxylate (2 g) and N,O-bis(trimethylsilyl)acetamide (3.79 ml) in tetrahydrofuran (20 ml) was added to the above activated acid solution at -30 °C, and the reaction mixture was stirred at -20 to -10 °C for 30 minutes. The mixture was added dropwise to diethyl ether (300 ml), and the precipitates were collected by filtration to give trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephe-4-carboxylate (syn isomer, 2.25 g).

IR (Nujol) : 1785, 1675 cm⁻¹
NMR (DMSO-d₆, δ) : 3.42 (2H, br. s), 3.89 (3H, s), 4.10 (3H, s), 5.23 (1H, d, J = 5Hz), 5.56 (2H, br. s), 5.89 (1H, dd, J = 8, 5Hz), 8.93 (1H, t, J = 3Hz), 7.41 (1H, s), 8.49 (1H, d, J = 3Hz), 8.52 (1H, s), 8.60 (1H, d, J = 3Hz), 9.70 (1H, d, J = 8Hz)

Example 2

Methanesulfonyle chloride (0.61 ml) was added to a solution of 2-[(2-aminothiazol-4-yl)-2-(3-thiantholoxyiminino)acetic acid (syn isomer, 0.99 g) and N,N-diisopropyl-N-ethylamine (1.33 ml) in N,N-dimethylformamide (20 ml) at -55 to -50 °C, and the mixture was stirred for 10 minutes to produce an activated acid solution. To a solution of bis(trifluoroacetic acid) salts of 7β-amino-3-(2-methyl-1-pyrazolio)methyl-3-cephe-4-carboxylate (2 g) and N,O-bis(trimethylsilyl)acetamide (3.79 ml) in tetrahydrofuran (20 ml) was added the above activated acid solution under ice-cooling, and the reaction mixture was stirred at the same temperature for an hour. The resultant mixture was poured into diethyl ether, and the precipitates were collected by filtration. The precipitates were suspended in water (20 ml), and the suspension was adjusted to pH 5 with 5% aqueous solution of sodium bicarbonate and subjected to column chromatography on macroporous non-ionic adsorption resin "Diaion HP-20" (Trademark, manufactured by Mitsubishi Chemical Industries) and eluted with 10% aqueous solution of isopropyl alcohol. The fractions containing the object compound were collected, evaporated in vacuo to remove isopropyl alcohol, and lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-(3-thiantholoxyiminino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephe-4-carboxylate (syn isomer, 0.5 g).

IR (Nujol) : 1770, 1660, 1605 cm⁻¹
NMR (D₂O, δ) : 3.2-3.8 (4H, m), 3.22, 3.63 (2H, ABq, J = 18Hz), 4.13 (3H, s), 5.10-5.32 (1H, m), 5.20, 5.54 (2H, ABq, J = 15Hz), 5.34 (1H, d, J = 5Hz), 5.89 (1H, d, J = 5Hz), 6.76-6.83 (1H, m), 7.03 (1H, s), 8.16-8.23 (2H, m)

The following compounds (Examples 3 to 18) were obtained according to similar manners to those of Examples 1 and 2.

Example 3

Trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-isopropoxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephe-4-carboxylate (syn isomer)

IR (Nujol) : 3400, 1770, 1650 cm⁻¹
NMR (DMSO-d₆, δ) : 1.28 (6H, d, J = 6Hz), 3.28, 3.63 (2H, ABq, J = 18Hz), 3.50 (1H, m), 4.13 (3H, s), 5.17 (1H, d, J = 5Hz), 5.45, 5.72 (2H, ABq, J = 15Hz), 5.78 (1H, dd, J = 5Hz, 8Hz), 6.93 (1H, t, J = 3Hz), 7.40 (1H, s), 8.53 (2H, m), 9.62 (1H, d, J = 8Hz)

Example 4

Trifluoroacetic acid salt of 7β-[2-(2-cyclopenten-1-yl oxyimino)-2-(2-formamidothiazol-4-yl)acetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephe-4-carboxylate (syn isomer)

IR (Nujol) : 3350, 1770, 1670 cm⁻¹
NMR (DMSO-d₆, δ) : 1.80-2.40 (4H, m), 2.48 (3H, s), 3.37 (2H, br. s), 3.90 (3H, s), 5.18 (1H, d, J = 5Hz),
Example 5

Trifluoroacetic acid salt of 7β-[2-(2-tetrahydropranyloxymimo)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 3150, 1775, 1675 cm⁻¹
NMR (DMSO-d₆, δ) : 1.50-1.93 (6H, m), 3.40 (2H, br. s), 3.50 (2H, m), 4.08 (3H, s), 5.20 (1H, d, J = 5Hz), 5.25 (1H, m), 5.53 (2H, br. s), 5.78 (1H, dd, J = 8Hz, 5Hz), 6.75 (1H, d, J = 2Hz), 7.15-7.60 (16H, m), 8.43 (1H, d, J = 2Hz), 8.56 (1H, d, J = 2Hz), 9.60 (1H, d, J = 8Hz)

Example 6

Trifluoroacetic acid salt of 7β-[2-difluoromethoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1780, 1660 cm⁻¹
NMR (DMSO-d₆, δ) : 2.43 (3H, s), 3.30-3.61 (2H, m), 3.84 (3H, s), 5.13 (2H, d, J = 5Hz), 5.47 (2H, br. s), 5.70 (1H, dd, J = 5Hz, 8Hz), 6.60-7.35 (18H, m), 8.27 (1H, s), 9.60 (1H, d, J = 8Hz)

Example 7

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3400, 1770, 1660, 1600, 1530 cm⁻¹
NMR (D₂O, δ) : 3.20, 3.50 (2H, ABq, J = 18Hz), 4.10 (3H, s), 5.25 (1H, d, J = 5Hz), 5.25, 5.50 (2H, ABq, J = 14Hz), 5.85 (1H, d, J = 5Hz), 6.75 (1H, t, J = 72Hz), 7.20 (1H, s), 8.17 (2H, m)

Example 8

7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxymimo)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1650, 1610, 1530 cm⁻¹
NMR (D₂O-NaHCO₃, δ) : 2.10 (2H, m), 2.35 (2H, m), 3.30, 3.50 (2H, ABq, J = 18Hz), 4.12 (3H, s), 5.25 (1H, d, J = 5Hz), 5.15-5.60 (3H, m), 5.80-6.30 (3H, m), 6.80 (1H, t, J = 2Hz), 7.00 (1H, s), 8.23 (2H, m)

Example 9

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1775, 1660, 1600 cm⁻¹
NMR (D₂O δ) : 3.21 and 3.53 (2H, ABq, J = 17Hz), 4.01 (3H, s), 4.13 (3H, s), 5.26 (1H, d, J = 5Hz), 5.28 and 5.52 (2H, ABq, J = 15Hz), 5.86 (1H, d, J = 5Hz), 6.80 (1H, t, J = 3Hz), 6.99 (1H, s), 8.22 (1H, d, J = 3Hz), 8.24 (1H, d, J = 3Hz)

Example 10

7β-[2-(2-Aminothiazol-4-yl)-2-isopropoxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1680, 1610, 1530 cm⁻¹
NMR (D₂O-NaHCO₃, δ) : 1.27(6H, d, J = 6Hz), 3.22, 3.53 (2H, ABq, J = 18Hz), 3.80 (1H, m), 4.12 (3H, s), 5.27 (1H, d, J = 5Hz), 6.80 (1H, t, J = 3Hz), 6.98 (1H, s), 8.23 (2H, m)

Example 11

7β-[2-(2-Aminothiazol-4-yl)-2-(2-tetrahydropranyloxymimo)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1775, 1680, 1620 cm⁻¹
Example 12

7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yl)oxyiminocacetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol): 3300, 1770, 1660, 1600 cm⁻¹

NMR (D₂O, δ): 1.40-1.95 (6H, m), 3.26, 3.50 (2H, ABq, J = 18Hz), 3.53-3.82 (2H, m), 4.09 (3H, s), 5.24 (1H, d, J = 5Hz), 5.26, 5.48 (2H, ABq, J = 15Hz), 5.40 (1H, m), 5.85 (1H, d, J = 5Hz), 6.73 (1H, t, J = 2Hz), 6.99 (1H, s), 8.16 (2H, br. s)

Example 13

7β-[2-(2-Aminothiazol-4-yl)-2-(hydroximino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol): 3320, 1775, 1660, 1620, 1600 cm⁻¹

NMR (D₂O, δ): 3.20, 3.51 (2H, ABq, J = 18Hz), 4.11 (3H, s), 5.25 (1H, d, J = 5Hz), 5.59, 5.50 (2H, ABq, J = 15Hz), 5.86 (1H, d, J = 5Hz), 6.76 (1H, t, J = 2Hz), 6.94 (1H, s), 8.18 (2H, d, J = 2Hz)

Example 14

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol): 3300, 1770, 1670, 1610 cm⁻¹

NMR (D₂O, δ): 2.43 (3H, s), 3.13, 3.43 (2H, ABq, J = 18Hz), 3.91 (3H, s), 5.18, 5.43 (2H, ABq, J = 15Hz), 5.22 (1H, d, J = 5Hz), 5.83 (1H, d, J = 5Hz), 6.56 (1H, d, J = 3Hz), 6.87 (1H, t, J = 7Hz), 7.18 (1H, s), 8.41 (1H, d, J = 3Hz)

Example 15

7β-[2-(2-Aminothiazol-4-yl)-2-(3-cyclopenten-1-yl)oxyiminocacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol): 3250, 3100, 1770, 1662, 1608 cm⁻¹

NMR (D₂O-NaHCO₃, δ): 2.65 (4H, m), 3.14, 3.44 (2H, ABq, J = 18Hz), 4.07 (3H, s), 5.0 (1H, m), 5.18 (1H, d, J = 5Hz), 5.21, 5.47 (2H, ABq, J = 16Hz), 5.68 (2H, s), 5.77 (1H, d, J = 5Hz), 6.73 (1H, m), 6.90 (1H, s), 8.13 (2H, m)

Example 16

7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yl)oxyiminocacetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol): 3260, 1765, 1660, 1605 cm⁻¹

NMR (D₂O, δ): 1.87-2.52 (4H, m), 3.27, 3.47 (2H, ABq, J = 18Hz), 4.07 (3H, s), 4.57 (2H, s), 5.20 (1H, d, J = 5Hz), 5.30 (1H, m), 5.39 (2H, br. s), 5.80 (1H, d, J = 5Hz), 5.82-6.23 (2H, m), 6.90 (1H, s), 8.14 (1H, s), 8.17 (1H, s)

Example 17

7β-[2-(2-Aminothiazol-4-yl)-2-(hydroximino)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol): 3200, 1765, 1660, 1600 cm⁻¹

NMR (D₂O, δ): 3.18, 3.49 (2H, ABq, J = 18Hz), 4.07 (3H, s), 4.56 (2H, s), 5.20, 5.45 (2H, ABq, J = 15Hz), 5.22 (1H, d, J = 5Hz), 5.82 (1H, d, J = 5Hz), 6.88 (1H, s), 8.18 (2H, s)
Example 18

Sulfuric acid salt of 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
NMR (D₂O, δ) : 3.33 and 3.57 (2H, ABq, J = 18Hz), 4.15 (3H, s), 5.30 (1H, d, J = 5Hz), 5.47 (2H, br. s), 5.87 (1H, d, J = 5Hz), 6.73-6.90 (1H, m), 7.0 (1H, t, J = 71Hz), 7.40 (1H, s), 8.20-8.35 (2H, m)

Example 19

To a solution of trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer, 2.2 g) in methanol (11 ml) was added conc. hydrochloric acid (0.78 ml) at room temperature, and the mixture was stirred at the same temperature for 2 hours. The reaction mixture was added to diethyl ether (300 ml), and the precipitates were collected by filtration. The precipitates were dissolved in water (20 ml) and the solution was adjusted to pH 5 with saturated aqueous solution of sodium bicarbonate. The solution was subjected to column chromatography on macroporous non-ionic adsorption resin "Diaion HP-20" and eluted with 15% aqueous solution of isopropyl alcohol. The fractions containing the product compound were collected and evaporated in vacuo to remove isopropyl alcohol. The solution was lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer, 0.78 g).

IR (Nujol) : 1775, 1660, 1600 cm⁻¹
NMR (D₂O, δ) : 3.21 and 3.53 (2H, ABq, J = 17Hz), 4.01 (3H, s), 4.13 (3H, s), 5.26 (1H, d, J = 5Hz), 5.28 and 5.52 (2H, ABq, J = 15Hz), 5.86 (1H, d, J = 5Hz), 6.80 (1H, t, J = 3Hz), 6.99 (1H, s), 8.22 (1H, d, J = 3Hz), 8.24 (1H, d, J = 3Hz)

The following compounds (Examples 20 to 28 were obtained according to a similar manner to that of Example 19.

Example 20

7β-[2-(2-Aminothiazol-4-yl)-2-(cyclopenten-1-ylxooimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 3300, 1770, 1650, 1610, 1530 cm⁻¹
NMR (D₂O-NaHCO₃, δ) : 2.10 (2H, m), 2.35 (2H, m), 3.30, 3.50 (2H, ABq, J = 18Hz), 4.12 (3H, s), 5.25 (1H, d, J = 5Hz), 5.15-5.60 (3H, m), 5.80-6.30 (3H, m), 6.80 (1H, t, J = 2Hz), 7.00 (1H, s), 8.23 (2H, m)

Example 21

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).
IR (Nujol) : 3400, 1770, 1660, 1600, 1530 cm⁻¹
NMR (D₂O, δ) : 3.20, 3.50 (2H, ABq, J = 18Hz), 4.10 (3H, s), 5.25 (1H, d, J = 5Hz), 5.25, 5.50 (2H, ABq, J = 14Hz), 5.85 (1H, d, J = 5Hz), 6.75 (1H, t, J = 72Hz), 7.20 (1H, s), 8.17 (2H, m)

Example 22

7β-[2-(2-Aminothiazol-4-yl)-2-isoproxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 3300, 1770, 1680, 1610, 1530 cm⁻¹
NMR (D₂O-NaHCO₃, δ) : 1.27 (6H, d, J = 6Hz), 3.22, 3.53 (2H, ABq, J = 18Hz), 3.80 (1H, m), 4.12 (3H, s), 5.27 (1H, d, J = 5Hz), 6.80 (1H, t, J = 3Hz), 6.98 (1H, s), 8.23 (2H, m)

Example 23

7β-[2-(2-Aminothiazol-4-yl)-2-(2-tetrahydropranyloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 3300, 1775, 1690, 1620 cm⁻¹
NMR (D₂O, δ) : 1.40-1.95 (6H, m), 3.28, 3.50 (2H, ABq, J = 18Hz), 3.53-3.82 (2H, m), 4.09 (3H, s), 5.24 (1H, d, J = 5Hz), 5.26, 5.48 (2H, ABq, J = 15Hz), 5.40 (1H, m), 5.85 (1H, d, J = 5Hz), 6.73 (1H, t, J = 2Hz), 6.99 (1H, s), 8.16 (2H, br. s)
Example 24
7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yl)oximes]acetamido]-3-(2,5-dimethyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1660, 1600 cm⁻¹
NMR (D₂O, δ) : 1.8-2.58 (4H, m), 2.43 (3H, s), 3.12, 3.42 (2H, ABq, J = 18Hz), 3.91 (3H, s), 5.17, 5.45 (2H, ABq, J = 15Hz), 5.19 (1H, d, J = 5Hz), 5.41 (1H, m), 5.80 (1H, d, J = 5Hz), 5.80-6.27 (2H, m), 6.58 (1H, d, J = 3Hz), 6.93 (1H, s), 8.05 (1H, d, J = 3Hz)

Example 25
7β-[2-(2-Aminothiazol-4-yl)-2-(3-thietanyloxymino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1660, 1605 cm⁻¹
NMR (D₂O, δ) : 3.2-3.8 (4H, m), 3.22, 3.83 (2H, ABq, J = 18Hz), 4.13 (3H, s), 5.10-5.32 (1H, m), 5.20, 5.54 (2H, ABq, J = 15Hz), 5.34 (1H, d, J = 5Hz), 5.89 (1H, d, J = 5Hz), 6.76-6.83 (1H, m), 7.03 (1H, s), 8.16-8.23 (2H, m)

Example 26
7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yl)oximes]acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3260, 1765, 1660, 1605 cm⁻¹
NMR (D₂O, δ) : 1.87-2.52 (4H, m), 3.27, 3.47 (2H, ABq, J = 18Hz), 4.07 (3H, s), 4.57 (2H, s), 5.20 (1H, d, J = 5Hz), 5.30 (1H, m), 5.39 (2H, brd, s), 5.80 (1H, d, J = 5Hz), 5.82-6.23 (2H, m), 6.90 (1H, s), 8.14 (1H, s), 8.17 (1H, s)

Example 27
7β-[2-(2-Aminothiazol-4-yl)-2-(2-hydroxyimino)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (Syn isomer)

IR (Nujol) : 3200, 1765, 1660, 1600 cm⁻¹
NMR (D₂O, δ) : 3.18, 3.49 (2H, ABq, J = 18Hz), 4.07 (3H, s), 4.56 (2H, s), 5.20, 5.45 (2H, ABq, J = 15Hz), 5.22 (1H, d, J = 5Hz), 5.82 (1H, d, J = 5Hz), 6.88 (1H, s), 8.18 (2H, s)

Example 28
Sulfuric acid salt of 7β-[2-(2-aminothiazol-4-yl)-2-difluorophenoximinato)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

NMR (D₂O, δ) : 3.33 and 3.57 (2H, ABq, J = 18Hz), 4.15 (3H, s), 5.30 (1H, d, J = 5Hz), 5.47 (2H, brd, s), 5.87 (1H, d, J = 5Hz), 6.73-6.90 (1H, m), 7.0 (1H, t, J = 7Hz), 7.40 (1H, s), 8.20-8.35 (2H, m)

Example 29
To a solution of trifluoroacetic acid salt of 7β-[2-(2-tetrahydropyran-4-yl)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer, 25.9 g), anisole (25 ml) and methylene chloride (25 ml) was added trifluoroacetic acid (50 ml) under ice-cooling with stirring. After stirred at the same temperature for 1 hour, the mixture was poured into diisopropyl ether (3500 ml).

The resulting precipitates were collected by filtration, washed with diisopropyl ether and the solid obtained was dissolved in water (700 ml). The solution was subjected to column chromatography on macro porous non-ionic adsorption resin "Diaion HP-20" and eluted with 30% aqueous solution of methanol. The fractions containing the product were collected, concentrated in vacuo, and lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer, 3.90 g).

IR (Nujol) : 3320, 1775, 1660, 1620, 1600 cm⁻¹
NMR (D₂O, δ) : 3.20, 3.51 (2H, ABq, J = 18Hz), 4.11 (3H, s), 5.25 (1H, d, J = 5Hz), 5.25, 5.50 (2H, ABq, J = 15Hz), 5.86 (1H, d, J = 5Hz), 6.76 (1H, t, J = 2Hz), 6.94 (1H, s), 8.18 (2H, d, J = 2Hz)
Example 30

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) was prepared from trifluoroacetic acid salt of 7β-[2-difluoromethoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) according to a similar manner to that of Example 29.

IR (Nujol): 3300, 1770, 1670, 1610 cm⁻¹

NMR (D₂O, δ): 2.43 (3H, s), 3.13, 3.43 (2H, ABq, J = 18Hz), 3.91 (3H, s), 5.18, 5.43 (2H, ABq, J = 15Hz), 5.22 (1H, d, J = 5Hz), 5.83 (1H, d, J = 5Hz), 6.56 (1H, d, J = 3Hz), 6.87 (1H, t, J = 7Hz), 7.18 (1H, s), 8.14 (1H, d, J = 3Hz)

Example 31

2-(3-Cyclopenten-1-yloxyimino)-2-(2-formamidothiazol-4-yl)acetlycic acid (syn isomer, 2.0 g) in tetrahydrofuran (20 ml) was activated with Willhmeier reagent prepared from N,N-dimethylformamide (0.66 ml) and phosphorus oxychloride (0.72 ml). To a solution of bis(trifluoroacetic acid) salts of 7β-amino-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (3.70 g) and N-mono(trimethylsilyl)acetamide (18.6 g) in tetrahydrofuran (37 ml) was added the activated acid solution obtained above under ice-cooling. After stirring at the same temperature for 1 hour, the reaction mixture was poured into a mixture of ethyl acetate (200 ml) and diisopropyl ether (200 ml). The solvent was removed by decantation. The residual glassy mass was washed with ethyl acetate by decantation and then dissolved in methanol (40 ml). To the solution was added conc. hydrochloric acid (8.2 ml) and the mixture was stirred at ambient temperature for 2 hours. The resultant solution was concentrated under reduced pressure and the residue was dissolved in water (80 ml). The solution was washed with ethyl acetate twice, and adjusted to pH 2.0 with diluted hydrochloric acid. The solution was subjected to column chromatography on macroporous non-ionic adsorption resin "Diaion HP-20", washed with water, and eluted with a mixture of 40% aqueous methanol. The fractions containing the object compound were collected, concentrated in vacuo and then lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-(3-cyclopenten-1-yloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer, 1.12 g).

IR (Nujol): 3250, 3100, 1770, 1662, 1608 cm⁻¹

NMR (D₂O-NaHCO₃, δ): 2.65 (4H, m), 3.14, 3.44 (2H, ABq, J = 18Hz), 4.07 (3H, s), 5.0 (1H, m), 5.18 (1H, d, J = 5Hz), 5.21, 5.47 (2H, ABq, J = 16Hz), 5.68 (2H, s), 5.77 (1H, d, J = 5Hz), 6.73 (1H, m), 6.90 (1H, s), 8.13 (2H, m)

Example 32

A mixture of 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]cerebrosporamic acid (syn isomer, 2 g), N-methylpyrazole (0.67 g), sodium iodide (4.2 g), water (0.7 ml) and acetonitrile (2.1 ml) was stirred at 63 to 65 °C for 3.5 hours. The reaction mixture was poured into water (130 ml) and adjusted to pH 2.0 with 10% hydrochloric acid. The solution was subjected to column chromatography on macroporous nonionic adsorption resin Diaion HP-20* (100 ml) and eluted with 30% aqueous solution of methanol. The fractions containing the object compound were collected, concentrated in vacuo, and lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer, 0.15 g).

IR (Nujol): 3400, 1770, 1600, 1600, 1530 cm⁻¹

NMR (D₂O, δ): 3.20, 3.50 (2H, ABq, J = 18Hz), 4.10 (3H, s), 5.25 (1H, d, J = 5Hz), 5.25, 5.50 (2H, ABq, J = 14Hz), 5.85 (1H, d, J = 5Hz), 6.75 (1H, t, J = 7Hz), 7.20 (1H, s), 8.17 (2H, m)

The following compounds (Examples 33 to 44 were obtained according to a similar manner to that of Example 32.

Example 33

7β-[2-(2-Aminothiazol-4-yl)-2-(3-cyclopenten-1-yloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol): 3300, 1770, 1650, 1610, 1530 cm⁻¹

NMR (D₂O-NaHCO₃, δ): 2.10 (2H, m), 2.35 (2H, m), 3.30, 3.50 (2H, ABq, J = 18Hz), 4.12 (3H, s), 5.25 (1H, d, J = 5Hz), 5.15-5.80 (3H, m), 5.80-6.30 (3H, m), 6.80 (1H, t, J = 2Hz), 7.00 (1H, s), 8.23 (2H, m)
Example 34

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol) : 1775, 1660, 1600 cm⁻¹
NMR (D₂O, δ ) : 3.21 and 3.53 (2H, ABq, J = 17Hz), 4.01 (3H, s), 4.13 (3H, s), 5.26 (1H, d, J = 5Hz), 5.28 and 5.52 (2H, ABq, J = 15Hz), 5.86 (1H, d, J = 5Hz), 6.80 (1H, t, J = 3Hz), 6.99 (1H, s), 8.22 (1H, d, J = 3Hz), 8.24 (1H, d, J = 3Hz)

Example 35

7β-[2-(2-Aminothiazol-4-yl)-2-(3-thietanyloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1770, 1660, 1605 cm⁻¹
NMR (D₂O, δ ) : 3.2-3.8 (4H, m), 3.22, 3.63 (2H, ABq, J = 18Hz), 4.13 (3H, s), 5.10-5.32 (1H, m), 5.20, 5.54 (2H, ABq, J = 15Hz), 5.34 (1H, d, J = 5Hz), 5.89 (1H, d, J = 5Hz), 6.76-6.83 (1H, m), 7.03 (1H, s), 8.16-8.23 (2H, m)

Example 36

7β-[2-(2-Aminothiazol-4-yl)-2-isopropoxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1660, 1610, 1530 cm⁻¹
NMR (D₂O-NaHCO₃, δ ) : 1.27 (6H, d, J = 6Hz), 3.22, 3.53 (2H, ABq, J = 18Hz), 3.80 (1H, m), 4.12 (3H, s), 5.27 (1H, d, J = 5Hz), 6.80 (1H, t, J = 3Hz), 6.98 (1H, s), 8.23 (2H, m)

Example 37

7β-[2-(2-Aminothiazol-4-yl)-2-(2-tetrahydropyanylloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1775, 1680, 1620 cm⁻¹
NMR (D₂O, δ ) : 1.40-1.95 (6H, m), 3.26, 3.50 (2H, ABq, J = 18Hz), 3.53-3.82 (2H, m), 4.09 (3H, s), 5.24 (1H, d, J = 5Hz), 5.26, 5.48 (2H, ABq, J = 15Hz), 5.40 (1H, m), 5.85 (1H, d, J = 5Hz), 6.73 (1H, t, J = 2Hz), 6.99 (1H, s), 8.16 (2H, br. s)

Example 38

7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(2,5-dimethyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1660, 1600 cm⁻¹
NMR (D₂O, δ ) : 1.83-2.58 (4H, m), 2.43 (3H, s), 3.12, 3.42 (2H, ABq, J = 18Hz), 3.91 (3H, s), 5.17, 5.45 (2H, ABq, J = 15Hz), 5.19 (1H, d, J = 5Hz), 5.41 (1H, m), 5.80 (1H, d, J = 5Hz), 5.80-6.27 (2H, m), 6.58 (1H, d, J = 3Hz), 6.93 (1H, s), 8.05 (1H, d, J = 3Hz)

Example 39

7β-[2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3320, 1775, 1660, 1620, 1600 cm⁻¹
NMR (D₂O, δ ) : 3.20, 3.51 (2H, ABq, J = 18Hz), 4.11 (3H, s), 5.25 (1H, d, J = 5Hz), 5.25, 5.50 (2H, ABq, J = 15Hz), 5.86 (1H, d, J = 5Hz), 6.76 (1H, t, J = 2Hz), 6.94 (1H, s), 8.18 (2H, d, J = 2Hz)

Example 40

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1670, 1610 cm⁻¹
NMR (D₂O, δ ) : 2.43 (3H, s), 3.13, 3.43 (2H, ABq, J = 18Hz), 3.91 (3H, s), 5.18, 5.43 (2H, ABq, J = 15Hz),
5.22 (1H, d, J = 5Hz), 5.83 (1H, d, J = 3Hz), 6.56 (1H, d, J = 3Hz), 6.87 (1H, t, J = 7Hz), 7.18 (1H, s), 8.14 (1H, d, J = 3Hz)

Example 41

7β-[2-(2-Aminothiazol-4-yl)-2-(3-cyclopenten-1-yloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3250, 3100, 1770, 1662, 1608 cm⁻¹

NMR (D₂O-NaHCO₃, δ) : 2.65 (4H, m), 3.14, 3.44 (2H, ABq, J = 18Hz), 4.07 (3H, s), 5.0 (1H, m), 5.18 (1H, d, J = 5Hz), 5.21, 5.47 (2H, ABq, J = 16Hz), 5.68 (2H, s), 5.77 (1H, d, J = 5Hz), 6.73 (1H, m), 6.90 (1H, s), 8.13 (2H, m)

Example 42

7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3260, 1765, 1660, 1605 cm⁻¹

NMR (D₂O, δ) : 1.87-2.52 (4H, m), 3.27, 3.47 (2H, ABq, J = 18Hz), 4.07 (3H, s), 4.57 (2H, s), 5.20 (1H, d, J = 5Hz), 5.30 (1H, m), 5.39 (2H, br. s), 5.80 (1H, d, J = 5Hz), 5.82-6.23 (2H, m), 6.90 (1H, s), 8.14 (1H, s), 8.17 (1H, s)

Example 43

7β-[2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3200, 1765, 1660, 1600 cm⁻¹

NMR (D₂O, δ) : 3.18, 3.49 (2H, ABq, J = 18Hz), 4.07 (3H, s), 4.56 (2H, s), 5.20, 5.45 (2H, ABq, J = 15Hz), 5.22 (1H, d, J = 5Hz), 5.82 (1H, d, J = 5Hz), 6.88 (1H, s), 8.18 (2H, s)

Example 44

Sulfuric acid salt of 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

NMR (D₂O, δ) : 3.33, 3.57 (2H, ABq, J = 18Hz), 4.15 (3H, s), 5.30 (1H, d, J = 5Hz), 5.47 (2H, br. s), 5.87 (1H, d, J = 5Hz), 6.73-6.90 (1H, m), 7.0 (1H, t, J = 7Hz), 7.40 (1H, s), 8.20-8.35 (2H, m)

Example 45

To a solution of benzhydryl 7β-[2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate chloride (syn isomer, 3.6 g), anisole (3.6 ml) and methylene chloride (15 ml) was added trifluoroacetic acid (7.2 ml) under ice-cooling with stirring. After stirred at the same temperature for 1 hour, the mixture was poured into diisopropyl ether (500 ml).

The resulting precipitates were collected by filtration, washed with diisopropyl ether and the solid was dissolved in water (100 ml). The solution was subjected to column chromatography on macroporous non-ionic adsorption resin "Diaion HP-20" and eluted with 30% aqueous solution of methanol. The fractions containing the object compound were collected, concentrated in vacuo, and lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer, 1.05 g).

IR (Nujol) : 3300, 1770, 1650, 1610, 1530 cm⁻¹

NMR (D₂O-NaHCO₃, δ) : 2.10 (2H, m), 2.35 (2H, m), 3.30, 3.50 (2H, ABq, J = 18Hz), 4.12 (3H, s), 5.25 (1H, d, J = 5Hz), 5.15-5.60 (3H, m), 5.80-6.30 (3H, m), 6.80 (1H, t, J = 2Hz), 7.00 (1H, s), 8.23 (2H, m)

The following compounds (Examples 46 to 55) were obtained according to a similar manner to that of Example 45.

Example 46

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 3400, 1770, 1660, 1600, 1530 cm\(^{-1}\)

NMR (D\(_2\)O, \(\delta\)) : 3.20, 3.50 (2H, ABq, J = 18Hz), 4.10 (3H, s), 5.25 (1H, d, J = 5Hz), 5.25, 5.50 (2H, ABq, J = 14Hz), 5.85 (1H, d, J = 5Hz), 6.75 (1H, t, J = 72Hz), 7.20 (1H, s), 8.17 (2H, m)

Example 47

7\(\beta\)-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1775, 1660, 1600 cm\(^{-1}\)
NMR (D\(_2\)O, \(\delta\)) : 3.21 and 3.53 (2H, ABq, J = 17Hz), 4.01 (3H, s), 4.13 (3H, s), 5.26 (1H, d, J = 5Hz), 5.28 and 5.52 (2H, ABq, J = 15Hz), 5.86 (1H, d, J = 5Hz), 6.80 (1H, t, J = 3Hz), 6.99 (1H, s), 8.22 (1H, d, J = 3Hz), 8.24 (1H, d, J = 3Hz)

Example 48

7\(\beta\)-[2-(2-Aminothiazol-4-yl)-2-(3-thiolyxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1770, 1660, 1605 cm\(^{-1}\)
NMR (D\(_2\)O, \(\delta\)) : 3.2-3.8 (4H, m), 3.22, 3.63 (2H, ABq, J = 18Hz), 4.13 (3H, s), 5.10-5.32 (1H, m), 5.20, 5.54 (2H, ABq, J = 15Hz), 5.34 (1H, d, J = 5Hz), 5.89 (1H, d, J = 5Hz), 6.76-6.83 (1H, m), 7.03 (1H, s), 8.16-8.23 (2H, m)

Example 49

7\(\beta\)-[2-(2-Aminothiazol-4-yl)-2-isopropoxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1660, 1610, 1530 cm\(^{-1}\)
NMR (D\(_2\)O-NaHCO\(_3\), \(\delta\)) : 1.27 (6H, d, J = 6Hz), 3.22, 3.53 (2H, ABq, J = 18Hz), 3.80 (1H, m), 4.12 (3H, s), 5.27 (1H, d, J = 5Hz), 6.80 (1H, t, J = 3Hz), 6.98 (1H, s), 8.23 (2H, m)

Example 50

7\(\beta\)-[2-(2-Aminothiazol-4-yl)-2-(2-tetrahydroxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1775, 1680, 1620 cm\(^{-1}\)
NMR (D\(_2\)O, \(\delta\)) : 1.40-1.95 (6H, m), 3.26, 3.50 (2H, ABq, J = 18Hz), 3.53-3.82 (2H, m), 4.09 (3H, s), 5.24 (1H, d, J = 5Hz), 5.26, 5.48 (2H, ABq, J = 15Hz), 5.40 (1H, m), 5.85 (1H, d, J = 5Hz), 6.73 (1H, t, J = 2Hz), 6.99 (1H, s), 8.16 (2H, br. s)

Example 51

7\(\beta\)-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yl-oxyimino)acetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1660, 1600 cm\(^{-1}\)
NMR (D\(_2\)O, \(\delta\)) : 1.83-2.58 (4H, m), 2.43 (3H, s), 3.12, 3.42 (2H, ABq, J = 18Hz), 3.91 (3H, s), 5.17, 5.45 (2H, ABq, J = 15Hz), 5.19 (1H, d, J = 5Hz), 5.41 (1H, m), 5.80 (1H, d, J = 5Hz), 5.80-6.27 (2H, m), 6.58 (1H, d, J = 3Hz), 6.93 (1H, s), 8.05 (1H, d, J = 3Hz)

Example 52

7\(\beta\)-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3320, 1775, 1660, 1620, 1600 cm\(^{-1}\)
NMR (D\(_2\)O, \(\delta\)) : 3.20, 3.51 (2H, ABq, J = 18Hz), 4.11 (3H, s), 5.25 (1H, d, J = 5Hz), 5.25, 5.50 (2H, ABq, J = 15Hz), 5.86 (1H, d, J = 5Hz), 6.76 (1H, t, J = 2Hz), 6.94 (1H, s), 8.18 (2H, d, J = 2Hz)
Example 53

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol): 3300, 1770, 1670, 1610 cm⁻¹
NMR (D₂O, δ): 2.43 (3H, s), 3.13, 3.43 (2H, ABq, J = 18Hz), 3.91 (3H, s), 5.18, 5.43 (2H, ABq, J = 15Hz), 5.22 (1H, d, J = 5Hz), 5.83 (1H, d, J = 5Hz), 6.56 (1H, d, J = 3Hz), 6.87 (1H, t, J = 7Hz), 7.18 (1H, s), 8.14 (1H, d, J = 3Hz)

Example 54

7β-[2-(2-Aminothiazol-4-yl)-2-(3-cyclopenten-1-yloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol): 3250, 3100, 1770, 1662, 1608 cm⁻¹
NMR (D₂O-NaHCO₃, δ): 2.65 (4H, m), 3.14, 3.44 (2H, ABq, J = 18Hz), 4.07 (3H, s), 5.0 (1H, m), 5.18 (1H, d, J = 5Hz), 5.21, 5.47 (2H, ABq, J = 16Hz), 5.68 (2H, s), 5.77 (1H, d, J = 5Hz), 6.73 (1H, m), 6.90 (1H, s), 8.13 (2H, m)

Example 55

Sulfuric acid salt of 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

NMR (D₂O, δ): 3.33 and 3.57 (2H, ABq, J = 18Hz), 4.15 (3H, s), 5.30 (1H, d, J = 5Hz), 5.47 (2H, br. s), 5.87 (1H, d, J = 5Hz), 6.73-6.90 (1H, m), 7.0 (1H, t, J = 7Hz), 7.40 (1H, s), 8.20-8.35 (2H, m)

Example 56

To a solution of benzhydrol 7β-[2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate chloride (syn isomer, 1.9 g), anisole (2 ml) and methylene chloride (6 ml) was added trifluoroacetic acid (4 ml) under ice-cooling with stirring. After stirring at the same temperature for 1 hour, the mixture was dissolved in water and the solution was adjusted to pH 4 with 5% aqueous solution of sodium bicarbonate. The solution was subjected to column chromatography on macroporous non-ionic adsorption resin "Diaion HP-20" and eluted with 3% aqueous solution of isopropyl alcohol. The fractions containing the object compound were collected, combined, concentrated, and finally lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer, 0.32 g).

IR (Nujol): 3200, 1765, 1660, 1600 cm⁻¹
NMR (D₂O, δ): 3.18, 3.49 (2H, ABq, J = 18Hz), 4.07 (3H, s), 4.56 (2H, s), 5.20, 5.45 (2H, ABq, J = 15Hz), 5.22 (1H, d, J = 5Hz), 5.82 (1H, d, J = 5Hz), 6.88 (1H, s), 8.18 (2H, s)

And further, the above-mentioned column was continuously eluted with 10% aqueous solution of isopropyl alcohol. The fractions containing the other object compound were collected, combined, concentrated, and finally lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer, 0.32 g).

IR (Nujol): 3260, 1765, 1660, 1605 cm⁻¹
NMR (D₂O, δ): 1.87-2.52 (4H, m), 3.27, 3.47 (2H, ABq, J = 18Hz), 4.07 (3H, s), 4.57 (2H, s), 5.20 (1H, d, J = 5Hz), 5.30 (1H, m), 5.39 (2H, br. s), 5.80 (1H, d, J = 5Hz), 5.82-6.23 (2H, m), 6.90 (1H, s), 8.14 (1H, s), 8.17 (1H, s)

Example 57

A mixture of benzhydrol 7β-[2-difluoromethoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-chloromethyl-3-cephem-4-carboxylate (syn isomer, 8.76 g), N-methylpyrazole (8.76 g), sodium iodide (1.5 g) and acetone (9 ml) was stirred at ambient temperature for 19 hours. The reaction mixture was evaporated, and ethyl acetate (200 ml) and 5% aqueous solution of sodium thiosulfate were added to the residue. The organic layer was separated and tetrahydrofuran (100 ml) was added thereto. The solution was dried over magnesium sulfate and evaporated and the residue was dissolved in a mixture of tetrahydrofuran (200 ml) and water (65 ml). The solution was subjected to column chromatography on an ion-exchange resin "Amberlite IRA-400"(Cl⁻ form), and eluted with a mixture of tetrahydrofuran and water (15:1 V/V). The
fractions containing the object compound were collected, combined and evaporated. The residue was triturated with disisopropyl ether to give benzhydryl 7β-[2-(difluoromethoxyimino-2-(2-tritylaminothiazol-4-yl)-acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate chloride (syn isomer, 8.0 g).

A solution of benzhydryl 7β-[2-(difluoromethoxyimino-2-(2-tritylaminothiazol-4-yl)-acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate chloride (syn isomer, 7.3 g) in methylene chloride (28 ml) was stirred at 0 to 5°C. Anisole (7 ml) and trifluoroacetic acid (28 ml) were added thereto, and the mixture was stirred for 1 hour at the same temperature. To the reaction mixture was added disisopropyl ether, and the precipitates were collected by filtration. The solid was washed with disisopropyl ether and dissolved in water (100 ml). The aqueous solution was adjusted to pH 2.0 with an aqueous solution of sodium bicarbonate and washed with ethyl acetate. The aqueous layer was subjected to column chromatography on macroporous non-ionic adsorption resin "Diaion HP-20" and eluted with 30% aqueous solution of methanol. The fractions containing the object compound were combined and concentrated. To the residual aqueous solution was added 1M sulfuric acid (2.2 ml) and the mixture was lyophilized to give sulfuric acid salt of 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer, 1.35 g).

NMR (D₂O, δ): 3.33 and 3.57 (2H, ABq, J = 18Hz), 4.15 (3H, s), 5.30 (1H, d, J = 5Hz), 5.47 (2H, br. s), 5.87 (1H, d, J = 5Hz), 6.73-6.90 (1H, m), 7.0 (1H, t, J = 7Hz), 7.40 (1H, s), 8.20-8.35 (2H, m)

Example 58

To a solution of 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer, 2.0 g) in water (100 ml) was added 1M sulfuric acid (3.5 ml) at ambient temperature, and the solution was lyophilized to give sulfuric acid salt of 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer, 2.25 g).

This product (2.1 g) was recrystallized from a mixture of water (8.4 ml) and acetone (33.6 ml) to give the purified crystals of the above compound (1.3 g).

IR (Nujol): 3220, 3075, 1790, 1690, 1665, 1640, 1610, 1600 and 1550 cm⁻¹
NMR (D₂O, δ): 3.33 and 3.57 (2H, ABq, J = 18Hz), 4.15 (3H, s), 5.30 (1H, d, J = 5Hz), 5.47 (2H, br. s), 5.87 (1H, d, J = 5Hz), 6.73-6.90 (1H, m), 7.0 (1H, t, J = 7Hz), 7.40 (1H, s), 8.20-8.35 (2H, m)

Example 59

To a solution of benzhydryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer) (2.1 g), anisole (2 ml) and methylene chloride (6 ml) was added trifluoroacetic acid (4 ml) under ice-cooling with stirring. After stirred at the same temperature for 1 hour, the mixture was poured into diethyl ether.

The resulting precipitates were collected by filtration, washed with diethyl ether and the solid was dissolved in water, then the solution was adjusted to pH 4 with 5% sodium bicarbonate aqueous solution.

The solution was subjected to column chromatography on macroporous non-ionic adsorption resin "Diaion HP-20" (30 ml) and eluted with 5% aqueous solution of isopropyl alcohol. The fractions containing the object compound were collected, concentrated in vacuo and lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) (0.63 g).

IR (Nujol): 3300, 1775, 1675, 1605 cm⁻¹
NMR (D₂O, δ): 3.18, 3.50 (2H, ABq, J = 18Hz), 3.84 (3H, s), 4.04 (3H, s), 5.16 and 5.44 (2H, ABq, J = 15Hz), 5.24 (1H, d, J = 5Hz), 5.83 (1H, d, J = 5Hz), 6.88 (1H, t, J = 7Hz), 7.16 (1H, s), 7.96 (2H, br. s)

Example 60

To a solution of benzhydryl 7β-[2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer) (2.5 g), anisole (2.5 ml) and methylene chloride (7.5 ml) was added trifluoroacetic acid (5 ml) under ice-cooling with stirring. After stirred at the same temperature for 1.5 hours, the mixture was poured into diethyl ether.

The resulting precipitates were collected by filtration, washed with diethyl ether and the solid was dissolved in water, then the solution was adjusted to pH 4 with 5% sodium bicarbonate aqueous solution.

The solution was subjected to column chromatography on macroporous non-ionic adsorption resin "Diaion HP-20" (50 ml) and first eluted with 3% aqueous solution of isopropyl alcohol. The fractions
containing the object compound were collected, concentrated in vacuo and lyophilized to give \(7\beta-[2-(2-
aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-
carboxylic acid (syn isomer) (0.345 g).

\[ \text{IR (Nujol): } 3250, 1765, 1660, 1600 \text{ cm}^{-1} \]

\[ \text{NMR (D}_2\text{O, } \delta: 3.17 \text{ and } 3.47 (2H, ABq, } J=18 \text{Hz, s), } 3.81 \text{ (3H, s), 4.01 (3H, s), 5.12 \text{ and } 5.41 (2H, ABq, } J=16 \text{Hz), 5.18 (1H, d, } J=5 \text{Hz), 5.78 (1H, d, } J=5 \text{Hz), 6.84 (1H, s), 7.97 (2H, s) } \]

Second, the elution was carried out with 15% aqueous solution of isopropyl alcohol. The fractions containing the object compound were collected, concentrated in vacuo and lyophilized to give \(7\beta-[2-(2-
aminothiazol-4-yl)-2-(2-cyclopenten-1-yl)oxyimino)acetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-
cephem-4-carboxylate (syn isomer) (0.162 g).

\[ \text{IR (Nujol): } 3300, 1675, 1600 \text{ cm}^{-1} \]

\[ \text{NMR (D}_2\text{O, } \delta: 1.69-2.56 (4H, m), 3.16, 3.46 (2H, ABq, } J=18 \text{Hz), 3.74 (3H, m), 4.03 (3H, m), 5.17 (1H, d, } J=5 \text{Hz), 5.33 (3H, m), 5.78 (1H, d, } J=5 \text{Hz), 5.77-6.22 (2H, m), 6.87 (1H, s), 7.97 (2H, s) } \]

The following compounds (Examples 61 to 78) were obtained according to a similar manner to that of Example 1.

Example 61

\(7\beta-[2-(2-Tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer)\)

\[ \text{IR (Nujol): } 3350, 1775, 1660, 1580 \text{ cm}^{-1} \]

\[ \text{NMR (DMSO-d}_6, \delta: 3.34 (2H, broad s), 3.77 (3H, s), 3.91 (3H, s), 5.11 (1H, d, } J=5 \text{Hz), 5.41 (2H, broad s), 5.69 (1H, dd, } J=8 \text{Hz and 5Hz), 6.94 (1H, d, } J=3 \text{Hz), 7.00-7.60 (16H, m), 8.32 (1H, d, } J=3 \text{Hz), 8.47 (1H, s), 8.70 (1H, s), 9.47 (1H, d, } J=8 \text{Hz} \]

Example 62

\(7\beta-[2-(2-Formamidothiazol-4-yl)-2-tertbutyloxycarbonylmethoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)\)

\[ \text{IR (Nujol): } 1770, 1670, 1605 \text{ cm}^{-1} \]

\[ \text{NMR (D}_2\text{O + DMSO-d}_6, \delta: 1.43 (9H, s), 3.07 and 3.38 (2H, ABq, } J=18 \text{Hz), 3.87 (3H, s), 4.63 (2H, s), 5.08 (1H, d, } J=5 \text{Hz), 5.20 and 5.44 (2H, ABq, } J=16 \text{Hz), 5.74 (1H, d, } J=5 \text{Hz), 6.87 (1H, m), 7.45 (1H, s), 8.22 (1H, d, } J=3 \text{Hz), 8.43 (1H, s), 8.47 (1H, s) } \]

Example 63

\(7\beta-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)\)

\[ \text{IR (Nujol): } 3350, 1770, 1660, 1610 \text{ cm}^{-1} \]

Example 64

\(7\beta-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-formamido-2-methyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer)\)

\[ \text{IR (Nujol): } 1775, 1675, 1605 \text{ cm}^{-1} \]

Example 65

\(7\beta-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2-methyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer)\)

\[ \text{IR (Nujol): } 3300, 1770, 1665 \text{ cm}^{-1} \]

Example 66

\(7\beta-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate\cdot trihydrochloride (syn isomer)\)

\[ \text{IR (Nujol): } 3300, 1770, 1660, 1630 \text{ cm}^{-1} \]
Example 67

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1765, 1660 cm\(^{-1}\)

Example 68

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1760, 1660, 1600 cm\(^{-1}\)

Example 69

7β-[2-(2-Aminothiazol-4-yl)-2-tert-butoxycarbonylmethoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate•trihydrochloride (syn isomer)

IR (Nujol) : 3300, 1775, 1715, 1670, 1630 cm\(^{-1}\)

Example 70

Benzhydryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate•trifluoroacetate (syn isomer)

IR (Nujol) : 1795, 1725, 1675, 1615 cm\(^{-1}\)

Example 71

Benzhydryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate•trifluoroacetate (syn isomer)

IR (Nujol) : 3200, 1790, 1720, 1680 cm\(^{-1}\)

Example 72

7β-[2-(2-Aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1760, 1650 cm\(^{-1}\)

Example 73

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1760, 1660, 1605 cm\(^{-1}\)

Example 74

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1640, 1600 cm\(^{-1}\)

Example 75

Benzhydryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer)

IR (Nujol) : 1785, 1720, 1675 cm\(^{-1}\)

Example 76

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
Example 77

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3250, 1765, 1665, 1600 cm⁻¹

Example 78

Trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3350, 1770, 1655 cm⁻¹

NMR (DMSO-d₆, δ) : 2.50 (3H, s), 3.40 (2H, broad s), 3.88 (3H, s), 4.03 (3H, s), 5.19 (1H, d, J = 5Hz), 5.52 (2H, broad s), 5.88 (1H, dd, J = 8Hz and 5Hz), 7.77 (1H, broad s), 7.35 (1H, s), 8.37 (1H, broad s), 8.50 (1H, s), 9.67 (1H, d, J = 8Hz)

Example 79

The Vilsmeier reagent was prepared in the usual manner. 2-(2-Formamidothiazol-4-yl)-2-methoxyiminoacetic acid (syn isomer) (1.19 g) was activated with Vilsmeier reagent in ethyl acetate (3 ml) and tetrahydrofuran (6 ml) under ice-cooling for 30 minutes. This activated acid solution was added to a solution of bis(trifluoroacetic acid) salts of 7β-amino-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (3 g) and bis(trimethylsilyl)acetamide (5.12 ml) in tetrahydrofuran (30 ml) under ice-cooling.

After being stirred at the same temperature for 1 hour, the reaction mixture was added dropwise to diethyl ether (300 ml), and the resulting precipitate was collected by filtration to give trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) (3.10 g).

IR (Nujol) : 3300, 1780, 1650 cm⁻¹

NMR (DMSO-d₆, δ) : 1.99 (3H, s), 3.41 (2H, broad s), 3.83 (3H, s), 3.88 (3H, s), 5.22 (1H, d, J = 5Hz), 5.46 (2H, broad s), 5.88 (1H, dd, J = 5Hz and 8Hz), 7.38 (1H, s), 8.27 (1H, s), 8.37 (1H, s), 8.49 (1H, s), 9.68 (1H, d, J = 5Hz)

Example 80

2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetic acid (syn isomer) activated by 1-hydroxy-1H-benzotriazole was prepared by reacting 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid (syn isomer) (24.14 g), dicyclohexylcarbodiimide (24.76 g), 1-hydroxy-1H-benzotriazole (16.12 g) and 4-(N,N-dimethylamino)pyridine (733 mg) according to a conventional manner. 1.04 g of activated acid thus obtained was added to a solution of bis(trifluoroacetic acid) salt of 7β-amino-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (1.5 g) in tetrahydrofuran (40 ml) and water (20 ml) at ambient temperature. The mixture was stirred for 4 hours keeping the pH 7 to 7.5 with saturated aqueous sodium bicarbonate solution, and the mixture was washed with ethyl acetate. The aqueous layer was adjusted to pH 3 with 1N hydrochloric acid and extracted with ethyl acetate five times. The solvent was evaporated in vacuo and the residue was subjected to a column chromatography on macroporous non-ionic adsorption resin "Diaion HP-20". The object compound was eluted with 5% aqueous isopropyl alcohol solution and lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) (407.5 mg).

IR (Nujol) : 3300, 1770, 1665, 1605 cm⁻¹

NMR (D₂O + NaHCO₃, δ) : 3.20 and 3.57 (2H, ABq, J = 18Hz), 3.98 (3H, s), 4.10 (3H, s), 5.26 (1H, d, J = 5Hz), 5.27 and 5.51 (2H, ABq, J = 15Hz), 5.65 (1H, d, J = 5Hz), 7.00 (1H, s), 8.34 (1H, s), 8.48 (1H, s), 8.50 (1H, s)

Example 81

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) was obtained according to a similar manner to that of Example 80.

IR (Nujol) : 3300, 1765, 1665, 1600 cm⁻¹
NMR (D₂O, δ) : 2.04 (3H, s), 3.20 and 3.53 (2H, ABq, J = 18Hz), 3.88 (3H, s), 3.99 (3H, s), 5.23 and 5.47 (2H, ABq, J = 15Hz), 5.25 (1H, d, J = 5Hz), 5.84 (1H, d, J = 5Hz), 6.99 (1H, s), 8.13 (1H, s), 8.43 (1H, s)

The following compounds (Examples 82 to 87) were obtained according to a similar manner to that of Example 19.

**Example 82**

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1760, 1660, 1605 cm⁻¹

NMR (D₂O, δ) : 2.54 (3H, s), 3.0-3.6 (2H, m), 4.03 (3H, s), 4.08 (3H, s), 5.1-5.7 (2H, m), 5.26 (1H, d, J = 5Hz), 5.86 (1H, d, J = 5Hz), 6.63 (1H, broad s), 7.00 (1H, s), 8.09 (1H, broad s)

**Example 83**

7β-[2-(2-Aminothiazol-4-yl)-2-carboxyethylthioiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1760, 1650 cm⁻¹

**Example 84**

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate·trihydrochloride (syn isomer)

IR (Nujol) : 3300, 1770, 1660, 1630 cm⁻¹

**Example 85**

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1765, 1660 cm⁻¹

**Example 86**

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1760, 1660, 1600 cm⁻¹

**Example 87**

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1765, 1640, 1600 cm⁻¹

**Example 88**

7β-[2-(2-Aminothiazol-4-yl)-2-tert-butoxycarbonylmethoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate·trihydrochloride (syn isomer) was obtained from 7β-[2-(2-formamidothiazol-4-yl)-2-tert-butoxycarbonylmethoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) according to a similar manner to that of Example 19.

IR (Nujol) : 3300, 1775, 1715, 1670, 1630 cm⁻¹

NMR (D₂O, δ) : 1.48 (9H, s), 3.25-3.50 (2H, m), 3.68 (3H, s), 4.68 (2H, s), 5.21 (2H, broad s), 5.24 (1H, d, J = 5Hz), 5.83 (1H, d, J = 5Hz), 5.93 (1H, d, J = 3Hz), 7.19 (1H, s), 7.82 (1H, d, J = 3Hz)

**Example 89**

To a solution of trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2,4-dimethyl-3-formamido-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) (3 g) in methanol (15 ml) was added concentrated hydrochloric acid (1.57 ml) at ambient temperature. After being stirred at the
same temperature for 4 hours, the reaction mixture was added dropwise to diethyl ether, and the resulting precipitate was collected by filtration. The precipitate was dissolved in water, and the solution was adjusted to pH 2 with aqueous 5% sodium bicarbonate solution and subjected to column chromatography on macroporous non-ionic adsorption resin "Diaion HP-20". The desired compound was eluted with aqueous 5% isopropyl alcohol solution. The objective fractions were collected and the isopropyl alcohol was evaporated. The resulting aqueous solution was lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) (763.5 mg).

IR (Nujol) : 3300, 1770, 1640, 1600 cm⁻¹

NMR (D₂O, δ) : 1.93 (3H, s), 3.08 and 3.33 (2H, ABq, J = 18Hz), 3.65 (3H, s), 3.98 (3H, s), 4.88 and 5.21 (2H, ABq, J = 15Hz), 5.18 (1H, d, J = 5Hz), 5.81 (1H, d, J = 5Hz), 6.97 (1H, s), 7.66 (1H, s)

The following compounds (Examples 90 to 95) were obtained according to a similar manner to that of Example 29.

Example 90

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3350, 1770, 1660, 1610 cm⁻¹

NMR (D₂O, δ) : 3.17 and 3.50 (2H, ABq, J = 18Hz), 3.93 (3H, s), 3.98 (3H, s), 5.20 and 5.44 (2H, ABq, J = 16Hz), 5.21 (1H, d, J = 5Hz), 5.81 (1H, d, J = 5Hz), 6.96 (1H, m), 6.97 (1H, s), 8.16 (1H, d, J = 3Hz), 8.43 (1H, s)

Example 91

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2-methyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1665 cm⁻¹

NMR (D₂O, δ) : 3.12 and 3.42 (2H, ABq, J = 18Hz), 3.87 (3H, s), 5.15 and 5.42 (2H, ABq, J = 16Hz), 5.19 (1H, d, J = 5Hz), 5.81 (1H, d, J = 5Hz), 6.75 (1H, d, J = 3Hz), 6.84 (1H, t, J = 7Hz), 7.11 (1H, s), 8.06 (1H, d, J = 3Hz), 8.43 (1H, s)

Example 92

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-formamido-2-methyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1775, 1675, 1605 cm⁻¹

NMR (D₂O, δ) : 3.20 and 3.50 (2H, ABq, J = 17Hz), 4.09 (3H, s), 5.22 and 5.50 (2H, ABq, J = 15Hz), 5.23 (1H, d, J = 5Hz), 5.83 (1H, d, J = 5Hz), 6.87 (1H, t, J = 7Hz), 7.13 (1H, s), 8.23 (1H, s), 8.39 (2H, s)

Example 93

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3250, 1765, 1665, 1600 cm⁻¹

NMR (D₂O, δ) : 2.03 (3H, s), 3.21 and 3.50 (2H, ABq, J = 18Hz), 3.83 (3H, s), 5.19 and 5.45 (2H, ABq, J = 15Hz), 5.29 (1H, d, J = 5Hz), 5.88 (1H, d, J = 5Hz), 6.93 (1H, t, J = 7Hz), 7.26 (1H, s), 8.07 (1H, s), 8.38 (1H, s)

Example 94

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1665, 1605 cm⁻¹
Example 95

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1765, 1665, 1600 cm⁻¹

The following compounds (Examples 96 to 116) were obtained according to a similar manner to that of Example 32.

Example 96

Benzhydryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate • trifluoroacetate (syn isomer)

IR (Nujol) : 3200, 1790, 1720, 1680 cm⁻¹

NMR (DMSO-d₆, δ) : 3.41 (2H, m), 3.67 (3H, s), 5.22 (1H, d, J = 5Hz), 5.40 (2H, m), 5.82 (1H, dd, J = 8Hz and 5Hz), 6.90 (1H, s), 8.93 (1H, s), 6.97 (1H, s), 7.02 (1H, t, J = 77Hz), 7.02-7.83 (25H, m), 8.22 (1H, s), 8.52 (1H, s), 8.88 (1H, s), 9.85 (1H, d, J = 8Hz)

Example 97

Benzhydryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate • trifluoroacetate (syn isomer)

IR (Nujol) : 1795, 1725, 1675, 1615 cm⁻¹

NMR (DMSO-d₆, δ) : 3.40 (2H, broad s), 3.83 (3H, s), 5.22 (1H, d, J = 5Hz), 5.41 (2H, broad s), 6.81 (1H, dd, J = 5Hz and 8Hz), 6.91 (1H, s), 6.95 (1H, s), 7.01 (1H, t, J = 78Hz), 7.03-7.63 (25H, m), 8.27 (1H, s), 8.48 (1H, s), 8.57 (1H, s), 8.86 (1H, s), 9.88 (1H, d, J = 8Hz), 10.81 (1H, s)

Example 98

Benzhydryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1785, 1720, 1675 cm⁻¹

NMR (DMSO-d₆, δ) : 1.98 (3H, s), 3.43 (2H, broad s), 3.64 (3H, s), 5.28 (1H, d, J = 5Hz), 5.44 (2H, broad s), 5.85 (1H, dd, J = 5Hz and 8Hz), 6.94 (1H, s), 7.02 (1H, s), 7.10 (1H, t, J = 72Hz), 7.12-7.64 (25H, m), 8.21 (1H, s), 8.43 (1H, s), 8.96 (1H, s), 9.95 (1H, d, J = 5Hz)

Example 99

7β-[2-(2-Tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3350, 1775, 1660, 1580 cm⁻¹

Example 100

7β-[2-(2-Formamidothiazol-4-yl)-2-tert-butoxy carbonylmethoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1770, 1670, 1605 cm⁻¹

Example 101

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3350, 1770, 1660, 1610 cm⁻¹

Example 102

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1775, 1675, 1605 cm⁻¹
Example 103

\[7\beta\)-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2-methyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer)\]

IR (Nujol) : 3300, 1770, 1665 cm\(^{-1}\)

Example 104

\[7\beta\)-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate•trihydrochloride (syn isomer)\]

IR (Nujol) : 3300, 1770, 1660, 1630 cm\(^{-1}\)

Example 105

\[7\beta\)-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)\]

IR (Nujol) : 3300, 1765, 1660 cm\(^{-1}\)

Example 106

\[7\beta\)-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)\]

IR (Nujol) : 1760, 1660, 1600 cm\(^{-1}\)

Example 107

\[7\beta\)-[2-(2-Aminothiazol-4-yl)-2-tert-butoxycarbonylmethoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate•trihydrochloride (syn isomer)\]

IR (Nujol) : 3300, 1775, 1715, 1670, 1630 cm\(^{-1}\)

Example 108

\[7\beta\)-[2-(2-Aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)\]

IR (Nujol) : 3300, 1760, 1650 cm\(^{-1}\)

Example 109

\[7\beta\)-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)\]

IR (Nujol) : 3300, 1760, 1660, 1605 cm\(^{-1}\)

Example 110

\[7\beta\)-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)\]

IR (Nujol) : 3300, 1770, 1640, 1600 cm\(^{-1}\)

Example 111

\[7\beta\)-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)\]

IR (Nujol) : 3250, 1765, 1665, 1600 cm\(^{-1}\)

Example 112

\[7\beta\)-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer)\]
Example 113

Trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephe-4-carboxylate (syn isomer)

IR (Nujol): 3300, 1765, 1640, 1600 cm⁻¹

Example 114

Trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephe-4-carboxylate (syn isomer)

IR (Nujol): 3300, 1780, 1650 cm⁻¹

Example 115

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephe-4-carboxylate (syn isomer)

IR (Nujol): 3300, 1770, 1665, 1605 cm⁻¹

Example 116

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephe-4-carboxylate (syn isomer)

IR (Nujol): 3300, 1765, 1665, 1600 cm⁻¹

Example 117

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephe-4-carboxylate (syn isomer) was obtained from benzhydryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephe-4-carboxylate. trifluoroacetate (syn isomer) according to a similar manner to that of Example 45.

IR (Nujol): 3300, 1770, 1665 cm⁻¹

NMR (D₂O, δ): 3.12 and 3.42 (2H, ABq, J = 18Hz), 3.87 (3H, s), 5.15 and 5.42 (2H, ABq, J = 16Hz), 5.19 (1H, d, J = 5Hz), 5.81 (1H, d, J = 5Hz), 6.75 (1H, d, J = 3Hz), 6.84 (1H, t, J = 7Hz), 7.11 (1H, s), 8.06 (1H, d, J = 3Hz), 8.43 (1H, s)

Example 118

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl3-cephe-4-carboxylate (syn isomer) was obtained from benzhydryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephe-4-carboxylate. trifluoroacetate (syn isomer) according to a similar manner to that of Example 45.

IR (Nujol): 1775, 1675, 1605 cm⁻¹

NMR (D₂O, δ): 3.20 and 3.50 (2H, ABq, J = 17Hz), 4.09 (3H, s), 5.22 and 5.50 (2H, ABq, J = 15Hz), 5.23 (1H, d, J = 5Hz), 5.83 (1H, d, J = 5Hz), 6.87 (1H, t, J = 7Hz), 7.13 (1H, s), 8.23 (1H, s), 8.39 (2H, s)

Example 119

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephe-4-carboxylate (syn isomer) was obtained from benzhydryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephe-4-carboxylate. trifluoroacetate (syn isomer) according to a similar manner to that of Example 45.

IR (Nujol): 3250, 1765, 1665, 1600 cm⁻¹

NMR (D₂O, δ): 2.03 (3H, s), 3.21 and 3.50 (2H, ABq, J = 18Hz), 3.83 (3H, s), 5.19 and 5.45 (2H, ABq, J = 15Hz), 5.29 (1H, d, J = 5Hz), 5.88 (1H, d, J = 5Hz), 6.93 (1H, t, J = 71Hz), 7.26 (1H, s), 8.07 (1H, s), 8.38 (1H, s)

The following compounds (Examples 120 to 131) were obtained according to a similar manner to that of
Example 45.

Example 120

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol): 3350, 1770, 1660, 1610 cm⁻¹

Example 121

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate•trihydrochloride (syn isomer)
IR (Nujol): 3300, 1770, 1680, 1630 cm⁻¹

Example 122

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol): 3300, 1765, 1660 cm⁻¹

Example 123

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol): 1760, 1660, 1600 cm⁻¹

Example 124

7β-[2-(2-Aminothiazol-4-yl)-2-carboxymethoxyiminoacytamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol): 3300, 1760, 1650 cm⁻¹

Example 125

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol): 3300, 1760, 1660, 1605 cm⁻¹

Example 126

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol): 3300, 1770, 1640, 1600 cm⁻¹

Example 127

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol): 3300, 1765, 1640, 1600 cm⁻¹

Example 128

Trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol): 3350, 1770, 1655 cm⁻¹
Example 129

Trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1780, 1650 cm\(^{-1}\)

Example 130

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1665, 1605 cm\(^{-1}\)

Example 131

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1765, 1665, 1600 cm\(^{-1}\)

Example 132

Concentrated hydrochloric acid (0.136 ml) was added to a suspension of 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) (0.2 g) in methanol (1 ml) at ambient temperature. After being stirred at the same temperature for 3 hours, the mixture was added dropwise to diethyl ether (100 ml), and the precipitate was collected by filtration.

The precipitate was dissolved in water and subjected to column chromatography on macroporous non-ionic adsorption resin "Dialion HP-20". The desired product was eluted with water, and lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-aminoo-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trihydrochloride (syn isomer) (71.20 mg).

IR (Nujol) : 3300, 1770, 1660, 1630 cm\(^{-1}\)

NMR (D₂O, δ) : 3.17 and 3.43 (2H, ABq, J = 18Hz), 3.66 (3H, s), 4.03 (3H, s), 5.18 (2H, broad s), 5.21 (1H, d, J = 5Hz), 5.78 (1H, d, J = 5Hz), 5.92 (1H, d, J = 3Hz), 7.08 (1H, s), 7.79 (1H, d, J = 3Hz)

Example 133

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-aminoo-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) was obtained from trifluoroacetic acid salt of 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer) according to a similar manner to that of Example 132.

IR (Nujol) : 3300, 1770, 1640, 1600 cm\(^{-1}\)

NMR (D₂O, δ) : 1.93 (3H, s), 3.08 and 3.33 (2H, ABq, J = 18Hz), 3.65 (3H, s), 3.98 (3H, s), 4.88 and 5.21 (2H, ABq, J = 15Hz), 5.18 (1H, d, J = 5Hz), 5.81 (1H, d, J = 5Hz), 6.97 (1H, s), 7.66 (1H, s)

The following compounds (Examples 134 to 136) were obtained according to a similar manner to that of Example 132.

Example 134

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-aminoo-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1765, 1690 cm\(^{-1}\)

NMR (DMSO-d₆, δ) : 2.94 and 3.22 (2H, ABq, J = 18Hz), 3.68 (3H, s), 4.96 and 5.27 (2H, ABq, J = 15Hz), 5.00 (1H, d, J = 5Hz), 5.57 (1H, dd, J = 8Hz and 5Hz), 5.75 (1H, d, J = 3Hz), 6.90 (1H, s), 7.01 (1H, t, J = 7Hz), 7.26 (2H, broad s), 8.01 (1H, d, J = 3Hz), 9.76 (1H, d, J = 8Hz)

Example 135

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-aminoo-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1760, 1680, 1600 cm\(^{-1}\)
Example 136

\[ 7\beta-2-(2-Aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolo)methyl-3-cephem-4-carboxylate (syn isomer)\]

IR (Nujol) : 3300, 1760, 1650 cm\(^{-1}\)

Example 137

\[ 7\beta-2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolo)methyl-3-cephem-4-carboxylate (syn isomer) \]

(432.3 mg) was obtained by reacting \[ 7\beta-2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolo)methyl-3-cephem-4-carboxylate (syn isomer) (923 mg) with concentrated hydrochloric acid (0.57 ml) in methanol (5 ml) according to a similar manner to that of Example 132.

IR (Nujol) : 3300, 1765, 1640, 1600 cm\(^{-1}\)

Example 138

To a suspension of \[ 7\beta-2-(2-aminothiazol-4-yl)-2-tert-butoxycarbonylthioiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolo)methyl-3-cephem-4-carboxylate \], trihydrochloride (syn isomer) (1.2 g) in anisole (1.2 ml) and methylene chloride (3.6 ml) was added dropwise trifluoroacetic acid (2.4 ml) under ice-cooling. After being stirred at ambient temperature for 3 hours, the mixture was added dropwise to isopropyl ether (200 ml). The resultant precipitate was collected by filtration. The precipitate was dissolved in water (30 ml) and the solution was adjusted to pH 2 with 5% aqueous sodium bicarbonate solution, and then subjected to column chromatography on macroporous non-ionic adsorption resin "Diaion HP-20". The desired product was eluted with 5% aqueous isopropyl alcohol solution, and isopropyl alcohol was evaporated. The aqueous layer was lyophilized to give \[ 7\beta-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolo)methyl-3-cephem-4-carboxylate (syn isomer) (131.3 mg).

IR (Nujol) : 3300, 1760, 1650 cm\(^{-1}\)

Example 139

To a suspension of Vilsmeier reagent prepared from N,N-dimethylformamide (0.158 ml) and phosphorus chloride (0.187 ml) in tetrahydrofuran (1 ml) was added a solution of 4-chloro-2-difluoromethoxyimino-3-oxobutyric acid (0.4 g) in tetrahydrofuran (4 ml) under ice-cooling with stirring. After stirred at the same temperature for 30 minutes, this activated acid solution was added to a solution of bis(trifluoroacetic acid) salt of \[ 7\beta-amino-3-(2-methyl-1-pyrazolo)methyl-3-cephem-4-carboxylate (0.80 g) \] and N-(trimethylsilyl)-acetamide (2.9 g) in tetrahydrofuran (20 ml) under ice-cooling. The mixture was stirred at the same temperature for 1.5 hours. To the resultant mixture was added a solution of thiourea (230 mg) in N,N-dimethylacetamide (2.3 ml) at ambient temperature. After stirred at 30-35 °C for 4 hours, the resultant solution was poured into a mixture of n-hexane (30 ml) and disopropyl ether (50 ml). The precipitated mass was triturated in ethyl acetate and dried under reduced pressure. The dried glassy mass was dissolved in water (20 ml) and the aqueous solution was washed with ethyl acetate twice, adjusted to pH 2.0 with 5% aqueous sodium bicarbonate solution, and subjected to column chromatography on macroporous nonionic adsorption resin "Diaion HP-20". The column was washed with water and the object compound was eluted with 30% aqueous methanol. The fraction containing the object compound was concentrated under reduced pressure and the residue was lyophilized to give \[ 7\beta-2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolo)methyl-3-cephem-4-carboxylate (syn isomer) (0.25 g).

IR (Nujol) : 3400, 1770, 1600, 1530 cm\(^{-1}\)

NMR (D\(_2\)O, 8) : 3.20 and 3.50 (2H, ABq, J = 18Hz), 4.10 (3H, s), 5.25 (1H, d, J = 5Hz), 5.25 and 5.50 (2H, ABq, J = 14Hz), 5.85 (1H, d, J = 5Hz), 6.75 (1H, t, J = 72Hz), 7.20 (1H, s), 8.17 (2H, m)
Example 140

4-Chloro-2-methoxyimino-3-oxobutyric acid, which was obtained in advance from tert-butyl 2-methoxyl
5 amino-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate according to a similar manner to that of
Example 139 to give 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-
3-cephem-4-carboxylate (syn isomer).
IR (Nujol) : 1775, 1660, 1600 cm\(^{-1}\)

The following compounds (Examples 141 to 177) were obtained according to a similar manner to that of
Example 139.

Example 141

Trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-1-
15 pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).
IR (Nujol) : 1785, 1675 cm\(^{-1}\)

Example 142

7β-[2-(2-Aminothiazol-4-yl)-2-(3-thietanyloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-
4-carboxylate (syn isomer).
IR (Nujol) : 1770, 1660, 1605 cm\(^{-1}\)

Example 143

Trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-isoproxyiminoacetamido]-3-(2-methyl-1-
15 pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 3400, 1770, 1650 cm\(^{-1}\)

Example 144

Trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-(2-formamidothiazol-4-yl)acetamido]-3-
20 (2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 3350, 1770, 1670 cm\(^{-1}\)

Example 145

Trifluoroacetic acid salt of 7β-[2-(2-cyclopenten-1-ylloxyimino)-2-(2-formamidothiazol-4-yl)acetamido]-3-
(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 3300, 3150, 1775, 1675 cm\(^{-1}\)

Example 146

Trifluoroacetic acid salt of 7β-[2-(2-tetrahydropyranyloxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-
(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 3300, 3150, 1775, 1675 cm\(^{-1}\)

Example 147

Trifluoroacetic acid salt of 7β-[2-(difluoromethoxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-(2,5-
40 dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 1780, 1680 cm\(^{-1}\)

Example 148

7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-ylloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-
45 cephem-4-carboxylate (syn isomer)
IR (Nujol) : 3300, 1770, 1650, 1610, 1530 cm\(^{-1}\)

Example 149

7β-[2-(2-Aminothiazol-4-yl)-2-isoproxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-
50 carboxylate (syn isomer)
IR (Nujol) : 3300, 1770, 1660, 1610, 1530 cm\(^{-1}\)
Example 149

7β-[2-(2-Aminothiazol-4-yl)-2-(2-tetrahydropyran-4-yl)amino]acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1775, 1680, 1620 cm⁻¹

Example 150

7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1660, 1600 cm⁻¹

Example 151

7β-[2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3320, 1775, 1660, 1620, 1600 cm⁻¹

Example 152

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1670, 1610 cm⁻¹

Example 153

7β-[2-(2-Aminothiazol-4-yl)-2-(3-cyclopenten-1-yloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3250, 3100, 1770, 1662, 1608 cm⁻¹

Example 154

7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3260, 1765, 1660, 1605 cm⁻¹

Example 155

7β-[2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3200, 1765, 1660, 1600 cm⁻¹

Example 156

Sulfuric acid salt of 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

NMR (D₂O, δ) : 3.33 and 3.57 (2H, ABq, J=18Hz), 4.15 (3H, s), 5.30 (1H, d, J=5Hz), 5.47 (2H, br. s), 5.87 (1H, d, J=5Hz), 6.73-6.90 (1H, m), 7.0 (1H, t, J=7Hz), 7.40 (1H, s), 8.20-8.35 (2H, m)

Example 157

7β-[2-(2-Tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3350, 1775, 1660, 1580 cm⁻¹
Example 158

7β-[2-(2-Formamidothiazol-4-yl)-2-tert-butoxycarbonylmethoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 1770, 1670, 1605 cm⁻¹

Example 159

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 3350, 1770, 1660, 1610 cm⁻¹

Example 160

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 1775, 1675, 1605 cm⁻¹

Example 161

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 3300, 1770, 1665 cm⁻¹

Example 162

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate•trihydrochloride (syn isomer)
IR (Nujol) : 3300, 1770, 1660, 1630 cm⁻¹

Example 163

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 3300, 1765, 1660 cm⁻¹

Example 164

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)
IR (Nujol) : 1760, 1660, 1600 cm⁻¹

Example 165

7β-[2-(2-Aminothiazol-4-yl)-2-tert-butoxycarbonyl methoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate•trihydrochloride (syn isomer)
IR (Nujol) : 3300, 1775, 1715, 1670, 1630 cm⁻¹

Example 166

Benzhydryl 7β-[2-(2-Tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate•trifluoroacetate (syn isomer)
IR (Nujol) : 1795, 1725, 1675, 1615 cm⁻¹

Example 167

Benzhydryl 7β-[2-(2-Tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate•trifluoroacetate (syn isomer)
Example 168

\[ 7\beta-[2-(2-Aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate \text{ (syn isomer)} \]
\[ \text{IR (Nujol)}: 3200, 1790, 1720, 1680 \text{ cm}^{-1} \]

Example 169

\[ 7\beta-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate \text{ (syn isomer)} \]
\[ \text{IR (Nujol)}: 3300, 1760, 1680 \text{ cm}^{-1} \]

Example 170

\[ 7\beta-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate \text{ (syn isomer)} \]
\[ \text{IR (Nujol)}: 3300, 1770, 1640, 1600 \text{ cm}^{-1} \]

Example 171

Benzhydryl \[ 7\beta-[2-(2-tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate \text{ (syn isomer)} \]
\[ \text{IR (Nujol)}: 1785, 1720, 1675 \text{ cm}^{-1} \]

Example 172

\[ 7\beta-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate \text{ (syn isomer)} \]
\[ \text{IR (Nujol)}: 3250, 1765, 1665, 1600 \text{ cm}^{-1} \]

Example 173

\[ 7\beta-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate \text{ (syn isomer)} \]
\[ \text{IR (Nujol)}: 3300, 1765, 1640, 1600 \text{ cm}^{-1} \]

Example 174

Trifluoroacetonic acid salt of \[ 7\beta-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate \text{ (syn isomer)} \]
\[ \text{IR (Nujol)}: 3350, 1770, 1655 \text{ cm}^{-1} \]

Example 175

Trifluoroacetonic acid salt of \[ 7\beta-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate \text{ (syn isomer)} \]
\[ \text{IR (Nujol)}: 3300, 1780, 1650 \text{ cm}^{-1} \]

Example 176

\[ 7\beta-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate \text{ (syn isomer)} \]
\[ \text{IR (Nujol)}: 3300, 1770, 1665, 1605 \text{ cm}^{-1} \]
Example 177

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol): 3300, 1765, 1665, 1600 cm\(^{-1}\)

The following compounds (Examples 178 to 185) were obtained according to a similar manner to that of Example 1.

Example 178

Benzhydryl 7β-[2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-[2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate chloride (syn isomer)

IR (Nujol): 3300, 1785, 1720, 1670, 1620, 1530 cm\(^{-1}\)

Example 179

Benzhydryl 7β-[2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate chloride (syn isomer).

IR (Nujol): 1785, 1720, 1675, 1630 cm\(^{-1}\)

Example 180

Benzhydryl 7β-[2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).

IR (Nujol): 1780, 1720, 1670, 1625, 1600 cm\(^{-1}\)

Example 181

Benzhydryl 7β-[2-(2-cyclopenten-1-yloxyimino)-2-(2-formamidothiazol-4-yl)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).

IR (Nujol): 1785, 1720, 1685, 1670 cm\(^{-1}\)

Example 182

Benzhydryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-difluoromethoxyiminoacetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).

IR (Nujol): 1790, 1720, 1685, 1605 cm\(^{-1}\)

Example 183

Benzhydryl 7β-[2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).

IR (Nujol): 1785, 1720, 1680, 1600 cm\(^{-1}\)

Example 184

Benzhydryl 7β-[2-(2-cyclopenten-1-yloxyimino)-2-(2-formamidothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate iodide (syn isomer).

IR (Nujol): 3300, 1780, 1720, 1670, 1540 cm\(^{-1}\)

Example 185

Benzhydryl 7β-[2-(2-cyclopenten-1-yloxyimino)-2-(2-formamidothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).

IR (Nujol): 3200, 1780, 1720, 1670, 1540 cm\(^{-1}\)
Example 186

To a mixture of benzhydryl 7β-[2-(cyclopenten-1-yl)oxyimino]-2-(2-formamidothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer, 4.9 g) in a mixture of methanol (50 ml) and tetrahydrofuran (10 ml) was added conc. hydrochloric acid (2.13 g) and the mixture was stirred at ambient temperature for 3 hours. Water (50 ml) and ethyl acetate (50 ml) were added thereto and the mixture was adjusted to pH 7.0 with 5% aqueous solution of sodium bicarbonate. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated to give benzhydryl 7β-[2-(cyclopenten-1-yl)oxyimino]acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate chloride (syn isomer, 3.66 g).

IR (Nujol) : 3300, 1785, 1720, 1670, 1620, 1530 cm⁻¹
NMR (DMSO-d₆, δ) : 2.00 (2H, m), 2.32 (2H, m), 3.50 (2H, m), 3.85 (3H, s), 5.28 (1H, d, J = 5Hz), 5.30-6.32 (5H, m), 6.73 (1H, s), 6.87 (1H, t, J = 2Hz), 6.95 (1H, s), 7.42 (10H, m), 8.45 (1H, d, J = 2Hz), 7.55 (1H, d, J = 2Hz), 9.58 (1H, d, J = 8Hz)

Example 187

Benzhydryl 7β-[2-(cyclopenten-1-yl)oxyimino]acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate chloride (syn isomer) was obtained according to a similar manner to that of Example 186.

IR (Nujol) : 1785, 1720, 1675, 1630 cm⁻¹
NMR (DMSO-d₆, δ) : 1.82-2.48 (4H, m), 3.48 (2H, br s), 3.83 (3H, s), 4.49 (2H, s), 5.28 (1H, d, J = 5Hz), 5.30 (1H, m), 5.48 (2H, br s), 5.90-6.18 (2H, m), 5.93 (1H, dd, J = 8Hz, 5Hz), 6.86 (1H, s), 6.91 (1H, s), 7.18-7.57 (10H, m), 8.33 (1H, s), 8.43 (1H, s), 9.74 (1H, d, J = 8Hz).

Example 188

Benzhydryl 7β-[2-(cyclopenten-1-yl)oxyimino]acetamido]-3-(4-methoxy-2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer) was obtained according to a similar manner to that of Example 186.

IR (Nujol) : 1780, 1720, 1670, 1625, 1600 cm⁻¹
NMR (DMSO-d₆, δ) : 1.72-2.53 (4H, m), 3.50 (2H, br s), 3.79 (6H, s), 5.28 (1H, d, J = 5Hz), 5.30 (1H, m), 5.47 (2H, br s), 5.80-6.18 (3H, m), 6.66 (1H, s), 6.91 (1H, s), 7.12-7.56 (10H, m), 8.33 (1H, s), 8.44 (1H, s), 9.68 (1H, d, J = 8Hz)

Example 189

4-Hydroxymethyl-1-methylpyrazole (2.5 ml) was added to a solution of benzhydryl 7β-[2-(cyclopenten-1-yl)oxyimino]-2-(2-formamidothiazol-4-yl)acetamido]-3-chloromethyl-3-cephem-4-carboxylate (syn isomer, 2.5 g) and sodium iodide (0.553 g) in acetone (2.5 ml) at ambient temperature. After stirring for 12 hours, the reaction mixture was poured into a mixture of ethyl acetate, tetrahydrofuran and water. The separated organic layer was washed with brine, dried over magnesium sulfate, and evaporated. The residue was dissolved in tetrahydrofuran, and the solution was subjected to column chromatography on Amberlite IRA-400 (CF₃COO⁻ form), and eluted with tetrahydrofuran. The fractions containing the object compound were collected and evaporated to give benzhydryl 7β-[2-(cyclopenten-1-yl)oxyimino]-2-(2-formamidothiazol-4-yl)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer, 2.25 g).

IR (Nujol) : 1785, 1720, 1685, 1670 cm⁻¹
NMR (DMSO-d₆, δ) : 1.87-2.52 (4H, m), 3.83 (2H, s), 3.82 (3H, s), 4.42 (2H, s), 5.28 (1H, d, J = 5Hz), 5.30 (1H, m), 5.43 (2H, br s), 5.87 (1H, dd, J = 8Hz, 5Hz), 5.88-6.18 (2H, m), 6.93 (1H, s), 7.18-7.52 (11H, m), 8.26 (1H, s), 8.40 (1H, s), 8.48 (1H, s), 9.64 (1H, s, J = 8Hz)

The following compounds (Examples 190 to 198) were obtained according to a similar manner to that of Example 189.

Example 190

Benzhydryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-difluoromethoxyiminoacetamido]-3-(4-methoxy-2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer)
Example 191

Benzhydryl 7β-[2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).

IR (Nujol) : 1785, 1720, 1680, 1600 cm⁻¹

NMR (DMSO-d₆, δ) : 3.49 and 3.76 (2H, ABq, J = 18Hz), 3.74 (6H, s), 5.19 (1H, d, J = 5Hz), 5.24 and 5.49 (2H, ABq, J = 16Hz), 5.77 (1H, dd, J = 8Hz, 5Hz), 6.86 (1H, s), 6.92 (1H, s), 6.97 (1H, t, J = 7Hz), 7.01-7.56 (25H, m), 8.13 (1H, s), 8.31 (1H, s), 8.83 (1H, s), 9.78 (1H, d, J = 8Hz).

Example 192

Benzhydryl 7β-[2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate chloride (syn isomer).

IR (Nujol) : 3300, 1785, 1720, 1670, 1620, 1530 cm⁻¹

Example 193

Benzhydryl 7β-[2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate chloride (syn isomer).

IR (Nujol) : 1785, 1720, 1675, 1630 cm⁻¹

Example 194

Benzhydryl 7β-[2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer)

IR (Nujol) : 1780, 1720, 1670, 1625, 1600 cm⁻¹

Example 195

Benzhydryl 7β-[2-(2-cyclopenten-1-yloxyimino)-2-(2-formamidothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate iodide (syn isomer).

IR (Nujol) : 3300, 1780, 1720, 1670, 1540 cm⁻¹

Example 196

Benzhydryl 7β-[2-(2-cyclopenten-1-yloxyimino)-2-(2-formamidothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).

IR (Nujol) : 3200, 1780, 1720, 1670, 1540 cm⁻¹

Example 197

7β-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol) : 3250, 1765, 1690, 1600 cm⁻¹

Example 198

7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol) : 3300, 1675, 1605 cm⁻¹

The following compounds (Examples 199 to 208) were obtained according to a similar manner to that of Example 139.
Example 199

Benzhydryl 7β-(2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxymino)acetamido)-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate chloride (syn isomer).

IR (Nujol): 3300, 1785, 1720, 1670, 1620, 1530 cm⁻¹

Example 200

Benzhydryl 7β-(2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxymino)acetamido)-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate chloride (syn isomer).

IR (Nujol): 1785, 1720, 1675, 1630 cm⁻¹

Example 201

Benzhydryl 7β-(2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxymino)acetamido)-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).

IR (Nujol): 1780, 1720, 1670, 1825, 1600 cm⁻¹

Example 202

Benzhydryl 7β-(2-(2-cyclopenten-1-yloxymino)-2-(2-formamidothiazol-4-yl)acetamido)-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).

IR (Nujol): 1785, 1720, 1685, 1670 cm⁻¹

Example 203

Benzhydryl 7β-(2-(2-tritylaminothiazol-4-yl)-2-difluoromethoxyiminoacetamido)-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).

IR (Nujol): 1790, 1720, 1685, 1605 cm⁻¹

Example 204

Benzhydryl 7β-[2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yloxymino)acetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).

IR (Nujol): 1785, 1720, 1680, 1600 cm⁻¹

Example 205

Benzhydryl 7β-[2-(2-cyclopenten-1-yloxymino)-2-(2-formamidothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate iodide (syn isomer).

IR (Nujol): 3300, 1780, 1720, 1670, 1540 cm⁻¹

Example 206

Benzhydryl 7β-[2-(2-cyclopenten-1-yloxymino)-2-(2-formamidothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).

IR (Nujol): 3200, 1780, 1720, 1670, 1540 cm⁻¹

Example 207

7β-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol): 3250, 1765, 1660, 1600 cm⁻¹

Example 208

7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxymino)acetamido]-3-(4-methoxy-2-methyl-1-pyrazolio). methyl-3-cephem-4-carboxylate (syn isomer).
Example 209

A mixture of benzhydryl 7β-[2-(2-cyclopenten-1-yloxyimino)-2-(2-formamidothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate 1-oxide iodide (syn isomer, 5.3 g) and N,N-dimethylformamide (50 ml) was stirred at -33 °C and phosphorus trichloride (1.68 g) was added thereto with stirring. The reaction mixture was stirred for 10 minutes at the same temperature, and poured into water (400 ml). Precipitates were collected by filtration and washed with water to give benzhydryl 7β-[2-(2-cyclopenten-1-yloxyimino)-2-(2-formamidothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate iodide (syn isomer, 4.95 g).

IR (Nujol): 3300, 1675, 1605 cm⁻¹

NMR (DMSO-δ6, δ): 2.20 (2H, m), 2.32 (2H, m), 3.30-3.75 (2H, m), 3.85 (3H, s), 5.30 (1H, d, J = 5Hz), 5.30-6.27 (5H, m), 6.90 (1H, t, J = 2Hz), 6.98 (1H, s), 7.43 (11H, m), 8.45 (1H, d, J = 2Hz), 8.54 (1H, s), 8.54 (1H, m), 9.68 (1H, d, J = 8Hz)

Example 210

Benzhydryl 7β-[2-(2-cyclopenten-1-yloxyimino)-2-(2-formamidothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate iodide (syn isomer, 4.9 g) was dissolved in tetrahydrofuran (18.75 ml) and water (1.25 ml), the solution was subjected to column chromatography on an ion-exchange resin Amberlite IRA-400* (Trademark, manufactured by Rohm and Haas Co.) (CF₃COO⁻ form) and eluted with a mixture of water and tetrahydrofuran (1:15). The fractions containing the object compound were collected and evaporated. The residue was triturated with diisopropyl ether to give benzhydryl 7β-[2-(2-cyclopenten-1-yloxyimino)-2-(2-formamidothiazol-4-yl)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer, 5.0 g).

IR (Nujol): 3200, 1780, 1720, 1670, 1540 cm⁻¹

NMR (DMSO-δ6, δ): 2.17 (2H, m), 2.33 (2H, m), 3.43 (2H, m), 3.82 (3H, s), 5.28 (1H, d, J = 5Hz), 5.33-6.25 (5H, m), 6.85 (1H, t, J = 2Hz), 7.37 (11H, m), 8.32 (1H, d, J = 2Hz), 8.47 (1H, br. s), 8.47 (1H, m), 9.62 (1H, d, J = 8Hz)

The following compounds (Examples 211 to 231) were obtained according to a similar manner to that of Example 209.

Example 211

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol): 3400, 1770, 1660, 1600, 1530 cm⁻¹

Example 212

Trifluoroacetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol): 1785, 1675 cm⁻¹

Example 213

7β-[2-(2-Aminothiazol-4-yl)-2-(3-thietanyloxyimino)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol): 1770, 1660, 1605 cm⁻¹

Example 214

7β-[2-(2-Aminothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol): 3300, 1770, 1650, 1610, 1530 cm⁻¹
Example 215

7β-[2-(2-Aminothiazol-4-yl)-2-isopropoxyiminoacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol) : 3300, 1770, 1660, 1610, 1530 cm⁻¹

Example 216

7β-[2-(2-Aminothiazol-4-yl)-2-{2-tetrahydropyran-2-yl}oxyimino]acacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol) : 3300, 1775, 1680, 1620 cm⁻¹

Example 217

7β-[2-(2-Aminothiazol-4-yl)-2-{cyclopent-1-1-yl}oxyimino]acacetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1660, 1600 cm⁻¹

Example 218

7β-[2-(2-Aminothiazol-4-yl)-2-{difuoromethoxyimino]acacetamido]-3-(2,5-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1670, 1610 cm⁻¹

Example 219

7β-[2-(2-Aminothiazol-4-yl)-2-{cyclopent-1-1-yl}oxyimino]acacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3250, 3100, 1770, 1662, 1608 cm⁻¹

Example 220

7β-[2-(2-Aminothiazol-4-yl)-2-{hydroxyimino]acacetamido]-3-(4-hydroxymethyl-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3200, 1765, 1660, 1600 cm⁻¹

Example 221

Sulfuric acid salt of 7β-[2-(2-aminothiazol-4-yl)-2-{difuoromethoxyimino]acacetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer)

NMR (D₂O, δ) : 3.33 and 3.57 (2H, ABq, J = 18Hz), 4.15 (3H, s), 5.30 (1H, d, J = 5Hz), 5.47 (2H, br. s), 5.87 (1H, d, J = 5Hz), 6.73-6.90 (1H, m), 7.0 (1H, t, J = 71Hz), 7.40 (1H, s), 8.20-8.35 (2H, m)

Example 222

7β-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol) : 3250, 1765, 1660, 1600 cm⁻¹

Example 223

7β-[2-(2-Aminothiazol-4-yl)-2-cyclopent-1-1-yl]oxyimino]acacetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol) : 3300, 1675, 1605 cm⁻¹
Example 224

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyliminoacetamido]-3-(3-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).
IR (Nujol) : 3350, 1770, 1660, 1610 cm⁻¹

Example 225

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-formamido-2-methyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer).
IR (Nujol) : 1775, 1675, 1605 cm⁻¹

Example 226

7β-[2-(2-Aminothiazol-4-yl)-2-tert-butoxycarbonylmethoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trihydrochloride (syn isomer).
IR (Nujol) : 3300, 1775, 1715, 1670, 1630 cm⁻¹

Example 227

Benzyldryl 7β-[2-(2-tritylaminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(4-formamido-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer).
IR (Nujol) : 1795, 1725, 1675, 1615 cm⁻¹

Example 228

7β-[2-(2-Aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-(3-amino-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).
IR (Nujol) : 3300, 1760, 1650 cm⁻¹

Example 229

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).
IR (Nujol) : 3300, 1770, 1640, 1600 cm⁻¹

Example 230

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-formamido-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).
IR (Nujol) : 3250, 1765, 1665, 1650 cm⁻¹

Example 231

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (syn isomer).
IR (Nujol) : 3300, 1765, 1640, 1600 cm⁻¹

The following compounds (Examples 232 and 233) were obtained according to a similar manner to that of Example 1.

Example 232

7β-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(4-methoxy-2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (syn isomer).
IR (Nujol) : 3250, 1765, 1660, 1600 cm⁻¹
Example 233

7β-[2-(2-Amino(thiazol-4-yl)-2-(2-cyclopenten-1-yl)-oxyimino)acetamido]-3-(4-methoxy-2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate (syn isomer).

IR (Nujol) : 3300, 1675, 1605 cm⁻¹

Example 234

Sodium carbonate (6.06 g) was added to a suspension of sulfuric acid salt of 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate (syn isomer) (35 g) in water (105 ml) and then the solution was allowed to stand at 3 to 5 °C for 14 hours. The resultant precipitates were collected by filtration, washed with cool water (50 ml) and dried to give crystals of 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate· dihydrate (syn isomer) (23.8 g).

mp : 249-251 °C

IR (Nujol) : 3480, 3150, 1775, 1650, 1610, 1530 cm⁻¹

Example 235

1N-Hydrochloric acid (3.9 ml) was added to a solution of 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate dihydrate (syn isomer) (2 g) in water (50 ml). The resultant aqueous solution was lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate hydrochloride (syn isomer) (21 g).

IR (Nujol) : 3210, 1780, 1670, 1630, 1530 cm⁻¹

NMR (D₂O, δ) : 3.28 and 3.60 (2H, ABq, J = 18Hz), 4.13 (3H, s), 5.30 (1H, d, J = 5Hz), 5.35 and 5.53 (2H, ABq, J = 14Hz), 5.87 (1H, d, J = 5Hz), 6.80 (1H, t, J = 3Hz), 6.87 (1H, t, J = 72Hz), 7.37 (1H, s), 8.23 (2H, d, J = 3Hz).

Example 236

7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate dihydrochloride (syn isomer) (1.02 g) was obtained by treating 7β-[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolyl)methyl-3-cephem-4-carboxylate dihydrate (syn isomer) (1 g) with 1N hydrochloric acid (3.9 ml) according to a similar manner to that of Example 235.

IR (Nujol) : 3200 (broad), 1780, 1670, 1630, 1540 cm⁻¹

NMR (D₂O, δ) : 3.33 and 3.65 (2H, ABq, J = 18Hz), 4.15 (3H, s), 5.33 (1H, d, J = 5Hz), 5.52 (2H, s), 5.88 (1H, d, J = 5Hz), 6.82 (1H, t, J = 3Hz), 6.98 (1H, t, J = 72Hz), 7.42 (1H, s), 8.25 (2H, d, J = 3Hz).

Preparation 31

A mixture of 2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetic acid (100 g) (syn isomer) (RS mixture), (R)-(+)-1-phenylethylamine (38.8 g) and ethanol (100 ml) was stirred at ambient temperature for 3 hours. The precipitates crystallized out of the solution were collected by filtration, washed with ethanol and disopropyl ether to give their crude salt (50 g). The salt was dissolved in ethanol (750 ml) under reflux, and cooled. The first precipitates were filtered off and the filtrate was allowed to stand at ambient temperature for 4 days. The precipitates crystallized out of the solution were collected by filtration, washed with ethanol and disopropyl ether to give (R)-(+)-1-phenylethylamine salt of one isomer of 2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetic acid (17.3 g) (syn isomer).

Sodium bicarbonate (7.1 g) was added to a solution of the salt obtained above (17 g) in ethyl acetate (200 ml) and water (200 ml), and the mixture was stirred at ambient temperature for 3 hours. The separated aqueous layer was adjusted to pH 2.5 with 6N-hydrochloric acid. The precipitates were collected by filtration, washed with water to give one isomer of 2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yloxyimino)acetic acid (11.2 g) (syn isomer).

mp : 160 °C (dec.)

[α]D = -25.5 ° (c = 1.0%, MeOH:H₂O = 1:1)

IR (Nujol) : 3200, 3100, 3050, 2570, 2400, 1705, 1690, 1590, 1550 cm⁻¹

Hereinafter this isomer is referred to as "A isomer" and a compound derived from this isomer is also
referred to as "A isomer".

Preparation 32

A mixture of 2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yl)oxime)acetic acid (syn isomer, RS mixture) (100 g) and (S)-(-)-1-phenylethylamine (38.8 g) in ethanol (500 ml) was stirred at ambient temperature for 18 hours. The precipitates crystallized out of the solution were collected by filtration, washed with ethanol and diisopropyl ether to give their crude salt (71.7 g).

The salt (70 g) was dissolved in ethanol (1050 ml) under reflux and then cooled. The resultant precipitates were collected by filtration, washed with ethanol and diisopropyl ether to give (S)-(-)-1-phenylethylamine salt of the other isomer of 2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yl)oxime)acetic acid (31.5 g).

This salt (30 g) was converted to free acid according to a similar manner to that of Preparation 31 to give the other isomer of 2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yl)oxime)acetic (syn isomer) (19.36 g).

mp: 164 °C (dec.)

[α]D = +22.3° (c = 1.0%, MeOH:H2O = 1:1)

IR (Nujol): 3200, 3100, 3050, 2570, 2400, 1715, 1710, 1595, 1560 cm⁻¹

Hereinafter this isomer is referred to as "B isomer" and a compound derived from this isomer is also referred to as "B isomer".

Example 237

N,N-Dimethylformamido (0.75 g) and phosphor chloride (1.57 ml) were mixed to prepare Vilsmeier reagent in a usual manner, and the resultant Vilsmeier reagent was suspended in dry ethyl acetate (22 ml).

To the suspension was added 2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yl)oxime)acetic acid (A isomer) (syn isomer) (2.3 g) under ice-cooling with stirring, and then the mixture was stirred for an hour to prepare an activated acid solution. To a solution of bis(trifluoracetic acid)jwas salt of 7β-amino-3-(2-methyl-1-pyrazolio)methyl-3-ceph-4-carboxylate (4.7 g) and N-monotrimethylsilyl)acetamide (11.8 g) in ethyl acetate (50 ml) was added the activated acid solution prepared above at 3 °C. After stirring at the same temperature for an hour, the mixture was poured into diisopropyl ether (500 ml). The precipitates were collected by filtration and successively washed with diisopropyl ether to give trifluoracetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yl)oxime)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-ceph-4-carboxylate (A isomer) (syn isomer) (6.02 g).

IR (Nujol): 3100, 1780, 1660, 1540 cm⁻¹

NMR (DMSO-d₆, δ): 2.07 (2H, m), 2.30 (2H, m), 3.38 (2H, broad s), 4.03 (3H, s), 5.17 (1H, d, J=5Hz), 5.40 (1H, m), 5.53 (2H, broad s), 5.87 (1H, dd, J=5Hz and 8Hz), 5.95 (2H, m), 6.87 (1H, t, J=3Hz), 7.32 (1H, s), 8.47 (1H, s), 8.57 (1H, d, J=3Hz), 9.60 (1H, d, J=8Hz)

Example 238

Trifluoracetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yl)oxime)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-ceph-4-carboxylate (B isomer) (syn isomer) was obtained from 2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yl)oxime)acetic acid (B isomer) (syn isomer) and bis(trifluoracetic acid) salt of 7β-amino-3-(2-methyl-1-pyrazolio)methyl-3-ceph-4-carboxylate according to a similar manner to that of Example 237.

IR (Nujol): 3150, 1780, 1660, 1540 cm⁻¹

NMR (DMSO-d₆, δ): 2.10 (2H, m), 2.33 (2H, m), 3.40 (2H, broad s), 4.07 (3H, s), 5.20 (1H, d, J=5Hz), 5.22 (1H, m), 5.57 (2H, broad s), 5.93 (1H, dd, J=5Hz and 8Hz), 5.80-6.20 (2H, m), 6.90 (1H, t, J=3Hz), 7.35 (1H, s), 8.50 (1H, s), 8.67 (1H, d, J=3Hz), 9.60 (1H, d, J=8Hz)

Example 239

Conc. hydrochloric acid (4.1 g) was added to a solution of trifluoracetic acid salt of 7β-[2-(2-formamidothiazol-4-yl)-2-(2-cyclopenten-1-yl)oxime)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-ceph-4-carboxylate (A isomer) (syn isomer) (5.8 g) in methanol (60 ml), and the mixture was stirred at ambient temperature for 2 hours. To the reaction mixture was added water (60 ml) and adjusted to pH 2.0 with 5% aqueous solution of sodium bicarbonate. The separated aqueous solution was subjected to column
chromatography on macroporous non-ionic adsorption resin "Dialion HP-20" (120 ml) and eluted with 30% aqueous solution of methanol. The fractions containing the object compound were collected and concentrated in vacuo, then lyophilized to give 7β-[2-(2-aminothiazol-4-yl)-2-(2-cyclopenten-1-yl oxymino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (A isomer) (syn isomer) (1.1 g).

\[ \alpha_0^p = +38.5^\circ (C = 1.0 \%, \text{MeOH}:\text{H}_2\text{O} = 1:1) \]
IR (Nujol): 3300, 1770, 1660, 1610, 1530 cm\(^{-1}\)
NMR (D\(_2\)O-NaHCO\(_3\), \(\delta\)): 2.10 (2H, m), 2.34 (2H, m), 3.13 and 3.43 (2H, ABq, J = 18Hz), 4.06 (3H, s), 5.16 (1H, d, J = 5Hz), 5.30 (1H, m), 5.18 and 5.48 (2H, ABq, J = 14Hz), 5.75 (1H, d, J = 5Hz), 5.88 (1H, m), 6.10 (1H, m), 6.70 (1H, t, J = 3Hz), 8.66 (1H, s), 8.10 (2H, m)

Example 240

7β-[2-(2-Amino thiazol-4-yl)-2-(2-cyclopenten-1-yl oxymino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (B isomer) (syn isomer) was obtained according to a similar manner to that of Example 239.

\[ \alpha_0^p = +64.0^\circ (C = 1.0 \%, \text{MeOH}:\text{H}_2\text{O} = 1:1) \]
IR (Nujol): 3250, 1760, 1660, 1600, 1615 cm\(^{-1}\)
NMR (D\(_2\)O-NaHCO\(_3\), \(\delta\)): 2.10 (2H, m), 2.32 (2H, m), 3.13 and 3.42 (2H, ABq, J = 18Hz), 4.06 (3H, s), 5.16 (1H, d, J = 5Hz), 5.30 (1H, m), 5.20 and 5.43 (2H, ABq, J = 14Hz), 5.75 (1H, d, J = 5Hz), 5.90 (1H, m), 6.10 (1H, m), 6.70 (1H, t, J = 3Hz), 8.67 (1H, s), 8.10 (2H, m)

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A new cephem compound of the formula:

![Chemical Structure](image.png)

wherein

- **R\(^1\)** is amino or protected amino,
- **R\(^2\)** is hydrogen, tetrahydropropyl amine, (C\(_1\)-C\(_6\))alkyl, dihalogenated (C\(_1\)-C\(_6\))alkyl, cyclo(C\(_3\)-C\(_8\))alkyl, thienyl, carboxy (C\(_1\)-C\(_6\))alkyl or protected carboxy (C\(_1\)-C\(_6\))alkyl,
- **R\(^3\)** is (C\(_1\)-C\(_6\))alkyl,
- **R\(^4\)** and **R\(^5\)** are each hydrogen, (C\(_1\)-C\(_6\))alkyl, hydroxy (C\(_1\)-C\(_6\))alkyl, (C\(_1\)-C\(_6\))alkoxy amino or protected amino,
- **R\(^6\)** is COO\(^-\), carboxy or protected carboxy,
- **X\(^\circ\)** is an anion, and
- **n** is 0 or 1,

with proviso that

(i) when **R\(^2\)** is carboxy (C\(_1\)-C\(_6\))alkyl or protected carboxy (C\(_1\)-C\(_6\))alkyl, then **R\(^4\)** is hydrogen and **R\(^5\)** is amino,

(ii) when **R\(^6\)** is COO\(^-\), then **n** is 0, and

(iii) when **R\(^6\)** is carbon or protected carboxy, then **n** is 1, and a pharmaceutically acceptable salt thereof.

2. A syn isomer of the compound of claim 1.

3. A compound of claim 2,

wherein

- **R\(^2\)** is hydrogen, tetrahydropropyl amine, (C\(_1\)-C\(_6\))alkyl, dihalogenated (C\(_1\)-C\(_6\))alkyl, cyclo(C\(_3\)-C\(_8\))alkenyl
4. A compound of claim 3, wherein
   \[ \text{R}^1 \text{ is amino,} \]
   \[ \text{R}^2 \text{ is } (\text{C}_1-\text{C}_6)\text{alkyl or dihalogenated } (\text{C}_1-\text{C}_6)\text{alkyl,} \]
   \[ \text{R}^3 \text{ and } \text{R}^5 \text{ are each hydrogen, } (\text{C}_1-\text{C}_6)\text{alkyl or amino, and} \]
   \[ \text{R}^6 \text{ is } \text{COO}^\circ. \]

5. A compound of claim 4, wherein
   \[ \text{R}^2 \text{ is dihalogenated } (\text{C}_1-\text{C}_6)\text{alkyl,} \]
   \[ \text{R}^3 \text{ and } \text{R}^5 \text{ are each hydrogen.} \]

6. A compound of claim 5, which is
   \[ 7\beta-[2-(2\text{-aminothiazol-4-yl})-2-(\text{difluoromethoxyimino})\text{acetamido}]3-(2\text{-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate } (\text{syn isomer}). \]

7. A compound of claim 5, which is
   \[ \text{sulfuric acid salt of } 7\beta-[2-(2\text{-aminothiazol-4-yl})-2-(\text{difluoromethoxyimino})\text{acetamido}]3-(2\text{-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylate } (\text{syn isomer}). \]

8. A compound of claim 4, wherein
   \[ \text{R}^4 \text{ is } (\text{C}_1-\text{C}_6)\text{alkyl, and} \]
   \[ \text{R}^5 \text{ is } \text{amino.} \]

9. A compound of claim 8, which is selected from a group consisting of:
   \[ 7\beta-[2-(2\text{-aminothiazol-4-yl})-2\text{-methoxyiminoacetamido}]3-(3\text{-amino-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate } (\text{syn isomer}) \] and
   \[ 7\beta-[2-(2\text{-aminothiazol-4-yl})-2-(\text{difluoromethoxyimino})\text{acetamido}]3-(3\text{-amino-2,4-dimethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate } (\text{syn isomer}). \]

10. A process for preparing a compound of claim 1, or its salt, which comprises
    \[ (1) \text{ reacting a compound of the formula :} \]

\[
\begin{align*}
H_2N & \quad \text{S} \quad \text{N} \quad \text{CH}_2 \quad \text{+} \quad \text{R}^5 \\
\text{O} & \quad \text{N} \quad \text{R}^6 \quad \text{R}^4 \quad \text{+} \quad X^\circ \quad \text{n}
\end{align*}
\]


wherein
\[ \text{R}^3, \text{R}^4, \text{R}^5, \text{X}^\circ \text{ and } n \text{ are each as defined above,} \]
or its reactive derivative at the amino group
or its salt with a compound of the formula :
wherein \( R^1 \) and \( R^2 \) are each as defined above, or its reactive derivative at the carboxy group or its salt, or

(2) subjecting a compound of the formula:

wherein

\( R^2, R^3, R^4, R^6, X^a \) and \( n \) are each as defined above, and

\( R^a \)

is protected amino,

or its salt to elimination reaction of the amino protective group in \( R^a \) to give a compound of the formula:

wherein

\( R^2, R^3, R^4, R^6, X^a \) and \( n \) are each as defined above,

or its salt, or

(3) reacting a compound of the formula:

wherein

\( R^1, R^2 \) are each as defined above,

\( R^6 \)

is carboxy or protected carboxy, and

\( Y \)

is a leaving group,
or its salt with a compound of the formula:

\[
\begin{align*}
\text{R}^3, \text{R}^4 \quad \text{and} \quad \text{R}^6 & \quad \text{are each as defined above,} \\
\text{or its salt, to give a compound of the formula:}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{X}^a \quad \text{and} \quad n & \quad \text{are each as defined above,} \\
\text{or its salt, or} \\
\text{(4) subjecting a compound of the formula:}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5 \quad \text{are each as defined above,} \\
\text{R}^6 & \quad \text{is protected carboxy, and} \\
n & \quad \text{is 1,} \\
\text{or its salt to elimination reaction of the carboxy protective group in} \text{R}^6 \text{to give a compound of the formula:}
\end{align*}
\]
wherein
R¹, R², R³, R⁴, R⁵ and X⁰ are each as defined above, and
R⁰ is COO⁻ or carboxy,
with proviso that
(i) when R⁰ is COO⁻, then n is 0 and
(ii) when R⁰ is carboxy, then n is 1,
or its salt, or
(5) subjecting a compound of the formula:

wherein
R¹, R², R³, R⁴, R⁵, R⁶, X⁰ and n are each as defined above, and
R⁰ is tetrahydropyranyl,
or its salt, to elimination reaction of the tetrahydropyranyl of R⁰ to give a compound of the formula:

wherein
R¹, R³, R⁴, R⁵, R⁶, X⁰ and n are each as defined above,
or its salt, or
(6) subjecting a compound of the formula:

\[
\begin{align*}
& R^1 \quad \text{N} \quad \text{C-CONH} \quad \text{N} \quad \text{O} \quad \text{R}^2 \quad \text{S} \\
& \quad \text{\{N} \quad \text{O} \quad \text{R}^2 \quad \text{CH}_2 \quad \text{N} \quad \text{R}^6 \\
& \quad \text{\{N} \quad \text{R}^3 \quad \text{R}^4 \quad \text{X}^\circ \quad \text{n}
\end{align*}
\]

wherein

\( R^1, R^2, R^3, R^4, R^6, X^\circ \) and \( n \) are each as defined above, and
\( R^5 \) is protected amino,

or its salt to elimination reaction of the amino protective group in \( R^5 \) to give a compound of the formula:

\[
\begin{align*}
& R^1 \quad \text{N} \quad \text{C-CONH} \quad \text{N} \quad \text{O} \quad \text{R}^2 \quad \text{S} \\
& \quad \text{\{N} \quad \text{NH}_2 \quad \text{R}^4 \quad \text{X}^\circ \quad \text{n}
\end{align*}
\]

wherein

\( R^1, R^2, R^3, R^4, R^6, X^\circ \) and \( n \) are each as defined above,

or its salt, or

(7) subjecting a compound of the formula:

\[
\begin{align*}
& R^1 \quad \text{N} \quad \text{C-CONH} \quad \text{N} \quad \text{O} \quad \text{R}^2 \quad \text{S} \\
& \quad \text{\{N} \quad \text{NH}_2 \quad \text{R}^4 \quad \text{X}^\circ \quad \text{n}
\end{align*}
\]

wherein

\( R^1, R^3, X^\circ \) and \( n \) are each as defined above, and
\( R^6 \) is protected carboxy(C1-C6)alkyl,

or its salt to elimination reaction of the carboxy protective group in \( R^6 \), to give a compound of the formula:
wherein
\[ R_1^1, R_2^1, R_3^1, X_0^1 \text{ and } n \]
are each as defined above, and
\[ R_2^2 \]
is carboxy(C_{1-6})alkyl,
or its salt, or
(8) reacting a compound of the formula:

\[
\begin{align*}
Z-\text{CH}_2\text{COCCONH} & \\
& \\
\text{O} \text{O} \text{R}_2^2
\end{align*}
\]
wherein
\[ R_1^2, R_2^2, R_3^2, X_0^2 \text{ and } n \]
are each as defined above, and
\[ Z \]
is an acid residue,
or its salt with a compound of the formula:

\[
\begin{align*}
\text{S} \text{H}_2\text{N-C-R}_1^1
\end{align*}
\]
wherein
\[ R_1^1 \]
is as defined above,
to give a compound of the formula:

\[
\begin{align*}
\text{R}_1^1 & \\
& \text{N} \text{C-CONH} \\
& \text{O} \text{O} \text{R}_2^2
\end{align*}
\]
wherein
\[ R_1^1, R_2^1, R_3^1, R_4^1, R_5^1, X_0^1 \text{ and } n \]
are each as defined above, or
reducing a compound of the formula:

wherein
R¹, R², R³, R⁴, R⁵, X⁰, and n are each as defined above,

or its salt.

11. A compound of the formula:

wherein
R³ is (C₁₋C₆)alkyl,
R⁴ and R⁶ are each hydrogen, (C₁₋C₆)alkyl, hydroxy(C₁₋C₆)alkyl, (C₁₋C₆)alkoxy, amino or protected amino,
with proviso that R⁴ and R⁶ are not hydrogens at the same time,
R⁶ is COO⁰, carboxy or protected carboxy,
X⁰ is an anion, and
n is 0 or 1,

with proviso that
(i) when R⁶ is COO⁰, then n is 0, and
(ii) when R⁶ is carboxy or protected carboxy,
then n is 1 and its salt.

12. A compound of the formula:

wherein
13. A compound of the formula:

![Chemical Structure Image]

wherein

- $R^1$ is amino or protected amino,
- $R^2$ is hydrogen, tetrahydropyranyl, $(C_1-C_6)$alkyl, dihalogenated $(C_1-C_6)$alkyl, cyclo$(C_3-C_6)$-alkenyl, thietanyl, carboxy$(C_1-C_6)$alkyl or protected carboxy$(C_1-C_6)$alkyl,
- $R^3$ is $(C_1-C_6)$alkyl,
- $R^4$ and $R^5$ are each hydrogen, $(C_1-C_6)$alkyl, hydroxy$(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxy, amino or protected amino,
- $R^6$ is COO$^\circ$, carboxy or protected carboxy,
- $X^o$ is an anion,
- $Z$ is an acid residue, and
- $n$ is 0 or 1,

with proviso that

(i) when $R^2$ is carboxy$(C_1-C_6)$alkyl or protected carboxy$(C_1-C_6)$alkyl, then $R^4$ is hydrogen and $R^6$ is amino,
(ii) when $R^6$ is COO$^\circ$, then $n$ is 0, and
(iii) when $R^6$ is carboxy or protected carboxy, then $n$ is 1, and its salt.

14. 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.

15. A use of a compound of claim 1 or pharmaceutically acceptable salt thereof for manufacture of an antimicrobial medicament.

16. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.
Claim for the following Contracting States: AT, ES

1. A process for preparing a new cepham compound of the formula:

   \[
   \text{\begin{align*}
   &\text{C-CONH} \quad \text{S} \quad \text{CH}_2 \\
   &\text{O-} \quad \text{R}^2 \quad \text{N} \quad \text{R}^4 \cdot (\text{X}^{-})_n
   \end{align*}}
   \]

   wherein
   \begin{itemize}
   \item \( R^1 \) is amino or protected amino,
   \item \( R^2 \) is hydrogen, tetrahydropranyl, (C\(_1\)-C\(_5\))alkyl, dihalogenated (C\(_1\)-C\(_5\))alkyl, cyclo(C\(_2\)-
   C\(_6\))alkenyl, thietyl, carboxy(C\(_1\)-C\(_8\))alkyl or protected carboxy(C\(_1\)-C\(_8\))alkyl,
   \item \( R^3 \) is (C\(_1\)-C\(_6\))alkyl,
   \item \( R^4 \) and \( R^5 \) are each hydrogen, (C\(_1\)-C\(_6\))alkyl, hydroxy(C\(_1\)-C\(_3\))alkyl, (C\(_1\)-C\(_6\))alkoxy, amino or pro-
   tection amino,
   \item \( R^6 \) is COO\(^-\), carboxy or protected carboxy,
   \item \( X^o \) is an anion, and
   \item \( n \) is 0 or 1,
   \end{itemize}

   with proviso that
   \begin{itemize}
   \item (i) when \( R^2 \) is carboxy(C\(_1\)-C\(_6\))alkyl or protected carboxy(C\(_1\)-C\(_6\))alkyl, then \( R^4 \) is hydrogen and \( R^5 \) is
   amino,
   \item (ii) when \( R^6 \) is COO\(^-\), then \( n \) is 0, and
   \item (iii) when \( R^6 \) is carboxy or protected carboxy, then \( n \) is 1,
   \end{itemize}

   or its reactive derivative at the amino group

   or its salt, which comprises
   \begin{itemize}
   \item (1) reacting a compound of the formula:
   \end{itemize}

   \[
   \text{\begin{align*}
   &\text{H}_2\text{N} \quad \text{CH}_2 \quad \text{R}^5 \\
   &\text{O} \quad \text{R}^6 \quad \text{N} \quad \text{R}^4 \cdot (\text{X}^{-})_n
   \end{align*}}
   \]

   wherein
   \begin{itemize}
   \item \( R^3, R^4, R^5, X^o \) and \( n \) are each as defined above,
   \end{itemize}

   or its reactive derivative at the amino group

   or its salt with a compound of the formula:

   \[
   \text{\begin{align*}
   &\text{R}^1 \quad \text{C-COOH} \\
   &\text{S} \quad \text{N} \\
   &\text{O-} \quad \text{R}^2
   \end{align*}}
   \]

   wherein \( R^1 \) and \( R^2 \) are each as defined above, or its reactive derivative at the carboxy group or its

   salt, or
(2) subjecting a compound of the formula:

\[
\begin{align*}
&\text{R}_a^1 \quad \text{N} \\
&\quad \text{C-CONH} \\
&\quad \{ \text{N} \} \\
&\quad \text{O-}\text{R}_2 \\
&\quad \text{R}_5^5 \quad (X^-)_n \\
&\quad \text{R}_4^4 \\
&\quad \text{R}_6^6 \\
&\quad \text{R}_3^3 \\
&\text{N} \\
&\text{C-CONH} \\
&\{ \text{N} \} \\
&\text{O-}\text{R}_2 \\
&\text{R}_5^5 \quad (X^-)_n \\
&\text{R}_4^4 \\
&\text{R}_6^6 \\
&\text{R}_3^3 \\
&\text{N}
\end{align*}
\]

wherein
\( R_a^1, R_3^3, R_4^4, R_5^5, R_6^6, X^\alpha \) and \( n \) are each as defined above, and
\( R_a^1 \) is protected amino,
or its salt to elimination reaction of the amino protective group in \( R_a^1 \) to give a compound of the formula:

\[
\begin{align*}
&\text{H}_2\text{N} \\
&\quad \text{C-CONH} \\
&\quad \{ \text{N} \} \\
&\quad \text{O-}\text{R}_2 \\
&\quad \text{R}_5^5 \quad (X^-)_n \\
&\quad \text{R}_4^4 \\
&\quad \text{R}_6^6 \\
&\quad \text{R}_3^3 \\
&\quad \text{N}
\end{align*}
\]

wherein
\( R_2^2, R_3^3, R_4^4, R_5^5, R_6^6, X^\alpha \) and \( n \) are each as defined above,
or its salt, or

(3) reacting a compound of the formula:

\[
\begin{align*}
&\text{R}_a^1 \\
&\quad \text{N} \\
&\quad \text{C-CONH} \\
&\quad \{ \text{N} \} \\
&\quad \text{O-}\text{R}_2 \\
&\quad \text{R}_6^6 \\
&\quad \text{R}_a^a \quad \text{Y}
\end{align*}
\]

wherein
\( R_1^1 \) and \( R_2^2 \) are each as defined above,
\( R_6^6 \) is carboxy or protected carboxy, and
\( Y \) is a leaving group,
or its salt with a compound of the formula:
wherein

\( R^0, R^4 \) and \( R^6 \) are each as defined above,
or its salt, to give a compound of the formula:

wherein

\( R^1, R^2, R^3, R^6, R^8, X^0 \) and \( n \) are each as defined above,
or its salt, or

(4) subjecting a compound of the formula:

wherein

\( R^1, R^2, R^3, R^6, X^0 \) are each as defined above,
\( R^0 \) is protected carboxy, and
\( n \) is 1,
or its salt to elimination reaction of the carboxy protective group in \( R^0 \) to give a compound of the formula:
wherein
\[ R^1, R^2, R^3, R^4, R^5 \text{ and } X^o \] are each as defined above, and
\[ R^6 \] is COO\(^-\) or carboxy,
with proviso that
(i) when \( R^6 \) is COO\(^-\), then \( n \) is 0 and
(ii) when \( R^6 \) is carboxy, then \( n \) is 1,
or its salt, or
(5) subjecting a compound of the formula:

\[
\begin{array}{c}
\text{R}^1 \begin{array}{c} \\
N
\end{array} \begin{array}{c}
S \\
\text{C-CONH}
\end{array} \begin{array}{c}
N
\end{array} \begin{array}{c}
S \\
\text{CH}_2
\end{array} \begin{array}{c}
N
\end{array} \begin{array}{c}
(\text{X}^-)_n
\end{array} \\
\text{R}^5 \\
\text{R}^4
\end{array}
\]

wherein
\[ R^1, R^2, R^3, R^4, R^5, X^o \] and \( n \) are each as defined above, and
\[ R^6 \] is tetrahydropyranyl,
or its salt, to elimination reaction of the tetrahydropyranyl of \( R^6 \) to give a compound of the formula:

\[
\begin{array}{c}
\text{R}^1 \begin{array}{c}
N
\end{array} \begin{array}{c}
S \\
\text{C-CONH}
\end{array} \begin{array}{c}
N
\end{array} \begin{array}{c}
S \\
\text{CH}_2
\end{array} \begin{array}{c}
N
\end{array} \begin{array}{c}
(\text{X}^-)_n
\end{array} \\
\text{R}^5 \\
\text{R}^4
\end{array}
\]

wherein
\[ R^1, R^2, R^3, R^4, R^5, X^o \text{ and } n \] are each as defined above,
or its salt, or
(6) subjecting a compound of the formula:

\[
\begin{array}{c}
\text{R}^1 \begin{array}{c}
N
\end{array} \begin{array}{c}
S \\
\text{C-CONH}
\end{array} \begin{array}{c}
N
\end{array} \begin{array}{c}
S \\
\text{CH}_2
\end{array} \begin{array}{c}
N
\end{array} \begin{array}{c}
(\text{X}^-)_n
\end{array} \\
\text{R}^5 \\
\text{R}^4
\end{array}
\]

wherein
\[ R^1, R^2, R^3, R^4, R^5, X^o \text{ and } n \] are each as defined above, and
\[ R^6 \] is protected amino,
or its salt to elimination reaction of the amino protective group in \( R^6 \) to give a compound of the formula:
wherein

- $R^1$, $R^2$, $R^3$, $R^4$, $X^\alpha$ and $n$ are each as defined above, or its salt, or

(7) subjecting a compound of the formula:

wherein

- $R^1$, $R^3$, $R^6$, $X^\alpha$ and $n$ are each as defined above, and
- $R^C$ is protected carboxy(C$_1$-C$_6$)alkyl,

or its salt to elimination reaction of the carboxy protective group in $R^C$, to give a compound of the formula:

wherein

- $R^1$, $R^3$, $R^6$, $X^\alpha$ and $n$ are each as defined above, and
- $R^C$ is carboxy(C$_1$-C$_6$)alkyl,

or its salt, or

(8) reacting a compound of the formula:
wherein

\( R^2, R^3, R^4, R^6, X^0 \) and \( n \) are each as defined above, and
\( Z \) is an acid residue,
or its salt with a compound of the formula:

\[
\begin{array}{c}
\text{H}_2N-C-R^1 \\
\end{array}
\]

wherein

\( R^1 \) is as defined above,
to give a compound of the formula:

wherein

\( R^1, R^2, R^3, R^4, R^6, X^0 \) and \( n \) are each as defined above, or
(9) reducing a compound of the formula:

wherein

\( R^1, R^2, R^3, R^4, R^6, X^0 \) and \( n \) are each as defined above,
or its salt.
Claims for the following Contracting State: GR

1. A process for preparing a new cepham compound of the formula:

\[
\begin{align*}
\text{R}^1 & \quad \text{is amino or protected amino,} \\
\text{R}^2 & \quad \text{is hydrogen, tetrahydropranyl, (C}_1\text{-C}_6\text{)alkyl, dihalogenated (C}_1\text{-C}_6\text{)alkyl, cyclo(C}_2\text{-C}_6\text{)alkenyl, thietanyl, carboxy(C}_1\text{-C}_8\text{)alkyl or protected carboxy(C}_1\text{-C}_8\text{)alkyl,} \\
\text{R}^3 & \quad \text{is (C}_1\text{-C}_6\text{)alkyl,} \\
\text{R}^4 \text{ and } \text{R}^6 & \quad \text{are each hydrogen, (C}_1\text{-C}_6\text{)alkyl, hydroxy(C}_1\text{-C}_6\text{)alkyl, (C}_1\text{-C}_6\text{)alkoxy, amino or protected amino,} \\
\text{R}^6 & \quad \text{is COO}^\text{a}, \text{ carboxy or protected carboxy,} \\
\text{X}^\text{a} & \quad \text{is an anion, and} \\
n & \quad \text{is 0 or 1,}
\end{align*}
\]

with proviso that

(i) when R\text{\textsuperscript{2}} \text{ is carboxy(C}_1\text{-C}_6\text{)alkyl or protected carboxy(C}_1\text{-C}_6\text{)alkyl, then R}\text{\textsuperscript{4}} \text{ is hydrogen and R}\text{\textsuperscript{6}} \text{ is amino,} \\
(ii) when R\text{\textsuperscript{6}} \text{ is COO}^\text{a}, \text{ then n is 0, and} \\
(iii) when R\text{\textsuperscript{6}} \text{ is carboxy or protected carboxy, then n is 1,} \\
or its salt, which comprises

(1) reacting a compound of the formula:

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{R}^4 \text{ and } \text{R}^6, \text{X}^\text{a} \text{ and n are each as defined above,} \\
& \quad \text{or its reactive derivative at the amino group or its salt with a compound of the formula:}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & \quad \text{is amino or protected amino,} \\
\text{R}^2 & \quad \text{is hydrogen, tetrahydropranyl, (C}_1\text{-C}_6\text{)alkyl, dihalogenated (C}_1\text{-C}_6\text{)alkyl, cyclo(C}_2\text{-C}_6\text{)alkenyl, thietanyl, carboxy(C}_1\text{-C}_8\text{)alkyl or protected carboxy(C}_1\text{-C}_8\text{)alkyl,} \\
\text{R}^3 & \quad \text{is (C}_1\text{-C}_6\text{)alkyl,} \\
\text{R}^4 \text{ and } \text{R}^6 & \quad \text{are each hydrogen, (C}_1\text{-C}_6\text{)alkyl, hydroxy(C}_1\text{-C}_6\text{)alkyl, (C}_1\text{-C}_6\text{)alkoxy, amino or protected amino,} \\
\text{R}^6 & \quad \text{is COO}^\text{a}, \text{ carboxy or protected carboxy,} \\
\text{X}^\text{a} & \quad \text{is an anion, and} \\
n & \quad \text{is 0 or 1,}
\end{align*}
\]

(2) reacting a compound of the formula:

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{R}^4 \text{ and } \text{R}^6, \text{X}^\text{a} \text{ and n are each as defined above,} \\
& \quad \text{or its reactive derivative at the carboxy group or its salt with a compound of the formula:}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & \quad \text{is amino or protected amino,} \\
\text{R}^2 & \quad \text{is hydrogen, tetrahydropranyl, (C}_1\text{-C}_6\text{)alkyl, dihalogenated (C}_1\text{-C}_6\text{)alkyl, cyclo(C}_2\text{-C}_6\text{)alkenyl, thietanyl, carboxy(C}_1\text{-C}_8\text{)alkyl or protected carboxy(C}_1\text{-C}_8\text{)alkyl,} \\
\text{R}^3 & \quad \text{is (C}_1\text{-C}_6\text{)alkyl,} \\
\text{R}^4 \text{ and } \text{R}^6 & \quad \text{are each hydrogen, (C}_1\text{-C}_6\text{)alkyl, hydroxy(C}_1\text{-C}_6\text{)alkyl, (C}_1\text{-C}_6\text{)alkoxy, amino or protected amino,} \\
\text{R}^6 & \quad \text{is COO}^\text{a}, \text{ carboxy or protected carboxy,} \\
\text{X}^\text{a} & \quad \text{is an anion, and} \\
n & \quad \text{is 0 or 1,}
\end{align*}
\]
(2) subjecting a compound of the formula:

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \\
\text{C} & \quad \text{CONH} \\
\text{N} & \quad \text{II} \\
\text{O} & \quad \text{R}^2 \\
\text{R}^5 & \quad \text{X}^\circ \quad \text{R}^4 \cdot (\text{X}^\circ)^n
\end{align*}
\]

wherein
\(\text{R}^1, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{X}^\circ\) and \(n\) are each as defined above, and
\(\text{R}^a\) is protected amino,
or its salt to elimination reaction of the amino protective group in \(\text{R}^a\) to give a compound of the formula:

\[
\begin{align*}
\text{H}_2 & \quad \text{N} \\
\text{C} & \quad \text{CONH} \\
\text{N} & \quad \text{II} \\
\text{O} & \quad \text{R}^2 \\
\text{R}^5 & \quad \text{X}^\circ \quad \text{R}^4 \cdot (\text{X}^\circ)^n
\end{align*}
\]

wherein
\(\text{R}^1, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{X}^\circ\) and \(n\) are each as defined above,
or its salt, or
(3) reacting a compound of the formula:

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \\
\text{C} & \quad \text{CONH} \\
\text{N} & \quad \text{II} \\
\text{O} & \quad \text{R}^2 \\
\text{R}^6 & \quad \text{CH}_2 - \text{Y}
\end{align*}
\]

wherein
\(\text{R}^1, \text{R}^2\) are each as defined above,
\(\text{R}^a\) is carboxy or protected carboxy, and
\(\text{Y}\) is a leaving group,
or its salt with a compound of the formula:
wherein

$R^3$, $R^4$, and $R^5$ are each as defined above, or its salt, to give a compound of the formula:

$$\text{R}^1 \text{N} \text{C-CONH} \text{S} \text{R}^6 \text{CH}_2 \text{N} \text{R}^5 \cdot (\text{X}^-)_n$$

wherein

$R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $X^n$ and $n$ are each as defined above, or its salt, or

(4) subjecting a compound of the formula:

$$\text{R}^1 \text{N} \text{C-CONH} \text{S} \text{R}^6 \text{CH}_2 \text{N} \text{R}^5 \cdot (\text{X}^-)_n$$

wherein

$R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $X^n$ are each as defined above, $R^6$ is protected carboxy, and $n$ is 1,

or its salt to elimination reaction of the carboxy protective group in $R^6$ to give a compound of the formula:

$$\text{R}^1 \text{N} \text{C-CONH} \text{S} \text{R}^6 \text{CH}_2 \text{N} \text{R}^5 \cdot (\text{X}^-)_n$$
wherein
\[ R^1, R^2, R^3, R^4, R^6 \] and \( X^0 \) are each as defined above, and
\[ R^6 \] is COO\(^{-}\) or carboxy,

with proviso that
(i) when \( R^6 \) is COO\(^{-}\), then \( n \) is 0 and
(ii) when \( R^6 \) is carboxy, then \( n \) is 1,

or its salt, or
(5) subjecting a compound of the formula:

![Chemical Structure 1](image1)

wherein
\[ R^1, R^3, R^4, R^6, X^0 \] and \( n \) are each as defined above, and
\[ R^6 \] is tetrahydropyranyl,

or its salt, to elimination reaction of the tetrahydropyranyl of \( R^6 \) to give a compound of the formula:

![Chemical Structure 2](image2)

wherein
\[ R^1, R^3, R^4, R^6, X^0 \] and \( n \) are each as defined above,
or its salt, or
(6) subjecting a compound of the formula:

![Chemical Structure 3](image3)

wherein
\[ R^1, R^2, R^3, R^4, R^6, X^0 \] and \( n \) are each as defined above, and
\[ R^6 \] is protected amino,
or its salt to elimination reaction of the amino protective group in \( R^6 \) to give a compound of the formula:

![Chemical Structure 4](image4)
wherein
R¹, R², R³, R⁴, R⁵, X⁰ and n are each as defined above, or its salt, or
(7) subjecting a compound of the formula:

wherein
R¹, R³, R⁶, X⁰ and n are each as defined above, and
R⁶ is protected carboxy(C₅₋C₆)alkyl, or its salt to elimination reaction of the carboxy protective group in R⁶ , to give a compound of the formula:

wherein
R¹, R³, R⁶, X⁰ and n are each as defined above, and
R⁶ is carboxy(C₅₋C₆)alkyl, or its salt, or
(8) reacting a compound of the formula:

$$Z - \text{CH}_2 \text{COCCONH} \quad \begin{array}{c}
\text{N} \\
\text{O} - \text{R}^2
\end{array}$$

wherein
$$R^2, R^3, R^4, R^5, R^6, X^0$$ and $$n$$ are each as defined above, and
$$Z$$ is an acid residue,

or its salt with a compound of the formula:

$$\quad \begin{array}{c}
S \\
\text{H}_2\text{N-C-R}^1
\end{array}$$

wherein
$$R^1$$ is as defined above,
to give a compound of the formula:

$$\quad \begin{array}{c}
\text{N} \\
\text{O} - \text{R}^2
\end{array}$$

wherein
$$R^1, R^2, R^3, R^4, R^5, X^0$$ and $$n$$ are each as defined above, or
(9) reducing a compound of the formula:

$$\quad \begin{array}{c}
\text{N} \\
\text{O} - \text{R}^2
\end{array}$$

wherein
$$R^1, R^2, R^3, R^4, R^5, X^0$$ and $$n$$ are each as defined above,
or its salt.
2. Modification of the process claimed in claim 1 which is characterized by bringing a compound or a non-toxic salt thereof, produced by a process claimed in claim 1, into pharmaceutically acceptable form by admixture or presentation of said compound with a pharmaceutically acceptable diluent or carrier.

5 Patentansprüche

Patentansprüche für folgende Vertragsstaaten: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Neue Cephemverbindung der Formel

![Chemical Structure](image)

worin bedeuten:

- \( R^1 \) Amino oder geschütztes Amino,
- \( R^2 \) Wasserstoff, Tetrahydropyranyl, \((C_1-C_6)\)-Alkyl, dihalogeniertes \((C_1-C_6)\)-Alkyl, Cyclo\((C_3-C_7)\)-alkeny1, Thietyl, Carboxy\((C_1-C_6)\)-alkyl oder geschütztes Carboxy\((C_1-C_6)\)-alkyl,
- \( R^3 \) \((C_1-C_6)\)-Alkyl,
- \( R^4 \) und \( R^5 \) jeweils Wasserstoff, \((C_1-C_6)\)-Alkyl, Hydroxy\((C_1-C_6)\)-alkyl, \((C_1-C_6)\)-Alkoxy, Amino oder geschütztes Amino,
- \( R^6 \) COO\(^{-}\), Carboxy oder geschütztes Carboxy,
- \( X^a \) ein Anion und
- \( n \) die Zahl 0 oder 1,

mit der Maßgabe, daß

i) wenn \( R^2 \) für Carboxy\((C_1-C_6)\)-alkyl oder geschütztes Carboxy\((C_1-C_6)\)-alkyl steht, dann \( R^6 \) Wasserstoff und \( R^5 \) Amino darstellen,

ii) wenn \( R^6 \) für COO\(^{-}\) steht, dann \( n = 0 \), und

iii) wenn \( R^6 \) für Carboxy oder geschütztes Carboxy steht, dann \( n = 1 \), und ein pharmazeutisch akzeptables Salz derselben.

2. syn-Isomer der Verbindung nach Anspruch 1.

3. Verbindung nach Anspruch 2, worin \( R^2 \) für Wasserstoff, Tetrahydropyranyl, \((C_1-C_6)\)-Alkyl, dihalogeniertes \((C_1-C_6)\)-Alkyl, Cyclo\((C_3-C_7)\)-alkeny1 oder Thietyl steht.

4. Verbindung nach Anspruch 3, worin bedeuten:

- \( R^1 \) Amino,
- \( R^2 \) \((C_1-C_6)\)-Alkyl oder dihalogeniertes \((C_1-C_6)\)-Alkyl,
- \( R^4 \) und \( R^5 \) jeweils Wasserstoff, \((C_1-C_6)\)-Alkyl oder Amino und
- \( R^6 \) COO\(^{-}\).

5. Verbindung nach Anspruch 4, worin bedeuten:

- \( R^2 \) dihalogeniertes \((C_1-C_6)\)-Alkyl,
- \( R^4 \) und \( R^5 \) jeweils Wasserstoff.

6. Verbindung nach Anspruch 5, bei der es sich handelt um

7ß-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-1-pyrazolio)methyl-3-cephem-4-carboxylat (syn-Isomer).
7. Verbindung nach Anspruch 5, bei der es sich handelt um
das Schwefelsäuresalz von 7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(2-methyl-
1-pyrazolio)methyl-3-cephem-4-carboxylat (syn-Isomer).

8. Verbindung nach Anspruch 4, worin bedeuten:
   \( R^4 \) (C\(_1\)-C\(_6\))-Alkyl und
   \( R^5 \) Amino.

9. Verbindung nach Anspruch 8, die ausgewählt wird aus der Gruppe, die besteht aus:
   7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)methyl-3-
cephem-4-carboxylat (syn-Isomer) und
   7β-[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-(3-amino-2,4-dimethyl-1-pyrazolio)-
methyl-3-cephem-4-carboxylat (syn-Isomer).

10. Verfahren zur Herstellung einer Verbindung nach Anspruch 1 oder ihres Salzes, das umfaßt
   1) die Umsetzung einer Verbindung der Formel

   \[
   \text{H}_2\text{N} - \text{N} - \text{S} - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{N} - \text{S} - \text{CH}_2 - \text{N} - \text{S} - \text{CH}_2 - \text{N} - \text{S} - \text{CH}_2 - \text{N} - \text{R}^4 - (X^-)^n
   \]

   worin \( R^3, R^4, R^5, X^- \) und \( n \) jeweils wie oben definiert sind,
oder ihres reaktionsfähigen Derivats an der Aminogruppe oder ihres Salzes mit einer Verbindung der
Formel

   \[
   \text{R}^1 - \text{N} - \text{S} - \text{COOH}
   \]

   \[
   \text{R}^2 - \text{O} - \text{R}^2
   \]

   worin \( R^1 \) und \( R^2 \) jeweils wie oben definiert sind,
oder ihrem reaktionsfähigen Derivat an der Carboxygruppe oder ihrem Salz oder
2) die Durchführung einer Reaktion zur Eliminierung der Aminoschutzgruppe in \( R^1_a \) aus einer
Verbindung der Formel

   \[
   \text{R}^1_a - \text{N} - \text{S} - \text{C} - \text{CONH} - \text{S} - \text{CH}_2 - \text{N} - \text{S} - \text{CH}_2 - \text{N} - \text{S} - \text{CH}_2 - \text{N} - \text{S} - \text{CH}_2 - \text{N} - \text{R}^5 - (X^-)^n
   \]

   worin \( R^2, R^3, R^4, R^5, X^- \) und \( n \) jeweils wie oben definiert sind und \( R^1_a \) für geschütztes Amino
steht,
or Ihrem Salz unter Bildung einer Verbindung der Formel

worin \( R^2, R^3, R^4, R^5, X^0 \) und \( n \) jeweils wie oben definiert sind,
or ihres Salzes oder
3) die Umsetzungschar einer Verbindung der Formel

worin \( R^1 \) und \( R^2 \) jeweils wie oben definiert sind, \( R^0_a \) für Carboxy oder geschütztes Carboxy und \( Y \) für eine austretende Gruppe stehen,
or ihres Salzes mit einer Verbindung der Formel

worin \( R^3, R^4 \) und \( R^5 \) jeweils wie oben definiert sind,
or ihrem Salz unter Bildung einer Verbindung der Formel

worin \( R^1, R^2, R^3, R^4, R^5, X^0 \) und \( n \) jeweils wie oben definiert sind,
or ihres Salzes oder
4) die Durchführung einer Reaktion zur Eliminierung der Carboxyschutzgruppe in \( R^0_b \) aus einer
Verbindung der Formel
worin $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ und $X^\circ$ jeweils wie oben definiert sind, $R^6$ für geschütztes Carboxyl und $n$ für die Zahl 1 stehen, oder ihrem Salz unter Bildung einer Verbindung der Formel.

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ und $X^\circ$ wie oben definiert sind und $R^6$ für COO$^\circ$ oder Carboxyl steht, mit der Maßgabe, daß
i) wenn $R^6$ für COO$^\circ$ steht, dann $n = 0$, und
ii) wenn $R^6$ für Carboxyl steht, dann $n = 1$,
oder ihres Salzes oder
5) die Durchführung einer Reaktion zur Eliminierung der Tetrahydropyranylgruppe von $R^6$, aus einer Verbindung der Formel.

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $X^\circ$ und $n$ jeweils wie oben definiert sind und $R^6$ für Tetrahydropyranyl steht, oder ihrem Salz unter Bildung einer Verbindung der Formel.

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $X^\circ$ und $n$ jeweils wie oben definiert sind und $R^6$ für Tetrahydropyranyl steht, oder ihrem Salz unter Bildung einer Verbindung der Formel.
worin R¹, R², R³, R⁴, R⁵, X⁶ und n jeweils wie oben definiert sind, oder ihres Salzes oder
6) die Durchführung einer Reaktion zur Eliminierung der Aminoschutzgruppe in R₅ₓ aus einer Verbindung der Formel

worin R¹, R², R³, R⁴, R⁵, X⁶ und n jeweils wie oben definiert sind und R₅ₓ für geschütztes Amino steht, oder ihres Salzes unter Bildung einer Verbindung der Formel

worin R¹, R², R³, R⁴, R⁵, X⁶ und n jeweils wie oben definiert sind, oder ihres Salzes oder
7) die Durchführung einer Reaktion zur Eliminierung der Carboxyschutzgruppe in R₇ₓ aus einer Verbindung der Formel

worin R¹, R², R³, R⁴, X⁶ und n jeweils wie oben definiert sind und R₇ₓ für geschütztes Carboxy(C₁-C₆)-alkyl steht, oder ihres Salzes unter Bildung einer Verbindung der Formel
worin $R^1$, $R^2$, $R^6$, $X^0$ und $n$ jeweils wie oben definiert sind und $R^6$ für Carboxy(C1-C6)-alkyl steht, oder ihres Salzes oder

8) die Umsetzung einer Verbindung der Formel

\[ \text{S} \]
\[ H_2N-C-R_1 \]

worin $R^1$ wie oben definiert ist, unter Bildung einer Verbindung der Formel

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^6$, $R^6$, $X^0$ und $n$ jeweils wie oben definiert sind, oder

9) die Reduktion einer Verbindung der Formel

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^6$, $X^0$ und $n$ jeweils wie oben definiert sind, oder ihres Salzes.
11. Verbindung der Formel

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{S} & \quad \text{N} \\
\text{CH}_2 & \quad \text{N} \\
\text{R}^5 & \quad \text{R}^4 \cdot (X^o)\_n
\end{align*}
\]

worin bedeuten:

- \( R^3 \) (C\(_1\)-C\(_6\))-Alkyl,
- \( R^a \) und \( R^b \) jeweils Wasserstoff, (C\(_1\)-C\(_6\))-Alkyl, Hydroxy(C\(_1\)-C\(_6\))-alkyl, (C\(_1\)-C\(_6\))-Alkoxy, Amino oder geschütztes Amino, mit der Maßgabe, daß \( R^a \) und \( R^b \) nicht gleichzeitig Wasserstoffatome darstellen,
- \( R^6 \) COO\(^o\), Carboxy oder geschütztes Carboxy,
- \( X^o \) ein Anion und
- \( n \) die Zahl 0 oder 1,

mit der Maßgabe, daß

i) wenn \( R^6 \) für COO\(^o\) steht, dann \( n = 0 \) und
ii) wenn \( R^6 \) für Carboxy oder geschütztes Carboxy steht, dann \( n = 1 \),

und ihr Salz.

12. Verbindung der Formel

\[
\begin{align*}
\text{Z} & \quad \text{CH}_2\text{COCONH} \\
\text{O} - \text{R}^2 & \quad \text{N} \\
\text{S} & \quad \text{N} \\
\text{CH}_2 & \quad \text{N} \\
\text{R}^5 & \quad \text{R}^4 \cdot (X^o)\_n
\end{align*}
\]

worin bedeuten:

- \( R^2 \) Wasserstoff, Tetrahydrofuran(C\(_1\)-C\(_6\))-alkyl, dihalogeniertes (C\(_1\)-C\(_6\))-Alkyl, Cyclo(C\(_2\)-C\(_6\))-alkenyl, Thietanyl, Carboxy(C\(_1\)-C\(_6\))-alkyl oder geschütztes Carboxy(C\(_1\)-C\(_6\))-alkyl,
- \( R^3 \) (C\(_1\)-C\(_6\))-Alkyl und
- \( R^a \) und \( R^b \) jeweils Wasserstoff, (C\(_1\)-C\(_6\))-Alkyl, Hydroxy(C\(_1\)-C\(_6\))-alkyl, (C\(_1\)-C\(_6\))-Alkoxy, Amino oder geschütztes Amino,
- \( R^6 \) COO\(^o\), Carboxy oder geschütztes Carboxy,
- \( X^o \) ein Anion,
- \( Z \) einen Säurerest und
- \( n \) die Zahl 0 oder 1,

mit der Maßgabe, daß

i) wenn \( R^2 \) für Carboxy(C\(_1\)-C\(_6\))-alkyl oder geschütztes Carboxy(C\(_1\)-C\(_6\))-alkyl steht, dann \( R^4 \) Wasserstoff und \( R^6 \) Amino bedeuten,
ii) wenn \( R^6 \) für COO\(^o\) steht, dann \( n = 0 \), und
iii) wenn \( R^6 \) für Carboxy oder geschütztes Carboxy steht, dann \( n = 1 \),

und ihr Salz.
13. Verbindung der Formel

worin bedeuten:

\[ R^1 \]  Amino oder geschütztes Amino,
\[ R^2 \]  Wasserstoff, Tetrahydropyranyl, \((C_1-C_6)\)-Alkyl, dihalogeniertes \((C_1-C_6)\)-Alkyl, Cyclo-
\[ R^3 \]  \((C_3-C_6)\)-alkenylen, Thietanyl, Carboxy\((C_1-C_6)\)-alkyl oder geschütztes Carboxy\((C_1-C_6)\)-
aldehyd,
\[ R^4 \]  \((C_1-C_6)\)-Alkyl,
\[ R^5 \]  jeweils Wasserstoff, \((C_1-C_6)\)-Alkyl, Hydroxy\((C_1-C_6)\)-alkyl, \((C_1-C_6)\)-Alkoxy, Amino oder
\[ R^6 \]  geschütztes Amino,
\[ X^o \]  COO\(^{-}\), Carboxy oder geschütztes Carboxy,
\[ n \]  die Zahl 0 oder 1,

mit der Maßgabe, daß

i) wenn \( R^6 \) für Carboxy\((C_1-C_6)\)-alkyl oder geschütztes Carboxy\((C_1-C_6)\)-alkyl steht, dann \( R^6 \) Wasser-

ii) wenn \( R^6 \) für COO\(^{-}\) steht, dann \( n = 0 \), und

iii) wenn \( R^6 \) für Carboxy oder geschütztes Carboxy steht, dann \( n = 1 \),

und ihr Salz.

14. Pharmazeutische Zusammensetzung, die als aktiven Bestandteil (Wirkstoff) eine Verbindung nach
Anspruch 1 oder ein pharmazeutisch akzeptables Salz derselben im Gemisch mit pharmazeutisch
akzeptablen Trägern enthält.

15. Verwendung einer Verbindung nach Anspruch 1 oder eines pharmazeutisch akzeptablen Salzes
derselben zur Herstellung eines antimikrobiellen Arzneimittels.

16. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salze derselben für die Verwen-
dung als Arzneimittel.

Patentansprüche für folgende Vertragsstaaten: AT, ES

1. Verfahren zur Herstellung einer neuen Cephemverbindung der Formel

worin bedeuten:
R¹ Amino oder geschütztes Amino,
R² Wasserstoff, Tetrahydropranyl, (C₁₋C₆)-Alkyl, dihalogeniertes (C₁₋C₆)-Alkyl, Cyclo-(C₃₋C₆)-alkenyl, Thietyl, Carboxy(C₁₋C₆)-alkyl oder geschütztes Carboxy(C₁₋C₆)-alkyl,
R³ (C₁₋C₆)-Alkyl,
R⁴ und R⁵ jeweils Wasserstoff, (C₁₋C₆)-Alkyl, Hydroxy(C₁₋C₆)-alkyl, (C₁₋C₆)-Alkoxy, Amino oder geschütztes Amino,
R⁶ COO⁰, Carboxy oder geschütztes Carboxy,
X⁰ ein Anion und
n die Zahl 0 oder 1,

mit der Maßgabe, daß
i) wenn R² für Carboxy(C₁₋C₆)-alkyl oder geschütztes Carboxy(C₁₋C₆)-alkyl steht, dann R⁴ Wasserstoff und R⁵ Amino darstellen,
ii) wenn R⁶ für COO⁰ steht, dann n = 0, und
iii) wenn R⁶ für Carboxy oder geschütztes Carboxy steht, dann n = 1,
oder eines Salzes derselben, das umfaßt
1) die Umsetzung einer Verbindung der Formel

worin R¹, R⁴, R⁵, X⁰ und n jeweils wie oben definiert sind,
or ihres reaktionsfähigen Derivats an der Aminogruppe oder ihres Salzes mit einer Verbindung der Formel

worin R¹ und R² jeweils wie oben definiert sind,
or ihrem reaktionsfähigen Derivat an der Carboxygruppe oder ihrem Salz oder
2) die Durchführung einer Reaktion zur Eliminierung der Aminoschutzgruppe in R¹ₐ aus einer Verbindung der Formel

worin R², R³, R⁴, R⁵, X⁰ und n jeweils wie oben definiert sind und R¹ₐ für geschütztes Amino
steht,
on ihrer Salz unter Bildung einer Verbindung der Formel

worin \( R^2, R^3, R^4, R^6, X^m \) und \( n \) jeweils wie oben definiert sind, oder ihres Salzes oder
3) die Umsetzung einer Verbindung der Formel

worin \( R^1 \) und \( R^2 \) jeweils wie oben definiert sind, \( R^6 \), für Carboxy oder geschütztes Carboxy und \( Y \) für eine austretende Gruppe stehen, oder ihres Salzes mit einer Verbindung der Formel

worin \( R^3, R^4 \) und \( R^5 \) jeweils wie oben definiert sind, oder ihrem Salz unter Bildung einer Verbindung der Formel

worin \( R^1, R^2, R^3, R^4, R^6, X^m \) und \( n \) jeweils wie oben definiert sind, oder ihres Salzes oder
4) die Durchführung einer Reaktion zur Eliminierung der Carboxyschutzgruppe in \( R^6 \), aus einer Verbindung der Formel
worin \( R^1, R^2, R^3, R^4, R^5 \) und \( X^0 \) jeweils wie oben definiert sind, \( R^6_p \) für geschütztes Carboxy und \( n \) für die Zahl 1 stehen,
or ihrem Salz unter Bildung einer Verbindung der Formel

worin \( R^1, R^2, R^3, R^4, R^5 \) und \( X^0 \) wie oben definiert sind und \( R^6_c \) für \( \text{COO}^\circ \) oder Carboxy steht,
mit der Maßgabe, daß
i) wenn \( R^6_c \) für \( \text{COO}^\circ \) steht, dann \( n = 0 \), und
ii) wenn \( R^6_c \) für Carboxy steht, dann \( n = 1 \),
oder ihres Salzes oder
5) die Durchführung einer Reaktion zur Eliminierung der Tetrahydropyranylgruppe von \( R^5_a \) aus einer
Verbindung der Formel

worin \( R^1, R^2, R^3, R^4, R^5, X^0 \) und \( n \) jeweils wie oben definiert sind und \( R^7_a \) für Tetrahydropyranyl
steht,
or ihrem Salz unter Bildung einer Verbindung der Formel
worin $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $X^0$ und $n$ jeweils wie oben definiert sind, oder ihres Salzes oder
6) die Durchführung einer Reaktion zur Eliminierung der Aminoschutzgruppe in $R^6_a$ aus einer Verbindung der Formel

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^6$, $X^0$ und $n$ jeweils wie oben definiert sind und $R^6_a$ für geschütztes Amino steht, oder ihrem Salz unter Bildung einer Verbindung der Formel

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^6$, $X^0$ und $n$ jeweils wie oben definiert sind, oder ihres Salzes oder
7) die Durchführung einer Reaktion zur Eliminierung der Carboxyschutzgruppe in $R^7_a$ aus einer Verbindung der Formel

worin $R^1$, $R^2$, $R^3$, $X^0$ und $n$ jeweils wie oben definiert sind und $R^7_b$ für geschütztes Carboxy($C_1$-$C_6$)-alkyl steht, oder ihrem Salz unter Bildung einer Verbindung der Formel
worin $R^1$, $R^3$, $R^5$, $X^0$ und $n$ jeweils wie oben definiert sind und $R^2$, für Carboxy(C$_1$-C$_6$)-alkyl steht, oder ihres Salzes oder

8) die Umsetzung einer Verbindung der Formel

[Chemische Strukturformel]

worin $R^2$, $R^3$, $R^5$, $R^6$, $X^0$ und $n$ jeweils wie oben definiert sind und $Z$ für einen Säurerest steht, oder ihres Salzes mit einer Verbindung der Formel

[Chemische Strukturformel]

worin $R^1$ wie oben definiert ist, unter Bildung einer Verbindung der Formel

[Chemische Strukturformel]

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^6$, $X^0$ und $n$ jeweils wie oben definiert sind, oder

9) die Reduktion einer Verbindung der Formel

[Chemische Strukturformel]

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^6$, $X^0$ und $n$ jeweils wie oben definiert sind, oder ihres Salzes.
Patentansprüche für folgenden Vertragsstaat: GR

1. Verfahren zur Herstellung einer neuen Cephamverbindung der Formel

\[ \text{R}^1 \] Amino oder geschütztes Amino,
\[ \text{R}^2 \] Wasserstoff, Tetrahydropranyl, (C₁₋C₆)-Alkyl, dihalogeniertes (C₁₋C₆)-Alkyl, Cyclo-(C₃₋C₆)-alkenyl, Thietanyl, Carboxy(C₁₋C₆)-alkyl oder geschütztes Carboxy(C₁₋C₆)-alkyl,
\[ \text{R}^3 \] (C₁₋C₆)-Alkyl,
\[ \text{R}^4 \] und \[ \text{R}^5 \] jeweils Wasserstoff, (C₁₋C₆)-Alkyl, Hydroxy(C₁₋C₆)-alkyl, (C₁₋C₆)-Alkoxy, Amino oder geschütztes Amino,
\[ \text{X}^\circ \] COO⁻, Carboxy oder geschütztes Carboxy,
\[ \text{n} \] die Zahl 0 oder 1,

mit der Maßgabe, daß

i) wenn \[ \text{R}^5 \] für Carboxy(C₁₋C₆)-alkyl oder geschütztes Carboxy(C₁₋C₆)-alkyl steht, dann \[ \text{R}^6 \] Wasserstoff und \[ \text{R}^6 \] Amino darstellen,

ii) wenn \[ \text{R}^6 \] für COO⁻ steht, dann \[ \text{n} = 0 \], und

iii) wenn \[ \text{R}^5 \] für Carboxy oder geschütztes Carboxy steht, dann \[ \text{n} = 1 \],

oder eines Salzes derselben, das umfaßt

1) die Umsetzung einer Verbindung der Formel

\[ \text{R}^3, \text{R}^4, \text{R}^5, \text{X}^\circ \] und \[ \text{n} \] jeweils wie oben definiert sind,
oder ihres reaktionsfähigen Derivats an der Aminogruppe oder ihres Salzes mit einer Verbindung der Formel

\[ \text{R}^1 \] und \[ \text{R}^2 \] jeweils wie oben definiert sind,
oder ihrem reaktionsfähigen Derivat an der Carboxygruppe oder ihrem Salz oder
2) die Durchführung einer Reaktion zur Eliminierung der Aminoschutzgruppe in R₁₈ aus einer
Verbindung der Formel

worin R₂, R₃, R₅, R₆, X₀ und n jeweils wie oben definiert sind und R₁₈ für geschütztes Amino
steht,
oDER iharem Salz unter Bildung einer Verbindung der Formel

worin R₂, R₃, R₄, R₅, R₆, X₀ und n jeweils wie oben definiert sind,
oDER ihrem Salzes oder
3) die Umsetzung einer Verbindung der Formel

worin R¹ und R² jeweils wie oben definiert sind, R₁₇ für Carboxy oder geschütztes Carboxy und Y für
eine austretende Gruppe stehen,
oDER ihrem Salzes mit einer Verbindung der Formel

worin R³, R⁴ und R⁵ jeweils wie oben definiert sind,
oDER ihrem Salz unter Bildung einer Verbindung der Formel
worin R¹, R², R³, R⁴, R⁵, X⁶ und n jeweils wie oben definiert sind, oder ihres Salzes oder
4) die Durchführung einer Reaktion zur Eliminierung der Carboxylschutzgruppe in R⁶, aus einer Verbindung der Formel

worin R¹, R², R³, R⁴, R⁵ und X⁶ jeweils wie oben definiert sind, R⁶, für geschütztes Carboxy und n für die Zahl 1 stehen, oder ihrem Salz unter Bildung einer Verbindung der Formel

worin R¹, R², R³, R⁴, R⁵ und X⁶ wie oben definiert sind und R⁶, für COO⁶ oder Carboxy steht, mit der Maßgabe, daß
i) wenn R⁶, für COO⁶ steht, dann n = 0, und
ii) wenn R⁶, für Carboxy steht, dann n = 1, oder ihres Salzes oder
5) die Durchführung einer Reaktion zur Eliminierung der Tetrahydropyranylgruppe von R², aus einer Verbindung der Formel
worin $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $X^\circ$ und $n$ jeweils wie oben definiert sind und $R^6_a$ für Tetrahydropyranyl steht, oder ihrem Salz unter Bildung einer Verbindung der Formel

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $X^\circ$ und $n$ jeweils wie oben definiert sind, oder ihres Salzes oder

6) die Durchführung einer Reaktion zur Eliminierung der Aminoschutzgruppe in $R^6_a$ aus einer Verbindung der Formel

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $X^\circ$ und $n$ jeweils wie oben definiert sind und $R^6_a$ für geschütztes Amino steht, oder ihrem Salz unter Bildung einer Verbindung der Formel

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $X^\circ$ und $n$ jeweils wie oben definiert sind, oder ihres Salzes oder

7) die Durchführung einer Reaktion zur Eliminierung der Carboxyschutzgruppe in $R^6_b$ aus einer Verbindung der Formel
worin R₁, R₂, R₃, X₀ und n jeweils wie oben definiert sind und R₃ₕ für geschütztes Carboxy(C₁-C₆)-alkyl steht, 
or dem ihrer Salz unter Bildung einer Verbindung der Formel

worin R₁, R₂, R₃, X₀ und n jeweils wie oben definiert sind und R₃ₕ für Carboxy(C₁-C₆)-alkyl steht, 
or dem ihrer Salzes oder
8) die Umsetzung einer Verbindung der Formel

worin R₂, R₃, R₄, R₅, R₆, X₀ und n jeweils wie oben definiert sind und Z für einen Säurerest steht, 
or dem ihrer Salzes mit einer Verbindung der Formel

worin R₁ wie oben definiert ist, 
unter Bildung einer Verbindung der Formel
worin $R^1$, $R^2$, $R^3$, $R^4$, $R^6$, $X^0$ und $n$ jeweils wie oben definiert sind, oder
9) die Reduktion einer Verbindung der Formel

worin $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $X^0$ und $n$ jeweils wie oben definiert sind,
oder ihres Salzes.

2. Modifikation des Verfahrens nach Anspruch 1, dadurch gekennzeichnet, daß man eine Verbindung oder
ein nicht-toxisches Salz derselben, hergestellt nach dem Verfahren nach Anspruch 1, durch Mischen
oder Präsentieren dieser Verbindung mit einem pharmazeutisch akzeptablen Verdünnungsmittel oder
Träger in eine pharmazeutisch akzeptable Form bringt.

Reivendications
Reivendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Nouveau composé de céphème de la formule:

50 dans laquelle

$R^1$ est un groupe amino ou amino protégé,
$R^2$ est un atome d’hydrogène, un groupe tétrahydropyranyle, alkyle en C$_1$-C$_6$, (alkyle en
C$_1$-C$_6$) dihalogéné, cyclo(alcényle en C$_2$-C$_3$), thétanyle, carboxy(alkyle en C$_1$-C$_6$) ou
carboxy (alkyle en C$_1$-C$_6$) protégé,
$R^3$ est un groupe alkyle en C$_1$-C$_6$,
$R^4$ et $R^5$ sont chacun un atome d’hydrogène, un groupe alkyle en C$_1$-C$_6$, hydroxy(alkyle en C$_1$-
C$_6$), alcoxy en C$_1$-C$_6$, amino ou amino protégé,
$R^6$ est COO$^-$, un groupe carboxy ou carboxy protégé,
\[ X^0 \text{ est un anion, et} \]
\[ n \text{ est 0 ou 1,} \]

à condition que :

(i) lorsque \( R^2 \) est un groupe carboxy(alkyle en C\(_1\)-C\(_6\)) ou carboxy(alkyle en C\(_1\)-C\(_6\)) protégé, \( R^2 \) soit alors un atome d’hydrogène et \( R^0 \) un groupe amino,

(ii) lorsque \( R^0 \) est un COO\(^n\), n soit alors 0, et

(iii) lorsque \( R^6 \) est un groupe carboxy ou carboxy protégé, n soit alors 1, et un de ses sels pharmaceutiquement acceptables.

2. Isomère syn du composé de la revendication 1.

3. Composé selon la revendication 2,

daufquelle

\[ R^2 \text{ est un atome d’hydrogène, un groupe tétrahydropyranyle, alkyle en C\(_1\)-C\(_6\), (alkyle en C\(_1\)-C\(_6\)}\) dihalogéné, cyclo(alcényle en C\(_2\)-C\(_6\)) ou thiétanyle.

4. Composé selon la revendication 3,

daufquelle

\[ R^1 \text{ est un groupe amino,} \]
\[ R^2 \text{ est un groupe alkyle en C\(_1\)-C\(_6\)) ou (alkyle en C\(_1\)-C\(_6\)) dihalogéné,} \]
\[ R^4 \text{ et } R^5 \text{ sont chacun un atome d’hydrogène, un groupe alkyle en C\(_1\)-C\(_6\) ou amino, et} \]
\[ R^6 \text{ est COO}\(^n\). \]

5. Composé selon la revendication 4,

daufquelle

\[ R^2 \text{ est un groupe (alkyle en C\(_1\)-C\(_6\)) dihalogéné,} \]
\[ R^4 \text{ et } R^5 \text{ sont chacun un atome d’hydrogène.} \]

6. Composé selon la revendication 5, qui est le 7β-[2-(2-aminothiazol-4-yl)-2-(difluorométhoxyimino)-acétamido]-3-(2-méthyl-1-pyrazolio)méthyl-3-céphème-4-carboxylate (isomère syn).

7. Composé selon la revendication 5, qui est le sel d’acide sulfurique du 7β-[2-(2-aminothiazol-4-yl)-2-(difluorométhoxyimino)acétamido]-3-(2-méthyl-1-pyrazolio)méthyl-3-céphème-4-carboxylate (isomère syn).

8. Composé selon la revendication 4,

daufquelle

\[ R^4 \text{ est un groupe alkyle en C\(_1\)-C\(_6\), et} \]
\[ R^5 \text{ est un groupe amino.} \]

9. Composé selon la revendication 8, qui est choisi dans le groupe constitué de :

\[ 7β-[2-(2-aminothiazol-4-yl)-2-méthoxyiminoacétamido]-3-(3-amino-2,4-diméthyl-1-pyrazolio)méthyl-3-céphème-4-carboxylate (isomère syn) \]
\[ et \]

\[ 7β-[2-(2-aminothiazol-4-yl)-2-(difluorométhoxyimino)acétamido]-3-(3-amino-2,4-diméthyl-1-pyrazolio)-méthyl-3-céphème-4-carboxylate (isomère syn). \]

10. Procédé pour préparer un composé de la revendication 1, ou son sel, qui comprend :

(1) le fait de faire réagir un composé de la formule :
dans laquelle
\( R^1, R^2, R^3, R^6, X^0 \) et \( n \) sont chacun tels que définis ci-dessus, ou son dérivé réactif au groupe amino, ou son sel avec un composé de la formule :

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \\
\text{N} & \quad \text{C-COOH} \\
\text{O-R}^2 & 
\end{align*}
\]

dans laquelle \( R^1 \) et \( R^2 \) sont chacun tels que définis ci-dessus, ou son dérivé réactif au groupe carboxy ou son sel, ou (2) le fait de soumettre un composé de la formule :

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \\
\text{N} & \quad \text{C-COONH} \\
\text{O-R}^2 & 
\end{align*}
\]

dans laquelle
\( R^2, R^3, R^4, R^6, X^0 \) et \( n \) sont chacun tels que définis ci-dessus, et
\( R^6 \) est un groupe amino protégé, ou son sel, à une réaction d'élimination du groupe protecteur du groupe amino dans \( R^6 \) pour donner un composé de la formule :

\[
\begin{align*}
\text{H}_2 & \quad \text{N} \\
\text{N} & \quad \text{C-COONH} \\
\text{O-R}^2 & 
\end{align*}
\]

dans laquelle
\( R^2, R^3, R^4, R^6, X^0 \) et \( n \) sont chacun tels que définis ci-dessus, ou son sel, ou
(3) le fait de faire réagir un composé de la formule :

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \quad \text{C-CONH} \quad \text{N} \quad \text{O-R}^2 \\
\text{S} & \quad \text{S} \quad \text{CH}_2 \cdot \text{Y} \\
\end{align*}
\]

dans laquelle
R\(^1\) et R\(^2\) sont chacun tels que définis ci-dessus,
R\(^a\) est un groupe carboxy ou carboxy protégé, et
Y est un groupe partant,
ou son sel avec un composé de la formule :

\[
\begin{align*}
\text{R} & \quad \text{N} \\
\text{N} & \quad \text{R}^4 \\
\text{R} & \quad \text{R}^5 \\
\end{align*}
\]

dans laquelle
R\(^3\), R\(^4\) et R\(^5\) sont chacun tels que définis ci-dessus,
ou son sel, pour donner un composé de la formule :

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \quad \text{C-CONH} \quad \text{N} \quad \text{O-R}^2 \\
\text{S} & \quad \text{S} \quad \text{CH}_2 \cdot \text{Y} \quad \text{R}^4 \cdot \text{X(\bigodot)}_n \\
\end{align*}
\]

dans laquelle
R\(^1\), R\(^2\), R\(^3\), R\(^4\), R\(^5\), X\(^\bigodot\) et n sont chacun tels que définis ci-dessus,
ou son sel, ou
(4) le fait de soumettre un composé de la formule :

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \quad \text{C-CONH} \quad \text{N} \quad \text{O-R}^2 \\
\text{S} & \quad \text{S} \quad \text{CH}_2 \cdot \text{Y} \quad \text{R}^4 \cdot \text{X(\bigodot)}_n \\
\end{align*}
\]

dans laquelle
R₁, R₂, R₃, R₄, R₅ et X₀ sont chacun tels que définis ci-dessus,
R₆ est un groupe carboxy protégé, et
n est 1.
ou son sel, à une réaction d'élaboration du groupe protecteur du groupe carboxy dans R₆ pour
donner un composé de la formule :

\[
\begin{align*}
\text{C}-&\text{CONH} \\
\text{S} & \text{N} \\
\text{O}-R^2
\end{align*}
\]

dans laquelle
R₁, R₂, R₃, R₄, R₅ et X₀ sont chacun tels que définis ci-dessus, et
R₆ est COO° ou un groupe carboxy,
à condition que :
(i) lorsque R₆ est COO°, n soit alors 0 et
(ii) lorsque R₆ est un groupe carboxy, n soit alors 1,
or son sel, ou
(5) le fait de soumettre un composé de la formule :

\[
\begin{align*}
\text{C}-&\text{CONH} \\
\text{S} & \text{N} \\
\text{O}-R^2
\end{align*}
\]

dans laquelle
R₁, R₂, R₃, R₄, R₅, X₀ et n sont chacun tels que définis ci-dessus, et
R₆ est un groupe tétrahydropyranyle,
or son sel, à une réaction d'élaboration du groupe tétrahydropyranyle dans R₆ pour donner un
composé de la formule :

\[
\begin{align*}
\text{C}-&\text{CONH} \\
\text{S} & \text{N} \\
\text{O} & \text{OH}
\end{align*}
\]

dans laquelle
R₁, R₂, R₃, R₄, R₅, R₆, X₀ et n sont chacun tels que définis ci-dessus,
or son sel, ou
(6) le fait de soumettre un composé de la formule :

\[
\begin{align*}
\text{R}_1 \quad &\text{N} \\
&\text{C-CONH} \\
&\text{O-R}_2 \\
&\text{R}_5 \\
&= (\text{X}^-)_n
\end{align*}
\]

dans laquelle
\(\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5, \text{X}^-\) et \(n\) sont chacun tels que définis ci-dessus, et
\(\text{R}_5\) est un groupe amine protégé,
ou son sel, à une réaction d'élimination du groupe protecteur du groupe amino dans \(\text{R}_5\) pour donner un composé de la formule :

\[
\begin{align*}
\text{R}_1 \quad &\text{N} \\
&\text{C-CONH} \\
&\text{O-R}_2 \\
&\text{R}_5 \\
&= (\text{X}^-)_n
\end{align*}
\]

dans laquelle
\(\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{X}^-\) et \(n\) sont chacun tels que définis ci-dessus,
or son sel, ou

(7) le fait de soumettre un composé de la formule :

\[
\begin{align*}
\text{R}_1 \quad &\text{N} \\
&\text{C-CONH} \\
&\text{O-R}_2 \\
&\text{R}_5 \\
&= (\text{X}^-)_n
\end{align*}
\]

dans laquelle
\(\text{R}_1, \text{R}_2, \text{R}_3, \text{X}^-\) et \(n\) sont chacun tels que définis ci-dessus, et
\(\text{R}_5\) est un groupe carboxy(alkyle en \(\text{C}_1-\text{C}_6\))protégé,
ou son sel, à une réaction d'élimination du groupe protecteur du groupe carboxy dans \(\text{R}_5\) pour donner un composé de la formule :
dans laquelle
\( R^1, R^3, R^6, X^o \) et \( n \) sont chacun tels que définis ci-dessus, et
\( R^c \) est un groupe carboxy(alkyle en C\(_1\)-C\(_6\)),
ou son sel, ou
(8) le fait de faire réagir un composé de la formule :

\[
\begin{align*}
\text{Z-CH}_2\text{COCONH-COOH} & \quad \text{O-R}^2 \\
\text{N} & \quad \text{O-R}^2 \\
\text{S} & \quad \text{H}_2\text{N-C-R}^1
\end{align*}
\]

dans laquelle \( R^2, R^3, R^6, X^o \) et \( n \) sont chacun tels que définis ci-dessus, et
\( Z \) est un radical acide,
ou son sel, avec un composé de la formule :

\[
\begin{align*}
\text{S} & \\
\text{II} & \\
\text{H}_2\text{N-C-R}^1
\end{align*}
\]

dans laquelle \( R^i \) est tel que défini ci-dessus,
pour donner un composé de la formule :

\[
\begin{align*}
\text{R}^1 & \quad \text{C-CONH-COOH} \\
\text{N} & \quad \text{O-R}^2 \\
\text{S} & \quad \text{R}^5 \cdot (X^o)_n
\end{align*}
\]

dans laquelle
\( R^1, R^2, R^3, R^6, R^6, X^o \) et \( n \) sont chacun tels que définis ci-dessus, ou
(9) le fait de réduire un composé de la formule :

\[
\begin{align*}
\text{R}^1 & : 
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{O} - \text{R}^2 
\end{array} 
\end{align*}
\]

\[
\begin{align*}
\text{CONH} & : 
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{N} \\
\text{CH}_2 \\
\text{N} \\
\text{R}^5 
\end{array} 
\end{align*}
\]

\[
\begin{align*}
\text{R}^{4} & : 
\begin{array}{c}
\text{O} - \text{R}^5 
\end{array} 
\end{align*}
\]

\[
\begin{align*}
\text{X} & : 
\begin{array}{c}
\text{X} \\
\text{N} \\
\text{R}^3 \\
\text{R}^6 
\end{array} 
\end{align*}
\]

\[
\begin{align*}
\text{n} & : 
\begin{array}{c}
\text{N} \\
\text{R}^7 \\
\text{R}^8 
\end{array} 
\end{align*}
\]

dans laquelle
\(\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{X} \) et \(\text{n}\) sont chacun tels que définis ci-dessus, ou son sel.

11. Composé de la formule :

\[
\begin{align*}
\text{H}_2\text{N} & : 
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{CH}_2 \text{N} \\
\text{R}^6 \\
\text{R}^3 \\
\text{R}^4 \\
\text{X} \end{array} 
\end{align*}
\]

dans laquelle
\(\text{R}^3\) est un groupe alkyle en \(\text{C}_1-\text{C}_6\),
\(\text{R}^4\) et \(\text{R}^5\) sont chacun un atome d’hydrogène, un groupe alkyle en \(\text{C}_1-\text{C}_6\), hydroxy(alkyle en \(\text{C}_1-\text{C}_6\), alcoxy en \(\text{C}_1-\text{C}_6\), amino ou amino protégé,
à condition que \(\text{R}^4\) et \(\text{R}^5\) ne soient pas en même temps un atome d’hydrogène,
\(\text{R}^6\) est \(\text{COO}^\circ\), un groupe carboxy ou carboxy protégé,
\(\text{X}^\circ\) est un anion, et
\(\text{n}\) est 0 ou 1,
à condition que :
(i) lorsque \(\text{R}^6\) est \(\text{COO}^\circ\), \(\text{n}\) soit alors 0, et
(ii) lorsque \(\text{R}^6\) est un groupe carboxy ou carboxy protégé, \(\text{n}\) soit alors 1, et son sel.

12. Composé de la formule:

\[
\begin{align*}
\text{Z-CH}_2 \text{COCONH} & : 
\begin{array}{c}
\text{N} \\
\text{O} - \text{R}^2 
\end{array} 
\end{align*}
\]

\[
\begin{align*}
\text{CONH} & : 
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{N} \\
\text{CH}_2 \\
\text{N} \\
\text{R}^5 
\end{array} 
\end{align*}
\]

\[
\begin{align*}
\text{R}^{4} & : 
\begin{array}{c}
\text{O} - \text{R}^5 
\end{array} 
\end{align*}
\]

\[
\begin{align*}
\text{X} & : 
\begin{array}{c}
\text{X} \\
\text{N} \\
\text{R}^3 \\
\text{R}^6 
\end{array} 
\end{align*}
\]

dans laquelle
\(\text{R}^2\) est un atome d’hydrogène, un groupe tétrahydropryranyle (alkyle en \(\text{C}_1-\text{C}_6\), (alkyle en
C₁−C₆) dihalogéné, cyclo(alcényle en C₃−C₆), thiétanyle, carboxy(alkyle en C₁−C₆) ou carboxy (alkyle en C₁−C₆) protégé,
R⁰ est un groupe alkyle en C₁−C₆, et
R⁰ et R⁰ sont chacun un atome d’hydrogène, un groupe alkyle en C₁−C₆, hydroxy(alkyle en C₁−C₆), alcoxy en C₁−C₆, amino ou amino protégé,
R⁶ est COO⁰, un groupe carboxy ou carboxy protégé,
X⁰ est un anion,
Z est un radical acide, et
n est 0 ou 1,
à condition que :
(i) lorsque R⁰ est un groupe carboxy(alkyle en C₁−C₆) ou un groupe carboxy(alkyle en C₁−C₆)−protégé, R⁰ soi alors un atome d’hydrogène et R⁰ soit un groupe amino,
(ii) lorsque R⁰ est COO⁰, n soit alors 0, et
(iii) lorsque R⁰ est un groupe carboxy ou carboxy protégé, n soit alors 1, et son sel.

13. Composé de la formule:

\[ \text{Structure de la molécule} \]

dans laquelle
R¹ est un groupe amino ou amino protégé,
R² est un atome d’hydrogène, un groupe tétrahydropyranyle, alkyle en C₁−C₆, (alkyle en C₁−C₆) dihalogéné, cyclo(alcényle en C₃−C₆), thiétanyle, carboxy(alkyle en C₁−C₆) ou carboxy (alkyle en C₁−C₆) protégé,
R³ est un groupe alkyle en C₁−C₆,
R⁴ et R⁵ sont chacun un atome d’hydrogène, un groupe alkyle en C₁−C₆, hydroxy(alkyle en C₁−C₆), alcoxy en C₁−C₆, amino ou amino protégé,
R⁶ est COO⁰, un groupe carboxy ou carboxy protégé,
X⁰ est un anion, et
n est 0 ou 1,
à condition que :
(i) lorsque R⁰ est un groupe carboxy(alkyle en C₁−C₆) ou carboxy(alkyle en C₁−C₆) protégé,
R⁰ soi alors un atome d’hydrogène et
R⁰ soit un groupe amino,
(ii) lorsque R⁰ est COO⁰, n soit alors 0, et
(iii) lorsque R⁰ est un groupe carboxy ou carboxy protégé, n soit alors 1, ou son sel.

14. Composition pharmaceutique qui comprend, comme ingrédient actif, un composé de la revendication 1, ou un de ses sels pharmaceutiquement acceptables en mélange avec des supports pharmaceutiquement acceptables.

15. Utilisation d’un composé de la revendication 1, ou de son sel pharmaceutiquement acceptable pour la fabrication d’un médicament antimicrobien.

16. Composé de la revendication 1 ou un de ses sels pharmaceutiquement acceptables pour utilisation comme médicamente.
Revenicdation pour les États contractants suivants : AT, ES

1. Procédé pour préparer un nouveau composé de céphème de la formule :

\[
\begin{align*}
&\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{X}^\ominus, \text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10} \\
&\text{est un groupe amino ou amino protégé,} \\
&\text{est un atome d'hydrogène, un groupe tétrahydropryranyle, alkyle en C}_{1}-C_{6}, \text{ (alkyle en C}_{1}-C_{6})\text{dihalogéné, cyclo(alkynyle en C}_{2}-C_{6}), \text{ thiényl, carboxy(alkyle en C}_{1}-C_{6}) \text{ ou carboxy (alkyle en C}_{1}-C_{6})\text{protégé,} \\
&\text{est un groupe alkyle en C}_{1}-C_{6}, \\
&\text{R}^4 \text{ et R}^5 \text{ sont chacun un atome d'hydrogène, un groupe alkyle en C}_{1}-C_{6}, \text{ hydroxy(alkyle en C}_{1}-C_{6})\text{, alcoxy en C}_{1}-C_{6}, \text{ amino ou amino protégé,} \\
&\text{R}^6 \text{ est COO}^\ominus, \text{ un groupe carboxy ou carboxy protégé,} \\
&\text{n est 0 ou 1,} \\
&\text{à condition que :} \\
&\text{(i) lorsque R}^2 \text{ est un groupe carboxy(alkyle en C}_{1}-C_{6}) \text{ ou carboxy(alkyle en C}_{1}-C_{6})\text{protégé, R}^4 \text{ soit alors un atome d'hydrogène et R}^5 \text{ un groupe amino,} \\
&\text{(ii) lorsque R}^6 \text{ est un groupe COO}^\ominus, n \text{ soit alors 0, et} \\
&\text{(iii) lorsque R}^6 \text{ est carboxy ou carboxy protégé, n soit alors 1,} \\
&\text{ou son sel, qui comprend :} \\
&\text{(1) le fait de faire réagir un composé de la formule :}
\end{align*}
\]

\[
\begin{align*}
&\text{R}^3, \text{R}^4, \text{R}^5, \text{X}^\ominus, \text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10} \\
&\text{sont chacun tels que définis ci-dessus,} \\
&\text{ou son dérivé réactif au groupe amino,} \\
&\text{ou son sel, avec un composé de la formule :}
\end{align*}
\]
dans laquelle
R₁ et R² sont chacun tels que définis ci-dessus, ou son dérivé réactif au groupe carboxy ou son sel,
ou
(2) le fait de soumettre un composé de la formule :

dans laquelle
R¹, R², R³, R⁴, R⁵, R⁶, X⁰ et n sont chacun tels que définis ci-dessus, et
R⁰ est un groupe amine protégé,
ou son sel, à une réaction d'élimination du groupe protecteur du groupe amine dans R⁰ pour donner un composé de la formule :

dans laquelle
R², R³, R⁴, R⁵, R⁶, X⁰ et n sont chacun tels que définis ci-dessus,
ou son sel, ou
(3) le fait de faire réagir un composé de la formule :

dans laquelle
R¹ et R² sont chacun tels que définis ci-dessus,
R⁶ est un groupe carboxy ou carboxy protégé, et
Y est un groupe partant,
ou son sel, avec un composé de la formule :

Dans laquelle
R³, R⁴ et R⁵ sont chacun tels que définis ci-dessus,
or son sel, pour donner un composé de la formule :

Dans laquelle
R¹, R², R³, R⁴, R⁵, R⁶, X⁰ et n sont chacun tels que définis ci-dessus,
or son sel, ou
(4) le fait de soumettre un composé de la formule :

Dans laquelle
R¹, R², R³, R⁴, R⁵ et X⁰ sont chacun tels que définis ci-dessus,
R⁶ est un groupe carboxy protégé, et
n est 1,
or son sel, à une réaction d'élimination du groupe protecteur du groupe carboxy dans R⁶ pour
donner un composé de la formule :
dans laquelle
R₁, R², R³, R⁴, R⁵ et X₈ sont chacun tels que définis ci-dessus, et
R₆ est COO₈ ou un groupe carboxy,
à condition que :
(i) lorsque R₆ est COO₈, n soit alors 0 et
(ii) lorsque R₆ est un groupe carboxy, n soit alors 1,
on son sel, ou
(5) le fait de soumettre un composé de la formule :

dans laquelle
R₁, R³, R⁴, R⁶, X₈ et n sont chacun tels que définis ci-dessus, et
R₆ est un groupe tétrahydropyranyle,
ou son sel, à une réaction d'élimination du groupe tétrahydropyranyle dans R₆ pour donner un
composé de la formule :

dans laquelle
R₁, R³, R⁴, R⁶, X₈ et n sont chacun tels que définis ci-dessus,
on son sel, ou
(6) le fait de soumettre un composé de la formule :

\[
\begin{align*}
& R^1, R^2, R^3, R^4, R^5, R^6, X^a \text{ et } n \\
& \text{sont chacun tels que définis ci-dessus, et} \\
& R^a \text{ est un groupe amino protégé,} \\
& \text{ou son sel, à une réaction d’élaboration du groupe protecteur du groupe amino dans } R^a \text{ pour donner} \\
& \text{un composé de la formule :}
\end{align*}
\]

\[
\begin{align*}
& \text{dans laquelle} \\
& R^1, R^2, R^3, R^4, R^6, X^a \text{ et } n \\
& \text{sont chacun tels que définis ci-dessus,} \\
& \text{ou son sel, ou}
\end{align*}
\]

(7) le fait de soumettre un composé de la formule :

\[
\begin{align*}
& R^1, R^2, R^3, X^a \text{ et } n \\
& \text{sont chacun tels que définis ci-dessus, et} \\
& R^a \text{ est un groupe carboxylé(alkyle en C1-C6) protégé,} \\
& \text{ou son sel, à une réaction d’élaboration du groupe protecteur du groupe carboxyl dans } R^a \text{ pour} \\
& \text{donner un composé de la formule :}
\end{align*}
\]
dans laquelle 
$R^1, R^2, R^3, X^\ominus$ et $n$ sont chacun tels que définis ci-dessus, et 
$R^4_S$ est un groupe carboxy(alkyle en $C_1-C_5$), 
ou son sel, ou 
(8) le fait de faire réagir un composé de la formule :

$$Z-CH_2-COCCONH$$

dans laquelle 
$R^2, R^3, R^4, R^5, R^6, X^\ominus$ et $n$ sont chacun tels que définis ci-dessus, et 
Z est un radical acide, 
ou son sel avec un composé de la formule :

$$S$$

$$H_2N-C-R^1$$

dans laquelle $R^1$ est tel que défini ci-dessus, 
pour donner un composé de la formule :

$$R^1-CH_2-COCCONH$$

dans laquelle 
$R^1, R^2, R^3, R^4, R^5, X^\ominus$ et $n$ sont chacun tels que définis ci-dessus, ou
(9) le fait de réduire un composé de la formule :

\[
\begin{align*}
R^1 & \quad N \quad S \quad C-CONH \quad S \quad CH_2 \quad N \quad R^6 \\
& \quad N \quad O-R^2 \quad \text{O} \quad R^5 \quad R^4 \quad (X^-)_n
\end{align*}
\]

dans laquelle \(R^1\), \(R^2\), \(R^3\), \(R^4\), \(R^5\), \(X^-\) et \(n\) sont chacun tels que définis ci-dessus, ou son sel.

**Revendications pour l’Etat contractant suivant : GR**

1. Procédé pour préparer un nouveau composé de céphème de la formule :

\[
\begin{align*}
R^1 & \quad N \quad S \quad C-CONH \quad S \quad CH_2 \quad N \quad R^6 \\
& \quad N \quad O-R^2 \quad \text{O} \quad R^5 \quad R^4 \quad (X^-)_n
\end{align*}
\]

dans laquelle

- \(R^1\) est un groupe amino ou amino protégé,
- \(R^2\) est un atome d’hydrogène, un groupe tétrahydropyranyle, alkyle en C\(_1\)-C\(_6\), (alkyle en C\(_1\)-C\(_6\))dihalogéné, un groupe cyclo (alcényle en C\(_5\)-C\(_6\)), thiétanyle, carboxy (alkyle en C\(_1\)-C\(_6\)) ou carboxy (alkyle en C\(_1\)-C\(_6\)) protégé,
- \(R^3\) est un groupe alkyle en C\(_1\)-C\(_6\),
- \(R^4\) et \(R^5\) sont chacun un atome d’hydrogène, un groupe alkyle en C\(_1\)-C\(_6\), hydroxy (alkyle en C\(_1\)-C\(_6\)), alcoxy en C\(_1\)-C\(_6\), amino ou amino protégé,
- \(R^6\) est COO\(^-\), un groupe carboxy ou carboxy protégé,
- \(X^-\) est un anion, et
- \(n\) est 0 ou 1,

à condition que :

(i) lorsque \(R^2\) est un groupe carboxy (alkyle en C\(_1\)-C\(_6\)) ou carboxy (alkyle en C\(_1\)-C\(_6\)) protégé, \(R^4\) soit alors un atome d’hydrogène et \(R^5\) un groupe amino,
(ii) lorsque \(R^6\) est COO\(^-\), \(n\) soit alors 0, et
(iii) lorsque \(R^6\) est un groupe carboxy ou carboxy protégé, \(n\) soit alors 1,

ou son sel, qui comprend :
(1) le fait de faire réagir un composé de la formule :

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{N} \quad \text{N} \quad \text{C} \quad \text{O} \\
\text{S} & \quad \text{N} \quad \text{CH}_2 & \quad \text{N} & \quad \text{N} & \quad \text{R}_5 \\
\text{R}_6 & \quad \text{R}_3 & \quad \text{R}_4 & \quad (\text{X}^\text{-})_n
\end{align*}
\]

dans laquelle
\( R^1, R^4, R^5, R^6, X^\text{a} \) et \( n \) sont chacun tels que définis ci-dessus,
or son dérivé réactif au groupe amino,
or son sel, avec un composé de la formule :

\[
\begin{align*}
\text{R}_1 & \quad \text{N} \quad \text{C} \quad \text{COOH} \\
\text{S} & \quad \text{N} \quad \text{O} & \quad \text{R}_2
\end{align*}
\]

dans laquelle \( R^1 \) et \( R^2 \) sont chacun tels que définis ci-dessus, ou son dérivé réactif au groupe carboxy ou son sel,
or

(2) le fait de soumettre un composé de la formule :

\[
\begin{align*}
\text{R}_1 & \quad \text{N} \quad \text{C} \quad \text{CONH} \\
\text{S} & \quad \text{N} \quad \text{O} & \quad \text{R}_2
\end{align*}
\]

dans laquelle
\( R^1, R^3, R^4, R^5, R^6, X^\text{a} \) et \( n \) sont chacun tels que définis ci-dessus, et
\( R^1_i \) est un groupe amino protégé,
or son sel, à une réaction d’élimination du groupe protecteur du groupe amino dans \( R^1_i \) pour donner un composé de la formule :

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dans laquelle
R², R³, R⁴, R⁵, X⁰ et n sont chacun tels que définis ci-dessus,
ou son sel, ou
(3) le fait de faire réagir un composé de la formule :

dans laquelle
R¹ et R² sont chacun tels que définis ci-dessus,
R⁶ est un groupe carboxy ou carboxy protégé, et
Y est un groupe partant,
ou son sel, avec un composé de la formule :

dans laquelle
R³, R⁴ et R⁵ sont chacun tels que définis ci-dessus,
ou son sel, pour donner un composé de la formule :

dans laquelle
R¹, R², R³, R⁴, R⁵, X⁰ et n sont chacun tels que définis ci-dessus, ou son sel, ou
(4) le fait de soumettre un composé de la formule :

\[
\text{Diagramme}
\]

dans laquelle
R¹, R², R³, R⁴, R⁵ sont chacun tels que définis ci-dessus, 
R⁶ est un groupe carboxy protégé, et 
n est 1, 
ou son sel, à une réaction d'élimination du groupe protecteur du groupe carboxy dans R⁶ pour donner un composé de la formule :

\[
\text{Diagramme}
\]

dans laquelle
R¹, R², R³, R⁴, R⁵ et X⁰ sont chacun tels que définis ci-dessus, et 
R⁶ est COO⁰ ou un groupe carboxy, 
à condition que :
(i) lorsque R⁶ est COO⁰, n soit alors 0 et 
(ii) lorsque R⁶ est un groupe carboxy, n soit alors 1, 
ou son sel, ou
(5) le fait de soumettre un composé de la formule :

\[
\text{Diagramme}
\]

dans laquelle
R¹, R³, R⁴, R⁵, X⁰ et n sont chacun tels que définis ci-dessus, et 
R⁶ est un groupe tétrahydropryranyle, 
ou son sel, à une réaction d'élimination du groupe tétrahydropryranyle de R⁶ pour donner un composé de la formule :

\[
\text{Diagramme}
\]
dans laquelle
R¹, R², R³, R⁴, R⁵, X⁰ et n sont chacun tels que définis ci-dessus,
ou son sel, ou
(6) le fait de soumettre un composé de la formule :

R¹
N
\[ \text{C-CONH-S-CH}_2\text{-}N^\langle \oplus \rangle \text{-}N^\langle \ominus \rangle \text{-}R^4 \cdot (X^\ominus)_n \]

R²
O-R²

R¹
N
\[ \text{C-CONH-S-CH}_2\text{-}N^\langle \oplus \rangle \text{-}N^\langle \ominus \rangle \text{-}R^4 \cdot (X^\ominus)_n \]

R⁰

R¹
N
\[ \text{C-CONH-S-CH}_2\text{-}N^\langle \oplus \rangle \text{-}N^\langle \ominus \rangle \text{-}R^4 \cdot (X^\ominus)_n \]

R²
O-R²

R¹
N
\[ \text{C-CONH-S-CH}_2\text{-}N^\langle \oplus \rangle \text{-}N^\langle \ominus \rangle \text{-}R^4 \cdot (X^\ominus)_n \]

R²

R¹
N
\[ \text{C-CONH-S-CH}_2\text{-}N^\langle \oplus \rangle \text{-}N^\langle \ominus \rangle \text{-}R^4 \cdot (X^\ominus)_n \]

R²

R¹
N
\[ \text{C-CONH-S-CH}_2\text{-}N^\langle \oplus \rangle \text{-}N^\langle \ominus \rangle \text{-}R^4 \cdot (X^\ominus)_n \]

R²

R¹
N
\[ \text{C-CONH-S-CH}_2\text{-}N^\langle \oplus \rangle \text{-}N^\langle \ominus \rangle \text{-}R^4 \cdot (X^\ominus)_n \]

R²

R¹
N
\[ \text{C-CONH-S-CH}_2\text{-}N^\langle \oplus \rangle \text{-}N^\langle \ominus \rangle \text{-}R^4 \cdot (X^\ominus)_n \]

R²

R¹
N
\[ \text{C-CONH-S-CH}_2\text{-}N^\langle \oplus \rangle \text{-}N^\langle \ominus \rangle \text{-}R^4 \cdot (X^\ominus)_n \]

R²

R¹
N
\[ \text{C-CONH-S-CH}_2\text{-}N^\langle \oplus \rangle \text{-}N^\langle \ominus \rangle \text{-}R^4 \cdot (X^\ominus)_n \]
(7) le fait de soumettre un composé de la formule :

\[ \text{dans laquelle} \]
\[ R_1^1, R_3^3, R_6^6, X^a \text{ et } n \text{ sont chacun tels que définis ci-dessus, et} \]
\[ R_2^2 \text{ est un groupe carboxy(alkyle en } C_1-C_6) \text{ protégé,} \]
ou son sel, à une réaction d’élimination du groupe protecteur du groupe carboxy dans \( R_2^2 \) pour donner un composé de la formule :

(8) le fait de faire réagir un composé de la formule :

\[ \text{dans laquelle} \]
\[ R_1^1, R_3^3, R_6^6, X^a \text{ et } n \text{ sont chacun tels que définis ci-dessus, et} \]
\[ R_2^2 \text{ est un groupe carboxy(alkyle en } C_1-C_6), \]
où son sel, ou

\[ \text{ou son sel, avec un composé de la formule :} \]

\[ \text{dans laquelle} \]
\[ R_2^2, R_3^3, R_6^6, X^a, X^b \text{ et } n \text{ sont chacun tels que définis ci-dessus, et} \]
\[ Z \text{ est un radical acide,} \]
où son sel, avec un composé de la formule :

\[ \text{dans laquelle } R_1^1 \text{ est tel que défini ci-dessus,} \]
\[ \text{pour donner un composé de la formule :} \]
2. Modification du procédé revendiqué dans la revendication 1, qui est caractérisé en ce qu'on amène un composé ou un de ses sels non toxiques, obtenus par un procédé revendiqué en revendication 1, sous une forme pharmaceutiquement acceptable par mélange ou présentation dudit composé avec un diluant ou un support pharmaceutiquement acceptable.