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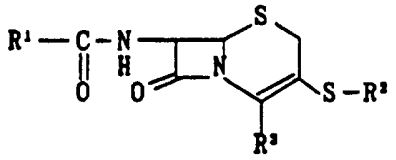
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(54) Title: CEPHEM COMPOUNDS AND PHARMACEUTICAL USE THEREOF



(I)

(57) Abstract

This invention relates to a new use of a cephem compound of formula (I), wherein R^1 is aryl(lower)alkyl which may have one or more suitable substituent(s), arylthio(lower)alkyl, lower alkenylthio(lower)alkyl which may have one or more suitable substituent(s), or a group of the formula: R^4-A- or R^4-S-A- in which R^4 is heterocyclic group which may have one or more suitable substituent(s), and A is lower alkylene which may have one or more suitable substituent(s) or lower alkenylene, R^2 is heterocyclic group which may have one or more suitable substituent(s), or heterocyclic(lower)-alkyl and R^3 is carboxy or protected carboxy, and a pharmaceutically acceptable salt thereof, which have antimicrobial activity against *Helicobacter pylori*, and are useful as anti-*Helicobacter pylori* agents, anti-gastritis agents, antiulcer agents and anticancer agents.

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DESCRIPTION

CEPHEM COMPOUNDS AND PHARMACEUTICAL USE THEREOF

Field of the Invention

This invention relates to new use of cephem compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to new use of the cephem compounds and pharmaceutically acceptable salts thereof, which have antimicrobial activity against *Helicobacter pylori*, to a pharmaceutical composition comprising said cephem compound or a pharmaceutically acceptable salt thereof and to a method for the prophylaxis and/or treatment of ulcer and the prophylaxis of stomach cancer in human being and animals.

Background Art

At present, acid secretion inhibitors such as H_2-blocker and proton pump inhibitor, and mucosalprotective factor enhancers, have been mainly used for the treatment of peptic ulcers such as gastric ulcer and duodenal ulcer. While the use of H_2-blocker and proton pump inhibitor shortens treatment period, the problem of possible recurrence of the disease still remains to be solved.

Helicobacter pylori (*H. pylori*) is a Gram negative bacterium found in the mucous layer on the gastric epithelium of humans, and infection with *H. pylori* has been found to induce gastrointestinal diseases, such as chronic gastritis and peptic ulcer (e.g., gastric ulcer and duodenal ulcer). There are an increasing number of reports on the effectiveness of the

eradication of *H. pylori* for treating intractable ulcers and prevention of ulcer recurrence. The drug having an antimicrobial action on *H. pylori* is useful for the treatment and/or prevention of gastritis and ulcer, and a new drug having such pharmacological action is desired.

Disclosure of the Invention

One object of this invention is to provide new use of cephem compounds and pharmaceutically acceptable salts thereof, which have antimicrobial activity against *Helicobacter pylori*.

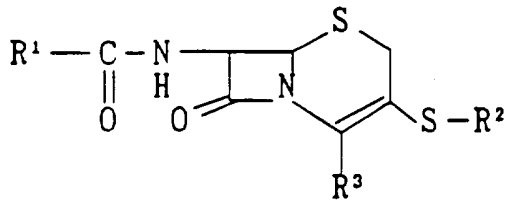
The cephem compounds and pharmaceutically acceptable salts thereof are useful as anti-*Helicobacter pylori* agents, anti-gastritis agents, antiulcer agents and anticancer agents. The cephem compounds and pharmaceutically acceptable salts thereof may be used as anti-*Helicobacter pylori* agents, anti-gastritis agents, antiulcer agents and anticancer agents in combination with an acid secretion inhibitor such as an H_2-blocker and a proton pump inhibitor.

A further object of this invention is to provide a pharmaceutical composition for the prophylactic and/or therapeutic treatment of diseases caused by *Helicobacter pylori* infection in human being or animals, comprising, as an active ingredient, said cephem compound or a pharmaceutically acceptable salt thereof.

A further object of this invention is to provide a therapeutical method for the prophylaxis and/or treatment of the diseases caused by *Helicobacter pylori* infection such as

gastritis, ulcer [e.g. peptic ulcer (e.g. gastric ulcer, duodenal ulcer, anastomotic ulcer etc.) etc.], MALT lymphoma, non-ulcer dyspepsia, and stomach cancer in human being and animals.

The cephem compounds used in the present invention can be represented by the following general formula (I) :



(I)

wherein R^1 is aryl(lower)alkyl which may have one or more suitable substituent(s), arylthio(lower)alkyl, lower alkenylthio(lower)alkyl which may have one or more suitable substituent(s), or

a group of the formula:

R^4-A- or R^4-S-A-

in which R^4 is heterocyclic group which may have one or more suitable substituent(s), and

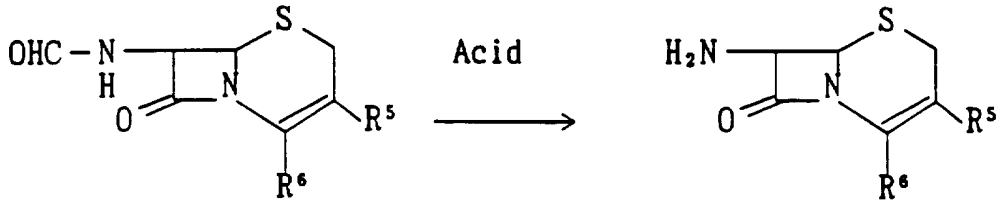
A is lower alkylene which may have one or more suitable substituent(s) or lower alkenylene,

R^2 is heterocyclic group which may have one or more suitable substituent(s), or heterocyclic(lower)-alkyl, and

R^3 is carboxy or protected carboxy.

The cephem compound (I) and a salt thereof can be prepared by processes as illustrated in the following reaction schemes.

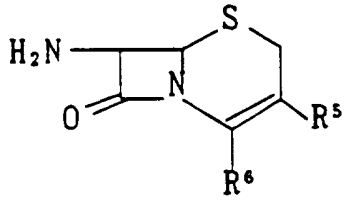
Process 1



(II)
or a salt thereof

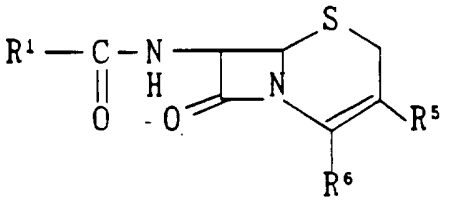
(III)
or a salt thereof

Process 2



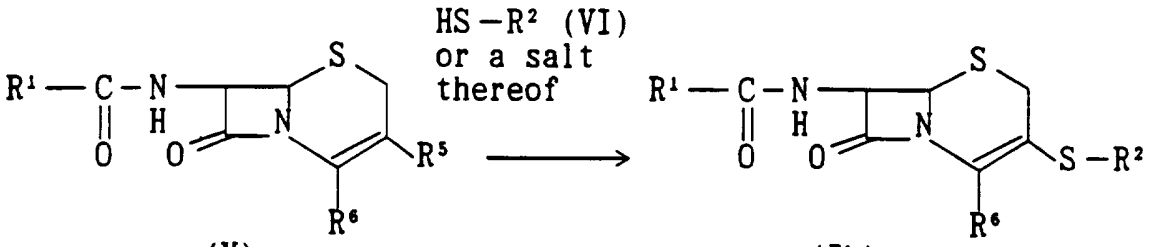
(III)
or its reactive derivative
at the amino group
or a salt thereof

R1-COOH
(IV)
or its reactive derivative
at the carboxyl group
or a salt thereof



(V)
or a salt thereof

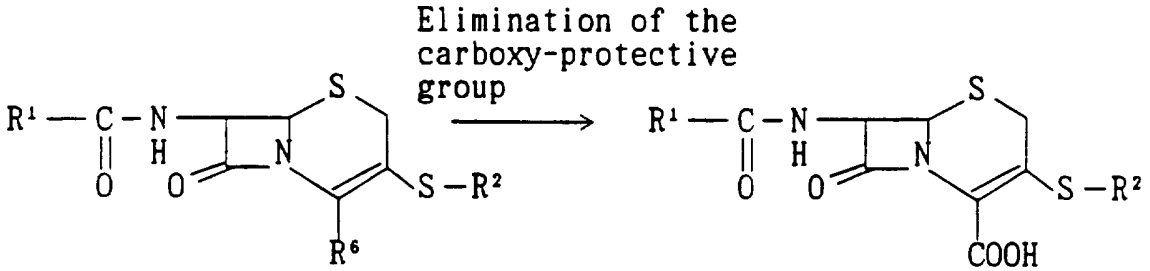
Process 3



(V)
or a salt thereof

(Ib)
or a salt thereof

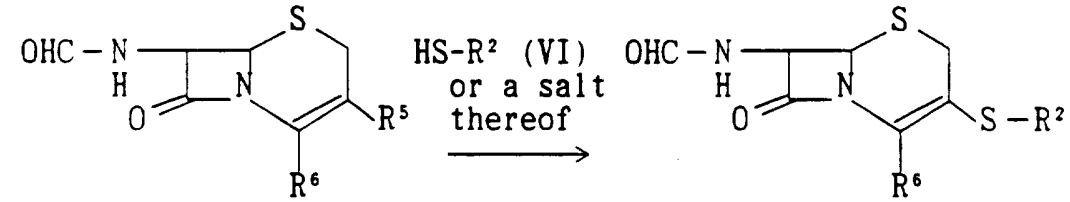
Process 4



(Ib)
or a salt thereof

(Ia)
or a salt thereof

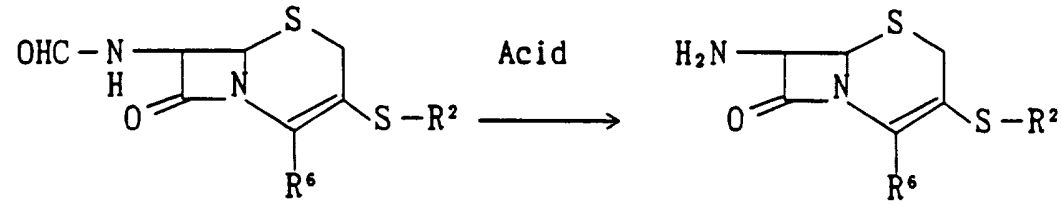
Process 5



(II)
or a salt thereof

(VII)
or a salt thereof

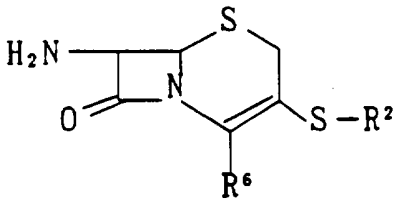
Process 6



(VII)
or a salt thereof

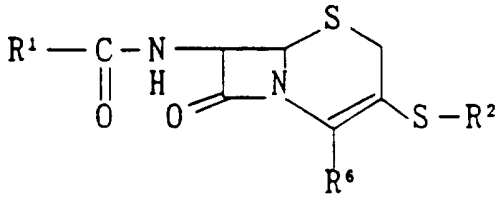
(VIII)
or a salt thereof

Process 7



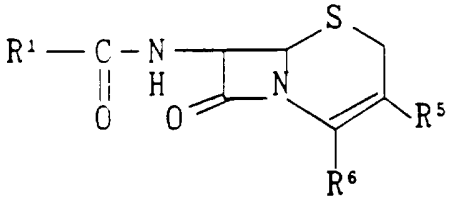
(VIII)
or its reactive derivative
at the amino group
or a salt thereof

R¹-COOH
(IV)
or its reactive derivative
at the carboxyl group
or a salt thereof



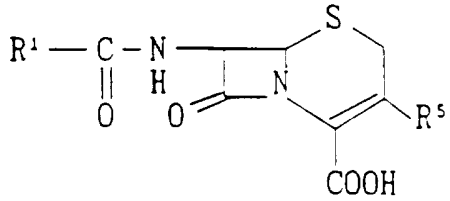
(Ib)
or a salt thereof

Process 8



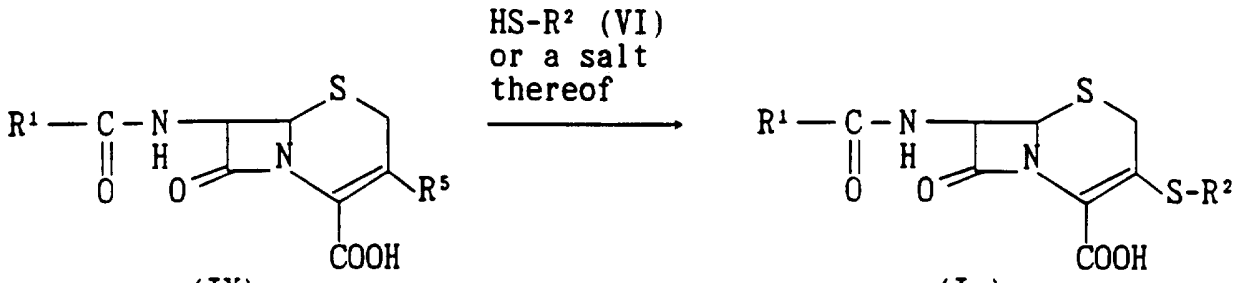
(V)
or a salt thereof

Elimination of the
carboxy-protective
group



(IX)
or a salt thereof

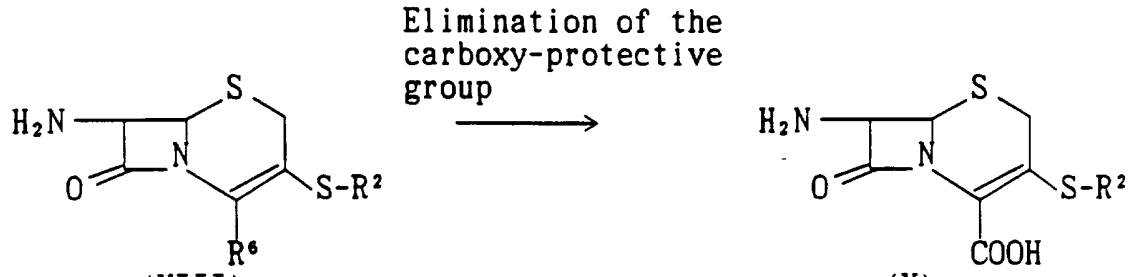
Process 9



(IX)
or a salt thereof

(Ia)
or a salt thereof

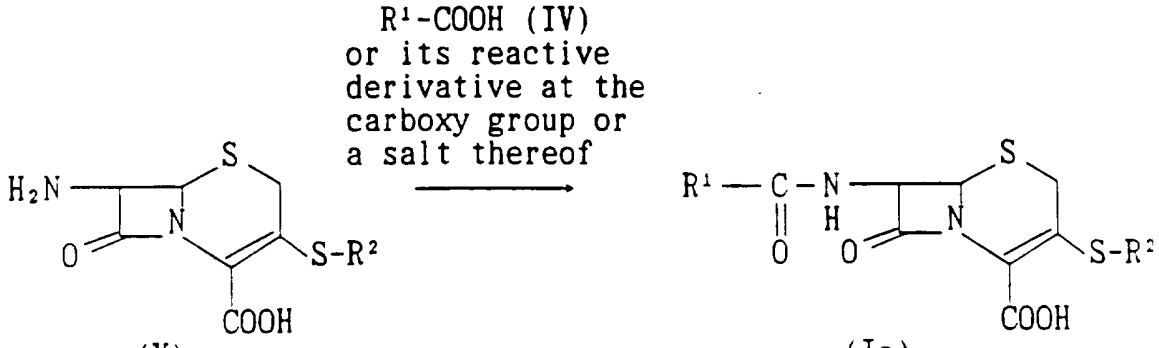
Process 10



(VIII)
or a salt thereof

(X)
or a salt thereof

Process 11



(X)
or its reactive derivative
at the amino group
or a salt thereof

(Ia)
or a salt thereof

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

R^5 is protected hydroxy, and

R^6 is protected carboxy.

Suitable examples of the various definitions of the cephem compound (I) used in the present invention to be included within the scope of the invention, which are given in the description of the present specification, are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise provided.

Suitable "lower alkyl" and "lower alkyl" moiety in "aryl(lower)alkyl", "arylthio(lower)alkyl", "lower alkenylthio(lower)alkyl", "lower alkylthio", "phenyl(lower) alkyl", "phenylthio(lower)alkyl", etc. include straight or branched ones having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl and hexyl, preferable ones having 1 to 4 carbon atoms.

Suitable "aryl" and "aryl" moiety in "aryl(lower)alkyl", "arylthio(lower)alkyl" and "arylthio" include C_6-C_{10} aryl, such as phenyl, naphthyl, tolyl, xylyl, mesityl and cumenyl, in which more preferred one is phenyl.

Suitable "aryl(lower)alkyl" includes benzyl, phenethyl, α-methylbenzyl and naphthylmethyl, in which more preferred one is phenyl(lower)alkyl and the most preferred one is benzyl.

The aryl(lower)alkyl mentioned above may have one or more, preferably 1 to 3 suitable substituent(s) on the aromatic ring,

such as lower alkyl, lower alkoxy, halogen, halo(lower)-alkyl, hydroxy, amino, lower alkylamino, acylamino, cyano, nitro, carboxy, acyl and lower alkylthio, in which more preferred ones are halogen, nitro, hydroxy, amino and lower alkyl.

Suitable "lower alkyl" moiety in "aryl(lower)alkyl which may have one or more suitable substituent(s)" may have one or more suitable substituent(s), such as hydroxy, amino and the like.

Suitable "arylthio(lower)alkyl" includes phenylthiomethyl, phenylthioethyl, phenylthiopropyl and phenylthiobutyl, in which more preferred one is phenylthio(lower)alkyl and the most preferred one is phenylthiomethyl.

Suitable "lower alkenyl" moiety in "lower alkenylthio(lower)alkyl" and "lower alkenylthio" includes straight or branched alkenyl having 2 to 6 carbon atoms, such as vinyl, 1-propenyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 1-pentenyl and 2-pentenyl, preferable ones having 2 to 4 carbon atoms.

Suitable "lower alkenylthio(lower)alkyl" includes vinylthiomethyl, vinylthioethyl, vinylthiopropyl, 1-propenylthiomethyl, 1-propenylthioethyl, allylthiomethyl and allylthioethyl, in which more preferred one is (C_2-C_6)-alkenylthio(C_1-C_6)alkyl.

The lower alkenylthio(lower)alkyl mentioned above may have one or more, preferably 1 to 3 suitable substituent(s) such as

cyano and carbamoyl.

Suitable "lower alkoxy" includes straight or branched ones such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy and hexyloxyl, preferable ones having 1 to 4 carbon atoms.

Suitable "halogen" includes chloro, bromo, fluoro and iodo.

Suitable "halo(lower)alkyl" includes chloromethyl, fluoromethyl, bromomethyl, difluoromethyl, dichloromethyl, trifluoromethyl, trichloromethyl and 2-fluoroethyl.

Suitable "lower alkylamino" includes mono- or di(lower)-alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, isobutylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, diisopropylamino, dipentylamino, dihexylamino and N-methyl-N-ethylamino.

Suitable "acyl" and "acyl" moiety in "acylamino" include carbamoyl, thiocarbamoyl, sulfamoyl, an aliphatic acyl and an aromatic acyl derived from carbamic, sulfonic, caboxylic acids or their thio acids.

The aliphatic acyl includes saturated or unsaturated, acyclic or cyclic ones, such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl), lower alkanesulfonyl (e.g. methanesulfonyl, ethanesulfonyl, propanesulfonyl), lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-

butoxycarbonyl), lower alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl), (C_3-C_7)cycloalkanecarbonyl (e.g. cyclohaxane-carbonyl), lower alkoxalyl (e.g. methoxalyl, ethoxalyl), lower alkanoylcarbonyl (e.g. pyruvoyl) and lower alkanoyloxy(lower)-alkanoyl (e.g. acetoxyacetyl, acetoxypropionyl).

The aromatic acyl includes aroyl (e.g. benzoyl, nitorobenzoyl, toluoyl, xyloyl) and arenesulfonyl (e.g. benzenesulfonyl, tosyl).

Suitable "lower alkylthio" includes methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, tert-butylthio, pentylthio, isopentylthio and hexylthio, in which more preferred one is (C_1-C_4)alkylthio.

Suitable "lower alkenylthio" includes vinylthio, 1-propenylthio, allylthio, isopropenylthio, 1-butenylthio, 2-butenylthio, 1-pentenylthio and 2-pentenylthio, in which more preferred one is (C_2-C_4)alkenylthio.

Suitable "arylthio" includes phenylthio, naphthylthio, tolylthio, xylylthio, mesitylthio and cumenylthio, in which more preferred one is phenylthio.

Suitable "heterocyclic" moiety in "heterocyclic group which may have one or more suitable substituent(s)" or "heterocyclic(lower)alkyl" includes heterocyclic groups such as:

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl,

pyrazolyl, pyridyl, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 2H-1,2,3-triazolyl), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur

atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.; and

unsaturated condensed heterocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, benzoxathiinyl, etc.

The heterocyclic group mentioned above may have one or more, preferably 1 to 3 suitable substituent(s) such as lower alkyl, amino, acylamino, lower alkylthio, arylthio, lower alkenylthio lower alkylamino, di(lower)alkylamino, pyrrolidinyl and morpholinyl.

Preferable examples of a "heterocyclic group" for R^2 include unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have lower alkyl, unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), and unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), more preferred ones are triazolyl, thiadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrazolyl, oxadiazolyl, quinolyl, isoquinolyl, benzothiazolyl and pyrimidinyl, and the most preferred ones are 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrazolyl, oxadiazolyl, quinolyl, isoquinolyl, benzothiazolyl and pyrimidinyl.

Preferable examples of "heterocyclic(lower)alkyl" for R^2 include lower alkyl having unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), more preferred one is (C_1-C_6)alkyl having pyrazolyl, and the most

preferred one is pyrazolylmethyl.

Preferable examples of a "heterocyclic group" for R^4 include unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), and unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s), and more preferred ones are thiazolyl, thiadiazolyl (e.g. 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl), tetrazolyl, pyridyl and thienyl.

Suitable "lower alkylene" in "lower alkylene which may have one or more suitable substituent(s)" includes straight or branched ones such as methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene and hexamethylene, in which more preferred one is C_1-C_4 alkylene, and the most preferred ones are methylene and ethylene.

Preferable examples of "suitable substituent(s)" in "lower alkylene which may have one or more suitable substituent(s)" include lower alkoxyimino, in which more preferred one is methoxyimino.

Suitable "lower alkenylene" includes straight or branched one having 2 to 6 carbon atom(s) such as vinylene, propenylene, 1-(or 2-)butenylene, 1-(or 2- or 3-)pentenylene, 1-(or 2- or 3-)hexenylene, methylvinylene, ethylvinylene, 1-(or 2- or 3-)methylpropenylene, 1-(or 2- or 3-)ethylpropenylene, 1-(or 2- or 3- or 4-)methyl-1-(or 2-)butenylene, and the like, in which

more preferred one is (C_2-C_4)alkenylene, and the most preferred one is vinylene.

Suitable "protected carboxy" includes carboxy group protected by conventional protective group such as substituted or unsubstituted lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, 2-(dimethylamino)ethoxycarbonyl, 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl), substituted or unsubstituted aryloxycarbonyl (e.g. phenoxycarbonyl, 4-nitrophenoxycarbonyl, 2-naphthyloxycarbonyl), and substituted or unsubstituted aryl(lower)alkoxycarbonyl, for example, mono or di or triphenyl(lower)alkoxycarbonyl which may be substituted with nitro (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, 4-nitrobenzyloxycarbonyl).

Suitable "protected hydroxy" includes hydroxy protected by conventional protective group, for example, a substituted lower alkoxy such as lower alkoxy(lower)alkoxy (e.g. methoxymethoxy), lower alkoxy(lower)alkoxy(lower)alkoxy (e.g. methoxyethoxy-methoxy), a substituted or unsubstituted aryl(lower)alkoxy (e.g. benzyloxy, nitrobenzyloxy); acyloxy such as lower alkanoyloxy (e.g. acetoxy, propionyloxy, pivaloyloxy), aroyloxy (e.g. benzoyloxy, fluorenecarbonyloxy), lower alkoxycarbonyloxy (e.g. methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, isopropoxycarbonyloxy, butoxycarbonyloxy, isobutoxycarbonyloxy, tert-butoxycarbonyloxy, pentyloxycarbonyloxy, hexyloxycarbonyl-

oxy), a substituted or unsubstituted aryl(lower)alkoxycarbonyl-oxy (e.g. benzyloxycarbonyloxy, bromobenzyloxycarbonyloxy), arenesulfonyloxy (e.g. benzensulfonyloxy, tosyloxy), alkanesulfonyloxy (e.g. methanesulfonyloxy, ethanesulfonyloxy); and tri(lower)alkylsilyloxy (e.g. trimethylsilyloxy).

Suitable salts of the object compound (I) are pharmaceutically acceptable salts such as conventional non-toxic salts and include an organic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate), an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate), an alkali metal salt (e.g. sodium salt, potassium salt) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt).

Suitable examples of the salts of the compounds (II), (III), (V), (VII), (VIII), (IX) and (X) in Processes 1 to 11 are to be referred to those as exemplified for the object compound (I).

Particularly, the preferred examples of the compound (I) used in the present invention are as follows:

1) the compound of the formula (I) wherein

R^1 is arylthio(lower)alkyl, and

R^2 is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s);

more preferred one is that wherein

R^1 is phenylthio(lower)alkyl, and

R^2 is triazolyl; and

the most preferred one is that wherein

R^1 is phenylthiomethyl, and

R^2 is 1,2,4-triazol-3-yl.

2) the compound of the formula (I) wherein

R^1 is arylthio(lower)alkyl, and

R^2 is unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s);

more preferred one is that wherein

R^1 is phenylthio(lower)alkyl, and

R^2 is thiadiazolyl; and

the most preferred one is that wherein

R^1 is phenylthiomethyl, and

R^2 is 1,3,4-thiadiazol-2-yl or 1,2,3-thiadiazol-5-yl.

3) the compound of the formula (I) wherein

R^1 is lower alkenylthio(lower)alkyl having cyano, and

R^2 is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s);

more preferred one is that wherein

R^1 is $(C_2\text{-}C_6)$alkenylthio$(C_1\text{-}C_6)$alkyl having cyano, and

R^2 is triazolyl; and

the most preferred one is that wherein

R^1 is ethenylthiomethyl having cyano, and

R^2 is 1,2,4-triazol-3-yl.

4) the compound of the formula (I) wherein

R^1 is aryl(lower)alkyl, and

R^2 is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) or unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have a suitable substituent;

more preferred one is that wherein

R^1 is phenyl(lower)alkyl, and

R^2 is triazolyl, thiadiazolyl or thiadiazolyl having lower alkyl; and

the most preferred one is that wherein

R^1 is benzyl, and

R^2 is 1,2,3-triazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl or 5-methyl-1,3,4-thiadiazol-2-yl.

5) the compound of the formula (I) wherein

R^1 is a group of the formula:

R^4-A- or R^4-S-A-

in which R^4 is unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have a suitable substituent, and

A is lower alkylene, and

R^2 is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s);

more preferred one is that wherein

R^1 is thiazolylmethyl having a suitable substituent, thiadiazolylmethyl which may have a suitable substituent or thiadiazolylthiomethyl having a suitable substituent, and

R^2 is triazolyl; and

the most preferred one is that wherein

R^1 is (1,2,5-thiadiazol-3-yl)methyl, (2-amino-thiazol-4-yl)-methyl, (2-formylamino-thiazol-4-yl)methyl or (5-methyl-1,3,4-thiadiazol-2-yl)thiomethyl, and

R^2 is 1,2,4-triazol-3-yl.

Other preferred examples of the compound (I) used in the present invention are as follows:

1) the compound of the formula (I) wherein

R^1 is arylthio(lower)alkyl, and

R^2 is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have 1 to 3 suitable substituent(s);

more preferred one is that wherein

R^1 is phenylthio(lower)alkyl, and

R^2 is triazolyl which may have lower alkyl; and

the most preferred one is that wherein

R^1 is phenylthiomethyl, and

R^2 is 1,2,4-triazol-3-yl or 1-methyl-1,3,4-triazol-2-yl.

2) the compound of the formula (I) wherein

R^1 is arylthio(lower)alkyl, and

R^2 is unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 suitable substituent(s);

more preferred one is that wherein

R^1 is phenylthio(lower)alkyl, and

R^2 is thiadiazolyl which may have lower alkyl; and

the most preferred one is that wherein

R^1 is phenylthiomethyl, and

R^2 is 1,3,4-thiadiazol-2-yl, 1,2,3-thiadiazol-5-yl or 5-methyl-1,3,4-thiadiazol-2-yl.

3) the compound of the formula (I) wherein

R^1 is lower alkenylthio(lower)alkyl having cyano, and

R^2 is a) lower alkyl having unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

b) unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), or

c) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s);

more preferred one is that wherein

R^1 is lower alkenylthio(lower)alkyl having cyano, and

R^2 is triazolyl, pyrazolyl(lower)alkyl or thiadiazolyl; and

the most preferred one is that wherein

R^1 is ethenylthiomethyl having cyano, and

R^2 is 1,2,4-triazol-3-yl, 1,2,3-triazol-5-yl,

(pyrazol-4-yl)methyl, 1,3,4-thiadiazol-2-yl or 1,2,3-thiadiazol-5-yl.

4) the compound of the formula (I) wherein

R^1 is aryl(lower)alkyl which may have 1 to 3 suitable substituent(s), and

R^2 is a) unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have 1 to 3 suitable substituent(s), or

b) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have a suitable substituent;

more preferred one is that wherein

R^1 is phenyl(lower)alkyl which may have a halogen, and

R^2 is triazolyl, thiadiazolyl, thiadiazolyl having lower alkyl, thiadiazolyl having amino, triazolyl having lower alkyl, thiazolyl or pyridyl; and

the most preferred one is that wherein

R^1 is benzyl, chlorobenzyl or fluorobenzyl, and

R^2 is 1,2,3-triazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl, 5-methyl-1,3,4-triazol-2-yl, 5-amino-1,3,4-thiadiazol-2-yl, 2-thiazolyl or 2-pyridyl.

5) the compound of the formula (I) wherein

R^1 is a group of the formula:

R^4-A- or R^4-S-A-

in which R^4 is a) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have a suitable substituent, or

b) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s), and

A is lower alkylene or lower alkenylene, and

R^2 is a) unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have 1 to 3 suitable substituent(s), or

b) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 suitable substituent(s);

more preferred one is that wherein

R^1 is thiazolylmethyl having a suitable substituent, thiadiazolylmethyl which may have a suitable substituent, thiadiazolylthiomethyl having a suitable substituent, or thienylmethyl, and

R^2 is triazolyl, thiadiazolyl, thiadiazolyl having methyl or thiadiazolyl having amino; and

the most preferred one is that wherein

R^1 is (1,2,5-thiadiazol-3-yl)methyl, (2-amino-thiazol-4-yl)-

methyl, (2-formylamino-thiazol-4-yl)methyl, (5-methyl-1,3,4-thiadiazol-2-yl)thiomethyl, 2-thienylmethyl or 3-thienylmethyl, and

R^2 is 1,2,4-triazol-3-yl, 1,3,4-thiadiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl or 5-amino-1,3,4-thiadiazol-2-yl.

Other preferred examples of the compound (I) used in the present invention are as follows:

the compound of the formula (I) wherein

R^1 is phenyl(lower)alkyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of halogen, nitro, hydroxy and amino;

phenylthio(lower)alkyl;

lower alkenylthio(lower)alkyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of cyano and acyl; or

a group of the formula:

R^4-A- or R^4-S-A-

in which R^4 is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s);

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 suitable substituent(s) selected from the group

consisting of amino, acylamino and lower alkyl; or

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s);

A is lower alkylene which may have 1 to 3 lower alkoxyimino; or

lower alkenylene; and

R^2 is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have 1 to 3 suitable substituent(s) selected from the group consisting of lower alkyl and amino;

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 suitable substituent(s) selected from the group consisting of lower alkyl, amino, acylamino, mono or di(lower)-alkylamino, pyrrolidinyl and morpholinyl;

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have 1 or 2 lower alkyl;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s);

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s); or

lower alkyl substituted by unsaturated 3 to 8-

membered heteromonocyclic group containing 1 to 4 nitrogen atom(s);

more preferred one is that wherein

R^1 is phenyl(lower)alkyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of halogen, nitro, hydroxy and amino;

phenylthio(lower)alkyl;

lower alkenylthio(lower)alkyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of cyano and carbamoyl; or

a group of the formula:

R^4-A- or R^4-S-A-

in which R^4 is pyridyl;

tetrazolyl;

thiazolyl which may have 1 or 2 suitable substituent(s) selected from the group consisting of amino, lower alkanoylamino and lower alkyl; or

thienyl;

A is lower alkylene which may have 1 to 3 lower alkoxyimino; or

lower alkenylene;

R^2 is triazolyl which may have 1 or 2 suitable substituent(s) selected from the group consisting of lower alkyl and amino;

thiadiazolyl which may have suitable

substituent(s) selected from the group consisting of lower alkyl, amino, lower alkylamino, di(lower)alkylamino, lower alkanoylamino, pyrrolidinyl and morpholinyl;
pyridyl;
pyrimidinyl;
pyrazolyl;
thiazolyl which may have amino;
oxadiazolyl which may have lower alkyl;
quinolyl;
isoquinolyl;
benzothiazolyl;
pyrazolyl(lower)alkyl; or
tetrazolyl which may have lower alkyl; and

R^3 is carboxy;

another more preferred one is that wherein

R^1 is phenyl(lower)alkyl which may have halogen, phenylthio(lower)alkyl, lower alkenylthio(lower)alkyl having cyano, thiazolyl(lower)alkyl which may have amino, or thienyl(lower)alkyl,

R^2 is triazolyl, thiadiazolyl, thiazolyl, pyridyl, triazolyl having lower alkyl, thiadiazolyl having lower alkyl, thiadiazolyl having amino, or thiadiazolyl having lower alkylamino, and

R^3 is carboxy;

another more preferred one is that wherein

R^1 is phenylthio(lower)alkyl,
phenyl(lower)alkyl, or
lower alkenylthio(lower)alkyl having cyano,

R^2 is triazolyl, thiadiazolyl, thiadiazolyl having lower alkyl, or thiadiazolyl having amino, and

R^3 is carboxy;

another more preferred one is that wherein

R^1 is phenyl(lower)alkyl,

R^2 is thiadiazolyl having lower alkyl or
thiadiazolyl having amino, and

R^3 is carboxy; and

the most preferred one is that wherein

R^1 is benzyl,

R^2 is 5-methyl-1,3,4-thiadiazol-2-yl or
5-amino-1,3,4-thiadiazol-2-yl, and

R^3 is carboxy.

Particularly preferred examples of the compound (I) are as follows:

1) the compound of the formula (I) wherein

R^1 is arylthio(lower)alkyl,

R^2 is a) unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have 1 to 3 suitable substituent(s), or

b) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3

nitrogen atom(s) which may have 1 to 3 suitable substituent(s), and

R^3 is carboxy;

more preferred one is that wherein

R^1 is phenylthio(lower)alkyl,

R^2 is triazolyl which may have lower alkyl or thiadiazolyl which may have lower alkyl, and

R^3 is carboxy; and

the most preferred one is that wherein

R^1 is phenylthiomethyl,

R^2 is 1,2,4-triazol-3-yl, 1-methyl-1,3,4-triazol-2-yl, 1,3,4-thiadiazol-2-yl, 1,2,3-thiadiazol-5-yl or 5-methyl-1,3,4-thiadiazol-2-yl, and

R^3 is carboxy.

2) the compound of the formula (I) wherein

R^1 is ethenylthiomethyl having cyano,

R^2 is 1,2,4-triazol-3-yl, 1,2,3-triazol-5-yl, (pyrazol-4-yl)methyl, 1,3,4-thiadiazol-2-yl or 1,2,3-thiadiazol-5-yl, and

R^3 is carboxy.

3) the compound of the formula (I) wherein

R^1 is benzyl which may have a halogen,

R^2 is triazolyl, thiadiazolyl, thiadiazolyl having lower alkyl, thiadiazolyl having amino, thiadiazolyl having lower alkylamino, triazolyl having lower alkyl, thiazolyl or pyridyl, and

R^3 is carboxy;

more preferred one is that wherein

R^1 is benzyl, chlorobenzyl or fluorobenzyl,

R^2 is 1,2,3-triazol-5-yl, 1,2,4-triazol-3-yl,
1,2,3-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl,
5-methyl-1,3,4-thiadiazol-2-yl,
5-methyl-1,3,4-triazol-2-yl,
5-amino-1,3,4-thiadiazol-2-yl,
5-methylamino-1,3,4-thiadiazol-2-yl,
2-thiazolyl or 2-pyridyl, and

R^3 is carboxy; and

the most preferred one is that wherein

R^1 is benzyl,

R^2 is 5-methyl-1,3,4-thiadiazol-2-yl or
5-amino-1,3,4-thiadiazol-2-yl, and

R^3 is carboxy.

4) the compound of the formula (I) wherein

R^1 is thiazolylmethyl which may have amino or
thienylmethyl,

R^2 is triazolyl, thiadiazolyl, thiadiazolyl having methyl,
thiadiazolyl having amino or thiadiazolyl having
lower alkylamino, and

R^3 is carboxy; and

the more preferred one is that wherein

R^1 is thiazol-4-yl-methyl, (2-amino-thiazol-4-yl)methyl,
2-thienylmethyl or 3-thienylmethyl,

R^2 is 1,2,4-triazol-3-yl, 1,3,4-thiadiazol-2-yl,
5-methyl-1,3,4-thiadiazol-2-yl,
5-amino-1,3,4-thiadiazol-2-yl or
5-methylamino-1,3,4-thiadiazolyl-2-yl, and
R^3 is carboxy.

The processes for preparing the cephem compound (I) used in the present invention are explained in detail in the following.

Process 1

The compound (III) or a salt thereof can be prepared by subjecting the compound (II) or a salt thereof to elimination of formyl group in the presence of an acid.

Suitable acid includes an organic acid (e.g. formic acid, acetic acid, propionic acid) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid).

The reaction is usually carried out in a solvent such as water, an alcohol (e.g. methanol, ethanol), methylene chloride, chloroform, tetrachloromethane, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction.

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

Process 2

The compound (V) or a salt thereof can be prepared by reacting the compound (III) or its reactive derivative at the

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

Suitable reactive derivative at the carboxy group of the compound (IV) includes an acid halide, an acid anhydride, an activated amide and an activated ester. Suitable exmaples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid (e.g. methanesulfonic acid), aliphatic carboxylic acid (e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid), or aromatic carboxylic acid (e.g. benzoic acid); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2N^+=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester) or an ester with a N-hydroxy compound (e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-

pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole). These reactive derivatives can optionally be selected from them according to the kind of the compound (IV) to be used.

Suitable salts of the compound (IV) and its reactive derivative include a base salt such as an alkali metal salt (e.g. sodium salt, potassium salt), an alkaline earth metal salt (e.g. calcium salt, magnesium salt), an ammonium salt and an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt).

Suitable reactive derivative at the amino group of the compound (III) includes Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (III) with a carbonyl compound such as aldehyde or ketone; a silyl derivative formed by the reaction of the compound (III) 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 (III) with phosphorus trichloride or phosgene.

The reaction is usually carried out in a solvent such as water, an alcohol (e.g. methanol, ethanol), acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other 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 (IV) 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'-morpholinoethyl-carbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)-carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropyl-carbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate (e.g. ethyl chloroformate, isopropyl chloroformate); triphenylphosphine; 2-ethyl-7-hydroxybenz-isoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; or so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride or oxalyl chloride.

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

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

Process 3

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

Suitable salts of the compound (VI) include alkali metal salts (e.g. sodium salt, potassium salt).

The reaction is usually carried out in the presence of a base. Suitable examples of the base include organic bases such as triethylamine, trimethylamine, N,N-diisopropylethylamine, dimethylamine, N-methylmorpholine and pyridine, and inorganic bases such as alkali metal hydroxides (e.g. sodium hydroxide, potassium hydroxide), alkali metal carbonates (e.g. sodium carbonate, potassium carbonate), and alkali metal hydrogencarbonates (e.g. sodium hydrogencarbonate, potassium hydrogencarbonate).

The reaction is usually carried out in a solvent such as water, acetone, acetonitrile, dioxane, tetrahydrofuran, N,N-dimethylformamide, dimethyl sulfoxide, 1,2-dimethoxyethane, a mixture thereof or any other solvent which does not adversely influence the reaction.

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

Process 4

The object compound (Ia) or a salt thereof can be prepared

by subjecting the compound (Ib) or a salt thereof to an elimination reaction of the carboxy-protective group.

In the present elimination reaction, all conventional methods used for the elimination of the carboxy-protective group, for example, hydrolysis, reduction, elimination using a Lewis acid, etc. are applicable. When the carboxy-protective group is an ester, it can be eliminated by hydrolysis or elimination using Lewis acid. The hydrolysis is preferably carried out in the presence of a base or an acid.

Suitable base includes, for example, inorganic bases such as alkali metal hydroxides (e.g. sodium hydroxide, potassium hydroxide), alkaline earth metal hydroxides (e.g. magnesium hydroxide, calcium hydroxide), alkali metal carbonates (e.g. sodium carbonate, potassium carbonate), alkaline earth metal carbonates (e.g. magnesium carbonate, calcium carbonate), alkali metal hydrogencarbonates (e.g. sodium hydrogencarbonate, potassium hydrogencarbonate), alkali metal acetates (e.g. sodium acetate, potassium acetate), alkaline earth metal phosphates (e.g. magnesium phosphate, calcium phosphate), and alkali metal hydrogen phosphates (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate); and organic bases such as trialkylamines (e.g. trimethylamine, triethylamine), picoline, N-methylpyrrolidine, N-methylmorpholine, and 1,5-diazabicyclo[4.3.0]non-5-one, 1,4-diazabicyclo[2.2.2]octane, and 1,5-diazabicyclo[5.4.0]undecene-5. The hydrolysis using a base is often carried out in water or a hydrophilic organic solvent

or a mixed solvent thereof.

Suitable acid includes organic acids (e.g. formic acid, acetic acid, propionic acid) and inorgnic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid). The present hydrolysis is usually carried out in water or an organic solvent or a mixed solvent thereof.

The reaction temperature is not critical, and it may be selected suitably in accordance with the kind of carboxy protective group and elimination method.

The elimination using a Lewis acid is preferable for eliminating a substituted or unsubstituted aryl(lower)alkyl ester, and carried out by reacting the compound (Ib) or a salt thereof with a Lewis acid. Examples of the Lewis acid are boron trihalides (e.g. boron trichloride, boron trifluoride), titanium tetrahalides (e.g. titanium tetrachloride, titanium tetrabromide), tin tetrahalides (e.g. tin tetrachloride, tin tetrabromide), aluminium halides (e.g. aluminium chloride, aluminium bromide), and trihaloacetic acids (e.g. trichloroacetic acid, trifluoroacetic acid). This elimination reaction is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol) and is usually carried out in a solvent such as nitroalkane (e.g. nitromethane, nitroethane), alkylene halide (e.g. methylene chloride, ethylene chloride), diethyl ether, carbon disulfide or any other solvent which does not adversely influence the reaction. These solvents may be used alone or upon mixing with one another.

The reduction elimination can be preferably conducted for eliminating a protective group such as halo(lower)alkyl (e.g 2-iodoethyl, 2,2,2-trichloroethyl) ester, and aryl(lower)alkyl (e.g. benzyl) ester.

The reduction applicable for the elimination reaction includes the reduction using a combination of a metal (e.g. zinc, zinc amalgam) or a salt of chromium compound (e.g. chromous chloride, chromous acetate) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid); and conventional catalytic reduction in the presence of a conventional metallic catalyst (e.g. palladium carbon, Raney nickel).

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

Process 5

The compound (VII) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (VI) or a salt thereof.

This reaction can be carried out in substantially the same manner as in Process 3, and therefore the reaction mode and reaction conditions (e.g. bases, solvent, reaction temperature) of this reaction are to be referred to those as explained in Process 3.

Process 6

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

subjecting the compound (VII) or a salt thereof to elimination of formyl group in the presence of an acid.

This reaction can be carried out in substantially the same manner as in Process 1, and therefore the reaction mode and reaction conditions (e.g. acids, solvent, reaction temperature) of this reaction are to be referred to those as explained in Process 1.

Process 7

The compound (Ib) or a salt thereof can be prepared by reacting the compound (VIII) or its reactive derivative at the amino group or a salt thereof with the compound (IV) or its reactive derivative at the carobxy group or a salt thereof.

This reaction can be carried out in substantially the same manner as in Process 2, and therefore the reaction mode and reaction conditions (e.g. reactive derivatives, condensing agents, solvent, reaction temperature) of this reaction are to be referred to those as explained in Process 2.

Process 8

The compound (IX) or a salt thereof can be prepared by subjecting the compound (V) or a salt thereof to an elimination reaction of the carboxy-protective group.

This reaction can be carried out in substantially the same manner as in Process 4, and therefore the reaction mode and reaction conditions (e.g. bases, acids, catalysts, solvent, reaction temperature) of this reaction are to be referred to those as explained in Process 4.

Process 9

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

This reaction can be carried out in substantially the same manner as in Process 3, and therefore the reaction mode and reaction conditions (e.g. bases, solvent, reaction temperature) of this reaction are to be referred to those as explained in Process 3.

Process 10

The compound (X) or a salt thereof can be prepared by subjecting the compound (VIII) or a salt thereof to an elimination reaction of the carboxy-protective group.

This reaction can be carried out in substantially the same manner as in Process 4, and therefore the reaction mode and reaction conditions (e.g. bases, acids, catalysts, solvent, reaction temperature) of this reaction are to be referred to those as explained in Process 4.

Process 11

The compound (Ia) or a salt thereof can be prepared by reacting the compound (X) or its reactive derivative at the amino group or a salt thereof with the compound (IV) or a salt thereof.

This reaction can be carried out in substantially the same manner as in Process 2, and therefore the reaction mode and reaction conditions (e.g. reactive derivatives, condensing

agents, solvent, reaction temperature) of this reaction are to be referred to those as explained in Process 2.

The starting compound (II) can be prepared by the known method such as disclosed in Japanese Patent Publication No. 52-83492.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography or reprecipitation.

It is to be noted that each of the object compound (I) may include one or more steroisomer such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) or double bond(s) and all such isomers and mixtures thereof are included within the scope of this invention.

The cephem compound (I) and a pharmaceutically acceptable salt thereof include a solvate [e.g., enclosure compound (e.g., hydrate, etc.)].

The cephem compound (I) and a pharmaceutically acceptable salt thereof include both their crystal form and non-crystal form.

The cephem compound (I) and pharmaceutically acceptable salts thereof are stable even in a strong acid such as gastric juice.

The cephem compound (I) and pharmaceutically acceptable salts thereof possess antimicrobial activity against

H. pylori, and are useful for the prophylaxis and/or treatment of gastritis, ulcer (e.g. gastric ulcer, duodenal ulcer, anastomotic ulcer), MALT lymphoma and non-ulcer dyspepsia and the prophylaxis of stomach cancer. The cephem compound (I) and pharmaceutically acceptable salts thereof may be administered in combination with an acid secretion inhibitor such as an H_2-blocker (e.g. cimetidine, ranitidine, famotidine, etc.) or a proton pump inhibitor (e.g. omeprazole, lansoprazole, etc.) for the prophylaxis and/or treatment of chronic gastritis, peptic ulcer (e.g. gastric ulcer, duodenal ulcer, anastomotic ulcer), MALT lymphoma and non-ulcer dyspepsia and the prophylaxis of stomach cancer.

The cephem compound (I) and pharmaceutically acceptable salts thereof are particularly effective for the prophylaxis and/or treatment of the diseases caused by *Helicobacter pylori* infection such as gastritis, ulcer [e.g. peptic ulcer (e.g. gastric ulcer, duodenal ulcer, anomatic ulcer, etc.) etc.], MALT lymphoma, non-ulcer-dyspepsia and stomach cancer when administered with an acid secretion inhibitor such as an H_2-blocker (e.g. cimetidine, ranitidine, famotidine, etc.) or a proton pump inhibitor (e.g. omeprazole, lansoprazole, etc.).

Particularly, since the cephem compound (I) and pharmaceutically acceptable salts thereof possess selective antimicrobial activity against *H. pylori*, they can act selectively on *H. pylori* without exerting adverse influence on other useful enterobacteria. Accordingly, the cephem compound

(I) and pharmaceutically acceptable salts thereof serve well for the eradication of *H. pylori* and are useful for the treatment of ulcers and/or prevention of recurrence of ulcers. The cephem compound (I) and pharmaceutically acceptable salts thereof may be administered in combination with an acid secretion inhibitor such as an H_2-blocker (e.g. cimetidine, ranitidine, famotidine, etc.) or a proton pump inhibitor (e.g. omeprazole, lansoprazole, etc.) for the treatment of ulcers and/or prevention of recurrence of ulcers.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used as they are, or in the form of pharmaceutical preparations containing one of said compounds as an active ingredient in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral or parenteral administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension or emulsion. If desired, there may be included, in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives such as lactose, sialic 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) will vary depending upon the age and condition of the patient, an average single

dose of about 0.1 mg, 1 mg, 10 mg, 25 mg, 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg and 2000 mg of the compound (I) may be effective for treating ulcer. In general, amounts between 0.1 mg/body and about 2,000 mg/body may be administered per day.

When the compound (I) is used in combination with an acid secretion inhibitor, a ratio by weight of the compound (I) to an acid secretion inhibitor is in the following range:

compound (I) / acid secretion inhibitor = 0.01/1 - 100/1

A preferred range is

compound (I) / acid secretion inhibitor = 1/1 - 100/1

A more preferred range is

compound (I) / acid secretion inhibitor = 2.5/1 - 50/1

Another preferred range is

compound (I) / acid secretion inhibitor = 0.1/1 - 10/1

According to the present invention, the followings are provided.

(1) A product comprising the cephem compound (I) or a pharmaceutically acceptable salt thereof and an acid secretion inhibitor as a combined preparation for simultaneous, separate or sequential use for the prevention and/or treatment of the diseases caused by *Helicobacter pylori* infection.

(2) The cephem compound (I) or a pharmaceutically acceptable salt thereof for adjuvant therapy of the diseases caused by *Helicobacter pylori* infection, with an acid secretion inhibitor.

(3) Use of the cephem compound (I) or a pharmaceutically

acceptable salt thereof and an acid secretion inhibitor for the manufacture of medicament for simultaneous, separate or sequential use for the prevention and/or treatment of the diseases caused by *Helicobacter pylori* infection.

(4) A product comprising the cephem compound (I) and an acid secretion inhibitor for simultaneous, separate or sequential use as a medicament.

(5) A pharmaceutical composition, comprising the cephem compound (I) and an acid secretion inhibitor and optionally pharmaceutically acceptable carriers or excipients.

(6) A pharmaceutical composition, characterized in that the composition is adapted for only oral administration and comprises, as an active ingredient, the cephem compound (I) or a pharmaceutically acceptable salt thereof and an acid secretion inhibitor.

(7) A product comprising:

a) the cephem compound (I) or a pharmaceutically acceptable salt thereof, and,

b) an acid secretion inhibitor in a ratio by weight of:
a) to b) of from 0.01/1 to 100/1.

(8) A method for treatment or inhibition of the diseases caused by *Helicobacter pylori* infection which comprises administering an effective amount of the cephem compound (I) to a patient in need of said treatment or inhibition.

(9) The method of the above (8) wherein the cephem compound (I) is administered to said patient in combination with an acid

secretion inhibitor in a ratio by weight of the cephem compound (I) to an acid secretion inhibitor in the range of from 0.01/1 to 100/1.

(10) A method for the veterinary treatment of an animal infected with *Helicobacter pylori* which comprises administering an effective amount of the cephem compound (I) to an animal in need of said treatment.

(11) The method of the above (10) wherein the cephem compound (I) is administered to said animal in combination with an acid secretion inhibitor in a ratio by weight of the cephem compound (I) to an acid secretion inhibitor in the range of from 0.01/1 to 100/1.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of the representative compound of the compound (I) are shown in the following.

Test 1 (Anti-microbial activity against *Helicobacter pylori*)

Test Method

In vitro anti-microbial activity against *Helicobacter pylori* was determined by the two-fold agar plate dilution method as described below.

Helicobacter pylori was cultured on a Brucella agar plate containing 3% horse serum and 2% starch at 37℃ for 3 days under 10% CO_2, and suspended in a Brucella broth to a turbidity

of McFarland No. 1. This suspension was inoculated on Brucella agar supplemented with 7% horse blood containing graded concentrations of the test compound, and the minimum inhibitory concentration (MIC) was expressed in terms of μg/ml after incubation at 37°C for 3 days under 10% CO_2.

Test Compound

7β-[2-(Phenylthio)acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylic acid (the compound of Example 2).

Test Result

MIC (μg/ml)

Test strain	Test Compound
H. pylori FP 1757	<0.02

Test 2 (Therapeutic effects in mouse model)

Test Method

1.5 ml of approx. 10^8 cfu/ml of *H. pylori* FP 1757 was orally infected into 4 weeks old male ICR mice (Nippon SLC, Hamamatsu, Japan) which had been fasted overnight. Four days after infection, the test compound was orally administered to the mice at the dose of 0.32 mg/kg/time twice per day, for 4 days. The test compound was suspended in 0.5% methylcellulose

and administered to the mice. The mice were sacrificed at 2 weeks after the final administration and the gastric mucosa was scraped and homogenized in 1 ml of 0.1 M phosphate buffered saline. 0.1 ml aliquots were inoculated onto Brucella agar plate containing 3% horse serum, 2% starch and antibiotics. All plates were incubated at 37°C under 10% CO_2 for 4 or 5 days. Colonies grown on the plate were counted, and the therapeutic effect was evaluated.

Test Compound

7β-(2-Phenylacetamido)-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylic acid (the compound of Example 16).

Test Result

	dose (mg/kg/time)	eradication(%)
Test Compound	0.32	71%

Test 3 (Subacute toxicity)

Test Method

The test compound suspended in 0.5% methylcellulose was orally administered to male rats at a dose of 100 or 32 mg/kg/day for 2 weeks.

Test Compound

(Z)-7β-[2-{(2-Cyanoethenyl)thio}acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylic acid (the compound of Example 8).

Test Result

	non toxicological dose (mg/kg/day)
Test Compound	100

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

Preparation 1

To a solution of benzhydryl 7β-formamido-3-methanesulfonyloxy-3-cephem-4-carboxylate (15.6 g) in methanol (78 ml) and tetrahydrofuran (20 ml) was added conc. hydrochloric acid (21.0 ml). After stirring at room temperature for 3 hours, the reaction mixture was poured into a mixture of ethyl acetate and water, and the mixture was adjusted to pH 6.0 with an aqueous sodium hydrogencarbonate solution. The separated organic layer was washed with a saturated aqueous

sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure to give benzhydryl 7β-amino-3-methanesulfonyloxy-3-cephem-4-carboxylate (6.64 g).

NMR ($CDCl_3$, δ) : 2.73 (3H, s),
3.71 (2H, dd, J=18.5Hz and 57.9Hz),
4.79 (1H, d, J=5.1Hz), 5.01 (1H, d, J=5.1Hz),
6.97 (1H, s), 7.2 - 7.5 (10H, m)

Preparation 2

A solution of phosphorus pentachloride (3.15 g) in dichloromethane (32 ml) was stirred at room temperature for 20 minutes. 3-Phenylthioacetic acid (2.42 g) was added to the solution at -15°C and the mixture was stirred at said temperature for 20 minutes. To a solution of benzhydryl 7β-amino-3-methanesulfonyloxy-3-cephem-4-carboxylate (6.63 g) in tetrahydrofuran (265 ml) were added N-trimethylsilylacetamide (3.78 g) and the acid chloride solution obtained above at 0°C. After stirring under ice-cooling for one hour, the reaction mixture was poured into a mixture of ethyl acetate and water. The separated organic layer was washed with a saturated aqueous sodium chloride solution three times, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent; n-hexane:ethyl acetate = 3:1(v/v)) to give benzhydryl 7β-[2-(phenylthio)acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate (6.36 g).

NMR ($CDCl_3$, δ) : 2.78 (3H, s),

3.65 (2H, dd, J=18.5Hz and 54.1Hz),

3.70 (2H, d, J=3.9Hz), 5.02 (1H, d, J=5.0Hz),

5.85 (1H, dd, J=5.0Hz and 9.3Hz), 6.95 (1H, s),

7.2 - 7.5 (15H, m), 7.51 (1H, d, J=9.3Hz)

Preparation 3

The following compound was prepared according to a method similar to that of Example 1.

Benzhydryl 7β-formamido-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate.

NMR ($CDCl_3$, δ) : 2.92 (2H, d, J=15.3Hz),

4.94 (1H, d, J=4.9Hz),

5.88 (1H, dd, J=4.9Hz and 9.0Hz), 6.93 (1H, s),

7.1 - 7.5 (11H, m), 8.19 (1H, s)

Mass (m/z) = 494

Preparation 4

To a solution of benzhydryl 7β-formamido-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate (13.14 g) in methanol (65.7 ml) was added conc. hydrochloric acid (11.0 ml). After stirring at room temperature for 1.5 hours, the reaction mixture was poured into a mixture of ethyl acetate and water, and the mixture was adjusted to pH 6.5 with an aqueous sodium hydrogencarbonate solution. The separated organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent; ethyl acetate) to give benzhydryl 7β-amino-3-

(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate (1.79 g).

NMR ($CDCl_3$, δ) : 3.44 (2H, dd, J=17.9Hz and 55.2Hz),
4.73 (1H, d, J=5.0Hz), 4.91 (1H, d, J=5.0Hz),
6.96 (1H, s), 7.1 - 7.5 (10H, m), 8.14 (1H, s)

Preparation 5

A mixture of benzhydryl 7β-amino-3-(1,2,4-triazol-3-yl)-thio-3-cephem-4-carboxylate (2.28 g) and N-trimethylsilyl-acetamide (3.21 g) in tetrahydrofuran (40 ml) was stirred at 0°C for 30 minutes. To the solution was dropwise added bromoacetyl bromide (0.60 ml) with stirring under ice-cooling. The mixture was stirred at said temperature for 4 hours. The reaction mixture was poured into a mixture of a saturated aqueous sodium hydrogencarbonate solution (20 ml) and ethyl acetate (100 ml) with stirring. The organic layer was separated, washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure. The resulting residue was subjected to column chromatography on silica gel (eluent; ethyl acetate). The fractions containing the desired compound were collected and evaporated under reduced pressure to give benzhydryl 7β-(2-bromoacetamido)-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate (1.93 g).

NMR ($CDCl_3$, δ) : 3.42 (2H, ABq, J=17.9Hz),
3.71 (2H, s), 4.96 (1H, d, J=4.72Hz),
5.82 (1H, dd, J=4.77Hz and 9.06Hz), 6.91 (1H, s),
7.10 - 7.55 (10H, m), 7.74 (1H, d, J=8.92Hz),
8.27 (1H, s)

Preparation 6

(Z)-Benzhydryl 7β-[2-{(2-cyanoethenyl)thio}acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 2 from benzhydryl 7β-amino-3-methanesulfonyloxy-3-cephem-4-carboxylate and (Z)-(2-cyanoethenyl)thioacetic acid.

NMR (DMSO-d_6, δ) : 3.19 (3H, s), 3.74 (2H, s),
3.90 (2H, dd, J=18.0Hz and 55.7Hz),
5.30 (1H, d, J=4.9Hz), 5.74 (1H, d, J=10.5Hz),
5.84 (1H, dd, J=4.9Hz and 8.2Hz),
6.93 (1H, s), 7.2 - 7.5 (10H, m),
7.66 (1H, d, J=10.5Hz), 9.32 (1H, d, J=8.2Hz)

Preparation 7

Benzhydryl 3-(5-amino-1,3,4-thiadiazol-2-yl)thio-7β-formamido-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 3 from benzhydryl 7β-formamido-3-methanesulfonyloxy-3-cephem-4-carboxylate and 5-amino-2-mercapto-1,3,4-thiadiazole.

NMR ($CDCl_3$, δ) : 1.79 (2H, br s), 3.38 (2H, br s),
4.90 (1H, d, J=4.78Hz), 5.79 - 5.90 (1H, m),
6.19 (2H, br s), 6.92 (1H, s), 7.10 - 7.70 (15H, m),
8.17 (1H, s)

Preparation 8

Benzhydryl 7β-amino-3-(5-amino-1,3,4-thiadiazol-2-yl)-thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 1 from benzhydryl 3-(5-amino-

1,3,4-thiadiazol-2-yl)thio-7β-formamido-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 2.44 (2H, br s),
3.55 (2H, ABq, J= 17.7Hz), 4.87 (1H, d, J=5.1Hz),
5.09 (1H, d, J=5.1Hz), 6.93 (1H, s),
7.20 - 7.70 (15H, m)

Preparation 9

The following compounds were prepared according to a method similar to that of Preparation 3 and Preparation 4.

(1) Benzhydryl 7β-amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)-thio-3-cephem-4-carboxylate

(2) Benzhydryl 7β-amino-3-(pyrazol-4-yl)methylthio-3-cephem-4-carboxylate

Preparation 10

A mixture of 2-amino-5-mercapto-1,3,4-triazole (1.0 g) and salicylaldehyde (2.10 g) in ethanol (15 ml) was refluxed for 2 hours. The reaction mixture was cooled, and the resulting precipitate was collected by filtration, washed with ethanol and dried to give 2-(2-hydroxybenzylidene)amino-5-mercapto-1,3,4-triazole (E,Z-unknown) (1.71 g).

NMR (DMSO-d_6, δ) : 6.9 - 7.1 (2H, m), 7.4 - 7.6 (1H, m),
7.7 - 7.8 (1H, m), 9.24 (1H, s), 11.33 (1H, s),
13.49 (1H, s), 13.64 (1H, br s)

APCI-Mass (m/z) = 221 ($M + H^+$)

Preparation 11

The addition of potassium hydroxide (540 mg) in water (0.33

ml) to 4-dimethylthiosemicarbazide (974 mg) in absolute ethanol produced a clear solution. Carbon disulfide (639 μl) was added with stirring. The solution was stirred at room temperature for 1.5 hours and at reflux temperature for 20 hours. The mixture was concentrated to dryness in vacuo, and the residue was dissolved in water (10 ml). The solution was filtered and the filtrate was adjusted to pH 2 - 3 with concentrated hydrochloric acid. The precipitate was collected by filtration, washed with water and dried to give 5-dimethylamino-2-mercapto-1,3,4-thiadiazole (0.90 g).

NMR (DMSO-d_6, δ) : 2.92 (6H, s), 13.47 (1H, br s)

APCI-Mass (m/z) = 162 ($M + H^+$)

Preparation 12

The addition of potassium hydroxide (860 mg) in water (0.53 ml) to morpholine-1-thiocarboxylic acid hydrazide (2.1 g) in absolute ethanol produced a clear solution. Carbon disulfide (1.02 ml) was added under ice-cooling with stirring. The solution was refluxed for 1.5 hours. The reaction mixture was cooled, and the resulting precipitate was collected by filtration, washed with ethanol and dried to give 2-mercapto-5-morpholino-1,3,4-thiadiazole potassium salt (2.06 g).

NMR (D_2O, δ) : 3.3 - 3.4 (4H, m), 3.8 - 3.9 (4H, m)

APCI-Mass (m/z) = 204 $(M + H)^+$

Preparation 13

To a solution of 2-aminothiazole (1.0 g) and ammonium thiocyanate (1.60 g) in acetic acid (5.0 ml) was added a

solution of bromine (1.60 g) in acetic acid (3.0 ml) at 10℃. After stirring at 20 ℃ for 1 hour, the mixture was poured into a mixture of tetrahydrofuran and water, and adjusted to pH 3.5. The separated organic layer was washed with a saturated aqueous sodium chloride solution three times, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent; n-hexane:ethyl acetate = 1:1(v/v)) to give 2-amino-5-thiocyanatothiazole (1.33 g).

NMR (DMSO-d_6, δ) : 7.43 (1H, s), 7.81 (2H, br s)

Preparation 14

To a solution of sodium hydroxide (1.32 g) in water (16.5 ml) was added 2-amino-5-thiocyanatothiazole (1.30 g). After refluxing for 10 minutes, the mixture was poured into tetrahydrofuran, and adjusted to pH 3.5. The separated organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent; ethyl acetate) to give 2-amino-5-mercaptothiazole (335 mg).

NMR (DMSO-d_6, δ) : 6.99 (1H, s), 7.62 (2H, br s)

FAB-Mass (m/z) = 133 ($M + H^+$)

Preparation 15

To a solution of 4-aminophenylacetic acid (453 mg) in a mixture of water (9 ml) and acetone (9 ml) were added triethylamine (395 mg) and di-t-butyl dicarbonate (851 mg).

After stirring at room temperature for 3 hours, the mixture was poured into a mixture of ethyl acetate and water, and adjusted to pH 7.6. The separated aqueous layer was poured into ethyl acetate and adjusted to pH 3.0. The separated organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure to give 4-(t-butoxycarbonylamino)phenylacetic acid (0.71 g).

NMR (DMSO-d_6, δ) : 1.47 (9H, s), 3.46 (2H, s),
7.11 (2H, d, J=8.5Hz), 7.37 (2H, d, J=8.5Hz),
9.27 (1H, br s), 12.23 (1H, br s)

Preparation 16

To a solution of benzhydryl 7β-(2-phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxylate (5.0 g) in a mixture of dichloromethane (15 ml) and anisole (5 ml) was added trifluoroacetic acid (10 ml) under ice-cooling. The mixture was stirred at the same temperature for an hour. The reaction mixture was poured into diisopropyl ether (250 ml). The precipitate was collected by filtration and dried to give 7β-(2-phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxylic acid (3.34 g).

NMR (DMSO-d_6, δ) : 3.42 (3H, s),
3.48 and 3.58 (2H, ABq, J=14Hz),
3.67 and 3.98 (2H, ABq, J=18Hz),
5.18 (1H, d, J=5Hz), 5.73 (1H, dd, J=5Hz and 8Hz),
7.2 - 7.4 (5H, m), 9.19 (1H, d, J=8Hz)

Preparation 17

To a solution of benzhydryl 7β-amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (31.5 g) in a mixture of dichloromethane (90 ml) and anisole (30 ml) was added trifluoroacetic acid (60 ml) at 15℃. The mixture was stirred at 15 - 25℃ for 70 minutes. The reaction mixture was poured into diisopropyl ether (1.3 L). The precipitate was collected by filtration and dried to give 7β-amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid trifluoroacetic acid salt (26.9 g).

Preparation 18

A solution of 7β-amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)-thio-3-cephem-4-carboxylic acid trifluoroacetic acid salt (25.3 g) in a mixture of tetrahydrofuran (400 ml), water (400 ml) and sodium hydrogencarbonate (9.50 g) was adjusted to pH 7.0 with 1N-hydrochloric acid (15 ml), and washed with ethyl acetate. To the aqueous solution was added a mixture of ethyl acetate (300 ml) and tetrahydrofuran (300 ml). The mixture was adjusted to pH 4.2 with 1N-hydrochloric acid (80 ml). The mixture was stirred under ice-cooling for an hour. The resulting precipitate was collected, washed successively with water, tetrahydrofuran and n-hexane, and dried to give 7β-amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid (16.5 g).

NMR (CF_3COOD, δ) : 3.15 (3H, s),
3.87 and 4.02 (2H, ABq, J=18Hz),

5.54 (1H, d, J=5Hz), 5.59 (1H, d, J=5Hz)

Preparation 19

A suspension of phosphorus pentachloride (14.2 g) in dichloromethane (210 ml) was stirred at ambient temperature for 30 minutes. To the mixture was added pyridine (553 ml) at -15°C with stirring. The mixture was stirred at -20°C to -15°C for 30 minutes. To the mixture was added benzhydryl 7β-(2-phenylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (28 g) at the same temperature. After being stirred at -10°C to -5°C for 1.5 hours, to the reaction mixture was added dropwise methanol (27.6 ml) at -20°C to -10°C for 10 minutes. After being stirred at ambient temperature for 50 minutes, to the reaction mixture was added water (56 ml) under ice-cooling, and the mixture was stirred at the same temperature for 30 minutes. The organic layer was separated, washed with water, dried over magnesium sulfate and concentrated in vacuo. The residue was triturated with ethyl acetate to give benzhydryl 7β-amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate hydrochloride (15.3 g).

NMR (DMSO-d_6, δ) : 2.73 (3H, s), 3.78 (2H, br s),
5.27 (1H, d, J=5Hz), 5.39 (1H, d, J=5Hz),
6.98 (1H, s), 7.2 - 7.5 (10H, m)

Preparation 20

Benzhydryl 7β-amino-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate hydrochloride was prepared according to a

method similar to that of Preparation 19, from benzhydryl 7β-(2-phenylacetamido)-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 3.82 (2H, m), 5.29 (1H, d, J=5Hz), 5.40 (1H, d, J=5Hz), 6.99 (1H, s), 7.2 - 7.5 (10H, m), 9.71 (1H, s)

Preparation 21

A suspension of phosphorus pentachloride (28.5 g) in dichloromethane (420 ml) was stirred at ambient temperature for 30 minutes. To the mixture was added dropwise pyridine (11.1 ml) at -10°C for 3 minutes and the mixture was stirred at -20°C to -5°C for 30 minutes. To the mixture was added benzhydryl 7β-(2-phenylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (56 g) at -20°C. After being stirred at -20°C to -5°C for 1.5 hours, to the mixture was added dropwise methanol (55.2 ml) at -35°C to -20°C for 3 minutes. After being stirred at 5 - 20°C for an hour, to the mixture was added water (110 ml) under ice-cooling, and the mixture was stirred at the same temperature for 30 minutes. The mixture was poured into a mixture of water (150 ml) and sodium bicarbonate (7.7 g) and adjusted to pH 7.5 with 1N sodium hydroxide solution. The mixture was concentrated in vacuo. The residue was triturated with water and ethyl acetate to give benzhydryl 7β-amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (38 g).

NMR (DMSO-d_6, δ) : 2.69 (3H, s),

3.51 and 3.85 (2H, ABq, J=18Hz),

4.93 (1H, d, J=5Hz), 5.15 (1H, d, J=5Hz),

6.94 (1H, s), 7.2 - 7.4 (10H, m)

Preparation 22

A suspension of phosphorus pentachloride (19.0 g) in dichloromethane (380 ml) was stirred at ambient temperature for an hour to give a clear solution. To the solution was added 2-(3-thienyl)acetic acid (12.4 g) at -20 ℃ with stirring. The mixture was stirred at -20℃ to -10℃ for 40 minutes to give an activated acid solution. On the other hand, to a solution of benzhydryl 7β-amino-3-methanesulfonyloxy-3-cephem-4-carboxylate (40 g) in dichloromethane (600 ml) was added N-trimethylsilylacetamide (57 g) at ambient temperature, and the mixture was stirred at the same temperature for 30 minutes. To the solution was added the activated acid solution prepared above at 20℃ and the mixture was stirred at -20℃ to -13℃ for 45 minutes. The mixture was poured into a solution of sodium hydrogencarbonate (61 g) in water (1.5 L). The solution was extracted with ethyl acetate (1.5 L) and tetrahydrofuran (0.5 L). The extract was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. The residue was triturated with diethyl ether to give benzhydryl 7β-[2-(3-thienyl)acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate (47.2 g).

NMR ($CDCl_3$, δ) : 2.79 (3H, s),

3.55 and 3.81 (2H, ABq, J=18Hz), 3.66 (2H, s),

5.03 (1H, d, J=5Hz), 5.88 (1H, dd, J=5Hz and 8Hz),
6.33 (1H, d, J=8Hz), 6.93 (1H, s),
7.01 (1H, dd, J=1Hz and 5Hz), 7.1 - 7.2 (1H, m),
7.2 - 7.4 (11H, m)

FAB-Mass (m/z) = 585.1 ($M + H^+$)

Preparation 23

Benzhydryl 7β-[2-(2-thienyl)acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate was prepared according to a similar method to that of Preparation 2.

NMR ($CDCl_3$, δ) : 2.80 (3H, s),
3.55 and 3.81 (2H, ABq, J=18Hz), 3.84 (2H, s),
5.03 (1H, d, J=5Hz), 5.88 (1H, dd, J=5Hz and 8Hz),
6.48 (1H, d, J=8Hz), 6.9 - 7.0 (2H, m),
6.93 (1H, s), 7.2 - 7.4 (11H, m)

FAB-Mass (m/z) = 585.1 ($M + H^+$)

Preparation 24

Benzhydryl 7β-formamido-3-(benzothiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a similar method to that of Preparation 3.

NMR (DMSO-d_6, δ) : 3.77 and 4.04 (2H, ABq, J=17.8Hz),
5.37 (1H, d, J=5.1Hz),
5.99 (1H, dd, J=5.1Hz and 8.0Hz), 6.96 (1H, s),
7.1 - 7.6 (12H, m), 7.92 (1H, d, J=7.1Hz),
8.07 (1H, d, J=7.6Hz), 8.17 (1H, s),
9.27 (1H, d, J=9.0Hz)

Preparation 25

Benzhydryl 7β-formamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a similar method to that of Preparation 3.

NMR ($CDCl_3$, δ) : 3.51 and 3.82 (2H, ABq, J=18.0Hz),
5.09 (1H, d, J=5.1Hz),
5.98 (1H, dd, J=5.1Hz and 9.3Hz),
6.69 (1H, d, J=9.3Hz), 6.99 (1H, s),
7.2 - 7.4 (10H, m), 8.26 (1H, s), 9.12 (1H, s)

Preparation 26

Benzhydryl 7β-formamido-3-(thiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a similar method to that of Preparation 3.

NMR ($CDCl_3$, δ) : 3.42 and 3.58 (2H, ABq, J=17.9Hz),
5.00 (1H, d, J=4.9Hz),
5.91 (1H, dd, J=4.9Hz and 9.2Hz),
6.65 (1H, d, J=9.2Hz), 6.98 (1H, s),
7.2 - 7.5 (11H, m), 7.86 (1H, d, J=3.4Hz),
8.20 (1H, s)

Preparation 27

To a solution of benzhydryl 7β-formamido-3-methanesulfonyloxy-3-cephem-4-carboxylate (20.0 g) in acetonitrile (150 ml) and N,N-dimethylformamide (50 ml) was added 5-mercapto-1,2,3-thiadiazole sodium salt (9.35 g) at -40℃. After stirring at -35℃ to -25℃ for 2 hours, the mixture was poured into a mixture of ice-water, 1N-hydrochloric acid and ethyl acetate. The separated organic layer was washed

with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure to give benzhydryl 7β-formamido-3-(1,2,3-thiadiazol-5-yl)thio-3-cephem-4-carboxylate (22.07 g).

NMR ($CDCl_3$, δ) : 3.24 and 3.43 (2H, ABq, J=17.9Hz),
5.03 (1H, d, J=5.0Hz),
5.94 (1H, dd, J=5.0Hz and 9.1 Hz),
6.77 (1H, d, J=9.1Hz), 7.00 (1H, s),
7.2 - 7.4 (10H, m), 8.24 (1H, s), 8.49 (1H, s)

Preparation 28

Benzhydryl 7β-formamido-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 27.

NMR ($CDCl_3$, δ) : 2.89 (1H, s), 2.95 (1H, s),
4.83 (1H, d, J=4.7Hz),
5.72 (1H, dd, J=4.7Hz and 9.1Hz),
6.85 (1H, d, J=9.1Hz), 6.91 (1H, s),
7.2 - 7.5 (10H, m), 7.68 (1H, s), 8.10 (1H, s)

Preparation 29

Benzhydryl 7β-amino-3-(benzothiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 1.

NMR (DMSO-d_6, δ) : 3.69 and 3.99 (2H, ABq, J=17.9Hz),
4.97 (1H, d, J=5.3Hz), 5.21 (1H, d, J=5.3Hz),
6.93 (1H, s), 7.1 - 7.6 (12H, m),
7.90 (1H, d, J=7.3Hz), 8.06 (1H, d, J=7.6Hz)

Preparation 30

Benzhydryl 7β-amino-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 1.

NMR (DMSO-d_6, δ) : 2.50 (2H, br s),
3.55 and 3.88 (2H, ABq, J=17.8Hz),
4.94 (1H, d, J=5.1Hz), 5.16 (1H, d, J=5.1Hz),
6.95 (1H, s), 7.2 - 7.4 (10H, m), 9.62 (1H, s)

Preparation 31

Benzhydryl 7β-amino-3-(thiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 1.

NMR (DMSO-d_6, δ) : 2.44 (2H, br s),
3.51 and 3.77 (2H, ABq, J=17.7Hz),
4.90 (1H, d, J=5.2Hz), 5.14 (1H, d, J=5.2Hz),
6.94 (1H, s), 7.2 - 7.5 (11H, m), 7.86 (1H, s)

Preparation 32

Benzhydryl 7β-amino-3-(1,2,3-thiadiazol-5-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 1.

NMR ($CDCl_3$, δ) : 1.80 (2H, br s),
3.25 and 3.56 (2H, ABq, J=17.9Hz),
4.82 (1H, d, J=5.2Hz), 4.98 (1H, d, J=5.2Hz),
7.03 (1H, s), 7.2 - 7.4 (10H, m), 8.41 (1H, s)

Preparation 33

Benzhydryl 7β-amino-3-(1,2,3-triazol-4-yl)thio-3-cephem-

4-carboxylate was prepared according to a method similar to that of Preparation 1.

NMR ($CDCl_3$, δ) : 3.23 (1H, s), 3.27 (1H, s),
3.49 (2H, br s), 4.72 (1H, d, J=5.0Hz),
4.92 (1H, d, J=5.0Hz), 6.98 (1H, s),
7.2 - 7.4 (10H, m), 7.74 (1H, s)

Preparation 34

Benzhydryl 7β-(2-phenylacetamido)-3-[2-(2-hydroxybenzylidene)amino-1,3,4-triazol-5-yl]thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 3.

NMR (DMSO-d_6, δ) : 3.4 - 3.7 (2H, m),
3.54 and 3.71 (2H, ABq, J=17Hz), 5.25 (1H, d, J=5Hz),
5.77 (1H, dd, J=5Hz and 8Hz), 6.9 - 7.0 (2H, m),
6.95 (1H, s), 7.1 - 7.6 (16H, m), 7.7 - 7.8 (1H, m),
9.19 (1H, d, J=8Hz), 9.44 (1H, s), 11.5 (1H, br s),
14.6 (1H, br s)

FAB-Mass (m/z) = 703.5 ($M + H^+$)

Example 1

To a solution of 3-mercapto-1,2,4-triazole (646 mg) in N,N-dimethylformamide (6 ml) was added N,N-diisopropylethylamine (635 mg) and the mixture was stirred at room temperature for one hour. To a solution of benzhydryl 7β-[2-(phenylthio)-acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate (3.0 g) in N,N-dimethylformamide (24 ml) was added the thiol solution

obtained above at -30℃. After stirring under ice-cooling for 4 hours, the reaction mixture was poured into a mixture of ethyl acetate and water, and the mixture was adjusted to pH 5.0 with 1N hydrochloric acid. The separated organic layer was washed with a saturated aqueous sodium chloride solution three times, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent; ethyl acetate:n-hexane = 2:1(v/v)) to give benzhydryl 7β-[2-(phenylthio)acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate (540 mg).

NMR ($CDCl_3$, δ) : 3.39 (2H, dd, J=18.0Hz and 60.5Hz), 3.59 (2H, d, J=4.4Hz), 4.94 (1H, d, J=4.9Hz), 5.81 (1H, dd, J=4.9Hz and 9.0Hz), 6.92 (1H, s), 7.1 - 7.4 (15H, m), 7.68 (1H, dd, J=9.0Hz), 8.12 (1H, s)

Example 2

To a solution of benzhydryl 7β-[2-(phenylthio)acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate (530 mg) in dichloromethane (1.59 ml) were added anisole (0.53 ml) and trifluoroacetic acid (1.06 ml) under ice-cooling. After stirring at said temperature for one hour, the reaction mixture was poured into diisopropyl ether. The resulting precipitate was collected by filtration and dissolved in a mixture of ethyl acetate and water. The mixture was adjusted to pH 7.0 with an aqueous sodium hydrogencarbonate solution. The separated aqueous layer was adjusted to pH 4.5 with 1N

hydrochloric acid and subjected to column chromatography on non-ionic adsorption resin, Diaion HP-20 (Trade mark, made by Mitsubishi Chemical Industries) (eluent; 10% aqueous acetonitrile). The fractions containing the desired compound were collected, concentrated under reduced pressure and freeze-dried to give 7β-[2-(phenylthio)acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylic acid (0.3 g).

IR (KBr) : 1763, 1608, 1540 (cm^{-1})

NMR (D_2O, δ) : 3.35 (2H, dd, J=17.3Hz and 57.7Hz),
3.77 (2H, d, J=3.5Hz), 5.09 (1H, d, J=4.7Hz),
5.57 (1H, d, J=4.7Hz), 7.2 - 7.5 (5H, m),
8.46 (1H, s)

Mass (m/z) = 449.8

Example 3

The following compound was prepared according to a method similar to that of Example 1.

Benzhydryl 7β-[2-(phenylthio)acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

NMR ($CDCl_3$, δ) : 3.60 (2H, dd, J=18.0Hz and 70.7Hz),
3.69 (2H, dd, J=17.0Hz and 25.3Hz),
5.04 (1H, d, J=5.1Hz),
5.87 (1H, dd, J=5.1Hz and 9.3Hz), 6.99 (1H, s),
7.0 - 7.2 (15H, m), 7.52 (1H, d, J=9.3Hz),
9.11 (1H, s)

Example 4

The following compound was prepared according to a method

similar to that of Example 2.

7β-[2-(Phenylthio)acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid.

IR (KBr) : 1770, 1670, 1616 (cm^{-1})

NMR (D_2O, δ) : 3.63 (2H, dd, J=17.7Hz and 82.4Hz),
3.82 (2H, d, J=3.2Hz), 5.20 (1H, d, J=4.9Hz),
5.66 (1H, d, J=4.9Hz), 7.3 - 7.6 (5H, m),
9.46 (1H, s)

Mass (m/z) = 467.0

Example 5

To a solution of benzhydryl 7β-[2-(phenylthio)acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate (1.0 g) in N,N-dimethylformamide (10 ml) was added 5-mercapto-1,2,3-thiadiazole sodium salt (356 mg) at -10°C. After stirring at 0°C for 1.5 hours, the reaction mixture was poured into a mixture of ethyl acetate and water, and the mixture was adjusted to pH 6.0 with 1N hydrochloric acid. The separated organic layer was washed with a saturated aqueous sodium chloride solution three times, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent; n-hexane:ethyl acetate = 2:1(v/v)) to give benzhydryl 7β-[2-(phenylthio)-acetamido]-3-(1,2,3-thiadiazol-5-yl)thio-3-cephem-4-carboxylate (755 mg).

NMR ($CDCl_3$, δ) : 3.32 (2H, dd, J=17.8Hz and 53.7Hz),
3.69 (2H, dd, J=12.2Hz and 26.7Hz),

4.99 (1H, d, J=5.1Hz),

5.85 (1H, dd, J=5.1Hz and 9.1Hz), 7.01 (1H, s),

7.10 - 7.35 (15H, m), 7.53 (1H, d, J=9.1Hz),

8.46 (1H, s)

Example 6

To a solution of benzhydryl 7β-[2-(phenylthio)acetamido]-3-(1,2,3-thiadiazol-5-yl)thio-3-cephem-4-carboxylate (720 mg) in dichloromethane (2.16 ml) were added anisole (0.72 ml) and trifluoroacetic acid (1.44 ml) under ice-cooling. After stirring at said temperature for 35 minutes, the reaction mixture was poured into diisopropyl ether. The resulting precipitate was collected by filtration. The precipitate was dissolved in a mixture of tetrahydrofuran (20 ml), ethyl acetate (20 ml) and an aqueous sodium hydrogencarbonate solution (96 mg/40 ml). The separated aqueous layer was added to ethyl acetate (40 ml), and the mixture was adjusted to pH 2 with 1N hydrochloric acid. The separated organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure. To the residue was added ether. The precipitate was collected by filtration and sequentially washed with ether and n-hexane to give 7β-[2-(phenylthio)acetamido]-3-(1,2,3-thiadiazol-5-yl)-thio-3-cephem-4-carboxylic acid (257 mg).

IR (KBr) : 3300, 1790, 1710, 1650, 1560, 1540, 1520, 1440, 1360 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.52 and 3.83 (2H, ABq, J=18Hz),

3.76 (2H, s), 5.21 (1H, d, J=5Hz),

5.80 (1H, dd, J=5Hz and 8Hz), 7.1 - 7.4 (5H, m),

8.92 (1H, s), 9.28 (1H, d, J=8Hz),

FAB-Mass (m/z) = 467.0 (M^+)

Example 7

The following compound was prepared according to a method similar to that of Preparation 2.

(Z)-Benzhydryl 7β-[2-{(2-cyanoethenyl)thio}acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate.

NMR ($CDCl_3$, δ) : 3.25 (2H, s),

3.43 (2H, dd, J=17.9Hz and 72.7Hz),

4.99 (1H, d, J=4.8Hz), 5.30 (1H, d, J=10.4Hz),

5.82 (1H, dd, J=4.8Hz and 8.8Hz), 6.95 (1H, s),

7.1 - 7.5 (11H, m), 7.72 (1H, d, J=8.8Hz),

8.20 (1H, s)

Example 8

The following compound was prepared according to a method similar to that of Example 2.

(Z)-7β-[2- {(2-Cyanoethenyl)thio}acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylic acid.

IR (KBr) : 2214, 1772, 1670, 1616 (cm^{-1})

NMR (D_2O, δ) : 3.47 (2H, dd, J=17.4Hz and 58.9Hz),

3.77 (2H, s), 5.20 (1H, d, J=4.7Hz),

5.57 (1H, d, J=10.5Hz), 5.65 (1H, d, J=4.7Hz),

7.48 (1H, d, J=10.5Hz), 8.46 (1H, s)

Mass (m/z) = 425.0

Example 9

To a solution of 3-mercapto-1,2,4-triazole (490 mg) in a mixture of tetrahydrofuran (5 ml) and 1,2-dimethoxyethane (5 ml) was added potassium t-butoxide (427 mg) at -10°C with stirring and the mixture was stirred at said temperature for 20 minutes. A solution of benzhydryl 7β-(2-phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxylate (2.0 g) in a mixture of tetrahydrofuran (10 ml) and 1,2-dimethoxyethane (10 ml) was dropwise added to the solution obtained above at -20°C, and the mixture was stirred at a temperature from -10°C to 5°C for 2 hours. The reaction mixture was poured into a mixture of 0.1N hydrochloric acid (20 ml) and ethyl acetate (30 ml). The organic layer was sequentially washed with water, an aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure to give a residue. The residue was subjected to column chromatography on silica gel (eluent; n-hexane:ethyl acetate = 1:2(v/v)). The fractions containing the desired compound were collected and evaporated under reduced pressure to give benzhydryl 7β-(2-phenylacetamido)-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate (351 mg).

NMR ($CDCl_3$, δ) : 3.21 and 3.59 (2H, ABq, J=17.8Hz),
3.47 (2H, s), 4.90 (1H, d, J=4.39Hz),
5.84 (1H, dd, J=4.82Hz and 9.31Hz), 6.87 (1H, s),
7.10 - 7.40 (15H, m), 8.34 (1H, brs)

Example 10

To a solution of benzhydryl 7β-(2-phenylacetamido)-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate (348 mg) in a mixture of dichloromethane (1.5 ml) and anisole (0.5 ml) was added trifluoroacetic acid (1 ml) with stirring under ice-cooling. The mixture was stirred at said temperature for one hour. The reaction mixture was poured into isopropyl ether (30 ml) and the resulting precipitate was collected by filtration and dried in vacuo. The precipitate was dissolved in a mixture of a saturated aqueous sodium hydrogencarbonate solution (10 ml), water (20 ml), tetrahydrofuran (10 ml) and ethyl acetate (10 ml). The aqueous layer was washed with a mixture of ethyl acetate (10 ml) and tetrahydrofuran (10 ml). Ethyl acetate (20 ml) and tetrahydrofuran (10 ml) were added to the aqueous layer and the mixture was adjusted to pH 2.0 with 1N hydrochloric acid with stirring. The organic layer was washed twice with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure to give a solid. The solid was collected by filtration, washed with ethyl acetate and dried in vacuo to give 7β-(2-phenylacetamido)-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylic acid (154 mg).

IR (Nujol) : 3250, 1755, 1660, 1530, 1300 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.30 and 3.60 (4H, m),
5.16 (1H, d, J=4.7Hz),
5.60 (1H, dd, J=4.8Hz and 8.3Hz), 7.10 - 7.30 (5H, m),
8.69 (1H, brs), 9.14 (1H, d, J=8.3Hz),

14.2 - 14.6 (1H, brs)

Example 11

To a solution of 2-mercapto-1,3,4-thiadiazole (572 mg) in a mixture of tetrahydrofuran (6 ml) and 1,2-dimethoxyethane (6 ml) was added potassium t-butoxide (427 mg) at a temperature from -20°C to -10°C with stirring, and the mixture was stirred at said temperature for 20 minutes. A solution of benzhydryl 7β-(2-phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxylate (2.0 g) in a mixture of tetrahydrofuran (10 ml) and 1,2-dimethoxyethane (10 ml) was dropwise added to the solution obtained above at -10°C, and the mixture was stirred at 0°C for 2 hours. The reaction mixture was poured into a mixture of 0.1N hydrochloric acid (20 ml) and ethyl acetate (30 ml). The organic layer was sequentially washed with water, an aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure to give a residue. The residue was subjected to column chromatography on silica gel (eluent; dichloromethane:acetone = 20:1(v/v)). The fractions containing the desired compound were collected and evaporated under reduced pressure to give benzhydryl 7β-(2-phenylacetamido)-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (740 mg).

NMR ($CDCl_3$, δ) : 3.43 and 3.78 (2H, ABq, J=18.0Hz),
3.64 (2H, d, J=1.93Hz), 5.03 (1H, d, J=5.02Hz),
5.90 (1H, dd, J=5.02Hz and 9.09Hz),

6.27 (1H, d, J=9.04Hz), 6.97 (1H, s),
7.20 - 7.40 (15H, m), 9.11 (1H, s)

Example 12

To a solution of benzhydryl 7β-(2-phenylacetamido)-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (0.74 g) in a mixture of dichloromethane (3 ml) and anisole (1 ml) was added trifluoroacetic acid (2 ml) under ice-cooling. The mixture was stirred at said temperature for one hour. The reaction mixture was poured into isopropyl ether (60 ml) and the resulting precipitate was collected by filtration and dried in vacuo. The precipitate was dissolved in a mixture of a saturated aqueous sodium hydrogencarbonate solution (12 ml), water (12 ml), tetrahydrofuran (12 ml) and ethyl acetate (12 ml). The aqueous layer was washed twice with a mixture of ethyl acetate (8 ml) and tetrahydrofuran (8 ml). Ethyl acetate (30 ml) was added to the aqueous layer and the mixture was adjusted to pH 2.0 with 1N hydrochloric acid. The organic layer was washed twice with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure to give a solid. The solid was filtrated, washed with ethyl acetate and dried in vacuo to give 7β-(2-phenylacetamido)-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid (172 mg).

IR (Nujol) : 1782, 1693, 1659, 1535 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.52 (2H, d, J=4.41Hz),
3.57 and 3.89 (2H, ABq, J=17Hz),
5.23 (1H, d, J=5.04Hz),

5.79 (1H, dd, J=5.02Hz and 8.31Hz),
7.21 - 7.40 (5H, m), 9.25 (1H, d, J=8.30Hz),
9.65 (1H, s)

FAB-Mass (m/z) = 434.9 (M^+)

Example 13

The following compound was prepared according to a method similar to that of Example 11.

Benzhydryl 7β-(2-phenylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 2.71 (3H, s), 3.53 (2H, d, J=3.71Hz),
3.57 and 3.87 (2H, ABq, J=17.7Hz),
5.26 (1H, d, J=4.98Hz),
5.85 (1H, dd, J=5.00Hz and 8.30Hz), 6.97 (1H, s),
7.20 - 7.50 (15H, m), 9.28 (1H, d, J=8.41Hz),

Example 14

The following compound was prepared according to a method similar to that of Example 12.

3-(5-Methyl-1,3,4-thiadiazol-2-yl)thio-7β-(2-phenyl-acetamido)-3-cephem-4-carboxylic acid.

NMR (DMSO-d_6, δ) : 2.73 (3H, s),
3.52 and 3.62 (2H, ABq, J=14.0Hz),
3.55 and 3.85 (2H, ABq, J=17.6Hz),
5.22 (1H, d, J=5.0Hz),
5.78 (1H, dd, J=5.03Hz and 8.28Hz),
7.15 - 7.35 (5H, m), 9.24 (1H, d, J=8.37Hz),.

FAB-Mass (m/z) = 448.9 (M^+)

Example 15

To a solution of benzhydryl 7β-(2-phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxylate (1.5 g) in a mixture of tetrahydrofuran (12 ml) and dimethoxyethane (12 ml) was added dropwise 5-mercapto-1,2,3-triazole sodium salt (443 mg) with stirring under ice-cooling. The mixture was stirred at said temperature for 3 hours. To the reaction mixture were added ethyl acetate (100 ml) and 1N hydrochloric acid (20 ml) with stirring. The organic layer was separated, sequentially washed with water, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure to give benzhydryl 7β-(2-phenylacetamido)-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylate (1.47 g).

NMR ($CDCl_3$, δ) : 3.61 (2H, s), 4.88 (1H, d, J=4.61Hz), 5.75 (1H, dd, J=4.64Hz and 8.44Hz), 6.91 (1H, s), 7.05 - 7.35 (15H, m), 7.45 (1H, d, J=7.35Hz), 7.64 (1H, s)

Example 16

The following compound was prepared according to a method similar to that of Example 12.

7β-(2-Phenylacetamido)-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylic acid.

IR (Nujol) : 1745, 1695, 1650, 1535 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.27 (2H, s), 3.51 (2H, ABq, J=13.9Hz and 18.3Hz),

5.09 (1H, d, J=4.70Hz),

5.62 (1H, dd, J=4.69Hz and 8.18Hz),

7.10 - 7.30 (5H, m), 8.32 (1H, brs),

9.11 (1H, d, J=8.25Hz)

FAB-Mass (m/z) = 417.9 (M^+)

Example 17

The following compound was prepared according to a method similar to that of Example 15.

Benzhydryl 7β-(2-phenylacetamido)-3-(1,2,3-thiadiazol-5-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 3.4 - 3.6 (2H, m),

3.50 and 3.85 (2H, ABq, J=18Hz),

5.24 (1H, d, J=5Hz),

5.87 (1H, dd, J=5Hz and 8Hz), 6.98 (1H, s),

7.2 - 7.4 (15H, m), 8.84 (1H, s),

9.28 (1H, d, J=8Hz)

Example 18

The following compound was prepared according to a method similar to that of Example 12.

7β-(2-Phenylacetamido)-3-(1,2,3-thiadiazol-5-yl)thio-3-cephem-4-carboxylic acid.

NMR (DMSO-d_6, δ) : 3.52 - 3.83 (2H, ABq, J=18Hz),

3.5 - 3.6 (2H, m), 5.20 (1H, d, J=17Hz),

5.79 (1H, dd, J=5Hz and 8Hz), 7.2 - 7.3 (5H, m),

8.92 (1H, s), 9.24 (1H, d, J=8Hz)

Example 19

To a solution of phosphorus pentachloride (738 mg) in a mixture of dichloromethane (8 ml) and tetrahydrofuran (4 ml) was added (1,2,5-thiadiazol-3-yl)acetic acid (488 mg) at -15°C and the mixture was stirred under ice-cooling for 30 minutes. To a solution of benzhydryl 7β-amino-3-(1,2,4-triazol-3-yl)-thio-3-cephem-4-carboxylate (1.5 g) in tetrahydrofuran (23 ml) was added N-trimethylsilylacetamide (1.27 g) under ice-cooling, and the mixture was stirred at said temperature for 30 minutes. Thereto was dropwise added the acid chloride solution obtained above under ice-cooling and the mixture was stirred at said temperature for one hour. The reaction mixture was poured into a mixture of a saturated aqueous sodium hydrogencarbonate solution (50 ml), water (50 ml) and ethyl acetate (100 ml) with stirring. The organic layer was separated, washed with an aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure to give benzhydryl 7β-[2-(1,2,5-thiadiazol-3-yl)acetamido]-3-(1,2,4-triazol-3-yl)-thio-3-cephem-4-carboxylate (1.90 g).

Example 20

To a solution of benzhydryl 7β-[2-(1,2,5-thiadiazol-3-yl)-acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate (1.90 g) in a mixture of dichloromethane (6 ml) and anisole (2 ml) was added trifluoroacetic acid (4 ml) with stirring under ice-cooling. The mixture was stirred at said temperature for one hour. The reaction mixture was poured into isopropyl ether (120 ml) and the resulting precipitate was collected by

filtration and dried in vacuo. The precipitate was dissolved in a mixture of a saturated aqueous sodium hydrogencarbonate solution (10 ml), water (50 ml), tetrahydrofuran (30 ml) and ethyl acetate (30 ml). The aqueous layer was washed with a mixture of ethyl acetate (20 ml) and tetrahydrofuran (20 ml), adjusted to pH 5.0 with 1N hydrochloric acid with stirring and evaporated under reduced pressure to remove the organic solvent. The resulting residue was adjusted to pH 5.0 with 1N hydrochloric acid and was subjected to column chromatography on non-ionic adsorption resin, Diaion HP-20, sequentially eluting with water (100 ml) and 10% isopropyl alcohol in water (300 ml). The fractions containing the desired compound were collected and evaporated under reduced pressure to remove the organic solvent. The resulting residue was adjusted to pH 2.0 with 1N hydrochloric acid and extracted twice with a mixture of tetrahydrofuran (100 ml) and ethyl acetate (100 ml). The organic layer was dried over magnesium sulfate and evaporated under reduced pressure to give a solid. The solid was washed with ethyl acetate and dried in vacuo to give 7β-[2-(1,2,5-thiadiazol-3-yl)acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylic acid (577 mg).

IR (Nujol) : 3263, 1757, 1660, 1554, 1298, 1232 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.45 (2H, ABq, J=17.2Hz),
4.02 (2H, s), 5.19 (1H, d, J=4.75Hz),
5.69 (1H, dd, J=4.75Hz and 8.19Hz),
8.72 (1H, brs), 8.75(1H, s), 9.31 (1H, d, J=8.25Hz),

14.5 (1H, brs)

FAB-Mass (m/z) = 425.9 (M^+)

Example 21

The following compound was prepared according to a method similar to that of Example 19.

Benzhydryl 7β-[2-(2-formylamino-1,3-thiazol-4-yl)acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate.

Example 22

The following compound was prepared according to a method similar to that of Example 20.

7β-[2-(2-Formylamino-1,3-thiazol-4-yl)acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylic acid.

NMR (DMSO-d_6, δ) : 3.45 (2H, ABq, J=17.2Hz),
3.60 (2H, s), 5.12 (1H, d, J=4.75Hz),
5.69 (1H, dd, J=4.62Hz and 8.19Hz), 6.95 (1H, s),
8.45 (1H, s), 8.72(1H, brs), 9.05 (1H, d, J=8.37Hz),
12.2 (1H, brs)

FAB-Mass (m/z) = 467.9 (M^+)

Example 23

To a solution of benzhydryl 7β-[2-(2-formylamino-1,3-thiazol-4-yl)acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate (1.88 g) in methanol (10 ml) was added conc. hydrochloric acid (1.31 ml) at ambient temperature, and the mixture was stirred at said temperature for 4 hours. The reaction mixture was added to a mixture of a saturated aqueous sodium hydrogencarbonate solution (30 ml), water (30 ml) and

ethyl acetate (50 ml) with stirring. The organic layer was separated, washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure to give a residue. The residue was washed with ethyl acetate (30 ml) and dried in vacuo to give benzhydryl 7β-[2-(2-amino-1,3-thiazol-4-yl)acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate (639 mg).

NMR (DMSO-d_6, δ) : 3.34 (2H, s),
3.47 (2H, ABq, J=17.3Hz), 5.24 (1H, d, J=4.78Hz),
5.77 (1H, dd, J=4.74Hz and 8.44Hz),
6.25 (1H, s), 6.80 - 7.60 (12H, m), 8.73 (1H, brs),
8.98 (1H, d, J=8.56Hz)

Example 24

The following compound was prepared according to a method similar to that of Example 20.

7β-[2-(2-Amino-1,3-thiazol-4-yl)acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylic acid.

NMR (DMSO-d_6, δ) : 3.37 (2H, s),
3.44 (2H, ABq, J=17.3Hz),
5.17 (1H, d, J=4.74Hz),
5.67 (1H, dd, J=4.64Hz and 8.28Hz), 6.24 (1H, s),
6.91 (2H, s), 8.67 (1H, brs), 8.93 (1H, d, J=8.41Hz)

FAB-Mass (m/z) = 439.9 (M^+)

Example 25

To a solution of 2-mercapto-5-methyl-1,3,4-thiadiazole (2.0 g) in a mixture of tetrahydrofuran (10 ml) and 1,2-

dimethoxyethane (10 ml) was added potassium t-butoxide (1.70 g) at -10°C, and the mixture was stirred in an ice-bath for 30 minutes. The resulting precipitate was collected by filtration, washed with 1,2-dimethoxyethane and dried in vacuo to give a solid (1.08 g). This solid (152 mg) was added to a solution of benzhydryl 7β-(2-bromoacetamido)-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate (0.5 g) in 1,2-dimethoxyethane (5 ml) at a temperature from 0°C to -10°C, and the mixture was stirred at said temperature for one hour. The reaction mixture was poured into a mixture of ethyl acetate (50 ml) and 1N hydrochloric acid (10 ml) with stirring. The organic layer was separated, washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure to give benzhydryl 7β-[2-{(5-methyl-1,3,4-thiadiazol-2-yl)-thio}acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate (346 mg).

Example 26

The following compound was prepared according to a method similar to that of Example 20.

7β-[2-{(5-Methyl-1,3,4-thiadiazol-2-yl)thio}acetamido]-3-(1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylic acid.

NMR (DMSO-d_6, δ) : 3.44 (2H, ABq, J=17.3Hz),
4.12 (2H, ABq, J=13.5Hz), 5.19 (1H, d, J=4.76Hz),
5.68 (1H, dd, J=4.89Hz and 8.18Hz), 8.72 (1H, brs),
9.28 (1H, d, J=8.22Hz), 14.5 (1H, brs)

FAB-Mass (m/z) = 471.8 (M^+)

Example 27

A solution of phosphorus pentachloride (949 mg) in dichloromethane (10 ml) was stirred at ambient temperature for 30 minutes. To the solution were added (2-formamido-thiazol-4-yl)acetic acid (849 mg) and tetrahydrofuran (5 ml) at -15°C with stirring. The mixture was stirred at a temperature from 0°C to 5°C for 30 minutes.

On the other hand, to a solution of benzhydryl 7β-amino-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (2.0 g) in tetrahydrofuran (30 ml) was added N-trimethylsilylacetamide (1.63 g) at a temperature from 30°C to 40°C and the mixture was stirred at the same temperature for 20 minutes. To the reaction mixture was added dropwise the solution obtained above on ice-bath and the mixture was stirred at the same temperature for 2 hours. The reaction mixture was poured into a mixture of water (50 ml) and ethyl acetate (100 ml).

The organic layer was separated, washed with aqueous sodium chloride solution, aqueous sodium hydrogencarbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give benzhydryl 7β-[2-(2-formamido-thiazol-4-yl)-acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (2.91 g).

NMR (DMSO-d_6, δ) : 3.61 (2H, s),
3.77 (2H, ABq, J=17.7Hz), 5.30 (1H, d, J=5.04Hz),
5.90 (1H, dd, J=5.02Hz and 8.46Hz), 6.96 (1H, s),

6.98 (1H, s), 7.20 - 7.50 (10H, m), 8.46 (1H, s),
9.22 (1H, d, J=8.50Hz), 9.65 (1H, s), 12.25 (1H, s)

Example 28

To a solution of benzhydryl 7β-[2-(2-formamido-thiazol-4-yl)acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (2.91 g) in a mixture of methanol (15 ml) and tetrahydrofuran (5 ml) was added conc. hydrochloric acid (1.86 ml) at ambient temperature and the mixture was stirred at the same temperature for 4 hours. The reaction mixture was poured into a mixture of aqueous sodium hydrogencarbonate solution (70 ml) and ethyl acetate (60 ml). The organic layer was separated, washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give benzhydryl 7β-[2-(2-amino-thiazol-4-yl)-acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (2.60 g).

NMR (DMSO-d_6, δ) : 3.38 (2H, s),
3.76 (2H, ABq, J=17.8Hz), 5.30 (1H, d, J=5.08Hz),
5.89 (1H, dd, J=5.03Hz and 8.47Hz), 6.25 (1H, s),
6.89 (2H, br s), 6.98 (1H, s),
9.09 (1H, d, J=8.57Hz), 9.65 (1H, s)

Example 29

7β-[2-(2-Amino-thiazol-4-yl)acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-[2-(2-amino-thiazol-4-yl)acetamido]-3-(1,3,4-

thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

IR (Nujol) : 1768, 1655, 1537, 1342 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.73 (2H, ABq, J=17.6Hz),
5.25 (1H, d, J=5.04Hz),
5.81 (1H, dd, J=5.01Hz and 8.40Hz), 6.33 (1H, s),
7.32 (2H, br s), 9.09 (1H, d, J=8.42Hz), 9.63 (1H, s)

FAB-Mass (m/z) = 457 (M^+)

Example 30

Benzhydryl 7β-[2-(2-formamido-thiazol-4-yl)acetamido]-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 27 from benzhydryl 7β-amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate and (2-formamido-thiazol-4-yl)acetic acid.

NMR (DMSO-d_6, δ) : 2.67 (3H, s), 3.60 (2H, s),
3.72 (2H, ABq, J=17.7Hz), 5.28 (1H, d, J=5.05Hz)
5.88 (1H, dd, J=5.05Hz and 8.42Hz), 6.96 (1H, s),
6.97 (1H, s), 8.45 (1H, s), 9.17 (1H, d, J=8.45Hz),
12.2 (1H, s)

Example 31

Benzhydryl 7β-[2-(2-amino-thiazol-4-yl)acetamido]-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 28 from benzhydryl 7β-[2-(2-formamido-thiazol-4-yl)acetamido]-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 2.68 (3H, s), 3.38 (2H, s),
3.71 (2H, ABq, J=17.8Hz), 5.27 (1H, d, J=5.04Hz),

5.87 (1H, dd, J=5.04Hz and 8.46Hz), 6.25 (1H, s), 6.88 (2H, s), 6.97 (1H, s), 7.20 - 7.50 (10H, m), 9.05 (1H, d, J=8.54Hz)

Example 32

7β-[2-(2-Amino-thiazol-4-yl)acetamido]-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-[2-(2-amino-thiazol-4-yl)acetamido]-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 2.72 (3H, s), 3.39 (2H, s), 3.69 (2H, ABq, J=17.6Hz), 5.23 (1H, d, J=5.02Hz), 5.78 (1H, dd, J=5.02Hz and 8.39Hz), 6.28 (1H, s), 7.06 (2H, br s), 9.02 (1H, d, J=8.43Hz)

FAB-Mass (m/z) = 471 (M^+)

Example 33

Benzhydryl 7β-[2-(2-formamido-thiazol-4-yl)acetamido]-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 27 from benzhydryl 7β-amino-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylate and (2-formamido-thiazol-4-yl)acetic acid.

Example 34

Benzhydryl 7β-[2-(2-amino-thiazol-4-yl)acetamido]-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 28 from benzhydryl 7β-[2-(2-formamido-thiazol-4-yl)acetamido]-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylate.

IR (Nujol) : 1778, 1664, 1608, 1524 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.33 (2H, s), 3.38 (2H, s),
5.18 (1H, d, J=4.7Hz),
5.75 (1H, dd, J=4.7Hz and 8.5Hz), 6.25 (1H, s),
6.89 (2H, br s), 6.95 (1H, s), 7.20 - 7.65 (10H, m),
8.26 (1H, br s), 8.94 (1H, d, J=8.5Hz)

Example 35

7β-[2-(2-Amino-thiazol-4-yl)acetamido]-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-[2-(2-amino-thiazol-4-yl)acetamido]-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 3.36 (2H, s), 5.11 (1H, d, J=4.7Hz),
5.65 (1H, dd, J=4.7Hz and 8.4Hz), 6.25 (1H, s),
6.92 (2H, br s), 8.26 (1H, br s),
8.89 (1H, d, J=8.4Hz)

FAB-Mass (m/z) = 440 (M^+)

Example 36

(Z)-Benzhydryl 7β-[2-{(2-cyanoethenyl)thio}acetamido]-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 5 from (Z)-benzhydryl 7β-[2-{(2-cyanoethenyl)thio }acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate and 5-mercapto-1,2,3-triazol sodium salt.

NMR ($CDCl_3$, δ) : 3.20 (2H, s), 3.53 (2H, s),
4.99 (1H, d, J=4.8Hz), 5.39 (1H, d, J=10.5Hz),

5.72 (1H, dd, J=4.8Hz and 8.7Hz),

6.92 (1H, d, J=8.7Hz), 6.97 (1H, s),

7.1 - 7.6 (11H, m), 8.02 (1H, s)

Example 37

(Z)-7β-[2-{(2-Cyanoethenyl)thio}acetamido]-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from (Z)-benzhydryl 7β-[2-{(2-cyanoethenyl)thio}acetamido]-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 2214, 1772, 1751, 1670 (cm^{-1})

NMR (D_2O, δ) : 3.37 (2H, dd, J=17.4Hz and 39.2Hz)

3.77 (2H, s), 5.13 (1H, d, J=4.7Hz),

5.57 (1H, d, J=10.5Hz), 5.01 (1H, d, J=4.7Hz),

7.49 (1H, d, J=10.5Hz), 8.12 (1H, s)

FAB-Mass (m/z) = 424.9

Example 38

(Z)-Benzhydryl 7β-[2-{(2-cyanoethenyl)thio}acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 11 from (Z)-benzhydryl 7β-[2-{(2-cyanoethenyl)thio}acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate and 2-mercapto-1,3,4-thiadiazole.

NMR ($CDCl_3$, δ) : 3.57 (2H, s),

3.64 (2H, dd, J=17.9Hz and 54.2Hz),

5.09 (1H, d, J=5.0Hz), 5.38 (1H, d, J=10.3Hz),

5.87 (1H, dd, J=5.0Hz and 9.0Hz), 6.99 (1H, s),

7.2 - 7.5 (11H, m), 7.54 (1H, d, J=9.0Hz),
9.15 (1H, s)

Example 39

(Z)-7β-[2-{(2-Cyanoethenyl)thio}acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from (Z)-benzhydryl 7β-[2-{(2-cyanoethenyl)thio}acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 2212, 1770, 1616 (cm^{-1})

NMR (D_2O, δ) : 3.71 (2H, dd, J=17.5Hz and 80.7Hz),
3.80 (2H, s), 5.29 (1H, d, J=4.9Hz),
5.60 (1H, d, J=10.5Hz), 5.72 (1H, d, J=4.9Hz),
7.51 (1H, d, J=10.5Hz), 9.43 (1H, s)

FAB-Mass (m/z) = 442.0

Example 40

(Z)-Benzhydryl 7β-[2-{(2-cyanoethenyl)thio}acetamido]-3-(1,2,3-thiadiazol-5-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 5 from (Z)-benzhydryl 7β-[2-{(2-cyanoethenyl)thio}acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate and 5-mercapto-1,2,3-thiadiazole sodium salt.

NMR ($CDCl_3$, δ) : 3.36 (2H, dd, J=17.8Hz and 38.4Hz),
3.55 (2H, s), 5.05 (1H, d, J=4.9Hz),
5.40 (1H, d, J=10.5Hz),
5.84 (1H, dd, J=4.9Hz and 8.8Hz), 7.01 (1H, s),
7.1 - 7.4 (12H, m), 8.50 (1H, s)

Example 41

(Z)-7β-[2-{(2-Cyanoethenyl)thio}acetamido]-3-(1,2,3-thiadiazol-5-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from (Z)-benzhydryl 7β-[2-{(2-cyanoethenyl)thio}acetamido]-3-(1,2,3-thiadiazol-5-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 2212, 1780, 1683 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.69 (2H, dd, J=17.5Hz and 64.1Hz),
3.73 (2H, s), 5.23 (1H, d, J=4.9Hz),
5.72 (1H, d, J=10.5Hz),
5.80 (1H, dd, J=4.9Hz and 8.2Hz),
7.65 (1H, d, J=10.5Hz), 8.93 (1H, s),
9.32 (1H, d, J=8.2Hz)

FAB-Mass (m/z) = 442.0

Example 42

Benzhydryl 7β-[2-(phenylthio)acetamido]-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 5 from benzhydryl 7β-[2-(phenylthio)acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate and 5-mercapto-1,2,3-triazole sodium salt.

NMR ($CDCl_3$, δ) : 3.09 (2H, dd, J=17.7Hz and 21.5Hz),
3.69 (2H, dd, J=16.8Hz and 22.7Hz),
4.91 (1H, d, J=4.8Hz),
5.74 (1H, dd, J=4.8Hz and 8.7Hz),
6.97 (1H, s), 7.1 - 7.8 (17H, m)

Example 43

7β-[2-(Phenylthio)acetamido]-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-[2-(phenylthio)acetamido]-3-(1,2,3-triazol-5-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 1759, 1683, 1616 (cm^{-1})

NMR (D_2O, δ) : 3.19 (2H, dd, J=17.3Hz and 35.6Hz),
3.77 (2H, dd, J=15.5Hz and 19.7Hz),
5.02 (1H, d, J=4.6Hz), 5.50 (1H, d, J=4.6Hz),
7.2 - 7.5 (5H, m), 8.09 (1H, s)

FAB-Mass (m/z) = 449.8

Example 44

Benzhydryl 7β-[2-(phenylthio)acetamido]-3-(5-methyl-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 11 from benzhydryl 7β-[2-(phenylthio)acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate and 5-methyl-1,3,4-triazole-2-thiol.

NMR ($CDCl_3$, δ) : 2.43 (3H, s),
3.40 (2H, dd, J=17.9Hz and 54.1Hz),
3.59 (2H, d, J=4.8Hz), 4.95 (1H, d, J=4.9Hz),
5.79 (1H, dd, J=4.8Hz and 9.0Hz),
6.90 (1H, s), 7.1 - 7.5 (15H, m),
7.66 (1H, d, J=9.0Hz)

Example 45

7β-[2-(Phenylthio)acetamido]-3-(5-methyl-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a

method similar to that of Example 2 from benzhydryl 7β-[2-(phenylthio)acetamido]-3-(5-methyl-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 1755, 1666, 1560 (cm^{-1})

NMR (DMSO-d_6, δ) : 2.37 (3H, s),
3.44 (2H, dd, J=14.9Hz and 32.6Hz), 3.75 (2H, s),
5.17 (1H, d, J=4.8Hz),
5.65 (1H, dd, J=4.8Hz and 8.2Hz), 7.1 - 7.4 (5H, m),
9.17 (1H, d, J=8.2Hz)

FAB-Mass (m/z) = 464.0

Example 46

Benzhydryl 7β-[2-(phenylthio)acetamido]-3-(1-methyl-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 11 from benzhydryl 7β-[2-(phenylthio)acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate and 1-methyl-1,3,4-triazole-2-thiol.

NMR ($CDCl_3$, δ) : 3.31 and 3.39 (2H, ABq, J=17.8Hz),
3.55 (3H, s), 3.69 (2H, d, J=5.8Hz),
4.96 (1H, d, J=4.9Hz),
5.82 (1H, dd, J=4.9Hz and 9.2Hz),
6.97 (1H, s), 7.1 - 7.5 (15H, m),
7.69 (1H, d, J=9.2Hz), 8.56 (1H, s)

Example 47

7β-[2-(Phenylthio)acetamido]-3-(1-methyl-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-[2-

(phenylthio)acetamido]-3-(1-methyl-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 1782, 1672, 1514 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.22 and 3.32 (2H, ABq, J=17.4Hz),
3.65 (3H, s), 3.75 (2H, s), 5.13 (1H, d, J=4.8Hz),
5.69 (1H, dd, J=4.8Hz and 8.2Hz),
7.1 - 7.4 (5H, m), 8.76 (1H, s),
9.17 (1H, d, J=8.2Hz)

FAB-Mass (m/z) = 463.9

Example 48

Benzhydryl 7β-[2-(phenylthio)acetamido]-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 11 from benzhydryl 7β-[2-(phenylthio)acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate and 5-methyl-1,3,4-thiadiazole-2-thiol.

NMR ($CDCl_3$, δ) : 2.75 (3H, s),
3.40 and 3.68 (2H, ABq, J=18.0Hz),
3.63 and 3.74 (2H, ABq, J=17.0Hz),
5.00 (1H, d, J=5.1Hz),
5.86 (1H, dd, J=5.1Hz and 9.3Hz), 6.97 (1H, s),
7.1 - 7.5 (15H, m), 7.54 (1H, d, J=9.3Hz)

Example 49

7β-[2-(Phenylthio)acetamido]-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-[2-(phenylthio)acetamido]-3-(5-methyl-1,3,4-

thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 1786, 1668, 1535 (cm^{-1})

NMR (DMSO-d_6, δ) : 2.73 (3H, s),
3.53 and 3.83 (2H, ABq, J=17.5Hz), 3.76 (2H, s),
5.23 (1H, d, J=5.0Hz),
5.79 (1H, dd, J=5.0Hz and 8.3Hz), 7.1 - 7.4 (5H, m),
9.27 (1H, d, J=8.3Hz)

FAB-Mass (m/z) = 480.9

Example 50

Benzhydryl 7β-[2-(phenylthio)acetamido]-3-(1-methyl-tetrazol-5-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 5 from benzhydryl 7β-[2-(phenylthio)acetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate and 5-mercapto-1-methyltetrazole sodium salt.

NMR ($CDCl_3$, δ) : 3.37 and 3.67 (2H, ABq, J=18.0Hz),
3.66 (2H, d, J=3.2Hz), 3.80 (3H, s),
5.03 (1H, d, J=5.1Hz),
5.89 (1H, dd, J=5.1Hz and 9.3Hz), 6.98 (1H, s),
7.1 - 7.4 (15H, m), 7.54 (1H, d, J=9.3Hz)

Example 51

7β-[2-(Phenylthio)acetamido]-3-(1-methyl-tetrazol-5-yl)-thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-[2-(phenylthio)acetamido]-3-(1-methyl-tetrazol-5-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 1782, 1670, 1523 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.38 (2H, d, J=6.9Hz),
3.39 and 3.62 (2H, ABq, J=17.4Hz), 3.76 (3H, s),
5.20 (1H, d, J=4.9Hz),
5.76 (1H, dd, J=4.9Hz and 8.3Hz), 7.1 - 7.4 (5H, m),
9.22 (1H, d, J=8.3Hz)

FAB-Mass (m/z) = 465.0

Example 52

Benzhydryl 7β-(2-phenylacetamido)-3-(5-methyl-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 11 from benzhydryl 7β-(2-phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxylate and 5-methyl-1,3,4-triazole-2-thiol.

NMR (DMSO-d_6, δ) : 2.38 (3H, s),
3.43 and 3.55 (2H, ABq, J=17.4Hz), 3.52 (2H, s),
5.22 (1H, d, J=4.7Hz),
5.73 (1H, dd, J=4.7Hz and 8.4Hz), 6.92 (1H, s),
7.1 - 7.4 (15H, m), 9.18 (1H, d, J=8.4Hz),
14.1 (1H, s)

Example 53

7β-(2-phenylacetamido)-3-(5-methyl-1,3,4-triazol-2-yl)-thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(2-phenylacetamido)-3-(5-methyl-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 1755, 1666, 1562 (cm^{-1})

NMR (DMSO-d_6, δ) : 2.36 (3H, s),
3.39 and 3.53 (2H, ABq, J=17.3Hz), 3.51 (2H, s),
5.16 (1H, d, J=4.7Hz),
5.64 (1H, dd, J=4.7Hz and 8.3Hz), 7.1 - 7.4 (5H, m),
9.15 (1H, d, J=8.3Hz)

FAB-Mass (m/z) = 432.0

Example 54

Benzhydryl 7β-(2-phenylacetamido)-3-(1-methyl-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 11 from benzhydryl 7β-(2-phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxylate and 1-methyl-1,3,4-triazole-2-thiol.

NMR ($CDCl_3$, δ) : 3.33 (2H, d, J=1.7Hz), 3.51 (3H, s),
3.64 (2H, s), 4.94 (1H, d, J=4.8Hz),
5.85 (1H, dd, J=4.8Hz and 9.0Hz),
6.64 (1H, d, J=9.0Hz), 6.94 (1H, s),
7.1 - 7.5 (15H, m), 8.34 (1H, s)

Example 55

7β-(2-Phenylacetamido)-3-(1-methyl-1,3,4-triazol-2-yl)-thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(2-phenylacetamido)-3-(1-methyl-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 1782, 1664, 1531 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.22 and 3.33 (2H, ABq, J=17.3Hz),
3.48 and 3.55 (2H, ABq, J=14.0Hz), 3.65 (3H, s),

5.12 (1H, d, J=4.8Hz),

5.68 (1H, dd, J=4.8Hz and 8.2Hz), 7.2 - 7.4 (5H, m),

8.76 (1H, s), 9.14 (1H, d, J=8.2Hz)

FAB-Mass (m/z) = 432.0

Example 56

Benzhydryl 7β-(2-phenylacetamido)-3-(1-methyl-tetrazol-5-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 5 from benzhydryl 7β-(2-phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxylate and 5-mercapto-1-methyltetrazole sodium salt.

NMR ($CDCl_3$, δ) : 3.39 and 3.76 (2H, ABq, J=18.0Hz),

3.55 (2H, s), 3.79 (3H, s), 5.04 (1H, d, J=5.0Hz),

5.91 (1H, dd, J=5.0Hz and 9.1Hz),

6.22 (1H, d, J=9.1Hz), 6.95 (1H, s),

7.1 - 7.4 (15H, m)

Example 57

7β-(2-Phenylacetamido)-3-(1-methyl-tetrazol-5-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(2-phenylacetamido)-3-(1-methyl-tetrazol-5-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 1784, 1666, 1531 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.42 and 3.62 (2H, ABq, J=17.4Hz),

3.52 (2H, d, J=5.2Hz), 4.05 (3H, s),

5.18 (1H, d, J=4.8Hz),

5.74 (1H, dd, J=4.9Hz and 8.3Hz), 7.1 - 7.4 (5H, m),

9.17 (1H, d, J=8.3Hz)

FAB-Mass (m/z) = 433.0

Example 58

Benzhydryl 7β-(2-phenylacetamido)-3-(thiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 11 from benzhydryl 7β-(2-phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxylate and 2-mercaptothiazole.

NMR (DMSO-d_6, δ) : 3.53 (2H, d, J=3.8Hz),
3.54 and 3.77 (2H, ABq, J=17.7Hz),
5.26 (1H, d, J=5.0Hz),
5.83 (1H, dd, J=5.0Hz and 8.4Hz), 6.97 (1H, s),
7.2 - 7.5 (15H, m), 7.90 (2H, s),
9.26 (1H, d, J=8.4Hz)

Example 59

7β-(2-Phenylacetamido)-3-(thiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(2-phenylacetamido)-3-(thiazol-2-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 1782, 1660, 1537 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.52 (2H, d, J=4.3Hz),
3.50 and 3.74 (2H, ABq, J=17.5Hz),
5.21 (1H, d, J=4.9Hz),
5.75 (1H, dd, J=4.9Hz and 8.3Hz), 7.1 - 7.4 (5H, m),
7.88 (2H, s), 9.22 (1H, d, J=8.3Hz)

FAB-Mass (m/z) = 434.0

Example 60

Benzhydryl 7β-(2-phenylacetamido)-3-(5-amino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 11 from benzhydryl 7β-(2-phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxylate and 5-amino-2-mercapto-1,3,4-thiadiazole.

NMR (DMSO-d_6, δ) : 3.53 (2H, d, J=3.3Hz),
3.56 and 3.65 (2H, ABq, J=18.6Hz),
5.22 (1H, d, J=4.9Hz),
5.78 (1H, dd, J=4.9Hz and 8.3Hz), 6.96 (1H, s),
7.2 - 7.6 (15H, m), 7.69 (2H, s),
9.20 (1H, d, J=8.3Hz)

Example 61

7β-(2-Phenylacetamido)-3-(5-amino-1,3,4-thiadiazol-2-yl)-thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(2-phenylacetamido)-3-(5-amino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 3261, 1770, 1656, 1537 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.52 (2H, d, J=4.2Hz),
3.47 and 3.63 (2H, ABq, J=17.5Hz),
5.16 (1H, d, J=4.8Hz),
5.70 (1H, dd, J=4.8Hz and 8.2Hz), 7.1 - 7.4 (5H, m),
7.63 (2H, s), 9.15 (1H, d, J=8.3Hz)

FAB-Mass (m/z) = 450.0

Example 62

Benzhydryl 7β-(2-phenylacetamido)-3-(pyridin-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 11 from benzhydryl 7β-(2-phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxylate and 2-mercaptopyridine.

NMR (DMSO-d_6, δ) : 3.53 (2H, d, J=4.0Hz),
3.56 and 3.89 (2H, ABq, J=17.6Hz),
5.29 (1H, d, J=5.0Hz),
5.83 (1H, dd, J=5.0Hz and 8.4Hz), 6.92 (1H, s),
7.1 - 7.4 (7H, m), 7.77 (1H, dt, J=1.9Hz and 7.7Hz),
8.48 (1H, d, J=3.9Hz), 9.29 (1H, d, J=8.4Hz)

Example 63

7β-(2-Phenylacetamido)-3-(pyridin-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(2-phenylacetamido)-3-(pyridin-2-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 1782, 1660, 1537 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.53 (2H, s),
3.51 and 3.88 (2H, ABq, J=17.5Hz),
5.26 (1H, d, J=4.9Hz),
5.77 (1H, dd, J=4.9Hz and 8.4Hz), 7.1 - 7.4 (7H, m),
7.75 (1H, dt, J=1.8Hz and 7.8Hz),
8.45 (1H, d, J=4.0Hz), 9.26 (1H, d, J=8.4Hz)

FAB-Mass (m/z) = 427.9

Example 64

Benzhydryl 7β-(2-phenylacetamido)-3-(pyrimidin-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 11 from benzhydryl 7β-(2-phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxylate and 2-mercaptopyrimidine.

NMR (DMSO-d_6, δ) : 3.53 (2H, d, J=5.6Hz),
3.71 and 3.94 (2H, ABq, J=17.7Hz),
5.27 (1H, d, J=5.0Hz),
5.84 (1H, dd, J=5.0Hz and 8.5Hz), 6.91 (1H, s),
7.1 - 7.4 (16H, m), 8.66 (2H, d, J=4.9Hz),
9.32 (1H, d, J=8.5Hz)

Example 65

7β-(2-Phenylacetamido)-3-(pyrimidin-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(2-phenylacetamido)-3-(pyrimidin-2-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 1788, 1656, 1560 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.54 (2H, d, J=5.4Hz),
3.69 and 3.98 (2H, ABq, J=17.4Hz),
5.24 (1H, d, J=5.0Hz),
5.78 (1H, dd, J=5.0Hz and 8.5Hz),
7.1 - 7.4 (6H, m), 8.66 (2H, d, J=4.9Hz),
9.29 (1H, d, J=8.5Hz)

FAB-Mass (m/z) = 429.2

Example 66

Benzhydryl 7β-(3-nitrophenyl)acetamido-3-(1,3,4-triazol-

2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 27 from benzhydryl 7β-amino-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate and 3-nitrophenylacetic acid.

Example 67

7β-(3-Nitrophenyl)acetamido-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(3-nitrophenyl)acetamido-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 3.44 (2H, ABq, J=17.2Hz),
3.72 (2H, s), 5.17 (1H, d, J=4.8Hz),
5.66 (1H, dd, J=4.8Hz and 8.2Hz),
7.55 - 7.75 (2H, m), 8.05 - 8.20 (2H, m),
8.70 (1H, br s), 9.26 (1H, d, J=8.2Hz),
14.5 (1H, br s)

FAB-Mass (m/z) = 463 (M^+ + 1)

Example 68

Benzhydryl 7β-(2-thienyl)acetamido-3-(1,3,4-triazol-2-yl)-thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 27 from benzhydryl 7β-amino-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate and 2-thienylacetic acid.

Example 69

7β-(2-Thienyl)acetamido-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method

similar to that of Example 2 from benzhydryl 7β-(2-thienyl)-acetamido-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 3.45 (2H, ABq, J=17.3Hz),
3.75 (1H, s), 5.18 (1H, d, J=4.8Hz),
5.67 (1H, dd, J=4.8Hz and 8.3Hz),
6.90 - 6.96 (2H, m), 7.35 (1H, dd, J=1.6Hz and 4.8Hz),
8.67 (1H, br s), 9.15 (1H, d, J=8.3Hz),
14.4 (1H, br s)

Example 70

Benzhydryl 7β-(3-thienyl)acetamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 27 from benzhydryl 7β-amino-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate and 3-thienylacetic acid.

NMR ($CDCl_3$, δ) : 3.62 (2H, ABq, J=17.9Hz),
3.67 (2H, s), 5.04 (1H, d, J=5.1Hz),
5.91 (1H, dd, J=5.1Hz and 9.2Hz),
6.37 (1H, d, J=9.2Hz), 6.90 - 7.40 (13H, m),
9.11 (1H, s)

Example 71

7β-(3-Thienyl)acetamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(3-thienyl)-acetamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 3.54 (2H, s),
3.73 (2H, ABq, J=17.6Hz), 5.24 (1H, d, J=5.0Hz),

5.79 (1H, dd, J=5.0Hz and 8.3Hz), 7.01 - 7.04 (1H, m),
7.26 (1H, m), 7.43 - 7.48 (1H, m),
9.19 (1H, d, J=8.3Hz), 9.65 (1H, s)

FAB-Mass (m/z) = 441 (M^+)

Example 72

Benzhydryl 7β-(2-thienyl)acetamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 27 from benzhydryl 7β-amino-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate and 2-thienylacetic acid.

NMR ($CDCl_3$, δ) : 3.62 (2H, ABq, J=18.0Hz),
3.86 (2H, s), 5.05 (1H, d, J=5.1Hz),
5.91 (1H, dd, J=5.1Hz and 9.2Hz),
6.47 (1H, d, J=9.2Hz), 6.90 - 7.45 (14H, m),
9.12 (1H, s)

Example 73

7β-(2-Thienyl)acetamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(2-thienyl)-acetamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

IR (Nujol) : 1784, 1660, 1535 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.73 (2H, ABq, J=17.6Hz),
3.76 (2H, s), 5.25 (1H, d, J=5.0Hz),
5.80 (1H, dd, J=5.0Hz and 8.3Hz), 6.92 - 7.00 (2H, m),
7.36 (1H, dd, J=2.2Hz and 4.8Hz),
9.28 (1H, d, J=8.3Hz), 9.65 (1H, s)

FAB-Mass (m/z) = 441 (M^+)

Example 74

Benzhydryl 7β-(3-fluorophenyl)acetamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 27 from benzhydryl 7β-amino-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate and 3-fluorophenylacetic acid.

NMR (DMSO-d_6, δ) : 3.50 - 3.60 (2H, m),
3.75 (2H, ABq, J=17.8Hz), 5.27 (1H, d, J=5.0Hz),
5.86 (1H, dd, J=5.0Hz and 8.3Hz),
6.97 (1H, s), 6.90 - 7.40 (14H, m),
9.32 (1H, d, J=8.3Hz), 9.63 (1H, s)

Example 75

7β-(3-Fluorophenyl)acetamido-3-(1,3,4-thiadiazol-2-yl)-thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(3-fluorophenyl)acetamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 3.56 (2H, m),
3.74 (2H, ABq, J=17.6Hz), 5.24 (1H, d, J=5.0Hz),
5.79 (1H, dd, J=5.0Hz and 8.3Hz), 7.0 - 7.45 (4H, m),
9.29 (1H, d, J=8.3Hz), 9.65 (1H, s)

FAB-Mass (m/z) = 451 (M^+ - 1)

Example 76

Benzhydryl 7β-(4-fluorophenyl)acetamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared

according to a method similar to that of Example 27 from benzhydryl 7β-amino-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate and 4-fluorophenylacetic acid.

NMR ($CDCl_3$, δ) : 3.60 (2H, ABq, J=17.9Hz), 3.62 (2H, s), 5.03 (1H, d, J=5.0Hz), 5.89 (1H, dd, J=5.0Hz and 9.1Hz), 6.52 (1H, d, J=9.1Hz), 6.92 (1H, s), 6.92 - 7.40 (14H, m), 9.11 (1H, s)

Example 77

7β-(4-Fluorophenyl)acetamido-3-(1,3,4-thiadiazol-2-yl)-thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(4-fluorophenyl)acetamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 3.51 (2H, s), 3.72 (2H, ABq, J=17.6Hz), 5.23 (1H, d, J=5.0Hz), 5.78 (1H, dd, J=5.0Hz and 8.3Hz), 7.05 - 7.35 (4H, m), 9.24 (1H, d, J=8.0Hz), 9.65 (1H, s)

FAB-Mass (m/z) = 453 (M^+ + 1)

Example 78

Benzhydryl 7β-(3-chlorophenyl)acetamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 27 from benzhydryl 7β-amino-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate and 3-chlorophenylacetic acid.

NMR ($CDCl_3$, δ) : 3.50 (2H, s), 3.61 (2H, ABq, J=17.9Hz),

5.03 (1H, d, J=5.0Hz),

5.89 (1H, dd, J=5.0Hz and 9.0Hz),

6.70 (1H, d, J=9.0Hz), 6.97 (1H, s),

7.05 - 7.40 (14H, m), 9.11 (1H, s)

Example 79

7β-(3-Chlorophenyl)acetamido-3-(1,3,4-thiadiazol-2-yl)-thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-(3-chlorophenyl)acetamido-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 3.50 - 3.60 (2H, m),

3.73 (2H, ABq, J=17.6Hz), 5.24 (1H, d, J=5.0Hz),

5.79 (1H, dd, J=5.0Hz and 8.3Hz), 7.15 - 7.40 (5H, m),

9.30 (1H, d, J=8.3Hz), 9.65 (1H, s)

FAB-Mass (m/z) = 469 (M^+)

Example 80

Benzhydryl 7β-[3-(3-thienyl)acryloylamino]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 27 from benzhydryl 7β-amino-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate and 3-(3-thienyl)acrylic acid.

NMR ($CDCl_3$, δ) : 3.63 (2H, ABq, J=18.0Hz),

5.09 (1H, d, J=5.0Hz),

6.07 (1H, dd, J=5.0Hz and 9.0Hz),

6.34 (1H, d, J=15.5Hz), 6.75 (1H, d, J=9.0Hz),

6.97 (1H, s), 7.20 - 7.50 (13H, m),

7.78 (1H, d, J=15.5Hz), 9.12 (1H, s)

Example 81

7β-[3-(3-Thienyl)acryloylamino]-3-(1,3,4-thiadiazol-2-yl)-thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-[3-(3-thienyl)acryloylamino]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 3.75 (2H, ABq, J=17.6Hz),
5.30 (1H, d, J=5.0Hz),
5.93 (1H, dd, J=5.0Hz and 8.4Hz),
6.55 (1H, d, J=15.7Hz), 7.33 (1H, d, J=5.0Hz),
7.54 (1H, d, J=15.7Hz),
7.62 (1H, dd, J=2.9Hz and 5.0Hz),
7.86 (1H, d, J=2.9Hz), 9.13 (1H, d, J=8.4Hz),
9.65 (1H, s)

FAB-Mass (m/z) = 453 (M^+)

Example 82

Benzhydryl 7β-[2-(phenylthio)acetamido]-3-(pyrazol-4-yl)-methylthio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 27 from benzhydryl 7β-amino-3-(pyrazol-4-yl)methylthio-3-cephem-4-carboxylate and phenylthioacetic acid.

NMR (DMSO-d_6, δ) : 3.78 (2H, s), 4.08 (2H, s),
4.57 (2H, s), 5.17 (1H, d, J=4.7Hz),
5.68 (1H, dd, J=4.7Hz and 8.3Hz), 6.86 (1H, s),
7.1 - 7.6 (15H, m), 7.81 (1H, s), 8.31 (1H, s),

9.21 (1H, d, J=8.3Hz)

Example 83

7β-[2-(Phenylthio)acetamido]-3-(pyrazol-4-yl)methylthio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-[2-(phenylthio)acetamido]-3-(pyrazol-4-yl)methylthio-3-cephem-4-carboxylate.

IR (KBr) : 1759, 1660, 1578 (cm^{-1})

NMR (D_2O, δ) : 3.38 (2H, dd, J=17.2Hz and 43.1Hz),
3.78 (2H, dd, J=3.9Hz and 12.2Hz),
3.92 (2H, dd, J=14.4Hz and 19.9Hz),
4.93 (1H, d, J=4.6Hz), 5.50 (1H, d, J=4.6Hz),
7.2 - 7.7 (7H, m)

FAB-Mass (m/z) = 463.0

Example 84

(Z)-Benzhydryl 7β-[2-{(2-cyanoethenyl)thio}acetamido]-3-(pyrazol-4-yl)methylthio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 27 from benzhydryl 7β-amino-3-(pyrazol-4-yl)methylthio-3-cephem-4-carboxylate and (Z)-(2-cyanoethenyl)thioacetic acid.

NMR (DMSO-d_6, δ) : 3.75 (2H, s), 3.88 (2H, s),
4.07 (2H, d, J=3.9Hz), 5.19 (1H, d, J=4.6Hz),
5.67 (1H, dd, J=4.6Hz and 8.1Hz),
5.74 (1H, d, J=10.6Hz), 6.85 (1H, s),
7.2 - 7.7 (12H, m), 7.68 (1H, d, J=10.6Hz),
9.27 (1H, d, J=8.1Hz)

Example 85

(Z)-7β-[2-{(2-Cyanoethenyl)thio}acetamido]-3-(pyrazol-4-yl)methylthio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from (Z)-benzhydryl 7β-[2-{(2-cyanoethenyl)thio}acetamido]-3-(pyrazol-4-yl)methylthio-3-cephem-4-carboxylate.

IR (KBr) : 2212, 1772, 1683, 1670 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.74 (2H, s), 3.79 (2H, d, J=4.3Hz),
4.02 (2H, d, J=3.5Hz), 5.11 (1H, d, J=4.5Hz),
5.58 (1H, dd, J=4.5Hz and 8.0Hz),
5.73 (1H, d, J=10.5Hz), 7.56 (2H, s),
7.67 (1H, d, J=10.5Hz), 9.22 (1H, d, J=8.0Hz)

FAB-Mass (m/z) = 438.0

Example 86

Benzhydryl 7β-[2-(3-thienyl)acetamido]-3-(5-amino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Example 27 from benzhydryl 7β-amino-3-(5-amino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate and 3-thienylacetic acid.

NMR (DMSO-d_6, δ) : 3.55 (2H, s),
3.52 and 3.66 (2H, ABq, J=17.5Hz),
5.23 (1H, d, J=4.9Hz),
5.79 (1H, dd, J=4.9Hz and 8.3Hz), 6.95 (1H, s),
7.02 (1H, d, J=4.9Hz), 7.2 - 7.6 (12H, m),
7.68 (2H, s), 9.15 (1H, d, J=8.3Hz)

Example 87

7β-[2-(3-Thienyl)acetamido]-3-(5-amino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2 from benzhydryl 7β-[2-(3-thienyl)acetamido]-3-(5-amino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate.

IR (KBr) : 3270, 1772, 1654, 1541 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.54 (2H, s),
3.45 and 3.63 (2H, ABq, J=17.4Hz),
5.17 (1H, d, J=4.9Hz),
5.70 (1H, dd, J=4.9Hz and 8.3Hz),
7.01 (1H, dd, J=1.2Hz and 4.9Hz), 7.25 (1H, s),
7.45 (1H, dd, J=3.0Hz and 4.9Hz), 7.62 (2H, s),
9.10 (1H, d, J=8.3Hz)

FAB-Mass (m/z) = 455.9

Example 88

Phosphorus oxychloride (268 μl) was added dropwise to a mixture of N,N-dimethylformamide (220 μl) and ethyl acetate (0.7 ml) under ice-cooling. After being stirred for 10 minutes at the same temperature, the mixture was cooled until a precipitate appeared. To the suspension was added tetrahydrofuran (10 ml). The suspension was stirred at the same temperature for 30 minutes. To the suspension was added 3-chlorophenylacetic acid (403 mg). The mixture was stirred at the same temperature for 30 minutes to give an activated acid solution. On the other hand, to a suspension of benzhydryl 7β-amino-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate (1.0 g)

in tetrahydrofuran (10 ml) was added N-trimethylsilylacetamide (845 mg). The suspension was stirred at room temperature for 30 minutes to give a clear solution. To the solution was added the activated acid solution prepared above at -20 °C and the mixture was stirred at -25°C to -10°C for an hour. The mixture was poured into a solution of sodium hydrogencarbonate (2 g) in water (50 ml). The solution was extracted with ethyl acetate (50 ml). The extract was washed with water and a saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. The residue was triturated with diethyl ether to give benzhydryl 7β-[2-(3-chlorophenyl)acetamido]-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate (955 mg).

IR (KBr) : 3400, 1790, 1730, 1670, 1530, 1490, 1380, 1280, 1220 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.3 - 3.7 (4H, m), 5.24 (1H, d, J=5Hz), 5.74 (1H, dd, J=5Hz and 8Hz), 6.93 (1H, s), 7.2 - 7.6 (14H, m), 8.70 (1H, br s), 9.23 (1H, d, J=8Hz), 14.5 (1H, br s)

APCI-Mass (m/z) = 618 ($M + H^+$)

Example 89

7β-[2-(3-Chlorophenyl)acetamido]-3-(1,3,4-triazol-2-yl)-thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2.

IR (KBr) : 3400, 3270, 2920, 1780, 1660, 1550, 1350, 1240 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.37 and 3.58 (2H, ABq, J=17Hz),
3.56 and 3.58 (total 1H, each s),
5.17 (1H, d, J=5Hz),
5.66 (1H, dd, J=5Hz and 8Hz), 7.2 - 7.4 (4H, m),
8.68 (1H, br s), 9.19 (1H, d, J=8Hz), 14.4 (1H, br s)
FAB-Mass (m/z) = 451.9 ($M + H^+$)

Example 90

To a suspension of benzhydryl 7β-amino-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate (1.0 g) and (Z)-2-(2-carbamoylethenylthio)acetic acid (451 mg) in tetrahydrofuran (30 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride under ice-cooling. The reaction mixture was stirred at the same temperature for 3.5 hours. The resulting viscus solid was washed with tetrahydrofuran. The viscus solid was dissolved in a mixture of tetrahydrofuran (10 ml) and water (20 ml). The solution was extracted with ethyl acetate (20 ml). The extract was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. The residue was triturated with ethyl acetate to give (Z)-benzhydryl 7β-[2-[(2-carbamoylethenyl)-thio]acetamido]-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate (443 mg).

NMR (DMSO-d_6, δ) : 3.39 and 3.58 (2H, ABq, J=17Hz),
5.26 (1H, d, J=5Hz), 5.76 (1H, dd, J=5Hz and 8Hz),
5.89 (1H, d, J=10Hz), 6.88 (2H, br s), 6.93 (1H, s),
7.04 (1H, d, J=10Hz), 7.2 - 7.6 (10H, m),

8.74 (1H, br s), 9.15 (1H, d, J=8Hz), 14.5 (1H, br s)

FAB-Mass (m/z) = 609.0 (M + H$^+$)

Example 91

To a solution of (Z)-benzhydryl 7β-[2-[(2-carbamoylethenyl)thio]acetamido]-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate (400 mg) in dichloromethane (1.2 ml) were added anisole (0.4 ml) and trifluoroacetic acid (0.8 ml) under ice-cooling. After stirring at the same temperature for an hour, the solution was poured into diisopropyl ether. The resulting precipitate was collected by filtration, dissolved in a mixture of ethyl acetate (30 ml), tetrahydrofuran (15 ml) and an aqueous sodium hydrogencarbonate solution (30 ml). The separated aqueous layer was adjusted to pH 5.0 with 1N-hydrochloric acid and subjected to column chromatography on non-ionic adsorption resin "Diaion HP-20" (20 ml) (eluent; 5 - 10% aqueous diisopropyl alcohol). The eluate was concentrated in vacuo and freeze-dried to give sodium (Z)-7β-[2-[(2-carbamoylethenyl)thio]acetamido]-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate (55 mg).

IR (KBr) : 3500-3200, 1763, 1657, 1610, 1570, 1394, 1354, 1261 cm^{-1}

NMR (D_2O, δ) : 3.33 and 3.73 (2H, ABq, J=17Hz), 3.58 (2H, s), 5.21 (1H, d, J=5Hz), 5.66 (1H, d, J=5Hz), 6.07 (1H, d, J=10Hz), 7.12 (1H, d, J=10Hz), 8.46 (1H, s)

FAB-Mass (m/z) = 465.0 (M + H$^+$)

Example 92

Benzhydryl 7β-[2-(4-pyridylthio)acetamido]-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 2.

NMR (DMSO-d_6, δ) : 3.35 and 3.54 (2H, ABq, J=17Hz),
3.90 (2H, s), 5.24 (1H, d, J=5Hz),
5.75 (1H, dd, J=5Hz and 8Hz), 6.92 (1H, s),
7.2 - 7.5 (12H, m), 8.3 - 8.4 (2H, m),
8.68 (1H, br s), 9.34 (1H, d, J=8Hz)

Example 93

To a solution of benzhydryl 7β-[2-(4-pyridylthio)-acetamido]-3-(1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate (900 mg) in a mixture of dichloromethane (3 ml) and anisole (1 ml) was added trifluoroacetic acid (2 ml) under ice-cooling. The mixture was stirred at the same temperature for an hour. The reaction mixture was poured into diisopropyl ether (50 ml). The precipitate was collected by filtration and dried over to give 7β-[2-(4-pyridylthio)acetamido]-3-(1,3,4-triazol-2-yl)-thio-3-cephem-4-carboxylic acid, trifluoroacetic acid salt (930 mg).

NMR (DMSO-d_6, δ) : 3.38 and 3.55 (2H, ABq, J=17Hz),
4.15 (2H, s), 5.19 (1H, d, J=5Hz),
5.68 (1H, dd, J=5Hz and 8Hz), 7.8 - 7.9 (2H, s),
8.6 - 8.7 (3H, m), 9.43 (1H, d, J=8Hz)

FAB-Mass (m/z) = 450.9 ($M + H^+$)

Example 94

The following compound was prepared according to a method similar to that of Preparation 2.

Benzhydryl 7β-[2-(thiazol-4-yl)acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxlate.

NMR (DMSO-d_6, δ) : 3.62 and 3.91 (2H, ABq, J=17Hz), 3.77 (2H, s), 5.30 (1H, d, J=5Hz), 5.90 (1H, dd, J=5Hz and 8Hz), 6.98 (1H, s), 7.2 - 7.6 (10H, m), 7.46 (1H, m), 9.02 (1H, m), 9.26 (1H, d, J=8Hz), 9.64 (1H, s)

FAB-Mass (m/z) = 608 ($M + H^+$)

Example 95

To a solution of benzhydryl 7β-[2-(thiazol-4-yl)-acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (470 mg) in a mixture of dichloromethane (1.4 ml) and anisole (0.47 ml) was added trifluoroacetic acid (0.94 ml) under ice-cooling. The mixture was stirred at the same temperature for 40 minutes. The reaction mixture was poured into diisopropyl ether (50 ml) and the resulting precipitate was collected by filtration and dried in vacuo. The precipitate was dissolved in a mixture of an aqueous sodium hydrogencarbonate solution (20 ml), tetrahydrofuran (10 ml) and ethyl acetate (30 ml). To the separated aqueous layer were added ethyl acetate (30 ml) and tetrahydrofuran (10 ml). The mixture was adjusted to pH 1.5 with 1N-hydrochloric acid. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. The residue was

triturated with ethyl acetate to give crude product (121 mg). The crude product (95 mg) was dissolved in a mixture of tetrahydrofuran (10 ml) and an aqueous sodium hydrogencarbonate solution (20 ml). The solution was washed with ethyl acetate (20 ml) and evaporated in vacuo to remove the organic solvent. The resulting residue was adjusted to pH 6.5 with 1N-hydrochloric acid, purified by high pressure liquid chromatography (R-ODS-C-15, YMC-pack) eluting with 0 - 15% acetonitrile-phosphate buffer (pH 6.0). The fractions containing the desired compound were collected and concentrated in vacuo. To the resulting solution was added tetrahydrofuran (50 ml) and ethyl acetate (150 ml) and the mixture was adjusted to pH 2 with 1N-hydrochloric acid. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was triturated with diethyl ether to give 7β-[2-(thiazol-4-yl) acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid (32 mg).

NMR (DMSO-d_6, δ) : 3.56 and 3.89 (2H, ABq, J=17Hz),
3.76 (2H, s), 5.26 (1H, d, J=5Hz),
5.82 (1H, dd, J=5Hz and 8Hz), 7.46 (1H, m),
9.02 (1H, m), 9.20 (1H, d, J=8Hz), 9.65 (1H, s)

FAB-Mass (m/z) = 441.9 ($M + H^+$)

Example 96

To a solution of benzhydryl 7β-amino-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (965 mg) in tetrahydrofuran (29

ml) was added N-trimethylsilylacetamide (788 mg). After stirring at room temperature for 10 minutes, the solution was cooled at 0°C and 2-(2-amino-thiazol-4-yl)-2-methoxyiminoacetyl chloride hydrochloride syn isomer (512 mg) was added to the cooled solution. After stirring under ice-cooling for 1 hour, the solution was poured into a mixture of ethyl acetate and water, and adjusted to pH 7 with an aqueous sodium hydrogen-carbonate solution. The separated organic layer was washed with a saturated aqueous sodium chloride solution three times, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent; ethyl acetate) to give benzhydryl 7β-[2-(2-amino-thiazol-4-yl)-2-methoxyiminoacetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate syn isomer (693 mg).

NMR (DMSO-d_6, δ) : 3.61 and 3.87 (2H, ABq, J=17.8Hz),
3.83 (3H, s), 5.35 (1H, d, J=5.0Hz),
5.96 (1H, dd, J=4.9Hz and 8.3Hz), 6.74 (1H, s),
6.97 (1H, s), 7.1 - 7.5 (10H, m), 9.64 (1H, s),
9.75 (1H, d, J=8.3Hz)

Example 97

7β-[2-(2-Amino-thiazol-4-yl)-2-methoxyiminoacetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2.

IR (KBr) : 1770, 1612, 1531 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.31 and 3.78 (2H, ABq, J=17.0Hz),
3.83 (3H, s), 5.15 (1H, d, J=5.0Hz),

5.69 (1H, dd, J=5.0Hz and 8.1Hz), 6.72 (1H, s),
7.21 (2H, br s), 9.51 (1H, s), 9.66 (1H, d, J=8.1Hz)

FAB-Mass (m/z) = 499.9 ($M + H^+$)

Example 98

Benzhydryl 7β-[2-(1-tetrazolyl)acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 2.

NMR (DMSO-d_6, δ) : 3.67 and 3.90 (2H, ABq, J=17.8Hz),
5.32 (1H, d, J=5.1Hz), 5.37 (2H, s),
5.93 (1H, dd, J=5.1Hz and 8.4Hz), 6.97 (1H, s),
7.2 - 7.5 (10H, m), 9.36 (1H, s), 9.64 (1H, s),
9.66 (1H, d, J=8.4Hz)

Example 99

7β-[2-(1-Tetrazolyl)acetamido]-3-(1,3,4-thiadiazol-2-yl)-thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2.

IR (KBr) : 1778, 1693, 1666, 1542 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.61 and 3.89 (2H, ABq, J=17.6Hz),
5.28 (1H, d, J=5.1Hz), 5.38 (2H, s),
5.86 (1H, dd, J=5.1Hz and 8.3Hz), 9.38 (1H, s),
9.64 (1H, d, J=8.3Hz), 9.66 (1H, s)

FAB-Mass (m/z) = 427.0 ($M + H^+$)

Example 100

Benzhydryl 7β-[2-(2-formamido-4-methylthiazol-5-yl)-acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of

Preparation 2.

NMR (DMSO-d_6, δ) : 2.19 (3H, s), 3.65 (2H, s),
3.62 and 3.89 (2H, ABq, J=17.8Hz),
5.30 (1H, d, J=5.1Hz),
5.87 (1H, dd, J=5.1Hz and 8.4Hz),
6.98 (1H, s), 7.2 - 7.5 (10H, m), 8.40 (1H, s),
9.31 (1H, d, J=8.4Hz), 9.64 (1H, s), 11.99 (1H, s)

Example 101

Benzhydryl 7β-[2-(2-amino-4-methylthiazol-5-yl)acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 1.

NMR (DMSO-d_6, δ) : 2.18 (3H, s), 3.65 (2H, d, J=3.8Hz),
3.60 and 3.88 (2H, ABq, J=17.9Hz),
5.29 (1H, d, J=5.1Hz),
5.84 (1H, dd, J=5.1Hz and 8.4Hz),
6.97 (1H, s), 7.1 - 7.4 (12H, m),
9.21 (1H, d, J=8.4Hz), 9.63 (1H, s)

Example 102

7β-[2-(2-Amino-4-methylthiazol-5-yl)acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2.

IR (KBr) : 1772, 1635, 1541 (cm^{-1})

NMR (DMSO-d_6, δ) : 2.00 (3H, s), 3.45 (2H, s),
3.61 and 3.85 (2H, ABq, J=17.8Hz),
5.20 (1H, d, J=5.1Hz),
5.71 (1H, dd, J=5.1Hz and 8.4Hz), 6.80 (2H, br s),

9.13 (1H, d, J=8.4Hz), 9.60 (1H, s)

FAB-Mass (m/z) = 470.9 ($M + H^+$)

Example 103

To a mixture of benzhydryl 7β-amino-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (1.93 g), D-2-(t-butoxycarbonylamino)-2-(4-hydroxyphenyl)acetic acid (1.28 g) and dichloromethane (40 ml) was added 1,3-dicyclohexylcarbodiimide (825 mg) at -10°C. After stirring at room temperature for 2 hours, ethyl acetate was added to the mixture and insoluble material was filtered off. The filtrate was adjusted to pH 6.8 and the separated organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated. The residue was subjected to column chromatography on silica gel (eluent; ethyl acetate:n-hexane = 3:2 (v/v)) to give benzhydryl 7β-[D-2-(t-butoxycarbonylamino)-2-(4-hydroxyphenyl)acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (1.43 g).

NMR (DMSO-d_6, δ) : 1.38 (9H, s),

3.53 and 3.81 (2H, ABq, J=17.8Hz),

5.16 (1H, d, J=7.7Hz), 5.21 (1H, d, J=5.1Hz),

5.56 (1H, d, J=7.7Hz),

5.90 (1H, dd, J=5.1Hz and 8.5Hz),

6.66 (2H, d, J=8.5Hz), 6.97 (1H, s),

7.1 - 7.6 (12H, m), 9.23 (1H, d, J=8.5Hz),

9.36 (1H, s), 9.62 (1H, s)

Example 104

7β-[D-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2.

IR (KBr) : 1770, 1614, 1516 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.48 and 3.79 (2H, ABq, J=17.8Hz),
5.00 (1H, s), 5.22 (1H, d, J=4.8Hz),
5.53 (1H, dd, J=4.8Hz and 8.5Hz),
6.74 (2H, d, J=8.5Hz), 7.09 (2H, d, J=8.5Hz),
8.66 (1H, d, J=8.5Hz), 9.43 (1H, s)

FAB-Mass (m/z) = 466.0 ($M + H^+$)

Example 105

Benzhydryl 7β-[2-[4-(t-butoxycarbonylamino)phenyl]-acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared according to a method similar to that of Preparation 2.

NMR (DMSO-d_6, δ) : 1.46 (9H, s), 3.44 (2H, d, J=5.3Hz),
3.61 and 3.89 (2H, ABq, J=17.8Hz),
5.27 (1H, d, J=5.0Hz), 5.85 (1H, dd, J=5.0 and 8.3Hz),
6.98 (1H, s), 7.13 (2H, d, J=8.5Hz),
7.2 - 7.5 (12H, m), 9.22 (1H, d, J=8.3Hz),
9.25 (1H, s), 9.63 (1H, s)

Example 106

7β-[2-(4-Aminophenyl)acetamido]-3-(1,3,4-thiadiazol-2-yl)-thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2.

IR (KBr) : 1772, 1652, 1618, 1514 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.31 (2H, d, J=5.3Hz),
3.54 and 3.86 (2H, ABq, J=17.6Hz),
5.21 (1H, d, J=4.9Hz),
5.74 (1H, dd, J=4.9Hz and 8.3Hz),
6.47 (2H, d, J=8.3Hz), 6.91 (2H, d, J=8.4Hz),
9.06 (1H, d, J=8.3Hz), 9.63 (1H, s)

FAB-Mass (m/z) = 450.0 ($M + H^+$)

Example 107

To a solution of D-mandelic acid (304mg), 4-dimethylaminopyridine (10mg) and pyridine (324mg) in dichloromethane (4ml) was added dropwise chlorotrimethylsilane (445mg) at room temperature. After stirring at room temperature for 4 hours, the solution was cooled to 0°C, and N,N-dimethylformamide (2 drops) and oxalyl chloride (261 mg) were added to the cooled solution at 0°C. After stirring at 0°C for 1 hour and continuously at room temperature for 30 minutes, the solution was cooled to 0°C again. A solution of benzhydryl 7β-amino-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (965mg) and N-trimethylsilylacetamide (788mg) in tetrahydrofuran (19ml) was added to the cooled solution prepared above. After stirring under ice-cooling for 2 hours, a solution of citric acid (423mg) in methanol (4ml) was added to the solution. After stirring under ice-cooling for 30 minutes, the mixture was poured into a mixture of ethyl acetate and water. The separated organic layer was washed with a saturated aqueous

sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure. The residure was subjected to column chromatography on silica gel (eluent; n-hexane:ethyl acetate = 2:3(v/v)) to give benzhydryl 7β-(D-2-hydroxy-2-phenylacetamido)-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (513mg).

NMR (DMSO-d_6, δ) : 3.60 and 3.85 (2H, ABq, J=17.7Hz),
5.10 (1H, d, J=5.5Hz), 5.26 (1H, d, J=5.1Hz),
5.87 (1H, dd, J=5.1Hz and 8.9Hz),
6.13 (1H, d, J=5.5Hz), 6.97 (1H, s),
7.2 - 7.5 (15H, m), 9.02 (1H, d, J=8.9Hz),
9.64 (1H, s)

FAB-Mass (m/z) = 617 ($M + H^+$)

Example 108

7β-(D-2-Hydroxy-2-phenylacetamido)-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2.

IR (KBr) : 1776, 1682, 1514 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.55 and 3.84 (2H, ABq, J=17.6Hz),
5.09 (1H, s), 5.22 (1H, d, J=5.1Hz),
5.80 (1H, dd, J=5.1Hz and 8.9Hz), 7.2 - 7.5 (5H, m),
8.95 (1H, d, J=8.9Hz), 9.64 (1H, s)

FAB-Mass (m/z) = 451.0 ($M + H^+$)

Example 109

Benzhydryl 7β-(L-2-hydroxy-2-phenylacetamido)-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate was prepared

according to a method similar to that of Example 107 using L-mandelic acid instead of D-mandelic acid.

NMR (DMSO-d_6, δ) : 3.63 and 3.87 (2H, ABq, J=17.7Hz),
5.04 (1H, d, J=5.1Hz), 5.28 (1H, d, J=5.1Hz),
5.80 (1H, dd, J=5.1Hz and 8.7Hz),
6.26 (1H, d, J=5.1Hz), 6.97 (1H, s),
7.2 - 7.5 (15H, m), 8.95 (1H, d, J=8.7Hz),
9.64 (1H, s)

Example 110

7β-(L-2-Hydroxy-2-phenylacetamido)-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2.

IR (KBr) : 1782, 1680, 1515 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.58 and 3.87 (2H, ABq, J=17.5Hz),
5.04 (1H, s), 5.23 (1H, d, J=5.1Hz),
5.74 (1H, dd, J=5.1Hz and 8.7Hz), 7.2 - 7.5 (5H, m),
8.87 (1H, d, J=8.7Hz), 9.65 (1H, s)

FAB-Mass (m/z) = 451.0 ($M + H^+$)

The compounds of Example 111 to Example 115 were prepared according to a method similar to that of Preparation 3.

Example 111

Benzhydryl 7β-(2-phenylacetamido)-3-(4-amino-5-methyl-1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 2.36 (3H, s), 3.2 - 3.6 (4H, m),
5.16 (1H, d, J=5Hz), 5.77 (1H, dd, J=5Hz and 8Hz),

5.94 (2H, br s), 6.93 (1H, s), 7.2 - 7.7 (15H, m),
9.18 (1H, d, J=8Hz)

FAB-Mass (m/z) = 613.2 ($M + H^+$)

Example 112

Benzhydryl 7β-(2-phenylacetamido)-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.08 (6H, s), 3.4 - 3.6 (2H, m),
3.58 and 3.69 (2H, ABq, J=17Hz), 5.22 (1H, d, J=5Hz),
5.80 (1H, dd, J=5Hz and 8Hz), 6.96 (1H, s),
7.2 - 7.6 (15H, m), 9.22 (1H, d, J=8Hz)

FAB-Mass (m/z) = 644.2 ($M + H^+$)

Example 113

Benzhydryl 7β-(2-phenylacetamido)-3-(5-methylamino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 2.90 (3H, d, J=5Hz), 3.4 - 3.6 (2H, m),
3.50 and 3.69 (2H, ABq, J=17Hz), 5.22 (1H, d, J=5Hz),
5.79 (1H, dd, J=5Hz and 8Hz), 6.96 (1H, s),
7.2 - 7.6 (15H, m), 8.11 (1H, q, J=5Hz),
9.21 (1H, d, J=8Hz)

FAB-Mass (m/z) = 630.2 ($M + H^+$)

Example 114

Benzhydryl 7β-(2-phenylacetamido)-3-[5-(pyrrolidin-1-yl)-1,3,4-thiadiazol-2-yl]thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 1.9 - 2.1 (4H, m), 3.3 - 3.8 (3H, m),
5.21 (1H, d, J=5Hz), 5.80 (1H, dd, J=5Hz and 8Hz),
6.96 (1H, s), 7.2 - 7.6 (15H, m),

9.22 (1H, d, J=8Hz)

FAB-Mass (m/z) = 670.1 (M + H$^+$)

Example 115

Benzhydryl 7β-(2-phenylacetamido)-3-[5-morpholino-1,3,4-thiadiazol-2-yl]thio-3-cephem-4-carboxylate.

NMR (DMSO-d_6, δ) : 3.3 - 3.8 (12H, m), 5.22 (1H, d, J=15Hz),
5.83 (1H, dd, J=5Hz and 8Hz), 6.96 (1H, s),
7.2 - 7.6 (15H, m), 9.22 (1H, d, J=8Hz)

FAB-Mass (m/z) = 686.3 (M + H$^+$)

The compounds of Example 116 to Example 120 were prepared according to a method similar to that of Example 2.

Example 116

7β-(2-Phenylacetamido)-3-(4-amino-5-methyl-1,2,4-triazol-3-yl)thio-3-cephem-4-carboxylic acid

NMR (DMSO-d_6, δ) : 2.33 (3H, s),
3.26 and 3.47 (2H, ABq, J=17Hz), 3.4 - 3.6 (2H, m),
5.06 (1H, d, J=5Hz), 5.63 (1H, dd, J=5Hz and 8Hz),
7.25 (5H, m), 9.09 (1H, d, J=8Hz)

FAB-Mass (m/z) = 447.0 (M + H$^+$)

Example 117

7β-(2-Phenylacetamido)-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid

IR (Nujol) : 3260, 1770, 1690, 1660, 1560, 1510, 1350,
1310, 1240, 1230 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.10 (6H, s), 3.4 - 3.6 (2H, m),

3.44 and 3.64 (2H, ABq, J=17Hz),

5.15 (1H, d, J=5Hz), 5.70 (1H, dd, J=5Hz and 8Hz),

7.26 (5H, m), 9.16 (1H, d, J=8Hz)

FAB-Mass (m/z) = 478.0 ($M + H^+$)

Example 118

7β-(2-Phenylacetamido)-3-(5-methylamino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid

IR (Nujol) : 3260, 1770, 1650, 1530, 1330, 1240 (cm^{-1})

NMR (DMSO-d_6, δ) : 2.90 (3H, d, J=5Hz), 3.4 - 3.6 (2H, m),

3.45 and 3.65 (2H, ABq, J=17Hz),

5.16 (1H, d, J=5Hz), 5.70 (1H, dd, J=5Hz and 8Hz),

7.27 (5H, m), 8.08 (1H, m), 9.16 (1H, d, J=8Hz)

FAB-Mass (m/z) = 463.9 ($M + H^+$)

Example 119

7β-(2-Phenylacetamido)-3-[5-(pyrrolidin-1-yl)-1,3,4-thiadiazol-2-yl]thio-3-cephem-4-carboxylic acid

IR (Nujol) : 3280, 1770, 1700, 1660, 1550, 1520, 1350,

1220 (cm^{-1})

NMR (DMSO-d_6, δ) : 1.9 - 2.1 (4H, m), 3.3 - 3.7 (8H, m),

5.16 (1H, d, J=5Hz), 5.71 (1H, dd, J=5Hz and 8Hz),

7.1 - 7.4 (5H, m), 9.17 (1H, d, J=8Hz), 14.0 (1H, br s)

FAB-Mass (m/z) = 504.1 ($M + H^+$)

Example 120

7β-(2-Phenylacetamido)-3-[5-morpholino-1,3,4-thiadiazol-2-yl]thio-3-cephem-4-carboxylic acid

IR (Nujol) : 3280, 1770, 1700, 1660, 1540, 1510, 1350,

1310, 1260, 1240, 1220 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.3 - 3.8 (12H, m),
5.16 (1H, d, J=5Hz), 5.72 (1H, dd, J=5Hz and 8Hz),
7.2 - 7.4 (5H, m), 9.18 (1H, d, J=8Hz), 14.0 (1H, br s)

FAB-Mass (m/z) = 520.2 ($M + H^+$)

Example 121

To a solution of benzhydryl 7β-(2-phenylacetamido)-3-[5-(2-hydroxybenzylidene)amino-1,3,4-triazol-2-yl]thio-3-cephem-4-carboxylate (0.70 g) in tetrahydrofuran (7 ml) was added 1N-hydrochloric acid (0.5 ml) under ice-cooling. The mixture was stirred at the same temperature for an hour. To the reaction mixture were added 1N-sodium hydroxide solution (0.5 ml), ethyl acetate (30 ml) and water (20 ml). The organic layer was washed with water and a saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was triturated with diethyl ether to give benzhydryl 7β-(2-phenylacetamido)-3-(5-amino-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate (396 mg).

NMR (DMSO-d_6, δ) : 3.4 - 3.7 (4H, m), 5.21 (1H, d, J=5Hz),
5.70 (1H, dd, J=5Hz and 8Hz), 6.29 (2H, br s),
6.91 (1H, s), 7.1 - 7.6 (15H, m), 9.15 (1H, d, J=8Hz),
12.46 (1H, br s)

FAB-Mass (m/z) = 599.1

Example 122

To a solution of benzhydryl 7β-(2-phenylacetamido)-3-(5-amino-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylate (370 mg) in a mixture of dichloromethane (1.2 ml) and anisole (0.4 ml) was added trifluoroacetic acid (0.8 ml) under ice-cooling. The mixture was stirred at the same temperature for 70 minutes. The reaction mixture was poured into diisopropyl ether (30 ml). The precipitate was collected by filtration and dried in vacuo. The precipitate was dissolved in a mixture of an aqueous sodium hydrogencarbonate solution (30 ml) and tetrahydrofuran (10 ml). The solution was washed twice with ethyl acetate (20 ml). The aqueous layer was adjusted to pH 2 with 1N-hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, and dried to give 7β-(2-phenylacetamido)-3-(5-amino-1,3,4-triazol-2-yl)thio-3-cephem-4-carboxylic acid (198 mg).

NMR (DMSO-d_6, δ) : 3.4 - 3.7 (2H, m),
3.46 and 3.56 (2H, ABq, J=17Hz),
5.14 (1H, d, J=5Hz), 5.61 (1H, dd, J=5Hz and 8Hz),
6.23 (2H, br s), 7.27 (5H, m), 9.10 (1H, d, J=8Hz),
12.4 (1H, br s)

FAB-Mass (m/z) = 433.0 ($M + H^+$)

Example 123

7β-(2-Phenylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-yl) thio-3-cephem-4-carboxlic acid was prepared according to a method similar to that of Preparation 3 from 7β-(2-

phenylacetamido)-3-methanesulfonyloxy-3-cephem-4-carboxlic and 2-mercapto-5-methyl-1,3,4-thiadiazole.

NMR (DMSO-d_6, δ) : 2.72 (3H, s), 3.4 - 3.6 (2H, m), 3.43 and 3.84 (2H, ABq, J=18Hz), 5.21 (1H, d, J=5Hz), 5.77 (1H, dd, J=5Hz and 8Hz), 7.1 - 7.4 (5H, m), 9.23 (1H, d, J=8Hz)

Example 124

To a suspension of 7β-amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid (200 mg) in tetrahydrofuran (4 ml) was added N-trimethylsilylacetamide (730 mg) and stirred at room temperature for 40 minutes to give a clear solution. To the solution was added dropwise a solution of phenylacetyl chloride (88 μl) in tetrahydrofuran (1 ml) at a temperature above -14℃ for 2 minutes. The mixture was stirred at -14 to -5℃ for 50 minutes. To the mixture were added water (5 ml) and ethyl acetate (15 ml). The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. The residue was triturated with ethyl acetate to give 7β-(2-phenylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid (150 mg).

IR (Nujol) : 3280, 1770, 1710, 1650, 1520, 1340, 1220 cm^{-1}

NMR (DMSO-d_6, δ) : 2.72 (3H, s), 3.48 and 3.57 (2H, ABq, J=14Hz), 3.53 and 3.85 (2H, ABq, J=18Hz), 5.22 (1H, d, J=5Hz), 5.78 (1H, dd, J=5Hz and 8Hz),

7.2 - 7.4 (5H, m), 9.22 (1H, d, J=8Hz)

Example 125

Phosphorus oxychloride (82 μl) was added dropwise to a mixture of N,N-dimethylformamide (67.3 μl) and ethyl acetate (0.2 ml) under ice-cooling. After being stirred at the same temperature for 10 minutes, the mixture was cooled until a precipitate appeared. To the suspension was added tetrahydrofuran (3 ml). The suspension was stirred at the same temperature for 30 minutes. To the suspension was added 4-fluorophenylacetic acid (103 mg). The mixture was stirred at the same temperature for 30 minutes to give an activated acid solution. On the other hand, to a suspension of 7β-amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid (200 mg) in tetrahydrofuran (3 ml) was added N-trimethylsilyl-acetamide (730 mg). The suspension was stirred at room temperature for 30 minutes to give a clear solution. To the solution was added the activated acid solution prepared above at -10℃ and the mixture was stirred at -10℃ to -5℃ for an hour. To the mixture were added water (5 ml) and ethyl acetate (12 ml). The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. The residue was triturated with ethyl acetate to give 7β-[2-(4-fluorophenyl) acetamido]-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid (166 mg).

IR (Nujol) ; 3290, 1770, 1710, 1660, 1530, 1510, 1410,

1350, 1220 (cm^{-1})

NMR (DMSO-d_6, δ) : 2.72 (3H, s),
3.48 and 3.56 (2H, ABq, J=14Hz),
3.53 and 3.84 (2H, ABq, J=18Hz),
5.21 (1H, d, J=5Hz), 5.77 (1H, dd, J=5Hz and 8Hz),
7.0 - 7.2 (2H, m), 7.2 - 7.4 (2H, m),
9.22 (1H, d, J=8Hz)

Example 126

To a solution of 7β-(2-phenylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid (3.0 g) in tetrahydrofuran (80 ml) was added a solution of sodium acetate (549 mg) in methanol (60 ml) at ambient temperature. The mixture was stirred at ambient temperature for 10 minutes. The resulting precipitate was collected by filtration and dried to give sodium 7β-(2-phenylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (2.3 g).

NMR (D_2O, δ) : 2.58 (3H, s),
3.21 and 3.63 (2H, ABq, J=17Hz), 3.5 - 3.6 (2H, m),
5.03 (1H, d, J=5Hz), 5.53 (1H, d, J=5Hz),
7.1 - 7.3 (5H, m)

Example 127

To a suspension of 7β-[2-(2-aminothiazol-4-yl)acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid (500 ml) in a mixutre of tetrahydrofuran (10 ml) and water (10 ml) was added sodium hydrogencarbonate (92 mg). The mixture was stirred at ambient temperature for an hour to give a clear

solution. The solution was concentrated in vacuo and freeze-dried to give sodium 7β-[2-(2-aminothiazol-4-yl)acetamido]-3-(1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (421 mg).

NMR (D_2O, δ) : 3.46 and 3.87 (2H, ABq, J=17Hz),
5.25 (1H, d, J=5Hz), 5.72 (1H, d, J=5Hz),
6.49 (1H, s), 9.41 (1H, s)

Example 128

To a solution of benzhydryl 7β-(2-phenylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (40 kg) in anisol (200 L) was added BF_3-etherate (18.5 kg) and dissolved at 0 - 10℃.

To the resultant solution were added BF_3-etherate (27.7 kg) and formic acid at 0 - 10℃. After stirring for 45 minutes, to the reaction mixture was added isopropyl alcohol (120 L). The reaction mixture and 12% aqueous sodium hydroxide (180 L) were added dropwise to water (400 L) during 20 - 40 minutes.

The aqueous layer was washed with ethyl acetate (200 L). An aqueous solution of hydrochloric acid was added dropwise in order to adjust the pH of the aqueous layer to 2.5. The resultant crystals were collected by centrifugation and washed with water (200 L).

To a suspension of this wet crystals in water (400 L) was added aqueous sodium hydroxide and the crystals were dissolved at 0 - 10℃ and pH below 8.0. An aqueous solution of hydrochloric acid was added in order to adjust the pH of the solution to 6.9 ± 0.1.

This aqueous solution was passed through the column packed with Diaion HP-20 resin and adsorbed onto the resin. The object compound was eluted. An aqueous solution of hydrochloric acid was added dropwise to the eluate in order to adjust the pH of the eluate to 2.5. The resultant crystals were collected by centrifugation and washed with water (120 L) and then dried under vacuum to give 7β-(2-phenylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid (19.9 kg).

The compounds of Example 129 to Example 131 were prepared according to a method similar to that of Preparation 3.

Example 129

Benzhydryl 7β-[2-(3-thienyl)acetamido]-3-(5-methylamino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 2.90 (3H, d, J=5Hz),
3.50 and 3.69 (2H, ABq, J=18Hz), 3.55 (2H, s),
5.23 (1H, d, J=5Hz), 5.80 (1H, dd, J=5Hz and 8Hz),
6.91 (1H, s), 7.04 (1H, m), 7.2 - 7.6 (12H, m),
8.11 (1H, q, J=5Hz), 9.17 (1H, d, J=8Hz)

FAB-Mass (m/z) = 636.0 ($M + H^+$)

Example 130

Benzhydryl 7β-[2-(2-thienyl)acetamido]-3-(5-methylamino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 2.89 (3H, d, J=5Hz),
3.50 and 3.68 (2H, ABq, J=18Hz), 3.77 (2H, s),
5.24 (1H, d, J=5Hz), 5.80 (1H, dd, J=5Hz and 8Hz),

6.8 - 7.0 (3H, m), 7.2 - 7.6 (11H, m),
8.11 (1H, q, J=5Hz), 9.23 (1H, d, J=8Hz)

FAB-Mass (m/z) = 636.1 (M + H$^+$)

Example 131

Benzhydryl 7β-[2-(2-thienyl)acetamido]-3-(5-amino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.51 and 3.69 (2H, ABq, q=17Hz),
3.76 (2H, s), 5.24 (1H, d, J=5Hz),
5.80 (1H, dd, J=5Hz and 8Hz),
6.8 - 7.0 (3H, m), 7.2 - 7.5 (1H, m),
7.69 (2H, br s), 9.23 (1H, d, J=8Hz)

FAB-Mass (m/z) = 622.0 (M + H$^+$)

Example 132

7β-[2-(3-Thienyl)acetamido]-3-(5-methylamino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2.

IR (Nujol) : 3250, 1770, 1640, 1520, 1330, 1250, 1220 (cm^{-1})

NMR (DMSO-d_6, δ) : 2.90 (3H, d, J=5Hz),
3.44 and 3.65 (2H, ABq, J=17Hz), 3.54 (2H, s),
5.17 (1H, d, J=5Hz), 5.71 (1H, dd, J=5Hz and 8Hz),
7.01 (1H, dd, J=1Hz and 5Hz), 7.25 (1H, m),
7.4 - 7.5 (1H, m), 8.07 (1H, q, J=5Hz),
9.13 (1H, d, J=8Hz)

FAB-Mass (m/z) = 470.0 (M + H$^+$)

Example 133

To a solution of benzhydryl 7β-[2-(2-thienyl)acetamido]-3-(5-methylamino-1,3,4-thiadiazol-2-yl)-3-cephem-4-carboxylate (1.32 g) in a mixture of dichloromethane (3.9 ml) and anisole (1.3 ml) was added trifluoroacetic acid (2.6 ml) under ice-cooling. The mixture was stirred at the same temperature for 70 minutes. The reaction mixture was poured into diisopropyl ether (60 ml). The precipitate was collected by filtration and dried in vacuo. The precipitate was dissolved in a mixture of an aqueous sodium hydrogencarbonate solution (30 ml) and tetrahydrofuran (10 ml). The solution was washed with ethyl acetate (20 ml). To the aqueous layer was added a mixture of tetrahydrofuran (10 ml) and ethyl acetate (30 ml), and the mixture was adjusted to pH 2.5 with 1N-hydrochloric acid. The mixture was stirred under ice-cooling for 30 minutes. The resulting precipitate was collected by filtration, washed successively with a mixture of tetrahydrofuran (10 ml) and ethyl acetate (20 ml), water and n-hexane, dried over in vacuo to give 7β-[2-(2-thienyl)acetamido]-3-(5-methylamino-1,3,4-thiadiazol-2-yl)-3-cephem-4-carboxylic acid (635 mg).

IR (Nujol) : 3300, 1780, 1660, 1530, 1400, 1350, 1260, 1240 (cm^{-1})

NMR (DMSO-d_6, δ) : 2.90 (3H, d, J=5Hz), 3.45 and 3.65 (2H, ABq, J=17Hz), 3.75 (2H, s), 5.18 (1H, d, J=5Hz), 5.72 (1H, dd, J=5Hz and 8Hz), 6.9 - 7.0 (2H, m), 7.36 (1H, dd, J=1Hz and 5Hz), 8.06 (1H, q, J=5Hz), 9.19 (1H, d, J=8Hz)

Example 134

7β-[2-(2-Thienyl)acetamido]-3-(5-amino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2.

IR (Nujol) : 3250, 1760, 1650, 1530, 1330, 1260, 1230 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.45 and 3.65 (2H, ABq, J=17Hz),
3.75 (1H, s), 5.18 (1H, d, J=5Hz),
5.71 (1H, dd, J=5Hz and 8Hz), 6.9 - 7.0 (2H, m),
7.36 (1H, dd, J=1.5Hz and 4.8Hz), 7.63 (2H, br s),
9.19 (1H, d, J=8Hz)

FAB-Mass (m/z) = 456.0 ($M + H^+$)

Example 135

To a solution of benzhydryl 7β-(2-phenylacetamido)-3-(5-amino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (1.5 g) in tetrahydrofuran (23 ml) was added dropwise acetyl chloride (191 μl) under ice-cooling. The mixture was stirred at the same temperature for 40 minutes. To the mixture was added dropwise pyridine (197 μl) at the same temperature, and the mixture was stirred at the same temperature for 30 minutes. To the reaction mixture were added water (50 ml) and ethyl acetate (50 ml). The organic layer was washed with water and a saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. The residue was triturated with diethyl ether to give benzhydryl 7β-(2-phenylacetamido)-3-(5-acetylamino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylate (1.33 g).

NMR (DMSO-d_6, δ) : 2.21 (3H, s),
3.48 and 3.57 (2H, ABq, J=14Hz),
3.54 and 3.80 (2H, ABq, J=18Hz),
5.25 (1H, d, J=5Hz), 5.85 (1H, dd, J=5Hz and 8Hz),
6.98 (1H, s), 7.1 - 7.5 (15H, m), 9.31 (1H, d, J=8Hz),
12.79 (1H, s)

FAB-Mass (m/z) = 658.1 ($M + H^+$)

Example 136

7β-(2-Phenylacetamido)-3-(5-acetylamino-1,3,4-thiadiazol-2-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2.

IR (Nujol) : 3260, 3180, 1780, 1680, 1650, 1530, 1300, 1220 (cm^{-1})

NMR (DMSO-d_6, δ) : 2.20 (3H, s), 3.4 - 3.6 (2H, m),
3.48 and 3.77 (2H, ABq, J=18Hz),
5.20 (1H, d, J=5Hz), 5.76 (1H, dd, J=5Hz and 8Hz),
7.1 - 7.4 (5H, m), 9.26 (1H, d, J=8Hz), 12.8 (1H, s)

FAB-Mass (m/z) = 492.1 ($M + H^+$)

The compounds of Example 137 to Example 143 were prepared according to a method similar to that of Preparation 3.

Example 137

Benzhydryl 7β-(2-phenylacetamido)-3-(1,2,4-thiadiazol-5-yl)thio-3-cephem-4-carboxylate

NMR ($CDCl_3$, δ) : 3.65 (2H, d, J=2.72Hz),
3.47 and 3.85 (2H, ABq, J=18.1Hz)

5.08 (1H, d, J=5.1Hz),

5.93 (1H, dd, J=5.1Hz and 9.0Hz)

6.15 (1H, d, J=9.0Hz), 6.97 (1H, s),

7.1 - 7.5 (15H, m), 8.48 (1H, s)

APCI-Mass (m/z) = 601 ($M + H^+$)

Example 138

Benzhydryl 7β-(2-phenylacetamido)-3-(thiophen-2-yl)thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.32 (2H, s), 3.53 (2H, d, J=2.7Hz),

5.18 (1H, d, J=4.7Hz),

5.70 (1H, dd, J=4.7Hz and 8.3Hz), 6.95 (1H, s)

7.1 - 7.6 (17H, m), 7.88 (1H, d, J=4.1Hz),

9.12 (1H, d, J=8.3Hz)

Example 139

Benzhydryl 7β-(2-phenylacetamido)-3-(benzothiazol-2-yl)-thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.55 (2H, d, J=4.1Hz),

3.75 and 4.02 (2H, ABq, J=17.9Hz),

5.33 (1H, d, J=5.1Hz),

5.89 (1H, dd, J=5.1Hz and 8.3Hz), 6.96 (1H, s)

7.1 - 8.1 (19H, m), 9.31 (1H, d, J=8.3Hz)

Example 140

Benzhydryl 7β-(2-phenylacetamido)-3-(pyrazol-4-yl)thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.31 (2H, d, J=4.0Hz),

3.53 (2H, d, J=2.6Hz), 5.12 (1H, d, J=4.6Hz),

5.65 (1H, dd, J=4.6Hz and 8.3Hz), 6.92 (1H, s)
7.1 - 7.7 (16H, m), 8.06 (1H, s),
9.09 (1H, d, J=8.3Hz), 13.39 (1H, s)

Example 141

Benzhydryl 7β-(2-phenylacetamido)-3-(5-methyl-1,3,4-oxadiazol-2-yl)thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.32 (3H, s), 3.54 (2H, s),
3.76 and 3.99 (2H, ABq, J=18.1Hz),
5.26 (1H, d, J=4.9Hz),
5.82 (1H, dd, J=4.9Hz and 8.4Hz),
6.92 (1H, s), 7.2 - 7.6 (15H, m),
9.21 (1H, d, J=8.4Hz)

Example 142

Benzhydryl 7β-(2-phenylacetamido)-3-(5-isoquinolyl)thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.28 and 3.38 (2H, ABq, J=17.4Hz),
3.51 (2H, d, J=2.7Hz), 5.23 (1H, d, J=4.8Hz),
5.77 (1H, dd, J=4.8Hz and 8.4Hz), 6.99 (1H, s),
7.1 - 7.5 (15H, m), 7.73 (1H, t, J=7.9Hz),
7.86 (1H, s), 7.89 (1H, s), 8.23 (1H, d, J=8.1Hz),
8.59 (1H, d, J=6.0Hz), 9.19 (1H, d, J=8.4Hz),
9.42 (1H, s)

Example 143

Benzhydryl 7β-(2-phenylacetamido)-3-(2-amino-thiazol-5-yl)thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.4 - 3.7 (4H, m),

5.17 (1H, d, J=4.6Hz),

5.68 (1H, dd, J=4.6Hz and 8.3Hz), 6.91 (1H, s),

7.2 - 7.7 (18H, m), 9.11 (1H, d, J=8.3Hz).

APCI-Mass (m/z) = 615 ($M + H^+$)

The compounds of Example 144 to Example 148 were prepared according to a method similar to that of Example 2.

Example 144

7β-(2-Phenylacetamido)-3-(1,2,4-thiadiazol-5-yl)thio-3-cephem-4-carboxylic acid

IR (KBr) : 1790, 1724, 1666, 1531 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.54 (2H, d, J=4.5Hz),

3.69 and 4.01 (2H, ABq, J=17.8Hz),

5.27 (1H, d, J=5.1Hz),

5.84 (1H, dd, J=5.1Hz and 8.4Hz),

7.1 - 7.4 (5H, m), 8.80 (1H, s), 9.30 (1H, d, J=8.4Hz)

FAB-Mass (m/z) = 435.0 ($M + H^+$)

Example 145

7β-(2-Phenylacetamido)-3-(thiophen-2-yl)thio-3-cephem-4-carboxylic acid

IR (KBr) : 1767, 1632, 1531 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.37 (2H, s), 3.51 (2H, d, J=4.2Hz),

5.11 (1H, d, J=4.7Hz),

5.61 (1H, dd, J=4.7Hz and 8.3Hz), 7.1 - 7.5 (7H, m),

7.85 (1H, d, J=4.1Hz), 9.08 (1H, d, J=8.3Hz)

FAB-Mass (m/z) = 432.9 ($M + H^+$)

Example 146

7β-(2-Phenylacetamido)-3-(benzothiazol-2-yl)thio-3-cephem-4-carboxylic acid

IR (KBr) : 1782, 1659, 1537 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.55 (2H, d, J=4.2Hz),
3.68 and 4.00 (2H, ABq, J=17.8Hz),
5.28 (1H, d, J=5.0Hz),
5.82 (1H, dd, J=5.0Hz and 8.4Hz),
7.1 - 7.6 (7H, m), 7.91 (1H, d, J=7.4Hz),
8.07 (1H, d, J= 7.2Hz), 9.27 (1H, d, J=8.4Hz)

FAB-Mass (m/z) = 483.8 ($M + H^+$)

Example 147

7β-(2-Phenylacetamido)-3-(pyrazol-4-yl)thio-3-cephem-4-carboxylic acid

IR (KBr) : 1759, 1659, 1537 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.27 (2H, d, J=2.7Hz),
3.48 and 3.54 (2H, ABq, J=13.9Hz),
5.04 (1H, d, J=4.6Hz),
5.55 (1H, dd, J=4.6Hz and 8.2Hz),
7.1 - 7.4 (5H, m), 7.85 (2H, s),
9.05 (1H, d, J=8.2Hz), 13.32 (1H, br s)

FAB-Mass (m/z) = 417.0 ($M + H^+$)

Example 148

7β-(2-Phenylacetamido)-3-(5-methyl-1,3,4-oxadiazol-2-yl)-thio-3-cephem-4-carboxylic acid

IR (KBr) : 1782, 1724, 1659, 1533 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.41 (3H, s), 3.53 (2H, d, J=5.6Hz),
3.65 and 3.95 (2H, ABq, J=18.0Hz),
5.18 (1H, d, J=4.9Hz),
5.72 (1H, dd, J=4.9Hz and 8.3Hz),
7.2 - 7.4 (5H, m), 9.17 (1H, d, J=8.3Hz)
FAB-Mass (m/z) = 433.0 (M + H^+)

Example 149

To a solution of benzhydryl 7β-(2-phenylacetamido)-3-(5-isoquinolyl)thio-3-cephem-4-carboxylate (820 mg) in dichloromethane (2.46 ml) were added trifluoroacetic acid (1.64 ml) and anisole (0.82 ml). After stirring at room temperature for 1 hour, the solution was poured into diisopropyl ether (40 ml). The resulting precipitate was collected by filtration. The obtained trifluoroacetic acid salt was dissolved in a mixture of water, tetrahydrofuran and ethyl acetate, and the solution was adjusted to pH 7.2 with an aqueous sodium hydrogencarbonate solution. To the separated aqueous layer was added ethyl acetate, the mixture was acidified to pH 2.5 with 1N-hydrochloric acid. The resulting precipitate was collected by filtration and washed successively with water, ethyl acetate and n-hexane to give 7β-(2-phenylacetamido)-3-(5-isoquinolyl)-thio-3-cephem-4-carboxylic acid (0.40 g).

IR (KBr) : 1772, 1655, 1527 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.18 and 3.35 (2H, ABq, J=17.3Hz),
3.50 (2H, d, J=3.3Hz), 5.16 (1H, d, J=4.8Hz),

5.68 (1H, dd, J=4.8Hz and 8.3Hz), 7.1 - 7.3 (5H, m),
7.75 (1H, t, J=7.5Hz), 7.94 (1H, d, J=6.2Hz),
8.04 (1H, d, J=6.0Hz), 8.22 (1H, d, J=8.2Hz),
8.64 (1H, d, J=6.0Hz), 9.15 (1H, d, J=8.3Hz),
9.42 (1H, s)

FAB-Mass (m/z) = 478.0 ($M + H^+$)

Example 150

7β-(2-Phenylacetamido)-3-(2-amino-thiazol-5-yl)thio-3-cephem-4-carboxylic acid was prepared according to a method similar to that of Example 2.

IR (KBr) : 1768, 1655, 1540, 1346 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.48 (2H, s), 3.52 (2H, d, J=4.5Hz),
5.10 (1H, d, J=4.6Hz),
5.59 (1H, dd, J=4.6Hz and 8.3Hz), 7.1 - 7.4 (6H, m),
7.56 (2H, br s), 9.08 (1H, d, J=8.3Hz)

FAB-Mass (m/z) = 449.0 ($M + H^+$)

The compounds of Example 151 to Example 153 were prepared according to a method similar to that of Preparation 2.

Example 151

Benzhydryl 7β-[2-(2-formamido-thiazol-4-yl)acetamido]-3-(1,2,3-thiadiazol-5-yl)thio-3-cephem-4-carboxylate

NMR ($CDCl_3$, δ) : 3.11 (2H, s), 3.69 (2H, s),
4.97 (1H, d, J=4.8Hz),
5.79 (1H, dd, J=4.8Hz and 8.4Hz), 6.72 (1H, s),
6.95 (1H, s), 7.1 - 7.5 (10H, m),

7.79 (1H, d, J=8.4Hz), 8.52 (1H, s), 8.55 (1H, s)

Example 152

Benzhydryl 7β-[2-(2-formamido-thiazol-4-yl)acetamido]-3-(thiazol-2-yl)thio-3-cephem-4-carboxylate

NMR ($CDCl_3$, δ) : 3.37 and 3.51 (2H, ABq, J=18.0Hz),
3.65 (2H, s), 4.97 (1H, d, J=4.9Hz),
5.88 (1H, dd, J=4.9Hz and 8.5Hz), 6.68 (1H, s),
6.94 (1H, s), 7.2 - 7.5 (10H, m),
7.45 (1H, d, J=3.4Hz), 7.85 (1H, d, J=3.4Hz),
8.04 (1H, d, J=8.5Hz), 8.48 (1H, s)

Example 153

Benzhydryl 7β-[2-(2-formamido-thiazol-4-yl)acetamido]-3-(benzothiazol-2-yl)thio-3-cephem-4-carboxylate

NMR (DMSO-d_6, δ) : 3.63 (2H, s),
3.76 and 4.03 (2H, ABq, J=17.8Hz),
5.35 (1H, d, J=5.1Hz),
5.92 (1H, dd, J=5.1Hz and 8.4Hz), 6.97 (1H, s),
6.97 (1H, s), 7.1 - 7.4 (10H, m),
7.4 - 7.6 (2H, m), 7.92 (1H, d, J=7.2Hz),
8.07 (1H, d, J=6.7Hz), 8.46 (1H, m),
9.24 (1H, d, J=8.4Hz)

The compounds of Example 154 to Example 156 were prepared according to a method similar to that of Preparation 1.

Example 154

Benzhydryl 7β-[2-(2-amino-thiazol-4-yl)acetamido]-3-

(1,2,3-thiadiazol-5-yl)thio-3-cephem-4-carboxylate

NMR ($CDCl_3$, δ) : 3.22 and 3.47 (2H, ABq, J=17.8Hz),
3.54 (2H, s), 5.01 (1H, d, J=5.0Hz),
5.13 (2H, br s), 5.92 (1H, dd, J=5.0Hz and 8.9Hz),
6.27 (1H, s), 6.94 (1H, s), 7.2 - 7.5 (10H, m),
8.09 (1H, d, J=8.9Hz), 8.48 (1H, s)

Example 155

Benzhydryl 7β-[2-(2-amino-thiazol-4-yl)acetamido]-3-(thiazol-2-yl)thio-3-cephem-4-carboxylate

NMR ($DMSO-d_6$, δ) : 3.38 (2H, s),
3.52 and 3.76 (2H, ABq, J=17.7Hz),
5.28 (1H, d, J=5.0Hz),
5.84 (1H, dd, J=5.0Hz and 8.5Hz), 6.24 (1H, s),
6.87 (2H, br s), 6.97 (1H, s), 7.1 - 7.5 (10H, m),
7.90 (1H, s), 7.90 (1H, s), 9.04 (1H, d, J=8.5Hz)

Example 156

Benzhydryl 7β-[2-(2-amino-thiazol-4-yl)acetamido]-3-(benzothiazol-2-yl)thio-3-cephem-4-carboxylate

NMR ($DMSO-d_6$, δ) : 3.40 (2H, s),
3.75 and 4.03 (2H, ABq, J=17.8Hz),
5.34 (1H, d, J=5.1Hz),
5.91 (1H, dd, J=5.1Hz and 8.4Hz), 6.26 (1H, s),
6.88 (2H, br s), 6.96 (1H, s), 7.1 - 7.4 (10H, m),
7.4 - 7.6 (2H, m), 7.92 (1H, d, J=7.1Hz),
8.07 (1H, d, J=6.8Hz), 9.10 (1H, d, J=8.4Hz)

The compounds of Example 157 to Example 159 were prepared according to a method similar to that of Example 2.

Example 157

7β-[2-(2-Amino-thiazol-4-yl)acetamido]-3-(1,2,3-thiadiazol-5-yl)thio-3-cephem-4-carboxylic acid

IR (KBr) : 1789, 1675, 1627 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.60 (2H, s),
3.58 and 3.83 (2H, ABq, J=17.6Hz),
5.23 (1H, d, J=5.0Hz),
5.82 (1H, dd, J=5.0Hz and 8.3Hz), 6.60 (1H, s),
8.83 (2H, br s), 8.93 (1H, s), 9.25 (1H, d, J=8.3Hz)

FAB-Mass (m/z) = 457.0 ($M + H^+$)

Example 158

7β-[2-(2-Amino-thiazol-4-yl)acetamido]-3-(thiazol-2-yl)-thio-3-cephem-4-carboxylic acid

IR (KBr) : 1772, 1684, 1623, 1558 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.56 (2H, s),
3.50 and 3.74 (2H, ABq, J=17.4Hz),
5.24 (1H, d, J=4.9Hz),
5.78 (1H, dd, J=4.9Hz and 8.3Hz), 6.57 (1H, s),
7.89 (1H, s), 8.69 (1H, br s), 9.22 (1H, d, J=8.3Hz)

FAB-Mass (m/z) = 456.0 ($M + H^+$)

Example 159

7β-[2-(2-Amino-thiazol-4-yl)acetamido]-3-(benzothiazol-2-yl)thio-3-cephem-4-carboxylic acid

IR (KBr) : 1774, 1655, 1543 (cm^{-1})

NMR (DMSO-d_6, δ) : 3.41 (2H, s),
3.67 and 4.00 (2H, ABq, J=17.6Hz),
5.29 (1H, d, J=5.1Hz),
5.83 (1H, dd, J=5.1Hz and 8.4Hz),
6.27 (1H, s), 6.96 (2H, br s), 7.3 - 7.6 (2H, m),
7.91 (1H, d, J=7.1Hz), 8.06 (1H, d, J=6.7Hz),
9.05 (1H, d, J=8.4Hz)
FAB-Mass (m/z) = 506.0 ($M + H^+$)

Formulation Example

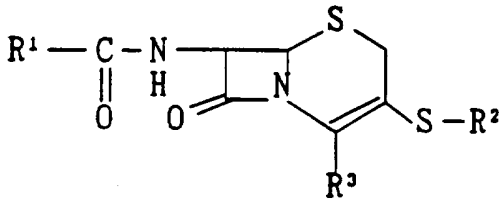
Tablets each having the following composition were manufactured.

7β-(2-Phenylacetamido)-3-(1,3,4-thiadiazol-2-yl)-thio-3-cephem-4-carboxylic acid (active ingredient)	25 mg
Lactose	150 mg
Corn starch	60 mg
Polyvinylpyrrolidone	10 mg
Magnesium stearate	5 mg

The active ingredient, lactose and corn starch were thoroughly blended and, then, wetted with 20% polyvinylpyrrolidone in ethanol. The composition was dried at 45°C. The granules thus obtained were mixed with magnesium stearate and the mixture was compressed into tablets.

CLAIMS

1. A pharmaceutical composition for the prophylactic and/or therapeutic treatment of the diseases caused by *Helicobacter pylori* infection which comprises, as an active ingredient, a cephem compound of the following formula :



(I)

wherein R^1 is aryl(lower)alkyl which may have one or more suitable substituent(s), arylthio(lower)alkyl, lower alkenylthio(lower)alkyl which may have one or more suitable substituent(s), or

a group of the formula:

R^4-A- or R^4-S-A-

in which R^4 is heterocyclic group which may have one or more suitable substituent(s), and

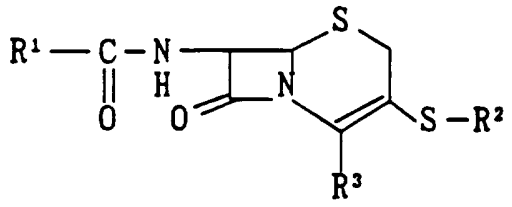
A is lower alkylene which may have one or more suitable substituent(s) or lower alkenylene,

R^2 is heterocyclic group which may have one or more suitable substituent(s), or heterocyclic(lower)-alkyl, and

R^3 is carboxy or protected carboxy,

or a pharmaceutically acceptable salt thereof.

2. Use of a cephem compound of the following formula :



(I)

wherein R^1 is aryl(lower)alkyl which may have one or more suitable substituent(s), arylthio(lower)alkyl, lower alkenylthio(lower)alkyl which may have one or more suitable substituent(s), or
a group of the formula:

R^4-A- or R^4-S-A-

in which R^4 is heterocyclic group which may have one or more suitable substituent(s), and

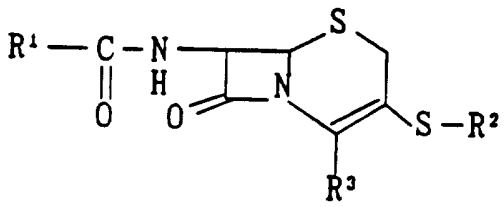
A is lower alkylene which may have one or more suitable substituent(s) or lower alkenylene,

R^2 is heterocyclic group which may have one or more suitable substituent(s), or heterocyclic(lower)-alkyl, and

R^3 is carboxy or protected carboxy,

or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the prophylactic and/or therapeutic treatment of the diseases caused by *Helicobacter pylori* infection.

3. A method for the prophylactic and/or therapeutic treatment of the diseases caused by *Helicobacter pylori* infection which comprises administering a cephem compound of the following formula :



(I)

wherein R^1 is aryl(lower)alkyl which may have one or more suitable substituent(s), arylthio(lower)alkyl, lower alkenylthio(lower)alkyl which may have one or more suitable substituent(s), or
a group of the formula:

R^4-A- or R^4-S-A-

in which R^4 is heterocyclic group which may have one or more suitable substituent(s), and

A is lower alkylene which may have one or more suitable substituent(s) or lower alkenylene,

R^2 is heterocyclic group which may have one or more suitable substituent(s), or heterocyclic(lower)-alkyl, and

R^3 is carboxy or protected carboxy,

or a pharmaceutically acceptable salt thereof to human being or animals.

4. A pharmaceutical composition of claim 1, use of claim 2 or a method of claim 3, in which the cephem compound (I) is the one wherein

R^1 is phenyl(lower)alkyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of halogen, nitro, hydroxy and amino;
phenylthio(lower)alkyl;
lower alkenylthio(lower)alkyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of cyano and acyl; or
a group of the formula:

R^4-A- or R^4-S-A-

in which R^4 is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s);
unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 suitable substituent(s) selected from the group consisting of amino, acylamino and lower alkyl; or
unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s);

A is lower alkylene which may have 1 to 3 lower alkoxyimino; or
lower alkenylene; and

R^2 is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have 1 to 3 suitable substituent(s) selected from the group consisting of lower alkyl and amino;
unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 suitable substituent(s) selected from the group consisting of lower alkyl, amino, acylamino, mono or di(lower)-alkylamino, pyrrolidinyl and morpholinyl;
unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have 1 or 2 lower alkyl;
unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s);
unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s); or
lower alkyl substituted with unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s).

5. A pharmaceutical composition of claim 4, use of claim 4 or a method of claim 4, in which the cephem compound (I) is the one

wherein

R^1 is phenyl(lower)alkyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of halogen, nitro, hydroxy and amino;

phenylthio(lower)alkyl;

lower alkenylthio(lower)alkyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of cyano and carbamoyl; or

a group of the formula:

R^4-A- or R^4-S-A-

in which R^4 is pyridyl;

tetrazolyl;

thiazolyl which may have 1 or 2 suitable substituent(s) selected from the group consisting of amino, lower alkanoylamino and lower alkyl; or

thienyl;

A is lower alkylene which may have 1 to 3 lower alkoxyimino; or

lower alkenylene;

R^2 is triazolyl which may have 1 or 2 suitable substituent(s) selected from the group consisting of lower alkyl and amino;

thiadiazolyl which may have suitable substituent(s) selected from the group consisting of lower alkyl, amino, lower alkylamino,

di(lower)alkylamino, lower alkanoylamino,
pyrrolidinyl and morpholinyl;
pyridyl;
pyrimidinyl;
pyrazolyl;
thiazolyl which may have amino;
oxadiazolyl which may have lower alkyl;
quinolyl;
isoquinolyl;
benzothiazolyl;
pyrazolyl(lower)alkyl; or
tetrazolyl which may have lower alkyl; and

R^3 is carboxy.

6. A pharmaceutical composition of claim 1, use of claim 2 or a method of claim 3, in which the cephem compound (I) is the one wherein

R^1 is arylthio(lower)alkyl, and

R^2 is a) unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have 1 to 3 suitable substituent(s); or

b) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 suitable substituent(s).

7. A pharmaceutical composition of claim 6, use of claim 6 or a method of claim 6, in which the cephem compound (I) is the one wherein

R^1 is phenylthio(lower)alkyl,

R^2 is triazolyl which may have lower alkyl or thiadiazolyl which may have lower alkyl, and

R^3 is carboxy.

8. A pharmaceutical composition of claim 1, use of claim 2 or a method of claim 3, in which the cephem compound (I) is the one wherein

R^1 is lower alkenylthio(lower)alkyl having cyano, and

R^2 is a) lower alkyl having unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

b) unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), or

c) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s).

9. A pharmaceutical composition of claim 8, use of claim 8 or a method of claim 8, in which the cephem compound (I) is the one wherein

R^1 is lower alkenylthio(lower)alkyl having cyano,

R^2 is triazolyl, pyrazolyl(lower)alkyl or thiadiazolyl and

R^3 is carboxy.

10. A pharmaceutical composition of claim 1, use of claim 2 or a method of claim 3, in which the cephem compound (I) is the one wherein

R^1 is aryl(lower)alkyl which may have 1 to 3 suitable substituent(s), and

R^2 is a) unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have 1 to 3 suitable substituent(s), or

b) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 suitable substituent(s).

11. A pharmaceutical composition of claim 10, use of claim 10 or a method of claim 10, in which the cephem compound (I) is the one wherein

R^1 is phenyl(lower)alkyl which may have a halogen,

R^2 is triazolyl which may have lower alkyl,

thiadiazolyl which may have a suitable substituent selected from the group consisting of lower alkyl, amino and lower alkylamino,

thiazolyl or pyridyl, and

R^3 is carboxy.

12. A pharmaceutical composition of claim 1, use of claim 2 or a method of claim 3, in which the cephem compound (I) is the one wherein

R^1 is a group of the formula:

R^4-A-

in which R^4 is a) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 suitable substituent(s), or

b) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s), and

A is lower alkylene, and

R^2 is a) unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have 1 to 3 suitable substituent(s), or

b) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 suitable substituent(s).

13. A pharmaceutical composition of claim 12, use of claim 12 or a method of claim 12, in which the cephem compound (I) is the one wherein

R^1 is thiazolyl(lower)alkyl which may have amino, or

thienyl(lower)alkyl,

R^2 is triazolyl, or thiadiazolyl which may have a suitable substituent selected from the group consisting of lower alkyl, amino and lower alkylamino, and

R^3 is carboxy.

14. A pharmaceutical composition of claim 1, use of claim 2 or a method of claim 3, in which the cephem compound (I) is the one wherein

R^1 is phenylthio(lower)alkyl, phenyl(lower)alkyl, or lower alkenylthio(lower)alkyl having cyano,

R^2 is triazolyl, thiadaizolyl, thiadiazolyl having lower alkyl or thiadiazolyl having amino, and

R^3 is carboxy.

15. A pharmaceutical composition of claim 14, use of claim 14 or a method of claim 14, in which the cephem compound (I) is the one wherein

R^1 is phenyl(lower)alkyl, and

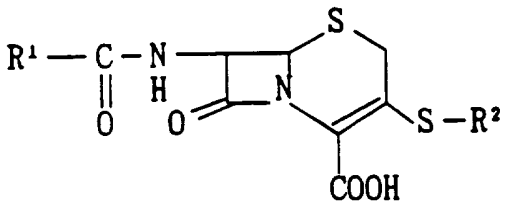
R^2 is thiadiazolyl having lower alkyl or thiadiazolyl having amino.

16. A pharmaceutical composition of claim 15, use of claim 15 or a method of claim 15, in which the cephem compound (I) is the one wherein

R^1 is benzyl, and

R^2 is 5-methyl-1,3,4-thiadiazol-2-yl or
5-amino-1,3,4-thiadiazol-2-yl.

17. A cephem compound of the following formula :



wherein R^1 is aryl(lower)alkyl which may have one or more suitable substituent(s), arylthio(lower)alkyl, lower alkenylthio(lower)alkyl which may have one or more suitable substituent(s), or
a group of the formula:

R^4-A- or R^4-S-A-

in which R^4 is heterocyclic group which may have one or more suitable substituent(s), and

A is lower alkylene which may have one or more suitable substituent(s) or lower alkenylene, and

R^2 is heterocyclic group which may have one or more suitable substituent(s), or heterocyclic(lower)-alkyl,

or a salt thereof.

18. A compound of claim 17, wherein

R^1 is arylthio(lower)alkyl, and

R^2 is a) unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have 1 to 3 suitable substituent(s), or

b) unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 suitable substituent(s).

19. A compound of claim 18, wherein

R^1 is phenylthio(lower)alkyl, and

R^2 is triazolyl which may have lower alkyl or thiadiazolyl which may have lower alkyl.

20. A compound of claim 19, wherein

R^1 is phenylthiomethyl, and

R^2 is 1,2,4-triazol-3-yl, 1-methyl-1,3,4-triazol-2-yl, 1,3,4-thiadiazol-2-yl, 1,2,3-thiadiazol-5-yl or 5-methyl-1,3,4-thiadiazol-2-yl.

21. A compound of claim 17, wherein

R^1 is ethenylthiomethyl having cyano, and

R^2 is 1,2,4-triazol-3-yl, 1,2,3-triazol-5-yl, (pyrazol-4-yl)methyl, 1,3,4-thiadiazol-2-yl or 1,2,3-thiadiazol-5-yl.

22. A compound of claim 17, wherein

R^1 is benzyl which may have a halogen, and

R^2 is triazolyl, thiadiazolyl, thiadiazolyl having lower alkyl, thiadiazolyl having amino, thiadiazolyl having lower alkylamino, triazolyl having lower alkyl, thiazolyl or pyridyl.

23. A compound of claim 22, wherein

R^1 is benzyl, chlorobenzyl or fluorobenzyl, and

R^2 is 1,2,3-triazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl, 5-methyl-1,3,4-triazol-2-yl, 5-amino-1,3,4-thiadiazol-2-yl, 5-methylamino-1,3,4-thiadiazol-2-yl, 2-thiazolyl or 2-pyridyl.

24. A compound of claim 23, wherein

R^1 is benzyl, and

R^2 is 5-methyl-1,3,4-thiadiazol-2-yl or 5-amino-1,3,4-thiadiazol-2-yl.

25. A compound of claim 17, wherein

R^1 is thiazolylmethyl which may have amino or thienylmethyl, and

R^2 is triazolyl, thiadiazolyl, thiadiazolyl having methyl, thiadiazolyl having amino or thiadiazolyl having

lower alkylamino.

26. A compound of claim 25, wherein

R^1 is thiazol-4-yl-methyl, (2-amino-thiazol-4-yl)-methyl, 2-thienylmethyl or 3-thienylmethyl, and

R^2 is 1,2,4-triazol-3-yl, 1,3,4-thiadiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl, 5-amino-1,3,4-thiadiazol-2-yl, or 5-methylamino-1,3,4-thiadiazol-2-yl.

27. A product comprising the cephem compound (I) used in claim 1 or a pharmaceutically acceptable salt thereof and an acid secretion inhibitor as a combined preparation for simultaneous, separate or sequential use for the prevention and/or treatment of the diseases caused by *Helicobacter pylori* infection.

28. The cephem compound (I) used in claim 1 or a pharmaceutically acceptable salt thereof for adjuvant therapy of the diseases caused by *Helicobacter pylori* infection, with an acid secretion inhibitor.

29. Use of the cephem compound (I) used in claim 1 or a pharmaceutically acceptable salt thereof and an acid secretion inhibitor for the manufacture of medicament for simultaneous, separate or sequential use for the prevention and/or treatment of the diseases caused by *Helicobacter pylori* infection.

30. A product comprising the cephem compound (I) used in claim 1 and an acid secretion inhibitor for simultaneous, separate or sequential use as a medicament.

31. A pharmaceutical composition, comprising the cephem compound (I) used in claim 1 and an acid secretion inhibitor and optionally pharmaceutically acceptable carriers or excipients.

32. A pharmaceutical composition, characterized in that the composition is adapted for only oral administration and comprises, as an active ingredient, the cephem compound (I) used in claim 1 or a pharmaceutically acceptable salt thereof and an acid secretion inhibitor.

33. A product comprising:

a) the cephem compound (I) used in claim 1 or a pharmaceutically acceptable salt thereof, and,

b) an acid secretion inhibitor in a ratio by weight of:

a) to b) of from 0.01/1 to 100/1.

34. A method for treatment or inhibition of the diseases caused by *Helicobacter pylori* infection which comprises administering an effective amount of the cephem compound (I) used in claim 1

to a patient in need of said treatment or inhibition.

35. The method of claim 34 wherein the cephem compound (I) used in claim 1 is administered to said patient in combination with an acid secretion inhibitor in a ratio by weight of the cephem compound (I) used in claim 1 to an acid secretion inhibitor in the range of from 0.01/1 to 100/1.

36. A method for the veterinary treatment of an animal infected with *Helicobacter pylori* which comprises administering an effective amount of the cephem compound (I) used in claim 1 to an animal in need of said treatment.

37. The method of claim 36 wherein the cephem compound (I) used in claim 1 is administered to said animal in combination with an acid secretion inhibitor in a ratio by weight of the cephem compound (I) used in claim 1 to an acid secretion inhibitor in the range of from 0.01/1 to 100/1.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/JP 95/02505

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D501/36 A61K31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 009 008 (CIBA-GEIGY AG) 19 March 1980 see claims	1-26
X	FR,A,2 293 935 (ELI LILLY AND COMPANY) 9 July 1976 see claims	1-26
X	FR,A,2 282 895 (CIBA-GEIGY AG) 26 March 1976 see claims	1-26
X	FR,A,2 318 642 (SHIONOGI) 18 February 1977 see claims	1-26
X	US,A,5 162 521 (VITTORIO FARINA ET AL) 10 November 1992 see claims	1-26

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 February 1996	11.03.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Luyten, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/JP 95/02505

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 123 528 (LOVJI D. CAMA ET AL) 31 October 1978 *Column 1-6* ---	1-26
X	EP,A,0 504 404 (MEIJI SEIKA KAISHA LTD) 23 September 1992 *Page 5: lines 17-18* see claims ---	1-26
P,X	WO,A,95 26966 (MICROCIDE PHARMACEUTICALS) 12 October 1995 see claims ---	1-26
A	CHEMICAL ABSTRACTS, vol. 115, no. 1, 8 July 1991, Columbus, Ohio, US; abstract no. 4979s, page 487 ;column 2 ; see abstract & EUR. J. CLIN. MICROBIOL. INFECT.DIS., vol.9, no.9, 1990 pages 691 - 693 -----	31

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 95/02505

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 34-37 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

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

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

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

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

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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