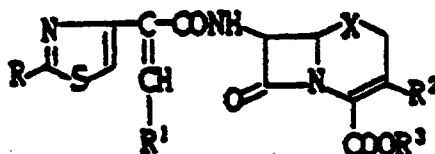


7-Beta-[2-(2-amino-4-thiazolyl)-2-alkenoylamino]-3-cephem-4-carboxylic Acid Ester Derivatives

The present invention relates to 7beta-[2-(2-amino-4-thiazolyl)-2-alkenoylamino]-3-cephem-4-carboxylic acid ester derivatives, to processes for the preparation thereof, and to composition containing them. The compounds are of use as antibacterial agents.

According to one aspect of the present invention there is provided a compound of the formula:



which exhibits very high oral availability when compared with free acid forms; and wherein R is amino or protected amino;

R¹ is methyl, ethyl, propyl, isopropyl, cyclopropyl, t-butyl, or cyclopentyl;

R² is hydrogen, chloro, methoxymethyl, propoxymethyl, isopropylloxymethyl, propenyloxymethyl, fluoroethoxymethyl, or carbamoyloxy-methyl;

R³ is a pharmaceutically or veterinarily acceptable ester group; and

X is sulfur or sulfinyl

The following explains the variable groups in the formula (I).

The amino protecting group in the protected amino R can be 1C to 8C alkanoyl or substituted alkanoyl (e.g., formyl,

acetyl, chloroacetyl, trifluoroacetyl), 7C to 20C aralkyl or substituted aralkyl (e.g., benzyl, diphenylmethyl, trityl, methoxybenzyl, nitrobenzyl, methylbenzyl), 1C to 8C substituted alkyl (e.g., trichloromethyl, trichloroethyl, tetrahydropyranyl), substituted arylthio, 1C to 8C alkylidene or substituted alkylidene, 7C to 14C aralkylidene or substituted aralkylidene (e.g., benzylidene, nitrobenzylidene), acyl (2C to 12C alkoxy-carbonyl or substituted alkoxy-carbonyl (in which the alkyl part can be methyl, ethyl, propyl, cyclopropylethyl, isopropyl, butyl, pentyl, hexyl, isobutyl, trichloroethyl, pyridylmethyl, cyclopentyl, cyclohexyl), 8C to 15C aralkoxy-carbonyl or substituted aralkoxy-carbonyl (in which the aralkyl part can be benzyl, diphenylmethyl, nitrobenzyl), dibasic acid acyl for example, trialkylsilyl, trialkylstannyl, acid addition salt group consisting of an amino group and an acid molecule, and other similar groups well known in the art. One or two of the protecting group can combine to the amino group.

The pharmaceutically or veterinarily acceptable ester group R^3 can be a group showing strong antibacterial potency on enteral or parenteral administration. Preferably, R^3 can be a 2C to 15C ester group, especially substituted alkyl ester, for example, straight, branched, cyclic or partially cyclic alkanoyloxyalkyl ester (e.g., acetoxymethyl ester, acetoxylethyl ester, pivaloyloxymethyl ester, pivaloyloxyethyl ester, cyclohexaneacetoxylethyl ester) or alkoxyformyloxyalkyl ester (e.g., ethoxycarbonyloxyethyl ester), alkoxyalkyl ester, 2-oxacycloalkyl ester, 2-oxo-1,3-dioxolylmethyl ester, (e.g., 4-methyl-2-oxo-1,3-dioxol-5-ylmethyl ester), or the like 1-oxygenated-1C to

12C-alkyl esters); substituted aralkyl ester (e.g., phenacyl ester, phthalidyl ester); aryl ester (e.g., phenyl ester, tolyl ester, xylyl ester, indanyl ester).

Some of the free acids of compound (I) and related

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compounds are claimed in Japanese Patent Application Kokai 57-93982, but none of pharmaceutically acceptable esters are disclosed. The present inventors found very high oral availability of the esters of the present invention.

- 5 The compounds (I) act as antibacterials against aerobic and anaerobic bacteria and are useful as an oral medicine. Characteristic features of compounds (I) are antibacterial potency against Gram-positive and Gram-negative bacteria, remarkable oral availability, excretion, distribution, etc.
- 10 For the prevention or treatment of human infections, compound (I) may be formulated by a conventional method and administered usually at a daily dose of 0.1 to 6 g (injection), 0.5 to 5 g (oral preparation), or 0.01 to 100 mg (topical or suppository preparation). The formulation may contain various additive,
- 15 other antibacterials. Further, compound (I) may be used as a starting material for producing other antibacterials or as a material for testing sensitivity of bacteria. The compound (I) having a protecting group is also useful as an intermediate for producing the said antibacterial compound (I).
- 20 Both of the geometric isomers at the double bond in the 7-side chain are antibacterials, but the isomer having the amido bond and R¹ group in cis position is a more potent antibacterial. The trans isomer is also useful as a starting material for producing the cis isomer.
- 25 Among the compounds (I), preferable ones for oral

availability are those having methyl, ethyl, propyl, isopropyl, or cyclopropyl as R¹, pivaloyloxymethyl or acetoxymethyl as R³, and propenyloxymethyl, fluoroethoxymethyl, methoxymethyl, isopropoxymethyl, carbamoyloxymethyl, hydrogen, or chloro as R².

Specific examples of preferable compounds include:

a compound wherein R is amino and wherein R¹ is ethyl R² is CH₂OCH₂CH=CH₂ R³ is pivaloyloxymethyl and X is sulfur or

R¹ is ethyl R² is CH₂OCH₂CH₂F R³ is pivaloyloxymethyl and X is sulfur or

R¹ is ethyl R² is CH₂OMe R³ is pivaloyloxymethyl and X is sulfur or

R¹ is ethyl R² is CH₂OCH(Me)₂ R³ is pivaloyloxymethyl and X is sulfur or

R¹ is ethyl R² is hydrogen R³ is pivaloyloxymethyl and X is sulfur or

R¹ is methyl R² is CH₂OCONH₂ R³ is pivaloyloxymethyl and X is sulfur or

R¹ is ethyl R² is CH₂OCONH₂ R³ is pivaloyloxymethyl and X is sulfur or

R¹ is ethyl R² is hydrogen R³ is ethoxy- carbonyloxyethyl and X is sulfur or

R¹ is ethyl R² is hydrogen R³ is pivaloyloxymethyl and X is sulfur or

R¹ is ethyl R² is hydrogen R³ is acetoxyethyl and X is sulfur or

R¹ is ethyl R² is hydrogen R³ is acetoxymethyl and X is sulfur or

R¹ is methyl R² is hydrogen R³ is pivaloyloxymethyl and X is sulfur or

R¹ is ethyl R² is CH₂OCONH₂ R³ is acetoxyethyl and X is sulfur or

R¹ is ethyl R² is CH₂OCONH₂ R³ is ethoxycarbonyloxyethyl and X is sulfur or

R¹ is tertiary butyl R² is hydrogen R³ is pivaloyloxymethyl and X is sulfur or

R¹ is cyclopropyl R² is hydrogen R³ is pivaloyloxymethyl and X is sulfur or

5 R¹ is ethyl R² is chloro R³ is pivaloyloxymethyl and X is sulfinyl or

R¹ is isopropyl R² is hydrogen R³ is pivaloyloxymethyl and X is sulfur or

10 R¹ is ethyl R² is hydrogen R³ is cyclohexaneacetoxymethyl and X is sulfur or

R¹ is ethyl R² is hydrogen R³ is 5-methyl-2-oxo-1,3-dioxol-5-ylmethyl and X is sulfur or

15 R¹ is propyl R² is hydrogen R³ is pivaloyloxymethyl and X is sulfur or

R¹ is ethyl R² is CH₂OCONH₂ R³ is pivaloyloxyethyl and X is sulfur or

R¹ is cyclopentyl R² is hydrogen R³ is pivaloyloxymethyl and X is sulfur.

20 The compound (I) having a protecting group is useful also as an intermediate for producing the said antibacterial compound (I).

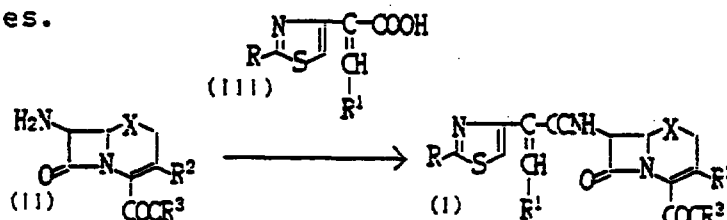
The compounds of this invention can, for example, be produced as follows. Generally,
25 protection and deprotection of a functional group (e.g., amino, hydroxy) in compounds (I) can be done conventionally according to methods described in various references, including patent publications.

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1) Amidation.

The amine (II) or its reactive derivative may be reacted with carboxylic acid (III) or its reactive derivative in a conventional manner to give the objective compound (I) or its derivatives.



typical reactive derivative of amine (II) have 7-amino activated by e.g. silyl (e.g., trimethylsilyl, methoxydimethylsilyl, t-butyldimethylsilyl), stannyl (e.g., trimethylstannyl), alkylene (as a part of the enamino of the amino with e.g., aldehyde, acetone, acetylacetone, acetoacetate ester, acetoacetonitrile, acetoacetanilide, cyclopentanedione, acetylbutyrolactone), alkylidene (e.g., 1-haloalkylidene, 1-haloaralkylidene, 1-alkoxyalkylidene, 1-alkoxyaralkylidene, 1-alkoxy-1-phenoxyalkylidene, alkylidene, aralkylidene), acid (as a salt of the amino with, e.g., mineral acid, carboxylic acid, sulfonic acid), easily removable acyl (e.g., alkanoyl), and include molecules protected at other functions of the molecule.

Carboxylic acid (III) may be used in the presence of a condensing reagent (carbodiimide (e.g., N,N'-diethylcarbodiimide, N,N'-dicyclohexylcarbodiimide), carbonyl compound (e.g., carbonyldiimidazole), isoxazolinium salt, acylamino compound

(e.g., 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline), for example. Reactive derivatives include acid anhydrides (e.g., symmetric anhydride, mixed anhydride [with a mineral acid (e.g., phosphoric acid, sulfuric acid, carbonic half ester), 5 organic acid (e.g., alkanic acid, aralkanic acid, sulfonic acid)], intramolecular acid anhydride (e.g., isocyanate, ketene), acid halide (i.e., a mixed anhydride of the acid with hydrogen halide)), acid halide, reactive ester (enol ester (e.g., vinyl ester, isopropenyl ester), aryl ester (e.g., 10 phenyl ester, halophenyl ester, nitrophenyl ester), heterocyclic ester (e.g., pyridyl ester, 1-hydroxybenzotriazolyl ester), ester with N-hydroxy compound, diacylhydroxylamine ester (ester with e.g., N-hydroxysuccinimide, N-hydroxyphthalimide), thiol ester (e.g., aralkylthiol ester, heterocyclic 15 thiol ester), for example], reactive amide (e.g., aromatic amide (e.g., amide with imidazole, triazole, 2-ethoxy-1,2-dihydroquinoline), diacylanilide], for example. The acid scavenger to be used with the said reactive derivatives include an inorganic base (e.g., oxide, hydroxide, carbonate, hydrogen 20 carbonate, alkali metal, alkaline earth metal), organic base (e.g., tertiary amine, aromatic base, oxirane (e.g., alkylene oxide, aralkylene oxide), pyridinium salt (e.g., tripyridiniumtriazine trichloride), adsorbent (e.g., Celite), for example.

2) Introduction of the 3-substituent.

Compound (I) but having a leaving group-substituted methyl at position 3 may be treated with a hetero aromatic thiol, aromatic base, or reactive derivative thereof giving objective compound 5 (I). Halogen, sulfonyloxy, alkanoyloxy, dihaloacetoxy, trihaloacetoxy, are the typical leaving groups. An alkali metal salt, ammonium salt, carboxylate ester,

are typical reactive derivatives of the thiol. The reaction may proceed at 0°C to 60°C even in anhydrous or 10 aqueous solvent. This reaction may be promoted by e.g. a dehydrating reagent, phosphoryl chlorides, thiocyanates.

Compound (I) having alkanoyloxymethyl or carbamoyloxymethyl at position 3 may be prepared from compound (I) but having hydroxymethyl at position 3 and protected carboxy at position 4 15 by treating with a reactive derivative of alkanonic acid or H-protected carbamic acid, and if required, deprotected at the stage where the objective group can remain in the target compound.

Compound (I) having no carbon atom attached to position 3 20 can be prepared by the reaction of 3-(hydroxy or oxo)-compound (if required, after activation by e.g. acylation, halogenation with e.g. a nucleophilic reagent, to give a 3-nucleophilic group substituted compound; or by elimination reaction of 3-(hydroxy, acyloxy, or halo)cepham compound by heat or with 25 base; reduction of a 3-(acyloxy or halo)-3-cephem compound

giving 3-unsubstituted compound for example, each in a conventional method.

3) Isomerization at position 7 side chain.

Each geometric isomer of Compound (I) can be transformed
5 into the other. This reaction may take place by the action of
acid, base or light. Here, the said acid includes a mineral
acid (e.g., hydrochloric acid, sulfuric acid, phosphoric acid),
carboxylic acid (e.g., formic acid, trifluoroacetic acid),
sulfonic acid (e.g., methanesulfonic acid, benzenesulfonic
10 acid), ; the said base includes an inorganic base (e.g.,
sodium hydroxide, sodium hydrogen carbonate, potassium
carbonate), strong organic base (e.g., triethylamine, potassium
t-butoxide, DBU).

4) Esterification of carboxy.

15 The carboxy group at position 4 can be esterified by a
known method, for example, a) A reaction of an alkali metal
salt of the carboxylic acid with a halide, sulfonate, for exam-
ple : of the ester group in the presence of an acid scavenger.
b) A reaction of the carboxylic acid or its reactive
20 derivative with alcohol having the ester group in the presence
of a condensing reagent. c) A reaction of the carboxylic acid
with a diazo compound having the ester group.

5) Introduction of an amino-protecting group.

When Compound (I) has amino in its molecule, the amino can be protected for example, as follows* a) an e.g. alkoxy-carbonyl, aralkoxycarbonyl, alkanoyl, group is introduced
5 by reacting 1 to 5 molar equivalents of halide, symmetric anhydride, or mixed anhydride of these groups in the presence of an acid scavenger at -30 to 50°C; b) an e.g. alkoxy-carbonyl, aralkoxycarbonyl, alkanoyl, arylsulfenyl, aralkyl, trialkyl-silyl, trialkylstannyl, group is introduced by reacting 1
10 to 5 molar equivalents of halide of the group in the presence of 1 to 10 molar equivalents of an acid scavenger in a solvent at -30 to 100°C for 1 to 10 hours; c) an e.g. tetrahydropyranyl, tetrahydrofuran, group is introduced by the reaction with e.g. dihydropyran, dihydrofuran, in a solvent for 1 to 10
15 hours. d) a trialkylsilyl group is introduced by the reaction with a derivative of disilazane, acetamido, for example (e.g., hexamethyldisilazane, bistrimethylsilylacetamide), in a conventional manner.

6) Deprotection of protected amino as R.

20 A protected amino group in compound (I) can be deprotected, for example, by the following conventional methods: a) an alkoxy-carbonyl group (e.g., tert-butoxycarbonyl), can be deprotected by reacting with an acid, for example, a strong acid (e.g., trifluoroacetic acid, trifluoromethanesulfonic

acid), or Lewis acid (e.g., aluminum chloride, tin chloride, titanium chloride, zinc chloride), if required in the presence of a cation scavenger (e.g., anisole, benzenethiol); b) an aralkoxycarbonyl group (e.g., carbobenzoxy, methylcarbobenzoxy, diphenylmethoxycarbonyl) or the like amino protecting group can be deprotected by reacting with a Lewis acid and a cation scavenger as given above; c) a lower alkanoyl group (e.g., formyl, acetyl, chloroacetyl), Schiff base forming group, i.e., a divalent carbon group (e.g., ethylidene, propylidene, benzylidene, substituted benzilidene), aralkyl (e.g., trityl, substituted trityl), arylthio (e.g., phenylsulfenyl), tetrahydropyranyl, silyl or stannyl (e.g., trimethylstannyl, trimethylsilyl), and other ones are deprotected by reacting with acid (e.g., hydrochloric acid, sulfuric acid, methanesulfonic acid); and d) some protecting groups have specific methods for deprotection (e.g., the reaction of thiourea or N-alkyldithiocarbamate for haloacetyl, hydrazine for a dibasic acid acyl, and phosphorus pentachloride and alkanol for amide).

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20 7) Sulfoxide formation

Compound (I) having sulfide group is oxidized, for example, by the following conventional methods. In this case, when the starting material has 2-double bond, the latter migrates to the position 3. a) peracid (an industrially available per-mineral

acid, percarboxylic acid, persulfonic acid,); b) ozone c) hydrogen peroxide; or d) peroxide (e.g., boron peroxide, nickel peroxide, sodium peroxide, urea peroxide) preferably in an inert solvent (e.g., halohydrocarbon, ester, water) to give the corresponding sulfoxide (I). These reactions may be accelerated with (e.g., phosphoric acid, polyphosphoric acid, phosphoric acid monoester, alkanolic acid, acid salts of VII group atom in the periodical table, e.g., tungstates). The reaction is preferably carried out with 1 to 2 molar equivalents of an oxidizing reagent at 0 to 35°C for 1 to 20 hours.

8) Reduction of the sulfoxide.

When compound (I) has sulfinyl in the molecule (e.g., when X is SO), it can be reduced by a conventional method to give the corresponding sulfide (I), for example, with 2 to 5 molar equivalents of a reducing reagent (e.g., trivalent phosphorus compound, stannous salt, iodide) in an inert solvent (e.g., dimethylformamide, dichloromethane, dioxane) at -20 to 50°C for 2 to 50 hours.

9) Reaction conditions

The reactions from 1) to 8) are usually carried out at -30°C to 100°C (preferably at -20°C to 50°C) for 10 minutes to 10 hours in a solvent, if required in a dry condition. Other conventional conditions may be applied to the reactions.

The typical reaction solvent can be a hydrocarbon (e.g., pentane, hexane, octane, benzene, toluene, xylene), halo-hydrocarbon (e.g., dichloromethane, chloroform, carbon tetrachloride, dichloroethane, trichloroethane, chlorobenzene),
5 ether (e.g., diethyl ether, methyl isobutyl ether, dioxane, tetrahydrofuran), ketone (e.g., acetone, methyl ethyl ketone, cyclohexanone), ester (e.g., ethyl acetate, isobutyl acetate, methyl benzoate), nitrohydrocarbon (e.g., nitromethane, nitrobenzene), nitrile (e.g., acetonitrile, benzonitrile),
10 amide (e.g., formamide, acetamide, dimethylformamide, dimethylacetamide, hexamethylphosphorotriamide), sulfoxide (e.g., dimethyl sulfoxide), carboxylic acid (e.g., formic acid, acetic acid, propionic acid), organic base (e.g., diethylamine, triethylamine, pyridine, picoline, collidine, quinoline),
15 alcohol (e.g., methanol, ethanol, propanol, hexanol, octanol, benzyl alcohol), water, or other industrial solvent or a mixture of two or more of these.

10) Work up

The objective products are recovered from the reaction
20 mixture by removing contaminant (e.g., unreacted starting materials, by-products, solvents) by conventional method (e.g., extraction, evaporation, washing, concentration, precipitation, filtration, drying), and by conventional purification (e.g., adsorption, elution,

distillation, precipitation, separation, chromatography).

The present invention further relates to a pharmaceutical or veterinary formulation comprising as active ingredient one or more compounds of formula (I) or physiologically acceptable salts thereof. Such compounds may be in unit dosage form and/or may include appropriate carriers, diluents or excipients.

EXAMPLES

The following non-limiting examples illustrate the embodiment of this invention. The physical constants of the products are listed on the tables. In the tables, IR shows cm^{-1} values and NMR shows delta values in ppm and J values shows coupling constants in Hz values.

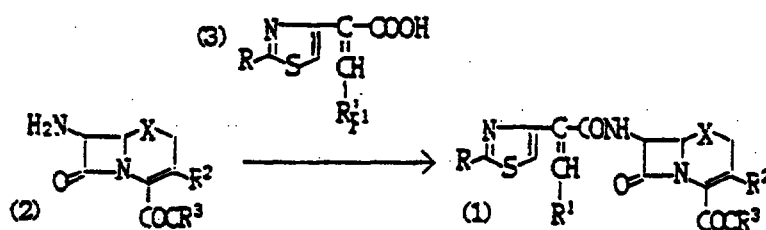
In Tables 1 and 2, all compounds have R^1 and amido groups in cis positions.

In the example, "part" shows weight per weight of starting beta-lactams and "molar equivalent" shows mole number per starting beta-lactams.

Work-up of the examples is done conventionally (if required after adding a solvent e.g., water, acid, dichloromethane) and the separated organic layer is washed with water, dried, and vacuum-distilled giving residue which may be purified conventionally (e.g., by chromatography over silica gel, crystallization, precipitation).

Example 1.

A 7beta-amino compound (2) (1 equivalent) is treated with carboxylic acid corresponding to the 7beta-side chain (3) or its reactive derivative to give the corresponding amide (1), for example, by an acylation represented by the following equation and as exemplified below:



- 1) In a mixture of dichloromethane (30 volumes), cyanuric chloride (1.1 equivalents), pyridine (4 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 5 minutes to 2 hours at -30°C to 10°C.
- 2) In a mixture of dichloromethane (3 volumes), phosphorus oxychloride (1.1 equivalents), triethylamine (1.5 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 20 minutes to 2 hours at -10°C to 10°C.
- 3) In a mixture of chloroform (3 volumes), toluene (1 volume), picoline (2 equivalents), oxalyl chloride (1 equivalent), and carboxylic acid (3) (1.1 equivalents), stirred for 10 minutes to 2 hours at -50°C to 10°C.
- 4) To a solution of 2-(2-t-butoxycarbonylaminothiazol-4-yl)-2-pentenoic acid (149 mg), triethylamine (83 microliter) in dichloromethane (5 ml) is added methanesulfonyl chloride

(0.04 ml) at -60°C. After stirring at the same temperature for 2 hours, a solution of 7beta-amino-3-cephem-4-carboxylic acid 1-acetoxyethyl ester (161 mg) and N-methylmorpholine (0.132 ml) in dichloromethane is added dropwise to the reaction mixture.

5 The mixture is stirred at -60 to -10°C for 3 hours, diluted with hydrochloric acid, and separated to obtain organic layer. The layer is washed with water, dried, and purified by column chromatography to give 7beta-[(2)-2-(2-t-butoxycarbonylamino-thiazol-4-yl)-2-pentenoylamino-3-cephem-4-carboxylic acid 10 1-acetoxyethyl ester (470 mg).

5) In a manner similar to that of above 1) to 4), the compounds listed on Table 2 are prepared.

Example 2 (Amino deprotection)

1) To a solution of a tertiary butoxycarbonylamino compound of 15 Table 2 in dichloromethane (0.3 to 3 parts) are added tri-fluoroacetic acid (0.3 to 3 parts) and anisole (0.5 to 5 parts). The mixture is stirred at -10 to 40°C for 10 minutes to 3 hours. The reaction mixture is concentrated to remove the solvent and reagents, and the resulting residue is washed with 20 benzene or ether to give the corresponding amino compound in Table 1. Yield: 70 to 80%.

2) To a solution of a chloroacetamido compound on Table 2 in a mixture of tetrahydrofuran (15 parts) and methanol (15 parts) are added thiourea or N-methyldithiocarbamate ester (4

equivalents) and sodium acetate (2 equivalents), and the mixture is kept at room temperature overnight. The mixture is concentrated, diluted with ethyl acetate, washed with water, dried, and concentrated to give the corresponding amino
5 compound on Table 1.

3) To a solution of a formamido or Schiff base compound of Table 2 in formic acid, acetic acid, or ethanol (10 parts) is added 1 to 3N-hydrochloric acid (0.1 to 3 parts), and the mixture is stirred at room temperature for 1 to 3 hours. The
10 reaction mixture is concentrated, diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate and water, dried, and concentrated to give the corresponding amino compound on Table 1.

4) To a solution of a formylamino, tertiary butoxycarbonyl-
15 amino, or benzyloxycarbonylamino compound on Table 2 in dichloromethane (5 to 9 parts) are added anisole (2 to 8 parts) and aluminum chloride, titanium tetrachloride, or tin tetrachloride (1 to 3 equivalents), and the mixture is stirred at -35 to 10 °C for 10 minutes to 24 hours. The reaction mixture
20 is extracted with diluted hydrochloric acid. The extract solution is passed through a column of adsorbent to remove salts, and eluate is concentrated to give the corresponding amino compound on Table 1.

5) A solution of 7beta-[(2)-2-(2-t-butoxycarbonylaminothiazol-
25 4-yl)-2-butenoyl]amino-3-carbamoyloxymethyl-3-cephem-4-

carboxylic acid pivaloyloxymethyl ester (160 mg) in trifluoroacetic acid (2 ml) is stirred at room temperature for 120 minutes and concentrated. To the resulting residue is added aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extract solution is purified by silica gel chromatography to give 7beta-[(2)-2-(2-aminothiazol-4-yl)-2-butenoyl]amino-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid pivaloyloxymethyl ester (75 mg).

6) In a manner similar to above 1) to 5), amino compounds on Table 1 are synthesized from the corresponding protected amino compounds.

Example 3. (Esterification)

(pivaloyloxymethyl ester)

1) To a solution of a potassium salt of a carboxylic acid in N,N-dimethylformamide (2 to 5 parts) is added iodoethyl pivalate (1 to 2 equivalents) at -50 to room temperature. After stirring for 15 minutes to 2 hours, the mixture is diluted with ethyl acetate, washed with ice water and aqueous sodium hydrogen carbonate, dried, and concentrated. The residue is crystallized from ethyl acetate to give the pivaloyloxymethyl ester. This pivaloyloxymethyl ester (250 mg), corn starch (150 mg), and magnesium stearate (5 mg) are mixed, granulated, and encapsulated in a conventional manner. This capsule (2 to 3 capsules) is given orally thrice a day to

treat a patient suffering from an infection caused by *Escherichia coli*.

In a similar manner, pivaloyloxymethyl compounds listed on Table 2 are prepared.

5 (acetoxymethyl ester)

2) In place of iodomethyl pivalate of above 1), bromomethyl acetate is used under the same condition to give the corresponding acetoxymethyl ester.

10 In a similar manner, acetoxymethyl compounds listed on Table 2 are prepared.

(acetoxymethyl ester)

3) In place of iodomethyl pivalate of above 1), bromoethyl acetate is used under the same condition to give the corresponding acetoxymethyl ester.

15 In a similar manner, acetoxymethyl compounds listed on Table 2 are prepared.

(1-pivaloyloxymethyl ester)

4) To a solution of 7beta-[2-(2-t-butoxycarbonylamino-4-thiazolyl)-2-pentenoylamino]-3-cephem-4-carboxylic acid (240
20 mg) in N,N-dimethylformamide (2.4 ml) is added potassium carbonate (138 mg) at -25 to 30°C and the mixture is stirred for several minutes. To the mixture is added pivaloyloxymethyl iodide (480 microliter) and the mixture is stirred for 60 minutes. The reaction mixture is diluted with ethyl acetate,
25 washed with aqueous saline and sodium hydrogen carbonate, and

water, dried and concentrated. The residue is chromatographed over silica gel to give the corresponding pivaloyloxyethyl ester (161 mg). Yield. 53%.

In a similar manner, pivaloyloxyethyl esters listed on
5 Table 2 are prepared.

(ethoxycarbonyloxyethyl ester)

5) To a solution of 7beta-[2-(2-t-butoxycarbonylamino-4-thiazolyl)-2-pentenoylamino]-3-cephem-4-carboxylic acid (240 mg) in N,N-dimethylformamide (2.4 ml) is added potassium
10 carbonate (138 mg) and 1-ethoxycarbonyloxyethyl bromide (150 mg) at -10°C. After stirring for 30 minutes, the mixture is diluted with ethyl acetate, washed with aqueous saline and sodium hydrogen carbonate, and water, dried and concentrated. The residue is chromatographed over silica gel to give the
15 corresponding ethoxycarbonyloxyethyl ester (191 mg). Yield. 64.1 %.

In a similar manner, ethoxycarbonyloxyethyl esters listed on Table 2 are prepared.

(5-methyl-2-oxo-1,3-dioxol-3-en-4-ylmethyl ester)

20 6) A mixture of 7beta-[(2)-2-(2-t-butoxycarbonylaminothiazol-4-yl)-2-pentenoylamino]-3-cephem-4-carboxylic acid (144 mg), potassium carbonate (83 mg), and dimethylformamide (3 ml) is stirred for 40 minutes at room temperature and mixed with 4-bromomethyl-5-methyl-1,3-dioxol-4-en-2-one (102 mg) in
25 dimethylformamide (1 ml). After stirring at 0°C for 30

minutes, the mixture is diluted with aqueous hydrochloric acid and extracted with ethyl acetate. The extract is purified by silica gel chromatography to give 7beta-[(2)-2-(2-t-butoxycarbonylaminothiazol-4-yl)-2-pentenoylamino-3-cephem-4-carboxylic acid 5-methyl-2-oxo-1,3-dioxol-4-en-4-ylmethyl ester (83 mg) as pale yellow powder.

(cyclohexaneacetoxylethyl ester)

- 7) To a solution of 7beta-[2-(2-t-butoxycarbonylamino-4-thiazolyl)-2-pentenoylamino-3-cephem-4-carboxylic acid (240 mg) in N,N-dimethylformamide (2.4 ml) is added potassium carbonate (138 mg) and 1-cyclohexaneacetoxylethyl iodide (355 mg) at -10°C. After stirring for 45 minutes, the mixture is diluted with ethyl acetate, washed with aqueous saline and sodium hydrogen carbonate, and water, dried and concentrated.
- 15 The residue is chromatographed over silica gel to give the corresponding cyclohexaneacetoxylethyl ester (152 mg).

In a similar manner, cyclohexaneacetoxylethyl esters listed on Table 2 are prepared.

- 8) In a manner similar to above, pharmacological esters on Table 2 can be prepared from the corresponding carboxylic acid.

Example 4 (Sulfoxide formation)

- 1) A sulfide is stirred with aqueous 30% hydrogen peroxide (1 equivalent) in a mixture of phosphoric acid (1 equivalent), dichloromethane (17 parts), and methanol (1 part) under ice

cooling for 10 minutes to give the corresponding sulfoxide.

2) To a solution of 7beta-[(2)-2-(2-t-butoxycarbonylamino-thiazol-4-yl)-2-pentenoyllamino-3-chloro-2-cephem-4-carboxylic acid pivaloyloxymethyl ester (410 mg) in dichloromethane (3 ml) 5 is added dropwise a solution of m-chloroperbenzoic acid (47.4 mg) in dichloromethane (1 ml) with stirring at 0°C. After stirring at the same temperature for 20 minutes, the reaction mixture is diluted with aqueous sodium hydrogen carbonate. The organic layer is separated, washed with water, dried, and 10 concentrated. The resulting residue is purified by silica gel column chromatography to give 7beta-[(2)-2-(2-t-butoxycarbonylaminothiazol-4-yl)-2-pentenoyllamino-3-chloro-3-cephem-4-carboxylic acid 1-oxide pivaloyloxymethyl ester (135 mg) as crystals.

15 Example 5 (Sulfoxide reduction)

1) To a solution of 7beta-[(2)-2-(2-t-butoxycarbonylamino-thiazol-4-yl)-2-pentenoyllamino-3-cephem-4-carboxylic acid 1-oxide pivaloyloxymethyl ester (61 mg) in dichloromethane (2 ml) is added phosphorus tribromide (19.3 microliter) at -30°C 20 and the mixture is stirred for 30 minutes. The reaction mixture is diluted with aqueous sodium hydrogen carbonate. The organic layer is separated, washed with water, dried, and concentrated. The residue is purified by silica gel column chromatography to give 7beta-[(2)-2-(2-t-butoxycarbonylamino-

thiazol-4-yl)-2-pentenoyllamino-3-cephem-4-carboxylic acid
pivaloyloxymethyl ester (51 mg).

- 2) In the reaction condition of above 1), phosphorus
tribromide in dichloromethane at -30°C for 30 minutes is
5 substituted by potassium iodide (6 molar equivalents) in
acetone (11 parts) for 1 hour under ice cooling or acetyl
chloride (13 equivalents) and stannous chloride (2.5 molar
equivalents) in N,N-dimethylformamide (12 parts) under ice
cooling for 21 hours to give the same sulfide.
- 10 3) In a manner similar to above, sulfides on Table 1 or Table
2 can be prepared by reducing the corresponding sulfoxides.

Example 6 (Acid addition salt)

- 1) [trifluoroacetate] A solution of 7beta-[(2)-2-(2-t-butoxy-
carbonylaminothiazol-4-yl)-2-pentenoyllamino-3-carbamoyloxy-
15 methyl-3-cephem-4-carboxylic acid pivaloyloxymethyl ester (450
mg) in trifluoroacetic acid (5 ml) is stirred at room
temperature for 120 minutes and then concentrated. The residue
is diluted with aqueous sodium hydrogen carbonate and extracted
with ethyl acetate. The extract is purified by silica gel
20 chromatography to give the corresponding free amine. This is
dissolved in dichloromethane (4 ml), mixed with trifluoroacetic
acid (1 ml), and vacuum-concentrated. The crystalline residue
is triturated in a mixture of ether and petroleum ether to give
7beta-[(2)-2-(2-aminothiazol-4-yl)-2-pentenoyllamino-3-carb-

amoyloxymethyl-3-cephem-4-carboxylic acid pivaloyloxymethyl ester trifluoroacetate (290 mg).

2) [Hydrochloride] A solution of 7beta-[(Z)-2-(2-t-butoxy-carbonylaminothiazol-4-yl)-2-pentenoylamino-3-cephem-4-carboxylic acid pivaloyloxymethyl ester (360 mg) in a mixture of anisole (2 ml) and trifluoroacetic acid (2 ml) is stirred at room temperature for 150 minutes and concentrated. The residue is dissolved in aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extract is purified by silica gel column chromatography to give 7beta-[(Z)-2-(2-aminothiazol-4-yl)-2-pentenoylamino-3-cephem-4-carboxylic acid pivaloyloxymethyl ester (250 mg). This is dissolved in dichloromethane, mixed with a solution of hydrochloric acid in ethyl acetate, and concentrated. The crystalline residue is washed with ether to give the hydrochloride of above ester.

3) In a manner similar to above, acid addition salts can be prepared from the corresponding amino compounds on Table 1.

Example 7

1) To a solution of aminothiazolyl compound in dichloromethane is added formic acid and acetic anhydride, chloroacetyl chloride and pyridine, or nitrobenzaldehyde and toluenesulfonic acid, and the mixture is stirred at -30 to room temperature for 1 to 3 hours. The mixture is treated in a usual manner to give the corresponding amino-protected compound as shown on Table 4.

Preparation 1

To a solution of 7beta-[(2)-2-(2-t-butoxycarbonylamino-thiazol-4-yl)-2-pentenoylamino-3-cephem-4-carboxylic acid 1-oxide diphenylmethyl ester (265 mg) in a mixture of anisole
5 (0.8 ml) and dichloromethane (1.5 ml) is added trifluoroacetic acid (1 ml) at 0°C with stirring. After 45 minutes' stirring, the mixture is concentrated in vacuum. The residue is washed with petroleum ether and ether to give 7beta-[(2)-2-(2-t-butoxycarbonylaminothiazol-4-yl)-2-pentenoylamino-3-cephem-
10 4-carboxylic acid 1-oxide (180 mg).

NMR (CDCl₃, -CD₃OD) δ : 1.11(t, J=7.5Hz, 3H), 1.55(s, 9H), 2.49(quintet, J=7.5Hz, 2H), 4.78(d, J=4.5Hz, 1H), 6.13(d, J=4.5Hz, 1H), 6.40(m, 1H), 6.45(t, J=7.5Hz, 1H), 6.79(s, 1H).

Preparation 2.

15 To a solution of 2-amino-1,3,4-thiadiazole-5-thiol (156 mg) in dimethylformamide (3 ml) is added a solution (0.3 ml) of 5.2N-sodium methoxide in methanol with stirring at 0°C to give the sodium salt. After neutralizing excess sodium methoxide with dry ice, a solution of 7beta-[(2)-2-(2-t-butoxycarbonyl-
20 aminothiazol-4-yl)-2-pentenoylamino-3-bromomethyl-3-cephem-4-carboxylic acid 1-oxide diphenylmethyl ester (590 mg) in dimethylformamide (2 ml) is added to the mixture. After stirring at 0°C for 30 minutes, the reaction mixture is poured into ice water and extracted with ethyl acetate to give crude

7beta-[(2)-2-(2-t-butoxycarbonylaminothiazol-4-yl)-2-pentenoyllamino-3-(2-amino-1,3,4-thiadiazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid 1-oxide diphenylmethyl ester in a quantitative yield.

5 NMR (CDCl₃) δ: 1.07(t, J=8Hz, 3H), 1.48(s, 9H), 2.52(quintet, J=8Hz, 2H), 3.61, 3.82(ABq, J=18Hz, 2H), 4.60, 3.70(ABq, J=18Hz, 2H), 4.55(d, J=5Hz, 1H), 5.60(brs, 2H), 6.15(dd, J=5Hz, J=9Hz, 1H), 6.40(t, J=8Hz, 1H), 6.74(s, 1H), 6.88(s, 1H), 7.20-7.45(m, 10H), 8.83(d, J=9Hz, 1H).

The ester group of this product is removed in a manner similar to that of Preparation 1 and the sulfoxide is reduced in a manner similar to that of Example 5-2) to give 7beta-[(2)-2-(2-t-butoxycarbonylaminothiazol-4-yl)-2-pentenoyllamino-3-(2-amino-1,3,4-thiadiazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

15 Preparation 3

(1) To a mixture of 2-(2-t-butoxycarbonylaminothiazol-4-yl)-pentenic acid (75 mg), triethylamine (0.041 ml), and dichloromethane (3 ml) is added dropwise methanesulfonyl chloride (0.02 ml) at -60°C with stirring. After stirring at 20 the same temperature for 5 hours, a solution of 7beta-amino-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid diphenylmethyl ester p-toluenesulphonate salt (153 mg) and N-methylmorpholine (0.05 ml) in dichloromethane (3 ml) is added dropwise to the mixture. After stirring for 3.5 hours, the mixture is quenched

with diluted hydrochloric acid. The organic layer is separated, washed with water, dried, and concentrated. The residue is purified by silica gel column chromatography to give 7beta-[(2)-2-(2-t-butoxycarbonylaminothiazol-4-yl)-2-penten-
5 oyllamino-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid diphenylmethyl ester (155 mg).

I R (CHCl₃) ν : 3430, 1785, 1726, 1672, 1543, 1326, 1158, 980.

NMR (CDCl₃) δ : 1.10(t, J=7.5Hz, 3H), 1.51(s, 9H), 2.55(quintet, J=7.5Hz, 2H), 3.16(s, 2H), 4.80, 4.97(ABq, J=14.4Hz, 2H), 4.82(s, 2H), 4.93(d, J=4.5Hz, 10 1H), 5.67(dd, J=4.5Hz, J=8Hz, 1H), 6.37(t, J=7.5Hz, 1H), 6.68(s, 1H), 6.80(s, 1H), 7.22-7.40(m, 10H), 7.82(d, J=8Hz, 1H), 10.0(brs, 1H).

(2) To an ice cold solution of 7beta-[(2)-2-(2-t-butoxycarbonylaminothiazol-4-yl)-2-pentenoyllamino-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid diphenylmethyl ester (855
15 mg), anisole (3.3 ml), and dichloromethane (2.3 ml) is added trifluoroacetic acid (1.93 ml) with stirring. After reacting at the same temperature for 30 minutes, the mixture is concentrated in vacuum. The residue is washed with petroleum ether and ether to give pale brown 7beta-[(2)-2-(2-t-butoxycarbonylaminothiazol-4-yl)-2-pentenoyllamino-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid (640 mg).

I R (CHCl₃) ν : 3425, 3360br, 1778, 1725, 1700, 1660, 1327, 1258, 1160, 1078.

NMR (CDCl₃, -CD₃OD) δ : 1.07(t, J=7.5Hz, 3H), 1.53(s, 9H), 2.41(quintet, J=7.5Hz, 2H), 3.43, 3.61(ABq, J=19.8Hz, 2H), 4.87, 5.10(ABq, J=14.4Hz, 2H), 5.08
25(d, J=5.0Hz, 1H), 5.85(d, J=5.0Hz, 1H), 6.41(t, J=7.5Hz, 1H), 6.80(s, 1H).

Experiment

Male rats weighing 20 to 25 gram are freely fed an aqueous solution of 40 % glucose and vitamins instead of chow diet for one day. Next day, a suspension of amoxicillin (the reference compound) or one of the esters (the test compounds) in aqueous 5 % arabic gum having a potency of 2 mg per milliliter was orally administered at a dose of 40 mg/kg each of the reference compound or the test compounds. Then, the blood is taken at 15 minutes intervals to determine the activity in the plasma. For the determination is used *Escherichia coli* for esters and *Micrococcus luteus* for amoxicillin by the agar plate dispersion method. The results are listed on the following table.

Table

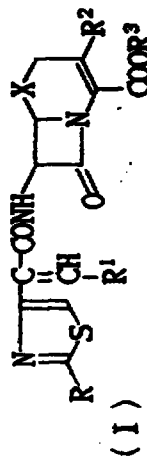
Maximum plasma level (gamma /ml) of Compound (I)

(in which R is amino and R'=pivaloyloxymethyl)

after oral administration to mice

No	R ¹	R ²	maximum serum level
1	Me	H	8.6
2	Me	CH ₃ COONH ₂	13.4
3	Et	H	14.1
4	Et	CH ₃ COONH ₂	9.3
amoxicillin			15.7

Table 1 Physical constants of pharmaceutical esters (1)



(Abbreviations) Ac=acetyl, AOE=acetoxyethyl, AOM=acetoxyethyl, BOC=t-butoxy-carbonyl, br=broad, Bu=butyl, Cbz=benzyloxycarbonyl, CHAE=cyclohexylacetoxymethyl, CPBA=m-chloroperbenzoic acid, cyc=cyclo-, DCM=dichloromethane, DMA=dimethylacetamide, DMF=dimethylformamide, DOL=4-methyl-2-oxo-1,3-dioxol-5-yl-methyl, ECE=ethoxycarbonyloxyethyl, Et=ethyl, Me=methyl, nd=not done, POE=pivaloyloxyethyl, POM=pivaloyloxyethyl, Pr=propyl, TFA=trifluoroacetic acid.

No	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃), cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
1	H ₂ N	Me	H	POM	S	nd	1.21(s, 9H), 1.33(d, J=7Hz, 3H), 3.40(dd, A of ABX, J=5Hz, J=18.9Hz, 1H), 3.60(dd, B of ABX, J=3Hz, J=18.9Hz, 1H), 5.03(d, J=5Hz, 1H), 5.80, 5.91(ABq, J=6Hz, 2H), 5.96(dd, J=5Hz, J=8Hz, 1H), 6.25(s, 1H), 6.49(q, J=7Hz, 1H), 6.59(dd, X of ABX, J=3Hz, J=5Hz, 1H), 8.40(d, J=8Hz, 1H).	2-1), 2-4)
2	H ₂ N	Me	CH ₂ COONH ₂	POM	S	3550, 3485, 3430, 3395, 1786, 1735, 1672, 1525, 1330, 1126.	1.21(s, 9H), 1.90(d, J=7Hz, 3H), 3.40, 3.52(ABq, J=18Hz, z, 2H), 4.76, 5.03(ABq, J=16.9Hz, 2H), 5.02(d, J=5Hz, 1H), 5.12(s, 2H), 5.54(brs, 2H), 5.77~5.95(m, 3H), 6.22(s, 1H), 6.45(q, J=7.0Hz, 1H), 8.45(d, J=9Hz, 1H).	2-5)
4	H ₂ N	Et	H	AOM	S	nd	1.05(t, J=8Hz, 3H), 2.11(s, 3H), 2.37(quintet, J=8Hz, 2H), 3.23~3.77(m, 2H), 5.02(d, J=5Hz, 1H), 5.26(s, 2H), 5.82, 5.92(ABq, J=6Hz, 2H), 5.98(dd, J=5Hz, J=9Hz, 1H), 6.32(s, 1H), 6.42(t, J=8Hz, 1H), 6.56~6.66(m, 1H), 8.10(d, J=9Hz, 1H).	2-1)

Table 1 Physical constants of pharmaceutical esters (2)

No	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃) cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
5	H ₂ N	Et	H	AOE	S	nd	1.05(t, J=8.0Hz, 3H), 1.54(d, J=6.0Hz, 3H), 2.07(s, 3H), 2.36(quintet, J=8.0Hz, 2H), 3.42(dd, A of ABX, J=7.0Hz, J=20Hz, 1H), 3.61(dd, B of ABX, J=4Hz, J=20Hz, 1H), 5.03(d, J=5Hz, 1H), 5.46(brs, 2H), 5.98(dd, J=5Hz, J=9Hz, 1H), 6.29(s, 1H), 6.42(t, J=8Hz, 1H), 6.58(dd, X of ABX, J=4.0Hz, J=7Hz, 1H), 6.99(q, J=6Hz, 1H), 8.19(d, J=9Hz, 1/2H), 8.26(d, J=9Hz, 1/2H).	2-1), 3-3)
6	H ₂ N	Et	H	POH	S	3475, 3380, 3325, 1783, 1750, 1674, 1522, 1285, 1123, 982.	1.02(t, J=7.5Hz, 3H), 1.20(s, 9H), 2.34(dq, J=7.5Hz, J=8Hz, 2H), 3.43(dd, A of ABX, J=7Hz, J=18.9Hz, 1H), 3.63(dd, B of ABX, J=3Hz, J=18.9Hz, 1H), 5.06(d, J=5Hz, 1H), 5.48(s, 2H), 5.84, 5.94(ABq, J=5.4Hz, 2H), 5.97(dd, J=5Hz, J=8Hz, 1H), 6.27(s, 1H), 6.42(t, J=8Hz, 1H), 6.63(dd, X of ABX, J=3Hz, J=7Hz, 1H), 8.36(d, J=8Hz, 1H).	2-1), 2-2), 2-3), 2-4), 3-1), 5-2)
7	H ₂ N HCl	Et	H	POH	S	3250, 2715br 1782, 1747, 1660, 1627, 1278, 1123, 982.	1.12(t, J=7.5Hz, 3H), 1.20(s, 9H), 2.37(quintet, J=7Hz, 2H), 3.75(dd, A of ABX, J=7Hz, J=19.8Hz, 1H), 3.71(dd, B of ABX, J=3.5Hz, J=19.8Hz, 1H), 5.17(d, J=5Hz, 1H), 5.82, 5.91(ABq, J=6.3Hz, 2H), 5.92(d, J=5Hz, 1H), 6.32(t, J=7.5Hz, 1H), 6.67(dd, X of ABX, J=3.5Hz, J=7.5Hz, 1H), 6.69(s, 1H).	6-2)

Table 1 Physical constants of pharmaceutical esters (3)

No	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃) cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
8	H ₂ N	Et	H	POE	S	nd	1.06(t, J=8Hz, 3H), 1.20(s, 9H), 1.53(d, J=5Hz, 3H), 2.38(quint-et, J=8Hz, 2H), 3.20-3.76(m, 2H), 5.02(d, J=5Hz, 1H), 5.23(brs, 2H), 5.87-6.06(m, 1H), 6.33(s, 1H), 6.42(t, J=8Hz, 1H), 6.52-6.62(m, 1H), 6.86-7.00(m, 1H), 7.96, 8.06(2xd, J=9Hz, 1H).	2-1)
9	H ₂ N	Et	H	ECE	S	nd	1.05(t, J=8Hz, 3H), 1.30(t, J=7Hz, 3H), 1.57(d, J=5Hz, 3H), 2.37(quintet, J=8Hz, 2H), 3.20-3.80(m, 2H), 4.20(q, J=7Hz, 2H), 5.01(d, J=5Hz, 1H), 5.23(brs, 2H), 5.96(dd, J=5Hz, J=9Hz, 1H), 6.33(s, 1H), 6.42(t, J=8Hz, 1H), 6.53-6.63(m, 1H), 6.80-7.00(m, 1H), 7.95(d, J=9Hz, 1H).	2-1)
10	H ₂ N	Et	H	DOL	S	3480, 3385, 3325, 1816, 1781, 1732, 1676, 1523, 1282, 1015.	1.05(t, J=7.5Hz, 3H), 2.19(s, 3H), 2.38(quintet, J=7.5Hz, 2H), 3.43(dd, A of ABX, J=6.0Hz, 1H), 3.70(dd, B of ABX, J=4.0Hz, J=19.8Hz, 1H), 4.95, 5.13(ABq, J=14Hz, 2H), 5.09(d, J=5Hz, 1H), 5.49(brs, 2H), 6.01(dd, J=5Hz, J=8.5Hz, 1H), 6.30(s, 1H), 6.44(t, J=7.5Hz, 1H), 6.63(dd, X of ABX, J=4Hz, J=6Hz, 1H), 8.35(d, J=8.5Hz, 1H).	2-1)

Table 1 Physical constants of pharmaceutical esters (4)

No	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃) cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
11	H ₂ N	Et	H	CHAE	S	nd	0.85-1.90(m, 11H), 1.06(t, J=8Hz, 3H), 1.53(d, J=5Hz, 3H), 2.20(d, J=6Hz, 2H), 2.38(quintet, J=8Hz, 2H), 3.20-3.76(m, 2H), 5.02(d, J=5Hz, 1H), 5.25(brs, 2H), 5.96(dd, J=5Hz, J=9Hz, 1H), 6.32(s, 1H), 6.42(t, J=8Hz, 1H), 6.53-6.63(m, 1H), 6.97(q, J=5Hz, 1H), 8.00, 8.05(2xd, J=9Hz, 1H).	2-1)
12	H ₂ N	Et	Cl	POM	S	3470, 3385, 3330, 1783, 1756, 1670, 1602, 1523, 1122, 1103.	1.05(t, J=7.5Hz, 3H), 1.22(s, 9H), 2.40(quintet, J=7.5 Hz, 2H), 3.51, 3.82(ABq, J=18.0Hz, 2H), 5.12(d, J=5.0 Hz, 1H), 5.27(bs, 2H), 5.83-6.01(m, 3H), 6.32(s, 1H), 6.41(t, J=7.5Hz, 1H), 8.27(d, J=8.0Hz, 1H).	2-1), 5-2)
13	H ₂ N	Et	Cl	POM	SO	3490, 3375, 1805, 1775, 1677, 1601, 1120, 987.	1.06(t, J=7.5Hz, 3H), 1.22(s, 9H), 2.47(quintet, J=7.5 Hz, 2H), 3.65, 3.87(ABq, J=18.0Hz, 2H), 4.66(d, J=5Hz, 1H), 5.47(brs, 2H), 5.86, 5.99(ABq, J=6Hz, 2H), 6.17 (dd, J=5Hz, J=10Hz, 1H), 6.38(s, 1H), 6.38(t, J=7.5Hz, 1H), 8.42(d, J=10Hz, 1H).	2-1)
14	H ₂ N	Et	CH ₂ OCH ₃	POM	S	3480, 3390, 2960, 1785, 1750, 1670, 1600, 1520, 1360, 1125.	1.06(t, J=8Hz, 3H), 1.22(s, 9H), 2.40(quintet, J=8Hz, 2H), 3.32(s, 3H), 3.56(s, 2H), 4.30(s, 2H), 5.06(d, J=5Hz, 1H), 5.23(brs, 2H), 5.90(s, 2H), 5.95(dd, J=5Hz, J=9Hz, 1H), 6.35(s, 1H), 6.45(t, J=8Hz, 1H), 8.06(d, J=9Hz, 1H).	2-1), 2-5)

Table 1 Physical constants of pharmaceutical esters (5)

No	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃) cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
15	H ₂ N	Et	CH ₃ O-i-Pr	POM	S	3470, 3370, 2950, 1775, 1740, 1670, 1595, 1360, 1115.	1.06(t, J=8Hz, 3H), 1.15(d, J=5Hz, 6H), 1.22(s, 9H), 2.37(quintet, J=8Hz, 2H), 3.57(s, 2H), 3.58(septet, J=5Hz, 1H), 4.35(s, 2H), 5.04(d, J=5Hz, 1H), 5.29(brs, 2H), 5.87(s, 2H), 5.92(dd, J=5Hz, J=9Hz, 1H), 6.32(s, 1H), 6.43(t, J=8Hz, 1H), 8.07(d, J=9Hz, 1H).	2-1)
16	H ₂ N	Et	CH ₃ O(pro- penyl)	POM	S	3480, 3390, 1785, 1750, 1675, 1600.	1.03(t, J=7Hz, 3H), 1.20(s, 9H), 2.17-2.52(m, 2H), 3.59(s, 2H), 3.97(m, 2H), 4.38(s, 2H), 5.08(d, J=5Hz, 1H), 5.13-5.36(m, 2H), 5.52(brs, 2H), 5.69-6.11(m, 4H), 6.28(s, 1H), 6.43(t, J=7Hz, 1H), 8.37(d, J=8Hz, 1H).	2-1)
17	H ₂ N	Et	CH ₃ OCH ₂ CH ₂ F	POM	S	3485, 3396, 1785, 1752, 1676, 1602, 1124.	1.05(t, J=8Hz, 3H), 1.23(s, 9H), 2.38(dq, J=8Hz, J=8Hz, 2H), 3.56(s, 2H), 3.66(dt, J=4.5Hz, J=28.8Hz, 2H), 4.40(s, 2H), 4.50(dt, J=4.5Hz, J=46.8Hz, 2H), 5.03(d, J=5Hz, 1H), 5.19(s, 2H), 5.85(s, 2H), 5.92(dd, J=5Hz, J=8.5Hz, 1H), 6.32(s, 1H), 6.41(t, J=8Hz, 1H), 8.02(d, J=8.5Hz, 1H).	2-1)

Table 1 Physical constants of pharmaceutical esters (6)

No	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃) cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
19	H ₂ N	Et	CH ₂ COONH ₂	AOE	S	3480, 3390, 1780, 1727, 1668, 1500, 1325, 1070.	1.05(t, J=7.5Hz, 3H), 1.53(d, J=6.0Hz, 3H), 2.07(s, 3H), 2.41(quintet, J=7.5Hz, 2H), 3.38, 3.55(ABq, J=15 Hz, 2H), 4.78, 5.02(ABq, J=13.5Hz, 2/2H), 4.81, 5.05 (ABq, J=13.5Hz, 2/2H), 4.99(s, 2H), 5.01(d, J=5.0Hz, 1H), 5.30(brs, 2H), 5.92(dd, J=5.0Hz, J=9Hz, 1H), 6.34 (s, 1H), 6.38(t, J=7.5Hz, 1H), 6.96(q, J=5Hz, 1/2H), 7.08(q, J=6.0Hz, 1/2H), 7.94(d, J=9.0Hz, 1/2H), 7.96 (d, J=9.0Hz, 1/2H).	2-1)
20	H ₂ N	Et	CH ₂ COONH ₂	POH	S	nd	1.05(t, J=8.0Hz, 3H), 1.23(s, 9H), 2.38(quintet, J=8 Hz, 2H), 3.44, 3.68(ABq, J=18.9Hz, 2H), 4.82, 5.08 (ABq, J=14.4Hz, 2H), 5.05(d, J=5.0Hz, 1H), 5.14(s, 2H), 5.51(s, 2H), 5.83-6.02(m, 3H), 6.34(s, 1H), 6.41 (t, J=8.0Hz, 1H), 8.17(d, J=8.5Hz, 1H).	2-1)
21	H ₂ N	Et	CH ₂ COONH ₂ TFA salt	POH	S	Anal. Calcd. (C ₂₁ H ₂₆ N ₂ O ₄ S ₂ F ₃): C, 44.05; H, 4.44; N, 10.28; F, 8.36. Found : C, 44.10; H, 4.62; N, 9.89; F, 8.40.		6-1)
22	H ₂ N	Et	CH ₂ COONH ₂	POE	S	3480, 3390, 2960, 1785, 1740, 1670, 1390, 1330, 1065.	1.08(t, J=8Hz, 3H), 1.20(s, 9H), 1.54(d, J=5Hz, 3H), 2.35(quintet, J=8Hz, 2H), 3.44, 3.58(ABq, J=18Hz, 2H), 4.80, 5.02(ABq, J=15Hz, 2H), 5.06(d, J=5Hz, 1H), 5.87, 5.92(2xd, J=5Hz, 1H), 6.36(s, 1H), 6.36(t, J=8Hz, 1H), 6.93, 7.02(2xq, J=5Hz, 1H). [CDCl ₃ +OD ₂]	2-1)

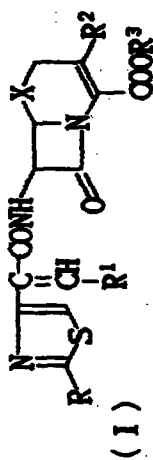
Table 1 Physical constants of pharmaceutical esters (7)

No.	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃) cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No.
23	H ₂ N	Et	CH ₂ CONH ₂	ECE	S	nd	1.06(t, J=7Hz, 3H), 1.30(t, J=7Hz, 3H), 1.56(d, J=6Hz, 3H), 2.35(quintet, J=7Hz, 2H), 3.50(brs, 2H), 4.22(q, J=7Hz, 2H), 4.82, 5.04(ABq, J=15Hz, 2H), 5.03, 5.06(2x d, J=5Hz, 1H), 5.86, 5.90(2x d, J=5Hz, 1H), 6.36(s, 1H), 6.36(t, J=7Hz, 1H), 6.86, 6.97(2x q, J=6Hz, 1H). [CDCl ₃ +CD ₃ OD]	2-1)
30	H ₂ N	n-Pr	H	POM	S	3480, 3390, 1790, 1750, 1675, 1640, 1600.	0.92(t, J=7Hz, 3H), 1.21(s, 9H), 1.47(brq, J=7Hz, 2H), 2.30(brq, J=7~8Hz, 2H), 3.23~3.78(m, 2H), 5.05(d, J=5 Hz, 1H), 5.60(brs, 2H), 5.82, 5.93(ABq, J=5Hz, 2H), 5.95(dd, J=8Hz, J=5Hz, 1H), 6.37(s, 1H), 6.41(t, J=8 Hz, 1H), 6.56~6.65(m, 1H), 8.23(d, J=8Hz, 1H).	2-1)
31	H ₂ N	i-Pr	H	POM	S	3480, 3390, 1780, 1740, 1670, 1635, 1600.	1.06(d, J=7Hz, 6H), 1.22(s, 9H), 2.73~3.13(m, 1H), 3.22~3.77(m, 2H), 5.00(d, J=5Hz, 1H), 5.43(brs, 2H), 5.81, 5.90(ABq, J=5Hz, 2H), 5.96(dd, J=8Hz, J=5Hz, 1H), 6.22(d, J=11Hz, 1H), 6.37(s, 1H), 6.53~6.73(m, 1H), 7.57(d, J=8Hz, 1H).	2-1)

Table 1 Physical constants of pharmaceutical esters (B)

No	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃) cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
32	H ₂ N	cyc-Pr	H	POM	S	3480, 3390, 1784, 1745, 1664, 1600, 1122.	0.5-1.03(m, 4H), 1.20(s, 9H), 2.0-2.5(m, 1H), 3.42(dd, J=7Hz, J=19.8Hz, (A of ABX), 1H), 3.60(dd, J=3Hz, J=19.8Hz, (B of ABX), 1H), 5.03(d, J=5Hz, 1H), 5.30(brs, 2H), 5.80(d, J=11Hz, 1H), 5.84, 5.93(ABq, J=5.4Hz, 2H), 6.03(dd, J=5Hz, J=9Hz, 1H), 6.33(s, 1H), 6.61(dd, J=3Hz, J=7Hz, (X of ABX), 1H), 8.06(d, J=9Hz, 1H).	2-1)
33	H ₂ N	t-Bu	H	POM	S	3480, 3390, 1788, 1745, 1678, 1496, 1123.	1.18(s, 9H), 1.21(s, 9H), 3.45(dd, A of ABX, J=6Hz, J=20Hz, 1H), 3.52(dd, B of ABX, J=4.0Hz, J=20Hz, 1H), 5.0(d, J=4.5Hz, 1H), 5.18(brs, 2H), 5.80, 5.88(ABq, J=5.5Hz, 2H), 5.98(dd, J=4.5Hz, J=8.5Hz, 1H), 6.33(s, 1H), 6.41(s1H), 6.56(dd, J=4Hz, J=6Hz, 1H), 6.74(d, J=8.5Hz, 1H).	2-1), 2-4)
35	H ₂ N	cyc-Pn	H	POM	S	3478, 3385, 1786, 1746, 1670, 1601, 1112.	1.22(s, 9H), 1.3-2.13(m, 8H), 2.75-3.20(m, 1H), 3.39(dd, J=6.3Hz, J=19.8Hz, (A of ABX), 1H), 3.58(dd, J=2.7Hz, J=19.8Hz, (B of ABX), 1H), 5.02(d, J=5Hz, 1H), 5.37(brs, 2H), 5.82, 5.94(ABq, J=7Hz, 2H), 6.00(dd, J=5Hz, J=8.5Hz, 1H), 6.35(d, J=10Hz, 1H), 6.38(s, 1H), 6.60(dd, J=2.7Hz, J=8.5Hz, (X of ABX), 1H), 7.96(d, J=8.5Hz, 1H).	3-1)

Table 2 Physical constants of protected pharmaceutical esters (I)



No	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃), cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
1	BOCNI	Me	H	POM	S	3415, 3100br 1786, 1746, 1725, 1678, 1545, 1280, 1155.	1.20(s, 9H), 1.51(s, 9H), 2.04(d, J=7Hz, 3H), 3.42 (dd, A of ABX, J=5Hz, J=9.9Hz, 1H), 3.61(dd, B of ABX, J=3Hz, J=9.9Hz, 1H), 5.02(d, J=5Hz, 1H), 5.85 (s, 2H), 5.94(dd, J=5Hz, J=8Hz, 1H), 6.42-6.62(m, 2H), 6.69(s, 1H), 8.01(d, J=8Hz, 1H), 9.62(brs, 1H).	3-1), 1-3)
2	BOCNI	Me	CH ₃ COONH ₂	POM	S	3550, 3415, 1787, 1730, 1678, 1545, 1300, 1155.	1.21(s, 9H), 1.51(s, 9H), 2.02(d, J=7Hz, 3H), 3.39, 4.13(ABq, J=17Hz, 2H), 4.81, 5.05(ABq, J=13.5Hz, 2H), 5.02(d, J=4.5Hz, 1H), 5.05(s, 2H), 5.87(s, 2H), 5.91(dd, J=4.5Hz, J=8.5Hz, 1H), 6.52(q, J=7Hz, 1H), 6.73(s, 1H), 7.90(d, J=8.5Hz, 1H), 8.47(brs, 1H).	3-1)

Table 2 Physical constants of protected pharmaceutical esters (2)

No.	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃), cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
4	BOC ₂ NH	Et	H	AOH	S	3410, 2960, 1785, 1720, 1670, 1540, 1370, 1285, 1155, 1005.	1.07(t, J=8Hz, 3H), 1.53(s, 9H), 2.10(s, 3H), 2.46 (quintet, J=8Hz, 2H), 3.20-3.76(m, 2H), 4.99(d, J=5 Hz, 1H), 5.82, 5.88(ABq, J=6Hz, 2H), 5.95(dd, J=5Hz, J=9Hz, 1H), 6.43(t, J=8Hz, 1H), 6.53-6.63(m, 1H), 6.75(s, 1H), 7.75(d, J=9Hz, 1H), 8.76(brs, 1H).	3-2)
5	BOC ₂ NH	Et	H	AOE	S	nd	1.07(t, J=7.5Hz, 3H), 1.53(s, 9H), 1.53(d, J=6.0Hz, 3H), 2.07(s, 3H), 2.48(quintet, J=7.5Hz, 2/2H), 2.50 (quintet, J=7.5Hz, 2/2H), 3.21-3.75(m, 2H), 4.94(d, J =4.5Hz, 1/2H), 4.99(d, J=4.5Hz, 1/2H), 5.79-6.02(m, 1H), 6.42(t, J=7.5Hz, 1H), 6.49-6.61(m, 1H), 6.74(s, 1H), 6.93(q, J=6.0Hz, 1/2H), 6.99(q, J=6.0Hz, 1/2H), 7.70(d, J=8.5Hz, 1/2H), 7.74(d, J=8.5Hz, 1/2H), 8.60 (brs, 1/2H), 9.55(brs, 1/2H).	1-2), 3-3)
6	BOC ₂ NH	Et	H	POH	S	nd	1.06(t, J=8Hz, 3H), 1.19(s, 9H), 1.52(s, 9H), 2.44 (quintet, J=8Hz, 2H), 3.43(dd, A of ABX, J=7Hz, J= 19.8Hz, 1H), 3.61(dd, B of ABX, J=4Hz, J=19.8Hz, 1H), 5.03(d, J=5Hz, 1H), 5.83, 5.90(ABq, J=4.5Hz, 2H), 5.97(dd, J=5Hz, J=8Hz, 1H), 6.45(t, J=8Hz, 1H), 6.58(dd, X of ABX, J=4Hz, J=7Hz, 1H), 6.73(s, 1H), 7.88(d, J=8Hz, 1H), 8.94(brs, 1H).	3-1), 5-1)

Table 2 Physical constants of protected pharmaceutical esters (3)

No.	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃) cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
6	CbzNH	Et	H	POM	S	3410, 3240br 1790, 1750, 1738, 1678, 1552, 1290, 1130, 1095.	1.03(t, J=7.5Hz, 3H), 1.20(s, 9H), 2.38(quintet, J=7.5Hz, 2H), 3.30(dd, A of ABX, J=6Hz, J=18.9Hz, 1H), 3.51(dd, B of ABX, J=3Hz, J=18.9Hz, 1H), 4.98(d, J=5.5Hz, 1H), 5.15, 5.30(ABq, J=13Hz, 2H), 5.78, 5.85(ABq, J=4.5Hz, 2H), 5.92(dd, J=5.5Hz, J=8Hz, 1H), 6.43(t, J=7.5Hz, 1H), 6.70(s, 1H), 7.36(s, 5H), 7.89(d, J=8Hz, 1H), 9.45(brs, 1H).	3-1)
	ONCNH					2970, 1790, 1755, 1705, 1680, 1550, 1290, 1130.	1.07(t, J=8Hz, 3H), 1.20(s, 9H), 2.37(quintet, J=8Hz, 2H), 3.20~3.76(m, 2H), 4.97(d, J=5Hz, 1H), 5.82(s, 2H), 5.92(dd, J=5Hz, J=9Hz, 1H), 6.45(t, J=8Hz, 1H), 6.50~6.62(m, 1H), 6.77(s, 1H), 7.93(d, J=9Hz, 1H), 8.49(s, 1H).	7-1)
	ClCH ₂ CONH					3500, 3370, 3230, 1790, 1755, 1685, 1640.	1.08(t, J=8Hz, 3H), 2.25~2.63(m, 2H), 3.23~3.78(m, 2H), 4.27(s, 2H), 5.02(d, J=5Hz, 1H), 5.86(s, 2H), 5.90(dd, J=8Hz, J=5Hz, 1H), 6.47(t, J=9Hz, 1H), 6.55~6.61(m, 1H), 6.85(s, 1H), 7.78(d, J=8Hz, 1H).	7-1)
	Ph-NO ₂ CH=N-					3410, 1785, 1745, 1675, 1635, 1520, 1345.	1.14(t, J=7Hz, 3H), 1.22(s, 9H), 2.56(q, J=7Hz, 2H), 3.23~3.82(m, 2H), 5.08(d, J=5Hz, 1H), 5.87, 5.97(ABq, J=5Hz, 2H), 6.03(dd, J=5Hz, J=8Hz, 1H), 6.57~6.69(m, 1H), 6.69(t, J=7Hz, 1H), 7.27(s, 1H), 7.71(d, J=8Hz, 1H), 8.16, 8.34(ABq, J=9Hz, 4H), 9.21(s, 1H).	7-1)

Table 2 Physical constants of protected pharmaceutical esters (4)

No.	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃), cm ⁻¹	NMR: δ (CDCl ₃), ppm	Ex. No
7	BOC ₂ NH	Et	H	POM	SO	3405, 3185br 1802, 1751, 1720, 1670, 1545, 1155.	1.08(t, J=7.5Hz, 3H), 1.21(s, 9H), 1.52(s, 9H), 2.52 (quintet, J=7.5Hz, 2H), 3.28(dd, A of ABX, J=1.5Hz, J=19.8Hz, 1H), 3.82(dd, B of ABX, J=6.0Hz, 19.8Hz, 1H), 4.59(dd, J=1.5Hz, J=4.5Hz, 1H), 5.84, 5.96(ABq, J=7Hz, 2H), 6.23(dd, J=4.5Hz, J=9Hz, 1H), 6.38(dd, X of ABX, J=1.5Hz, J=6Hz, 1H), 6.47(t, J=7.5Hz, 1H), 6.72(s, 1H), 8.81(brs, 1H), 8.94(d, J=9Hz, 1H).	3-1), 4-1)
8	BOC ₂ NH	Et	H	POE	S	3410, 1785, 1740, 1726, 1675, 1545, 1290, 1155, 1070.	1.08(t, J=8Hz, 3H), 1.20(s, 9H), 1.53(s, 9H), 1.53 (d, J=5Hz, 3H), 2.25-2.65(m, 2H), 3.20-3.80(m, 2H), 4.97, 5.02(2xd, J=5Hz, 1H), 5.95(dd, J=5Hz, J=9Hz, 1H), 6.40(t, J=8Hz, 1H), 6.49-6.59(m, 1H), 6.74(s, 1H), 6.90, 6.96(2xq, J=7Hz, 1H), 7.40, 7.45(2xd, J=9 Hz, 1H).	3-4)
9	BOC ₂ NH	Et	H	ECE	S	3420, 2960, 1785, 1765, 1730, 1675, 1550, 1370, 1290, 1155, 1080	1.07(t, J=7Hz, 3H), 1.30(t, J=7Hz, 3H), 1.53(s, 9H), 1.56(d, J=5Hz, 3H), 2.30-2.66(m, 2H), 3.10-3.80(m, 2H), 4.20(q, J=7Hz, 2H), 4.94, 5.00(2xd, J=5Hz, 1H), 5.85, 5.95(2xq, J=5Hz, J=9Hz, 1H), 6.43(t, J=7Hz, 1H), 6.46-6.63(m, 1H), 6.73(s, 1H), 6.84, 6.90(2xq, J=5Hz, 1H), 7.72(d, J=9Hz, 1H).	3-5)

Table 2 Physical constants of protected pharmaceutical esters (5)

No.	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃) cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
10	BOC ₂ NH	Et	H	DOL	S	3408, 3220br 1818, 1783, 1725, 1722, 1670, 1523, 1288, 1153.	1.07(t, J=7.5Hz, 3H), 1.52(s, 9H), 2.17(s, 3H), 2.96 (quintet, J=7.5Hz, 2H), 3.40(dd, A of ABX, J=7Hz, J= 19Hz, 1H), 3.62(dd, B of ABX, J=3Hz, J=19.0Hz, 1H), 4.97(s, 2H), 5.00(d, J=5Hz, 1H), 5.94(dd, J=5Hz, J=9 Hz, 1H), 6.43(t, J=7.5Hz, 1H), 6.56(dd, X of ABX, J= 3Hz, J=7Hz, 1H), 6.74(s, 1H), 7.74(d, J=9Hz, 1H), 8.72(brs1H).	3-6)
11	BOC ₂ NH	Et	H	CHAE	S	3410, 2930, 1790, 1755, 1730, 1680, 1540, 1290, 1160, 1075.	0.85~1.95(m, 14H), 1.07(t, J=8Hz, 3H), 1.53(s, 9H), 2.15~2.65(m, 4H), 3.20~3.80(m, 2H), 4.92, 5.00(2xd, J =5Hz, 1H), 5.82, 5.95(2xdd, J=5Hz, J=9Hz, 1H), 6.43 (t, J=8Hz, 1H), 6.48~6.58(m, 1H), 6.73(s, 1H), 6.92, 6.98(2xq, J=5Hz, 1H), 7.72, 7.74(2xd, J=9Hz, 1H).	3-7)
13	BOC ₂ NH	Et	Cl	POH	SO	3395, 3180br 1802, 1753, 1719, 1668, 1547, 1152, 985.	1.08(t, J=7.5Hz, 3H), 1.22(s, 9H), 1.52(s, 9H), 2.51 (quintet, J=7.5Hz, 2H), 3.64, 3.93(ABq, J=16.2Hz, 2 H), 4.76(d, 5.0Hz, 1H), 5.89, 6.00(ABq, J=5.4Hz, 2H), 6.19(dd, J=5.0Hz, J=10.0Hz, 1H), 6.48(t, J=7.5Hz, 1H), 6.73(s, 1H), 8.94(d, J=10Hz, 1H), 8.96(brs, 1H)	3-1), 4-2)

Table 2 Physical constants of protected pharmaceutical esters (6)

No.	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃ ,) cm ⁻¹	NMR: δ (CDCl ₃ ,) ppm	Ex. No
14	BOC ₂ NH	Et	CH ₂ OCH ₃	POM	S	3420, 2980, 1790, 1750, 1730, 1680, 1550, 1375, 1160.	1.07(t, J=8Hz, 3H), 1.20(s, 9H), 1.53(s, 9H), 2.45 (quintet, J=8Hz, 2H), 3.31(s, 3H), 3.53(s, 2H), 4.28 (s, 2H), 5.03(d, J=5Hz, 1H), 5.86(s, 2H), 5.90(dd, J=5Hz, J=9Hz, 1H), 6.43(t, J=8Hz, 1H), 6.73(s, 1H), 7.77(d, J=9Hz, 1H), 8.53(brs, 1H).	3-1)
15	BOC ₂ NH	Et	CH ₂ O-i-Pr	POM	S	3410, 2960, 1780, 1750, 1720, 1670, 1540, 1365, 1150, 1120, 1095	1.07(t, J=8Hz, 3H), 1.15(d, J=6Hz, 6H), 1.22(s, 9H), 1.53(s, 9H), 2.46(quintet, J=8Hz, 2H), 3.58(s, 2H), 3.60(septet, J=6Hz, 1H), 4.36(s, 2H), 5.05(d, J=5Hz, 1H), 5.88(s, 2H), 5.90(dd, J=5Hz, J=9Hz, 1H), 6.45 (t, J=8Hz, 1H), 6.75(s, 1H), 7.80(d, J=9Hz, 1H).	3-1)
16	BOC ₂ NH	Et	CH ₂ O(pro- penyl)	POM	S	3410, 1785, 1750, 1725, 1675.	1.08(t, J=7Hz, 3H), 1.23(s, 9H), 1.53(s, 9H), 2.27~ 2.60(m, 2H), 3.58(s, 2H), 3.97(m, 2H), 4.36(s, 2H), 5.04(d, J=5Hz, 1H), 5.13~5.33(m, 2H), 5.67~6.10(m, 4H), 6.41(t, J=7Hz, 1H), 6.73(s, 1H), 7.64(d, J=8Hz, 1H).	3-1)
17	BOC ₂ NH	Et	CH ₂ OCH ₂ CH ₂ F	POM	S	3420, 1792, 1755, 1726, 1678, 1548, 1156.	1.07(t, J=8Hz, 3H), 1.22(s, 9H), 1.52(s, 9H), 2.47 (dq, J=8Hz, J=8Hz, 2H), 3.58(s, 2H), 3.68(dt, J=2.5 Hz, J=30Hz, 2H), 4.42(s, 2H), 4.54(dt, J=4.5Hz, J=48 Hz, 2H), 5.04(d, J=4.5Hz, 1H), 5.87(s, 2H), 5.94(dd, J=4.5Hz, J=8Hz, 1H), 6.44(t, J=8Hz, 1H), 6.73(s, 1H), 7.81(d, J=8Hz, 1H), 8.55(brs, 1H).	3-1)

Table 2 Physical constants of protected pharmaceutical esters (7)

No	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃) cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
19	BOC ₂ NH	Et	CH ₂ OOCNH ₂	AOE	S	3520, 3405, 1778, 1722, 1663, 1540, 1149, 1070.	1.06(t, J=7.5Hz, 3H), 1.46(d, J=6Hz, 3H), 1.51(s, 9H), 2.06(s, 3H), 2.45(quintet, J=7.5Hz, 2/2H), 2.50(quintet, J=7.5Hz, 2/2H), 3.44(brs, 2H), 4.12-5.31(m, 5H), 5.63-5.92(m, 1H), 6.38(t, J=7.5Hz, 1H), 6.72(s, 1H), 6.89(q, J=6Hz, 1/2H), 7.04(q, J=6Hz, 1/2H), 7.76(d, J=8.0Hz, 1H).	3-3)
20	BOC ₂ NH	Et	CH ₂ OOCNH ₂	POM	S	nd	1.07(t, J=7.5Hz, 3H), 1.23(s, 9H), 1.54(s, 9H), 2.47(quintet, J=7.5Hz, 2H), 3.40, 3.56(ABq, J=18Hz, 2H), 4.79, 5.07(ABq, J=13.5Hz, 2H), 5.02(d, J=5Hz, 1H), 5.03(s, 2H), 5.87(s, 2H), 5.90(dd, J=5Hz, J=8.5Hz, 1H), 6.41(t, J=7.5Hz, 1H), 6.76(s, 1H), 7.74(d, J=8.5Hz, 1H), 9.11(s, 1H).	1-2), 3-2)
22	BOC ₂ NH	Et	CH ₂ OOCNH ₂	POE	S	3500, 3410, 2960, 1775, 1730, 1720, 1670, 1540, 1150, 1070.	1.07(t, J=8Hz, 3H), 1.20(s, 9H), 1.53(s, 9H), 1.46-1.60(m, 3H), 2.25-2.70(m, 2H), 3.20-3.80(m, 2H), 4.60-5.30(m, 5H), 5.70-6.03(m, 1H), 6.43(t, J=8Hz, 1H), 6.76(s, 1H), 6.83-7.16(m, 1H), 7.76, 7.81(2xd, J=9Hz, 1H).	3-4)

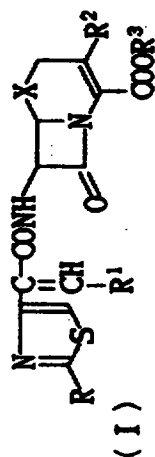
Table 2 Physical constants of protected pharmaceutical esters (8)

No	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃) cm ⁻¹	NMR: δ (CDCl ₃) ppm	Ex. No
23	BOCNH	Et	CH ₂ COONH ₂	ECE	S	3520, 3410, 2960, 1780, 1760, 1730, 1720, 1670, 1540, 1370, 1325, 1150, 1075.	1.08(t, J=8Hz, 3H), 1.32(t, J=7Hz, 3H), 1.55(s, 9H), 1.56(d, J=6Hz, 3H), 2.42(quintet, J=8Hz, 2H), 3.46, 3.62(ABq, J=20Hz, 2H), 4.23(q, J=7Hz, 2H), 4.86, 5.07 (ABq, J=15Hz, 2H), 5.02, 5.08(2xd, J=5Hz, 1H), 5.53 (brs, 2H), 5.87(d, J=5Hz, 1H), 6.43(t, J=8Hz, 1H), 6.77(s, 1H), 6.87, 7.00(q, 2x6Hz, 1H). [CDCl ₃ +D ₂ O]	3-5)
30	BOCNH	n-Pr	H	POM	S	3500, 3400, 3200, 1785, 1750, 1720, 1665, 1640.	0.96(t, J=7Hz, 3H), 1.22(s, 9H), 1.53(s, 9H), 1.40~ 1.63(m, 2H), 2.40(brq, J=7Hz, 2H), 3.23~3.77(m, 2H), 5.02(d, J=5Hz, 1H), 5.82, 5.90(ABq, J=6Hz, 2H), 5.97 (dd, J=8Hz, J=5Hz, 1H), 6.43(t, J=8Hz, 1H), 6.52~6.63 (m, 1H), 6.75(s, 1H), 7.50(d, J=8Hz, 1H).	3-1)
31	BOCNH	i-Pr	H	POM	S	3500, 3400, 3220, 1785, 1745, 1720, 1675, 1635.	1.07(d, J=7Hz, 6H), 1.20(s, 9H), 1.53(s, 9H), 2.71~ 3.18(m, 1H), 3.27~3.80(m, 2H), 5.03(d, J=5Hz, 1H), 5.83, 5.92(ABq, J=5Hz, 2H), 5.97(dd, J=8Hz, J=5Hz, 1H), 6.30(d, J=11Hz, 1H), 6.53~6.65(m, 1H), 6.79(s, 1H), 7.67(d, J=8Hz, 1H), 8.33(brs, 2H).	3-1)

Table 2 Physical constants of protected pharmaceutical esters (9)

No	R	R ¹	R ²	R ³	X	IR: ν (CHCl ₃) cm ⁻¹	NMR: δ (OCl ₃) ppm	Ex. No
32	BOC ₂ H	cyc-Pr	H	POH	S	3415, 1788, 1750, 1726, 1670, 1545, 1157.	0.5-1.02(m, 4H), 1.22(s, 9H), 1.53(s, 9H), 2.10-2.45 (m, 1H), 3.42(dd, J=5.4Hz, J=18Hz, A of ABX, 1H), 3.61(dd, J=2.7Hz, J=18Hz, B of ABX, 1H), 5.02(d, J=5 Hz, 1H), 5.78(d, J=12Hz, 1H), 5.80, 5.89(ABq, J=5Hz, 2H), 5.99(dd, J=5Hz, J=8.5Hz, 1H), 6.55(dd, J=2.7Hz, J=5.4Hz, X of ABX, 1H), 7.79(d, J=8.5Hz, 1H).	3-1)
33	BOC ₂ H	t-Bu	H	POH	S	3415, 1793, 1750, 1726, 1682, 1545, 1157, 1003.	1.17(s, 9H), 1.21(s, 9H), 1.52(s, 9H), 3.38(dd, A of ABX, J=6Hz, J=18.5Hz, 1H), 3.57(dd, B of ABX, J=3Hz, J=18.5Hz, 1H), 5.00(d, J=5.0Hz, 1H), 5.81, 5.90(ABq, J=5.5Hz, 2H), 6.0(dd, J=5Hz, J=9Hz, 1H), 6.41(s, 1H), 6.56(dd, X of ABX, J=3Hz, J=6Hz, 1H), 6.70(s, 1H), 7.76(d, J=9Hz, 1H), 8.83(brs, 1H).	3-1)

Table 3 Synthesis of Pharmaceutical esters (I)



No	R	R ¹	R ²	R ³	X	Ex. No	Start. Mat. (mg)	Solvent (ml)	Reagent	Subreagent	hr °C	Yld. %/mg
1	H ₂ N	Me	H	POM	S	2-1)	R=BOCNH 100	-	TFA 1 ml		1 rt	85 70
						2-4)	R=BOCNH 150	DCM 1	AlCl ₃ , 51 mg 1.5 eq	anisole 0.5 ml	0.1 -30	74 92
2	H ₂ N	Me	CH ₂ COONH ₂	POM	S	2-5)	R=BOCNH 160	-	TFA 2 ml		2 rt	55 75
4	H ₂ N	Et	H	AOM	S	2-1)	R=BOCNH 163	-	TFA 3 ml		1 rt	87 116
5	H ₂ N	Et	H	AOE	S	2-1)	R=BOCNH 90	-	TFA 1.5 ml		1 rt	59 45
						3-3)	R ³ =H 95	DMF 1	AOEBr 165 μl	K ₂ CO ₃ , 110 mg	2.5 -30-0	33 38

Table 3 Synthesis of Pharmaceutical esters (2)

No.	R	R ¹	R ²	R ³	X	Ex. No	Start. Mat. (mg)	Solvent (ml)	Reagent	Subreagent	hr/°C	Yld. %/mg
6	H ₂ N	Et	H	POM	S	2-1)	R=BOCNH 480	-	TFA 5 ml		1 rt	87 340
						2-2)	R=ClCH ₂ - CONH 143	THF 2	NH ₄ CSNH ₂ 76 mg 4 eq	AcONa 41 mg 2 eq MeOH 2 ml	4 rt	80 99
						2-3)	R=HOCNH 183	HOAc 2	N-HCl 0.3 ml		3.5 rt	63 110
						2-4)	R=BOCNH 120	DCM 1	AlCl ₃ 80 mg 3 eq	anisole 0.5 ml	0.1 -30	81 80
						3-1)	R ³ =H 114	DMF 1.5	POM 56 μ l 1.1 eq	K ₂ CO ₃ 62 mg 2 eq	0.5 -30	33 49
7	H ₂ N	Et	H HCl salt	POM	S	5-2)	X=SO 100	DCM 4	PBr ₂ 40 μ l 2 eq		0.8 -30	66 78
						6-2)	R=NH ₂ 82	DCM 1	HCl/EtOAc	rinsed with Et ₂ O	- -	87 63
8	H ₂ N	Et	H	POE	S	2-1)	R=BOCNH 160	-	TFA 3 ml		1 rt	47 63

Table 3 Synthesis of Pharmaceutical esters (3)

No	R	R ¹	R ²	R ³	X	Ex. No	Start. Mat. (mg)	Solvent (ml)	Reagent	Subreagent	hr/°C	Yld. %/mg
9	H ₂ N	Et	H	EOE	S	2-1)	R=BOCNH 189	-	TFA 3.5 ml		1 rt	76 119
10	H ₂ N	Et	H	DOL	S	2-1)	R=BOCNH 83	-	TFA 1 ml		1.5 rt	62 43
11	H ₂ N	Et	H	CHAE	S	2-1)	R=BOCNH 150	-	TFA 3 ml		1 rt	69 88
12	H ₂ N	Et	Cl	POM	S	2-1)	R=BOCNH 130	-	TFA 1.5 ml		2 rt	64 70
						5-2)	X-SO 51	DCM 2	PBr ₃ , 19 μ l		1 -30	83 41
14	H ₂ N	Et	CH ₂ OCH ₃	POM	S	2-1)	R=BOCNH 173	-	TFA 3.5 ml		1 rt	90 131
						2-4)	R=BOCNH 173	DCM 1.5	AlCl ₃ , 72 mg 2 eq	anisole 1 ml	0.2 -30	86 125
15	H ₂ N	Et	CH ₂ O-i-Pr	POM	S	2-1)	R=BOCNH 150	-	TFA 3 ml		1 rt	33 42

Table 3 Synthesis of Pharmaceutical esters (5)

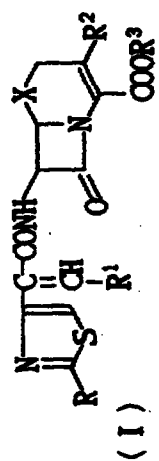
No.	R	R ¹	R ²	R ³	X	Ex. No.	Start. Mat. (mg)	Solvent (ml)	Reagent	Subreagent	hr °C	Yld. %/mg
30	H ₂ N	n-Pr	H	POM	S	2-1)	R=BOCNH 201	-	TFA 1 ml		3 rt	60 100
31	H ₂ N	i-Pr	H	POM	S	2-1)	R=BOCNH 186	-	TFA 1 ml		3 rt	70 108
32	H ₂ N	cyc-Pr	H	POM	S	2-1)	R=BOCNH 133	-	TFA 2.6 ml		1 rt	59 65
33	H ₂ N	t-Bu	H	POM	S	2-1)	R=BOCNH 53	-	TFA 1 ml		2 rt	90 40
35	H ₂ N	cyc-Pn	H	POM	S	3-1)	R ³ =H 102	DMF 2	POM 50 μ l 1.2 eq	K ₂ CO ₃ , 67 mg	1 -25	53 69
								DCM 1	SnCl ₄ , 40 μ l 2 eq.	anisole 1 ml	1 -10	85 75

Table 4 Synthesis of protected pharmaceutical esters (1)

(Abbreviations)

Q*=cephem nucleus

Q*=side chain acid minus carboxy



No	R	R ¹	R ²	R ³	X	Ex. No	Start. Mat. (mg)	Solvent (ml)	Reagent	Subreagent	hr °C	Yld. %/mg
1	BOCNH	Me	H	POM	S	3-1)	R ³ =H 100	DMF 1	POM 45 μl	K ₂ CO ₃ 45 mg	0.5 -30	80 100
						1-3)	H ₂ NQ* 157	DCM 10	Q*COOH 142 mg, (COCl) ₂ 42.6 μl 1 eq	picoline 98 μl 2 eq	0.5 -40	56 162
2	BOCNH	Me	CH ₂ COONH ₂	POM	S	3-1)	R ³ =H 216	DMF 4	POM 78 μl	K ₂ CO ₃ 110 mg	0.7 -20	57 150
4	BOCNH	Et	H	AOE	S	3-2)	R ³ =H 240	DMF 2.4	AOEBr 115 mg	K ₂ CO ₃ 138 mg	0.7 0	48 132
5	BOCNH	Et	H	AOE	S	1-4)	H ₂ NQ* 161	DCM 8	Q*COOH 149 mg, MeSO ₂ Cl 40 μl	NEt ₃ 83 μl, Me-m orpholine 132 μl	3 -60	83 235

Table 4 Synthesis of protected pharmaceutical esters (2)

No.	R	R ¹	R ²	R ³	X	Ex. No.	Start. Mat. (mg)	Solvent (ml)	Reagent	Subreagent	hr °C	Yld. %/mg
5	BOC ₂ NH	Et	H	AOE	S	3-3)	R ³ =H 170	DMF 2	AOEBr 230 μ l	K ₂ CO ₃ 152 mg, KI 300 mg	1.5 -20	32 65
6	BOC ₂ NH	Et	H	POM	S	3-1)	R ³ =H 572	DMF 8	POMI 223 μ l	K ₂ CO ₃ 329 mg	1 -30	68 485
						5-1)	X=SO 61	DCM 2	PBr, 19.3 μ l 2 eq		0.5 -30	86 51
	CbzNH			POM	S	3-1)	R ³ =H 153	DMF 3	POMI 65 μ l	K ₂ CO ₃ 92 mg	0.5 -20	72 136
	OHCONH			POM	S	7-1)	R=H ₂ N 50	-	HOOH 26 μ l	Ac ₂ O 66 μ l	0.5 rt	90 47
	ClCH ₂ CONH			POM	S	7-1)	R=H ₂ N 50	DCM 1	ClCH ₂ COCl 12 μ l	pyridine 12 μ l	0.5 -20	95 54
	NO ₂ PhCH=N			POM	S	7-1)	R=H ₂ N 50	DCM 3	O ₂ NC ₆ H ₄ CHO 23 mg	MeC ₆ H ₄ SO ₃ H 1 mg	2.5 45	32 20
8	BOC ₂ NH	Et	H	POE	S	3-4)	R ³ =H 240	DMF 2.4	POEI 460 μ l, POECl 320 μ l	K ₂ CO ₃ 138 mg	1 -25-30	53 161

Table 4 Synthesis of protected pharmaceutical esters (3)

No.	R	R ¹	R ²	R ³	X	Ex. No	Start. Mat. (mg)	Solvent (ml)	Reagent	Subreagent	hr °C	Yld. %/mg
9	BOC ₂ NH	Et	H	ECE	S	3-5)	R ³ =H 240	DMF 2.4	EOCBr 150 mg 1.5 eq	K ₂ CO ₃ 138 mg	0.5 -10	64 191
10	BOC ₂ NH	Et	H	DOL	S	3-6)	R ³ =H 144	DMF 4	DOLBr 102 mg 1.5 eq	K ₂ CO ₃ 83 mg	0.5 0	47 83
11	BOC ₂ NH	Et	H	CHAE	S	3-7)	R ³ =H 240	DMF 2.4	CHAEI 355 mg	K ₂ CO ₃ 138 mg	0.8 -30	47 152
13	BOC ₂ NH	Et	Cl	POM	SO	3-1)	R ³ =H 106	DMF 2	POMI 38 μ l 1.1 eq	K ₂ CO ₃ 55 mg	0.7 -30	58 75
						4-2)	X=S 410	DCM 4	m-CPBA 47.4 mg		0.3 0	30 135
14	BOC ₂ NH	Et	CH ₂ OCH ₃	POM	S	3-1)	R ³ =H 159	DMF 1.5	POMI 77 μ l	K ₂ CO ₃ 84 mg	1 -30	90 173
15	BOC ₂ NH	Et	CH ₂ O-i-Pr	POM	S	3-1)	R ³ =H 120	DMF 1.2	POMI 55 μ l	K ₂ CO ₃ 152 mg	1 -30	97 140
16	BOC ₂ NH	Et	CH ₂ O(pro- penyl)	POM	S	3-1)	R ³ =H 193	DMF 3	POMI 120 μ l 2 eq	K ₂ CO ₃ 97 mg	2 -40	55 128

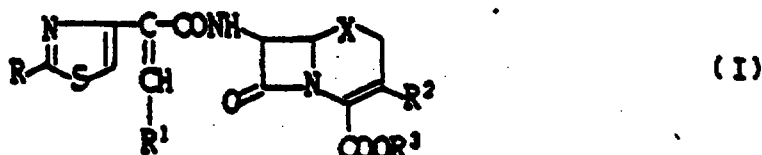
Table 4 Synthesis of protected pharmaceutical esters (4)

Table 4 Synthesis of protected pharmaceutical esters (5)

No	R	R ¹	R ²	R ³	X	Ex. No.	Start. Mat. (mg)	Solvent (ml)	Reagent	Subreagent	hr °C	Yld. %/mg
30	BOC ₂ NH	n-Pr	H	POM	S	3-1)	R ³ =H 289	DMF 4	POMI 200 μ l	K ₂ CO ₃ , 163 mg	1 -20	70 201
31	BOC ₂ NH	i-Pr	H	POM	S	3-1)	R ³ =H 259	DMF 4	POMI 170 μ l	K ₂ CO ₃ , 138 mg	2/3 -30	63 186
32	BOC ₂ NH	cyc-Pr	H	POM	S	3-1)	R ³ =H 312	DMF 3	POMI 118 μ l 1.2 eq	K ₂ CO ₃ , 128 mg	1.5 -30	47 133
33	BOC ₂ NH	t-Bu	H	POM	S	3-1)	R ³ =H 120	DMF 2	POMI 43 μ l	K ₂ CO ₃ , 61 mg	1 -30	31 43
35	BOC ₂ NH	cyc-Pn	H	POM	S	3-1)	R ³ =H 236	DMF 3	POMI 78 μ l 1.2 eq	K ₂ CO ₃ , 107 mg	1 -25	79 216

CLAIMS

1. A compound of the formula:



which exhibits very high oral availability when compared with free acid forms; and wherein R is amino or protected amino;

R₁ is methyl, ethyl, propyl, isopropyl, cyclopropyl, t-butyl, or cyclopentyl;

R₂ is hydrogen, chloro, methoxymethyl, propoxymethyl, isopropoxyethyl, propenyloxyethyl, fluoroethoxymethyl, or carbamoyloxyethyl;

R₃ is a pharmaceutically or veterinarily acceptable ester group; and

X is sulfur or sulfinyl

2. A compound as claimed in claim 1 wherein R is amino, t-butoxycarbonylamino, benzyloxycarbonylamino, formamido, chloroacetyl amino, or p-nitrobenzyl amino.

3. A compound as claimed in claim 1 or claim 2 wherein R₃ is 1-acetoxymethyl, acetoxylethyl, pivaloyloxyethyl, pivaloyloxyethyl, cyclohexane-acetoxylethyl, ethoxycarbonyloxyethyl, or 4-methyl-2-oxo-1,3-dioxol-5-ylmethyl.

4. A compound as claimed in any one of claims 1



to 3 wherein X is sulfur.

5. A compound wherein R is amino and wherein
R¹ is ethyl R² is CH₂OCH₂CH=CH₂ R³ is
5 pivaloyloxymethyl and X is sulfur or
R¹ is ethyl R² is CH₂OCH₂CH₂F R³
is pivaloyloxymethyl and X is sulfur or
R¹ is ethyl R² is CH₂OMe R³ is
pivaloyloxymethyl and X is sulfur or
10 R¹ is ethyl R² is CH₂OCH(Me)₂ R³ is
pivaloyloxymethyl and X is sulfur or
R¹ is ethyl R² is hydrogen R³ is
pivaloyloxymethyl and X is sulfur or
R¹ is methyl R² is CH₂OCONH₂ R³ is
15 pivaloyloxymethyl and X is sulfur or
R¹ is ethyl R² is CH₂OCONH₂ R³ is
pivaloyloxymethyl and X is sulfur or
R¹ is ethyl R² is hydrogen R³ is
ethoxycarbonyloxyethyl and X is sulfur or
20 R¹ is ethyl R² is hydrogen R³ is
pivaloyloxymethyl and X is sulfur or
R¹ is ethyl R² is hydrogen R³ is
acetoxylethyl and X is sulfur or
R¹ is ethyl R² is hydrogen R³ is
25 acetoxymethyl and X is sulfur or
R¹ is methyl R² is hydrogen R³ is
pivaloyloxymethyl and X is sulfur or
R¹ is ethyl R² is CH₂OCONH₂ R³ is
acetoxylethyl and X is sulfur or
30 R¹ is ethyl R² is CH₂OCONH₂ R³ is
ethoxycarbonyloxyethyl and X is sulfur or
R¹ is tertiary butyl R² is hydrogen R³
is pivaloyloxymethyl and X is sulfur or
R¹ is cyclopropyl R² is hydrogen R³ is
35 pivaloyloxymethyl and X is sulfur or
R¹ is ethyl R² is chloro R³ is



- 59.

pivaloyloxymethyl and X is sulfinyl or

R¹ is isopropyl R² is hydrogen R³ is
pivaloyloxymethyl and X is sulfur or

R¹ is ethyl R² is hydrogen R³ is
5 cyclohexaneacetoxyethyl and X is sulfur or

R¹ is ethyl R² is hydrogen R³ is
5-methyl-2-oxo-1,3-dioxol-5-ylmethyl and X is sulfur
or

R¹ is propyl R² is hydrogen R³ is
10 pivaloyloxymethyl and X is sulfur or

R¹ is ethyl R² is CH₂OCONH₂ R³ is
pivaloyloxyethyl and X is sulfur or

R¹ is cyclopentyl R² is hydrogen R³ is
pivaloyloxymethyl and X is sulfur.

15

6. A compound as claimed in claim 1, wherein R,
R¹, R², R³ and/or X are/is selected from
examples thereof given hereinbefore.

20 7. A compound as claimed in claim 1 and referred
to hereinbefore.

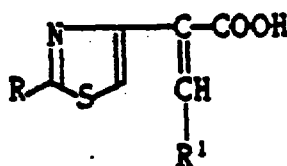
8. A compound as claimed in any one of claims 1
to 7 wherein the amido bond and R¹ group is in the
25 cis position.

9. An acid addition salt of a compound as claimed
in any one of claims 1 to 8.

30 10. A process for preparing a compound as claimed
in claim 1, which process comprises one or more of
the following steps:

(a) reacting a compound of the formula:

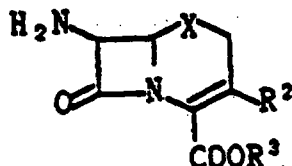
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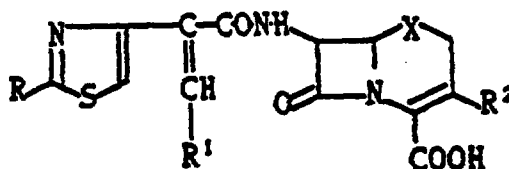
or a reactive derivative thereof with a compound of formula:

5



- 10 or a reactive derivative thereof;
(b) treating a compound of formula:

15



or a reactive derivative thereof with an esterifying reagent of formula;

20



wherein Y is a leaving group;

- (c) isomerizing a compound as claimed in claim 1 at the 7-position side chain;
- 25 (d) esterifying a compound as claimed in claim 1 at the 4-position when there is there present a carboxy group;
- (e) introducing an amino-protecting group when a compound as claimed in claim 1 has an amino group in
- 30 the molecule;
- (f) deprotecting a protected amino group in a compound as claimed in claim 1;
- (g) forming a sulfoxide from a compound as claimed in claim 1 which has a sulfide group;
- 35 (h) reducing a sulfoxide in a compound as claimed in claim 1 which has a sulfinyl group.



- 61

11. A process as claimed in claim 10 wherein the reaction is effected in an appropriate solvent at a temperature of -30°C to 100°C .

5

12. A process as claimed in claim 10 and substantially as hereinbefore described.

13. A process as claimed in claim 10 and substantially as hereinbefore described in any one of Examples 1 to 6 or the Tables.

14. A pharmaceutical or veterinary formulation comprising a compound as claimed in any one of claims 1 to 8 or a salt as claimed in claim 9 formulated, in either case, for pharmaceutical or veterinary use, respectively.

15. A formulation as claimed in claim 14 also comprising an acceptable diluent, carrier or excipient.

16. A formulation as claimed in claim 14 or claim 15 and in unit dosage form.

25

17. A formulation as claimed in any one of claims 14 to 16 substantially as hereinbefore described, with reference to the Preparations.

18. A compound as claimed in any one of claims 1 to 8, or a salt as claimed in claim 9 for use as an antibacterial agent or for testing bacterial sensitivity or as an intermediate in the production of other antibacterials.

35
