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Fortsættes ...

DESCRIPTION

TECHNICAL FIELD

[0001] The compounds of the subject invention are related to 2-substituted cephem compounds, which have a wide antimicrobial spectrum, in particular exhibit potent antimicrobial activity against beta-lactamase producing Gram negative bacteria, and pharmaceutical compositions comprising the same.

BACKGROUND

[0002] To date, a variety of beta-lactam drugs have been developed and beta-lactam drugs have become clinically extremely important antimicrobial drugs. However, there are increasing number of bacterial types which have obtained resistance against beta-lactam drugs by producing beta-lactamase, which degrade beta-lactam drugs.

[0003] According to the Ambler molecular classification, beta-lactamases are largely classified into four classes. Specifically, these are Class A (TEM type, SHV type, CTX-M type, KPC type and the like), Class B (IMP type, VIM type, L-1 type and the like), Class C (AmpC type) and Class D (OXA type and the like). Amongst these, Classes A, C and D types are largely classified into serine-beta-lactamase, on the other hand, Class B type is classified into metallo-beta-lactamase. It has been known that both have respectively different mechanisms to each other in terms of hydrolysis of beta-lactam drugs.

[0004] Recently, clinical problem has been occurring due to the existence of Gram negative bacteria which have become highly resistant to a number of beta-lactam drugs including Cephems and Carbapenems by producing Class A (ESBL) and D types serine-beta-lactamases which have an extended substrate spectrum, and Class B type metallo-beta-lactamase which have an extended substrate spectrum. Particularly, metallo-beta-lactamase is known to be one of the causes of obtaining multidrug-resistance in Gram negative bacteria. Cephem compounds which exhibit intermediate activity against metallo-beta-lactamase producing Gram negative bacteria are known (e.g., International Publication No. 2007/119511 pamphlet and Applied Microbiology and Biotechnology (1994), 40(6), 892-7). However, there is a demand for development of Cephem compounds which exhibit more potent antimicrobial activity, in particular more effective against a variety of beta-lactamase producing Gram negative bacteria.

[0005] One of the known antimicrobials having high anti-Gram negative bactericidal activity is Cephem compounds having a catechol group intramolecularly (e.g., The Journal of Antibiotics, vol. 61, pp. 36-39 (2008) ; The Journal of Antibiotics, vol.43, pp.1617-1620 (1990) The Journal of Antibiotics, vol.42, pp. 795-806 (1989)). The action thereof is that the catechol group forms

a chelate with Fe^{3+} , thereby the compound is efficiently incorporated into the bacterial body through the Fe^{3+} transportation system on the cellular membrane (tonB-dependent iron transport system). Therefore, research has been conducted on compounds having catechol or similar structure thereto, on the 3-side chain or 7-side chain moiety on the Cephem backbone.

[0006] Examples in the non-patent literature (i.e., e.g., see, Applied Microbiology and Biotechnology (1994), 40 (6), 892-7) and patent literature (i.e., see Japanese Laid-Open Publication No. 4-364189; Japanese Laid-Open Publication No. 3-173893; Japanese Laid-Open Publication No. 2-15090; Japanese Laid-Open Publication No. 2-28187; Japanese Laid-Open Publication No. 2-117678; Japanese Laid-Open Publication No. 2-28185), respectively, describe catechol type derivatives having a catechol group on the 3-side chain moiety on the Cephem backbone. Other patent documents (i.e., e.g., Japanese Laid-Open Publication No. 2-15090; Japanese Laid-Open Publication No. 2-28187; Japanese Laid-Open Publication No. 6-510523; and Japanese Laid-Open Publication No. 5-213971) describe pseudo-catechol type derivatives having a hydroxypyridone group on the 3-side chain moiety on the Cephem backbone. Patent Documents, International Publication No. 2007/096740 pamphlet and International Publication No. 2003/078440 pamphlet disclose Cephem compounds having a quaternary ammonium group, but do not describe a catechol type derivative.

[0007] Moreover, in the above documents, which describe Cephem compounds having a catechol group in their structure, there is no description of Class B type metallo-beta-lactamase and specific antimicrobial activity against a wide variety of Gram negative bacteria including Class B type.

[0008] Additionally, specific patent literature documents (i.e., e.g., European Patent Publication No. 35357 and US patent No. 3,487,079) and non-patent literature documents (i.e., e.g.,

[0009] Chemical & Pharmaceutical Bulletin, vol.31, 1482-1493 (1983); Journal of Medicinal Chemistry, vol.14, 420-425 (1971); and International Journal of Peptide & Protein Research, vol.10, 51-59 (1977)), respectively, describe cephem compounds having a substituent at position 2 of the cephem skeleton. However, these compounds do not have a quaternary ammonium group and a catechol group at position 3 of the cephem skeleton.

[0010] Non-patent literature (e.g., The Journal of Antibiotics, vol.41, pp. 1154-1157 (1988); The Journal of Antibiotics, vol. 43, pp. 357-371 (1989)) describe oxa-cephem compounds having a substituent at position 2 of the oxa-cephem skeleton. However, these compounds do not have a catechol group at position 3 of the oxa-cephem skeleton.

[0011] The present applicant has filed patent applications of cephem compounds having catechol type substituents (e.g., International Publication No. 2010/050468 pamphlet; International Publication No. 2011/125966 pamphlet; International Publication No. 2011/125967 pamphlet and International Publication No. 2011/136268 pamphlet). However, these applications do not disclose a compound having a substituent at position 2 of the cephem skeleton.

SUMMARY OF INVENTION

Problems to be solved by the Invention

[0012] The subject invention provides 2-substituted cephem compounds having a quaternary ammonium group on the 3-side chain, preferably together with a cathechol group, which exhibit potent antimicrobial spectrum against a variety of bacteria including Gram negative bacteria and/or Gram positive bacteria. Preferably, the compounds are effective against beta-lactamase producing Gram negative bacteria, including multidrug-resistant bacteria, in particular, Class B type metallo-beta-lactamase producing Gram negative bacteria, and extended-spectrum beta-lactamase (ESBL) producing bacteria. Furthermore, the subject invention provides preferably cephem compounds having antimicrobial activity against strains resistant to 2-unsubstituted cephem compounds.

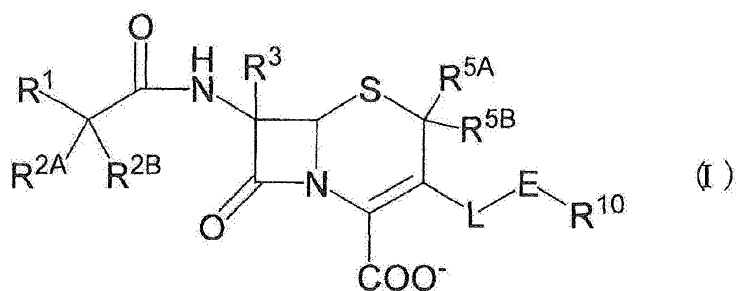
Means for Solving the Problem

[0013] The subject invention provides cephem compounds which have solved the above-mentioned problems with the following structural characteristics:

1. 1) a substituent group (s) at the position 2, preferably an alkyl group.
2. 2) a quaternary ammonium group on the 3-side chain.
3. 3) a cathechol group at the terminal or in the quaternary ammonium group of the 3-side chain as a preferable embodiment.

[0014] The subject invention provides the following inventions: 1. A compound of the formula (I):

[Chemical Formula 1]



an ester at carboxyl group, an amino-protected compound when the amino is present on a ring in the 7-side chain, or a pharmaceutically acceptable salt thereof, wherein,

R^1 is an optionally substituted carbocyclic group or an optionally substituted heterocyclic group;

with regard to R^{2A} and R^{2B} ,

1. a) R^{2A} is hydrogen, optionally substituted amino, $-\text{SO}_3\text{H}$, optionally substituted amino sulfonyl, carboxyl, optionally substituted (lower alkyl)oxycarbonyl, optionally substituted carbamoyl, hydroxyl, or substituted carbonyloxy; and R^{2B} is hydrogen, provided that R^{2A} and R^{2B} are not hydrogen at the same time, or
2. b) R^{2A} and R^{2B} are taken together to form optionally substituted methyldiene or optionally substituted hydroxyimino;

R^3 is hydrogen, $-\text{OCH}_3$ or $-\text{NH}-\text{CH}(=\text{O})$;

with regard to R^{5A} and R^{5B} ,

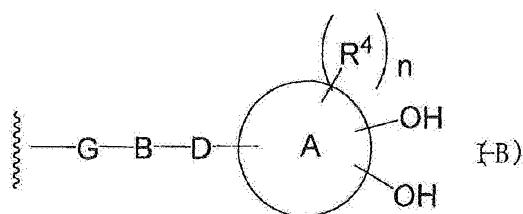
1. a) R^{5A} and R^{5B} are each independently hydrogen, or lower alkyl and R^{5A} and R^{5B} are not hydrogen at the same time,
2. b) R^{5A} and R^{5B} may be taken together with the neighboring atom to form optionally substituted carbocycle or a optionally substituted heterocyclic group, or
3. c) R^{5A} and R^{5B} may be taken together to form optionally substituted methyldiene;

L is $-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{CH}_2-$, $-\text{S}-$, $-\text{CH}_2-\text{S}-$, $-\text{CH}=\text{CH}-\text{S}-$ or $-\text{CH}=\text{CH}-\text{CH}_2-\text{S}-$;

E is an optionally substituted divalent group having at least one quaternary ammonium ion;

R^{10} is hydrogen or a group represented by the formula (I-B) :

[Chemical Formula 2]



wherein,

ring A is a benzene ring, monocyclic heterocycle or fused heterocycle;

n is an integer from 0 to 2;

each R^4 is independently hydrogen, halogen, oxo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{O}-\text{C}(=\text{O})-\text{R}^9$, $-\text{C}(=\text{O})-\text{R}^9$, $-\text{C}(=\text{O})-\text{OH}$, $-\text{C}(=\text{O})-\text{OR}^9$, $-\text{OR}^9$, $-\text{NR}^9\text{R}^9$, $-\text{SO}_2\text{R}^9$, $-\text{SR}^9$, $-\text{NR}^9-\text{C}(=\text{O})-\text{R}^9$, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; provided that two hydroxyl groups on ring A bind respectively to carbon atoms each

adjacently locates;

each R^9 is independently lower alkyl or halo(lower)alkyl;

G is a single bond, optionally substituted lower alkylene, optionally substituted alkenylene or optionally substituted alkynylene;

B is non-existent, a single bond or a 5- or 6-membered heterocyclic group containing at least 1-3 nitrogen atoms;

D is non-existent, a single bond, $-C(=O)-$, $-O-C(=O)-$, $-C(=O)-O-$, $-NR^6-$, $-NR^6-C(=O)-$, $-C(=O)-NR^6-$, $-C(=O)-C(=O)-$, $-NR^6-C(=O)-NR^6-$, $-C(=O)-C(=O)-NR^6-$, $-C(=O)-NR^6-C(=O)-$, $-NR^6-C(=O)-C(=O)-$, $-NR^6-NR^6-C(=O)-$, $-C(=O)-NR^6-NR^6-$, $-N=N-C(=O)-$, $-C(=O)-N=N-$, $-C=N-NR^6-C(=O)-$, $-C=N-C(=O)-$, $-N=C-C(=O)-$, $-C=N-C(=O)-NR^6-$, $-NR^6-C(=O)-C(=N-OR^6)-$, $-C(=N-OR^6)-C(=O)-NR^6-$, $-NR^6-C(=N-OR^6)-$, $-C(=N-OR^6)-NR^6-$, $-C(=O)-C(=N-OR^6)-$, $-C(=N-OR^6)-C(=O)-$, $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-NR^6-$, $-NR^6-S(=O)_2-$, $-NR^6-CH_2-$, $-CH_2-NR^6-$ or $-S(=O)_3-$;

each R^6 is independently hydrogen or optionally substituted lower alkyl;

provided that when R^{10} is hydrogen, E is an optionally substituted divalent cyclic group having at least one quaternary ammonium ion and at least two hydroxyl groups which bind respectively to carbon atoms each adjacently locates on the cyclic group.

Effects of the Invention

[0015] The compounds of the subject invention are useful as a pharmaceutical product having at least one of the following features:

1. 1) the compounds exhibit potent antimicrobial spectrum against a variety of bacteria including Gram negative bacteria and/or Gram positive bacteria;
2. 2) the compounds exhibit potent antimicrobial activity against beta-lactamase producing Gram negative bacteria;
3. 3) the compounds exhibit potent antimicrobial activity against multidrug-resistant bacteria, in particular, Class B type metallo-beta-lactamase producing Gram negative bacteria;
4. 4) the compounds exhibit potent antimicrobial activity against extended-spectrum beta-lactamase (ESBL) producing bacteria;
5. 5) the compounds do not exhibit cross resistance with known cephem drugs and/or carbapenem drugs; and
6. 6) the compounds do not exhibit side effects such as toxicity and fever after administration into the body;
7. 7) the compounds are stable for storage and/or well soluble in water;

8. 8) the compounds of the present invention have excellent features regarding kinetics in the body, such as high blood concentration, high bioavailability, long duration of effects, and/or high tissue migration; and
9. 9) the compounds of the present invention also may exhibit or have antimicrobial activity against biothreat organisms, which may include, but are not limited to those biothreat organisms, such as *Yersinia pestis*, *Bacillus anthracis*, *Francisella tularensis*, *Burkholderia mallei*, *Burkholderia pseudomallei*, *Brucella suis*, *Brucella melitensis* or *Brucella abortus*.

[Preferable Embodiments for Carrying out the Invention]

[0016] It should be understood that, throughout the present specification, the expression of a singular form (e.g., "a", "an", "the", and the like; and in other languages, corresponding articles, adjectives, and the like) includes the concept of its plural form unless specified otherwise. Furthermore, it should be understood that the terms used herein are used in a meaning normally used in the art unless specified otherwise. Thus, unless defined otherwise, all technical and scientific terms used herein have the same meaning as those generally understood by those skilled in the art in the field to which the subject invention pertains. Each specific definition of terms specifically used herein is described below. Each term used herein means, alone or in combination with another word, as below.

[0017] "Halogen" includes fluoro, chloro, bromo and iodo. Preferably, halogen is fluoro, chloro or bromo, and more preferably is chloro.

[0018] "Lower alkyl" includes linear or branched alkyl having 1-8 carbons, preferably 1-6 carbons, and more preferably 1-4 carbons, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, isohexyl, n-heptyl, isoheptyl, n-octyl, and the like.

[0019] "Lower alkylene" includes linear alkylene having 1-8 carbons, preferably 1-6 carbons, more preferably 1-4 carbons, and most preferably one or two carbons, for example, methylene, ethylene, n-propylene, n-butylene, n-pentylene, n-hexylene, and the like.

[0020] "Lower alkenylene" includes linear alkenylene having 2-8 carbons, preferably 2-6 carbons, more preferably 2-4 carbons, and at least one double bond at any position, and includes, for example, vinylene, allylene, propenylene, butenylene, prenylene, butadienylene, pentenylene, pentadienylene, hexenylene, hexadienylene, and the like.

[0021] "Lower alkynylene" includes linear alkynylene having 2-8 carbons, preferably 2-6 carbons, more preferably 2-4 carbons, and at least one triple bond at any position, for example, ethynylene, propynylene, butynylene, pentynylene, hexynylene, and the like.

[0022] "Halo (lower) alkyl" refers to a group in which at least one position of said "lower alkyl" is substituted with the above "halogen", and includes, for example, monofluoromethyl, difluoromethyl, trifluoromethyl, monochloromethyl, dichloromethyl, trichloromethyl, monobromomethyl, monofluoroethyl, monochloroethyl, chlorodifluoromethyl, and the like. Preferably is trifluoromethyl or trichloromethyl.

[0023] "Aralkyl" includes the above lower alkyl substituted with one to three groups selected from "aryl" mentioned below, preferably wherein the carbon number of alkyl is 1 to 4, more preferably is 1 or 2, for example, benzyl, phenethyl, phenylpropyl, trityl, and the like.

[0024] "Heteroaralkyl" includes the above lower alkyl substituted with one to three groups selected from "heteroaryl" mentioned below, preferably wherein the carbon number of alkyl is 1 to 4, more preferably is 1 or 2, for example, furylmethyl, thienylmethyl, pyrrolylmethyl, pyridylmethyl, thienylethyl, furylethyl, imidazolylmethyl, benzothienylmethyl, thiazolylmethyl, and the like.

[0025] "Acyl" includes formyl, optionally substituted lower alkylcarbonyl (e.g., acetyl, propionyl, butyl, isobutyl, valeryl, isovaleryl, pivaloyl, hexanoyl, octanoyl, methoxyethylcarbonyl, 2,2,2-trifluoroethylcarbonyl), optionally substituted alkenyloxycarbonyl (e.g., alloc, cinnamyloxy carbonyl), alkoxycarbonyl (e.g., ethoxycarbonylmethylcarbonyl), (lower)alkoxy(lower)alkylcarbonyl (e.g., methoxyethylcarbonyl), (lower)alkylcarbamoyl(lower)alkylcarbonyl (e.g., methylcarbamoylethylcarbonyl), optionally substituted arylcarbonyl (e.g., benzoyl, toluoyl), optionally substituted cycloalkyloxy carbonyl (e.g., cyclohexyloxycarbonyl), optionally substituted aralkyloxy carbonyl (e.g., benzyloxycarbonyl, p-nitrobenzyloxycarbonyl), optionally substituted heteroaralkyl carbonyl (e.g., thienylmethyl carbonyl) and the like.

[0026] Substituents of "optionally substituted amino" or "optionally substituted carbamoyl" include optionally substituted lower alkyl (e.g., methyl, ethyl, isopropyl, benzyl, carbamoylalkyl (e.g., carbamoylmethyl), mono- or di-(lower)alkylcarbamoyl(lower)alkyl (e.g., dimethylcarbamoylethyl), hydroxy(lower)alkyl, heterocyclyl(lower)alkyl (e.g., morpholinoethyl, tetrahydropyranylethyl), alkoxycarbonyl(lower)alkyl (e.g., ethoxycarbonylmethyl, ethoxycarbonylethyl), mono- or di-(lower)alkylamino(lower)alkyl (e.g., dimethylaminoethyl)); (lower)alkoxy(lower)alkyl (e.g., methoxyethyl, ethoxymethyl, ethoxyethyl, isopropoxyethyl, and the like); acyl (e.g., formyl, optionally substituted lower alkylcarbonyl (e.g., acetyl, propionyl, butyl, isobutyl, valeryl, isovaleryl, pivaloyl, hexanoyl, octanoyl, methoxyethylcarbonyl, 2,2,2-trifluoroethylcarbonyl, alkoxycarbonyl (e.g., ethoxycarbonylmethylcarbonyl), (lower)alkoxy(lower)alkylcarbonyl (e.g., methoxyethylcarbonyl), (lower)alkylcarbamoyl(lower)alkylcarbonyl (e.g., methylcarbamoylethylcarbonyl), optionally substituted arylcarbonyl (e.g., benzoyl, toluoyl); optionally substituted aralkyl (e.g., benzyl, 4-fluorobenzyl); hydroxy; optionally substituted lower alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, isopropylsulfonyl, 2,2,2-trifluoroethanesulfonyl, benzylsulfonyl, methoxyethylsulfonyl); arylsulfonyl optionally having a lower alkyl or halogen as a substituent

(e.g., benzenesulfonyl, toluenesulfonyl, 4-fluorobenzenesulfonyl), cycloalkyl (e.g., cyclopropyl); aryl optionally having lower alkyl as a substituent (e.g., phenyl, tolyl); lower alkylaminosulfonyl (e.g., methylaminosulfonyl, dimethylaminosulfonyl); lower alkylaminocarbonyl (e.g., dimethylaminocarbonyl); lower alkoxy carbonyl (e.g., ethoxy carbonyl); cycloalkyl carbonyl (e.g., cyclopropyl carbonyl, cyclohexyl carbonyl); optionally substituted sulfamoyl (e.g., sulfamoyl, methylsulfamoyl, dimethylsulfamoyl); lower alkyl carbonylamino (e.g., methyl carbonylamino); heterocyclic group (e.g., morpholino, tetrahydropyranyl); optionally substituted amino (e.g., mono- or di-alkylamino (e.g., dimethylamino), formylamino), and the like.

[0027] The above substituted amino or substituted carbamoyl may be mono-substituted or di-substituted.

[0028] "Lower alkenyl" refers to a linear or branched alkenyl having 2 to 8 carbons and having one or more double bonds on said "lower alkyl". The examples include vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,3-butadienyl, 3-methyl-2-butenyl, and the like. Preferred is alkenyl having 2 to 6 carbons, more preferably 2 to 4 carbons.

[0029] With regard to "optionally substituted amino" or "optionally substituted carbamoyl", two substituents of the amino group may be taken together with the adjacent nitrogen atom to form a nitrogen-containing heterocycle which optionally includes a sulfur atom and/or an oxygen atom in the ring (preferably, the heterocycle is a 5- to 7-membered ring, and is preferably saturated). The heterocycle is optionally substituted with oxo or hydroxy. When a sulfur atom forms the heterocycle, said sulfur atom may be substituted with oxo. Examples thereof include 5- or 6-membered rings such as piperazinyl, piperidino, morpholino, pyrrolidino, 2-oxopiperidino, 2-oxopyrrolidino, 4-hydroxymorpholino, and the like.

[0030] Substituents of "optionally substituted lower alkyl" include at least one group selected from Substituent Group alpha. The substitution may be of plurality and the substituents are same or different.

[0031] Substituents of "optionally substituted lower alkylene", "optionally substituted lower alkenylene" and "optionally substituted lower alkynylene" include at least one group selected from Substituent Group alpha. The substitution may be of plurality and the substituents are same or different.

[0032] Substituents of "optionally substituted cycloalkyl" include at least one group selected from Substituent Group alpha. The substitution may be of plurality and the substituents are same or different.

[0033] Substituents of "optionally substituted aryl" include at least one group selected from Substituent Group alpha. The substitution may be of plurality and the substituents are same or different.

[0034] Substituents of "optionally substituted heteroaryl" include at least one group selected

from Substituent Group alpha. The substitution may be of plurality and the substituents are same or different.

[0035] Substituents of "optionally substituted aminosulfonyl" include substituted lower alkyl and at least one group selected from Substituent Group alpha.

[0036] Substituents of "optionally substituted lower alkyloxycarbonyl" include at least one group selected from Substituent Group alpha.

[0037] Substituents of "substituted carbonyloxy" means "-O-C(=O)-substituent", including optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, an optionally substituted carbocyclic group, an optionally substituted heterocyclic group, amino optionally substituted with a heterocyclic group, and at least one group selected from Substituent Group alpha.

[0038] Substituents of "optionally substituted carboxyl" include an optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, an optionally substituted carbocyclic group, and an optionally substituted heterocyclic group.

[0039] "Optionally substituted acyl group" includes carbonyl substituted with optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, an optionally substituted carbocyclic group, or an optionally substituted heterocyclic group.

[0040] Substituents of an "optionally substituted, saturated or unsaturated, monocyclic or fused cyclic quaternary ammonium group" include an optionally substituted lower alkyl, one group selected from Substituent Group alpha, or any two substituents taken together may form a carbocyclic group or heterocyclic group. Lower alkylene, as a substituent in a heterocycle containing a quaternary ammonium group, may form a bridged structure between the quaternary ammonium group and any carbon atom in the heterocycle.

[0041] "Substituent Group alpha" consists of halogen, hydroxy, lower alkoxy, lower alkylene, hydroxy(lower)alkoxy, (lower)alkoxy(lower)alkoxy, carboxy, amino, acylamino, lower(alkyl)amino, imino, hydroxyimino, lower(alkoxy)imino, lower(alkyl)thio, carbamoyl, lower(alkyl)carbamoyl, hydroxy(lower)alkylcarbamoyl, sulfamoyl, lower(alkyl)sulfamoyl, lower(alkyl)sulfinyl, cyano, nitro, a carbocyclic group, and a heterocyclic group.

[0042] The lower alkyl moiety in "lower alkoxy", "hydroxy(lower)alkoxy", "(lower)alkoxy(lower)alkoxy", "lower(alkyl)amino", "lower(alkoxy)imino", "lower (alkyl) thio", "lower(alkyl)carbamoyl", "hydroxy(lower)alkylcarbamoyl", and "lower (alkyl)sulfamoyl", "lower(alkyl)sulfinyl", "lower(alkyl)oxycarbonyl", "lower(alkyl)sulfonyl", is as defined as the above "lower alkyl".

[0043] The lower alkenyl moiety in "lower(alkenyl)oxy", is as defined as the above "lower alkenyl".

[0044] The aryl moiety in "aryloxy" is as defined as "aryl" mentioned below.

[0045] Preferred embodiments of substituents in "optionally substituted lower alkyl" include fluoro, chloro, bromo, hydroxy, carboxy, methoxy, ethoxy, hydroxymethoxy, hydroxyethoxy, methoxymethoxy, methoxyethoxy, amino, acetylamino, methylamino, dimethylamino, imino, hydroxyimino, methoxyimino, methylthio, carbamoyl, methylcarbamoyl, hydroxymethylcarbamoyl, sulfamoyl, methylsulfamoyl, lower alkylsulfamoyl, cyano, nitro, phenyl, cyclopropyl, cyclobutyl, cyclohexyl, pyridyl, morpholinyl, and the like.

[0046] Preferred embodiments of "optionally substituted lower alkyl" include methyl, ethyl, isopropyl, tert-butyl, halo(lower)alkyl (e.g., monochloromethyl, dichloromethyl, trichloromethyl, monofluoromethyl, difluoromethyl, trifluoromethyl), carboxymethyl, carboxyethyl, carbamoylmethyl, carbamoylethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, methylthiomethyl, ethylthiomethyl, benzyl, phenethyl, 4-hydroxybenzyl, 4-methoxybenzyl, 4-carboxybenzyl, and the like.

[0047] Preferred embodiments of substituents in "optionally substituted cycloalkyl" include fluoro, chloro, bromo, hydroxy, carboxy, methoxy, ethoxy, hydroxymethoxy, hydroxyethoxy, methoxymethoxy, methoxyethoxy, amino, acetylamino, methylamino, dimethylamino, imino, hydroxyimino, methoxyimino, methylthio, carbamoyl, methylcarbamoyl, hydroxymethylcarbamoyl, sulfamoyl, methylsulfamoyl, lower alkylsulfamoyl, cyano, nitro, phenyl, cyclopropyl, cyclobutyl, cyclohexyl, pyridyl, morpholinyl, and the like.

[0048] "Carbocyclic group" includes cycloalkyl, cycloalkenyl, aryl and non-aromatic fused carbocyclic groups, and the like.

[0049] "Cycloalkyl" has 3-10 carbons, preferably 3-8 carbons, and more preferably 3-6 carbons, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, and the like.

[0050] "Cycloalkenyl" is cycloalkyl which contains at least one double bond at any position(s), and includes, for example, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptynyl, cyclooctynyl, and cyclohexadienyl, and the like.

[0051] "Aryl" includes phenyl, naphthyl, anthryl, phenanthryl, and the like, and phenyl is preferable.

[0052] "Aromatic carbocycle" means a ring derived from aryl as described below.

[0053] "Aromatic heterocycle" means an aromatic ring, which is monocyclic or bicyclic or more, having same or different one or more hetero atom selected independently from O, S or N.

[0054] The aromatic heterocyclic group which is bicyclic or more includes those wherein a

monocyclic or bicyclic or more aromatic heterocycle is condensed with "aromatic carbocycle" described above.

[0055] "Non-aromatic carbocyclic group" includes the above "cycloalkyl" and "cycloalkenyl", for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptynyl, cyclooctynyl, and cyclohexadienyl and the like.

[0056] "Non-aromatic fused carbocyclic group" includes a group in which one or more cyclic group selected from said "cycloalkyl" and "cycloalkenyl" is fused to said "cycloalkyl" "cycloalkenyl" or "aryl", and includes, for example, indanyl, indenyl, tetrahydronaphthyl, and fluorenyl, and the like.

[0057] "Heterocyclic group" includes heterocyclic groups having at least one hetero atom arbitrarily selected from O, S, and N in the ring, and includes, for example, 5- or 6-membered monocyclic non-aromatic heterocyclic group such as pyrrolidyl, piperidiny, piperadiny, morpholinyl, tetrahydrofuranyl, tetrahydrothienyl, and the like; 5- or 6-membered monocyclic heteroaryl such as pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazolyl, triazinyl, tetrazolyl, isoxazolyl, oxazolyl, oxadiazolyl, isothiazolyl, thiazolyl, thiadiazolyl, furyl, thienyl, and the like; 9- or 10-membered bicyclic fused heterocyclic groups such as indolyl, isoindolyl, indazolyl, indoliziny, indoliny, isoindoliny, quinolyl, isoquinolyl, cinnoliny, phthalazinyl, quinazolinyl, naphthyridinyl, quinoxalinyl, purinyl, pteridinyl, benzopyranyl, benzimidazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, benzoxadiazolyl, benzisothiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, imidazopyridyl, pyrazolopyridine, triazolopyridyl, imidazothiazolyl, pyrazinopyridazinyl, quinazolinyl, quinolyl, isoquinolyl, naphthyridinyl, dihydrobenzofuryl, tetrahydroquinolyl, tetrahydroisoquinolyl, dihydrobenzoxazine, tetrahydrobenzothienyl, and the like; tricyclic fused heterocyclic groups such as carbazolyl, acridinyl, xanthenyl, phenothiadiny, phenoxathiinyl, phenoxazinyl, dibenzofuryl, imidazoquinolyl, and the like; non-aromatic heterocyclic groups such as dioxanyl, thioranyl, oxiranyl, oxathiolanyl, azetidiny, thianyl, thiazolidine, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, thiomorpholino, dihydropyridyl, dihydrobenzimidazolyl, tetrahydropyridyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiazolyl, tetrahydroisothiazolyl, dihydrooxazinyl, hexahydroazepinyl, tetrahydrodiazepinyl, and the like. Preferably, the heterocyclic group is a 5- or 6-membered monocyclic heterocyclic group or 9- or 10-membered bicyclic fused heterocyclic group, and more preferably, a 5- or 6-membered heteroaryl or 9- or 10-membered bicyclic fused heterocyclic group.

[0058] "Heteroaryl" means an aromatic heterocyclic group described above. Preferred is 5- or 6-membered monocyclic heteroaryl or 9- or 10-membered bicyclic heteroaryl.

[0059] "Heterocycle" means a ring derived from a heterocyclic group as described above. Preferred is 5- or 6-membered monocyclic heterocycle or 9- or 10-membered bicyclic heterocycle.

[0060] "Fused heterocycle" means a ring condensed with at least one heterocycle, includes those wherein monocyclic, bicyclic or more heterocycle is condensed with "carbocycle" described above. Preferred is 9- or 10-membered bicyclic heterocycle having at least one nitrogen atom.

[0061] "Monocyclic heterocycle" is preferably 5- to 7-membered heterocycle, and more preferably 6-membered heterocycle having at least one nitrogen atom.

[0062] "Non-aromatic heterocyclic group" means a group which does not show aromatic character of the "heterocyclic group".

[0063] Substituents of "optionally substituted carbocyclic group", "optionally substituted heterocyclic group", "optionally substituted non-aromatic carbocyclic group", and "optionally substituted non-aromatic heterocyclic group" include optionally substituted lower alkyl, and at least one group selected from Substituent Group alpha.

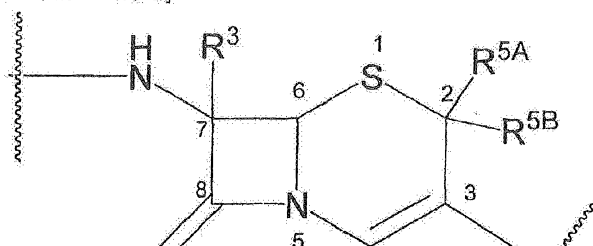
[0064] Preferred embodiments of substituents in "optionally substituted carbocyclic group", "optionally substituted heterocyclic group", "optionally substituted non-aromatic carbocyclic group" and "optionally substituted non-aromatic heterocyclic group" include methyl, ethyl, isopropyl, tert-butyl, a fluorine atom, a chlorine atom, a bromine atom, hydroxy, carboxy, methoxy, ethoxy, hydroxymethoxy, hydroxyethoxy, methoxymethoxy, methoxyethoxy, amino, acetylamino, methylamino, dimethylamino, imino, hydroxyimino, methoxyimino, methylthio, carbamoyl, methylcarbamoyl, hydroxymethylcarbamoyl, sulfamoyl, methylsulfamoyl, lower alkylsulfamoyl, cyano, nitro, phenyl, cyclopropyl, cyclobutyl, cyclohexyl, pyridyl, morpholinyl, and the like.

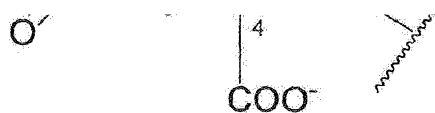
[0065] "5- or 6-membered aromatic heterocyclic group having 1-3 nitrogen atoms" includes pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazolyl, triazinyl, isoxazolyl, oxazolyl, oxadiazolyl, isothiazolyl, thiazolyl, thiadiazolyl, furyl, thienyl, and the like.

[0066] Examples of "optionally substituted carbocyclic group" or "optionally substituted heterocyclic group" of R^1 include phenyl, aminothiazole, aminothiadiazole, thiophene, furan, benzothiazole, pyridine, pyrimidine, pyridazine, aminopyridine, and the like, each optionally substituted with hydroxyl and/or halogen.

[0067] The nomenclature of the substitution position on the cephem skeleton of Formula (I) is as follows. As used herein, 3-side chain, 4-side chain and 7-side chain respectively refer to groups binding to the 3-position, 4-position and the 7-position of the cephem skeleton

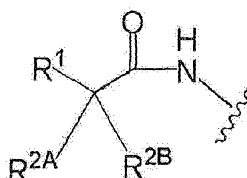
[Chemical Formula 104]





[0068] Esters of Formula (I) preferably include those at the 7-side chain. Esters at the carboxyl group on the 7-side chain include compounds, wherein any carboxyl group of optionally substituted amino, optionally substituted aminosulfonyl, carboxyl, optionally substituted (lower)alkyloxycarbonyl, optionally substituted carbamoyl, substituted carbonyloxy, or the like at the terminal of R^1 , R^{2A} or R^{2B} shown in the formula:

[Chemical Formula 105]



wherein each symbol is as defined above, is esterified. For example, in the case of carboxyl (-COOH), such esters are represented by the structural formula $-COOR^a$, wherein R^a is an ester residue such as a carboxyl-protecting group or the like. Such esters include those easily metabolized in the body to form a carboxylic state.

[0069] The aforementioned protecting groups for carboxyl or the like may be any group as long as it can be protected and/or deprotected by a method described in Protective Groups in Organic Synthesis, written by T. W. Greene, John Wiley & Sons Inc. (1991), or the like. Examples thereof include lower alkyl (e.g., methyl, ethyl, t-butyl), (lower)alkylcarbonyloxymethyl (e.g., pivaloyl), optionally substituted aralkyl (e.g., benzyl, benzhydryl, phenethyl, p-methoxybenzyl, p-nitrobenzyl), silyl groups (t-butyldimethylsilyl, diphenyl(t-butyl)silyl), and the like.

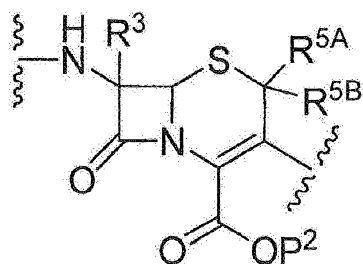
[0070] Amino-protected compounds at the amino on the 7-side chain of Formula (I) refer to the structures in which the amino on the ring (e.g., thiazole, thiadiazole) has been protected;

[0071] The amino protected group is represented by the formula $-NHR^c$ wherein R^c represents an amino-protecting group. Such amino-protecting groups include those groups that are readily metabolized in the body to form amino. The aforementioned amino-protecting groups may be any group as long as it can be protected and/or deprotected by a method described in Protective Groups in Organic Synthesis, written by T. W. Greene, John Wiley & Sons Inc. (1991), or the like. Examples thereof include (lower)alkoxycarbonyl (e.g., t-butoxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl), optionally substituted aralkanoyl (e.g., benzoyl, p-nitrobenzoyl), acyl (e.g., formyl, chloroacetyl), and the like.

[0072] The Compound (I) of the subject invention is not limited to particular isomers, but includes any possible isomers (e.g., keto-enol isomer, imine-enamine isomer, diastereoisomer, geometrical isomer, optical isomer, rotamer, etc.), racemates and a mixture thereof.

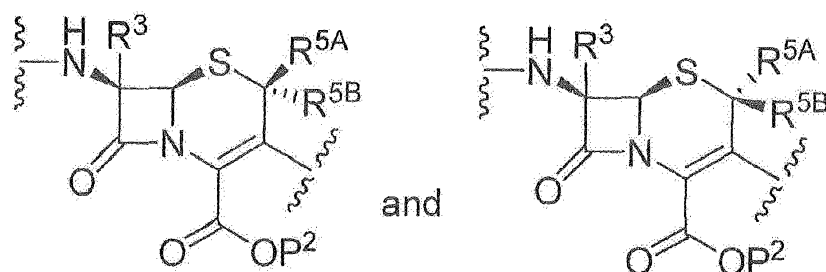
[0073] For example, the Formula (I):

[Chemical Formula 106]



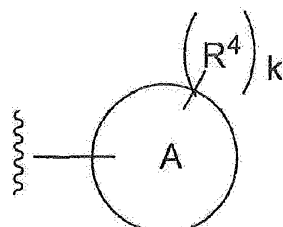
includes

[Chemical Formula 107]



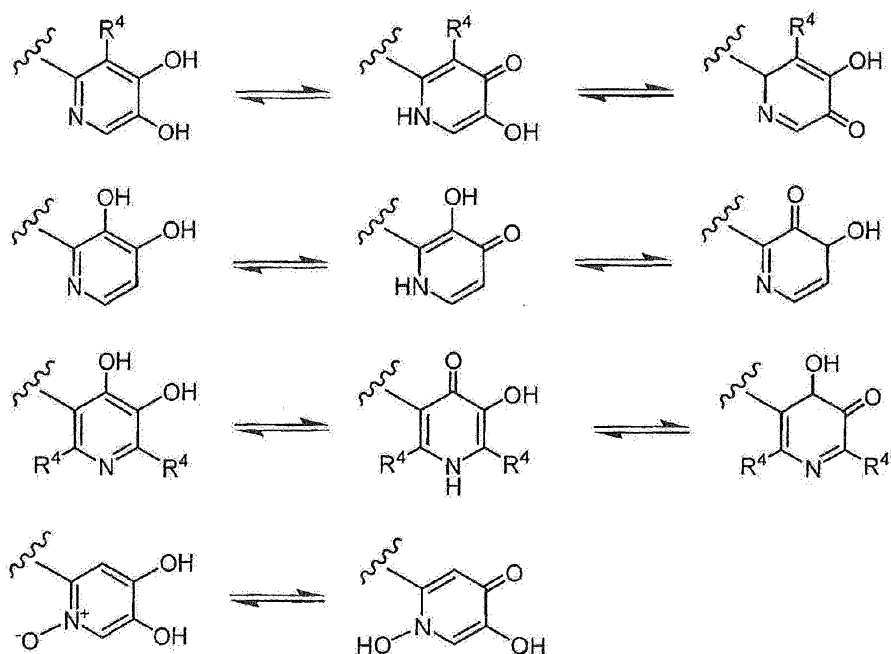
[0074] For example, the formula:

[Chemical Formula 108]



wherein each symbol is as defined above, includes the following resonance structures:

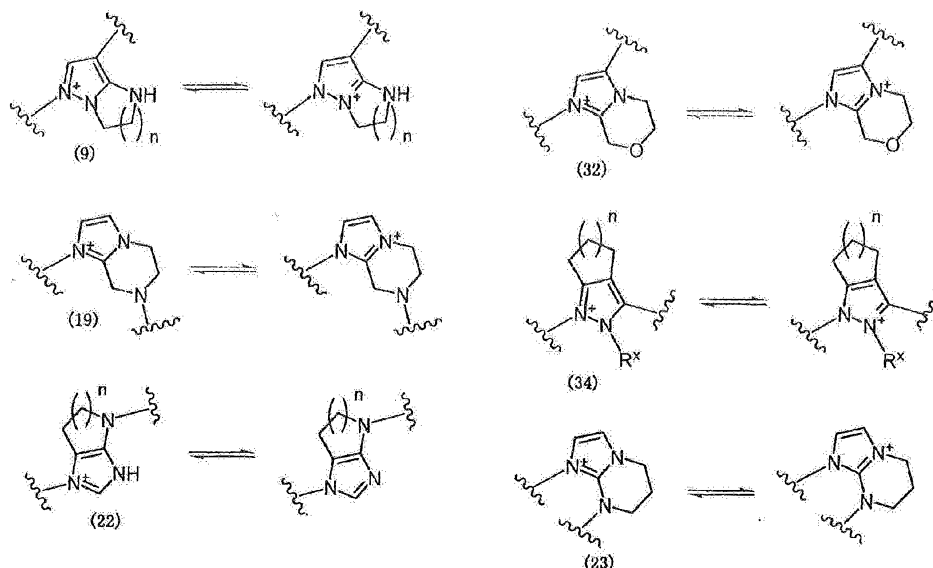
[Chemical Formula 109]



wherein R^4 is as defined above.

[0075] Also, the group "E" in Formula (I), for example, includes the following resonance structures:

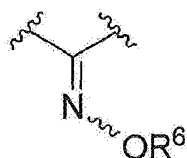
[Chemical Formula 110]



wherein each symbol is as defined above.

[0076] For example, the formula:

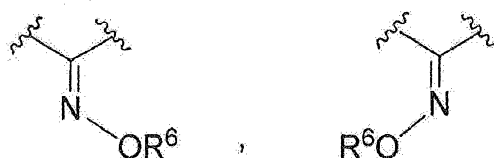
[Chemical Formula 111]



wherein, R_6 is as defined above;

includes

[Chemical Formula 112]



and a mixture thereof.

[0077] At least one hydrogen atom, carbon atom and/or another atom may be replaced with an isotope of said hydrogen atom, carbon atom and/or another atom. Examples of such isotope include hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine, iodine and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{123}I and ^{36}Cl . The compound of Formula (I) include compounds having an atom replaced with such isotope. Such compound replaced with an isotope are useful as a pharmaceutical product, and such compound include all of radiolabeled compound of Formula (I). Also, the subject invention includes any method of radioactive labeling for the production of such radiolabeled compound, and thus, it is useful in a research for metabolic pharmacokinetics, binding assay and/or as a diagnostic tool.

[0078] A radiolabeled compound of Formula (I) may be prepared according to the technique well known in the art. For example, tritium can be introduced into a specific compound of Formula (I) by catalytic dehalogenation using tritium to prepare a tritium-labeled compound of Formula (I). This method comprises reaction of a precursor which is a compound of Formula (I) appropriately halogenated with tritium gas in the presence of appropriate catalyst, such as Pd/C, in the presence or absence of a base. For another method for the preparation of a tritium-labeled compound, see the literature, *Isotopes in the Physical and Biomedical Sciences*, Vol.1, Labeled Compounds (Part A), Chapter 6 (1987) . ^{14}C -labeled compound can be prepared using a starting material having ^{14}C .

[0079] Salts of a compound of Formula (I) include those formed with an inorganic or organic acid by a carboxyl group in the 7-side chain and/or an amino group in the 7-side chain; and those formed with a counter anion by a quaternary amine moiety in the 3-side chain.

[0080] Pharmaceutically acceptable salts of a compound of Formula (I) include, for example, salts formed with alkali metal (e.g. lithium, sodium, potassium, etc.), alkaline earth metal (e.g. calcium, barium, etc.), magnesium, transition metal (e.g. zinc, ferrum, etc.), ammonia, organic base (e.g. trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine, meglumine, diethanolamine, ethylenediamine, pyridine, picoline, quinoline, etc.) and amino acid, or salts formed with inorganic acid (e.g. hydrochloric acid, sulphuric acid, nitric acid, carbonic acid, hydrobromic acid, phosphoric acid, hydroiodic acid, etc.), or organic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, citric acid, lactic acid, tartaric acid, oxalic acid, maleic acid, fumaric acid, mandelic acid, glutaric acid, malic acid, benzoic acid, phthalic acid, ascorbic acid, benzenesulphonic acid, p-toluenesulfonic acid, methanesulphonic acid, ethanesulphonic acid, etc, particularly, salts formed with hydrochloric acid, sulphuric acid, phosphoric acid, tartaric acid, methanesulphonic acid. These salts can be formed according to the conventional method.

[0081] The compound of Formula (I) or pharmaceutically acceptable salts thereof may form a solvate (e.g., hydrate) and/or a crystalline polymorphism, and the subject invention also includes such solvates and crystalline polymorphisms. In such "solvate", any number of solvent molecules (e.g., water molecule, etc.) maybe coordinated to the compound of Formula (I) . By leaving the compound of Formula (I) or pharmaceutically acceptable salt thereof in the atmosphere, it may absorb moisture to adhere with absorbed water or form a hydrate thereof. Also, a crystalline polymorphism of the compound of Formula (I) or pharmaceutically acceptable salt thereof can be formed by recrystallization.

[0082] The compound of Formula (I) or pharmaceutically acceptable salt thereof may form a prodrug, and the subject invention includes such prodrugs. Prodrug is a derivative of the compound of the invention having a group chemically- or metabolically-degradable to be transformed into a pharmacologically active compound by solvolysis or under physiological condition in vivo. Prodrug includes compounds which can be transformed into the compound of Formula (I) by enzymatically oxidization, reduction or hydrolysis under physiological condition

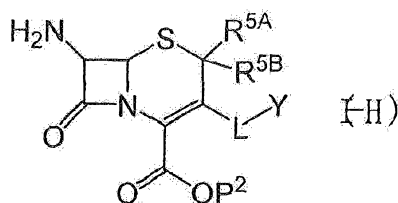
in vivo, or transformed into the compound of Formula (I) by hydrolysis with gastric acid, etc. Methods for selection and production of appropriate prodrug derivative can be found, for example, in Design of Prodrugs, Elsevier, Amsterdam 1985.

[0083] Prodrug may be active compound in itself.

[0084] When the compound of Formula (I) or pharmaceutically acceptable salt thereof has hydroxyl, acyloxy derivatives or sulfonyloxy derivatives can be prepared as a prodrug. For example, such compound having hydroxyl may be reacted with an appropriate acyl halide, acid anhydride or an appropriate sulfonyl chloride, sulfonyl anhydride, mixed anhydride, etc., or may be reacted using a coupling agent, such as for examples, those having $\text{CH}_3\text{COO}-$, $\text{C}_2\text{H}_5\text{COO}-$, $\text{t-BuCOO}-$, $\text{C}_{15}\text{H}_{31}\text{COO}-$, $\text{PhCOO}-$, $(\text{m-NaOOCPh})\text{COO}-$, $\text{NaOOCCH}_2\text{CH}_2\text{COO}-$, $\text{CH}_3\text{CH}(\text{NH}_2)\text{COO}-$, $\text{CH}_2\text{N}(\text{CH}_3)_2\text{COO}-$, CH_3SO_3- , $\text{CH}_3\text{CH}_2\text{SO}_3-$, CF_3SO_3- , CH_2FSO_3- , $\text{CF}_3\text{CH}_2\text{SO}_3-$, $\text{p-CH}_3\text{-O-PhSO}_3-$, PhSO_3- , $\text{p-CH}_3\text{PhSO}_3-$.

[0085] For the synthesis of a compound of Formula (I), A compound of the formula (I-H):

[Chemical formula 34]



wherein,

Y is a leaving group; P^2 is a protecting group;

$\text{R}^{5\text{A}}$, $\text{R}^{5\text{B}}$ and L are as defined above,

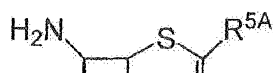
or a pharmaceutically acceptable salt thereof is preferred as an intermediate.

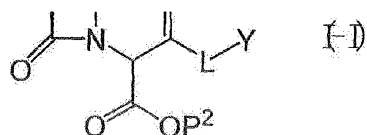
[0086] The compound of the formula (I-H), or a salt thereof, wherein P^2 is benzhydryl group, p-methoxybenzyl group, trityl group, 2,6-dimethoxybenzyl group, methoxymethyl group, benzyloxymethyl group or 2-(trimethylsilyl)ethoxymethyl group is preferred as an intermediate.

[0087] The compound of the formula (I-H), or a salt thereof, wherein $\text{R}^{5\text{A}}$ is methyl and $\text{R}^{5\text{B}}$ is hydrogen is preferred as an intermediate.

[0088] For the synthesis of a compound of Formula (I), a compound of the formula (I-I):

[Chemical formula 35]





or a salt thereof,
wherein,

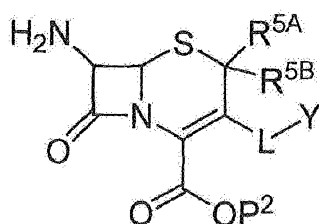
Y is a leaving group; P² is a protecting group;

R^{5A} and L are as defined above ,

or a pharmaceutically acceptable salt thereof is preferred as an intermediate.

[0089] For the synthesis of a compound of Formula (I), a compound of the formula:

[Chemical Formula 113]



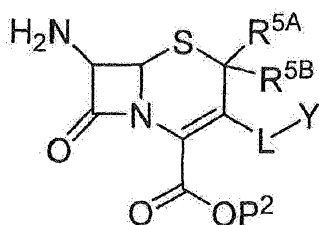
wherein, Y is a leaving group; P² is a protecting group; R^{5A}, R^{5B} and L are as defined above,

or a pharmaceutically acceptable salt thereof is preferred as an intermediate. The 7-amino can be formed with a counter anion (Z⁻) to be a salt (-NH₃⁺Z⁻)

[0090] The leaving group includes halogen (Cl, Br, I, F), acetoxy, methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy, etc.

[0091] Preferred example of a compound of the formula:

[Chemical Formula 114]

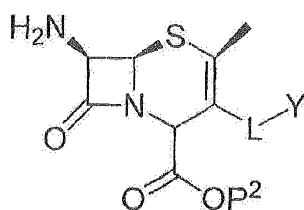


wherein, Y is a leaving group; P² is a protecting group; R^{5A},

R^{5B} and L are as defined above,

is a compound of the formula:

[Chemical Formula 115]



wherein, Y is a leaving group; P2 is a protecting group; L is as defined above.

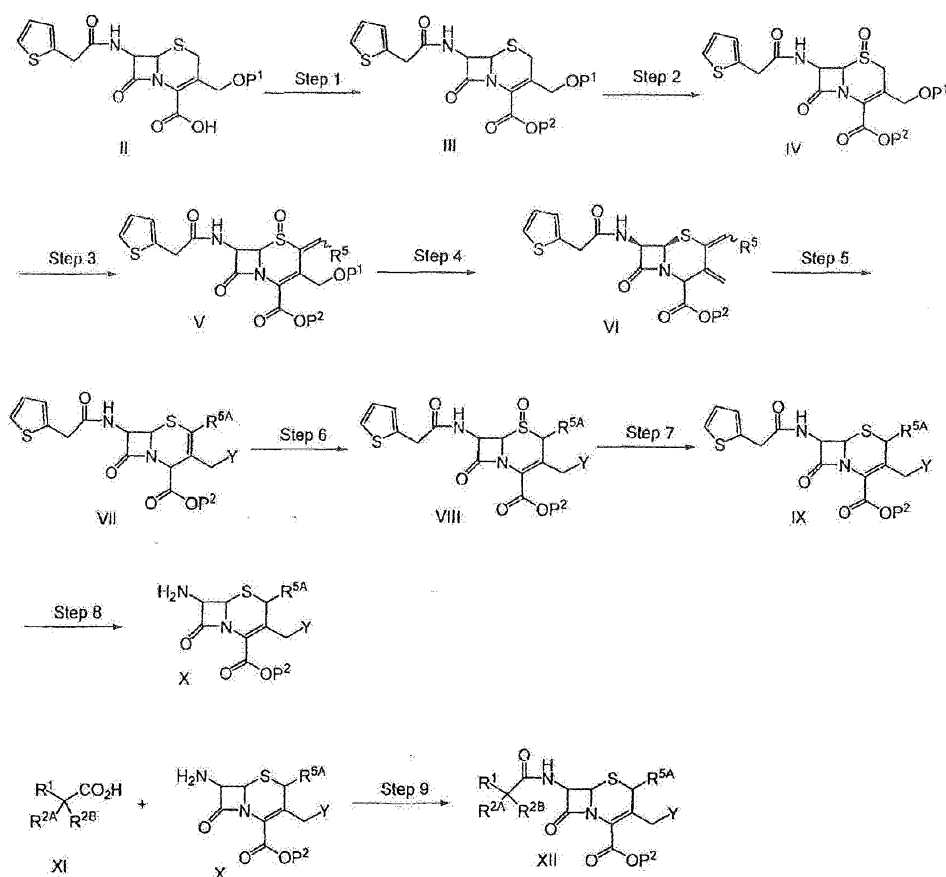
[0092] As described in the following General Synthesis and Examples, an intermediate compound described above is reacted with side chain moieties at the 3-, 4- and 7-positions of the cephem skeleton to obtain a compound of Formula (I). Examples of the protecting group "P²" include those described in the following General Synthesis, and preferably, benzhydryl, p-methoxybenzyl, trityl, 2,6-dimethoxybenzyl, methoxymethyl, benzyloxymethyl or 2-(trimethylsilyl)ethoxymethyl, etc.

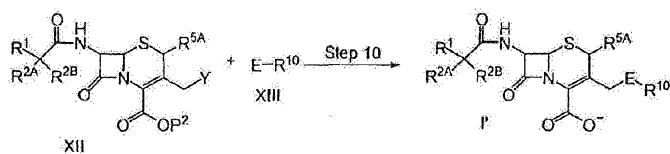
(General Synthesis Method)

[0093] Scheme 1 represents a general scheme for the preparation of compounds of the present invention.

[Chemical Formula 116]

Scheme 1





wherein, P^1 and P^2 are protecting groups; Y is a leaving group (e.g., a halogen (Cl, Br, I, F), methanesulfonyloxy, p-toluenesulfoxy) ; R5 is hydrogen or lower alkyl; other symbols are as defined above.

1) Formation of 2-methyl cephem: Synthesis of Compound (X)

Step 1

[0094] The 4-carboxyl group of the compound (II) is protected with a carboxyl-protecting group by a conventional method to give the compound (III). The carboxyl-protecting group is exemplified by diphenyl methyl, p-methoxybenzyl etc.

[0095] The reaction solvents include, for example, ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), dimethylsulfoxide, water and a mixed solvent thereof.

[0096] The reaction temperature is usually in the range of from about -100°C to 100°C , preferably from about -80°C to 80°C , more preferably from about -60°C to 60°C . The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

Step 2

[0097] The compound (IV) is obtained by subjecting the compound (III) to oxidation reaction using an oxidation agent well-known to those skilled in the art (e.g., m-chloroperoxybenzoic acid, acetic peroxide).

[0098] The reaction solvents include, for example, ethers (e.g., anisole, dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, n-butyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-

methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), nitros (e.g., nitromethane, nitroethane, nitrobenzene), dimethylsulfoxide, water, and a mixed solvent selected from two or more of these solvents. The reaction temperature is usually in the range of from about -100°C to 100°C, preferably from about -80°C to 50°C, more preferably about -60°C to -30°C. The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is carried out for 0.5 to 24 hours.

Step 3

[0099] The compound (IV) is reacted with aldehyde (i.e. R^5CHO) and a primary or secondary amine to give the compound (V).

[0100] Aldehyde include, for example, formaldehyde and lower alkyl aldehyde (e.g. acetaldehyde, propionaldehyde). Aldehyde is generally used in an amount of about 1 to 100 moles, preferably 1 to 30 moles, for 1 mole of the compound (IV).

[0101] A primary or secondary amine include, for example, methylamine, dimethylamine, ethylamine and diethylamine. A primary or secondary amine, including its salt, is generally used in an amount of about 1 to 100 moles, preferably 1 to 30 moles, for 1mole of the compound (IV).

[0102] The reaction solvents include, for example, ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetarachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), dimethylsulfoxide, water, and a mixed solvent thereof.

[0103] The reaction temperature is usually in the range of from about -100°C to 100°C, preferably from about -80°C to 80°C, more preferably from about 0°C to 80°C. The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

Step 4

[0104] The compound (V) is reacted with a reductant (e.g., zinc, copper, mixture thereof) and an acid (e.g., Hydrochloric acid, acetic acid, formic acid) to give the compound (VI).

[0105] Zinc is generally used in an amount of about 1 to 100 moles, preferably 1 to 30 moles, for 1mole of the compound (V). Acid (e.g., Hydrochloric acid, acetic acid, formic acid) is

generally used in an amount of about 1 to 100 moles, preferably 1 to 30 moles, for 1mole of the compound (V).

[0106] The reaction solvents include, for example, ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), acid (e.g., Hydrochloric acid, acetic acid, formic acid), dimethylsulfoxide, water, and a mixed solvent thereof.

[0107] The reaction temperature is usually in the range of from about -100°C to 100°C, preferably from about -80°C to 80°C, more preferably from about -20°C to 60°C. The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

Step 5

[0108] The compound (VI) is reacted with hydrohalic acid such as hydrochloric acid, etc. to give the compound (VII). Hydrohalic acid is generally used in an amount of about 1 to 100 moles, preferably 1 to 30 moles, for 1mole of the compound (VI) . The reaction solvents include, for example, ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), dimethylsulfoxide, water, and a mixed solvent thereof.

[0109] The reaction temperature is usually in the range of from about -100°C to 100°C, preferably from about -80°C to 80°C, more preferably from about -20°C to 60°C. The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

Step 6

[0110] The compound (VII) is reacted with a peroxyacid (e.g., meta-Chloroperoxybenzoic acid, peroxyacetic acid), etc. to give the crude sulfoxide compound. Furthermore, the crude sulfoxide compound is reacted with a base (e.g. triethylamine, sodium acetate, sodium bicarbonate, sodium hydrogen carbonate) to give the single stereoisomer sulfoxide compound(VIII). Peroxyacid is generally used in an amount of about 1 to 100 moles, preferably 1 to 30 moles,

for 1 mole of Compound (III). The reaction solvents include, for example, alcohols (e.g., methanol, ethanol), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone). The reaction temperature is usually in the range of from about -100°C to 100°C, preferably from about -80°C to 50°C, more preferably from about -20°C to 0°C. The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

Step 7

[0111] The compound (VIII) is reacted with a reductant (e.g., phosphorus trichloride, phosphorus tribromide) to give the compound (IX).

The reductant (e.g., phosphorus trichloride, phosphorus tribromide) is generally used in an amount of about 1 to 100 moles, preferably 1 to 30 moles, for 1 mole of Compound (VIII).

The reaction solvents include, for example, halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone). The reaction temperature is usually in the range of from about -100°C to 100°C, preferably from about -80°C to 50°C, more preferably from about -60°C to 0°C. The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

Step 8

[0112] The compound (X) is obtained by subjecting Compound (IX) to a hydrolysis reaction to make amide on 7-side chain to an amino group, followed by treating the compound with a hydrohalic acid such as hydrochloric acid. The reaction solvents include, for example, ethers (e.g., anisole, dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, n-butyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), nitros (e.g., nitromethane, nitroethane, nitrobenzene), dimethylsulfoxide, water, and a mixed solvent selected from two or more thereof. The reaction temperature is usually in the range of from about -100°C to 100°C, preferably from about -50°C to 50°C, more preferably from about -40°C to 30°C. The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

2) Formation of the 7-saide chain: Synthesis of the compound (XII).

Step 9

[0113] The compound (X) is subjected to condensation reaction with the compound (XI) to give the compound (XII). The reaction solvents include, for example, water, ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), dimethylsulfoxide, water, and a mixed solvent thereof.

[0114] The reaction temperature is usually in the range of from about -100°C to 100°C, preferably from about -80°C to 80°C, more preferably from about -60°C to 50°C. The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

3) Formation of the 3-side chain: Synthesis of the compound (I)**Step 10**

[0115] The compound (I') is obtained by subjecting the compound (XII) to a substitution reaction with the compound (XIII) and then subjecting it to deprotection reaction. The reaction solvents used in the reaction between the compound (XII) and the compound (XIII) include, for example, ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), dimethylsulfoxide, water, and a mixed solvent thereof. The reaction temperature is usually in the range of from about -100°C to 100°C, preferably from about -80°C to 80°C, more preferably from about -20°C to 30°C. The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

[0116] The protecting group to be used in the above reaction such as amino-protecting groups, hydroxy-protecting groups, etc. includes, for example, protecting groups described in Protective Groups in Organic Synthesis, written by T. W. Greene, John Wiley & Sons Inc. (1991), etc. Methods for the introduction and removal of a protecting group are methods

commonly used in synthetic organic chemistry (see, for example, methods described in *Protective Groups in Organic Synthesis*, written by T. W. Greene, John Wiley & Sons Inc. (1991)), etc., or can be obtained by a modified method thereof. Furthermore, a functional group included in each substituent can be converted by a known method (e.g., those described in *Comprehensive Organic Transformations*, written by R. C. Larock (1989), etc.) in addition to the above production methods. Some of the compounds of the present invention can be used as a synthetic intermediate, leading to a new derivative. Intermediates and desired compounds produced in each of the above production methods can be isolated and purified by a purification method commonly used in synthetic organic chemistry, for example, neutralization, filtration, extraction, washing, drying, concentration, recrystallization, any kind of chromatography, etc. Furthermore, intermediates can be subjected to a next reaction without any purification.

[0117] Examples of an amino-protecting group include phthalimide, lower alkoxy carbonyl (butoxycarbonyl (Boc) etc.), lower alkenyloxy carbonyl (allyloxy carbonyl (Alloc), etc.), benzyloxy carbonyl, p-nitrobenzyloxy carbonyl, optionally substituted aralkanoyl (p-nitrobenzoyl, etc.), acyl (formyl, chloroacetyl, etc.), optionally substituted aralkyl (trityl, etc.), benzhydryl (BH), and the like.

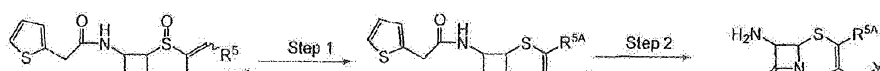
[0118] Examples of a hydroxy-protecting group include lower alkoxy carbonyl such as a C1-C4 alkoxy carbonyl (e.g., t-butyloxy carbonyl), halogenated lower alkoxy carbonyl such as a halogenated (C1-C3) alkoxy carbonyl (e.g., 2-iodo ethyloxy carbonyl, 2,2,2-trichloroethyloxy carbonyl), aryl-(lower) alkoxy carbonyl such as a phenyl-(C1-C4) alkoxy carbonyl having optionally a substituent (s) on the benzene ring (benzyloxy carbonyl, o-nitrobenzyloxy carbonyl, p-nitrobenzyloxy carbonyl, p-methoxybenzyloxy carbonyl), p-methoxybenzyl (PMB), tri-lower alkylsilyl such as tri-(C1-C4) alkylsilyl (e.g., trimethylsilyl, t-butyldimethylsilyl), a substituted methyl such as C1-C4 alkoxymethyl (e.g., methoxymethyl), C1-C4 alkoxy-(C1-C4) alkoxymethyl (e.g., 2-methoxyethoxymethyl), C1-C4 alkylthiomethyl (e.g., methylthiomethyl), tetrahydropyranyl, and the like.

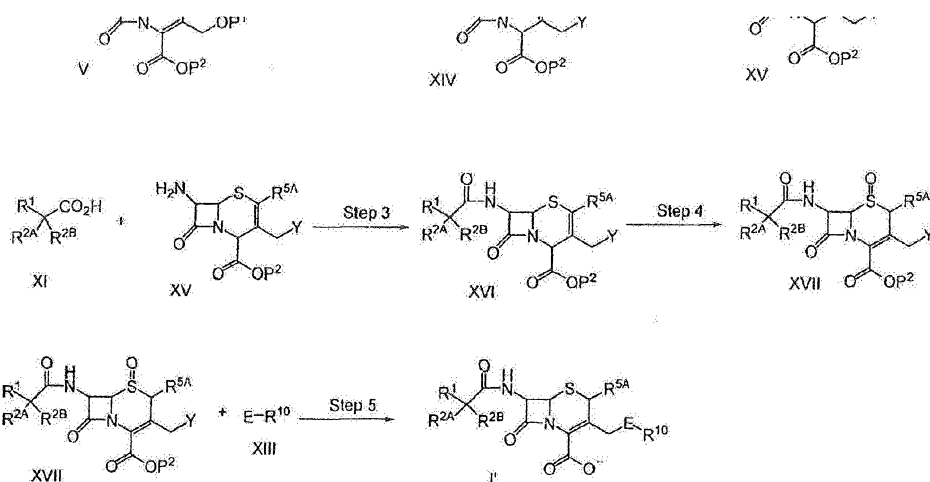
[0119] The above-mentioned deprotecting reaction is carried out in a solvent such as tetrahydrofuran, dimethylformamide, diethyl ether, dichloromethane, toluene, benzene, xylene, cyclohexane, hexane, chloroform, ethyl acetate, butyl acetate, pentane, heptane, dioxane, acetone, acetonitrile, or a mixed solvent thereof, using a Lewis acid (e.g., AlCl_3 , SnCl_4 , TiCl_4), a protonic acid (e.g., HCl , HBr , H_2SO_4 , HCOOH), and the like.

[0120] The obtained compound is further chemically modified, and thereby an ester, or a compound of which amino on the thiazole or thiadiazole ring at the 7-position thereof is protected, or a pharmaceutically acceptable salt, or a solvate thereof can be synthesized.

[Chemical Formula 117]

Scheme 2





wherein, P¹ and P² are protecting groups; Y is a leaving group (e.g., a halogen (Cl, Br, I, F), methanesulfonyloxy, pe-toluenesulfoxy); R⁵ is lower alkyl; other symbols are as defined above.

(1) Synthesis of the compound (XV)

Step 1

[0121] The compound (V) is reacted with a reductant (e.g., phosphorus trichloride, phosphorus tribromide), followed by treating the resultant with a hydrohalic acid such as hydrochloric acid, etc. to give the compound (IX).

[0122] The reaction solvents include, for example, ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), dimethylsulfoxide, water, and a mixed solvent thereof.

[0123] The reaction temperature is usually in the range of from about -100°C to 100°C, preferably from about -80°C to 80°C, more preferably from about -20°C to 60°C. The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

Step2

[0124] The compound (XV) is obtained by subjecting Compound (XIV) to a hydrolysis reaction to make amide on 7-side chain to an amino group, followed by treating the compound with a hydrohalic acid such as hydrochloric acid. The reaction solvents include, for example, ethers

(e.g., anisole, dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, n-butyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), nitros (e.g., nitromethane, nitroethane, nitrobenzene), dimethylsulfoxide, water, and a mixed solvent selected from two or more thereof. The reaction temperature is usually in the range of from about -100°C to 100°C, preferably from about -50°C to 50°C, more preferably from about -40°C to 30°C. The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

2) Formation of the 7-saïde chain: Synthesis of the compound (XVII).

Step 3

[0125] The compound (XV) is subjected to condensation reaction with the compound (XI) to give the compound (XVI). The reaction solvents include, for example, water, ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), dimethylsulfoxide, water, and a mixed solvent thereof.

[0126] The reaction temperature is usually in the range of from about -100°C to 100°C, preferably from about -80°C to 80°C, more preferably from about -60°C to 50°C. The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

Step 4

[0127] The compound (XVII) is obtained by subjecting the compound (XVI) to oxidation reaction using an oxidation agent well-known to those skilled in the art (e.g., m-chloroperbenzoic acid, acetic peroxide).

[0128] The reaction solvents include, for example, ethers (e.g., anisole, dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, n-butyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene,

toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), nitros (e.g., nitromethane, nitroethane, nitrobenzene), dimethylsulfoxide, water, and a mixed solvent selected from two or more thereof. The reaction temperature is usually in the range of from about -100°C to 100°C , preferably from about -80°C to 50°C , more preferably from about -60°C to -30°C . The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is carried out for 0.5 to 24 hours.

[0129] The obtained compound (XVII) can be purified by column chromatography to obtain each 2-methyl stereoisomer.

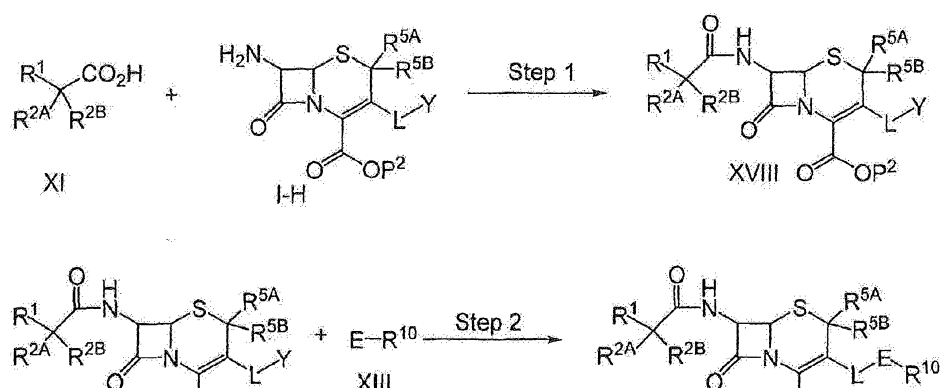
3) Formation of the 3-side chain: Synthesis of the compound (I)

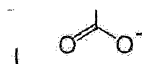
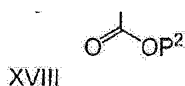
Step 5

[0130] Compound (I') is obtained by subjecting Compound (XVII) to a substitution reaction with Compound (XIII) by a method well-known to those skilled in the art, followed by reducing it with a reduction agent well-known to those skilled in the art (e.g., phosphorus chloride, phosphorus tribromide), and then subjecting it to a deprotection reaction. The reaction solvents include, for example, ethers (e.g., anisole, dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether), esters (e.g., ethyl formate, ethyl acetate, n-butyl acetate, isopropyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, toluene), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), nitriles (e.g., MeCN, propionitrile), nitros (e.g., nitromethane, nitroethane, nitrobenzene), dimethylsulfoxide, water, and a mixed solvent selected from two or more thereof. The reaction temperature is usually in the range of from about -100°C to 100°C , preferably from about -80°C to 50°C , more preferably from about -40°C to 0°C . The reaction time may vary according to the reagents, solvents or reaction temperature to be employed, but usually is 0.5 to 24 hours.

[Chemical Formula 118]

Scheme 3





wherein, P^2 is protecting groups; Y is a leaving group (e.g., a halogen (Cl, Br, I, F), methanesulfonyloxy, pe-toluenesulfoxy); other symbols are as defined above.

(1) Synthesis of the compound (I)

Step 1

[0131] The compound (XVIII) is obtained by reaction of the compound (XI) and the compound (I-H) as the similar procedure described in Step 9 of Scheme 1.

Step 2

[0132] The compound (I) is obtained by reaction of the compound (XVIII) and the compound (XIII) as the similar procedure described in Step 10 of Scheme 1.

[0133] The compounds of the present invention have a wide antimicrobial activity spectrum, and may be used for prevention or therapy against a variety of diseases caused by causative bacteria in a variety of mammals including humans, for example, airway infectious diseases, urinary system infectious diseases, respiratory system infectious diseases, sepsis, nephritis, cholecystitis, oral cavity infectious diseases, endocarditis, pneumonia, bone marrow membrane myelitis, otitis media, enteritis, empyema, wound infectious diseases, opportunistic infection, etc.

[0134] The compounds of the present invention exhibit high antimicrobial activity in particular against Gram negative bacteria, preferably, Gram negative bacteria of enterobacteria (*E. coli*, *Klebsiella*, *Serratia*, *Enterobacter*, *Citrobacter*, *Morganella*, *Providencia*, *Proteus*, etc.), Gram negative bacteria colonized in respiratory system (*Haemophilus*, *Moraxella*, etc.), and Gram negative bacteria of glucose non fermentation (*Pseudomonas aeruginosa*, *Pseudomonas* other than *P. aeruginosa*, *Stenotrophomonas*, *Burkholderia*, *Acinetobacter*, etc.). The compounds are stable against beta-lactamase belonging to Classes A, B, C and D which is produced by these Gram negative bacteria, and have high antimicrobial activity against a variety of beta-lactam drug resistant Gram negative bacteria, such as ESBL producing bacteria, etc. These are extremely stable against metallo-beta-lactamase belonging to Class B including in particular IMP type, VIM type, L-1 type, etc. Thus, these are effective against a variety of beta-lactam drug resistant Gram negative bacteria including Cephem and Carbapenem. Moreover, the compounds of the present invention have antimicrobial activity against Gram positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), etc. Still more preferable compounds have features

regarding kinetics in the body, such as high blood concentration, long duration of effects, and/or significant tissue migration. More preferable compounds are safe in terms of side effects, such as fever and nephrotoxicity. More preferable compounds have high water solubility, and thus preferable as an injecting drug, in particular.

[0135] The compounds of the present invention can be administered either orally or parenterally. The compounds of the present invention, when administered orally, can be used in any dosage form of normal formulations, for example, solid drug such as tablet, powder, granule, capsule, etc.; solution drug; oleaginous suspension drug; or liquid drug such as syrup or elixir. The compounds of the present invention, when administered parenterally, can be used as an aqueous or oleaginous suspended injecting agent, or nasal drops. In preparation thereof, a conventional excipient, binder, lubricant, aqueous solvent, oleaginous solvent, emulsifier, suspending agent, preservative, stabilizer, etc. can be optionally used. A formulation of the present invention is produced by combining (for example, mixing) a therapeutically effective amount of a compound of the present invention with a pharmaceutically acceptable carrier or diluent.

[0136] The compounds of the present invention may be administered either parenterally or orally as an injecting agent, capsules, tablets, and granules, and preferably administered as an injecting agent. The dosage of the present compound may usually be, per 1 kg of body weight of a patient or animal, about 0.1 to 100 mg/day, preferably, about 0.5 to 50 mg/day, if desired, divided into 2-4 times per day. Carriers when used in an injecting agent are, for example, distilled water, brine, etc., and a base and the like may be used for pH adjustment. When used as capsules, granules, or tablets, carriers may be known excipients (e.g., starch, lactose, sucrose, calcium carbonate, calcium phosphate, etc.), binders (e.g., starch, acacia gum, carboxymethyl cellulose, hydroxypropyl cellulose, crystalline cellulose, etc.), lubricants (e.g., magnesium stearate, talc, etc.), etc.

General Method

[0137] Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). Unless otherwise indicated, all reactions are conducted under an inert atmosphere at ambient temperature.

[0138] All temperatures are given in degrees Celsius, all solvents are highest available purity and all reactions run under anhydrous conditions in an argon (Ar) or nitrogen (N₂) atmosphere where necessary.

[0139] ¹H NMR (hereinafter also "NMR") spectra were recorded on Bruker AVANCE-400 spectrometers. CDCl₃ is deuteriochloroform, d₆-DMSO is hexadeuteriodimethylsulfoxide, D₂O is Deuterium oxide, and CD₃OD is tetradeuteriomethanol. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns

describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). □

[0140] Mass spectra were run on Waters Open Architecture System, UPLC SQD MS analytical system. The compound is analyzed using a reverse phase column, e.g., Xbridge-C18, Sunfire-C18, Thermo Aquasil/Aquasil C18, Acquity HPLC C18, Acquity UPLC BEH C18, Shim-pack XR-ODS, Thermo Hypersil Gold eluted using an acetonitrile and water gradient with a low percentage of an acid modifier such as 0.02% TFA or 0.1% formic acid.

[0141] Analytical HPLC was run using an Agilent system (1100 series) with variable wavelength UV detection using Luna C18 column and eluting with an acetonitrile/water gradient containing a 0.05% or 0.1% TFA modifier (added to each solvent).

[0142] Unless otherwise indicated, flash chromatography was run on a Teledyne Isco Combiflash RF using disposable Redi-Sep flash columns (normal or reverse stationary phase as indicated), and a detector with UV wavelength at 254 nm. A styrenic adsorbent resin, DIAION™ HP20SS, was used in the workup and purification of cephalosporin analogs, and is referred to simply as HP20SS resin in the following examples.

EXAMPLES

[0143] Hereinafter, the present invention is described in more details with Examples, Reference Examples, Experiments and Formulation Examples. However, the present invention is not construed to be limited thereto.

[0144] The meaning of each abbreviation is as described below.

Ac: Acetyl

Allooc: Allyloxycarbonyl

BH or Bzh: Benzhydryl

Boc: tert-Butoxycarbonyl

Bn: Benzyl

Bt: benzotriazole

Cbz: carbobenzoxy

DMF: N,N-dimethylformamide

EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

Et: Ethyl

HOBt: 1-hydroxybenzotriazole

i-Pr: isopropyl

mCPBA: m-chloroperoxybenzoic acid

Me: methyl

ODS: Octadecylsilyl

PMB: para-Methoxybenzyl

TBS : tert-butyldimethylsilyl

t-Bu: tert-butyl

TFA: trifluoroacetic acid

Tr: Trityl

WSCD: N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide

rt: room temperature

TFA: trifluoroacetic acid

THF: tetrahydrofuran

DCM: dichloromethane

MeOH: methanol

EA or EtOAc: ethyl acetate

Pd/C: palladium on carbon

NaBH(OAc)₃: sodium triacetoxyborohydride

Pd₂(dba)₃: tris(dibenzylideneacetone)dipalladium (0)

XPhos: dicyclohexyl[2',4',6'-tris(1-methylethyl)-2-biphenyl]phosphane

SEMCl: 2-(trimethylsilyl)ethoxymethyl chloride

CDI: 1,1'-carbonyldiimidazole

AlCl₃: aluminum chloride

LAH: lithium aluminium hydride

DIBAL-H: diisobutylaluminium hydride

PyBOP: (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

HATU:

2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V)

DIPEA or DIEA: diisopropylethylamine

K_2CO_3 : potassium carbonate

TMS: tetramethylsilane

CDCl₃: deuteriochloroform

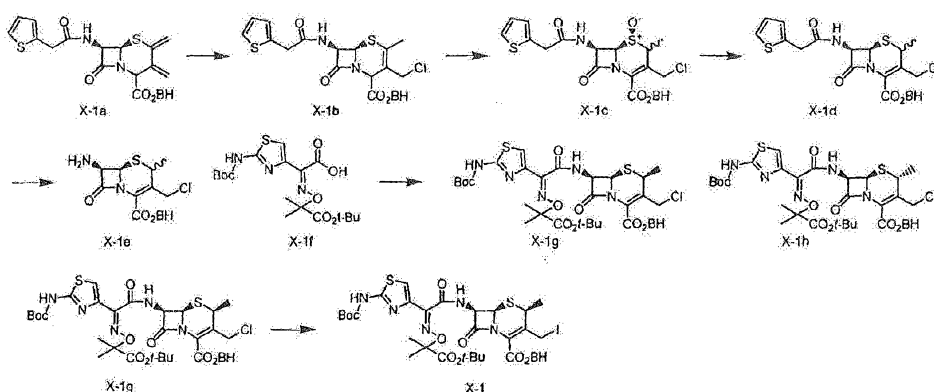
CD₃OD: tetradeuteriomethanol

DMSO- d_6 : hexadeuteriodimethylsulfoxide

Reference Example 1: Synthesis of Compound X-1

[0145]

[Chemical Formula 119]



Step (1): Compound X-1a → Compound X-1b

[0146] Compound X-1a (26.47 g, 51.2 mmol) which was synthesized according to the synthesis in US4463172A1 was dissolved into dioxane (200 mL), and thereto was then added 4 mol/L hydrochloric acid solution in dioxane (25.6 ml, 102 mmol) at rt. The mixture was stirred at rt for 1 hour. The reaction mixture was concentrated under reduced pressure. The precipitated solid was then collected by filtration, and washed with diisopropyl ether/dichloromethane to yield compound X-1b (21.1 g, 75%).

$^1\text{H-NMR}$ (CDCl_3) δ : 7.37-7.26 (11H, m), 7.03-6.99 (2H, m), 6.87 (1H, s), 6.36 (1H, d, $J = 8.7$ Hz), 5.63-5.59 (1H, m), 5.23-5.20 (2H, m), 4.31 (1H, d, $J = 12.3$ Hz), 4.09 (1H, d, $J = 12.3$ Hz), 3.86 (2H, s), 1.99 (3H, s).

Step (2): Compound X-1b $\rightarrow$ Compound X-1c

[0147] Compound X-1b (5.53 g, 10 mmol) was dissolved into dichloromethane (60 mL), and thereto was then added dropwise a solution of m-chloroperoxybenzoic acid (3.45 g, 13 mmol) in dichloromethane (40 mL) at -40°C . The mixture was stirred at -40°C for 1 hour. The reaction mixture was diluted with an aqueous sodium thiosulfate solution, then separated and washed with saturated sodium hydrogen carbonate solution, and dried over magnesium sulfate. Magnesium sulfate was filtrated off, and then the liquid was concentrated under reduced pressure. The precipitated solid was then collected by filtration, and washed with methanol to yield compound X-1c (3.79 g, 67%).

MS(M+1) = 569

Step (3): Compound X-1c $\rightarrow$ Compound X-1d

[0148] Compound X-1c (3.79 g, 6.6 mmol) was dissolved into dimethylformamide (35 mL), and thereto was then added phosphorus trichloride (1.7 mL, 20 mmol) at -50°C . The mixture was stirred at -20°C for 30 minutes. The reaction mixture was diluted with water and ethyl acetate, then separated and washed with water and a saturated salt solution, and dried over magnesium sulfate. Magnesium sulfate was filtrated off, and then the liquid was concentrated under reduced pressure. The compound-containing liquid was subjected to silica gel column chromatography to elute out the desired compound with hexane/ethyl acetate. The desired-compound-containing fraction was concentrated under reduced pressure to yield compound X-1d (1.98 g, 54%).

MS(M+1) = 553

Step (4): Compound X-1d $\rightarrow$ Compound X-1e

[0149] Phosphorus pentachloride (1.47 g, 7.1 mmol) was suspended into dichloromethane (20 mL), and thereto were then added pyridine (0.63 mL, 7.8 mmol) and compound X-1d (1.95 g, 3.5 mmol) at 0°C . The mixture was stirred at 0°C for 1 hour. Thereto was then added methanol (10 mL) at -40°C . The mixture was stirred at 0°C for 30 minutes. The mixture was diluted with a saturated sodium hydrogen carbonate solution and dichloromethane, then separated and dried over magnesium sulfate. Magnesium sulfate was filtrated off, and then ethyl acetate (20 mL) was added and concentrated under reduced pressure to yield the ethyl acetate solution of compound X-1e. This solution was used as it was, without being purified, in the next reaction.

Step (5): Compound X-1e + Compound X-1f → Compound X-1g, Compound X-1h

[0150] Compound X-1f (1.82 g, 4.2 mmol) and triethylamine (0.68 mL, 4.9 mmol) were dissolved into dimethylacetamide (20 mL), and thereto was then added methanesulfonyl chloride (0.36 mL, 4.6 mmol) at -20°C. The mixture was stirred at -10°C for 20 minutes. Pyridine (0.57 mL, 7.1 mmol) and the reaction mixture were added to the ethyl acetate solution of compound X-1e (3.5 mmol) at 0°C. The mixture was stirred at 0°C for 20 minutes. The reaction mixture was diluted with water and ethyl acetate, then separated and washed with water and a saturated salt solution, and dried over magnesium sulfate. Magnesium sulfate was filtrated off, and then the liquid was concentrated under reduced pressure. The compound-containing liquid was subjected to silica gel column chromatography to elute out the desired compound with hexane/ethyl acetate. The desired-compound-containing fraction was concentrated under reduced pressure to yield Compound X-1g (0.13 g, 4.4%), compound X-1h (1.17 g, 40%).

Compound X-1g

[0151] ¹H-NMR (CDCl₃) δ: 8.18-8.16 (2H, m), 7.42-7.30 (11H, m), 6.93 (1H, s), 6.03 (1H, dd, *J* = 9.0, 5.0 Hz), 5.23 (1H, d, *J* = 5.0 Hz), 4.83 (1H, d, *J* = 12.3 Hz), 4.21 (1H, d, *J* = 12.3 Hz), 4.01 (1H, q, *J* = 7.2 Hz), 1.64 (3H, s), 1.61 (3H, s), 1.57 (3H, d, *J* = 7.2 Hz), 1.53 (9H, s), 1.41 (9H, s).

compound X-1h

[0152] ¹H-NMR (CDCl₃) δ: 8.22-8.19 (2H, m), 7.46-7.30 (11H, m), 7.01 (1H, s), 6.13 (1H, dd, *J* = 9.0, 5.1 Hz), 5.19 (1H, d, *J* = 5.1 Hz), 4.43 (1H, d, *J* = 11.5 Hz), 4.18 (1H, d, *J* = 11.5 Hz), 3.85 (1H, q, *J* = 7.3 Hz), 1.63 (3H, s), 1.60 (3H, s), 1.58 (3H, d, *J* = 7.3 Hz), 1.53 (9H, s), 1.39 (9H, s).

Step (6) : Compound X-1g → Compound X-1

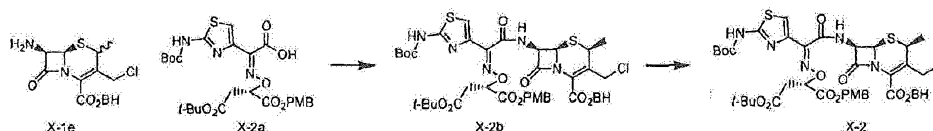
[0153] Compound X-1g (77.6 g, 92 mmol) was dissolved into tetrahydrofuran (770 mL), and thereto was then added sodium iodide (41.5 g, 277 mmol) at 15°C. The resultant solution was stirred at 15°C for 1 day. The reaction mixture was diluted with an aqueous sodium bisulfite solution and ethyl acetate, then separated and washed with water and a saturated salt solution, and dried over magnesium sulfate. Magnesium sulfate was filtrated off, and then the liquid was concentrated under reduced pressure to yield compound X-1 (85.2 g, 99%). Compound X-1g yielded was used as it was, without being purified, in the next reaction.

[0154] $^1\text{H-NMR}$ (CDCl_3) δ : 8.24 (1H, d, $J = 8.8$ Hz), 7.42-7.29 (12H, m), 6.94 (1H, s), 5.94 (1H, dd, $J = 8.8, 4.9$ Hz), 5.27 (1H, d, $J = 4.9$ Hz), 4.97 (1H, d, $J = 9.8$ Hz), 4.07-4.00 (2H, m), 1.64 (3H, s), 1.61 (3H, s), 1.55-1.53 (12H, m), 1.41 (9H, s).

Reference Example 2: Synthesis of Compound X-2

[0155]

[Chemical Formula 120]



[0156] Step (1): Compound X-1e + Compound X-2a $\rightarrow$ Compound X-2b Compound X-1e (8.3 g, 15 mmol) and compound X-2a (10.4 g, 18 mmol) were used to synthesize the target compound in the same way as in step 4 and 5 of Reference Example 1.

Yielded amount: 10.4 g,(70%)

[0157] $^1\text{H-NMR}$ (CDCl_3) δ : 8.27 (1H, d, $J = 8.1$ Hz), 8.09 (1H, s), 7.43-7.29 (11H, m), 7.23 (2H, d, $J = 8.5$ Hz), 6.94 (1H, s), 6.82 (2H, d, $J = 8.5$ Hz), 5.92 (1H, dd, $J = 8.1, 4.9$ Hz), 5.36 (1H, dd, $J = 8.4, 4.6$ Hz), 5.23 (1H, d, $J = 4.9$ Hz), 5.14 (1H, d, $J = 11.9$ Hz), 5.05 (1H, d, $J = 11.9$ Hz), 4.85 (1H, d, $J = 12.3$ Hz), 4.23 (1H, d, $J = 12.3$ Hz), 4.00 (1H, q, $J = 7.4$ Hz), 3.76 (3H, s), 2.92 (1H, dd, $J = 16.4, 8.4$ Hz), 2.83 (1H, dd, $J = 16.4, 4.6$ Hz), 1.57 (3H, d, $J = 7.4$ Hz), 1.54 (9H, s), 1.41 (9H, s).

Step (2): Compound X-2b $\rightarrow$ Compound X-2

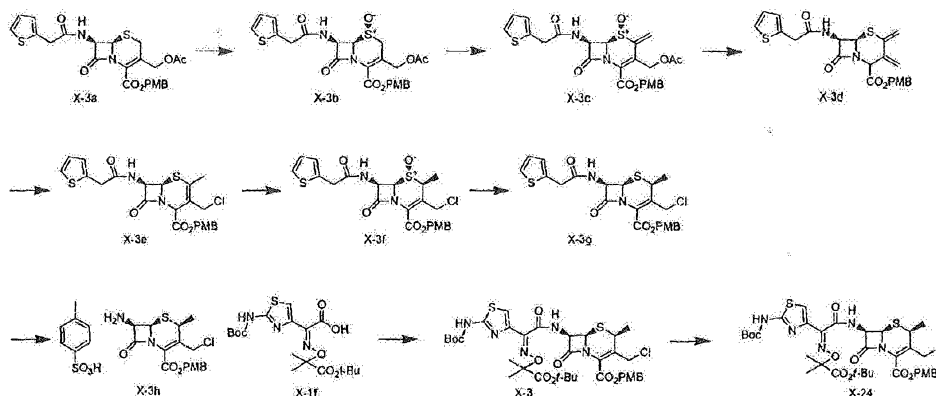
[0158] Compound X-2b (10.4 g, 11 mmol) was used to synthesize the target compound in the same way as in step 6 of Reference Example 1. Yielded amount: 10.7 g,(95%)

$^1\text{H-NMR}$ (CDCl_3) δ : 8.30 (1H, d, $J = 7.9$ Hz), 8.11 (1H, s), 7.44-7.29 (11H, m), 7.23 (2H, d, $J = 8.7$ Hz), 6.95 (1H, s), 6.82 (2H, d, $J = 8.7$ Hz), 5.84 (1H, dd, $J = 7.9, 4.8$ Hz), 5.37 (1H, dd, $J = 8.3, 4.8$ Hz), 5.27 (1H, d, $J = 4.8$ Hz), 5.14 (1H, d, $J = 11.8$ Hz), 5.05 (1H, d, $J = 11.8$ Hz), 4.99 (1H, d, $J = 9.8$ Hz), 4.06-4.01 (2H, m), 3.76 (3H, s), 2.92 (1H, dd, $J = 16.4, 8.3$ Hz), 2.84 (1H, dd, $J = 16.4, 4.8$ Hz), 1.54-1.52 (12H, m), 1.41 (9H, s).

Reference Example 3: Synthesis of Compound X-3 and X-24

[0159]

[Chemical Formula 121]



Step (1): Compound X-3a → Compound X-3b → Compound X-3c

[0160] To a pre-cooled solution of compound X-3a (50 g, 97 mmol), which was synthesized according to the synthesis in Tetrahedron Letter, 37, 1971-1974 (1996), in dichloromethane (450 mL) at -10 °C was added peracetic acid (19.82 g, 102 mmol, 37%Wt) . The mixture was stirred at -10 to -5 °C. To the resulting mixture was added a solution of sodium bisulfite (12.1 g, 116 mmol) in water (200 mL) . Water (150 mL) was added to the mixture, and then an organic layer was separated. The organic layer was washed with water (250 mL), 10% aqueous solution of sodium chloride (250 mL) . The aqueous layers were successively extracted with dichloromethane (150 mL) . The combined organic layers were dried over magnesium sulfate and filtered. To the filtrate was added dimethylformamide (200 mL) and then the solution was concentrated. The residue was placed in a reaction bottle with dimethylformamide (30 mL) and then to the solution was added formaldehyde (15.7 g, 194 mmol, 37%Wt) and dimethylamine hydrochloride (7.89 g, 97 mmol). The mixture was stirred at 60 °C for 3 hours and then cooled in ice bath. To the mixture was added water (250 mL) dropwise over 8 minutes. The resulting mixture was stirred for 3.5 hr. The precipitated material was collected by filtration and washed with water (250 mL) and ethanol (250 mL). The solid was dried under air for 3 days to afford compound X-3c (48.5 g, 92%).

¹H-NMR (DMSO-D₆) δ: 8.61 (1H, d, *J* = 8.3 Hz), 7.39-7.35 (3H, m), 6.98-6.93 (4H, m), 6.40 (1H, s), 6.21 (1H, s), 5.95 (1H, dd, *J* = 8.3, 5.1 Hz), 5.31-5.26 (2H, m), 5.21 (1H, d, *J* = 11.9 Hz), 5.07 (1H, d, *J* = 5.1 Hz), 4.74 (1H, d, *J* = 12.5 Hz), 3.91 (1H, d, *J* = 15.4 Hz), 3.83 (1H, d, *J* = 15.4 Hz), 3.75 (3H, s), 1.96 (3H, s).

Step (2) : Compound X-3c → Compound X-3d → Compound X-3e

[0161] To a pre-cooled suspension of compound X-3c (25.0 g, 45.9 mmol) in 1,4-dioxane (175 mL) and dichloromethane (50 mL) in ice bath was added zinc (15.01 g, 230 mmol) with dichloromethane (15 mL). To the mixture in ice bath was added concentrated hydrochloric acid (19.1 mL, 230 mmol, 12 M) dropwise over 45 minutes and then washed with dichloromethane (10 mL). The mixture was stirred in ice bath for 1 hour, and then filtered through Celite and it washed with dichloromethane (300 mL). The filtrate was washed with water (500 mL) and water (125 mL) successively. The aqueous layers were successively extracted with dichloromethane (75 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The residue was dissolved with 1,4-dioxane (75 mL) to remove dichloromethane and then cooled in ice bath. To the mixture was added hydrochloric acid in 1,4-dioxane (23.0 mL, 4M) and then stirred in ice bath for 2 hr. To the resulting mixture was added isopropyl ether (122 mL) and stirred in ice bath for 1.5 hr. The precipitated material was collected by filtration and washed with isopropyl ether. The solid was dried under air over night to afford compound X-3e (15.3g, 58%).

$^1\text{H-NMR}$ (DMSO- D_6) δ : 9.27 (1H, d, $J = 7.8$ Hz), 7.38-7.34 (3H, m), 6.97-6.92 (4H, m), 5.48 (1H, dd, $J = 7.8, 3.8$ Hz), 5.19 (1H, d, $J = 3.8$ Hz), 5.15-5.08 (3H, m), 4.64 (1H, d, $J = 12.2$ Hz), 4.31 (1H, d, $J = 12.2$ Hz), 3.77-3.74 (5H, m), 2.04 (3H, s).

Step (3): Compound X-3e $\rightarrow$ Compound X-3f

[0162] To a pre-cooled suspension of compound X-3e (50.0 g, 94 mmol) in dichloromethane (500 mL) in ice bath was added peracetic acid (18.4 g, 94 mmol, 39%Wt) dropwise over 10 minutes. The mixture was stirred in ice bath for 3 hours. An aqueous solution of sodium bisulfite (11.8 g, 113 mmol) in water (250 mL) was added. Water (250 mL) was further added. The organic layer was washed with water (500 mL) and 10% aqueous solution of sodium chloride (500 mL). The aqueous layers were successively extracted with dichloromethane (50 mL). The combined organic layers were concentrated while replaced a solvent to acetonitrile by adding twice (250 mL, 100 mL). To the residual suspension (approx. 250 mL) was added acetonitrile (612 mL) and water (150 mL). To the mixture was added 10% aqueous solution of sodium acetate (100 mL) and then pH showed 6.29. The mixture was stirred at room temperature with monitoring pH for 1.5 hours. 2mol/L hydrochloric acid (24.5 mL) was added to quench. The insoluble material was collected by filtration and washed with water (200 mL) and acetonitrile (150 mL). The solid was dried under air over 3 days to afford compound X-3f (32.6 g, 66%).

$^1\text{H-NMR}$ (DMSO- D_6) δ : 8.53 (1H, d, $J = 8.3$ Hz), 7.38-7.36 (3H, m), 6.97-6.93 (4H, m), 5.88 (1H, dd, $J = 8.3, 4.9$ Hz), 5.30 (1H, d, $J = 12.0$ Hz), 5.21 (1H, d, $J = 12.0$ Hz), 5.10 (1H, d, $J = 4.9$ Hz), 4.81 (1H, d, $J = 12.3\text{Hz}$), 4.42 (1H, d, $J = 12.3\text{Hz}$), 3.90-3.79 (3H, m), 3.76 (3H, s), 1.61 (3H, d, $J = 7.5$ Hz).

Step (4): Compound X-3f $\rightarrow$ Compound X-3g

[0163] To a pre-cooled suspension of compound X-3f (30.0 g, 57.4 mmol) in dimethylformamide (240 mL) with stirring at -40 °C was added phosphorus trichloride (23.6 g, 172 mmol) over 10 minutes. The mixture was stirred at -35 °C for 1 hour. To the resulting mixture was added dichloromethane (300 mL) and water (300 mL). The organic layer was separated, and then washed with water (300 mL) and 10% aqueous solution of sodium chloride (300 mL). The aqueous layers were successively extracted with dichloromethane (90 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to approx. 150mL. To the residual suspension was added 2-propanol (180 mL) and then the suspension was concentrated to approx. 150 mL again. To the residue was added 2-propanol (14 mL) and diisopropyl ether (120 mL). The mixture was stirred for 3 hours. The insoluble material was collected by filtration and dried under air for 3 days to afford compound X-3g (20.8g, 71%).

¹H-NMR (DMSO-D₆) δ: 9.21 (1H, d, *J* = 8.4 Hz), 7.38-7.34 (3H, m), 6.96-6.91 (4H, m), 5.73 (1H, dd, *J* = 8.4, 5.0 Hz), 5.33 (1H, d, *J* = 5.0 Hz), 5.27 (1H, d, *J* = 11.9 Hz), 5.17 (1H, d, *J* = 11.9 Hz), 4.66 (1H, d, *J* = 12.0 Hz), 4.49 (1H, d, *J* = 12.0 Hz), 4.08 (1H, q, *J* = 7.2 Hz), 3.75 (5H, s), 1.53 (3H, d, *J* = 7.2 Hz).

Step (5): Compound X-3g → Compound X-3h

[0164] To a pre-cooled suspension of phosphorus pentachloride (8.21 g, 39.4 mmol) in dichloromethane (90 mL) with stirring at -5 °C was added pyridine (3.43 g, 43.4 mmol) and compound X-3g (10.0 g, 19.7 mmol). The mixture was stirred at 10 to 15 °C for 1 hour. The resulting mixture was poured into pre-cooled methanol (25 mL) in ice bath, and then water (50 mL) was added. The organic layer was separated and washed with water (100 mL). The aqueous layers were successively extracted with dichloromethane (40 mL). The combined organic layers were dried over magnesium sulfate, filtered. To the filtrate was added p-toluenesulfonic acid mono-hydrate (3.75 g, 19.7 mmol) and ethyl acetate (60 mL). The mixture was concentrated to remove dichloromethane. To the residual suspension was added ethyl acetate (50 mL). The mixture was stirred at 35 °C, and then stirred in ice bath for 2.5 hours. The insoluble material was collected by filtration and washed with ethyl acetate. The solid was dried through air circulation to afford compound X-3h (7.30 g, 63%).

¹H-NMR (DMSO-D₆) δ: 9.02 (3H, br s), 7.48 (2H, d, *J* = 7.7 Hz), 7.36 (2H, d, *J* = 8.3 Hz), 7.12 (2H, d, *J* = 7.7 Hz), 6.94 (2H, d, *J* = 8.3 Hz), 5.45 (1H, d, *J* = 5.0 Hz), 5.29-5.17 (3H, m), 4.68 (1H, d, *J* = 12.0 Hz), 4.51 (1H, d, *J* = 12.0 Hz), 4.21 (1H, q, *J* = 7.2 Hz), 3.75 (3H, s), 2.29 (3H, s), 1.57 (3H, d, *J* = 7.2 Hz).

Step (6): Compound X-3h + Compound X-1f → Compound X-3

[0165] To a pre-cooled suspension of compound X-1f (9.29 g, 21.6 mmol) and compound X-3h (12.0 g, 21.6 mmol) in ethyl acetate (120 mL) at -40 °C was added phenyl dichlorophosphate

(6.84 g, 4.82 mmol) and N-methyl morpholine (7.65 g, 76 mmol). The mixture was stirred at -40°C for 1.5 hours. 0.5mol/L hydrochloric acid (130 mL) was added to quench. The organic layer was separated and washed with water (120 mL), 5% aqueous solution of sodium bicarbonate (120 mL), and 10% aqueous solution of sodium chloride (120 mL). The aqueous layers were successively extracted with ethyl acetate (60 mL). The combine organic layers were dried over magnesium sulfate, filtered and concentrated to give a crude material (19.7g). 6.58 g of the crude residue was purified by silica gel column chromatography eluted with n-hexane and ethyl acetate to afford compound X-3 (5.77 g).

$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 11.84 (1H, s), 9.58 (1H, d, $J = 8.3$ Hz), 7.36 (2H, d, $J = 8.2$ Hz), 7.26 (1H, s), 6.94 (2H, d, $J = 8.2$ Hz), 5.87 (1H, dd, $J = 8.1, 5.0$ Hz), 5.40 (1H, d, $J = 4.9$ Hz), 5.26 (1H, d, $J = 11.8$ Hz), 5.18 (1H, d, $J = 11.8$ Hz), 4.67 (1H, d, $J = 12.2$ Hz), 4.48 (1H, d, $J = 12.0$ Hz), 4.06 (1H, q, $J = 7.2$ Hz), 3.76 (3H, s), 1.52 (3H, d, $J = 7.2$ Hz), 1.46-1.44 (15H, m), 1.39 (9H, s).

Step (7): Compound X-3 $\rightarrow$ Compound X-24

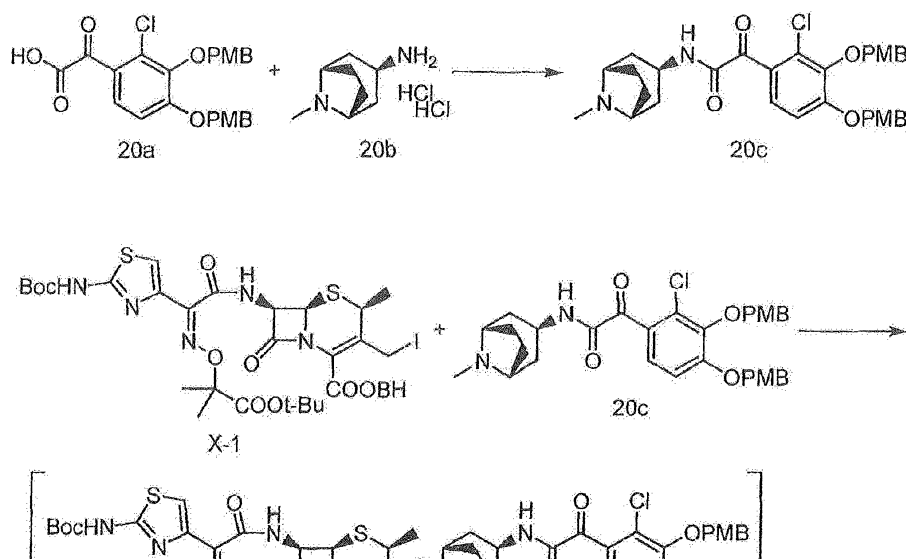
[0166] Compound X-3 (25.6 g, 30.0 mmol) was used to synthesize Compound X-24 in the same way as in step (6) of Reference Example 1. Yielded amount: 28.08 g, (106%)

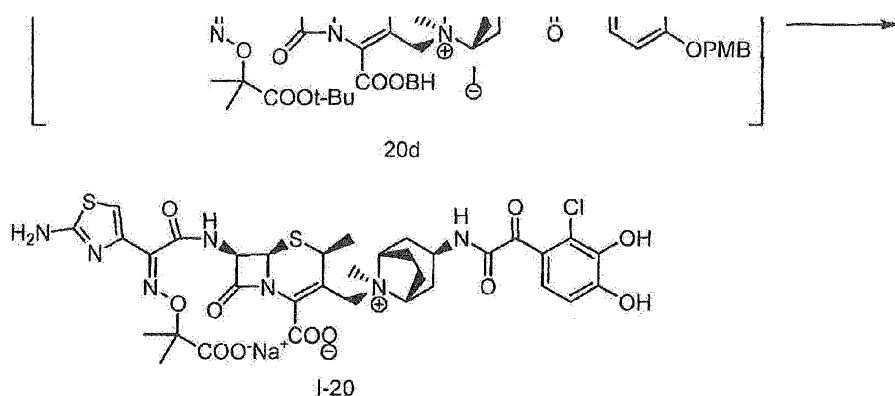
$^1\text{H-NMR}$ (CDCl_3) δ : 8.14 (1H, d, $J = 8.9$ Hz), 7.35-7.33 (3H, m), 6.91 (2H, d, $J = 8.4$ Hz), 5.91 (1H, dd, $J = 8.9, 4.9$ Hz), 5.27 (1H, d, $J = 11.9$ Hz), 5.21-5.18 (2H, m), 5.05 (1H, d, $J = 10.4$ Hz), 4.09-4.07 (2H, m), 3.82 (3H, s), 1.62 (3H, s), 1.60 (3H, s), 1.55 (3H, d, $J = 7.3$ Hz), 1.53 (9H, s), 1.41 (9H, s).

Example 20: Synthesis of Compound 1-20

[0167]

[Chemical Formula 165]





Step (1): Compound 20a + Compound 20b → Compound 20c

[0168] A solution of Compound 20a (1.00 g, 2.19 mmol) in 1 dichloromethane (10 mL) was cooled with ice, and thereto was added DIEA (573 μ L, 3.28 mmol), and Diphenyl chlorophosphate (681 μ L, 3.28 mmol). The liquid was stirred at 0°C for 30 minutes.

[0169] A solution of Compound 20b (513 g, 2.41 mmol) in 1 dichloromethane (10 mL) was cooled with ice, and thereto was added triethylamine (698 μ L, 5.03 mmol), and phosphate solution. After stirring at room temperature for 1 hour, aqueous sodium hydroxide was added to the reaction mixture, followed by extraction with ethyl acetate twice time. The combined organic layer was washed with water, then saturated brine, and then dried with anhydrous magnesium sulfate. The inorganic substance was removed by filtration, and then concentrated and subsequently drying under reduced pressure to yield Compound 20c as a yellow powder oil. Yielded amount: 1.00 g (79%)

$^1\text{H-NMR}$ (CDCl_3) δ : 1.75 (3H, d, J = 14.56 Hz), 1.86 (2H, dd, J = 15.31, 6.65 Hz), 2.18-2.21 (2H, m), 2.28-2.30 (2H, m), 2.33 (3H, s), 3.23 (2H, s), 3.80 (3H, s), 3.83 (3H, s), 4.96 (2H, s), 5.11 (2H, s), 6.83 (2H, d, J = 8.53 Hz), 6.91-6.96 (3H, m), 7.33-7.36 (4H, m), 7.65 (1H, d, J = 8.78 Hz).

Step (2): Compound X-1 + Compound 20c → Compound 20d → Compound 1-20

[0170] A solution of Compound 20c (579 mg, 1.0 mmol) in dimethylformamide (2.0 mL) was cooled with ice. The reaction vessel was then degassed under reduced pressure, and thereto was added Compound X-1 (932 mg, 1.0 mmol). After stirring at 0 °C for 7 hours, the reaction mixture was slowly added to 5% aqueous sodium chloride and sodium hydrogen sulfite cooled with ice. The precipitated solid was collected by filtration, washed with water, and suspended into water. The suspension was freeze-dried to yield Compound 20d as a brown solid. Compound 20d yielded was used as it was, without being purified, in the next reaction.

[0171] The total amount of compound 20d yielded was dissolved in dichloromethane (12 mL),

and the solution was cooled to -40°C . Thereto were then added anisole (1.09 mL, 10 mmol) and a 2 mol/L aluminum chloride solution (5.0 mL, 10 mmol) in nitromethane in turn. The liquid was stirred at 0°C for 30 minutes. To the reaction liquid were added diisopropyl ether and a small amount of water, and the resultant was stirred to generate a precipitate. The supernatant was removed by decantation. To the insoluble matter adhering to the vessel were added a diluted aqueous hydrochloric acid solution, and acetonitrile. The resultant was stirred to dissolve the matter completely. Thereto was then added diisopropyl ether, and the water phase was separated to be collected. The organic phase was again subjected to extraction with water, and then all of the resultant water phases were combined with each other. Thereto was added HP20-SS resin. Acetonitrile was then distilled off therefrom under reduced pressure. The resultant mixed liquid was purified by ODS column chromatography. The desired-compound-containing fraction was concentrated under reduced pressure, and then freeze-dried to yield compound 1-20 as a yellow powder.

Yielded amount: 385 mg (43%)

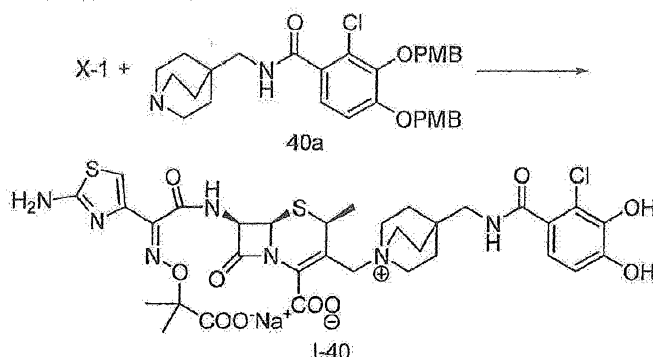
[0172] $^1\text{H-NMR}$ (D_2O) δ : 1.51 (3H, s), 1.53 (3H, s), 1.58 (3H, d, $J = 7.15$ Hz), 2.17 (2H, d, $J = 16.81$ Hz), 2.37-2.61 (5H, m), 2.71-2.85 (2H, m), 3.10 (3H, s), 3.95 (1H, s), 4.04-4.11 (3H, m), 4.24 (1H, t, $J = 7.53$ Hz), 5.46 (1H, d, $J = 4.89$ Hz), 5.83 (1H, d, $J = 4.89$ Hz), 6.90 (1H, d, $J = 8.66$ Hz), 7.02 (1H, s), 7.37 (1H, d, $J = 8.66$ Hz).

MS ($m+1$) = 820.28

Example 40: Synthesis of Compound 1-40

[0173]

[Chemical Formula 185]



Step (1): Compound X-1 + Compound 40a $\rightarrow$ Compound 1-40

[0174] From Compound X-1 (932 mg, 1.0 mmol) and Compound 40a (543 mg, 1.0 mmol),

Compound I-40 was obtained as a white powder using the same method as Example 20.

Yield: 523 mg, (64%)

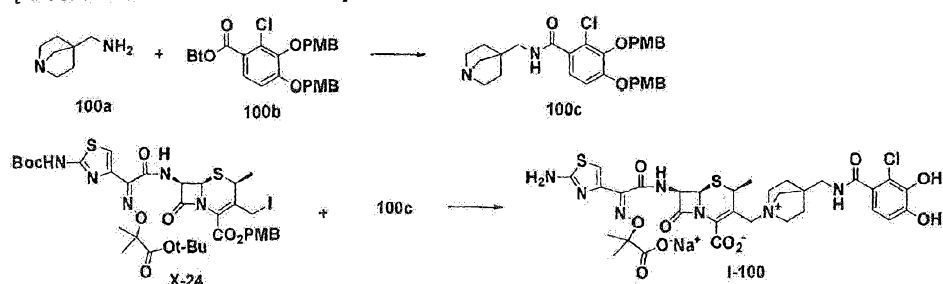
$^1\text{H-NMR}$ (D_2O) δ : 1.51 (3H, s), 1.53 (3H, s), 1.56 (3H, d, $J = 7.15$ Hz), 1.96 (6H, t, $J = 7.59$ Hz), 3.35 (2H, s), 3.45-3.57 (6H, m), 4.05-4.09 (2H, m), 4.64 (1H, d, $J = 14.31$ Hz), 5.45 (1H, d, $J = 4.89$ Hz), 5.85 (1H, d, $J = 4.89$ Hz), 6.90 (1H, d, $J = 8.41$ Hz), 6.95 (1H, d, $J = 8.41$ Hz), 7.00 (1H, s).

MS ($m+1$) = 792.01

Example 100: Synthesis of Compound 1-100

[0175]

[Chemical Formula 244]



Step (1): Compound 100a + Compound 100b $\rightarrow$ Compound 100c

[0176] To a solution of 100b (28.9 g, 53 mmol) in THF (250 ml) was added 100a (6.69 g, 53 mmol) in THF (50 ml) at 0°C . The mixture was stirred at rt for 1 h. The reaction mixture was diluted with ethyl acetate, washed with an aqueous sodium hydroxide solution, water and a saturated salt solution, and dried over magnesium sulfate. Magnesium sulfate was filtrated off, and then the liquid was concentrated under reduced pressure. The precipitated solid was then collected by filtration, and washed with diisopropyl ether to yield compound 100c (24.1 g, 85%)

compound 100c

[0177] $^1\text{H-NMR}$ (DMSO-D_6) δ : 8.40 (1H, t, $J = 6.0$ Hz), 7.43 (2H, d, $J = 8.5$ Hz), 7.33 (2H, d, $J = 8.5$ Hz), 7.19 (1H, d, $J = 8.7$ Hz), 7.13 (1H, d, $J = 8.7$ Hz), 6.98 (2H, d, $J = 8.5$ Hz), 6.89 (2H, d, $J = 8.5$ Hz), 5.16 (2H, s), 4.89 (2H, s), 3.78 (3H, s), 3.76 (3H, s), 3.53 (2H, d, $J = 6.0$ Hz), 2.85-2.78 (2H, m), 2.57-2.54 (2H, m), 2.25 (2H, s), 1.62-1.57 (2H, m), 1.24-1.18 (2H, m).

Step (2): Compound X-24 + Compound 100c $\rightarrow$ Compound I-100

[0178] Compound X-24 (886 mg, 1 mmol) and compound 100c (537 mg, 1mmol) were used to synthesize the target compound in the same way as Example 86.

Yielded amount: 500 mg (63%)

[0179] $^1\text{H-NMR}$ (D_2O) δ : 7.01 (1H, s), 6.95 (1H, d, $J = 8.4$ Hz), 6.89 (1H, d, $J = 8.4$ Hz), 5.82 (1H, d, $J = 4.8$ Hz), 5.45 (1H, d, $J = 4.8$ Hz), 4.92 (1H, d, $J = 14.6\text{Hz}$), 4.28 (1H, d, $J = 14.6\text{Hz}$), 4.07-4.02 (1H, m), 3.71-3.56 (6H, m), 3.44-3.42 (1H, br m), 3.35-3.33 (1H, br m), 2.24 (2H, br s), 2.01 (2H, br s), 1.57 (3H, d, $J = 7.2$ Hz), 1.52 (3H, s), 1.50 (3H, s).

$[\text{M}+\text{H}]=778.19$

Compound (I) of the invention was evaluated for in vitro antimicrobial activity thereof.

(Method)

[0180] Measurement of Minimum Inhibitory Concentration (MIC: $\mu\text{g/mL}$) was conducted according to CLSI (Clinical and Laboratory Standards Institute) method, and the amount of bacteria for inoculation was 5×10^5 cfu/mL, and cation-adjusted Iso-Sensitest broth containing human Apo-transferrin was used as a test medium, and the experiment was conducted using broth microdilution method. The bacteria used are listed below.

[Table 8]

No.	Species	Strain Name	Enzyme Produced	Strain Type
1	E.Coli	JMI1890	PER-1, TEM-1	ESBL producing strain
2	A.baumannii	JMI7	PER-1, OXA-23, 51	ESBL and OXA-type carbapenemase producing strain
3	A.baumannii	JMI2346	OXA-51, TEM	ESBL and OXA-type carbapenemase producing strain
4	K.pneumoniae	SR01358	KPC-2	ESBL and KPC-type carbapenemase producing strain

(Results)

[0181] The test results are shown in Tables below. The values of inhibitory activity are expressed in microgram/mL ($\mu\text{g/ml}$).

[Table 9]

Compound	E.Coli JMI:1890	A.baumannii JMI:7	A.baumannii JMI:2346	K.pneumoniae SR01358
I-40	0.5	1	4	0.063

[Table 11]

Compound	E.Coli JMI:1890	A.baumannii JMI:7	A.baumannii JMI:2346	K.pneumoniae SR01358
I-100	0.125	0.5	1	0.063

[0182] As shown above, Compounds (I) of the invention have a wide antimicrobial spectrum, in particular, potent antimicrobial spectrum against Gram negative bacteria, and/or effectiveness against multidrug-resistant bacteria, and further to exhibit high stability against beta-lactamase producing Gram negative bacteria.

Formulation Example 1

[0183] Powder of a compound of the present invention is formulated to prepare an injecting agent.

INDUSTRIAL APPLICABILITY

[0184] The compounds of the present invention have a wide antimicrobial spectrum against Gram negative bacteria and Gram positive bacteria, and are effective as an antimicrobial drug having high stability against beta-lactamase producing Gram negative bacteria. Moreover, the present compounds have good disposition, and high water solubility, and thus particularly effective as an injecting agent.

REFERENCES CITED IN THE DESCRIPTION

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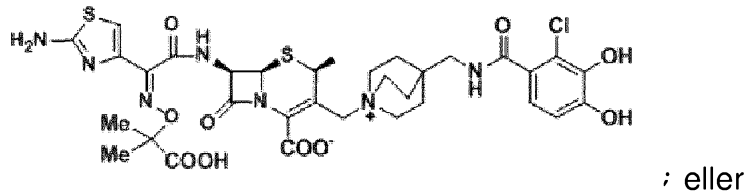
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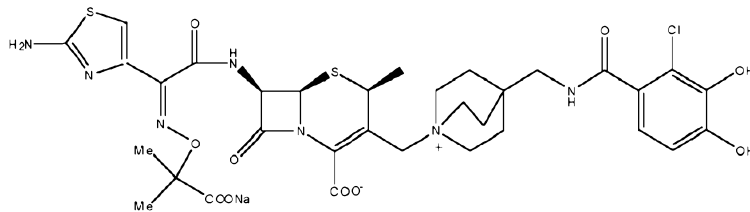
Patentkrav

1. Forbindelse, som er:



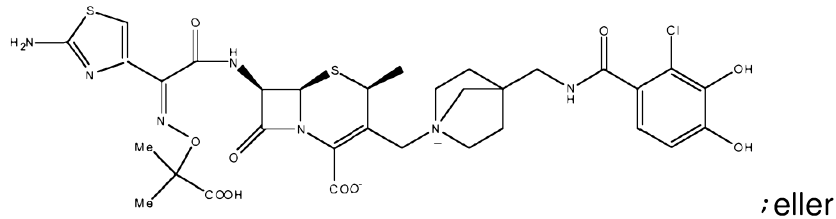
5 et farmaceutisk acceptabelt salt deraf.

2. Forbindelse ifølge krav 1, som er:



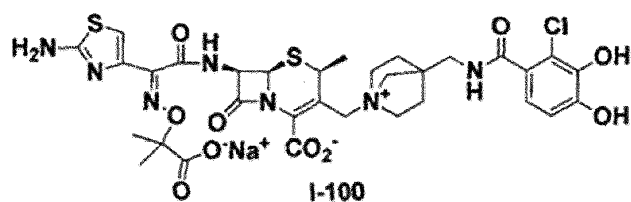
10

3. Forbindelse, som er:



15 et farmaceutisk acceptabelt salt deraf.

4. Forbindelse ifølge krav 3, som er:



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5. Forbindelse ifølge krav 1 eller krav 3, hvor det farmaceutisk acceptable salt er udvalgt blandt salte, der er dannet med lithium, natrium, kalium, calcium, barium, magnesium, zink, ferrum, ammoniak, trimethylamin, triethylamin, dicyclohexylamin, ethanolamin, diethanolamin, triethanolamin, meglumin, diethanolamin, ethylenediamin, pyridin, picolin, quinolin, aminosyre, saltsyre, svovlsyre, salpetersyre, kulsyre, hydrobromsyre, phosphorsyre, hydrogeniodidsyre, myresyre, eddikesyre, propionsyre, trifluoreddikesyre, citronsyre, mælkesyre, vinsyre, oxalsyre, maleinsyre, fumarsyre, mandelsyre, glutarsyre, æblesyre, benzoesyre, phthalsyre, ascorbinsyre, benzensulfonsyre, p-toluen-sulfonsyre, methansulfonsyre eller ethansulfonsyre.
6. Forbindelse ifølge krav 5, hvor det farmaceutisk acceptable salt er udvalgt blandt salte dannet med lithium, natrium, kalium, aminosyre, saltsyre, svovlsyre, salpetersyre, kulsyre, hydrobromsyre, phosphorsyre eller hydrogeniodidsyre.
7. Farmaceutisk sammensætning omfattende en forbindelse eller et farmaceutisk acceptabelt salt deraf ifølge et af kravene 1 til 6 og mindst et eller flere farmaceutisk acceptable hjælpestoffer.
8. Forbindelse eller et farmaceutisk acceptabelt salt deraf ifølge et af kravene 1 til 6 eller en farmaceutisk sammensætning ifølge krav 7, til anvendelse i antimikrobiel terapi.
9. Forbindelse eller et farmaceutisk acceptabelt salt deraf ifølge et af kravene 1 til 6 eller en farmaceutisk sammensætning ifølge krav 7, til anvendelse i terapi mod infektion af gramnegative bakterier.
10. Forbindelse eller et farmaceutisk acceptabelt salt deraf ifølge et af kravene 1 til 6 eller en farmaceutisk sammensætning ifølge krav 7, til anvendelse i terapi mod infektion af beta-lactamase-producerende gramnegative bakterier.
11. Forbindelse eller et farmaceutisk acceptabelt salt deraf ifølge et af kravene 1 til 6 eller en farmaceutisk sammensætning ifølge krav 7, til anvendelse i terapi mod infektion af:

- gramnegative bakterier udvalgt blandt gramnegative bakterier af enterobakterier f.eks. *E. coli*, *Klebsiella*, *Serratia*, *Enterobacter*, *Citrobacter*, *Morganella*, *Providencia* eller *Proteus*;
 - gramnegative bakterier, der er koloniseret i åndedrætssystemet, udvalgt blandt *Haemophilus* eller *Moraxella*;
 - gramnegative bakterier af glukose ikke-fermentering udvalgt blandt *Pseudomonas aeruginosa*, *Pseudomonas*, der ikke er *P. aeruginosa*, *Stenotrophomonas*, *Burkholderia* eller *Acinetobacter*;
 - gramnegative bakterier, der er multiresistente over for lægemidler, og som er udvalgt blandt klasse B-type metallo-beta-lactamase-producerende gramnegative bakterier; og
 - bakterier, der producerer beta-lactamase med udvidet spektrum (ESBL).
- 12.** Sammensætning eller et farmaceutisk acceptabelt salt deraf ifølge et af kravene 1 til 6, eller en farmaceutisk sammensætning ifølge krav 7, til anvendelse i terapi mod infektion af grampositive bakterier udvalgt blandt methicillin-resistente *Staphylococcus aureus* (MRSA) eller penicillin-resistente *Streptococcus pneumoniae* (PRSP).
- 13.** Sammensætning eller et farmaceutisk acceptabelt salt deraf ifølge et af kravene 1 til 6 eller en farmaceutisk sammensætning ifølge krav 7, til anvendelse i behandling af bakterieinfektion, som er en luftvejsinfektion, urinvejsinfektion, åndedrætssysteminfektion, sepsisinfektion, nefritis, cholecystitis, infektion i mundhulen, endocarditis, lungebetændelse, knoglemarvsmembran-myelitis, otitis media, enteritis, empyem, sårinfektion eller en opportunistisk infektion.