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DESCRIPTION

Glycosylated Glycopeptide Antibiotic Derivatives

[Technical Field]

[0001]

The present invention relates to glycosylated glycopeptide antibiotic derivatives, a process for producing the same, and their intermediates thereof.

[Background Art]

[0002]

A glycopeptide antibiotic is an antibiotic having a complicated polycyclic peptide structure which is produced by a variety of microorganisms, and is provided as an antibacterial agent effective for most of Gram-positive bacteria. In recent years, penicillin and cephalosporin resistant bacteria have appeared, and infection with multidrug resistant bacteria and methicillin-resistant *Staphylococcus aureus* (MRSA) lead to important problems in the medical field. A glycopeptide-based antibiotic such as vancomycin is typically effective for such microorganisms, and vancomycin has become the last resort drug for infection with MRSA and other resistant bacteria. However, particular microorganism such as vancomycin-resistant Enterococci (VRE) have begun to obtain resistance to vancomycin. In addition, recently, *Staphylococcus aureus* (VRSA) which has acquired VRE resistance has been found out.

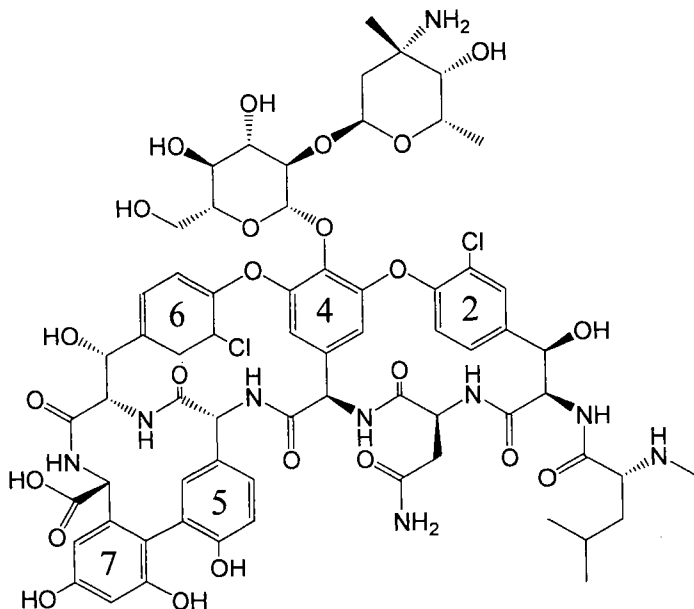
[0003]



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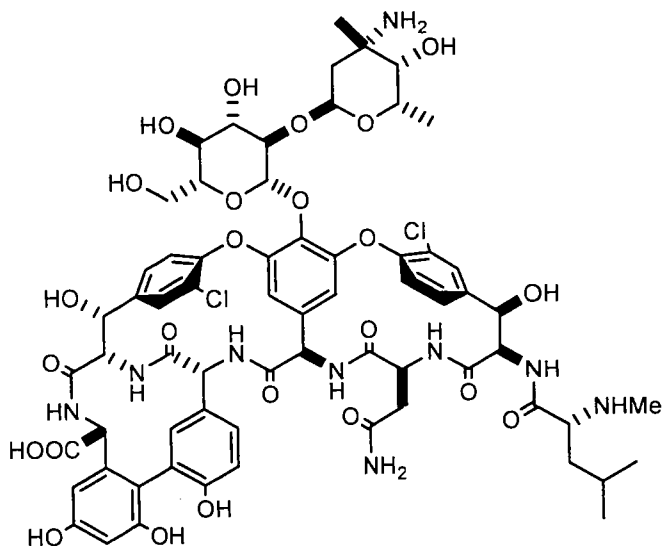
Vancomycin has a structure represented by the following formula:

[Chemical formula 1]



, more specifically, the following formula:

[Chemical formula 2]



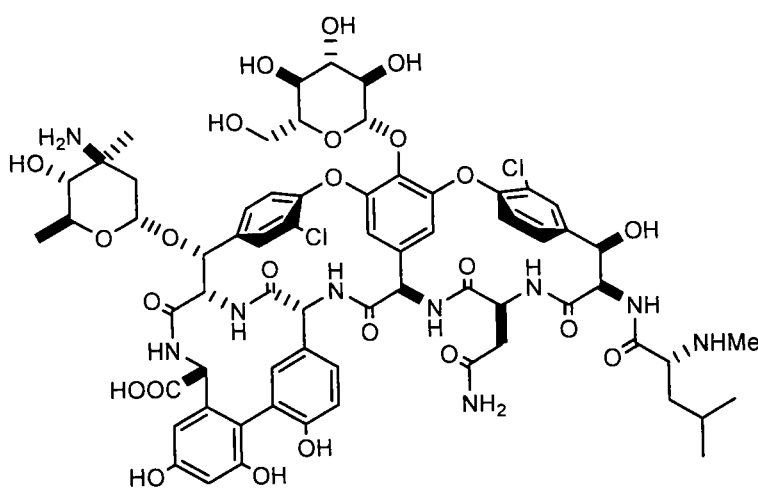
, and the aromatic ring of amino acid residues which are the second and sixth position from N-terminal is substituted with a chlorine atom. Vancomycin

derivatives are generally also termed glycopeptide antibiotics and, more academically, a generic name of dalbaheptides derived from D-alanyl-D-alanine binding antibiotics with a heptapeptidic structure has been proposed. The dalbaheptide has a peptide chain consisting of seven amino acids including aromatic amino acids as a common fundamental skeleton.

[0004]

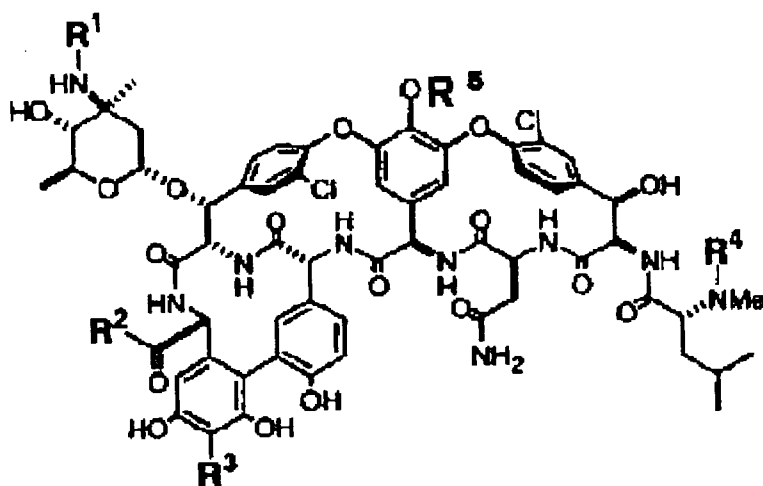
Previously, vancomycin, and other glycopeptide antibiotics having these common peptide chain as fundamental skeleton have been variously modified. For example, chloroorienticin B having the following structure (Patent Literature 1: JP-A No. 1-240196) and derivatives thereof (Patent Literature 2: JP-A No. 2001-163898) are known.

[Chemical formula 3]



Chloroorienticin B

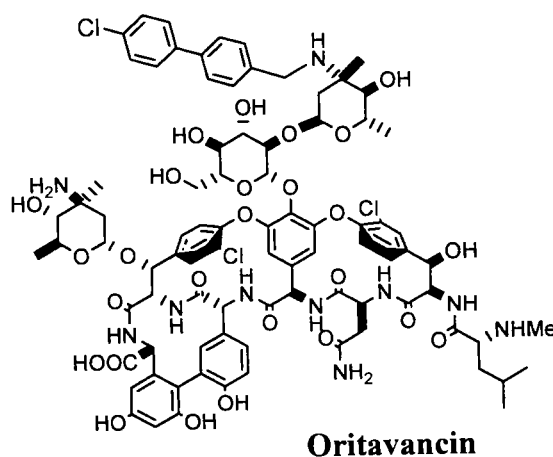
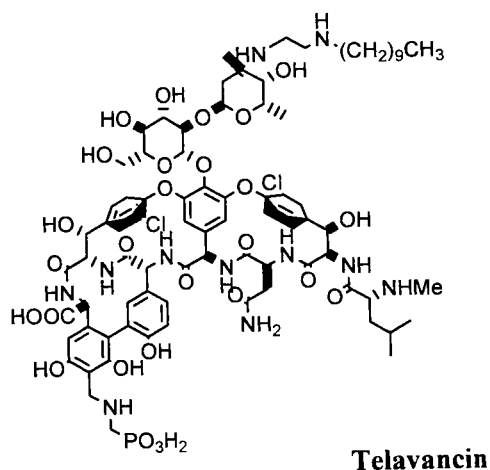
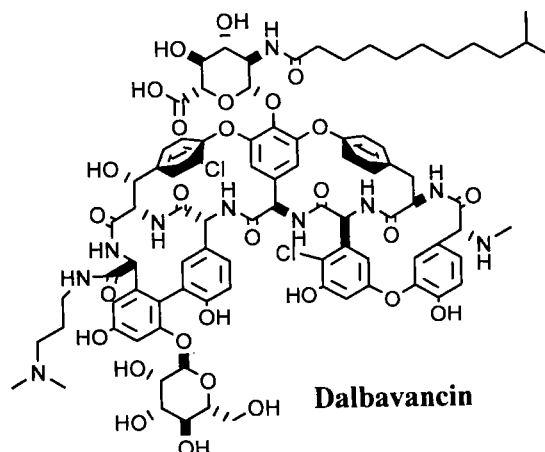
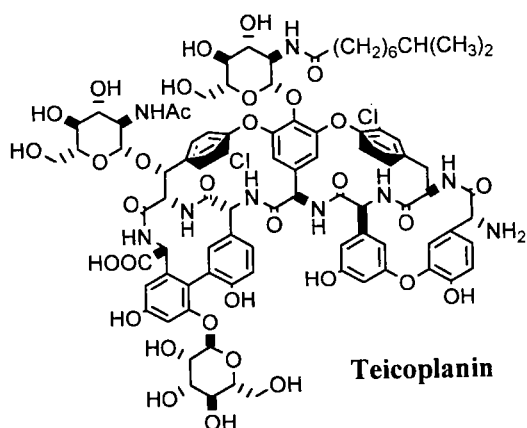
[Chemical formula 4]



(wherein R⁵ is hydrogen, glucosyl, or (4-epi-vancosaminyloxy)-O-glucosyl)

As other glycopeptide antibiotics, for example, the following compounds are known.

[Chemical formula 5]



In addition, glycopeptide compounds in which the amino sugar of vancomycin is modified are also known (e.g., Patent Literature 18).

However, development of antibacterial agents with novel structure in which antibacterial activity to drug-resistant bacteria, water solubility, distribution, safety and the like are further improved is desired.

On the other hand, as methods of chemically modifying glycopeptide antibiotics, methods using various glycosylase have been reported (e.g., Patent Literature 3, Non-Patent Literatures 1 to 5).

In addition, a glycopeptide compounds in which a sugar side chain

consisting of 1 or 2 sugars, to which an aminomethylene-type substituent is bound, is bound to the aromatic ring part of the fourth amino acid residue of the glycopeptide antibiotic are known (e.g., Patent Literatures 4 to 17, Non-Patent Literatures 5 to 17).

Among them, in Non-Patent Literature 11 (Angewandte Chemie, International Edition (2003), 42(38), 4657-4660), a vancomycin derivative in which $\text{-CH}_2\text{NH}_2$ is bound to galactose at the sugar chain terminal is described, but no compound in which the amino group is further chemically modified is described.

In addition, recent trend of study regarding glycopeptide compounds has been reported (e.g., Non-Patent Literature 18)

[0005]

[Patent Literature 1] JP-A No. 1-240196

[Patent Literature 2] JP-A No. 2001-163898

[Patent Literature 3] WO2006003456

[Patent Literature 4] US2005239689A1

[Patent Literature 5] US2003068669A1

[Patent Literature 6] US2004259228A1

[Patent Literature 7] US2005266523A1

[Patent Literature 8] WO2004019970

[Patent Literature 9] WO2001081373

[Patent Literature 10] WO2001081372

[Patent Literature 11] WO2000069893

[Patent Literature 12] WO2000059528

[Patent Literature 13] WO2000042067

[Patent Literature 14] WO2000004044

[Patent Literature 15] WO9303060

[Patent Literature 16] EP301785A1

[Patent Literature 17] EP273727A1

[Patent Literature 18] WO2006057303

[Non-Patent Literature 1] Journal of the American Chemical Society (2005), 127(30), 10747-10752

[Non-Patent Literature 2] Proceedings of the National Academy of Sciences of the United States of America (2004), 101(13), 4390-4395

[Non-Patent Literature 3] Chemistry-An Asian Journal (2006), 1, 445-452

[Non-Patent Literature 4] Current Opinion in Biotechnology 2005, 16:622-630

[Non-Patent Literature 5] Nature Biotechnology (2003), 21(12), 1467-1469

[Non-Patent Literature 6] ACS Chemical Biology (2006), 1(8), 499-504

[Non-Patent Literature 7] Activity Research (2006), 72(1) 20-33

[Non-Patent Literature 8] Bioorganic & Medical Chemistry Letters (2005), 15(16), 3801-3805

[Non-Patent Literature 9] Organic Letters (2005), 7(8), 1513-1515

[Non-Patent Literature 10] Chemistry & Biology (2005), 12(1), 131-140

[Non-Patent Literature 11] Angewandte Chemie, International, Edition (2003), 42(38), 4657-4660

[Non-Patent Literature 12] Journal of Medicinal Chemistry (2003), 46(13), 2755-2764

[Non-Patent Literature 13] Tetrahedron (2002), 58(32), 6585-6594

[Non-Patent Literature 14] Bioorganic & Medicinal Chemistry Letters (2002),

12(6), 849-852

[Non-Patent Literature 15] Chemistry - A European Journal (2001), 7(17), 3798-3823

[Non-Patent Literature 16] Journal of the American Chemical Society (2000), 122(50), 12608-12609

[Non-Patent Literature 17] Journal of Antibiotics (1998), 51(5), 525-527

[Non-Patent Literature 18] Expert Opinion on Therapeutic Patents (2004) 14(2) 141-173

[Disclosure of the Invention]

[Problems to be solved by the Invention]

[0006]

The present invention provides novel glycopeptide compounds having antibacterial activities. The present invention provides glycopeptide compounds which are preferably also effective for drug-resistant bacteria (e.g., VRSA, VRE), and are further preferably excellent in water solubility, distribution, safety or the like. Further, the present invention provides a method of glycosylating glycopeptide antibiotics utilizing glycosyltransferase and a process for producing glycopeptide compounds utilizing the same, as well as their intermediates therefor.

[Means to solve the Problems]

[0007]

The present inventors have intensively studied and, as a result, succeeded in further glycosylation by performing an enzymatic reaction on a

sugar which binds to an aromatic ring of a fourth amino acid residue of a glycopeptide antibiotic such as chloroorienticin B, and the like. The present inventors have succeeded in introducing an amino side chain regioselectively by oxidizing hydroxymethylene at the further glycosylated sugar chain terminal into aldehyde by an enzymatic reaction, or the like, and chemically modifying the aldehyde group.

The greatest characteristic of the glycopeptide compounds of the present invention is in that the compounds have a partial structure including aromatic ring of the fourth amino acid residue of the glycopeptide antibiotic, and two or more connected sugars are bound to the aromatic ring via an ether bond.

In the glycopeptide compound of the present invention, preferably, among two or more connected sugars, a sugar which is bound to an aglycone of a glycopeptide antibiotic is a β -D-glucosyl group and, more preferably, a sugar at the terminal is a β -D-galactosyl group.

In the glycopeptide compounds of the present invention, more preferably, $-\text{CH}_2\text{OH}$ or $-\text{COH}$ is bound to the sugar at the terminal and, further preferably, an optionally substituted aminomethylene group formed by chemical modification of them is bound thereto.

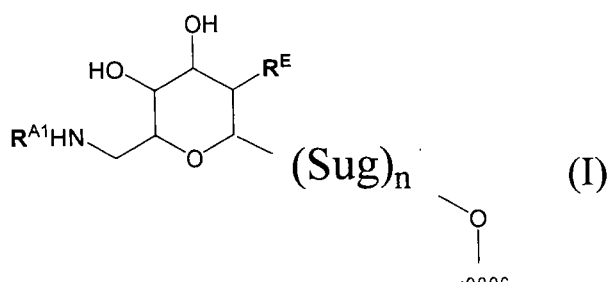
Therefore, according to the present invention, various glycopeptide compounds in which a side chain containing the glycosylated sugar on aromatic ring of the fourth amino acid residue of the glycopeptide antibiotics is bound via an ether bond are provided.

The present invention specifically provides the following compounds.

- (1) A glycopeptide compound, a pharmaceutically acceptable salt thereof,

or a solvate thereof, which is characterized in that a sugar residue (I) represented by the formula:

[Chemical Formula 6]



wherein

n is an integer of 1 to 5;

Sugs are each independently a monosaccharide, $(Sug)_n$ is a divalent sugar residue formed by binding same or different 1 to 5 monosaccharides;

R^{A1} is optionally substituted lower alkyl, optionally substituted lower alkenyl, or optionally substituted cycloalkyl; and

R^E is OH or $NHAc$ (Ac is acetyl);

is bound to an aromatic ring of the fourth amino acid residue in a glycopeptide skeleton.

[0008]

More particularly, the present invention provides compounds represented by the following (2) to (32).

(2) The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (1), wherein the monosaccharide is selected from the group consisting of glucose, galactose,

fructose, fucose, mannose, rhamnose, galactosamine, glucosamine, N-acetylgalactosamine, N-acetylglucosamine, vancosamine, epi-vancosamine, glucuronic acid, sialic acid, deoxyglucose, and deoxygalactose.

(3) The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (1), wherein the monosaccharide is glucose.

(4) The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of above (1) to (3), wherein n is 1 or 2.

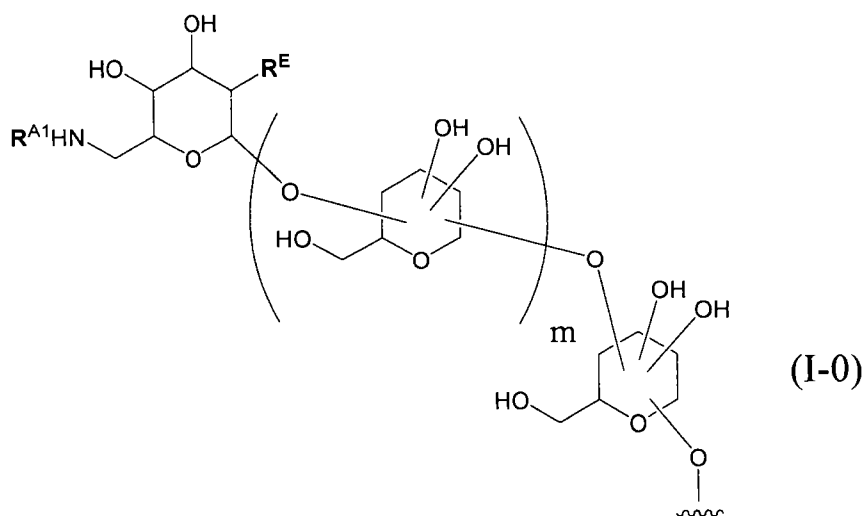
(5) The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (1), wherein the monosaccharide is glucose; and n is 1 or 2.

[0009]

(6) The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (1), wherein the sugar residue

(I) is a sugar residue (I-0) represented by the formula:

[Chemical Formula 7]



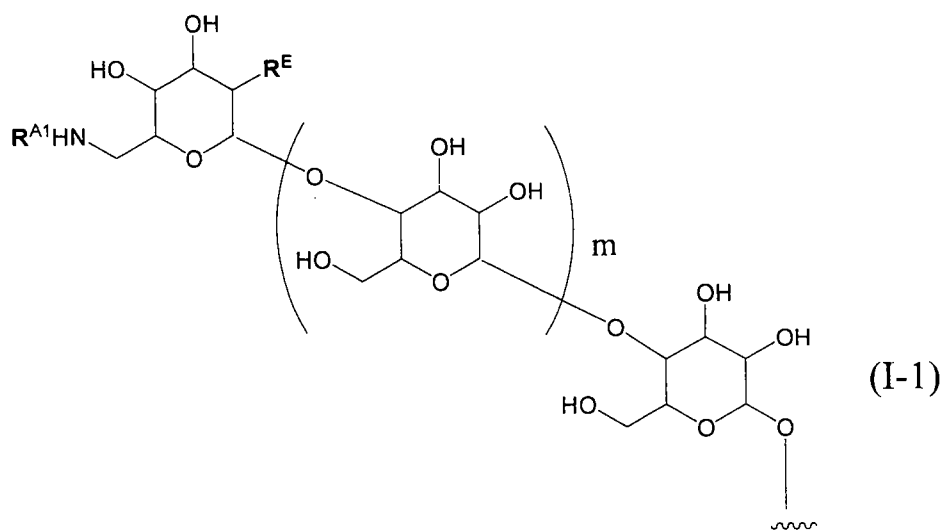
wherein

m is an integer of 0 to 4; and

R^{A1} and R^E are each as defined in above (1).

(7) The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (1), wherein the sugar residue (I) is a sugar residue (I-1) represented by the formula:

[Chemical formula 8]



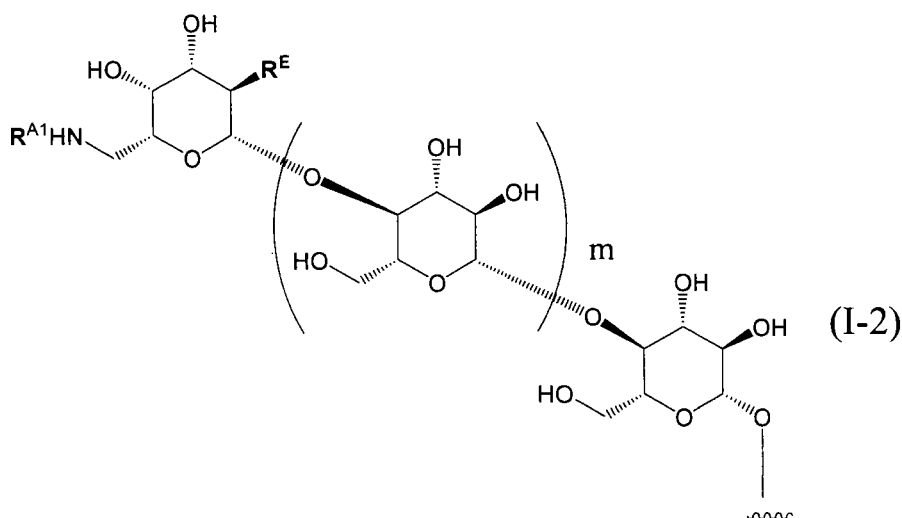
wherein

m is an integer of 0 to 4; and

R^{A1} and R^E are each as defined in above (1).

(8) The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (1), wherein the sugar residue (I) is a sugar residue (I-2) represented by the formula:

[Chemical formula 9]



wherein

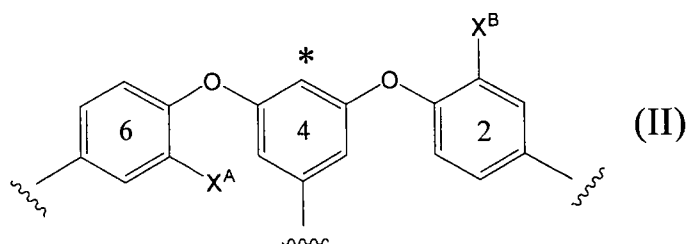
m is an integer of 0 to 4; and

R^{A1} and R^E are each as defined in above (1).

[0010]

(9) The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of above (1) to (8), wherein the compound has a partial structure (II) represented by the formula:

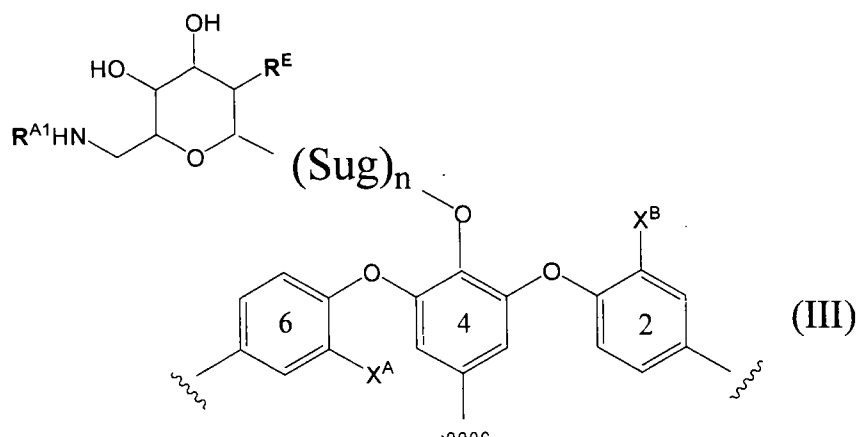
[Chemical formula 10]



wherein the ring 2, the ring 4 and the ring 6 represent aromatic rings of the second, fourth and sixth amino acid residues of a glycopeptide antibiotic, respectively; X^A and X^B each represent independently hydrogen or halogen; and * represents a binding position with a sugar residue.

(10) The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (1), wherein the compound has a partial structure (III) represented by the formula:

[Chemical formula 11]

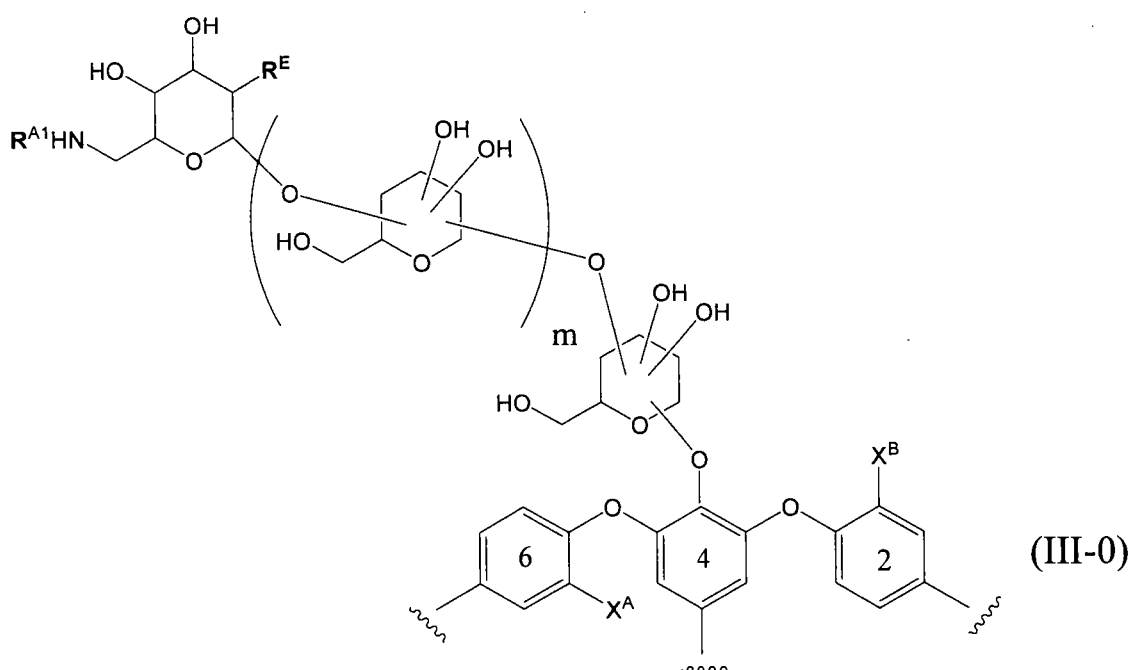


wherein the ring 2, the ring 4 and the ring 6 represent aromatic rings of the second, fourth and sixth amino acid residues of a glycopeptide antibiotic,

respectively; X^A and X^B each represent independently hydrogen or halogen; and other symbols are each as defined in above (1).

(11) The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (10), wherein the partial structure (III) is a partial structure (III-0) represented by the formula:

[Chemical formula 12]

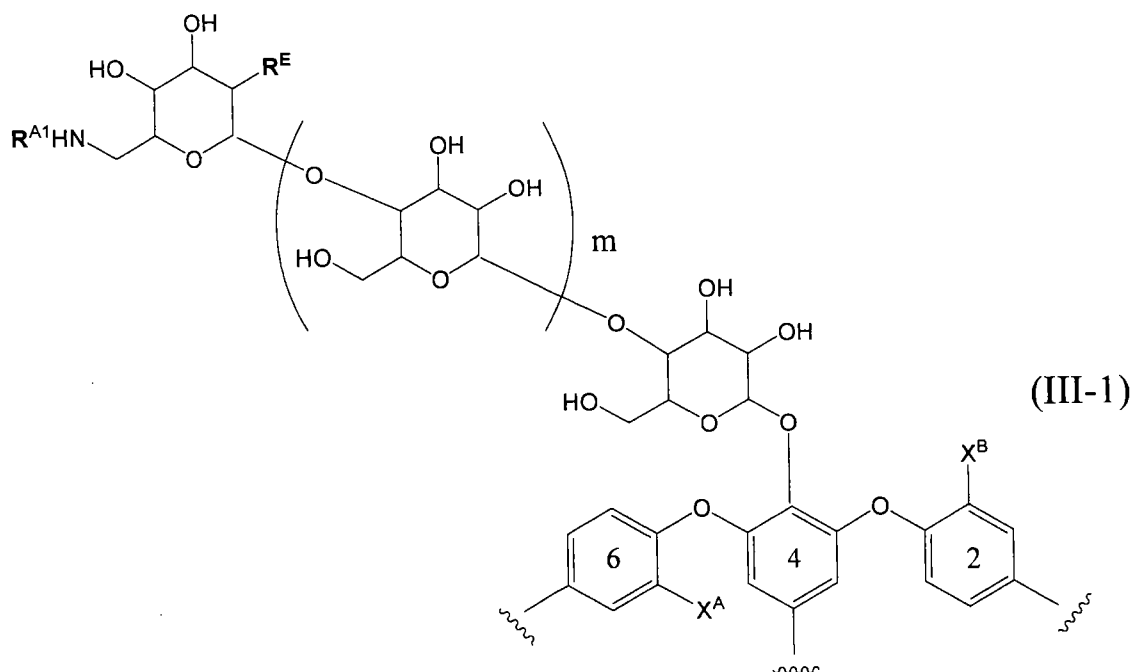


wherein the ring 2, the ring 4 and the ring 6 represent aromatic rings of the second, fourth and sixth amino acid residues of a glycopeptide antibiotic; X^A and X^B each represent independently hydrogen or halogen; m is an integer of 0 to 4; and R^{A1} and R^E are each as defined in above (1).

(12) The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (10), wherein the partial

structure (III) is a partial structure (III-1) represented by the formula:

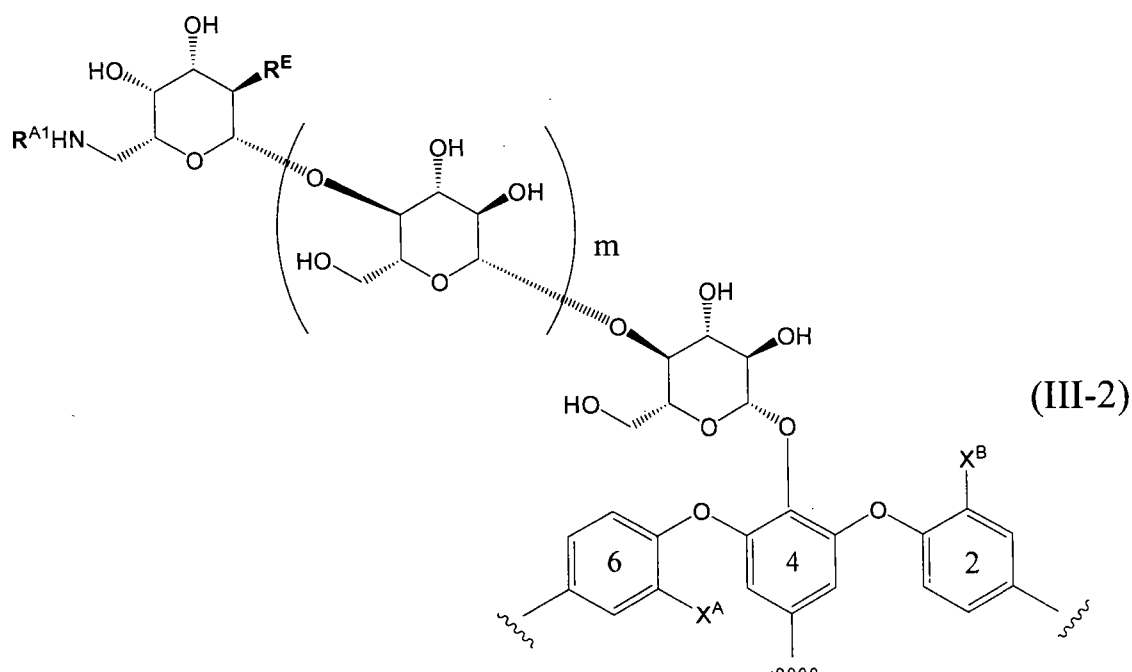
[Chemical formula 13]



wherein the ring 2, the ring 4 and the ring 6 represent aromatic rings of the second, fourth and sixth amino acid residue of a glycopeptides antibiotic, respectively; X^A and X^B each represents independently hydrogen or halogen; m is an integer of 0 to 4; and R^{A1} and R^E are each as defined in above (1).

(13) The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (10), wherein the partial structure (III) is a partial structure (III-2) represented by the formula:

[Chemical formula 14]



wherein the ring 2, the ring 4 and the ring 6 represent aromatic rings of the second, fourth and sixth amino acid residues of a glycopeptide antibiotic, respectively; X^A and X^B each represent independently hydrogen or halogen; m is an integer of 0 to 4; and R^{A1} and R^E are each as defined in above (1).

(14) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of above (1) to (13), wherein the glycopeptide compound is a chloroorienticin B derivative or a vancomycin derivative.

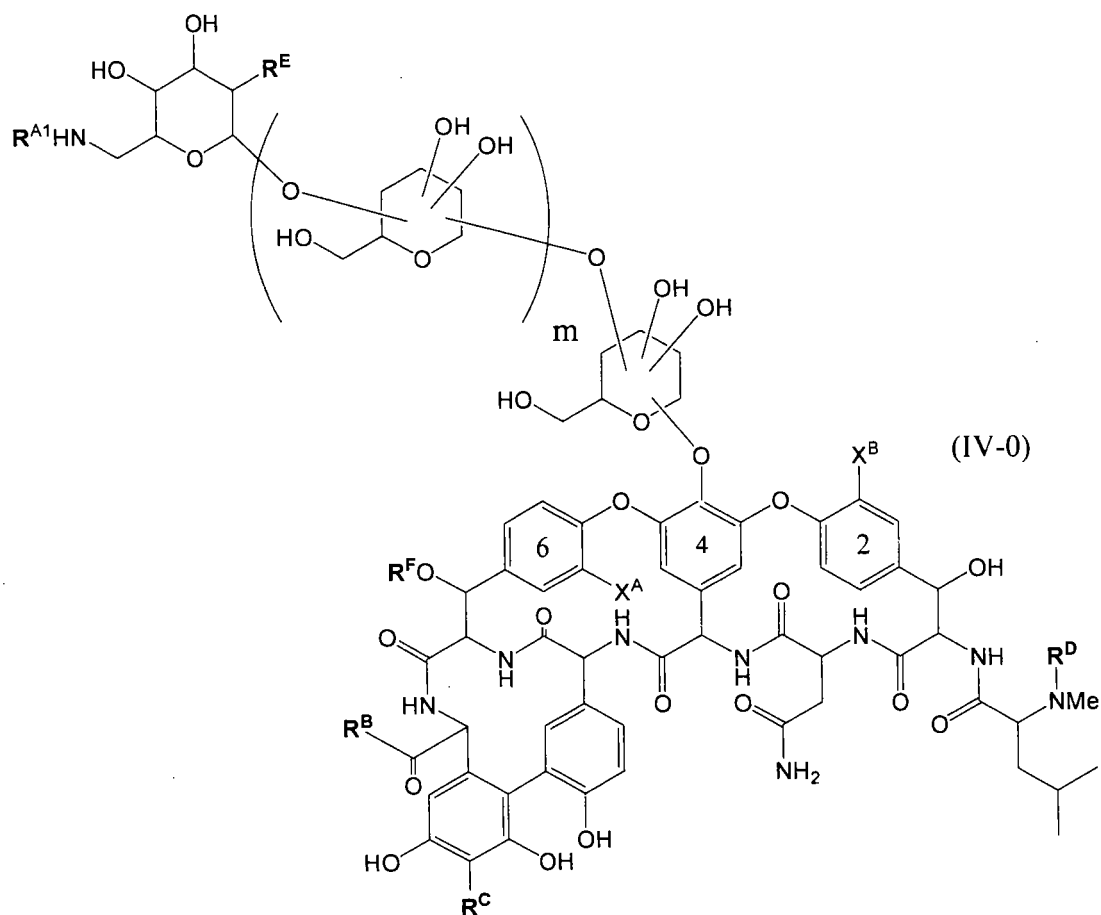
[0011]

(15) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (1), wherein the compound is represented by the formula:

[Chemical formula 15]

by the formula:

[Chemical formula 16]



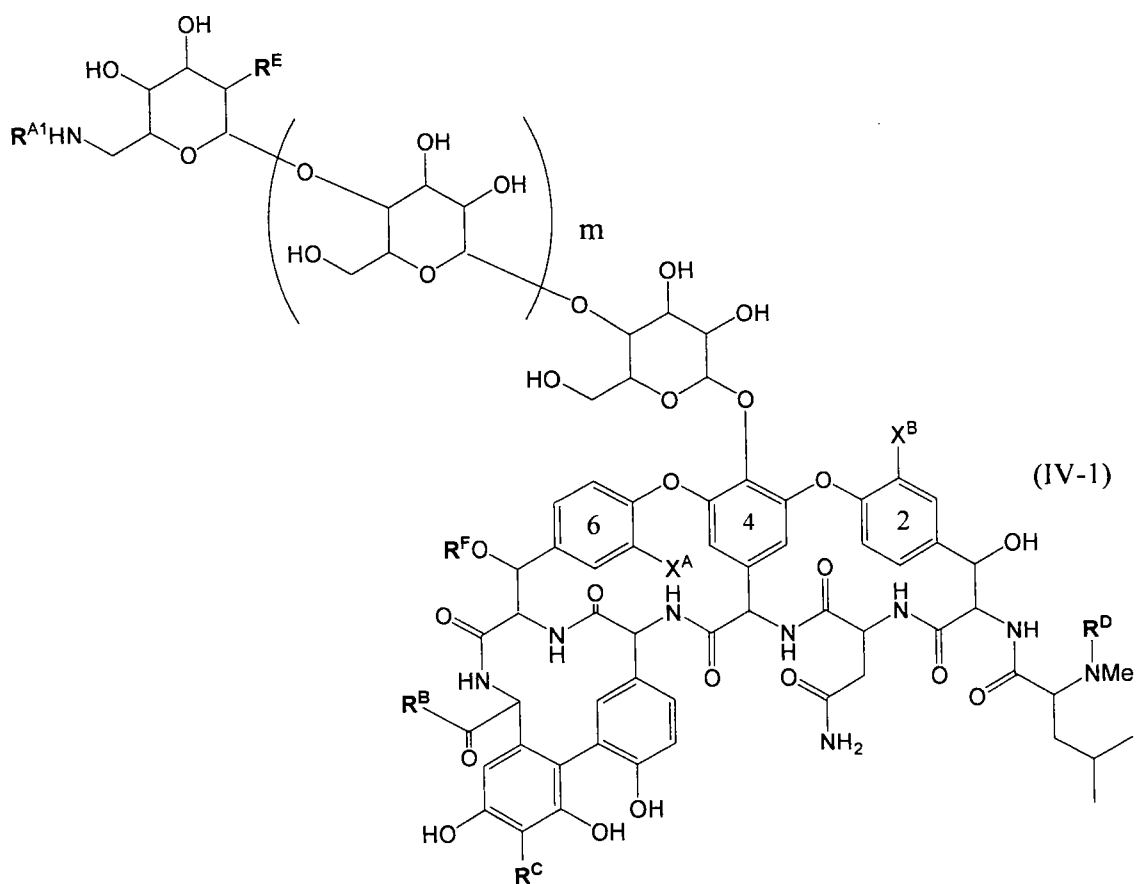
wherein

m is an integer of 0 to 4; and

other symbols are each as defined in above (15).

(17) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (16), wherein the compound is represented by the formula:

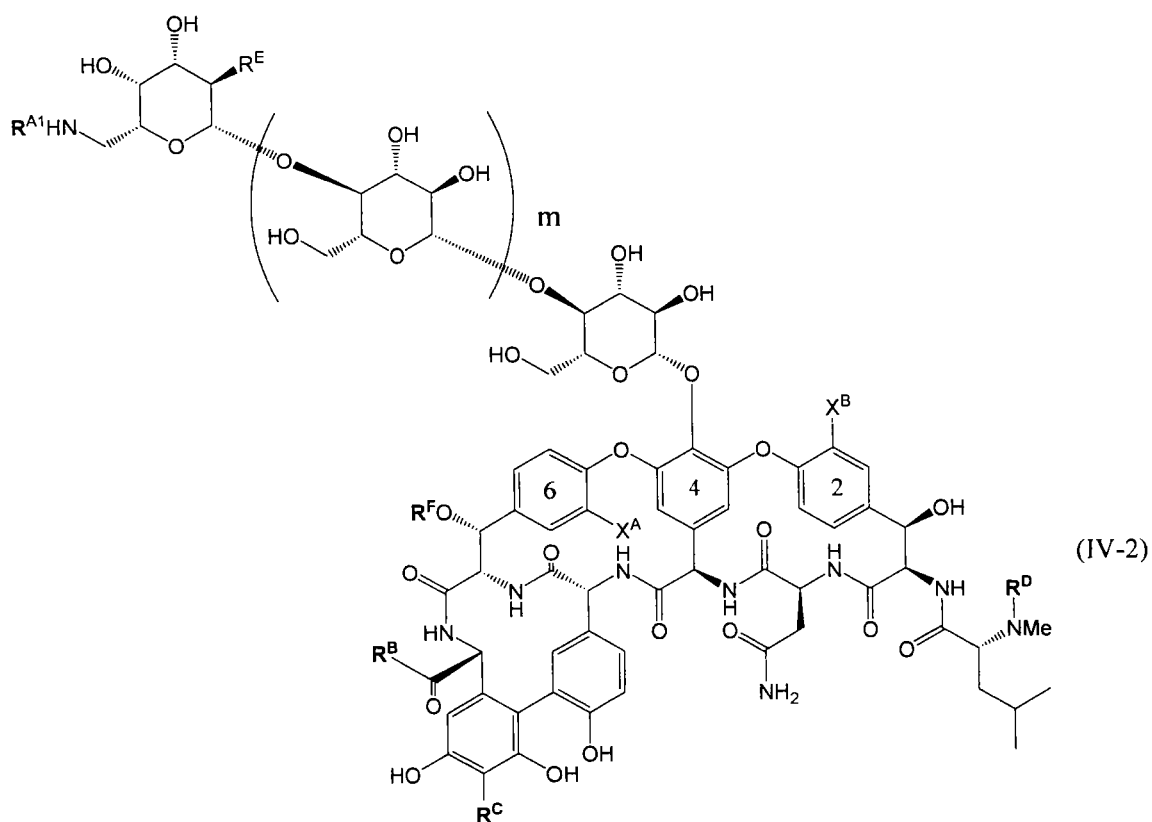
[Chemical formula 17]



wherein respective symbols are each as defined in above (16).

(18) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (16), wherein the compound is represented by the formula:

[Chemical formula 18]

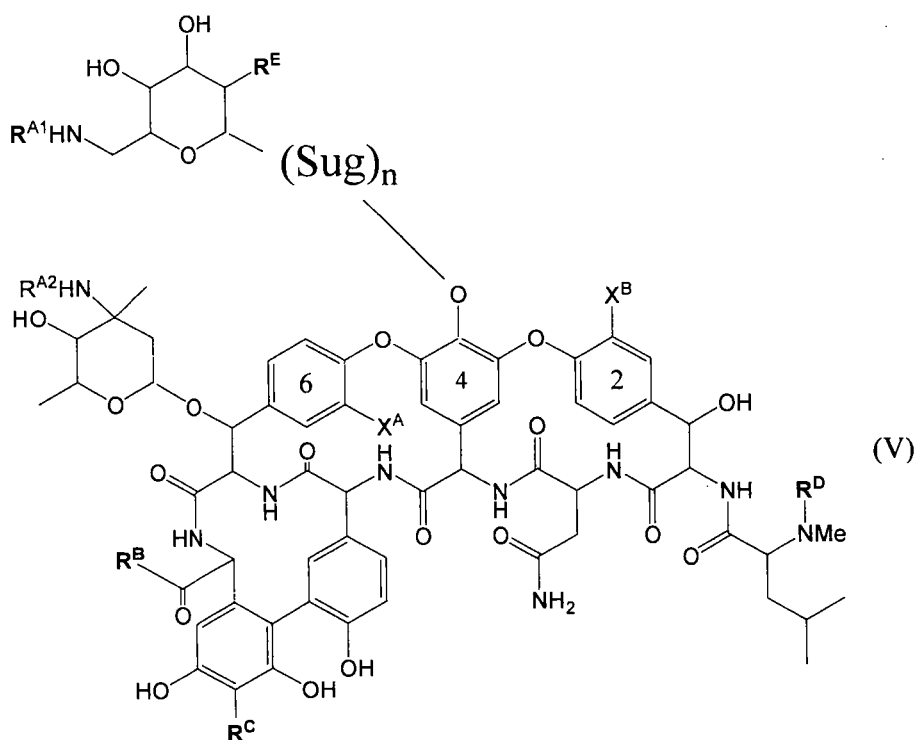


wherein respective symbols are each as defined in above (16).

[0012]

(19) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (1), wherein the compound is represented by the formula:

[Chemical formula 19]



wherein

R^{A2} is hydrogen or optionally substituted lower alkyl;

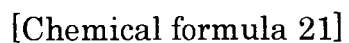
R^B is $-OH$, $-NR^5R^{5'}$ (wherein R^5 and $R^{5'}$ are each independently hydrogen, optionally substituted lower alkyl, optionally substituted lower alkyloxy, optionally substituted amino or amino sugar residue) or a $-OR^6$ (wherein R^6 is optionally substituted lower alkyl (a hetero atom group may intervene in the lower alkyl part));

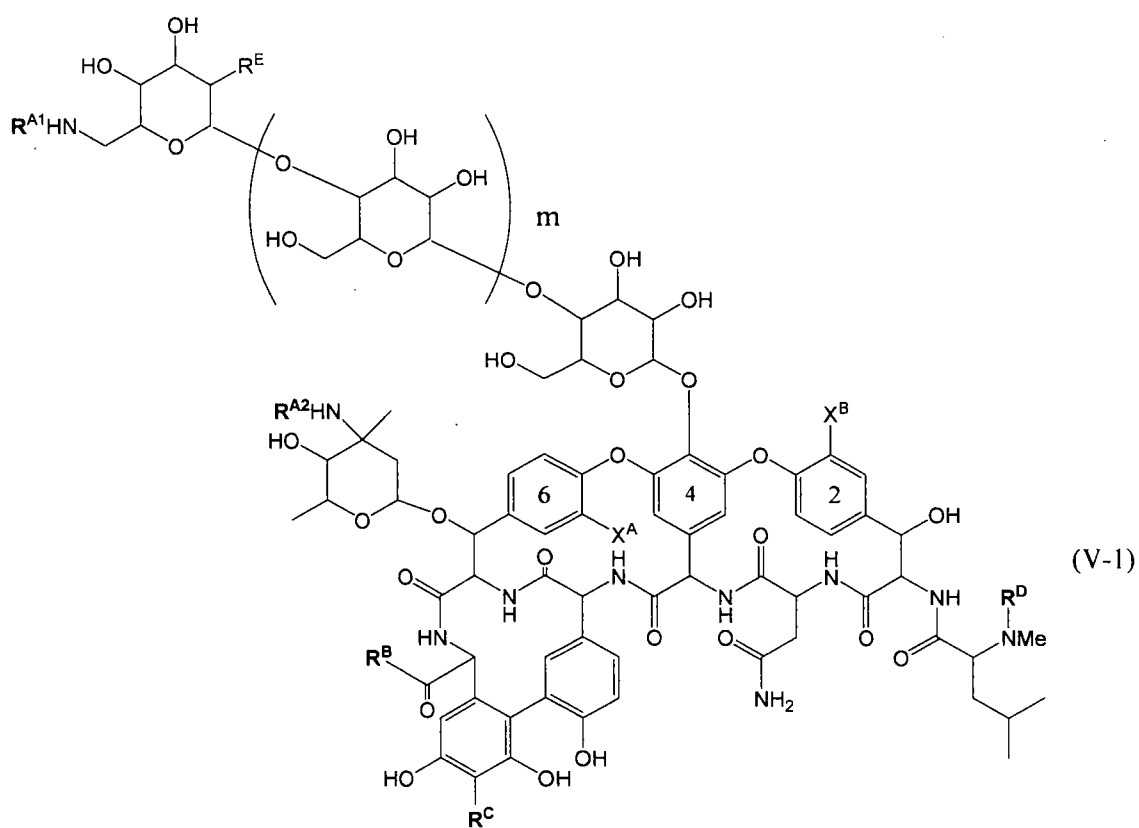
R^C is hydrogen or optionally substituted lower alkyl (a hetero atom group may intervene in the lower alkyl part);

R^D is hydrogen or lower alkyl;

X^A and X^B are each independently hydrogen or halogen; and other symbols are each as defined in above (1).

[Chemical formula 20]

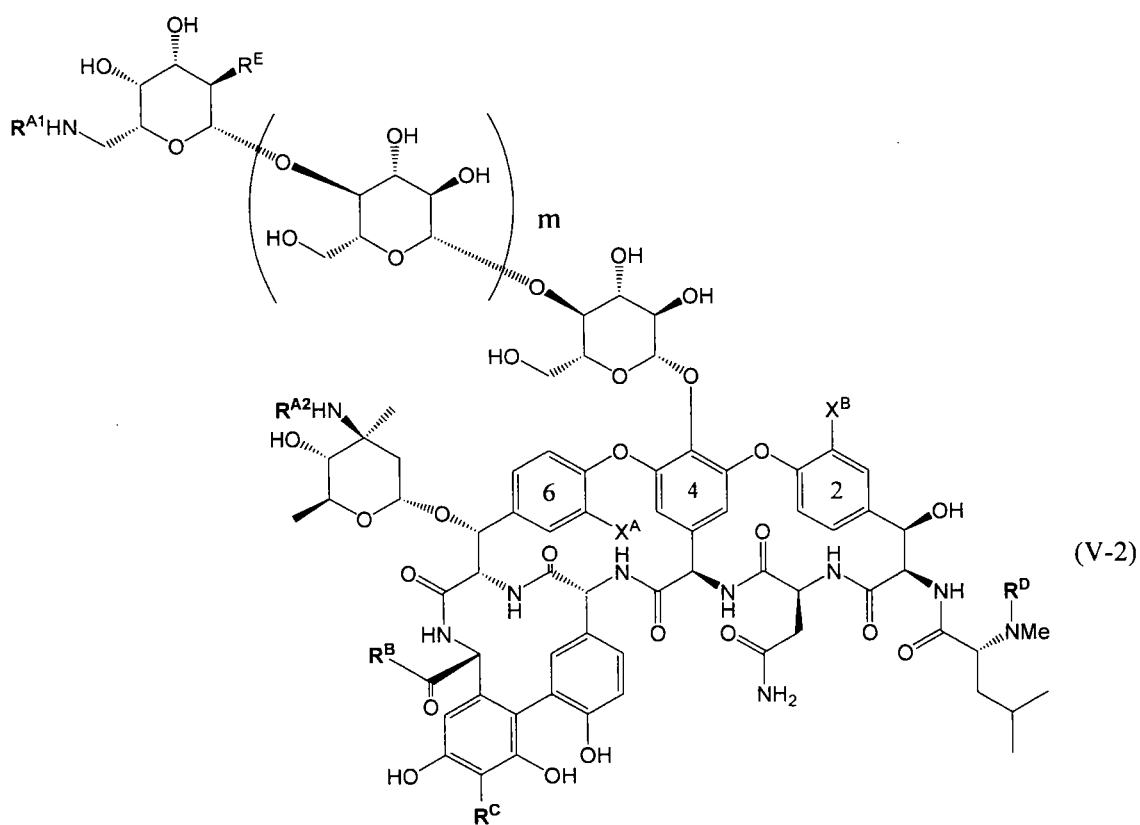




wherein respective symbols are as defined in above (20).

(22) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (20), wherein the compound is represented by the formula:

[Chemical formula 22]

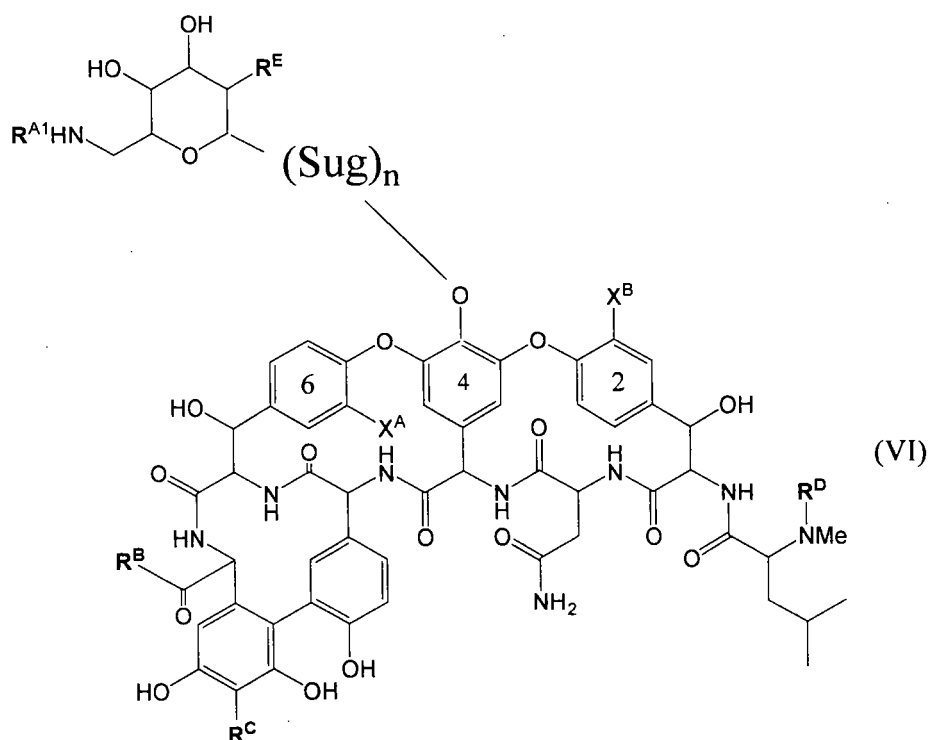


wherein respective symbols are each as defined in above (20).

[0013]

(23) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (1), wherein the compound is represented by the formula:

[Chemical formula 23]



wherein

R^B is $-OH$, $-NR^5R^{5'}$ (wherein R^5 and $R^{5'}$ are each independently hydrogen, optionally substituted with lower alkyl, optionally substituted lower alkyloxy, or optionally substituted amino or amino sugar residue) or $-OR^6$ (wherein R^6 is optionally substituted lower alkyl (a hetero atom group may intervene in the lower alkyl part));

R^C is hydrogen or optionally substituted lower alkyl (a hetero atom group may intervene in the lower alkyl part);

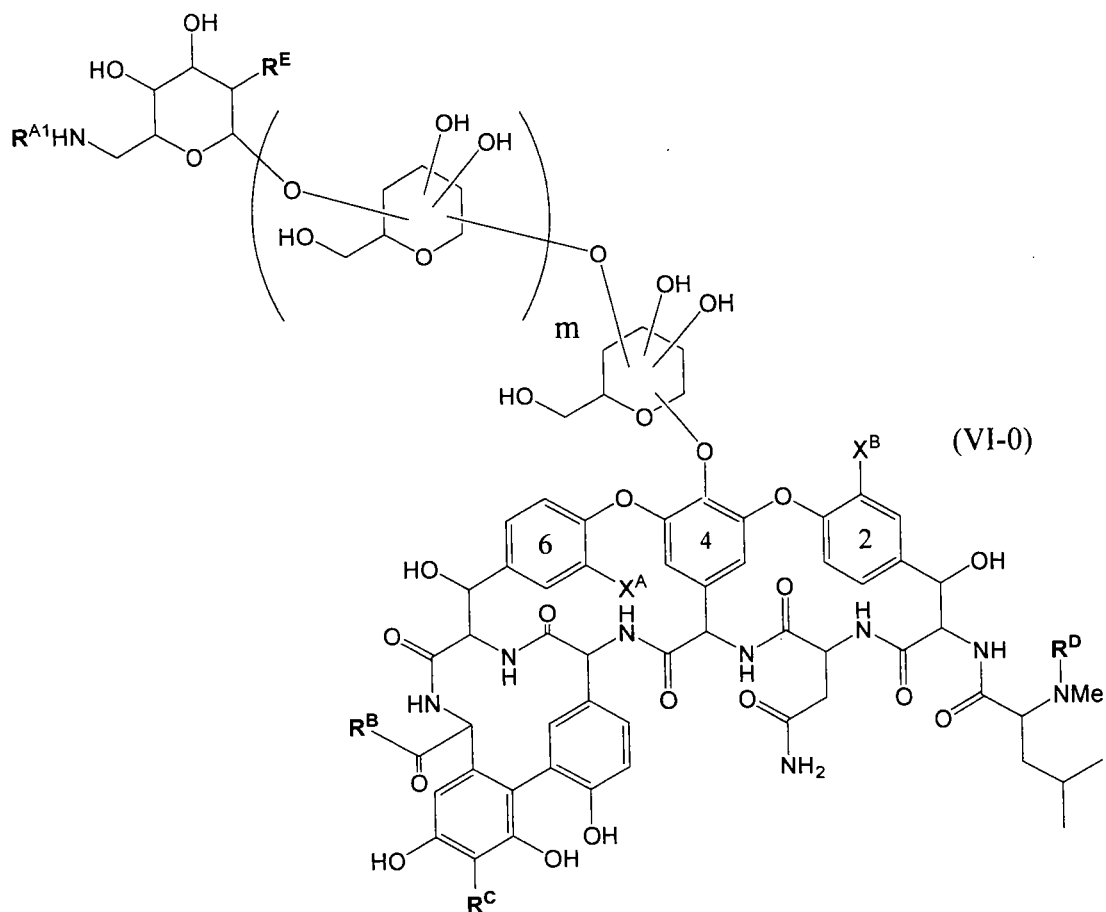
R^D is hydrogen or lower alkyl; and

X^A and X^B are each independently hydrogen or halogen; and other symbols are as defined in above (1).

(24) The compound, a pharmaceutically acceptable salt thereof, or a

solvate thereof according to above (23), wherein the compound is represented by the formula:

[Chemical formula 24]



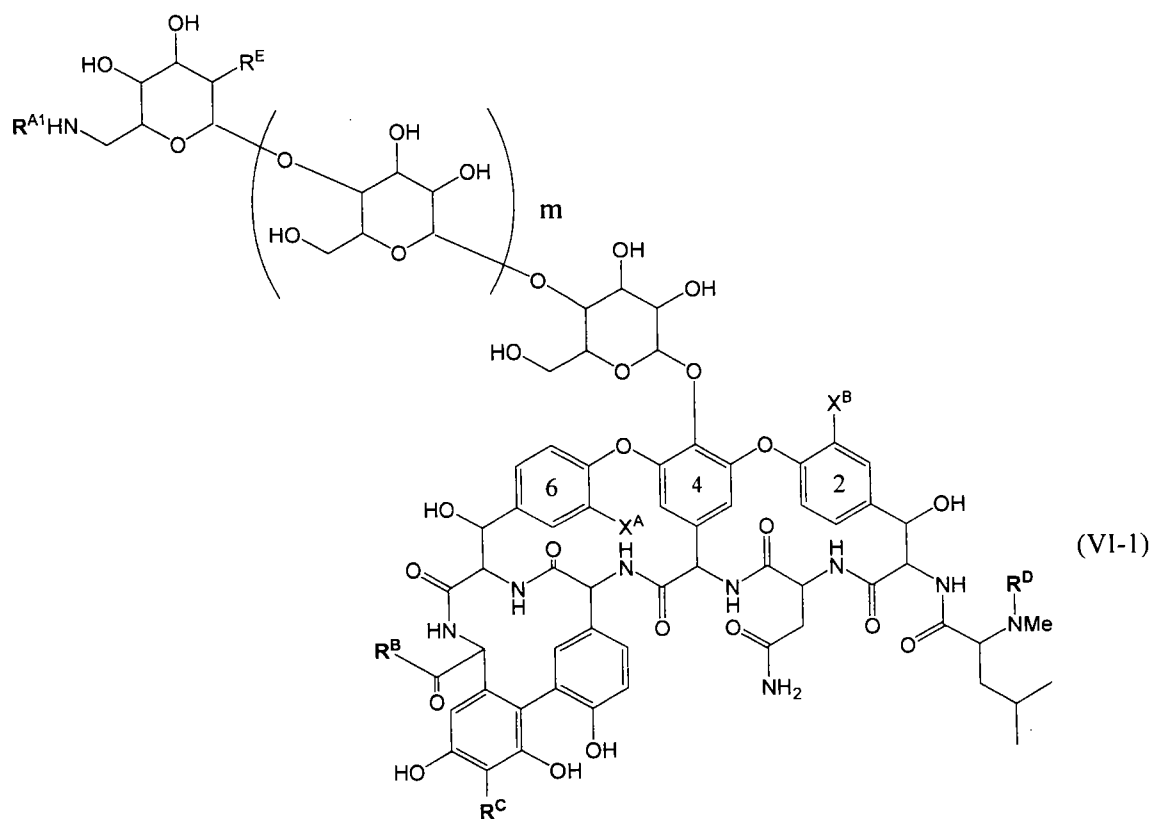
wherein

m is an integer of 0 to 4; and

other symbols are each as defined in above (23).

(25) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (24), wherein the compound is represented by the formula:

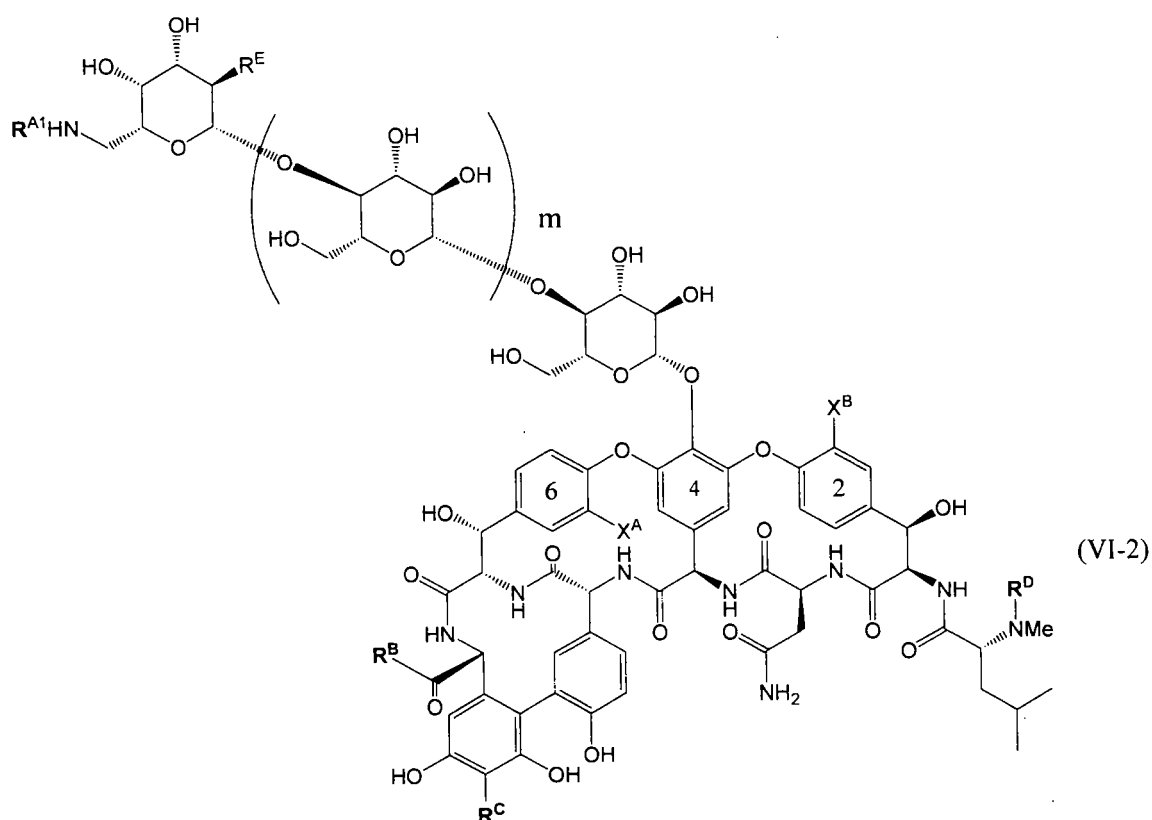
[Chemical formula 25]



wherein respective symbols are as defined in above (24).

(26) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (24), wherein the compound is represented by the formula:

[Chemical formula 26]



wherein respective symbols are each as defined in above (24).

(27) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of above (6) to (8), (11) to (13), (16) to (18), (20) to (22), and (24) to (26), wherein m is 0 or 1.

(28) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of above (1) to (27), wherein R^E is OH .

(29) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of above (1) to (28), wherein each substituents in optionally substituted lower alkyl, optionally substituted

lower alkenyl, or optionally substituted cycloalkyl, of R^{A1} are selected from the following Substituent group A.

Substituent group A: optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, optionally substituted aralkylthio, optionally substituted heteroaralkylthio, optionally substituted cycloalkyl, optionally substituted lower alkyloxy, optionally substituted aralkyloxy, optionally substituted aryloxy, optionally substituted arylsulfonylamino, and optionally substituted amino

(30) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (29), wherein each substituents of “optionally substituted” groups in Substituent group A of above (29) are selected from the following Substituent group B.

Substituent group B: optionally substituted arylaminocarbonylamino, optionally substituted arylcarbonylamino, oxo, halogen, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthio, optionally substituted arylsulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted amino, optionally substituted aralkylcarbonylamino, optionally substituted aralkylaminocarbonyl, optionally substituted aralkylsulfinyl, optionally substituted arylsulfonylamino, optionally substituted aralkylthio, halo lower alkyl, halo lower alkyloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, and optionally substituted aryl lower alkenyl

(30') The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (29), wherein each substituent of

“optionally substituted” groups in Substituent group A of above (29) is selected from the following Substituent group B.

Substituent group B: optionally substituted arylaminocarbonylamino, optionally substituted arylaminocarbonyl, optionally substituted arylcarbonyl, optionally substituted arylcarbonylamino, optionally substituted arylcarbonylaminoalkyl, oxo, halogen, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthio, optionally substituted arylamino, optionally substituted arylaminoalkyl, optionally substituted arylaminocarbonylalkyl, optionally substituted arylsulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted amino, optionally substituted aralkylcarbonylamino, optionally substituted aralkylamino, optionally substituted aralkylaminocarbonyl, optionally substituted aralkylsulfinyl, optionally substituted arylsulfonylamino, optionally substituted arylaminosulfonyl, optionally substituted aralkylthio, halo lower alkyl, lower alkyloxy, lower alkylamino, halo lower alkyloxy, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylthio, optionally substituted aryl lower alkenyl, optionally substituted heteroaryl lower alkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkyloxy, optionally substituted cycloalkylthio, optionally substituted cycloalkylaminocarbonyl, optionally substituted cycloalkyl lower alkenyl, optionally substituted cycloalkylsulfonyl, optionally substituted cycloalkylaminocarbonylamino, optionally substituted cycloalkylaminoalkyl, optionally substituted

cycloalkyl lower alkylamino, optionally substituted cycloalkylamino, optionally substituted cycloalkyl lower alkyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonylamino, optionally substituted cycloalkylcarbonylamino, optionally substituted cycloalkylcarbonylaminoalkyl, optionally substituted cycloalkyl lower alkylaminocarbonyl, optionally substituted cycloalkylsulfonylamino, optionally substituted cycloalkylaminocarbonylalkyl, and optionally substituted cycloalkylaminosulfonyl

(31) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to above (30) or (30'), wherein each substituents of "optionally substituted" groups in Substituent group B of above (30) or (30') are selected from the following Substituent group C.

Substituent group C: lower alkyl, lower alkyloxy, lower alkylsulfonyl, nitro, aralkyloxy, halogen, cyano, halo lower alkyl, halo lower alkyloxy, and di-lower alkylamino

(32) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of above (15) to (31), and (30'), wherein R^B is OH; R^C is H; and R^D is H.

[0014]

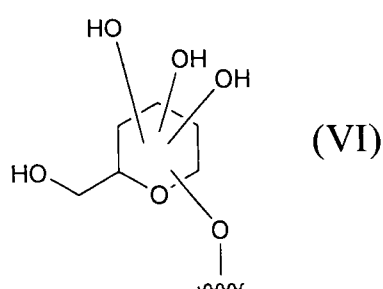
In addition, the present invention provides a process for producing the compounds described in above (1) to (32), and (30'), shown in the following (33) to (38).

(33) A process for producing the glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof as defined in above (6) including the following steps:

(step 1)

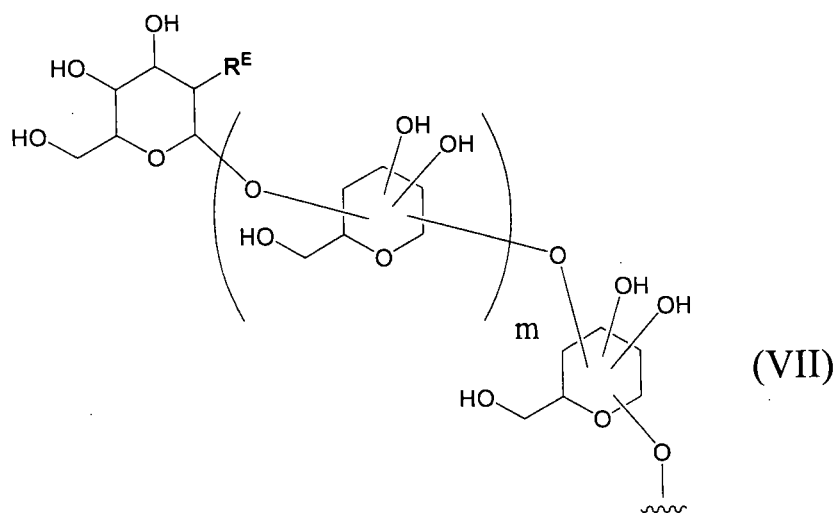
a step converting a sugar residue (VI) represented by the formula:

[Chemical formula 27]



into a group (VII) represented by the formula:

[Chemical formula 28]



wherein R^E is OH or NHAc; and m is an integer of 0 to 2;

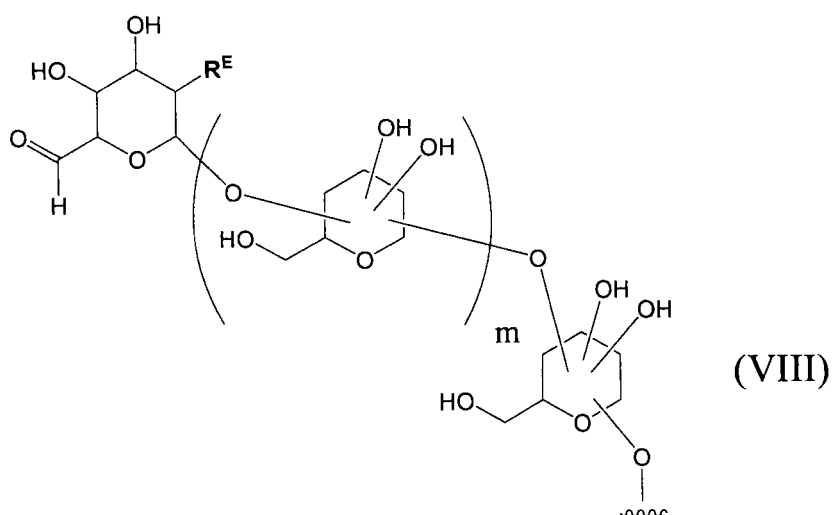
by performing $1+m$ (m is an integer of 0 to 2) times of glycosylating reaction in the presence of glycosyltransferase and a sugar donor using a glycopeptide

compound, a salt thereof, or a solvate thereof as a raw material,
 wherein the aromatic ring of the fourth amino acid residue is substituted
 with the sugar residue (VI).

(step 2)

a step converting the hydroxymethylene part in the sugar at the end of the
 group (VII) into a group (VIII) represented by the formula:

[Chemical formula 29]



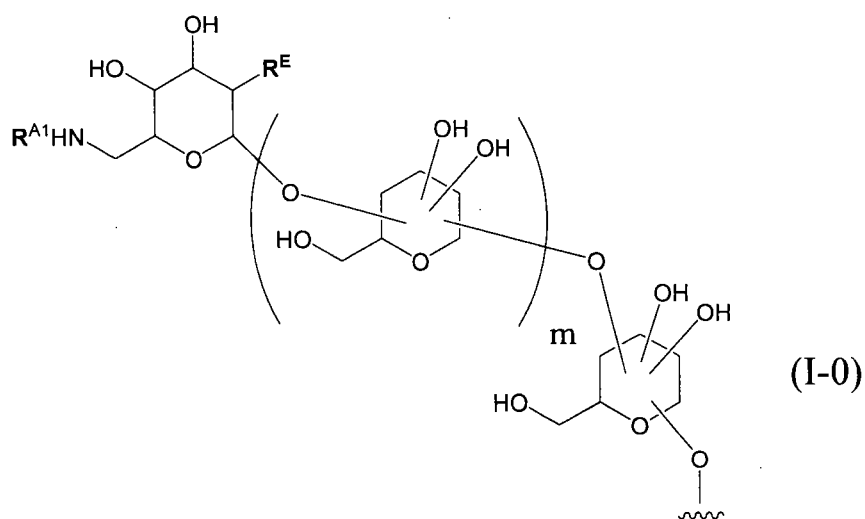
wherein respective symbols are as defined above;

by an oxidation reaction; and

(step 3)

a step converting the group (VIII) into a sugar residue (I-0) represented by
 the formula:

[Chemical formula 30]



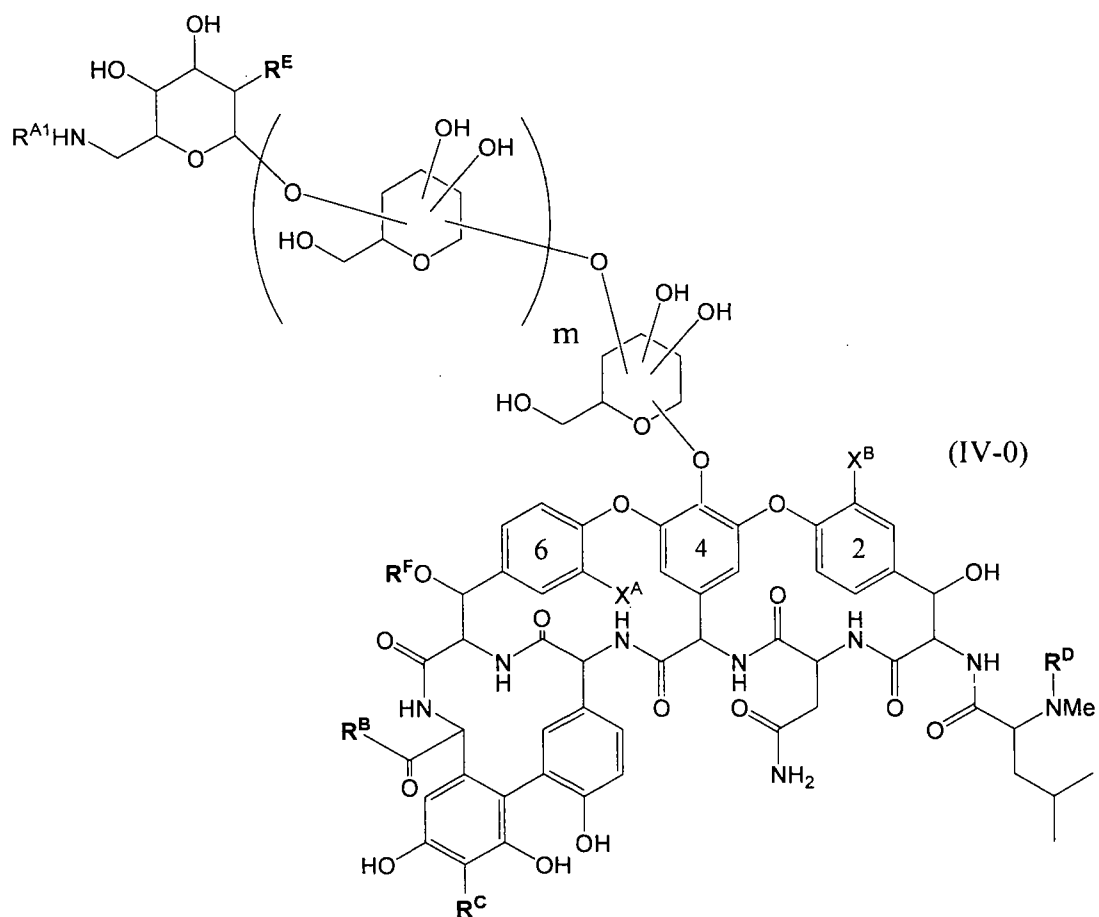
wherein respective symbols are as defined above

by reductive amination reaction of the aldehyde group of the group (VIII) with a compound (A) represented by the formula $R^{A1}NH_2$.

[0015]

(34) A process for producing the compound (IV-0), a pharmaceutically acceptable salt thereof or a solvate thereof as defined in above (16) represented by the formula:

[Chemical formula 34]



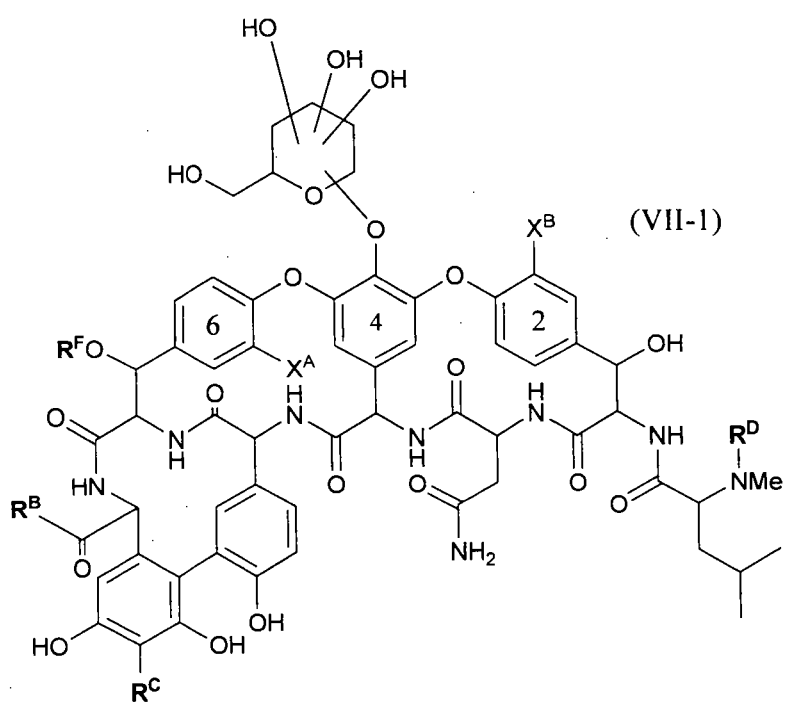
wherein respective symbols are as defined below,

including the following steps:

(step 1)

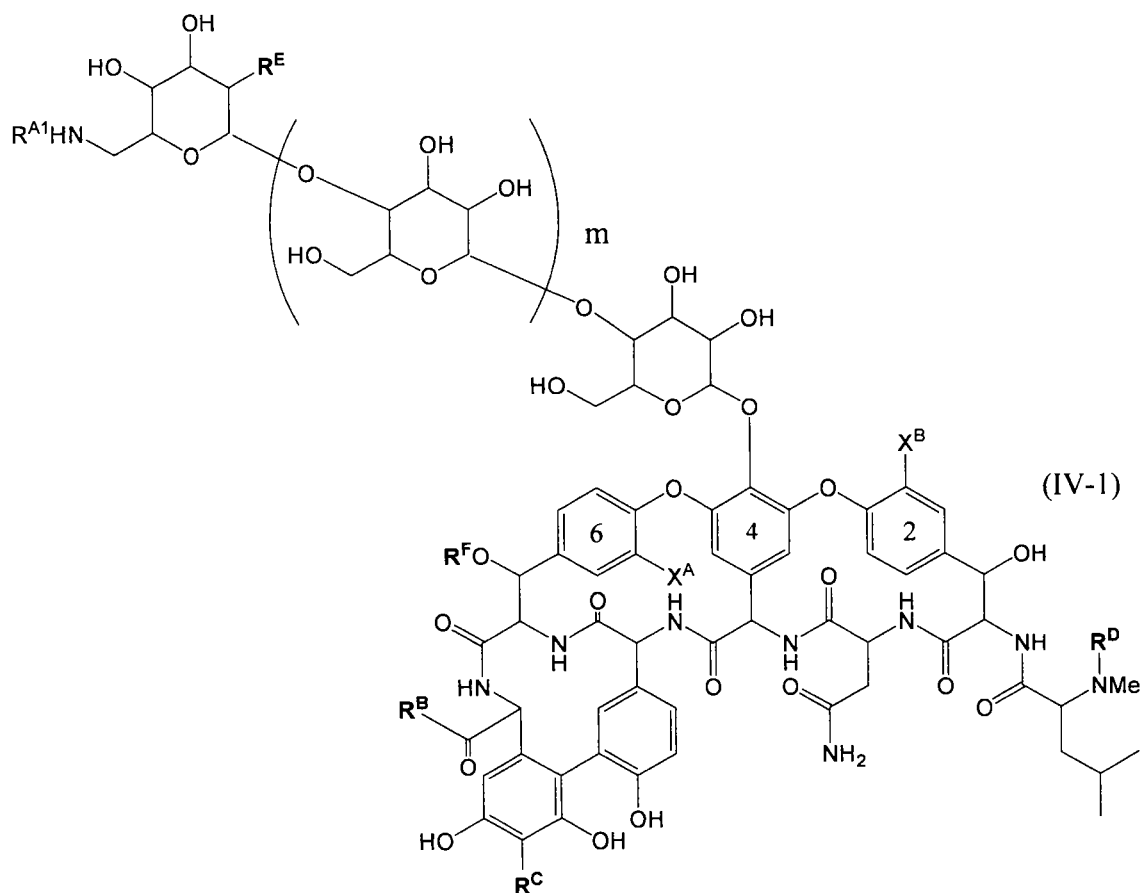
a step of reacting 1+m (m is an integer of 0 to 2) times of glycosylating reaction in the presence of glycosyltransferase and a sugar donor using a compound (VII-1) as a raw material represented by the formula:

[Chemical formula 31]



wherein respective symbols are as defined in above (15),
to obtain a compound (VIII-1), a salt thereof, or a solvate thereof represented
by the formula:
[Chemical formula 32]

[Chemical formula 38]



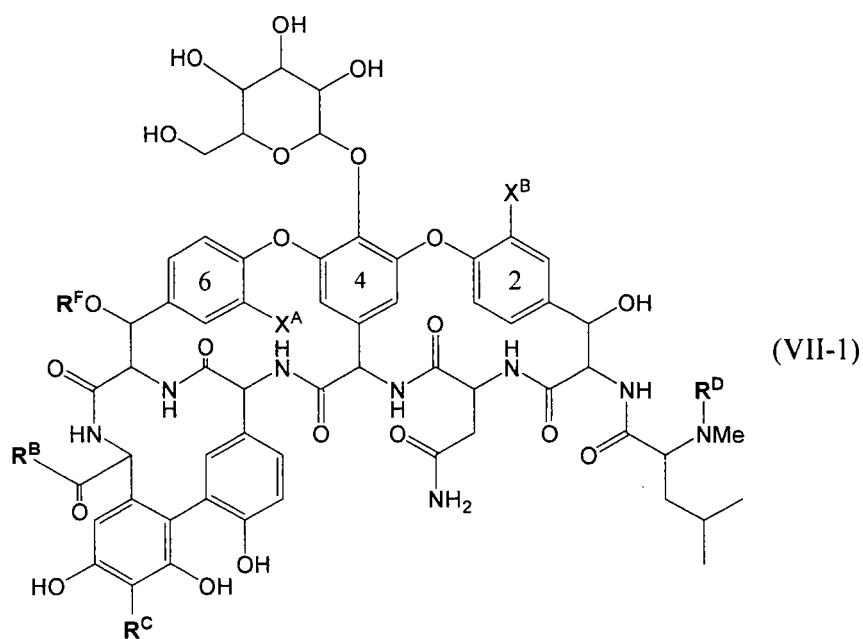
wherein respective symbols are as defined below,

including the following steps:

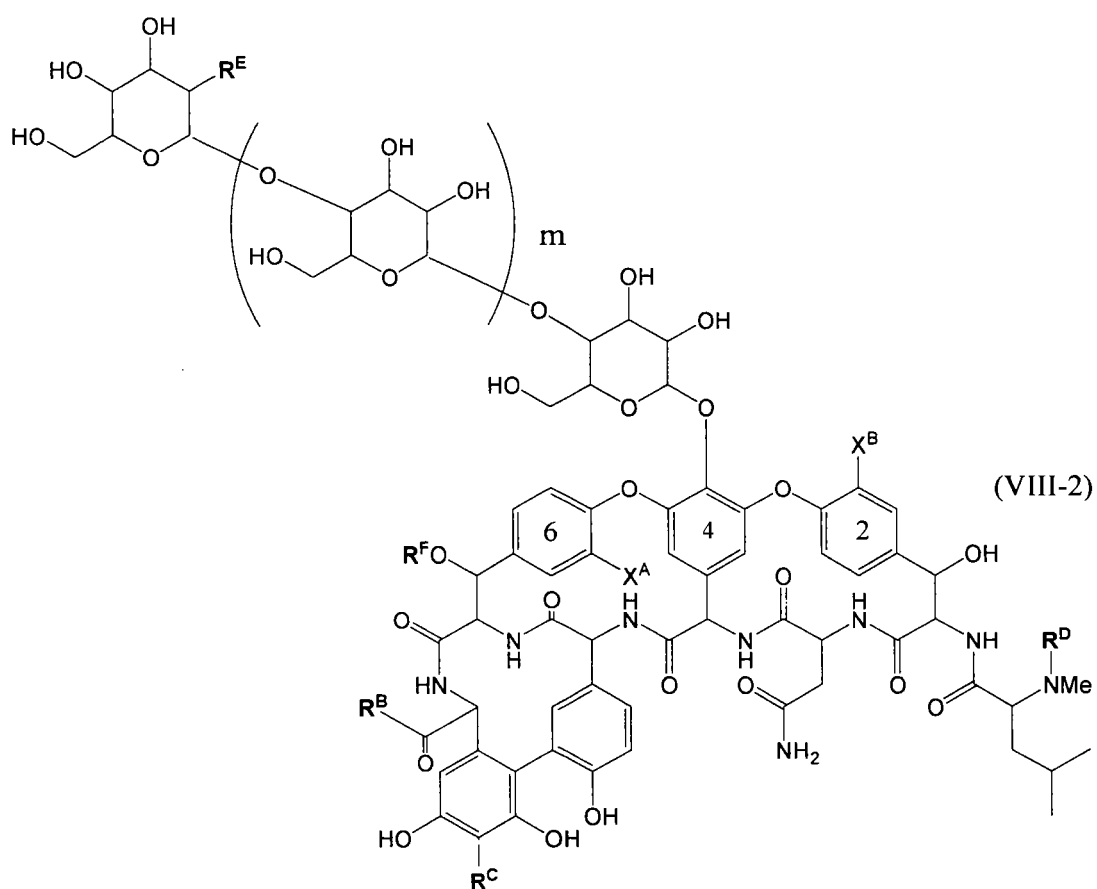
(step 1)

a step of reacting 1+m (m is an integer of 0 to 2) times of glycosylating reaction in the presence of glycosyltransferase and a sugar donor using a compound (VII-1) as a raw material represented by the formula:

[Chemical formula 35]



wherein respective symbols are as defined in above (15),
to obtain a compound (VIII-2), a salt thereof, or a solvate thereof,
represented by the formula:
[Chemical formula 36]

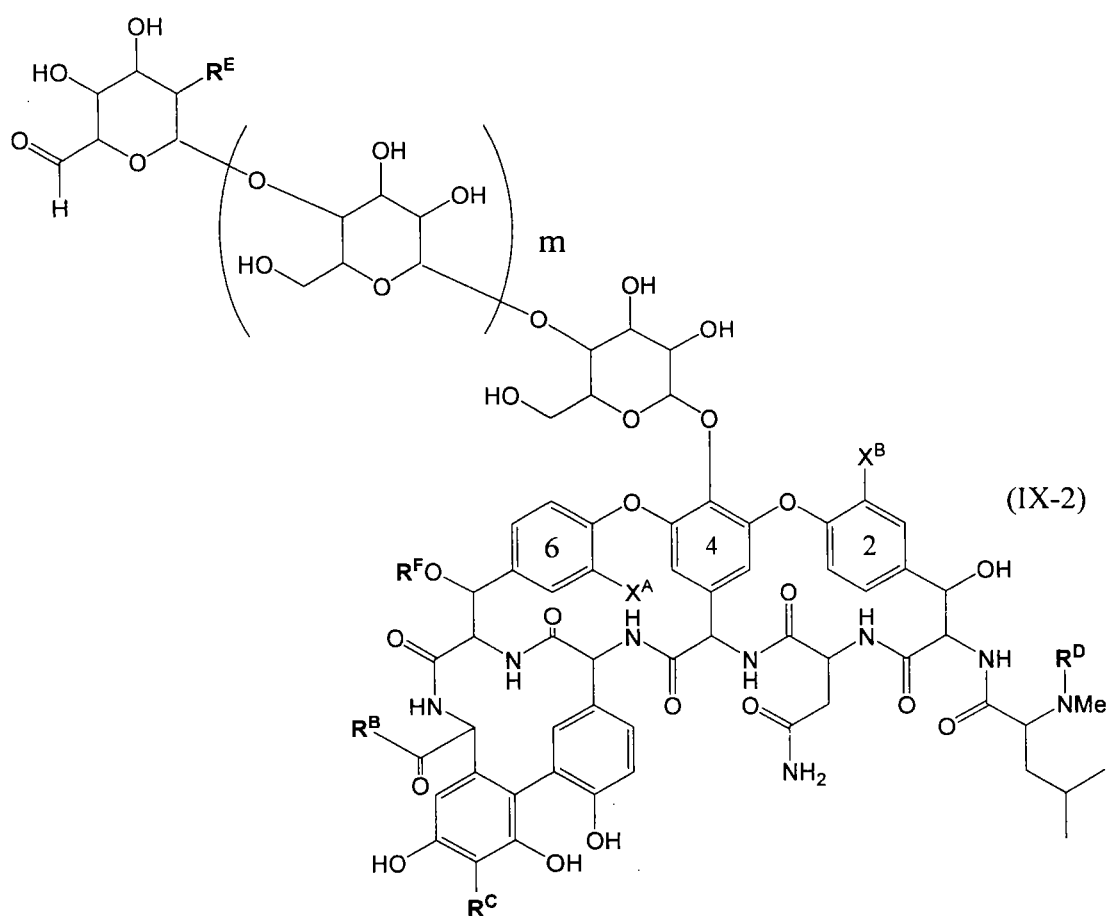


wherein R^E is OH or NHAc; and other symbols are as defined above,

(step 2)

a step of subjecting the compound (VIII-2), a salt thereof, or a solvate thereof to an oxidation reaction to obtain a compound (IX-2), a salt thereof, or a solvate thereof represented by the formula:

[Chemical formula 37]



wherein respective symbols are as defined above; and

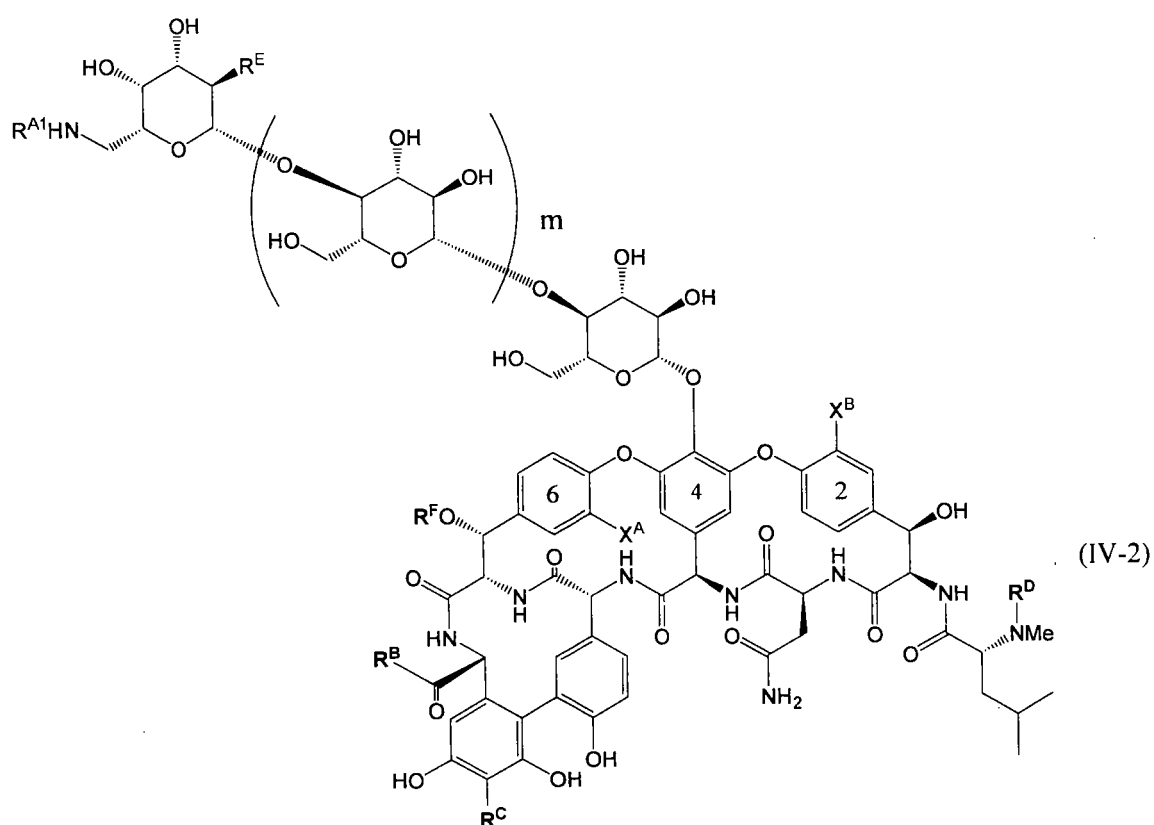
(step 3)

a step of subjecting the compound (IX-2), a salt thereof, or a solvate thereof to a reductive amination reaction with a compound (A) represented by the formula: R^{A1}NH₂.

[0017]

(36) A process for producing a compound (IV-2), a pharmaceutically acceptable salt thereof, or a solvate thereof, as defined in above (18) represented by the formula:

[Chemical formula 42]



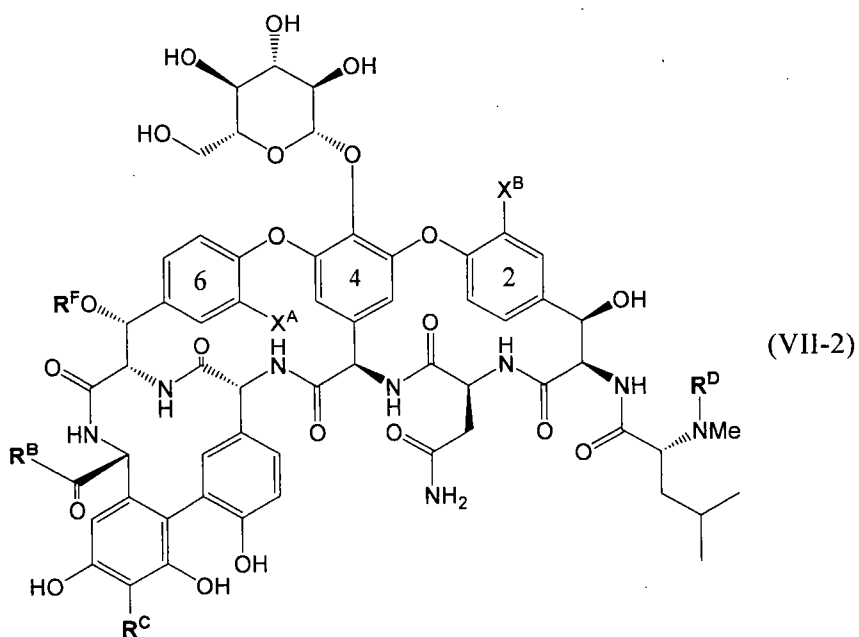
wherein respective symbols are as defined below;

including the following steps:

(step 1)

a step of reacting 1+m (m is an integer of 0 to 2) times of glycosylating reaction in the presence of glycosyltransferase and a sugar donor using a compound (VII-2) as a raw material represented by the formula:

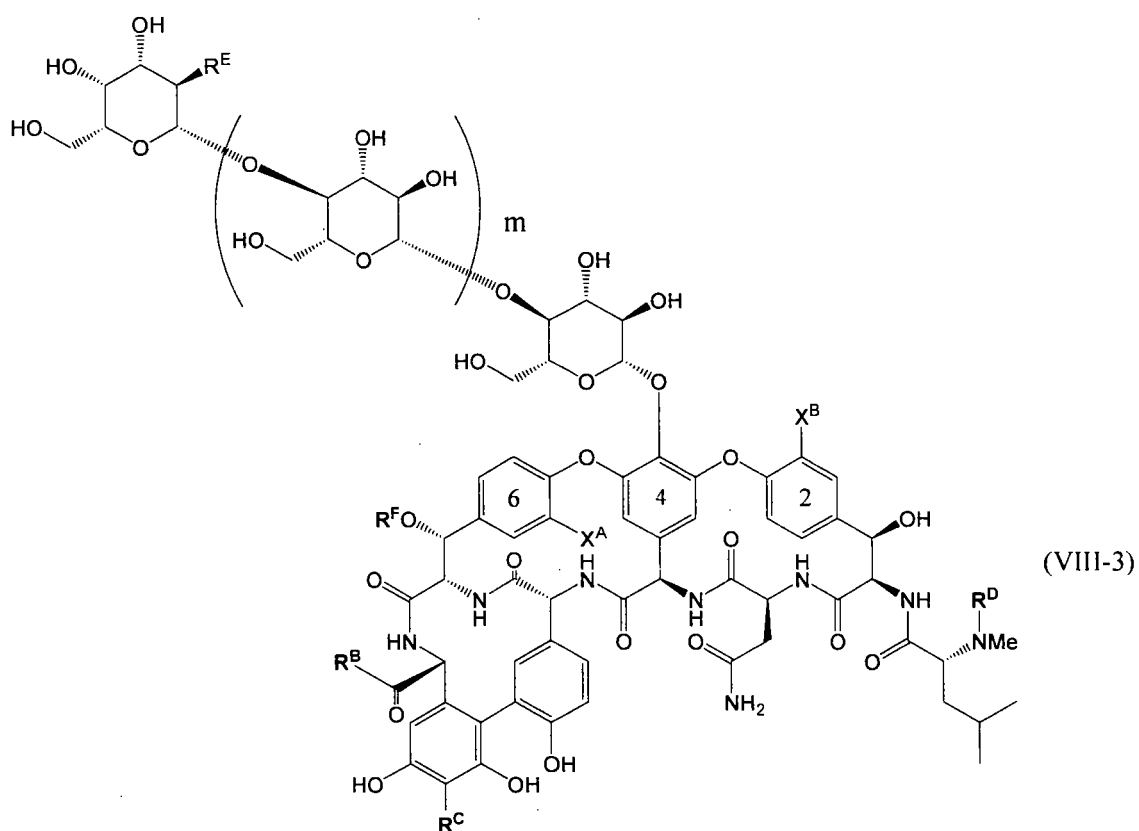
[Chemical formula 39]



wherein respective symbols are as defined in above (15),

to obtain a compound (VIII-3), a salt thereof, or a solvate thereof represented by the formula:

[Chemical formula 40]



wherein R^E is OH or NHAc; and other symbols are as defined above,

(step 2)

a step of subjecting the compound (VIII-3), a salt thereof, or a solvate thereof to an oxidation reaction to obtain a compound (IX-3), a salt thereof, or a solvate thereof represented by the formula:

[Chemical formula 41]

in the step 2, the oxidation reaction is performed with galactose oxidase.

(38) The process according to any one of above (33) to (36), wherein in the step 1, the glycosyltransferase is galactosyltransferase; and, after addition of glucose by an optional first glycosylating reaction, galactose is further added by a second glycosylating reaction; and, in the step 2, the oxidation reaction is performed with galactose oxidase.

[0019]

Further, the present invention also provides compounds shown by the following above (39) and (40), which are useful as an intermediate for producing the compounds as defined in any one of above (1) to (32), and (30').

(39) The compound (VIII-1), a salt thereof, or a solvate thereof as defined in above (34).

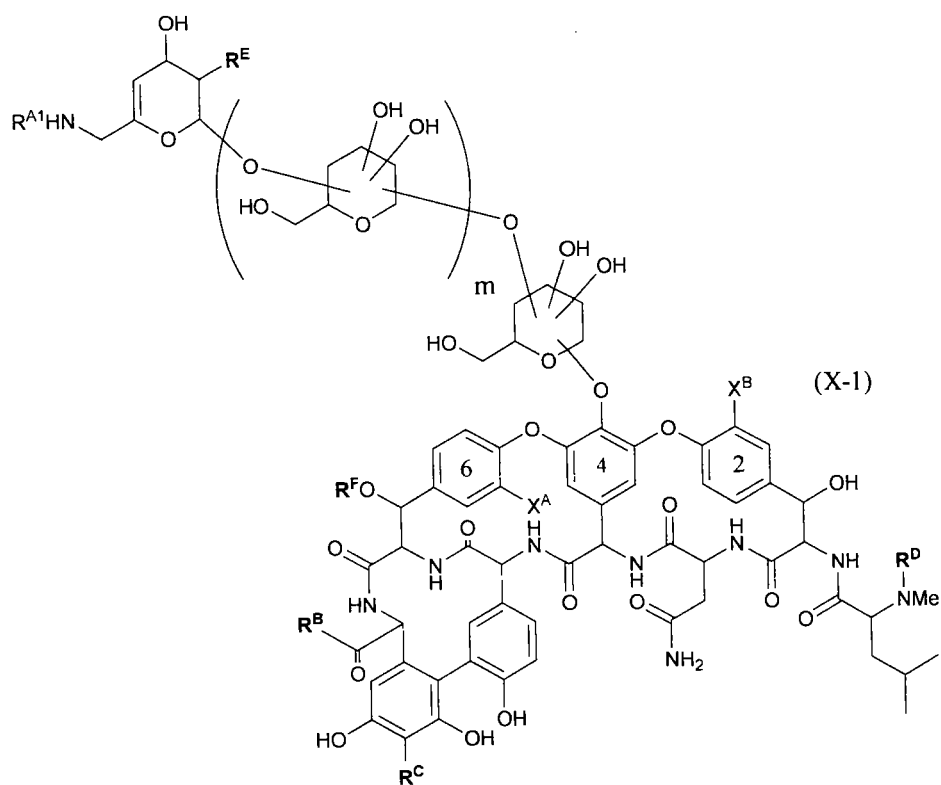
(40) The compound (IX-1), a salt thereof, or a solvate thereof as defined in (34).

[0020]

The present invention further provides following dehydrated material of a sugar at the side chain terminal.

(41) A compound, a pharmaceutically acceptable salt thereof, or a solvate thereof represented by the formula:

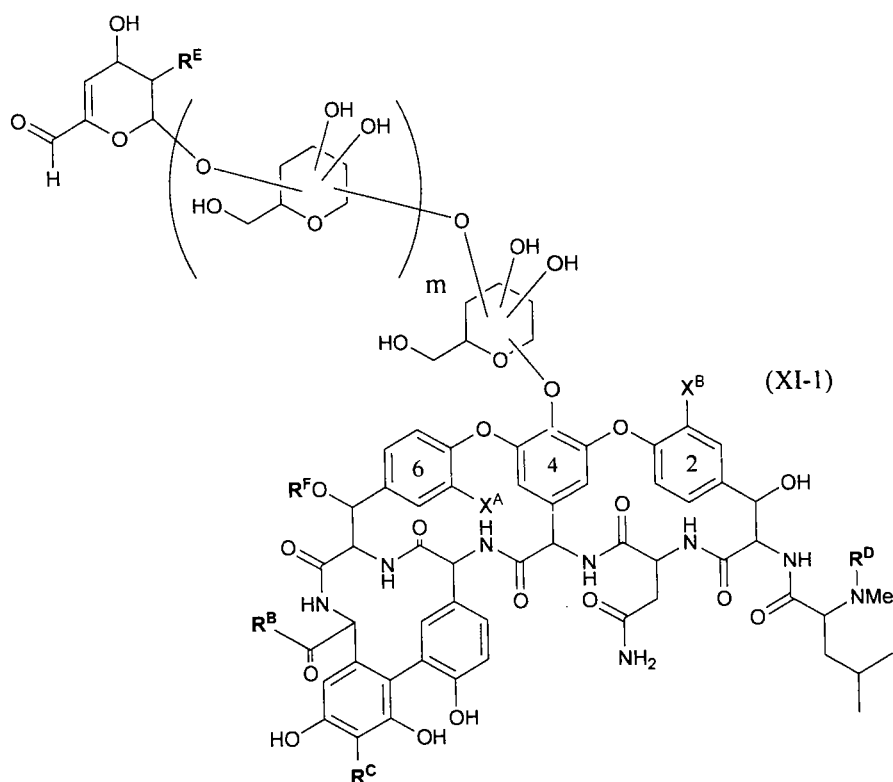
[Chemical formula 43]



wherein respective symbols are each as defined in above (16).

(42) A compound, a pharmaceutically acceptable salt thereof, or a solvate thereof represented by the formula:

[Chemical formula 44]



wherein respective symbols are as defined above.

(43) A pharmaceutical composition containing the compound as defined in any one of above (1) to (32), (30'), and (39) to (42), or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Effects of the Invention]

[0021]

The glycopeptide antibiotic derivative of the present invention, a pharmaceutically acceptable salt thereof, or a solvate thereof exhibits an antibacterial activity in an In Vitro and/or In Vivo test against various bacterium such as *Staphylococcus* including MRSA, *Streptococcus*, *Pneumococcus*, *Enterococcus*, and the like. Particularly, the compound of

the present invention is also effective for vancomycin-resistant bacterium derived therefrom and, particularly, for vancomycin-resistant *Enterococcus* (VRE) and vancomycin-resistant *Staphylococcus aureus* (VRSA). Therefore, the compound of the present invention is useful for treating or preventing various bacterial infections such as complicated skin and skin tissue infection, meningitis, sepsis, pneumonia, arthritis, peritonitis, bronchitis, empyema, endocarditis, catheter bloodstream infection and the like. In addition, the more preferable compound of present invention has high water solubility, is better in disposition, and/or is safe in toxicity (renal toxicity, hepatic toxicity, histamine freeing activity, hERG channel inhibition, antigenicity, etc.).

[Best Mode for carrying out the Invention]

[0022]

Herein, the “glycopeptide antibiotic” means an arbitrary glycopeptide compound having a peptide chain consisting of seven amino acids including an aromatic amino acid as a common fundamental skeleton, and a derivative thereof, represented by vancomycin and chloroorienticins. In addition, the “glycopeptide skeleton” means a cyclic fundamental structure consisting of the peptide chain which is commonly possessed by glycopeptide antibiotics. Examples of the known glycopeptide antibiotics are disclosed in JP-A No. 61-251699 gazette, JP-A No. 7-258289 gazette, International Publication WO 96/30401 pamphlet, International Publication WO 00/39156 pamphlet, JP-A No. 2000-302687 gazette, International Publication WO 2004/44222 pamphlet; US Patent Nos. 4,639,433; 4,643,987; 4,497,802; 4,698,327;

5,591,714; 5,840,684; and 5,843,889; EP0802199; EP0801075; EP0667353; WO 97/28812; WO 97/38702; WO 98/52589; WO 98/52592; as well as J. Am. Chem. Soc., 1996, 118, 13107-13108; J. Am. Chem. Soc., 1997, 119, 12041-12047; and J. Am. Chem. Soc., 1994, 116, 4573-4580.

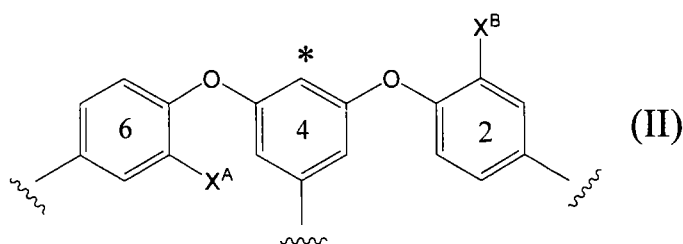
[0023]

More specific examples of the glycopeptide antibiotics include vancomycin, teicoplanin, ristomycin, ristocetin, actaplanin, actinoidin, ardacin, avoparcin, azureomycin, balhimycin, chloroorienticin A, chloroorienticin B, chloropolyspoin, decaplanin, N-demethylvancomycin, eremomycin, galacardin, helvecardin, izupeptin, kibdelin, mannopeptin, orienticin, parvodicin, synmonicin, oritavancin, telavancin (TD-6424), dalbavancin, and A-40926.

[0024]

In the present invention, the "glycopeptide skeleton" preferably has the following partial structure (II) as an aglycone part,

[Chemical formula 45]



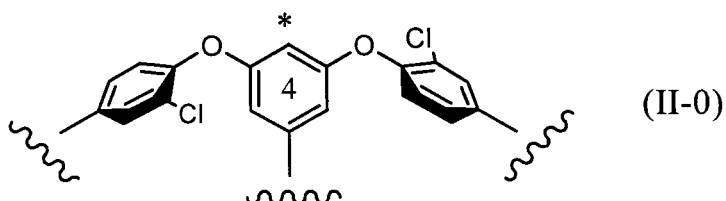
(wherein the ring 2, the ring 4 and the ring 6 represent aromatic rings of the second, fourth and sixth amino acid residues of a glycopeptide antibiotic, respectively; X^A and X^B are each independently hydrogen or halogen; and * represents a binding position with a sugar residue).

X^A and X^B are preferably both halogen, further preferably Cl.

[0025]

Further preferably, the glycopeptides skeleton has the following partial structure (II-0):

[Chemical formula 46]

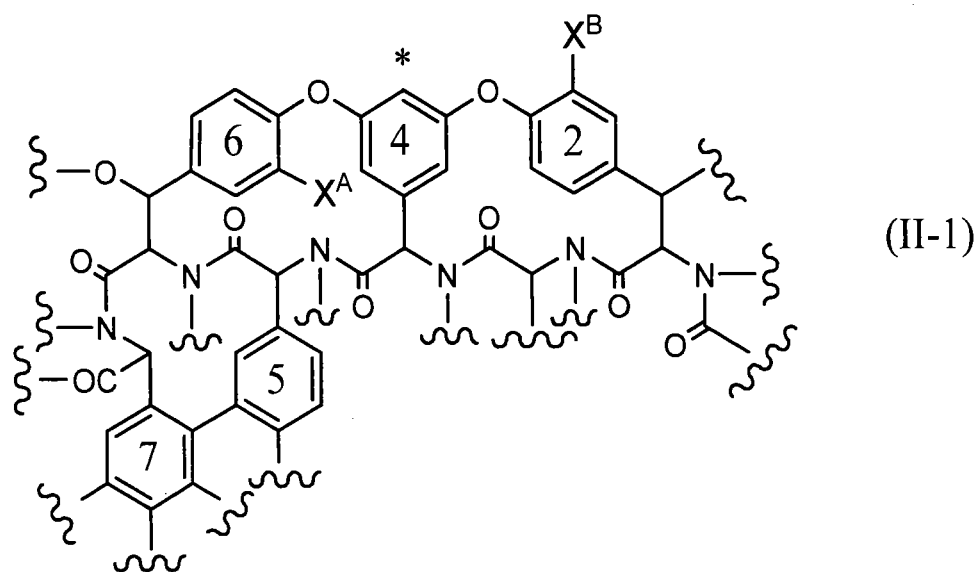


(wherein the ring 4 represents an aromatic ring of the fourth amino acid residue of a glycopeptide antibiotic; and * represents a binding position with a sugar residue).

[0026]

Further preferably, the glycopeptide skeleton has the following partial structure (II-1):

[Chemical formula 47]

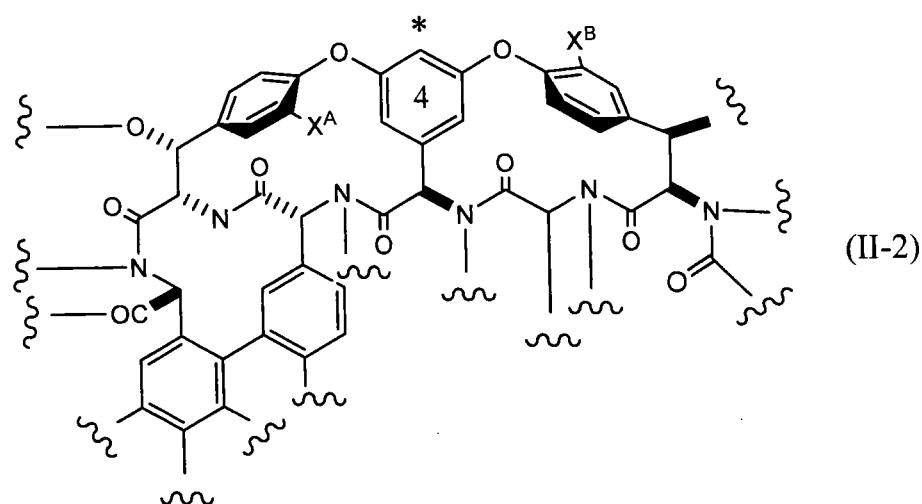


(wherein the rings 2, 4, 5, 6 and 7 represent aromatic rings at the second, fourth, fifth, sixth and seventh amino acid residues of a glycopeptide antibiotic, respectively; X^A and X^B are each independently hydrogen or halogen; and * represents a binding position with a sugar residue).

[0027]

Further preferably, the glycopeptide skeleton has the following partial structure (II-2):

[Chemical formula 48]



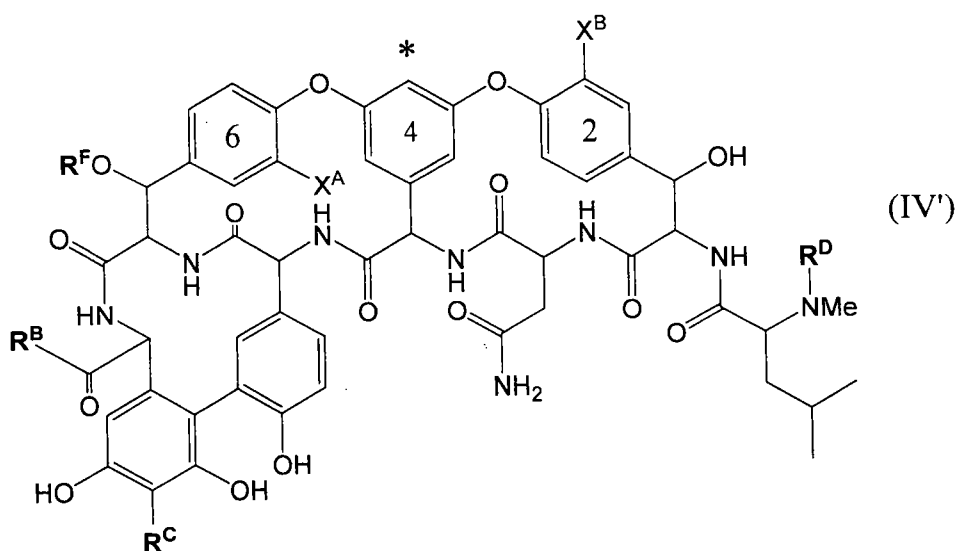
(wherein, respective symbols are as defined above).

The aglycone part may be optionally substituted with a substituent which is well-known to a person skilled in the art or can be synthesized by a person skilled in the art. For example, a C-terminal, an N-terminal, a resorcinol part or the like in a vancomycin derivative, a teicoplanin derivative, a chloroorienticin B derivative or the like may be optionally chemically modified. In addition, a sugar may be bound to a part other than carbon represented by *.

[0028]

Further preferably, the glycopeptide skeleton has the following partial structure (IV'):

[Chemical formula 49]



(wherein R^F is hydrogen or a sugar residue;

R^B is $\cdot\text{OH}$, $\cdot\text{NR}^5\text{R}^{5'}$ (wherein R^5 and $R^{5'}$ are each independently hydrogen, optionally substituted lower alkyl, optionally substituted lower alkyloxy, optionally substituted amino or amino sugar residue) or $\cdot\text{OR}^6$ (wherein OR^6 is optionally substituted lower alkyl (a hetero atom group may intervene in the lower alkyl part));

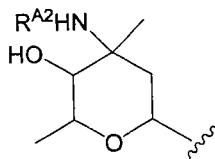
R^C is hydrogen or optionally substituted lower alkyl (a hetero atom group may intervene in the lower alkyl part);

R^D is hydrogen or lower alkyl;

other symbols are as defined above; and

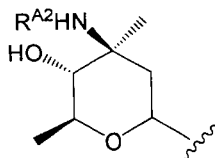
R^F is preferably a sugar residue, more preferably a sugar residue represented by the formula:

[Chemical formula 50]



(wherein R^{A2} is hydrogen or optionally substituted lower alkyl),
still more preferably a sugar residue represented by the formula:

[Chemical formula 51]



(wherein respective symbols are as defined above).

R^{A2} is preferably hydrogen; or lower alkyl optionally substituted with optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocycle or hydroxyl. As a substituent of the “optionally substituted aryl”, the “optionally substituted heteroaryl”, or the “optionally substituted heterocycle”, arylcarbonylamino optionally substituted with halo lower alkyloxy is preferable. R^{A2} is more preferably hydrogen).

R^B is preferably -OH, or -NHR⁵ (wherein R⁵ is lower alkyl optionally substituted with hydroxyl or dialkylamino, lower alkyloxy optionally substituted with lower alkyloxy, or lower alkylamino). More preferably, R^B is -OH.

R^C is preferably hydrogen, or lower alkyl optionally substituted with optionally substituted amino. As a substituent of the “optionally

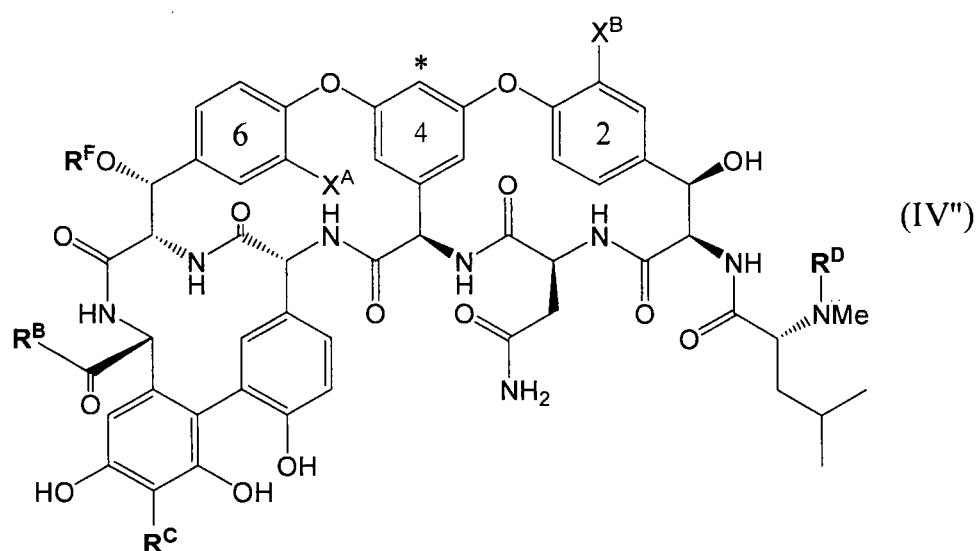
substituted amino", SO₃H, hydroxy, or lower alky optionally substituted with tri-lower alkylammonium; or heteroaralkyl is preferable. R^C is more preferably hydrogen.

R^D is preferably hydrogen.

[0029]

Further preferably, the glycopeptide skeleton has the following partial structure (IV''):

[Chemical formula 52]

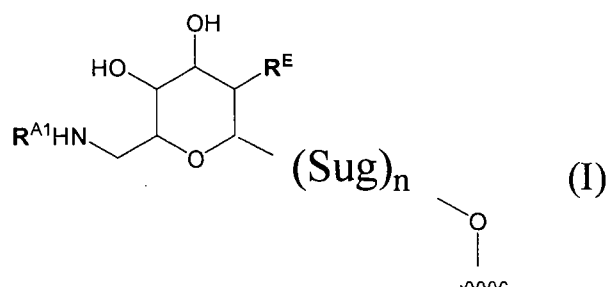


(wherein respective symbols are as defined above).

[0030]

The present compound has an aglycone represented by the partial structure. The compound is a glycopeptide compound in which, further, various sugar residues are bound to the aromatic ring of the fourth amino acid residue in the glycopeptide skeleton. The sugar residue is represented by the following structure:

[Chemical formula 53]



(wherein

n is an integer of 1 to 5;

Sugs are each independently a monosaccharide, $(\text{Sug})_n$ is a divalent sugar residue formed by binding same or different 1 to 5 monosaccharides;

R^{A1} is optionally substituted lower alkyl, optionally substituted lower alkenyl, or optionally substituted cycloalkyl; and

R^E is OH or NHAc (Ac is acetyl)).

n is preferably 1 or 2.

Sug is preferably glucose, galactose, fructose, fucose, mannose, rhamnose, galactosamine, glucosamine, N-acetylgalactosamine, N-acetylglucosamine, vancosamine, epi-vancosamine, glucuronic acid, sialic acid, deoxyglucose, or deoxygalactose. More preferable is glucose (e.g., β -D-glucose) or galactose (e.g., β -D-galactose).

When n is 1, Sug is further preferably glucose (e.g., β -D-glucose).

When n is 2, it is particularly preferable that two Sugs are glucose (e.g., β -D-glucose) at the same time.

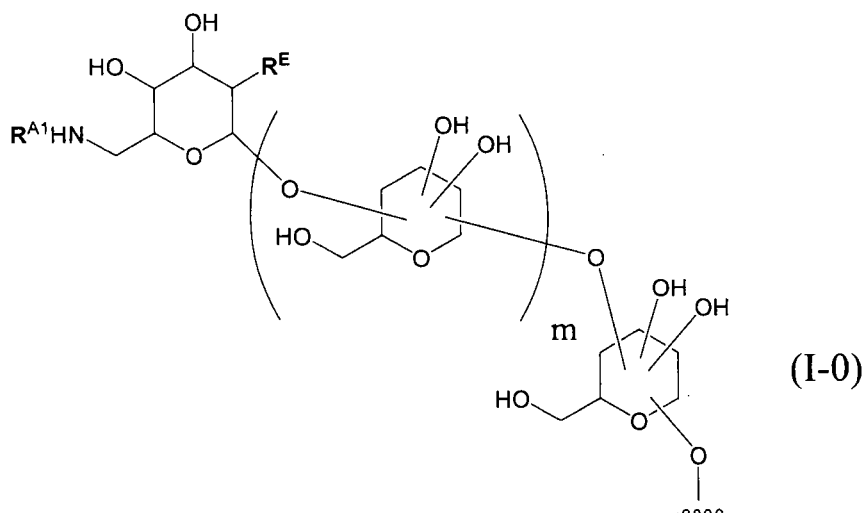
R^{A1} is preferably optionally substituted lower alkyl, or optionally substituted cycloalkyl, more preferably optionally substituted lower alkyl.

R^E is preferably OH.

[0031]

The sugar residue (I) is preferably the following sugar residue (I-0):

[Chemical formula 54]



(wherein

m is an integer of 0 to 4; and

R^{A1} and R^E are each as defined above).

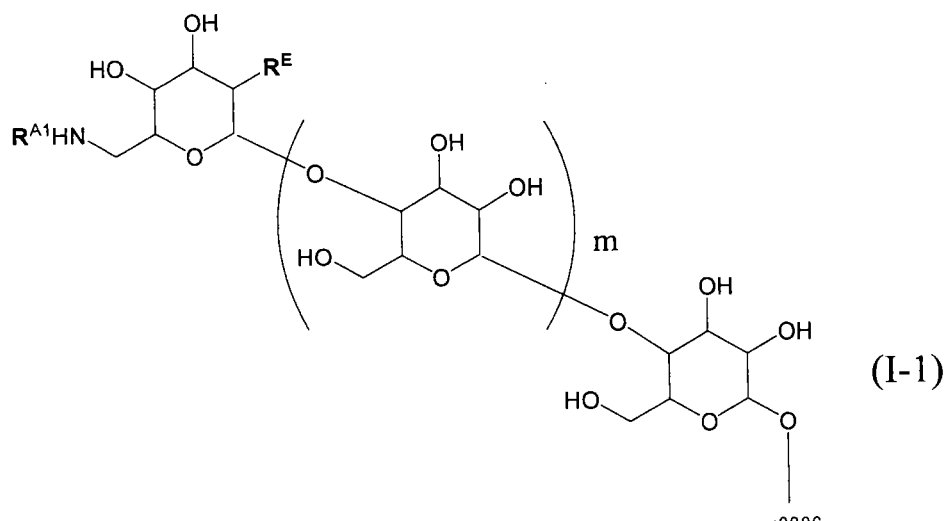
In the formula (I-0), positions of two hydroxyl groups which bind to each monosaccharide other than the terminal sugar are not particularly limited, but each hydroxyl group is preferably bound to the 2-position and the 3-position of one monosaccharide. In addition, the binding manner of two adjacent monosaccharides is not particularly limited, but monosaccharides are preferably bound to the 1-position and the 4-position. In addition, the binding position of the sugar which binds to an aglycone part is also not particularly limited, but the sugar preferably forms a glycoside bond with an aglycone at the 1-position of the monosaccharide.

m is preferably 0 or 1.

[0032]

The sugar residue (I-0) is preferably the following sugar residue (I-1):

[Chemical formula 55]



(wherein respective symbols are as defined above).

A monosaccharide adjacent to an aglycone is preferably glucose (e.g., β -D-glucose).

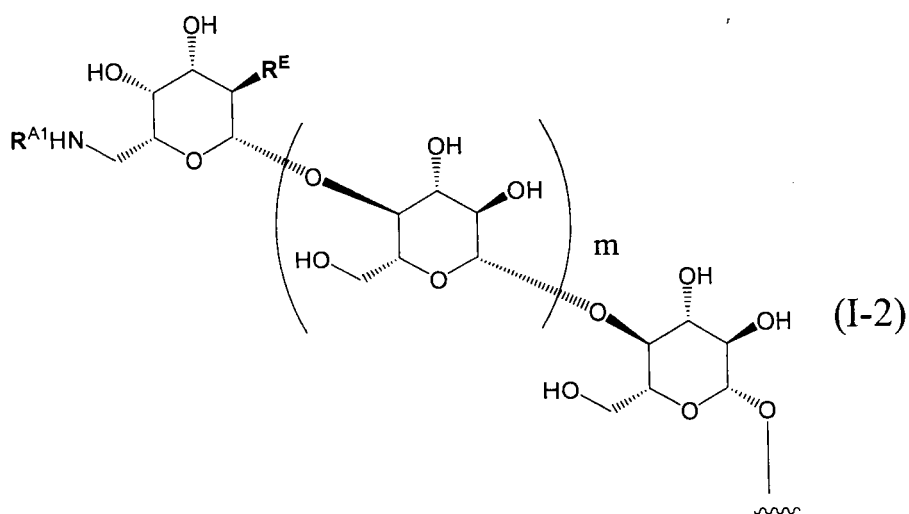
A monosaccharide situated at the terminal is preferably a monosaccharide in which the 6-positional hydroxyl of galactose or N-acetylgalactosamine is substituted with optionally substituted amino. More preferable is a monosaccharide in which the 6-positional hydroxyl of galactose (e.g., β -D-galactose) is substituted with optionally substituted amino.

A monosaccharide constituting other sugar residue is preferably glucose or galactose, more preferably glucose (e.g., β -D-glucose).

[0033]

The sugar residue (I-1) is preferably the following sugar residue (I-2):

[Chemical formula 56]



(wherein respective symbols are as defined above).

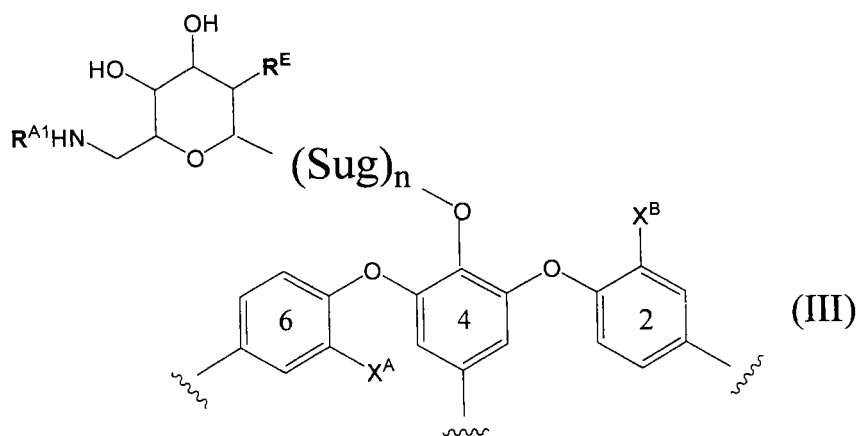
In the glycopeptide compound of the present invention, the sugar residue exemplified above is bound to carbon represented by * of the aglycone exemplified above.

[0034]

The present compound preferably has the following partial structure

(III):

[Chemical formula 57]

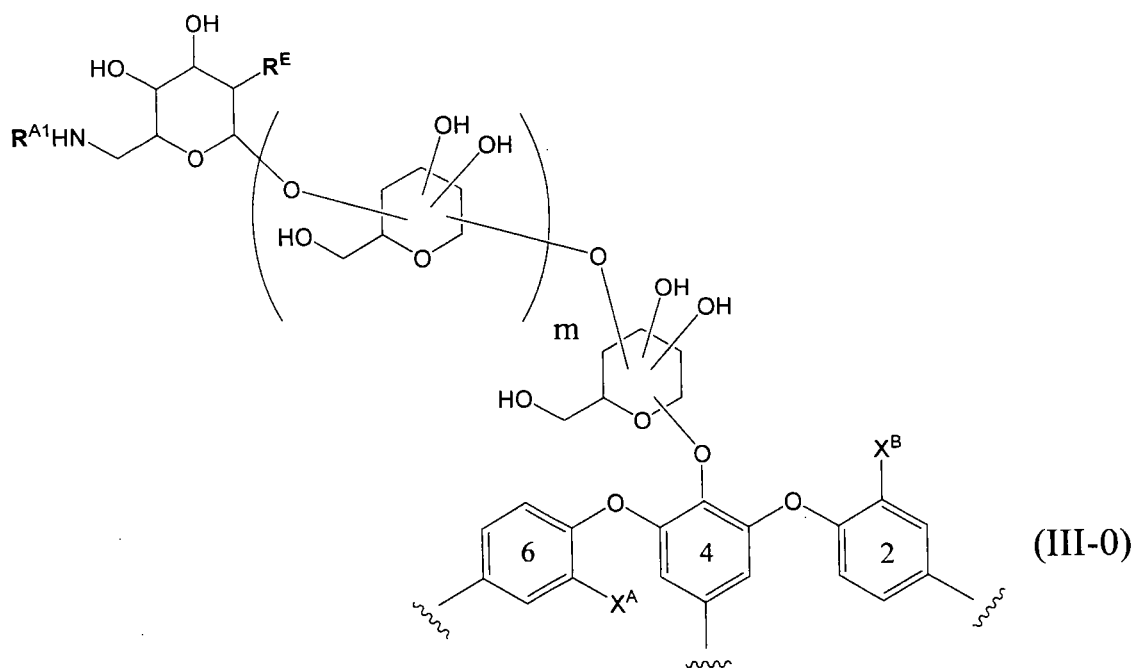


(wherein respective symbols are as defined above).

[0035]

The partial structure (III) is preferably the following partial structure (III-0):

[Chemical formula 58]

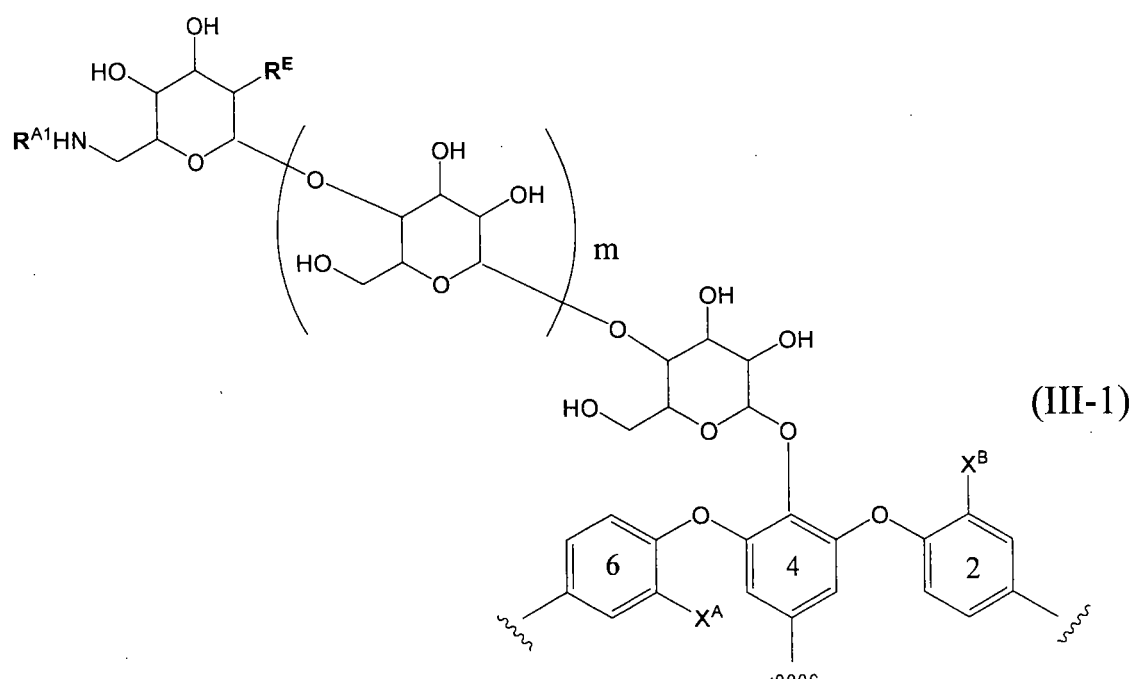


(wherein respective symbols are as defined above).

[0036]

The partial structure (III-0) is preferably the following partial structure (III-1):

[Chemical formula 59]



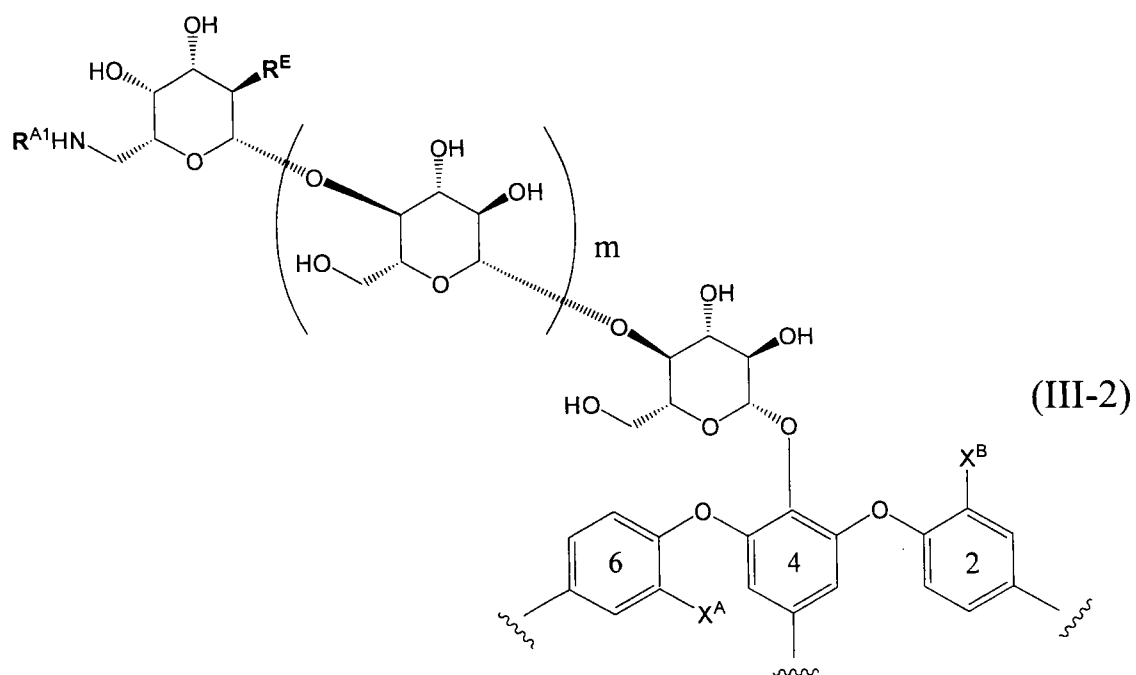
(wherein respective symbols are as defined above).

[0037]

The partial structure (III-1) is preferably the following structure

(III-2):

[Chemical formula 60]

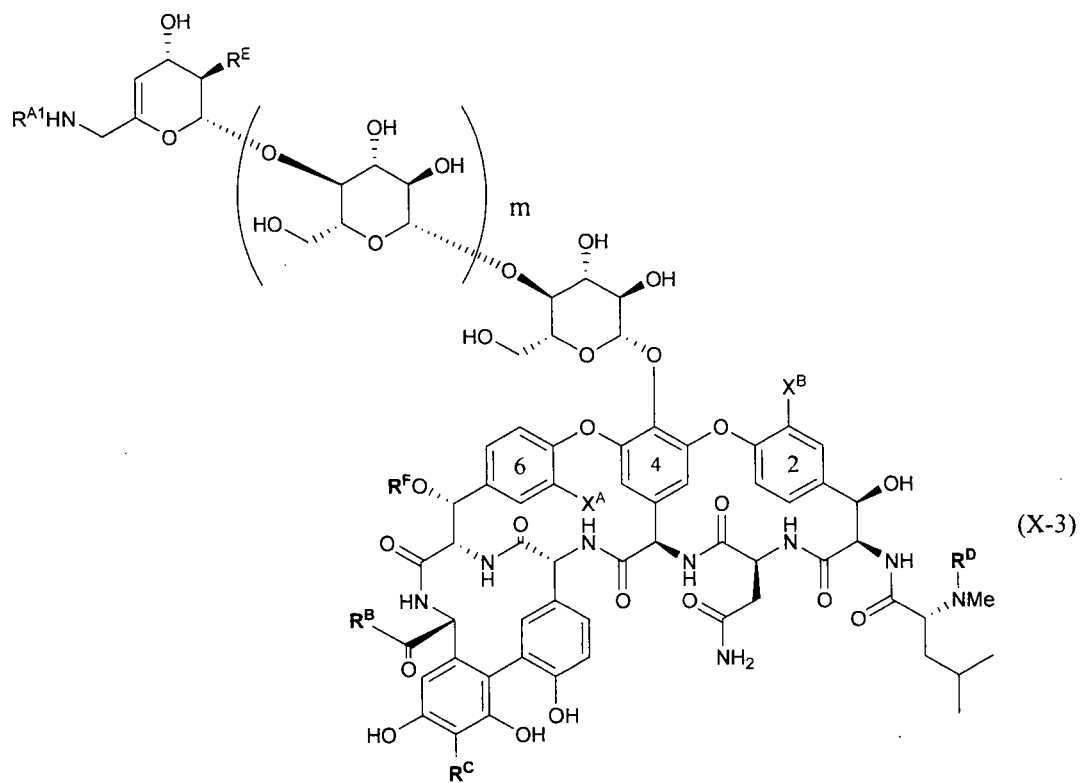


(wherein respective symbols are as defined above).

[0038]

The compound (X-1) is preferably the following compound (X-2):

[Chemical formula 61]

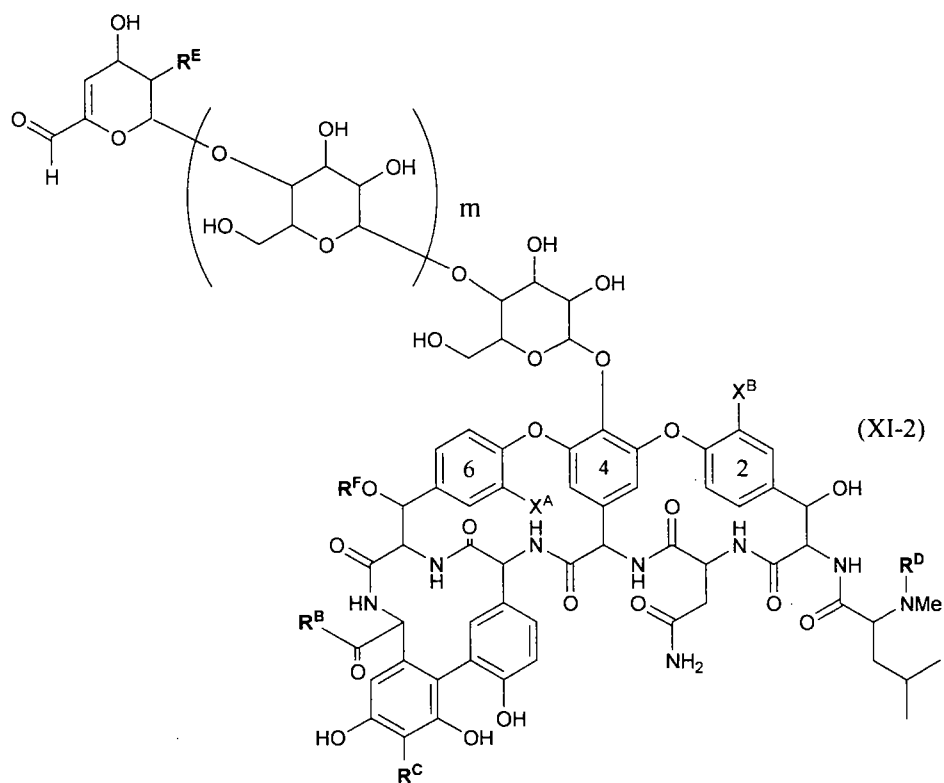


(wherein respective symbols are as defined above).

[0039]

The compound (XI-1) is preferably the following compound (XI-2):

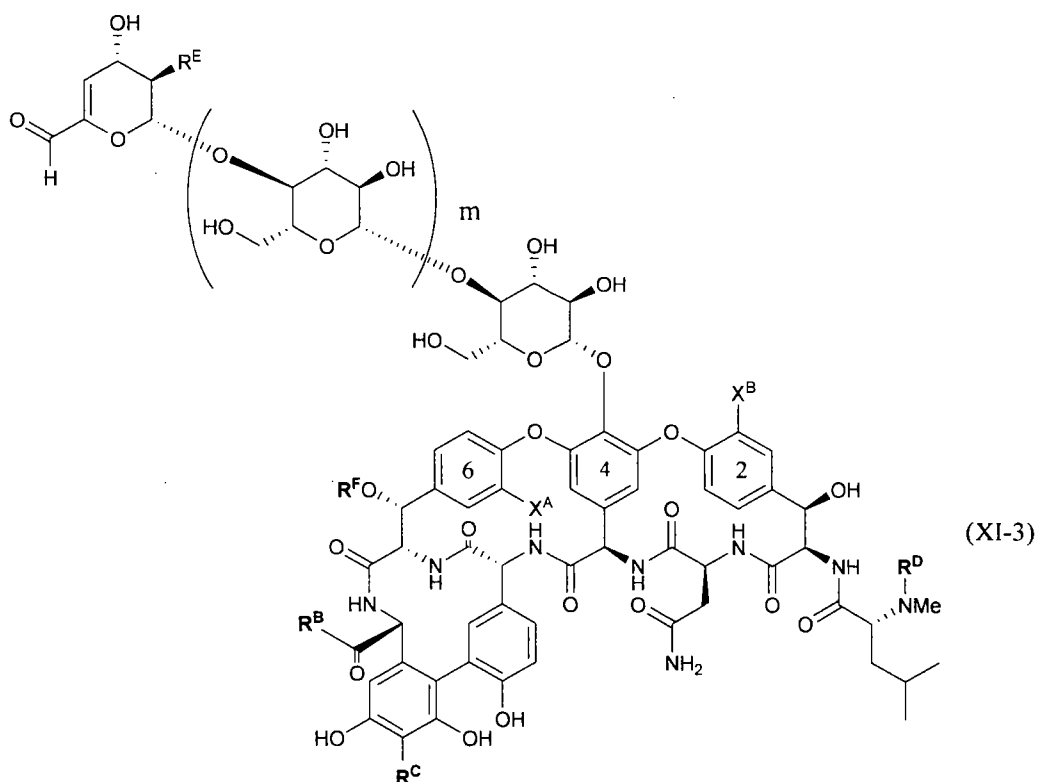
[Chemical formula 63]



(wherein respective symbols are as defined above),

further preferably a compound (XI-3):

[Chemical formula 64]



(wherein respective symbols are as defined above).

[0040]

The present compound further preferably includes a structure in which the sugar residue (I), (I-0), (I-1) or (I-2) is bound to the partial structure (II-0).

The present compound further preferably includes a structure in which the sugar residue (I), (I-0), (I-1) or (I-2) is bound to the partial structure (II-1).

The present compound further preferably includes a structure in which the sugar residue (I), (I-0), (I-1) or (I-2) is bound to the partial structure (II-2).

The present compound further preferably includes a structure in

which the sugar residue (I), (I-0), (I-1) or (I-2) is bound to the partial structure (IV').

The present compound further preferably includes a structure in which the sugar residue (I), (I-0), (I-1) or (I-2) is bound to the partial structure (IV'').

[0041]

In addition, the compounds (IV-0) and (X-1), the compounds (IV-1) and (X-2), the compounds (IV-2) and (X-3), the compounds (IX-1) and (XI-1), the compounds (IX-2) and (XI-2), as well as the compounds (IX-3) and (XI-3) may be each a composition consisting of the mixture.

[0042]

As used herein, the "sugar residue" means a remaining part when one OH is removed from a monosaccharide, or a polysaccharide in which the same or different plural monosaccharides are connected in straight or branched manner.

As used herein, as the "monosaccharide", glucose, galactose, fructose, fucose, mannose, rhamnose, galactosamine, glucosamine, N-acetylgalactosamine, N-acetylglucosamine, vancosamine, epi-vancosamine, glucuronic acid, sialic acid, deoxyglucose, and deoxygalactose are preferably. As a monosaccharide constituting a root part of a sugar residue which binds to the aromatic ring of the fourth amino acid residue of a glycopeptide skeleton, glucose (e.g., β -D-glucose) is particularly preferable. As a monosaccharide constituting the terminal part of a sugar residue which binds to the aromatic ring of the fourth amino acid residue of a glycopeptide skeleton, galactose or N-acetylgalactosamine is more preferable.

Particularly, galactose (e.g., β -D-galactose) is preferable.

As used herein, the “amino sugar residue” expresses the “sugar residue” having an amino group or a substituted amino group. Examples of the representative amino sugar residue include L-vancosaminyl, 3-desmethyl-vancosaminyl, 3-epi-vancosaminyl, 4-epi-vancosaminyl, 4-keto-vancosaminyl, acosaminyl, actinosaminyl, daunosaminyl, 3-epi-daunosaminyl, ristosaminyl, N-methyl-D-glucaminyl, N-acetyl-D-glucosaminyl, or N-acyl-D-glucosaminyl. Actinosaminyl, acosaminyl, 4-epi-vancosaminyl, 4-keto-vancosaminyl, ristosaminyl, or vancosaminyl is preferable. Particularly, L-4-epi-vancosaminyl is preferable.

[0043]

As used herein, the term “lower alkyl” which is used alone or in combination with other terms includes straight or branched monovalent hydrocarbon group, having 1 to 15, preferably 1 to 10 carbon atoms. Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, isohexyl, n-heptyl, n-octyl and the like. More preferably, examples include C1-C6 alkyl. Further preferably, examples include C1-C3 alkyl.

[0044]

As used herein, the “lower alkenyl” which is used alone or in combination with other terms includes straight or branched monovalent hydrocarbon group having 2 to 15, preferably 2 to 10 carbon atoms, and one or two or more double bonds. Examples include vinyl, allyl, 1-propenyl, 2-propenyl, crotonyl, isopentenyl, various butenyl isomers and the like.

Preferably, examples include C2-C6 alkenyl. Preferably, a double bond exists between the 1-positional and the 2-positional carbon atoms. Further preferably, examples include C2-C4 alkenyl.

[0045]

As used herein, examples of the “lower alkyloxy” include methyloxy, ethyloxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, s-butyloxy, t-butyloxy, n-pentyloxy, n-hexyloxy and the like. Preferably, examples include C1-C6 alkyloxy. Further preferably, examples include C1-C3 alkyloxy.

As used herein, the “cycloalkyl” which is used alone or in combination with other terms includes cycloalkyl having 3 to 8 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Preferably, examples include C3-C6 cycloalkyl. These may be cross-linked via 1 to 3 carbon atoms between two carbon atoms which constitute ring and are not adjacent.

As cycloalkyl in R^{A1} , cyclopropyl and cyclopentyl are particularly preferable.

As cycloalkyl in the substituent group A, cross-linked cyclohexyl is preferable.

[0046]

As used herein, the “aryl” which is used alone or in combination with other terms includes monocyclic or condensed cyclic aromatic hydrocarbon group having 6 to 14 carbon numbers. Examples include phenyl, 1-naphthyl, 2-naphthyl, anthryl and the like. Preferably, examples include phenyl, 1-naphthyl, and 2-naphthyl. Further preferably, examples include

phenyl, and 2-naphthyl.

[0047]

As used herein, the “heteroaryl” which is used alone or in combination with other terms means, for example, monocyclic aromatic heterocyclic group and condensed aromatic heterocyclic group containing hetero atom selected from nitrogen atom, sulfur atom and oxygen atom in the ring. The monocyclic aromatic heterocyclic group means group optionally having bond at a replaceable optional position, which is derived from 5- to 8- membered aromatic ring optionally containing 1 to 4 of oxygen atom, sulfur atom and/or nitrogen atom in the ring. The condensed aromatic heterocyclic group means group optionally having bond at a replaceable optional position, in which 5- to 8-membered aromatic ring optionally containing 1 to 4 of oxygen atom, sulfur atom, and/or nitrogen atom in the ring is condensed with 1 to 4 of 5- to 8-membered aromatic carbocycles or other 5- to 8-membered aromatic heterocycles.

[0048]

Examples of the specific “heteroaryl” include furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-4-yl), tetrazolyl (e.g., 1-tetrazolyl, 2-tetrazolyl, 5-tetrazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), thiadiazolyl, isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl,

4-pyridyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), furazanyl (e.g., 3-furazanyl), pyrazinyl (e.g., 2-pyrazinyl), oxadiazolyl (e.g., 1,3,4-oxadiazol-2-yl), benzofuryl (e.g., 2-benzo[b]furyl, 3-benzo[b]furyl, 4-benzo[b]furyl, 5-benzo[b]furyl, 6-benzo[b]furyl, 7-benzo[b]furyl), benzothienyl (e.g., 2-benzo[b]thienyl, 3-benzo[b]thienyl, 4-benzo[b]thienyl, 6-benzo[b]thienyl, 7-benzo[b]thienyl), benzimidazolyl (e.g., 1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl), dibenzofuryl, benzoxazolyl, quinoxalyl (e.g., 2-quinoxalyl, 5-quinoxalyl, 6-quinoxalyl), cinnolinyl (e.g., 3-cinnolinyl, 4-cinnolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, 8-cinnolinyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl, 5-quinazolyl, 6-quinazolyl, 7-quinazolyl, 8-quinazolyl), quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), phthalazinyl (e.g., 1-phthalazinyl, 5-phthalazinyl, 6-phthalazinyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), puryl, pteridinyl (e.g., 2-pteridinyl, 4-pteridinyl, 6-pteridinyl, 7-pteridinyl), carbazolyl, phenanthridinyl, acridinyl (e.g., 1-acridinyl, 2-acridinyl, 3-acridinyl, 4-acridinyl, 9-acridinyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), isoindolyl, phenazinyl (e.g., 1-phenazinyl, 2-phenazinyl) or phenothiazinyl (e.g., 1-phenothiazinyl, 2-phenothiazinyl, 3-phenothiazinyl, 4-phenothiazinyl).

As the "heteroaryl" in the substituent group A, a 5- or 6-membered ring (e.g., thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl) is preferable.

As the “heteroaryl” in the substituent group B, 5- or 6-membered ring (e.g., thienyl, pyrrolyl, pyridyl) is preferable.

As the “heteroaryl” as a substituent of “optionally substituted lower alkyl” in R^{A2}, 5- or 6-membered ring (e.g., imidazolyl, pyridyl) is preferable.
[0049]

As used herein, the “heterocycle” means, for example, monocyclic non-aromatic heterocyclic group and condensed non-aromatic heterocyclic group containing hetero atom selected from nitrogen atom, sulfur atom and oxygen atom in the ring. The monocyclic non-aromatic heterocyclic group means group optionally having bond at a replaceable optional position, which is derived from 5- to 8-membered non-aromatic ring optionally containing 1 to 4 of oxygen atom, sulfur atom and/or nitrogen atom in the ring. The condensed non-aromatic heterocyclic group means group optionally having bond at a replaceable optional position, in which 5- to 8-membered non-aromatic ring optionally containing 1 to 4 of oxygen atom, sulfur atom and/or nitrogen atom in the ring is condensed with 1 to 4 of 5- to 8-membered aromatic carbocycle, 5- to 8-membered aromatic heterocycle, 5- to 8-membered non-aromatic carbocycle, or another 5- to 8-membered non-aromatic heterocycle.

[0050]

Examples of the specific “heterocycle” include pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, pyrrolinyl (e.g., 3-pyrrolinyl), imidazolidinyl (e.g., 2-imidazolidinyl), imidazoliny (e.g., imidazoliny), pyrazolidinyl (e.g., 1-pyrazolidinyl, 2-pyrazolidinyl), pyrazoliny (e.g., pyrazoliny), piperidyl (e.g., piperidino, 2-piperidyl), piperazinyl (e.g., 1-piperazinyl), indoliny (e.g.,

1-indoliny], isoindoliny] (e.g., isoindoliny], morpholiny] (e.g., morpholino, 3-morpholiny], dihydropyridyl, tetrahydropyridyl, tetrahydroquinolyl, tetrahydrofuryl, dihydropyranyl, tetrahydropyranyl, 1,3-benzodioxolanyl, 1,4-benzodioxanyl, 1-benzoxolanyl, oxetanyl, azetidiny], diazetidiny], chromanyl and the like.

As the “heterocycle” in the substituent group A, 5- or 6-membered ring (e.g., piperidyl, piperaziny], morpholiny]) is preferable.

As the “heterocycle” as the substituent of “optionally substituted lower alkyl” in R^{A2}, 5- or 6-membered ring (e.g., morpholiny]) is preferable.

[0051]

Examples of the “aryloxy” used herein include phenyloxy, naphthyloxy, and the like. Preferably, examples include phenyloxy.

Examples of the “arylsulfonylamino” used herein include phenylsulfonylamino, naphthylsulfonylamino and the like. Preferably, examples include naphthylsulfonylamino.

Examples of the “arylcarbonylamino” used herein include benzoylamino, naphthylcarbonylamino and the like. Preferably, examples include benzoylamino.

Examples of the “arylaminocarbonylamino” used herein include phenylaminocarbonylamino, naphthylaminocarbonylamino and the like. Preferably, examples include phenylaminocarbonylamino.

Examples of the “heteroaryloxy” used herein include pyridyloxy, furyloxy, pyrrolyloxy, thienyloxy and the like. Preferably, examples include pyridyloxy.

Examples of the “arylaminocarbonyl” used herein include

phenylaminocarbonyl, naphthylaminocarbonyl and the like. Preferably, examples include phenylaminocarbonyl.

Examples of the "arylcarbonyl" used herein include phenylcarbonyl, naphthylcarbonyl and the like. Preferably, examples include phenylcarbonyl.

Examples of the "arylthio" used herein include phenylthio, naphthylthio and the like. Preferably, examples include phenylthio.

Examples of the "arylamino" used herein include phenylamino, naphthylamino, phenylmethyldamino and the like. Preferably, examples include phenylamino.

Examples of the "arylaminoalkyl" used herein include phenylamino lower alkyl, naphthylamino lower alkyl, phenylmethyldamino lower alkyl and the like. Preferably, examples include phenylamino lower alkyl.

Examples of the "arylsulfonyl" used herein include phenylsulfonyl, naphthylsulfonyl and the like. Preferably, examples include phenylsulfonyl.

Examples of the "arylaminosulfonyl" used herein include phenylaminosulfonyl, naphthylaminosulfonyl and the like. Preferably, examples include phenylaminosulfonyl.

Examples of the "heteroarylalkyl" used herein include pyridyl lower alkyl, furyl lower alkyl, pyrrolyl lower alkyl, thienyl lower alkyl and the like. Preferably, examples include pyridyl lower alkyl, and thienyl lower alkyl.

Examples of the "heteroarylcarbonyl" used herein include pyridylcarbonyl, furylcabonyl, pyrrolylcabonyl, thienylcarbonyl and the like. Preferably, examples include pyridylcarbonyl, and thienylcarbonyl.

Examples of the "heteroarylthio" used herein include pyridylthio and the like.

[0052]

As used herein, the "aralkyl" which is used alone or in combination with other terms is the "lower alkyl" substituted with one or more of the "aryl"s, and these can replace at all possible positions. Examples include benzyl, phenylethyl (e.g., 2-phenylethyl etc.), phenylpropyl (e.g., 3-phenylpropyl etc.), naphthylmethyl (e.g., 1-naphthylmethyl, 2-naphthylmethyl etc.), anthrylmethyl (e.g., 9-anthrylmethyl etc.), biphenylmethyl (e.g., 4-biphenylmethyl etc.) and the like. Preferably, examples include benzyl, and phenylethyl. More preferably, examples include benzyl.

As used herein, the "heteroaralkyl" which is used alone or in combination with other term is the "lower alkyl" substituted with one or two or more of "heteroaryl"s at an optional position, and these can replace at all possible positions. Examples include oxazolylmethyl (e.g., 2-oxazolylmethyl, 4-oxazolylmethyl), thiazolylmethyl (e.g., 2-thiazolylmethyl, 4-thiazolylmethyl), oxazolylethyl (e.g., 5-oxazolyl-2-ethyl), thiazolylethyl (e.g., 5-thiazolyl-2-ethyl), benzoxazolylmethyl (e.g., benzoxazol-2-ylmethyl), benzothiazolylmethyl (e.g., benzothiazol-2-ylmethyl), indolylmethyl (e.g., indol-3-ylmethyl), imidazolylmethyl (e.g., 4-imidazolylmethyl), indazolylmethyl (e.g., 1-indazolylmethyl), benzotriazolylmethyl (e.g., 1-benzotriazolylmethyl), benzoquinolylmethyl (e.g., 2-benzoquinolylmethyl), benzimidazolylmethyl (e.g., benzimidazol-2-methyl), pyridylmethyl (e.g., 4-pyridylmethyl), furylmethyl (e.g., furan-2-ylmethyl), thienylmethyl (e.g.,

thiophen-2-ylmethyl) and the like.

A substituent of the “optionally substituted lower alkyl” in R^C is preferably “optionally substituted amino”. A substituent of the “optionally substituted amino” is preferably heteroaralkyl (e.g., pyridylethyl).

[0053]

Examples of the “aralkyloxy” used herein include phenyl C1-C3 alkyloxy, naphthyl C1-C3 alkyloxy and the like. Preferably, examples include benzyloxy.

Examples of the “aralkylthio” used herein include phenyl C1-C3 alkylthio, naphthyl C1-C3 alkylthio and the like. Preferably, examples include benzylthio.

Examples of the “aralkylamino” used herein include phenyl C1-C3 alkylamino, naphthyl C1-C3 alkylamino and the like. Preferably, examples include benzylamino.

Examples of the “aralkylcarbonylamino” used herein include phenyl C1-C3 alkylcarbonylamino, naphthyl C1-C3 alkylcarbonylamino and the like. Preferably, examples include benzylcarbonylamino.

Examples of the “aralkylaminocarbonyl” used herein include phenyl C1-C3 alkylaminocarbonyl, naphthyl C1-C3 alkylaminocarbonyl and the like. Preferably, examples include benzylaminocarbonyl.

Examples of the “aralkylsulfinyl” used herein include phenyl C1-C3 alkylsulfinyl, naphthyl C1-C3 alkylsulfinyl and the like. Preferably, examples include benzylsulfinyl.

Examples of the “heteroaralkylthio” used herein include pyridyl C1-C3 alkylthio, furyl C1-C3 alkylthio, pyrrolyl C1-C3 alkylthio, thienyl

C1-C3 alkylthio and the like. Preferably, examples include furylmethylthio.

Examples of the "aryl lower alkenyl" used herein include phenyl C2-C4 alkenyl, naphthyl C2-C4 alkenyl and the like. Preferably, examples include 2-phenylethenyl.

[0054]

As used herein, the "halogen" means fluorine, chlorine, bromine, and iodine. Preferably, examples include fluorine, chlorine and bromine.

As used herein, a term "halo lower alkyl" which is used alone or in combination with other term includes the "lower alkyl" substituted with the "halogen" at 1 to 8 places, preferably 1 to 5 places. Examples include trifluoromethyl, trichloromethyl, difluoromethyl, trifluoroethyl, dichloroethyl, trichloroethyl and the like. Preferably, examples include C1-C3 alkyl substituted with the "halogen" at 1 to 5 places. Particularly preferably, examples include trifluoromethyl.

As used herein, as the "halo lower alkyloxy", C1-C3 alkyloxy substituted with the "halogen" at 1 to 5 places is preferable. Particularly preferably, examples include trifluoromethyloxy.

Examples of the "di-lower alkylamino" used herein include dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, ethylmethylamino, methyl n-propylamino, methylisopropylamino, ethyl n-propylamino, ethylisopropylamino and the like. Preferably, examples include dimethylamino.

[0055]

Examples of a substituent of the "optionally substituted lower alkyl", the "optionally substituted alkenyl", the "optionally substituted aryl", the

“optionally substituted heteroaryl”, the “optionally substituted cycloalkyl”,
 the “optionally substituted heterocycle”, the “optionally substituted aralkyl”,
 the “optionally substituted aralkylthio”, the “optionally substituted
 heteroaralkylthio”, the “optionally substituted lower alkyloxy”, the
 “optionally substituted aralkyloxy”, the “optionally substituted aryloxy”, the
 “optionally substituted arylsulfonylamino”, the “optionally substituted
 arylaminocarbonylamino”, the “optionally substituted arylcarbonyl amino”,
 the “optionally substituted aralkylcarbonylamino, the “optionally
 substituted aralkylaminocarbonyl”, the “optionally substituted
 aralkylsulfinyl”, the “optionally substituted heteroaryloxy”, the “optionally
 substituted arylaminocarbonyl”, the “optionally substituted arylcarbonyl”,
 the “optionally substituted arylthio”, the “optionally substituted arylamino”,
 the “optionally substituted arylaminoalkyl”, the “optionally substituted
 arylsulfonyl”, the “optionally substituted aralkylamino”, the “optionally
 substituted arylaminosulfonyl”, the “optionally substituted heteroarylalkyl”,
 the “optionally substituted heteroarylcarbonyl”, the “optionally substituted
 heteroarylthio”, the “optionally substituted aryl lower alkenyl”, and the
 “optionally substituted amino” include hydroxy, carboxy, halogen (F, Cl, Br, I),
 halo lower alkyl (e.g., CF₃, CH₂CF₃, CH₂CCl₃), C1-C6 alkyl (e.g., methyl,
 ethyl, isopropyl, tert-butyl), C2-C6 alkenyl (e.g., vinyl), C3-C6 alkynyl (e.g.,
 ethynyl), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl),
 cycloalkenyl (e.g., cyclopropenyl), alkoxy (e.g., methoxy, ethoxy, propoxy,
 butoxy), alkenyloxy (e.g., vinyloxy, allyloxy etc.), alkoxycarbonyl (e.g.,
 methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl etc.), nitro, nitroso,
 optionally substituted amino (e.g., amino, lower alkylamino (e.g.,

methylamino, ethylamino, dimethylamino), acylamino (e.g., acetylamino, benzoylamino), aralkylamino (e.g., benzylamino, tritylamino), hydroxyamino), azido, aryl (e.g., phenyl), aralkyl (e.g., benzyl), cyano, isocyano, isocyanato, thiocyanato, isothiocyanato, mercapto, lower alkylthio (e.g., methylthio), lower alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl), optionally substituted carbamoyl (e.g., lower alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl)), sulfamoyl, acyl (e.g., formyl, acetyl), formyloxy, haloformyl, oxalo, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, sulfinio, sulfo, sulfoamino, hydrazine, azido, ureido, amidino, guanidino, phthalimido, oxo, optionally substituted aryl (e.g., phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 1-naphthyl, 2-naphthyl), optionally substituted heteroaryl (e.g., pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, isoxazol-3-yl, isoxazol-5-yl, pyrrol-2-yl, pyrazol-3-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, imidazol-2-yl, oxazol-2-yl, thiazol-2-yl and the like).

[0056]

Examples of a substituent of the “optionally substituted aryl”, the “optionally substituted heteroaryl”, the “optionally substituted cycloalkyl”, the “optionally substituted heterocycle”, the “optionally substituted aralkyl”, the “optionally substituted aralkylthio”, the “optionally substituted heteroaralkylthio”, the “optionally substituted aralkyloxy”, the “optionally substituted aryloxy”, the “optionally substituted arylsulfonylamino”, the

“optionally substituted arylaminocarbonylamino”, the “optionally substituted arylcarbonylamino”, the “optionally substituted aralkylcarbonylamino”, the “optionally substituted aralkylaminocarbonyl”, the “optionally substituted aralkylsulfinyl”, the “optionally substituted heteroaryloxy”, the “optionally substituted arylaminocarbonyl”, the “optionally substituted arylcarbonyl”, the “optionally substituted arylthio”, the “optionally substituted arylamino”, the “optionally substituted arylaminoalkyl”, the “optionally substituted arylsulfonyl”, the “optionally substituted aralkylamino”, the “optionally substituted arylaminosulfonyl”, the “optionally substituted heteroarylalkyl”, the “optionally substituted heteroarylcarbonyl”, the “optionally substituted heteroarylthio”, the “optionally substituted aryl lower alkenyl”, and the “optionally substituted cycloalkyl” alone or in combination with other term include the above exemplified substituents. The aryl, the heteroaryl, the cycloalkyl, and the heterocycle may be substituted with these substituents at replaceable optional positions, and the number of substituents is 1 to 3.

[0057]

R^{A1} is preferably various lipophilic groups. More preferable is optionally substituted lower alkyl, optionally substituted lower alkenyl, or optionally substituted cycloalkyl. Further preferable is optionally substituted lower alkyl or optionally substituted cycloalkyl. Particularly preferable is optionally substituted lower alkyl. A substituent of the “optionally substituted” group is one or more same or different substituents selected from the substituent group A.

Substituent group A: optionally substituted aryl, optionally

substituted heteroaryl, optionally substituted heterocycle, optionally substituted aralkylthio, optionally substituted heteroaralkylthio, optionally substituted cycloalkyl, optionally substituted lower alkyloxy, optionally substituted aralkyloxy, optionally substituted aryloxy, optionally substituted arylsulfonylamino, and optionally substituted amino.

A substituent of the “optionally substituted” group in the substituent group A is one or more same or different substituents selected from the substituent group B.

Substituent group B: optionally substituted arylaminocarbonylamino, optionally substituted arylaminocarbonyl, optionally substituted arylcarbonyl, optionally substituted arylcarbonylamino, optionally substituted arylcarbonylaminoalkyl, oxo, halogen, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthio, optionally substituted arylamino, optionally substituted arylaminoalkyl, optionally substituted arylaminocarbonylalkyl, optionally substituted arylsulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted amino, optionally substituted aralkylcarbonylamino, optionally substituted aralkylamino, optionally substituted aralkylaminocarbonyl, optionally substituted aralkylsulfinyl, optionally substituted arylsulfonylamino, optionally substituted arylaminosulfonyl, optionally substituted aralkylthio, halo lower alkyl, lower alkyloxy, lower alkylamino, halo lower alkyloxy, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylthio, optionally substituted aryl lower alkenyl,

optionally substituted heteroaryl lower alkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkyloxy, optionally substituted cycloalkylthio, optionally substituted cycloalkylaminocarbonyl, optionally substituted cycloalkyl lower alkenyl, optionally substituted cycloalkylsulfonyl, optionally substituted cycloalkylaminocarbonylamino, optionally substituted cycloalkylaminoalkyl, optionally substituted cycloalkyl lower alkylamino, optionally substituted cycloalkylamino, optionally substituted cycloalkyl lower alkyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonylamino, optionally substituted cycloalkylcarbonylamino, optionally substituted cycloalkylcarbonylaminoalkyl, optionally substituted cycloalkyl lower alkylaminocarbonyl, optionally substituted cycloalkylsulfonylamino, optionally substituted cycloalkylaminocarbonylalkyl, and optionally substituted cycloalkylaminosulfonyl.

A substituent of the “optionally substituted” in the substituent group B is one or more same or different substituents selected from the substituent group C.

Substituent group C: lower alky, lower alkyloxy, lower alkylsulfonyl, nitro, aralkyloxy, halogen, cyano, halo lower alkyl, halo lower alkyloxy, and di-lower alkylamino.

[0058]

A preferable embodiment of R^{A1} includes the following groups.

(1-1) -CH₂-(substituted)Ph-CONR-(substituted)Ph

(1-2) -CH₂-(substituted)Ph-NR-CONR-(substituted)Ph

- (1-3) $\text{-CH}_2\text{-(substituted)Ph-CH}_2\text{-CONR-(substituted)Ph}$
- (1-4) $\text{-CH}_2\text{-(substituted)Ph-CH}_2\text{-NRCO-(substituted)Ph}$
- (1-5) $\text{-CH}_2\text{-(substituted)Ph-X-CONR-(substituted) Ph}$
- (1-6) $\text{-CH}_2\text{-(substituted)Ph-X-NRCO-(substituted) Ph}$
- (1-7) $\text{-CH}_2\text{-(substituted)Het-CONR-(substituted)Ph}$
- (1-8) $\text{-CH}_2\text{-(substituted)Het-NRCO-(substituted)Ph}$
- (1-9) $\text{-CH}_2\text{-(substituted)Ph-CONR-CH}_2\text{-(substituted)Ph}$
- (1-10) $\text{-CH}_2\text{-(substituted)Ph-NRCO-CH}_2\text{-(substituted)Ph}$
- (1-11) $\text{-CH}_2\text{-(substituted)Ph-CH}_2\text{-CONR-CH}_2\text{-(substituted)Ph}$
- (1-12) $\text{-CH}_2\text{-(substituted)Ph-CH}_2\text{-NRCO-CH}_2\text{-(substituted)Ph}$
- (1-13) $\text{-CH}_2\text{-(substituted)Ph-X-CONR-CH}_2\text{-(substituted)Ph}$
- (1-14) $\text{-CH}_2\text{-(substituted)Ph-X-NRCO-CH}_2\text{-(substituted)Ph}$
- (1-15) $\text{-CH}_2\text{-(substituted)Het-CONR-CH}_2\text{-(substituted)Ph}$
- (1-16) $\text{-CH}_2\text{-(substituted)Het-NRCO-CH}_2\text{-(substituted)Ph}$
- (1-17) $\text{-(CH}_2\text{)}_m\text{-(substituted)Ph-CONR-(substituted)Ph}$
- (1-18) $\text{-(CH}_2\text{)}_m\text{-(substituted)Ph-NRCO-(substituted)Ph}$
- (1-19) $\text{-(CH}_2\text{)}_m\text{-(substituted)Ph-CH}_2\text{-CONR-(substituted)Ph}$
- (1-20) $\text{-(CH}_2\text{)}_m\text{-(substituted)Ph-CH}_2\text{-NRCO-(substituted)Ph}$
- (1-21) $\text{-(CH}_2\text{)}_m\text{-(substituted)Ph-X-CONR-(substituted)Ph}$
- (1-22) $\text{-(CH}_2\text{)}_m\text{-(substituted)Ph-X-NRCO-(substituted)Ph}$
- (1-23) $\text{-(CH}_2\text{)}_m\text{-(substituted)Het-CONR-(substituted)Ph}$
- (1-24) $\text{-(CH}_2\text{)}_m\text{-(substituted)Het-NRCO-(substituted)Ph}$
- (1-25) $\text{-(CH}_2\text{)}_m\text{-(substituted)Het-X-CONR-(substituted)Ph}$
- (1-26) $\text{-(CH}_2\text{)}_m\text{-(substituted)Het-X-NRCO-(substituted)Ph}$
- (1-27) $\text{-(CH}_2\text{)}_m\text{-S-CH}_2\text{-(substituted)Ph}$

- (1-28) $\text{-(CH}_2\text{)-(substituted)Het-(substituted)Ph}$
- (1-29) $\text{-(CH}_2\text{)-CH[(substituted)Ph]}_2$
- (1-30) $\text{-(substituted)cAlk-X-CH}_2\text{-(substituted)Ph}$
- (1-31) $\text{-CH}_2\text{-(substituted)cAlk}$
- (1-32) $\text{-(CH}_2\text{)}_m\text{-X-(CH}_2\text{)}_m\text{-H}$
- (1-33) $\text{-(CH}_2\text{)}_m\text{-X-(substituted)Ph}$
- (1-34) $\text{-CH}_2\text{-(substituted)Ph}$
- (1-35) $\text{-CH}_2\text{-(substituted)Het-CH}_2\text{-(substituted)Ph}$
- (1-36) $\text{-CH}_2\text{-(substituted)Ph-(substituted)Ph}$
- (1-37) $\text{-(CH}_2\text{)}_m\text{-S-CH}_2\text{-(substituted)Het}$
- (1-38) $\text{-CH}_2\text{-(substituted)Ph-X-(substituted)Ph}$
- (1-39) $\text{-(CH}_2\text{)}_m\text{-(substituted)Het-CH}_2\text{-(substituted)Ph}$
- (1-40) $\text{-CH}_2\text{-(substituted)Ph-X-(substituted)Het}$
- (1-41) $\text{-CH}_2\text{-(substituted)Ph-(substituted)Het}$
- (1-42) $\text{-(CH}_2\text{)}_m\text{-(substituted)Het}$
- (1-43) $\text{-CH}_2\text{-(substituted)Ph-SO-CH}_2\text{-(substituted)Ph}$
- (1-44) $\text{-(substituted)cAlk-(substituted)Ph}$
- (1-45) $\text{-CH}_2\text{-(substituted)Ph-S-CH}_2\text{-(substituted)Ph}$
- (1-46) $\text{-CH}_2\text{-(substituted)Het-(substituted)Het}$
- (1-47) $\text{-CH}_2\text{-(substituted)Ph-CO-(substituted)Ph}$
- (1-48) $\text{-CH}_2\text{-(substituted)Het-CO-(substituted)Ph}$
- (1-49) $\text{-CH}_2\text{-(substituted)Het-CH=CH-(substituted)Ph}$
- (1-50) $\text{-CH}_2\text{-(substituted)Het-X-CH}_2\text{-(substituted)Ph}$
- (1-51) $\text{-CH}_2\text{-(substituted)Het-CH}_2\text{-X-(substituted)Ph}$
- (1-52) $\text{-CH}_2\text{-(substituted)Het-SO}_2\text{-(substituted)Ph}$

(1-53) $-\text{CH}_2\text{-(substituted)Het-X-(substituted)Ph}$

(1-54) $-\text{CH}_2\text{-CH=CH-(substituted)Het-(substituted)Ph}$

In the above formulas, Ph is phenyl; X is O, S or NR; R is hydrogen or lower alkyl; Het is optionally condensed heteroaryl or heterocycle (preferably 5- or 6-membered); cAlk is cycloalkyl (preferably 3- to 6-membered); m is 2 or 3; and (substituted) indicates optionally substituted.

Among the aforementioned groups, a particularly preferable embodiment of R^{A1} is (1-28).

[0059]

Examples of chemical modification in R^{B} , R^{C} and R^{D} include substituents described in JP-A No. 2001-163898. Specifically, the following are exemplified.

R^{b} is selected from the group consisting of the following (2-1) to (2-7):

(2-1) Hydroxy:

(2-2) Mono- or di-alkylamino optionally substituted (provided that (2-4) is excluded), wherein two alkyls may be bound to form a ring, the substituent is amino, monoalkylamino, dialkylamino, trialkylammonium, hydroxy, guanidino, carboxy, alkyloxycarbonyl, carbamoyl optionally substituted with cyano, mono- or di-alkylcarbamoyl, mono- or di-arylcarbamoyl, aryl, alkylamide or arylamide, alkylurea or arylurea, $-(\text{C}=\text{O})\text{N}\cdot\text{N}^+(\text{R}^{\text{X}})_3$, $\cdot\text{N}^+(\text{R}^{\text{X}})_2(\text{CH}_2)_m\text{COOR}^{\text{Y}}$, $\cdot\text{N}^+(\text{R}^{\text{X}})_2(\text{CH}_2)_m\text{N}^+(\text{R}^{\text{X}})_3$, $-\text{SO}_2\cdot\text{OR}^{\text{Y}}$ (wherein m is 1 to 3, R^{X} is C1-C3 alkyl, and R^{Y} is hydrogen or C1-C3 alkyl), or $-\text{P}=\text{O}(\text{OR}^{\text{Y}})_2$ (wherein R^{Y} is hydrogen or C1-C3 alkyl), or a combination thereof, wherein alkyl in the substituent may be further substituted with amino optionally substituted with alkyloxycarbonyl or aryloxycarbonyl, and an aryl ring in the

substituent can be further substituted with halogen, nitro, amino, hydroxy, carboxy, alkyloxycarbonyl, alkyl optionally substituted with amino, or optionally acylated hydroxyalkyl or thioalkyl, or a combination thereof;

(2-3) Amino, or cycloalkylamino optionally substituted with hydroxy;

(2-4) Di-substituted methylamino-NHCHR⁶R⁷, wherein R⁶ is selected from carboxy, alkyloxycarbonyl optionally having a substituent, carbamoyl, or monoalkylcarbamoyl optionally having a substituent, or cycloalkylcarbamoyl optionally having a substituent, wherein the substituent is amino, monoalkylamino, dialkylamino, trialkylammonium, carboxy, hydroxy, $-(C=O)N^--N^+(R^X)_3$, aryl optionally substituted with $-(CH_2)_mCOOR^X$ (wherein m is 1 to 3, R^X is C1-C3 alkyl), $-N^+(R^X)_2(CH_2)_mCOOR^Y$ (wherein R^Y is hydrogen or C1-C3 alkyl), or $-N^+(R^X)_2(CH_2)_mN^+(R^X)_3$, or a combination thereof, R⁷ is indole or thioindole in which a nitrogen is optionally substituted with C1-C3 alkyl, or imidazolyl;

(2-5) Tripeptide R-A¹-A²-A³-; wherein A¹, A², and A³ are an arbitrary amino acid unit, respectively, R represents hydroxy, amino, or mono- or di-alkylamino optionally substituted, at the carboxy terminal of the tripeptide, the substituent is amino, monoalkylamino, dialkylamino, trialkylammonium, guanidino, or aryl;

(2-6) Hydrazino optionally having a substituent, or hydroxamic acid, wherein the substituent is alkyl, or arylalkyl optionally substituted with alkyl; and

(2-7) Alkoxy optionally having a substituent, wherein the substituent is arylcarbonyl optionally further substituted with nitro, hydroxamic acid, or alkyl;

provided that, in (2-2) to (2-7), the existing aryl ring may contain

hetero atom, and the existing carbon-carbon single bond may be interrupted with hetero atom, or hetero group selected from $-\text{O}(\text{P}=\text{O})(\text{OR}^{\text{F}})\text{O}-$ (wherein R^{F} is hydrogen, alkyloxycarbonyl or aryloxycarbonyl), and imino, in some cases;

R^{B} is preferably $-\text{OH}$, $-\text{NHR}^5$, or $-\text{NR}^5\text{R}^{5'}$ (wherein R^5 and $\text{R}^{5'}$ are hydrogen, optionally substituted lower alkyl, $-\text{NH}\cdot\text{R}$, $-\text{NH}\cdot\text{COR}$, $-\text{NH}\cdot\text{CONHR}$, $-\text{O}\cdot\text{R}$ (each R is independently hydrogen or optionally substituted lower alkyl, respectively), or amino sugar residue). Preferably, one of R^5 and $\text{R}^{5'}$ is hydrogen. More preferable is $-\text{OH}$ or $-\text{NHR}^5$ (wherein R^5 is substituted lower alkyl, or optionally substituted lower alkyloxy).

As a substituent of the optionally substituted lower alkyl and the optionally substituted lower alkyloxy, hydrophilic substituent is preferable. For example, the same or different 1 to 10, preferably 1 to 6 substituents selected from amino, mono- or di-lower alkylamino, tri-lower alkylamine, amino lower alkylamino, hydroxyl lower alkylamino, hydroxy, carboxy, lower alkoxy, carbonyl, SO_3H , PO_3H_2 , optionally substituted carbamoyl, quaternary ammonium group (e.g., tri-lower alkylamino (e.g., $-\text{N}^+(\text{CH}_3)_3$)), optionally substituted heterocyclic group (heterocycle or heteroaryl), optionally substituted heterocyclic thio, guanidino, NHSO_2NH_2 , and hydroxy lower alkoxy are exemplified. An N atom part in the heterocycle may be quaternarized to form a salt. As a substituent of the optionally substituted heterocycle, hydroxy, amino, carboxy, amino lower alkyl, and quaternary ammonium lower alkyl are exemplified. Alternatively, a lower alkyl group on the quaternary ammonium group may be further substituted with the substituted lower alkyl (substituent: carboxy, hydroxy, quaternary

ammonium group). More preferable is optionally substituted lower amino, hydroxy, or lower alkoxy.

[0060]

R^C is selected from the group consisting of the group (3-1) to (3-4):

(3-1) Hydrogen;

(3-2) Alkyl, cycloalkyl, or aminomethyl optionally substituted with alkylene, which may each have a substituent, wherein the substituent is amino optionally substituted with alkyloxycarbonyl or aryloxycarbonyl, monoalkylamino, dialkylamino, trialkylammonium, aryl optionally substituted with cycloalkyl, pyridyl, hydroxy, guanidino, $-O-(P=O)(OH)_2$, carboxy, SO_3H , $-N^+(R^X)_2(CH_2)_mN^+(R^X)_3$, or $-(C=O)-N-N^+(R^X)_3$ (wherein m is 1 to 3, R^X is C1-C3 alkyl), or a combination thereof, wherein alkyl in the monoalkylamino or dialkylamino substituent may be further substituted with amino in some cases;

(3-3) Alkynyl optionally having a substituent, wherein the substituent is amino optionally substituted with alkyloxycarbonyl or aryloxycarbonyl, or aryl; and

(3-4) Halogen;

provided that, in (3-2) and (3-3), an existing aryl ring may contain hetero atom, and an existing carbon-carbon single bond is interrupted with heteroatom, or hetero group selected from $-O(P=O)(OR^J)O-$ (wherein R^J is hydrogen, alkyloxycarbonyl or aryloxycarbonyl), amido and imino in some cases.

R^C is preferably hydrogen or optionally substituted lower alkyl. A substituent of the optionally substituted lower alkyl is preferably the $-NHR^5$,

or substituents of optionally substituted lower alkyl in R^5 are exemplified. More preferable is the $-NHR^5$. Herein, R^5 is preferably optionally substituted aralkyl, optionally substituted heteroaralkyl, or optionally substituted lower alkyl. A substituent of the optionally substituted aralkyl, the optionally substituted heteroaralkyl, or the optionally substituted lower alkyl is preferably $-NH_2$, $-SO_3H$, or $-OH$.

As a preferable combination of R^B and R^C , the case where R^B is $-OH$, $-NHR^5$ (R^5 is mono- or di-lower alkylamino lower alkyl, tri-lower alkylammonium lower alkyl, or amino sugar residue), $-NR^5R^{5'}$ (R^5 and $R^{5'}$ are both hydroxy lower alkyl), or $-NHCH_2CON^+(Me)_3$, and R^C is hydrogen, mono- or di-substituted amino lower alkyl (examples of substituent: lower alkyl, mono- or di-lower alkylamino lower alkyl, tri-lower alkylammonium lower alkyl, hydroxy lower alkyl, hydroxy lower alkoxy lower alkyl, $-CH_2CON^+(Me)_3$, lower alkyl substituted with 1 to 6 hydroxys, and lower alkyl substituted with carboxy, hydroxy, oxo, optionally substituted carbamoyl, guanidido, sulfonic acid group, phosphoric acid group, $NHCO_2NH_2$ and/or amino, optionally substituted heterocyclic lower alkyl (substituent: amino lower alkyl), optionally substituted quaternary ammonium lower alkyl (substituent: carboxy, hydroxy, quaternary ammonium group)) is exemplified. Specifically, cases in Table 6 to Table 8 described later are exemplified.

As a particularly preferable combination of R^B and R^C , R^B is $-OH$, and R^C is hydrogen.

[0061]

R^D is selected from the group consisting of the following (4-1) to (4-6):

(4-1) Hydrogen;

(4-2) Alkyl optionally substituted, wherein the substituent is alkyloxycarbonyl, amino, optionally alkylated aryl, arylcarbonyl, carbamoyl, mono- or di-alkylcarbamoyl or mono- or di-arylalkylcarbamoyl or a combination thereof, wherein alkyl or aryl in the substituent may be further substituted with amino optionally substituted with alkyloxycarbonyl or aryloxycarbonyl, or hydroxy;

(4-3) Alkyloxycarbonyl optionally substituted, wherein the substituent is optionally alkylated aryl;

(4-4) Arylamide or arylthioamide;

(4-5) Optionally alkylated amino or amidino; and

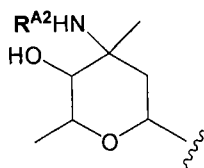
(4-6) Nitroso; provided that in (4-2) to (4-5), aryl ring can have hetero atom, and carbon-carbon single bond is interrupted with hetero atom in some cases.

R^D is preferably hydrogen or lower alkyl optionally having substituent. Particularly preferable is hydrogen.

Alternatively, an N-terminal part may be de-leucinated to convert it into -NH₂, or it may be further acylated according to a method described in the literature (e.g., Expert Opin. Ther. Patents (2004) 14, pp.141-173), [0062]

R^F is hydrogen or sugar residue. Preferable is a sugar residue. More preferable is amino sugar residue. Further preferable is amino sugar residue represented by the following formula:

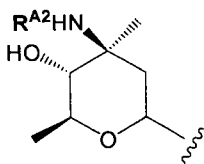
[Chemical formula 65]



(wherein R^{A2} is hydrogen or optionally substituted lower alkyl).

Particularly preferable is amino sugar residue represented by the following formula:

[Chemical formula 66]



(wherein R^{A2} is as defined above).

Examples of a substituent of optionally substituted lower alkyl in R^{A2} include hydroxy, carboxy, halogen (F, Cl, Br, I), halo lower alkyl (e.g., CF_3 , CH_2CF_3 , CH_2CCl_3), C1-C6 alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl) optionally substituted with hydroxy, C2-C6 alkenyl (e.g., vinyl), C3-C6 alkynyl (e.g., ethynyl), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), cycloalkenyl (e.g., cyclopropenyl), alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy), alkenyloxy (e.g., vinyloxy, allyloxy etc.), alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl etc.), nitro, nitroso, optionally substituted amino (e.g., amino, lower alkylamino (e.g., methylamino, ethylamino, dimethylamino), acylamino (e.g., acetylamino, benzoylamino), aralkylamino (e.g., benzylamino, tritylamino), hydroxyamino), azido, aryl (e.g., phenyl), aralkyl (e.g., benzyl), cyano,

isocyano, isocyanato, thiocyanato, isothiocyanato, mercapto, lower alkylthio (e.g., methylthio), lower alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl), optionally substituted carbamoyl (e.g., lower alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl)), sulfamoyl, acyl (e.g., formyl, acetyl), formyloxy, haloformyl, oxalo, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, sulfinio, sulfo, sulfoamino, hydrazine, azido, ureido, amidino, guanidino, phthalimido, oxo, optionally substituted aryl (e.g., phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 1-naphthyl, 2-naphthyl), optionally substituted heteroaryl (e.g., pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, isoxazol-3-yl, isoxazol-5-yl, pyrrol-2-yl, pyrazol-3-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, imidazol-2-yl, oxazol-2-yl, thiazol-2-yl), optionally substituted heterocycle (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolinyl, 2-imidazolidinyl, imidazolinyl, 1-pyrazolidinyl, 2-pyrazolidinyl, pyrazolinyl, piperidino, 2-piperidyl, 1-piperazinyl, morpholino, 3-morpholinyl, tetrahydrofuryl, tetrahydropyranylyl) and the like. Preferable is hydroxy, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocycle. More preferable is hydroxy, pyridin-3-yl, imidazol-2-yl, morpholino, or 3-(3-trifluoromethoxybenzoylamino) phenyl.

A particularly preferable embodiment of R^{A2} is hydrogen.

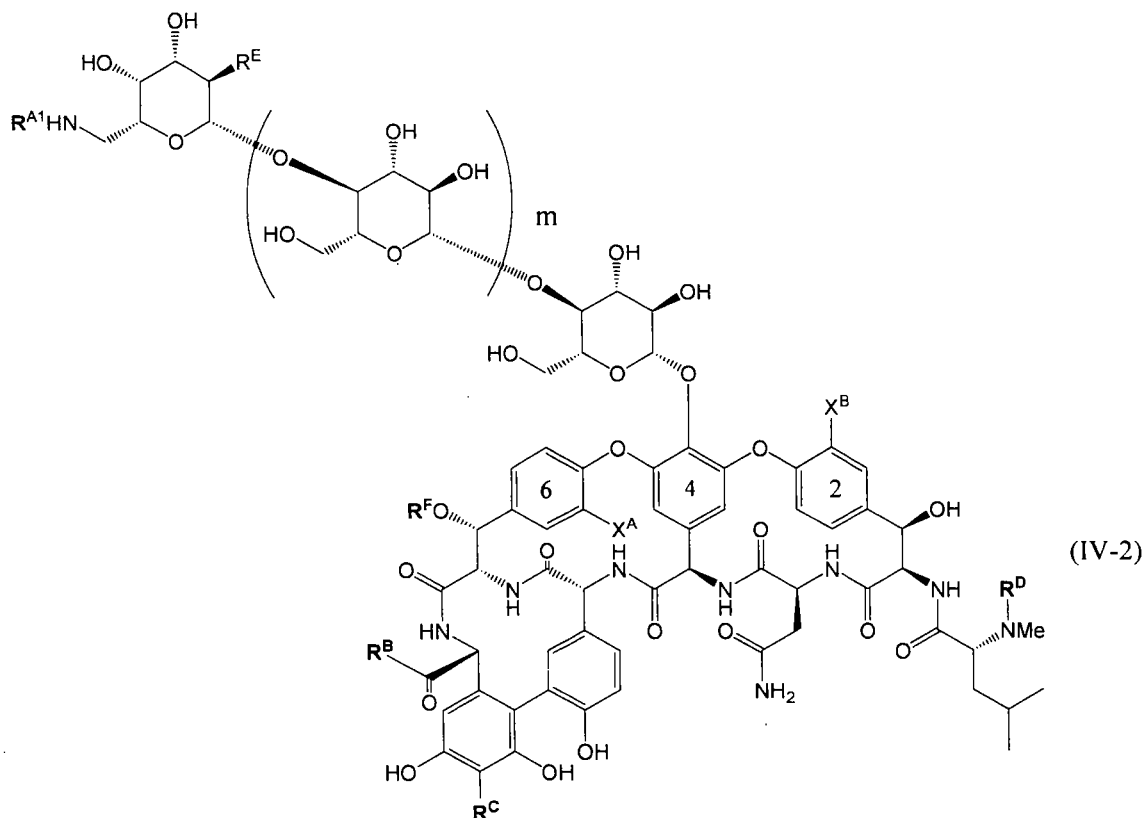
[0063]

Preferable compounds of the present invention can be classified into

the following categories.

In a compound represented by the formula (IV-2):

[Chemical formula 67]



(wherein respective symbols are as defined above):

- 1) A compound, a pharmaceutically acceptable salt thereof, or a solvate thereof in which R^{A1} is optionally substituted lower alkyl;
- 2) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to 1), wherein R^{A1} is lower alkyl optionally substituted with a substituent selected from the following substituent group A;

Substituent group A: optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, optionally substituted aralkylthio, optionally substituted heteroaralkylthio, optionally substituted

cycloalkyl, optionally substituted lower alkyloxy, optionally substituted aralkyloxy, optionally substituted aryloxy, optionally substituted arylsulfonylamino, and optionally substituted amino;

3) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to 2), wherein a substituent of the “optionally substituted” group in the substituent group A of 2) is selected from the following substituent group B;

Substituent group B: optionally substituted arylaminocarbonylamino, optionally substituted arylaminocarbonyl, optionally substituted arylcarbonyl, optionally substituted arylcarbonylamino, optionally substituted arylcarbonylaminoalkyl, oxo, halogen, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthio, optionally substituted arylamino, optionally substituted arylaminoalkyl, optionally substituted arylaminocarbonylalkyl, optionally substituted arylsulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted amino, optionally substituted aralkylcarbonylamino, optionally substituted aralkylamino, optionally substituted aralkylaminocarbonyl, optionally substituted aralkylsulfinyl, optionally substituted arylsulfonylamino, optionally substituted arylaminosulfonyl, optionally substituted aralkylthio, halo lower alkyl, lower alkyloxy, lower alkylamino, halo lower alkyloxy, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylthio, optionally substituted aryl lower alkenyl, optionally substituted heteroaryl lower alkenyl, optionally substituted

cycloalkyl, optionally substituted cycloalkyloxy, optionally substituted cycloalkylthio, optionally substituted cycloalkylaminocarbonyl, optionally substituted cycloalkyl lower alkenyl, optionally substituted cycloalkylsulfonyl, optionally substituted cycloalkylaminocarbonylamino, optionally substituted cycloalkylaminoalkyl, optionally substituted cycloalkyl lower alkylamino, optionally substituted cycloalkylamino, optionally substituted cycloalkyl lower alkyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonylamino, optionally substituted cycloalkylcarbonylamino, optionally substituted cycloalkylcarbonylaminoalkyl, optionally substituted cycloalkyl lower alkylaminocarbonyl, optionally substituted cycloalkylsulfonylamino, optionally substituted cycloalkylaminocarbonylalkyl, and optionally substituted cycloalkylaminosulfonyl;

4) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to 3), wherein a substituent of the “optionally substituted” group in the substituent group B of 3) is selected from the following substituent group C;

Substituent group C: lower alkyl, lower alkyloxy, lower alkylsulfonyl, nitro, aralkyloxy, halogen, cyano, halo lower alkyl, halo lower alkyloxy, and di-lower alkylamino;

5) A compound, a pharmaceutically acceptable salt thereof, or a solvate thereof in which R^B is -OH, -NHR⁵, or -NR⁵R^{5'} (wherein R⁵ and R^{5'} are hydrogen, optionally substituted lower alkyl, -NH-R, -NH-COR, -NH-CONHR, -O-R (each R are independently hydrogen or optionally

substituted lower alkyl), or amino sugar residue);

6) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to 5), wherein R^B is $-OH$ or $-NHR^5$ (wherein R^5 is lower alkyl optionally substituted with same or different 1 to 6 substituents selected from the following substituent group D, or lower alkyloxy optionally substituted with same or different 1 to 6 substituents selected from the following substituent D;

Substituent group D: amino, mono- or di-lower alkylamino, tri-lower alkylamino, amino lower alkylamino, hydroxy lower alkylamino, hydroxy, carboxy, lower alkoxy carbonyl, SO_3H , PO_3H_2 , optionally substituted carbamoyl, quaternary ammonium group, optionally substituted heterocyclic group, optionally substituted heterocyclic thio, guanidino, $NHSO_2NH_2$, and hydroxy lower alkoxy),;

7) A compound, a pharmaceutically acceptable salt thereof, or a solvate thereof in which R^C is hydrogen or optionally substituted lower alkyl;

8) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to 7), wherein R^C is hydrogen, or lower alkyl optionally substituted with amino optionally substituted with a substituent selected from the following substituent group E;

Substituent group E: aralkyl optionally substituted $-NH_2$, $-SO_3H$, or $-OH$; heteroaralkyl optionally substituted $-NH_2$, $-SO_3H$, or $-OH$; or lower alkyl optionally substituted with $-NH_2$, $-SO_3H$, or $-OH$;

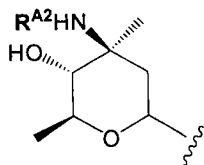
9) A compound, a pharmaceutically acceptable salt thereof, or a solvate thereof in which R^D is hydrogen, or lower alkyl optionally having a substituent;

10) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to 9), wherein R^D is hydrogen;

11) A compound, a pharmaceutically acceptable salt thereof, or a solvate thereof in which R^F is hydrogen or a sugar residue;

12) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to 11), wherein R^F is an amino sugar residue represented by the formula:

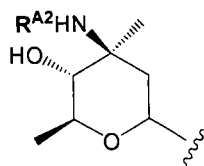
[Chemical formula 68]



(wherein R^{A2} is hydrogen or optionally substituted lower alkyl);

13) The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to 12), wherein R^F is an amino sugar residue represented by the formula:

[Chemical formula 69]



(wherein R^{A2} is hydrogen, hydroxy, pyridin-3-yl, imidazol-2-yl, morpholino, or lower alkyl optionally substituted with 3-(3-trifluoromethoxybenzoylamino)phenyl);

14) A compound, a pharmaceutically acceptable salt thereof, or a solvate

thereof in which X^A and X^B are both Cl;

15) A compound, a pharmaceutically acceptable salt thereof, or a solvate thereof in which R^E is -OH;

16) A compound, a pharmaceutically acceptable salt thereof, or a solvate thereof in which R^E is -NHAc;

17) A compound, a pharmaceutically acceptable salt thereof, or a solvate thereof in which m is 0 or 1.

Each category of the 1) to 17) can optionally constitute a compound with a combination of two or more.

[0064]

As a combination of R^B , R^C and R^D , the case where R^B is hydroxy, -NHR⁵ (R^5 is mono- or di-lower alkylamino lower alkyl, tri-lower alkylammonium lower alkyl, or an amino sugar residue), -NR⁵R^{5'} (R^5 and $R^{5'}$ are both hydroxy lower alkyl), or -NHCH₂CON·N⁺(Me)₃, R^C is hydrogen, mono- or di-substituted amino lower alkyl (examples of substituent: lower alkyl, mono- or di-lower alkylamino lower alkyl, tri-lower alkylammonium lower alkyl, hydroxy lower alkyl, hydroxy lower alkoxy lower alkyl, -CH₂CON·N⁺(Me)₃, lower alkyl optionally substituted with 1 to 6 of hydroxys, and lower alkyl substituted with carboxy, hydroxy, oxo, optionally substituted carbamoyl, guanidino, sulfonic acid residue, phosphoric acid group, NHSO₂NH₂ and /or amino, optionally substituted with heterocyclic lower alkyl (substituent: amino lower alkyl), optionally substituted quaternary ammonium lower alkyl (substituent: carboxy, hydroxy, quaternary ammonium group)) and R^D is hydrogen is exemplified. Specifically, the cases of Tables 1 to 8 are exemplified.

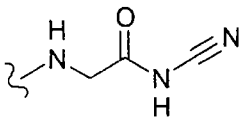
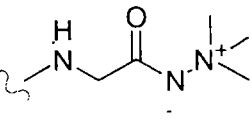
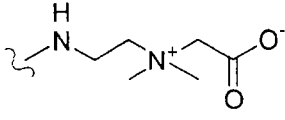
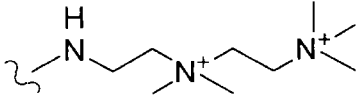
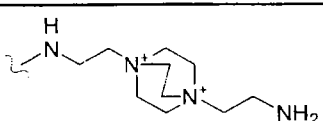
[0065]

[Table 1]

R^B	R^C	R^D
$-\text{NH}(\text{CH}_2)_2\text{NMe}_2$	H	H
$-\text{NH}(\text{CH}_2)_2\text{N}^+\text{Me}_3$	H	H
$-\text{NH}(\text{CH}_2)_3\text{NMe}_2$	H	H
$-\text{NH}(\text{CH}_2)_3\text{N}^+\text{Me}_3$	H	H
$-\text{NH}(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2\text{NH}_2$	H	H

[0066]

[Table 2]

R^B	R^C	R^D
$-\text{NH}(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2\text{OH}$	H	H
$-\text{N}[(\text{CH}_2)_2\text{OH}]_2$	H	H
$-\text{NHCH}_2\text{CO}_2\text{H}$	H	H
$-\text{NH}(\text{CH}_2)_2\text{CO}_2\text{H}$	H	H
$-\text{NH}(\text{CH}_2)_2\text{SO}_3\text{H}$	H	H
$-\text{NH}(\text{CH}_2)_2\text{PO}_3\text{H}_2$	H	H
	H	H
	H	H
	H	H
	H	H
	H	H

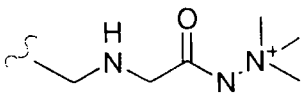
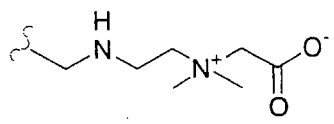
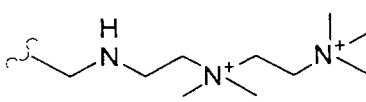
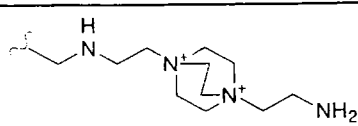
[0067]

[Table 3]

R ^B	R ^C	R ^D
	H	H
	H	H
	H	H
	H	H
	H	H
	H	H
	H	H
	H	H
	H	H
OH	-CH ₂ NHMe	H
OH	-CH ₂ NH(CH ₂) ₂ NH ₂	H

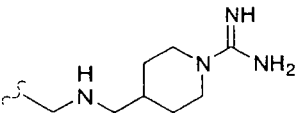
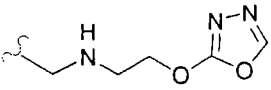
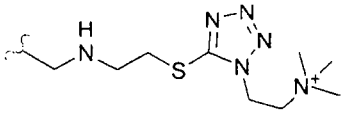
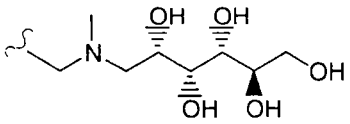
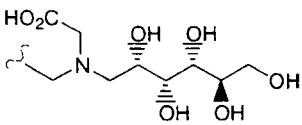
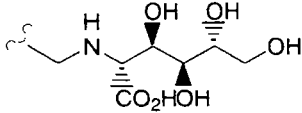
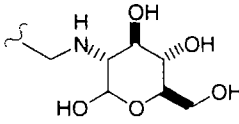
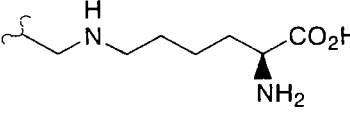
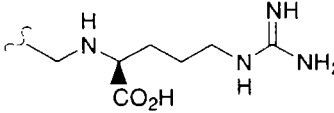
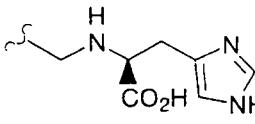
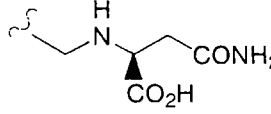
[0068]

[Table 4]

R^B	R^C	R^D
OH	$-\text{CH}_2\text{NH}(\text{CH}_2)_2\text{NMe}_2$	H
OH	$-\text{CH}_2\text{NH}(\text{CH}_2)_2\text{N}^+\text{Me}_3$	H
OH	$-\text{CH}_2\text{N}[(\text{CH}_2)_2\text{OH}]_2$	H
OH	$-\text{CH}_2\text{NHCH}_2\text{CO}_2\text{H}$	H
OH	$-\text{CH}_2\text{NH}(\text{CH}_2)_2\text{CO}_2\text{H}$	H
OH	$-\text{CH}_2\text{NH}(\text{CH}_2)_2\text{SO}_3\text{H}$	H
OH	$-\text{CH}_2\text{NHCH}_2\text{PO}_3\text{H}_2$	H
OH		H
OH		H
OH		H
OH		H

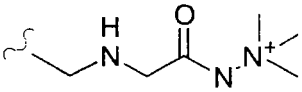
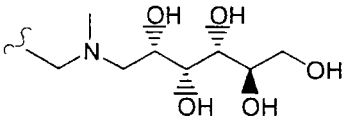
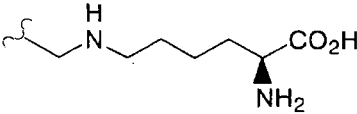
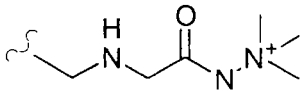
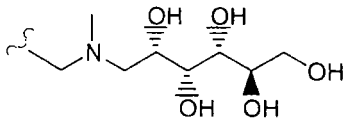
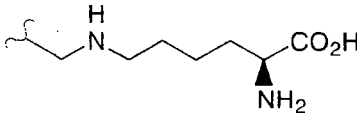
[0069]

[Table 5]

R ^B	R ^C	R ^D
OH		H
OH		H
OH		H
OH		H
OH		H
OH		H
OH		H
OH		H
OH		H
OH		H
OH		H

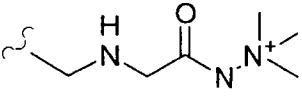
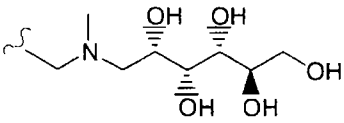
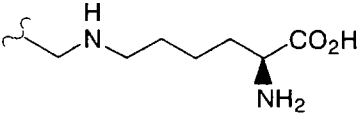
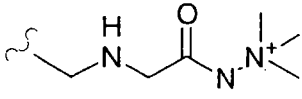
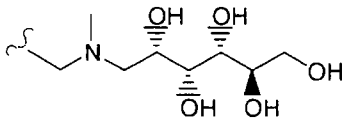
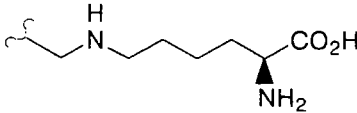
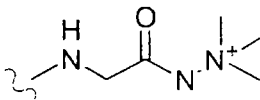
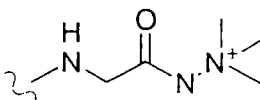
[0070]

[Table 6]

R^B	R^C	R^D
$-\text{NH}(\text{CH}_2)_3\text{NMe}_2$	$-\text{CH}_2\text{NH}(\text{CH}_2)_2\text{N}^+\text{Me}_3$	H
$-\text{NH}(\text{CH}_2)_3\text{NMe}_2$	$-\text{CH}_2\text{N}[(\text{CH}_2)_2\text{OH}]_2$	H
$-\text{NH}(\text{CH}_2)_3\text{NMe}_2$		H
$-\text{NH}(\text{CH}_2)_3\text{NMe}_2$		H
$-\text{NH}(\text{CH}_2)_3\text{NMe}_2$		H
$-\text{NH}(\text{CH}_2)_2\text{N}^+\text{Me}_3$	$-\text{CH}_2\text{NH}(\text{CH}_2)_2\text{N}^+\text{Me}_3$	H
$-\text{NH}(\text{CH}_2)_2\text{N}^+\text{Me}_3$	$-\text{CH}_2\text{N}[(\text{CH}_2)_2\text{OH}]_2$	H
$-\text{NH}(\text{CH}_2)_2\text{N}^+\text{Me}_3$		H
$-\text{NH}(\text{CH}_2)_2\text{N}^+\text{Me}_3$		H
$-\text{NH}(\text{CH}_2)_2\text{N}^+\text{Me}_3$		H
$-\text{N}[(\text{CH}_2)_2\text{OH}]_2$	$-\text{CH}_2\text{NH}(\text{CH}_2)_2\text{N}^+\text{Me}_3$	H

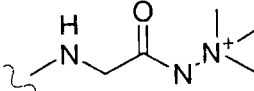
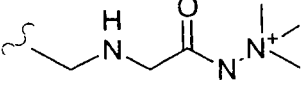
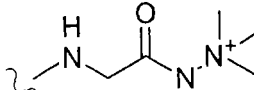
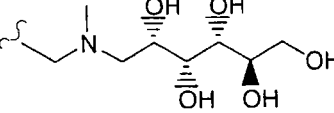
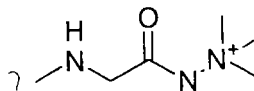
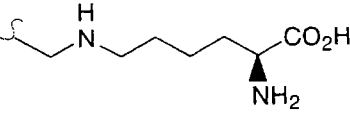
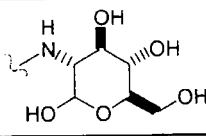
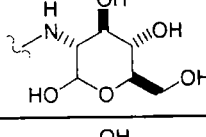
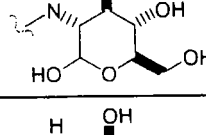
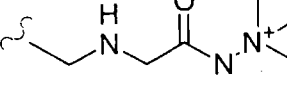
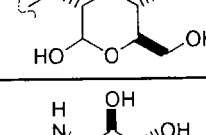
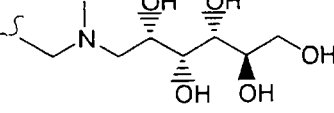
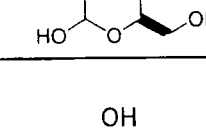
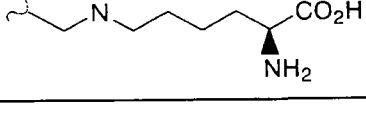
[0071]

[Table 7]

R^B	R^C	R^D
$-N[(CH_2)_2OH]_2$	$-CH_2N[(CH_2)_2OH]_2$	H
$-N[(CH_2)_2OH]_2$		H
$-N[(CH_2)_2OH]_2$		H
$-N[(CH_2)_2OH]_2$		H
$-NH(CH_2)_2CO_2H$	$-CH_2NH(CH_2)_2N^+Me_3$	H
$-NH(CH_2)_2CO_2H$	$-CH_2N[(CH_2)_2OH]_2$	H
$-NH(CH_2)_2CO_2H$		H
$-NH(CH_2)_2CO_2H$		H
$-NH(CH_2)_2CO_2H$		H
	$-CH_2NH(CH_2)_2N^+Me_3$	H
	$-CH_2N[(CH_2)_2OH]_2$	H

[0072]

[Table 8]

R ^B	R ^C	R ^D
		H
		H
		H
	-CH ₂ NH(CH ₂) ₂ N ⁺ Me ₃	H
	-CH ₂ N[(CH ₂) ₂ OH] ₂	H
		H
		H
		H
OH	H	H

[0073]

More specific present compounds are exemplified below. Table 9 and Table 10 below are examples of R^{A1} which is composed of each combinations of R^B, R^C and R^D.

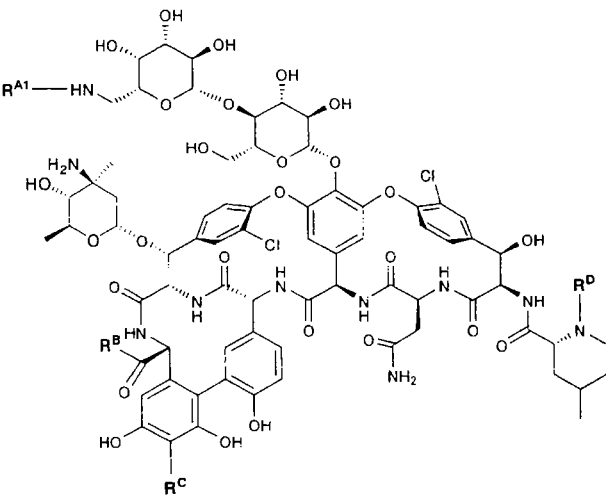
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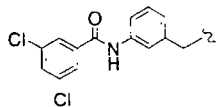
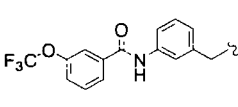
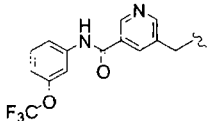
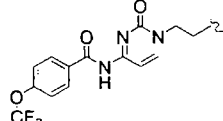
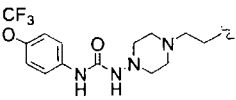
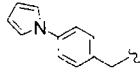
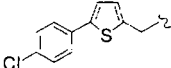
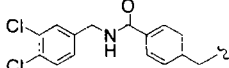
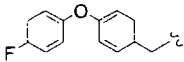
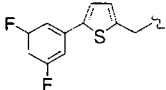
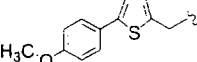
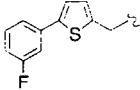
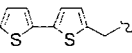
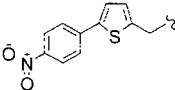
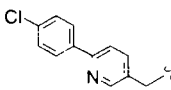
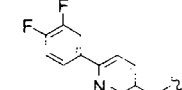
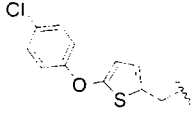
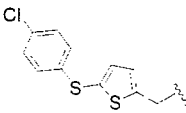
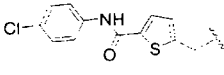
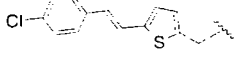
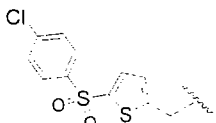
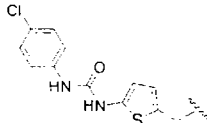
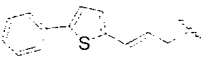
Structural formula	R ^B	R ^C	R ^D
	OH	H	H

R ^{A1}			

[0074]

[Table 10]

Structural formula		R ^B	R ^C	R ^D
		OH	H	H

R ^{A1}			
			
			
			
			
			
			

[0075]

The present invention includes the aforementioned compounds, pharmaceutically acceptable salts thereof, and solvates thereof.

Theoretically possible all tautomers, geometric isomers, and the like of the present compounds are within a scope of the present invention.

[0076]

“Pharmaceutically acceptable” means not harmful preventively or therapeutically. Examples of the pharmaceutically acceptable salt of the present compound include, as basic salt, alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt and the like; ammonium salt; aliphatic amine salts such as trimethylamine salt, triethylamine salt, dicyclohexylamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, procaine salt, meglumine salt, diethanolamine salt and ethylenediamine salt; aralkylamine salts such as N,N-dibenzylethylenediamine salt, benethamine salt and the like; heterocyclic aromatic amine salts such as pyridine salt, picoline salt, quinoline salt, isoquinoline salt and the like; quaternary ammonium salts such as tetramethylammonium salt, tetraethylammonium salt, benzyltrimethylammonium salt, benzyltriethylammonium salt, benzyltributylammonium salt, methyltrioctylammonium salt, tetrabutylammonium salt and the like; and basic amino acid salts such as arginine salt, lysine salt and the like. Examples of acidic salt include inorganic acid salts such as hydrochloride, sulfate, nitrate, phosphate, carbonate, bicarbonate, perchlorate and the like; organic acid salts such as acetate, propionate, lactate, maleate, fumarate, tartarate, malate, citrate,

ascorbate and the like; sulfonates such as methanesulfonate, isethionate, benzenesulfonate, p-toluenesulfonate and the like; and acidic amino acid salts such as aspartate, glutamate and the like.

In addition, a solvate, various solvates of the present compound are also within a scope of the present invention, and examples include monosolvate, disolvate, monohydrate, dihydrate and the like.

[0077] General process

A representative process of the present compound is described below, but it is not particularly limited to the production process.

[0078]

A starting material of the present invention can be prepared by variously chemically modifying an amino part (R^{A2}) of an amino sugar which binds to the sixth amino acid residue of a glycopeptides skeleton of chloroorienticin B or the known derivative thereof, or a C-terminal part (R^B), a resorcinol part (R^C), or an N-terminal part, a methylamino part (R^D) of chloroorienticin B, vancomycin or the known derivative thereof.

Alternatively, an aglycone obtained by once eliminating a sugar side chain which binds to the aromatic ring of the fourth amino acid residue of a glycopeptide skeleton can be also used as a raw material. Alternatively, as a starting material, chloroorienticin B, vancomycin or the known derivative thereof may be used without chemical modification.

[0079]

The chemical modification may be performed, for example, according to the method described in International Publication WO 2006/057303 pamphlet which constitutes a part of the present description. Specifically,

the chemical modification is as follows.

1) Modification of R^{A2} part

Representatively, using chloroorienticin B as a raw material, corresponding various aldehydes are reacted with an amino part of an amino sugar optionally in the presence of an acid or a base to form a Schiff base which is an intermediate, this may be subsequently reduced to be N-alkylated, thereby to form an objective secondary amine.

[0080]

More particularly, a reaction of forming a Schiff base is performed at a temperature of about 0°C to about 100°C optionally in the presence of an acid or a base in a polar solvent such as dimethyl sulfoxide, dimethylformamide, methanol, acetonitrile or water, or a mixed solvent thereof, optionally under the inert atmosphere such as nitrogen or argon. Preferably, the reaction is performed at a temperature of about 20°C to about 40°C for about 1 minute to 2 hours. As the base used, alkylamine (e.g., diisopropylethylamine) is exemplified. At this time, when a raw material compound has a substituent which is an obstacle of the present reaction, the substituent may be protected by the method described in Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) or the like, and the protective group may be removed at a desired step.

[0081]

Then, a Schiff base of an intermediate may be reduced or catalytic-reduced with metal hydride complex, preferably without isolation. As the metal hydride complex, metal borohydride such as sodium borohydride or sodium cyanoborohydride can be used. Catalytic reduction

is performed using hydrogen, in the presence of homogeneous or heterogeneous catalyst such as Crabtree catalyst, Wilkinson catalyst, palladium charcoal, platinum charcoal or rhodium charcoal. The reducing reaction is performed at a temperature of about 0°C to about 100°C for about 1 minute to 24 hours. Preferably, the reaction is performed at about 20°C to about 40°C in the solvent using excessive amount (e.g., 3 to 5 mole equivalent) of sodium cyanoborohydride.

The reaction of forming Schiff base and the reducing reaction may be performed simultaneously, or it is also possible to obtain objective compound by performing the reaction of forming Schiff base in the presence of a reducing agent.

[0082]

2) Modification of R^B part

Representatively, by amidating a carboxylic acid part which is the C-terminal, by a conventional method, using chloroorienticin B, vancomycin or the like as a raw material, the raw material can be converted into various amide derivatives which have R^B=-NR⁵R^{5'}.

[0083]

3) Modification of R^C part

Representatively, using chloroorienticin B, vancomycin or the like as a raw material, the resorcinol part is alkylated by a conventional method.

[0084]

4) Modification of R^D part

Representatively, using chloroorienticin B, vancomycin or the like as a raw material, the methylamine part of the N-terminal part may be,

example, N-alkylated by a conventional method.

5) Preparation of aglycone

Representatively, using chloroorienticin B, vancomycin or the like as a raw material, the raw material may be de-glycosylated by the known method such as acid hydrolysis and the like. Specifically, the aglycone can be prepared by the method described in J. Med. Chem. (1965),8,18-22, J. Chem. Soc., Chem. Commun. (1988),1306-1307, Biochemistry (2001), 40(15)4745-4755 or the like.

[0085]

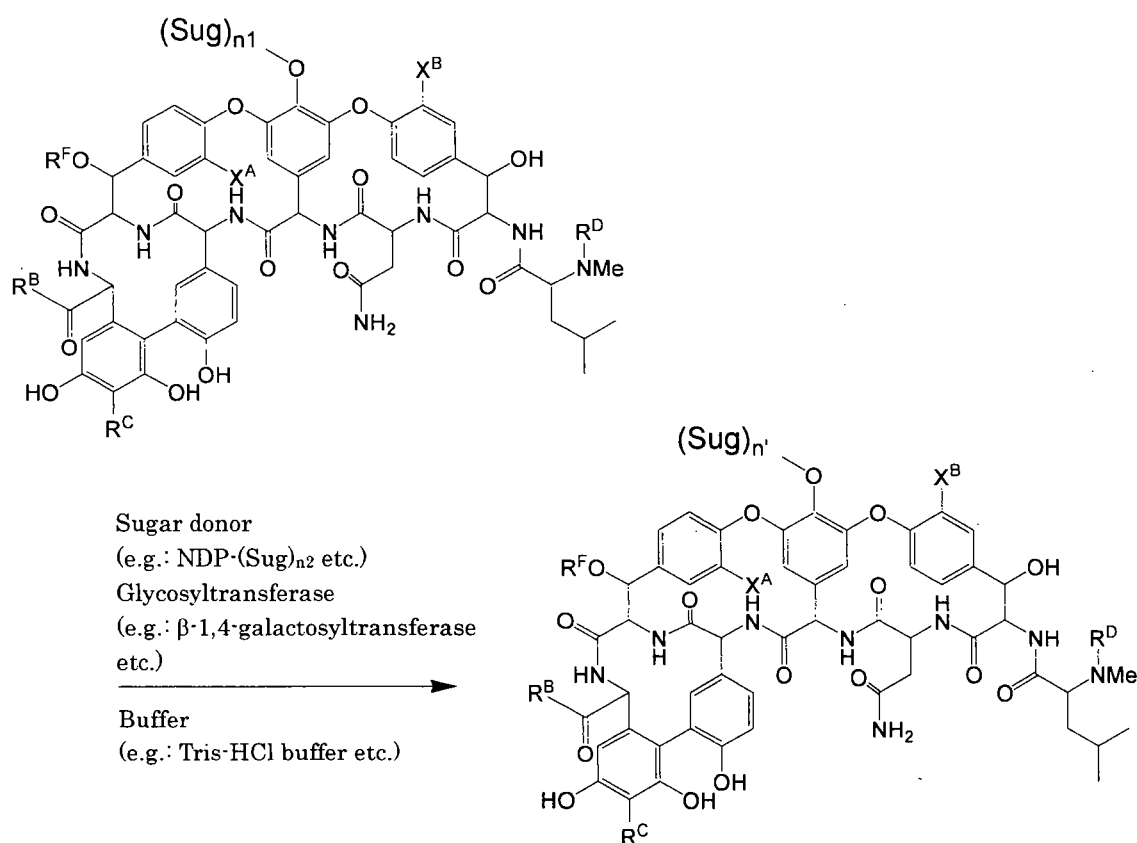
The present compound can be preferably synthesized by binding a monosaccharide to an OH part of an aromatic ring of the fourth amino acid residue of the glycopeptide skeleton of a starting material prepared by the aforementioned method, or a sugar residue which binds to it using glycosyltransferase or the like, elongating the sugar chain, oxidizing a hydroxymethyl group of the sugar residue at the terminal into an aldehyde group, reacting amine corresponding to R^{A1} in the presence of an acid or a base, if desired, to form a Schiff base which is an intermediated and, subsequently, N-alkylating the base by reduction, to form objective secondary amine. Specifically, the synthesis is as follows.

[0086]

6) Elongation of sugar chain

A method of elongating a sugar chain is shown below, regarding representative compounds.

[Chemical formula 70]



(wherein n1 is an integer of 0 to 5; n2 is an integer of 1 to 6;

n' is n1+n2 (wherein n' is 6 or less);

R^B, R^C, R^D, R^F, X^A, X^B, and Sug are as defined above; and

NDP is nucleotide-diphosphate; provided that, when n1 is 0, (Sug)_{n1} represents H.)

Sugar chain modification may be performed on a starting material prepared by any method of 1) to 5), or a method of a combination thereof to form the sugar residue (I). The sugar chain modification is preferably performed by an enzymatic reaction. For example, for the enzymatic reaction, a sugar chain is elongated by reacting with a sugar donor in the presence of glycosyltransferase optionally in buffer. When a sugar chain is elongated by 2 or more monosaccharides, the reaction may be repeated

plural times, or as described later, a sugar donor in which plurality of monosaccharides are connected in advance may be used.

As the buffer, buffers such as combination of a salt of an organic base such as Tris and the like, and an acid (e.g., Tris-HCl buffer, HEPES buffer, MES buffer etc); borate buffer; citrate buffer; acetate buffer; carbonate buffer and the like; are exemplified and preferable examples include Tris-HCl buffer, and MES buffer.

As the glycosyltransferase, β -1,4-galactosyltransferase, α -1,3-galactosyltransferase, β -1,3-galactosyltransferase, β -1,6-galactosyltransferase, α -2,6-sialyltransferase, α -1,4-galactosyltransferase, ceramidgalactosyltransferase, α -1,2-fucosyltransferase, α -1,3-fucosyltransferase, α -1,4-fucosyltransferase, α -1,6-fucosyltransferase, α -1,3-N-acetylgalactosaminyltransferase, α -1,6-N-acetylgalactosaminyltransferase, β -1,4-N-acetylgalactosaminyltransferase, polypeptide N-acetylgalactosaminyltransferase, β -1,4-N-acetylglucosaminyltransferase, β -1,2-N-acetylglucosaminyltransferase, β -1,3-N-acetylglucosaminyltransferase, β -1,6-N-acetylglucosaminyltransferase, α -1,4-N-acetylglucosaminyltransferase, β -1,4-mannosyltransferase, α -1,2-mannosyltransferase, α -1,3-mannosyltransferase, α -1,4-mannosyltransferase, α -1,6-mannosyltransferase, α -1,2-glucosyltransferase, α -1,3-glucosyltransferase, α -2,3-sialyltransferase, α -2,8-sialyltransferase, α -1,6-glucosaminyltransferase, α -1,6-xylosyltransferase, β -xylosyltransferase, (proteoglycan core structure

synthesizing enzyme), β -1,3-glucuronosyltransferase, hyaluronic acid synthesizing enzyme, glycosyltransferase Gtf A to E described in J. Am. Chem. Soc. (2005), 127(30), 10747-10752, Proc. Natl. Acad. Sci. U.S.A. (2004), 101(13), 4390-4395, Chem. Asian. J. (2006)., 1, 445-452 or the like, macrolide glycosyltransferase described in International Publication WO 2006/003456 pamphlet and the like are exemplified, and preferable is β -1,4-galactosyltransferase.

As the sugar donor, compounds (NDP-Sugar) in which various nucleotide diphosphates such as uridine diphosphate (UDP), thymidine diphosphate (TDP) and like, and monosaccharides such as galactose, glucose, fructose, fucose, galactosamine, glucosamine, N-acetylgalactosamine, N-acetylglucosamine, vancosamine, epi-vancosamine, glucuronic acid, sialic acid and like, or sugar chains in which 2 to 5 same or different monosaccharides are connected linearly or branched are bound, in addition to oligosaccharides, and polysaccharides such as sucrose, starch and the like can be used. Preferable examples include UDP-galactose, UDP-N-acetylgalactosamine, and UDP-glucose. When a part which is to be the terminal of a sugar chain of an objective compound is elongated, a sugar donor in which the terminal is galactose is particularly preferable.

Optionally, a salt of a metal (e.g., Mg, Mn, Ca, Co, Zn, Cu etc.) and an inorganic acid (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid etc.) may be added. The metal salt is preferably MnCl_2 or the like.

Further, optionally, additive for enhancing reaction efficiency may be present together such as additive for enhancing the enzyme activity of

lactoalbumin or the like; additive to decompose byproduct (e.g., alkaline phosphatase or the like); surfactant (e.g., Triton-X and the like);

The reaction temperature may be in conformity with an optimal temperature of glycosyltransferase. The temperature is 0 to 80°C, preferably 10 to 50°C, more preferably 20 to 40°C.

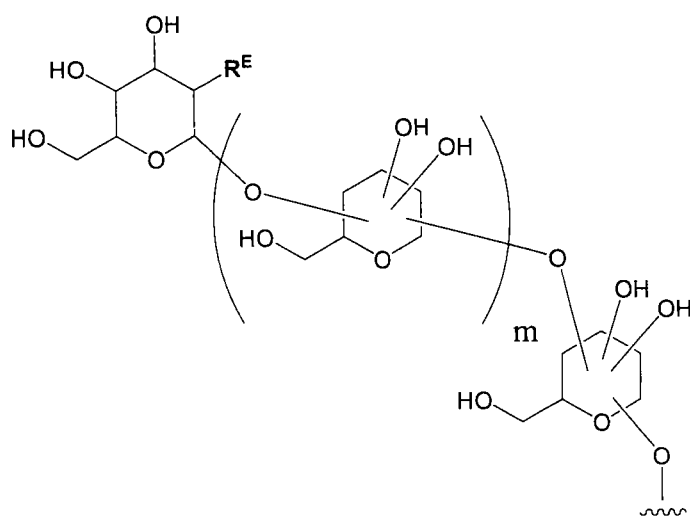
The reaction time is usually 1 to 100 hours, preferably 2 to 60 hours, more preferably 3 to 48 hours.

The pH of the buffer may be adjusted to an optimal pH of glycosyltransferase. Preferable pH is 2.0 to 12.0, more preferable is pH is 5.0 to 9.0, further preferable pH is 5.0 to 6.0.

In the sugar residue (Sug)_n, the sugar on the root side is preferably glucose (e.g., β-D-glucose). On the other hand, the sugar on the terminal side is preferably galactose or N-acetylgalactosamine, more preferably galactose (e.g., β-D-galactose).

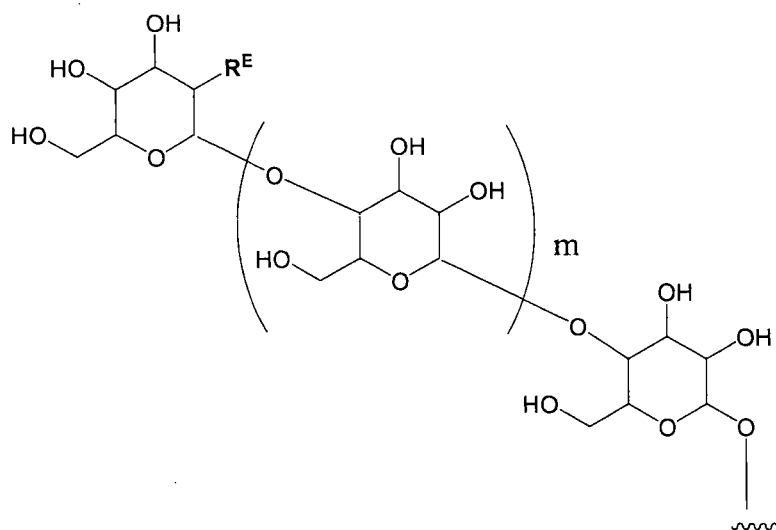
The sugar residue (Sug)_n is preferably a sugar residue represented by the formula:

[Chemical formula 71]



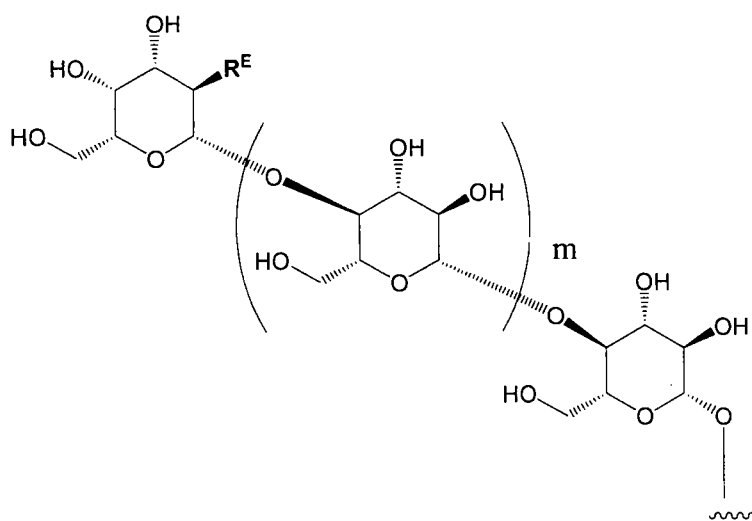
(wherein R^E is $-OH$ or $-NHAc$ (Ac is acetyl)). More preferable is a sugar residue represented by the formula:

[Chemical formula 72]



(wherein m is an integer of 0 to 4; and R^E is as defined above). Further preferable is a sugar residue represented by the formula:

[Chemical formula 73]

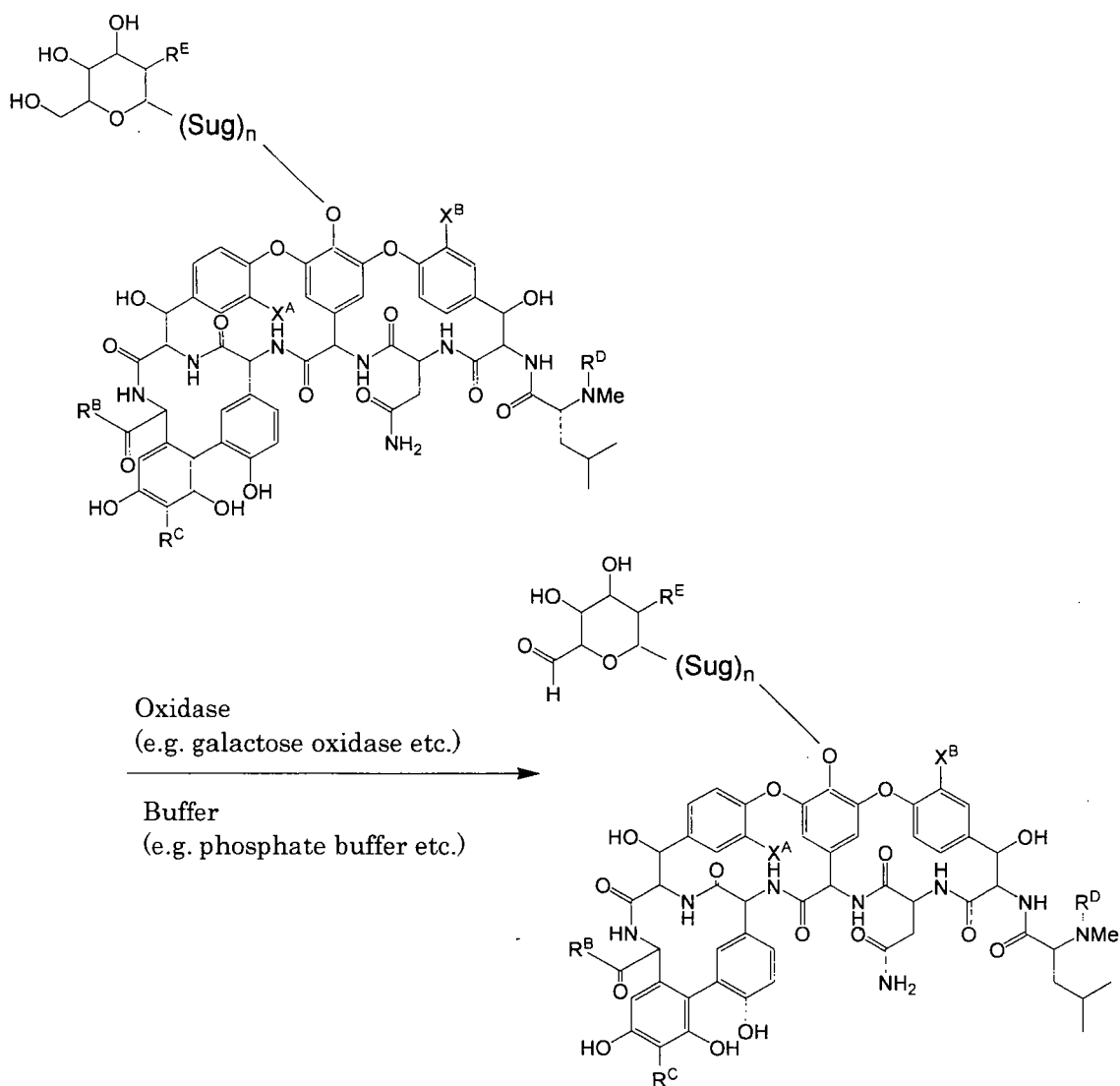


(wherein respective symbols are as defined above).

[0087]

7) Oxidation of hydroxymethyl group

[Chemical formula 74]



(wherein respective symbols are as defined above.)

A method of oxidizing the primary hydroxy group into aldehyde may be by oxidation with organic reagent, or oxidation with enzyme, and is

preferably the following method of oxidation with oxidase. According to the oxidation method, the objective hydroxy group can be selectively oxidized.

For the intermediate in which the sugar chain is elongated in above 6), the hydroxymethyl group is oxidized in the presence of oxidase optionally in buffer, to obtain the objective aldehyde intermediate.

As the buffer, phosphate buffer, borate buffer, citrate buffer, acetate buffer, carbonate buffer and the like are exemplified, and preferable is phosphate buffer.

As the oxidase, galactose oxidase and the like are exemplified.

Optionally, additive for improving the reaction efficiency to decompose byproduct (e.g., catalase and the like) may be present together.

The reaction temperature may be adjusted to an optimal temperature of the oxidase. Usually, the temperature is 0 to 80°C, preferably 10 to 50°C, more preferably 20 to 40°C.

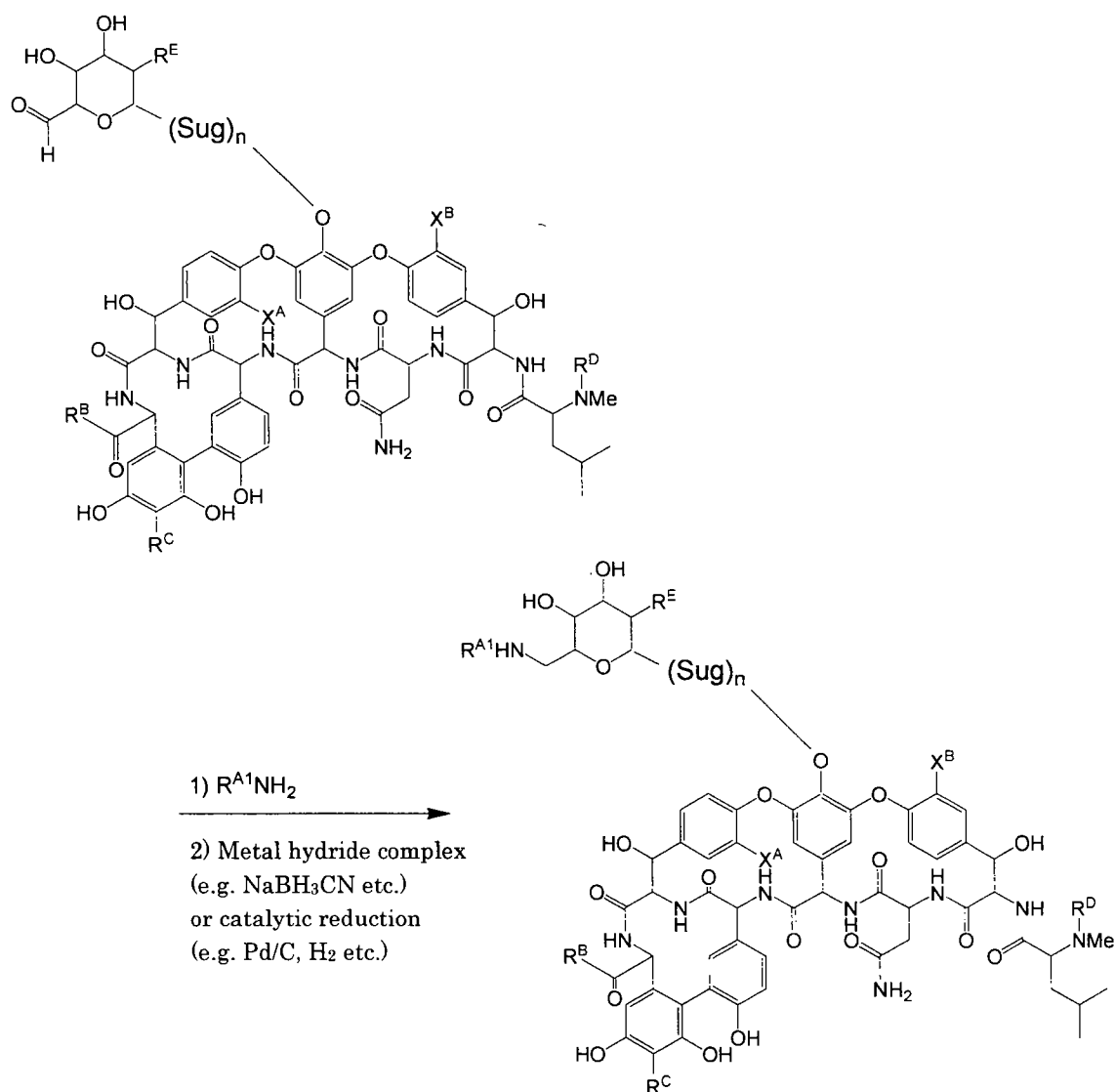
The reaction time is usually 1 to 100 hours, preferably 2 to 96 hours, more preferably 2 to 30 hours.

The pH of the buffer may be adjusted to an optimal pH of the oxidase. Preferable pH is 2.0 to 12.0, more preferably pH is 5.0 to 9.0, further preferably pH is 5.0 to 7.0.

[0088]

8) Modification of R^{A1} part

[Chemical formula 75]



(wherein respective symbols are as defined above.)

The objective compound is obtained by reacting the aldehyde intermediate obtained in 7), and amine $R^{A1}NH_2$ corresponding to objective R^{A1} , preferably by the same method as that of modification of the R^{A2} part in 1). The amine reagent ($R^{A1}NH_2$) is commercially available product, or can be synthesized according to the method described in International Publication WO 2006/057303.

According to the aforementioned method, the sugar residues (I-0), (I-1) and (I-2) are similarly formed.

In addition, the compound (X-1), (X-2) or (X-3) is present, as a byproduct, in admixture with the product obtained in 8) in some cases, and the compounds (IV-0) and (X-1), and compounds (IV-1) and (X-2) or the compounds (IV-2) and (X-3) can be each separated and isolated via a optional purification step (e.g., chromatography).

[0089]

9) Production of dehydrated material

The compound (X-1), (X-2) or (X-3) can be also produced by the following method.

In the presence of water or organic solvent, or in the presence of mixed solvent thereof, the aldehyde compound (XI-1), (XI-2) or (XI-3) in which the sugar terminal is the dehydrated material is produced by adding a base to react the compound (IX-1), (IX-2) or (IX-3) in which the sugar terminal is aldehyde.

Examples of the base include diisopropylethylamine, triethylamine, 4-dimethylaminopyridine and the like.

The reaction temperature is 0°C to 80°C, preferably 10°C to 60°C, more preferably 15°C to 40°C.

The reaction time is 1 to 100 hours, preferably 1 to 24 hours, more preferably 3 to 12 hours.

The produced aldehyde compound (XI-1), (XI-2) or (XI-3) in which the sugar terminal is dehydrated material can be subjected to modification of the

R^{A1} part by the same method as that of above 8), and the objective compound (X-1), (X-2) or (X-3) can be obtained.

[0090]

Pharmaceutical composition

The present invention also includes a pharmaceutical composition containing the novel glycopeptide derivative of the present invention. Therefore, the glycopeptide compound in a form of a pharmaceutically acceptable salt can be preferably formulated for oral or parenteral administration for treating or preventing bacterial infection.

[0091]

In the case of oral administration, the present compound can be also used as a conventional preparation, for example, as any dosage form of solid agents such as tablets, powders, granules, capsules; solutions; oily suspensions; or liquid agents such as syrups or elixirs. In the case of parenteral administration, the present compound can be used as aqueous or oily suspension injectables, or nose drops. Upon preparation thereof, conventional excipients, binders, lubricants, aqueous solvents, oily solvents, emulsifiers, suspending agents, preservatives, stabilizers and the like can be optionally used. As an antibacterial drug, particularly, oral agents, intravenous injectables or the like are preferable.

[0092]

Preparations of the present invention are produced by combining (for example, mixing) a therapeutically effective amount of the present compound with a pharmaceutically acceptable carrier or diluent. A preparation of the present compound can be produced using well-known

easily available ingredients by the known method.

[0093]

Upon production of a pharmaceutically composition of the present invention, an active ingredients is mixed with a carrier, or diluted with a carrier, or is placed into a carrier in a form of capsules, sachets, papers or other containers. When a carrier works as a diluent, the carrier is a solid, semi-solid or liquid material which works as a medium, and they can be formulated into tablets, pills, powders, pastille, elixirs, suspending agents, emulsions, solutions, syrups, aerosols (solids in liquid medium), ointments, and contain an up to 10% active compound. It is preferable that the present compound is formulated into preparations prior to administration.

[0094]

A person skilled in the art can use any of known suitable carriers for this formulation into preparations. In such preparations, a carrier is a solid, a liquid, or a mixture of a solid and a liquid. For example, for intravenous injection, the present compound is dissolved in a 4% dextrose/0.5% sodium citrate aqueous solution. A solid preparation includes powders, tablets and capsules. A solid carrier is one or more substances which serve also as a material for formulation into perfumes, lubricants, solubilizers, suspending agents, binders, tablets, disintegrating agents, or capsules. Tablets for oral administration contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, and calcium phosphate together with disintegrating agents such as corn starch, and alginic acid and/or binders such as gelatin and acacia, and lubricants such as magnesium stearate, stearic acid, and talc.

[0095]

In powders, a carrier is a finely divided solid, which is mixed with a finely divided active ingredient. In tablets, an active ingredient is mixed with a carrier having necessary binding property at a suitable ratio, and is solidified into a desired form and size. Powders and tablets contain about 1 to about 99% by weight of an active ingredient which is the novel compound of the present invention. A suitable solid carrier is magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth gum, methylcellulose, sodium carboxymethylcellulose, low melting point wax, and cocoa butter.

[0096]

Liquid preparations include suspending agents, emulsions, syrups and elixirs. An active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier such as sterile water, a sterile organic solvent, or a mixture of both of them. An active ingredient can be often dissolved in a suitable organic solvent, for example, an aqueous propylene glycol solution. Other compositions can be also produced by scattering a finely divided active ingredient in aqueous starch, a sodium carboxymethylcellulose solution, or a suitable oil.

[0097]

A dose of the present compound is different depending on an administration method, an age, a weight and condition of a patient and a kind of a disease and, usually, in the case of oral administration, about 0.1 mg to 7000 mg, preferably about 0.5 mg to 2000 mg may be administered per adult a day, if necessary, by division. In addition, in the case of parenteral

administration, about 0.1 mg to 1000 mg, preferably about 0.5 mg to 500 mg is administered per adult a day.

[0098]

The following Examples and Test Examples illustrate the present invention in more detail below, but the present invention is not limited by them.

In Examples, the following abbreviations are used.

Me: Methyl,

Et: Ethyl,

Ph: Phenyl,

Ms: Methanesulfonyl,

DMF: Dimethylformamide,

DMSO: Dimethyl sulfoxide,

THF: Tetrahydrofuran

DIPEA: Diisopropylethylamine,

TFA: Trifluoroacetic acid,

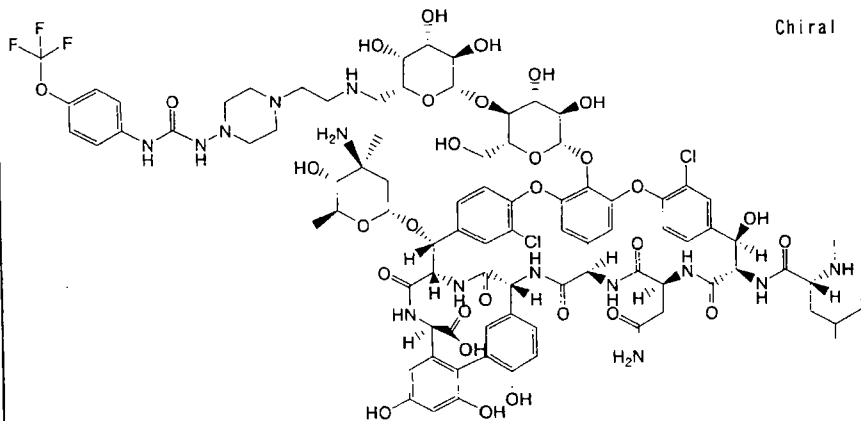
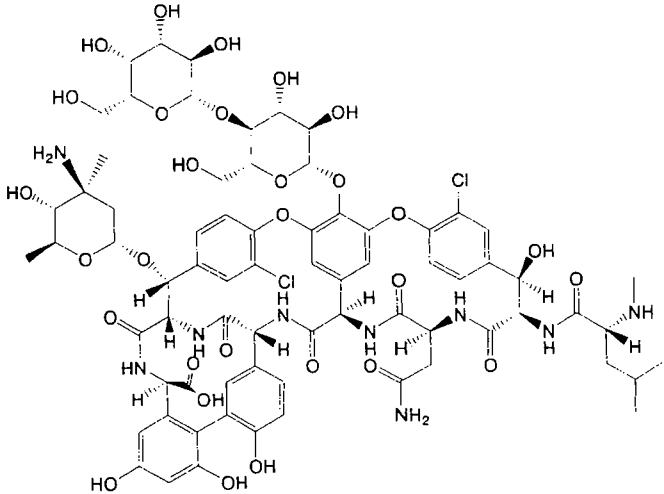
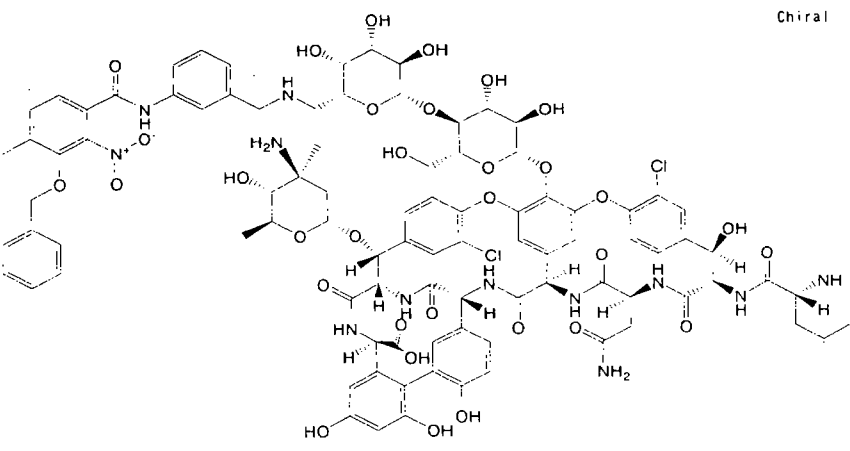
EDCI: N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide,

GalT: β -1,4-galactosyltransferase

[0099]

The compounds described in Table 11 to Table 51 were produced.

[Table 11]

Example	Structure	Mass Spectrometry	Elementary analysis
1	Chiral 	$[M+1]^+$ =1939	Calculated value for $C_{86}H_{103}Cl_{12}F_3N_{14}O_{30}$ $13.2H_{2O} \cdot 4HCl$ C: 44.44%, H: 5.78%, N: 8.44%, Cl: 9.15%, F: 2.45% Measured value C: 44.35%, H: 5.59%, N: 8.53%, Cl: 9.17%, F: 2.53%
2	Chiral 	$[M+1]^+$ =1610	Calculated value for $C_{72}H_{85}Cl_{12}N_9O_{29}$ $2.1HCl \cdot 13.8H_{2O}$ C: 44.65%, H: 5.97%, N: 6.51%, Cl: 7.51% Measured value C: 44.60%, H: 5.77%, N: 6.68%, Cl: 7.48%
3	Chiral 	$[M+1]^+$ =1983	Calculated value for $C_{94}H_{104}Cl_{12}N_{12}O_{32}$ $3.5HCl \cdot 14.9H_{2O}$ C: 47.42%, H: 5.81%, N: 7.06%, Cl: 8.19% Measured value C: 47.33%, H: 5.57%, N: 7.31%, Cl: 8.20%

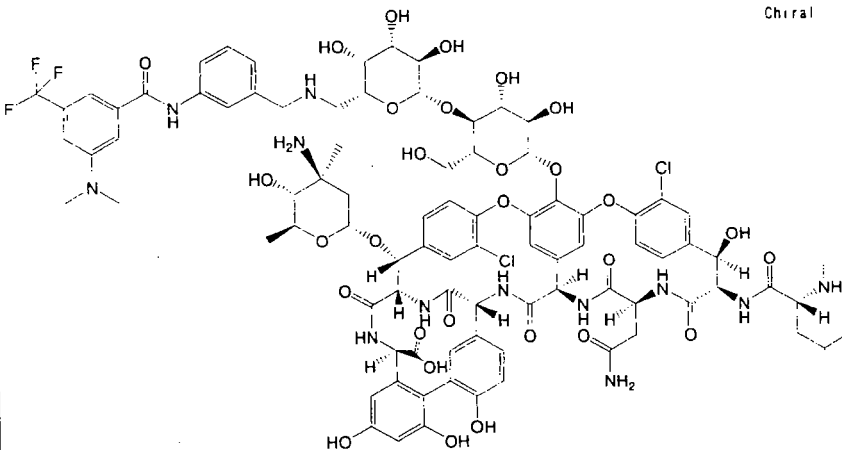
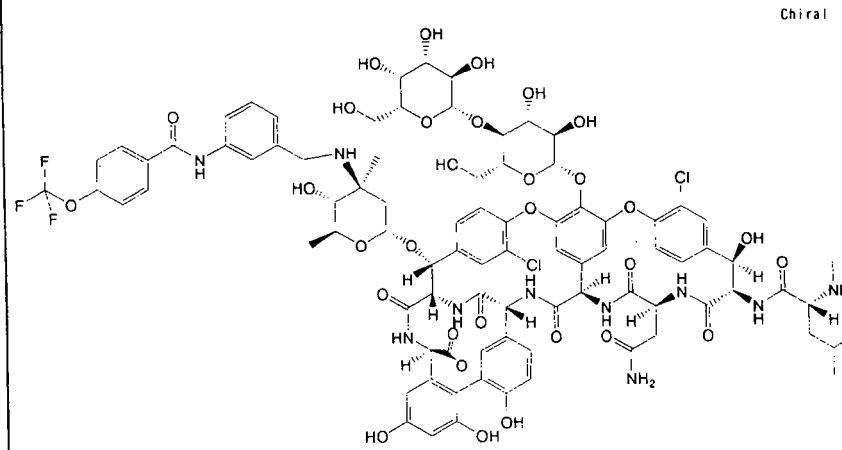
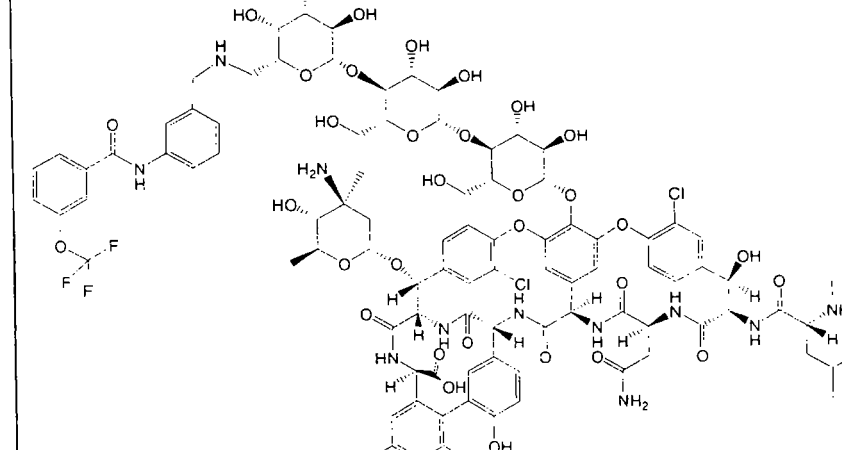
[0100]

[Table 12]

Example	Structure	Mass Spectrometry	Elementary analysis
4	Chiral	[M+1]⁺ =1938	Calculated value for C₉₄H₁₀₅Cl₁₂N₁₁O₃₀ · 3.3HCl · 14H₂O C: 48.83%, H: 5.94%, N: 6.66%, Cl: 8.13% Measured value C: 48.59%, H: 5.74%, N: 6.90%, Cl: 8.09%
5	Chiral	[M+1]⁺ =1886	Calculated value for C₈₆H₉₅Cl₁₄N₁₁O₂₉ · 3.4HCl · 13.6H₂O C: 45.39%, H: 5.65%, N: 6.77%, Cl: 11.53% Measured value C: 45.33%, H: 5.24%, N: 6.84%, Cl: 11.45%
6	Chiral	[M+1]⁺ =1902	Calculated value for C₈₇H₉₆Cl₁₂F₃N₁₁O₃₀ · 3HCl · 12.9H₂O C: 46.54%, H: 5.60%, N: 6.86%, Cl: 7.89%, F: 2.54% Measured value C: 46.45%, H: 5.24%, N: 6.96%, Cl: 7.85%, F: 2.48%

[0101]

[Table 13]

Example	Structure	Mass Spectrometry	Elementary analysis
7	 Chiral	[M+1] ⁺ =1929	Calculated value for C₈₉H₁₀₁C₁₂F₃N₁₂O₂₉ · 3.4HCl · 15.9H₂O C: 45.66%, H: 5.86%, N: 7.18%, Cl: 8.18%, F: 2.43% Measured value C: 45.69%, H: 5.72%, N: 7.27%, Cl: 8.21%, F: 2.26%
8	 Chiral	[M+1] ⁺ =1903	Calculated value for C₈₇H₉₅C₁₂F₃N₁₀O₃₁ · 2.4HCl · 16H₂O C: 45.82%, H: 5.72%, N: 6.14%, Cl: 6.84%, F: 2.50% Measured value C: 45.85%, H: 5.64%, N: 6.00%, Cl: 6.91%, F: 2.48%
9	 Chiral	[M+1] ⁺ =2064	Calculated value for C₉₃H₁₀₆C₁₂F₃N₁₁O₃₅ · 3.4HCl · 18.4H₂O C: 44.30%, H: 5.84%, N: 6.11%, Cl: 7.59%, F: 2.26% Measured value C: 44.27%, H: 5.72%, N: 6.14%, Cl: 7.53%, F: 2.33%

[0102]

[Table 14]

Example	Structure	Mass Spectrometry	Elementary analysis
10	Chiral	[M+]⁺ =1903	Calculated value for C₈₆H₉₅Cl₁₂F₃N₁₂O₃₀ · 12.4H₂O · 4.1HCl: C: 45.35%, H: 5.48%, N: 7.38%, Cl: 9.50%, F: 2.50% Measured value C: 45.33%, H: 5.45%, N: 7.46%, Cl: 9.57%, F: 2.63%
11	Chiral	[M+]⁺ =1934	Calculated value for C₈₆H₉₆Cl₁₂F₃N₁₃O₃₁ · 12.8H₂O · 3.6HCl: C: 44.96%, H: 5.49%, N: 7.93%, Cl: 8.64%, F: 2.48% Measured value C: 44.78%, H: 5.33%, N: 8.33%, Cl: 8.67%, F: 2.82%
12	Chiral	[M+]⁺ =1827	Calculated value for C₈₁H₉₄Cl₁₄N₁₁O₂₈S · 11.2H₂O · 3.2HCl: C: 45.29%, H: 5.61%, N: 6.52%, Cl: 11.88%, S: 1.49% Measured value C: 45.29%, H: 5.59%, N: 6.65%, Cl: 11.83%, S: 1.51%

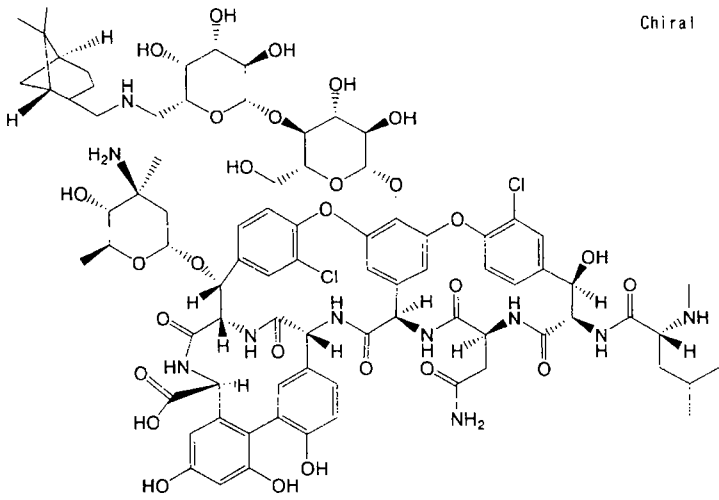
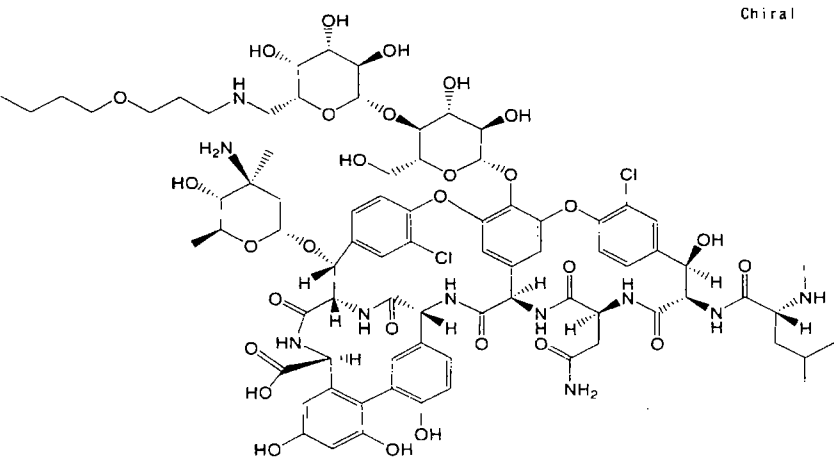
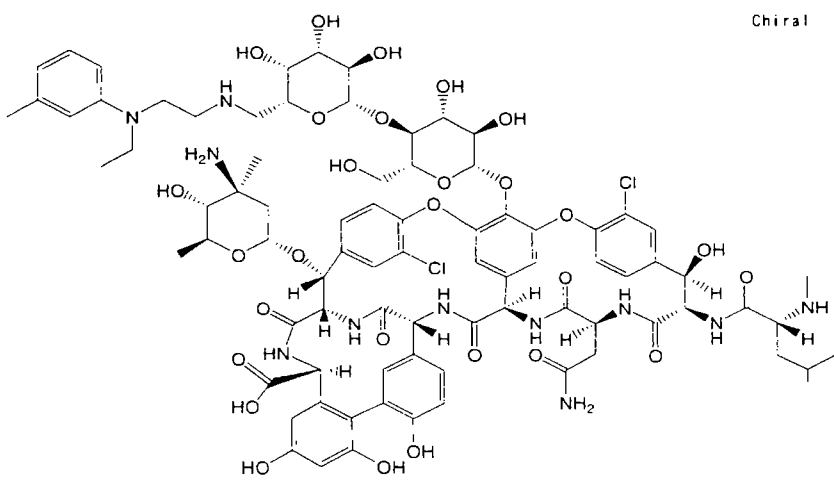
[0103]

[Table 15]

Example	Structure	Mass Spectrometry	Elementary analysis
13	Chiral	[M+1]⁺ = 1815	Calculated value for C₈₃H₉₃Cl₃N₁O₂₈ · 11.1H₂O · 2.8HCl C: 47.04%, H: 5.61%, N: 6.61%, Cl: 9.70%, S: 1.51% Measured value C: 46.99%, H: 5.57%, N: 6.70%, Cl: 9.68%, S: 1.35%
14	Chiral	[M+1]⁺ = 1789	Calculated value for C₈₆H₉₈Cl₂N₁O₂₈ C: 48.98%, H: 5.96%, N: 6.64%, Cl: 8.07% Measured value C: 48.97%, H: 5.81%, N: 6.71%, Cl: 8.01%
15	Chiral	[M+1]⁺ = 1783	Calculated value for C₈₄H₁₀₀Cl₂N₁O₂₉ · 10.7H₂O · 3.3HCl C: 48.09%, H: 5.99%, N: 6.68%, Cl: 8.96% Measured value C: 48.09%, H: 6.10%, N: 6.78%, Cl: 8.93%

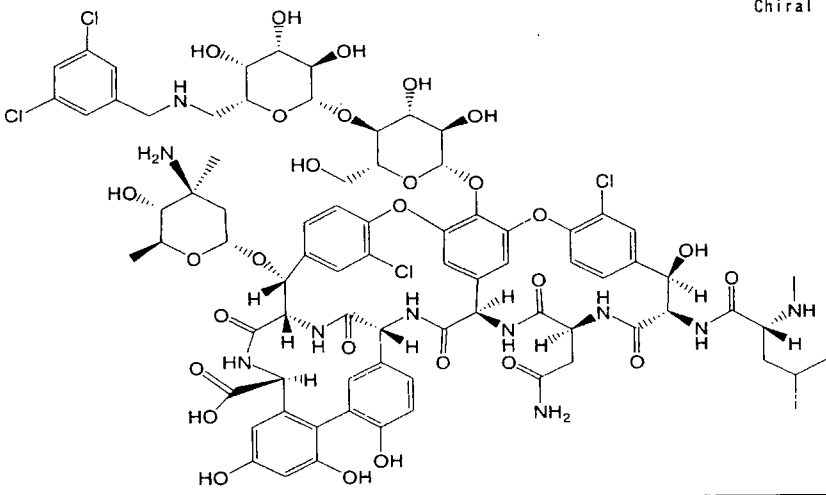
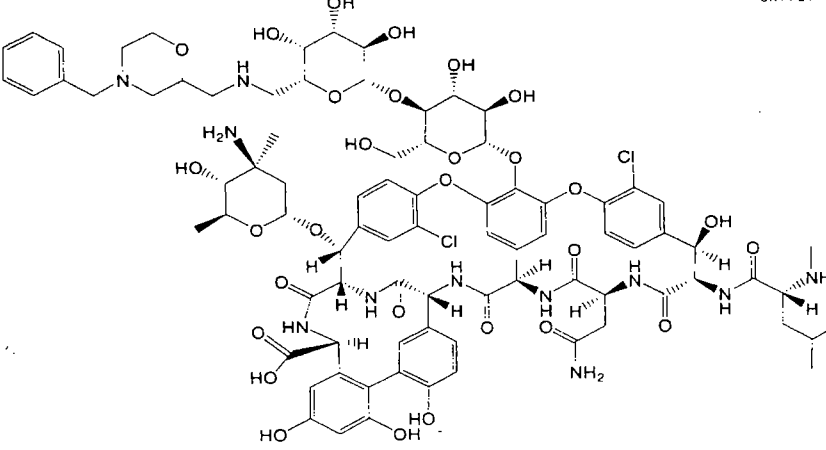
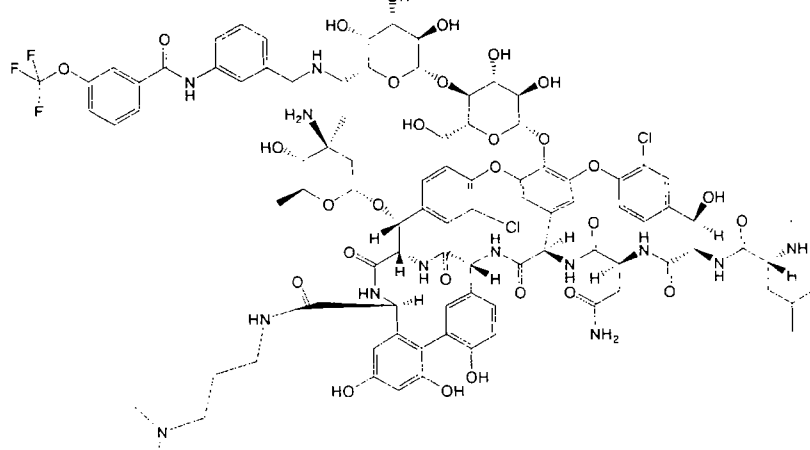
[0104]

[Table 16]

Example	Structure	Mass Spectrometry	Elementary analysis
16	Chiral 	[M+1] ⁺ =1745	Calculated value for C₈₂H₁₀₂Cl₁₂N₁₀O₂₈ · 12.1H₂O · 2.8HCl C: 47.65%, H: 6.29%, N: 6.78%, Cl: 8.23% Measured value C: 47.63%, H: 6.17%, N: 6.90%, Cl: 8.21%
17	Chiral 	[M+1] ⁺ =1723	Calculated value for C₇₉H₁₀₀Cl₁₂N₁₀O₂₉ · 11.9H₂O · 2.8HCl C: 46.49%, H: 6.25%, N: 6.86%, Cl: 8.34% Measured value C: 46.46%, H: 6.13%, N: 6.99%, Cl: 8.41%
18	Chiral 	[M+1] ⁺ =1770	Calculated value for C₈₃H₁₀₁Cl₁₂N₁₀O₂₈ · 11.9H₂O · 3.4HCl C: 47.25%, H: 6.12%, N: 7.30%, Cl: 9.07% Measured value C: 47.22%, H: 6.07%, N: 7.44%, Cl: 9.03%

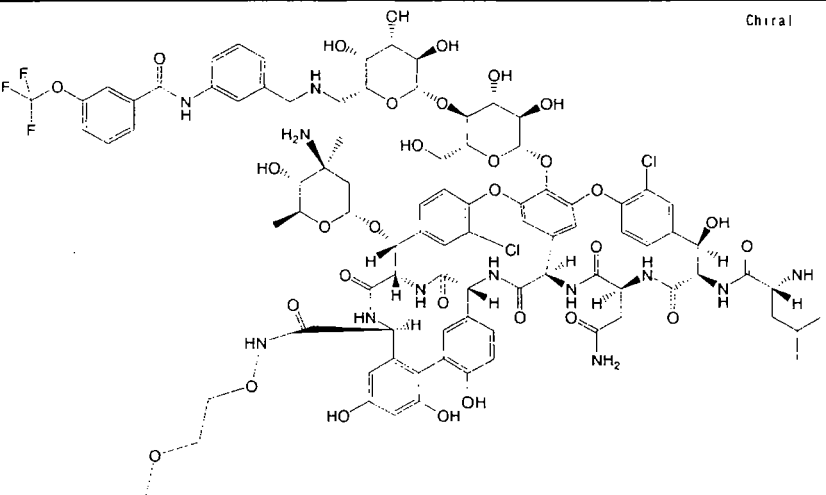
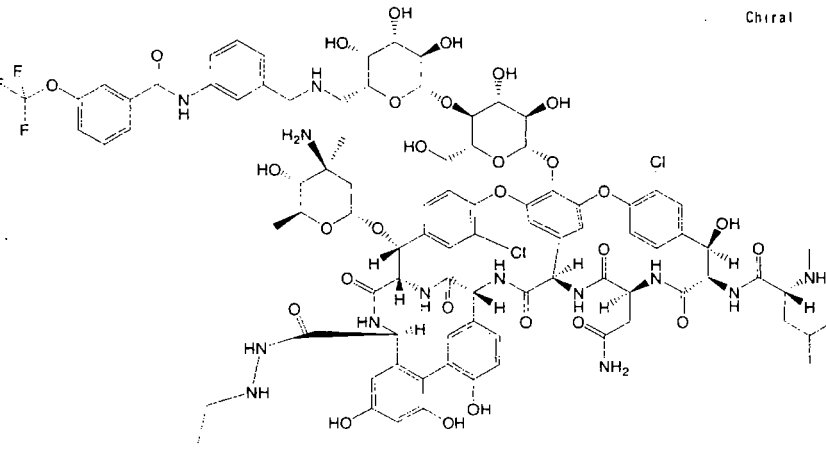
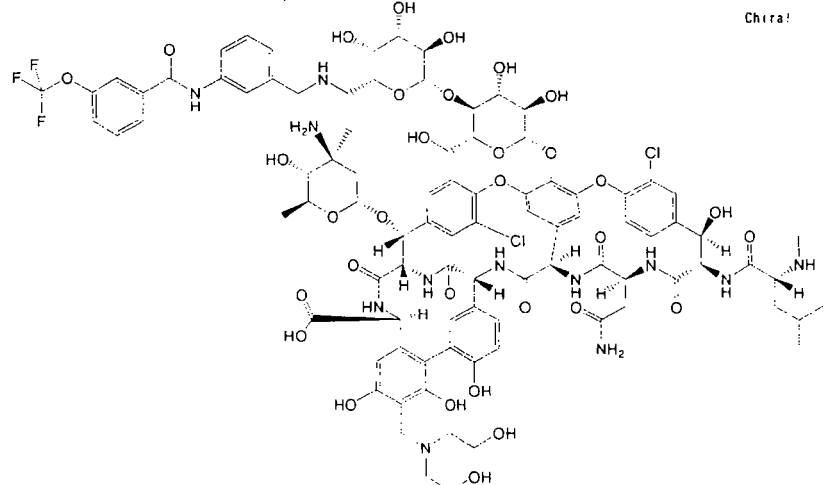
[0105]

[Table 17]

Example	Structure	Mass spectrometry	Elementary analysis
19	Chiral 	[M+1] =1767	Calculated value for C₇₉H₉₀Cl₄N₁ O₀₂₈ · 9.8H₂O · 3.9HCl C: 45.44%. H: 5.48%. N: 6.71%. Cl: 13.41% Measured value C: 45.12%. H: 5.52%. N: 6.89%. Cl: 13.41%
20	Chiral 	[M+1] =1798	Calculated value for C₈₄H₁₀₁Cl₂N₁ O₁₀₂₉ · 12.9H₂O · 4.2HCl C: 46.17%. H: 6.04%. N: 7.05%. Cl: 10.06% Measured value C: 46.15%. H: 5.99%. N: 7.15%. Cl: 10.00%
21	Chiral 	[M+1] =1986	Calculated value for C₉₂H₁₀₈Cl₂F₁ O_{3N13029} · 10.8H₂O · 4HCl C: 47.46%. H: 5.78%. N: 7.82%. Cl: 9.14%. F: 2.15% Measured value C: 47.46%. H: 5.75%. N: 7.87%. Cl: 9.18%. F: 2.37%

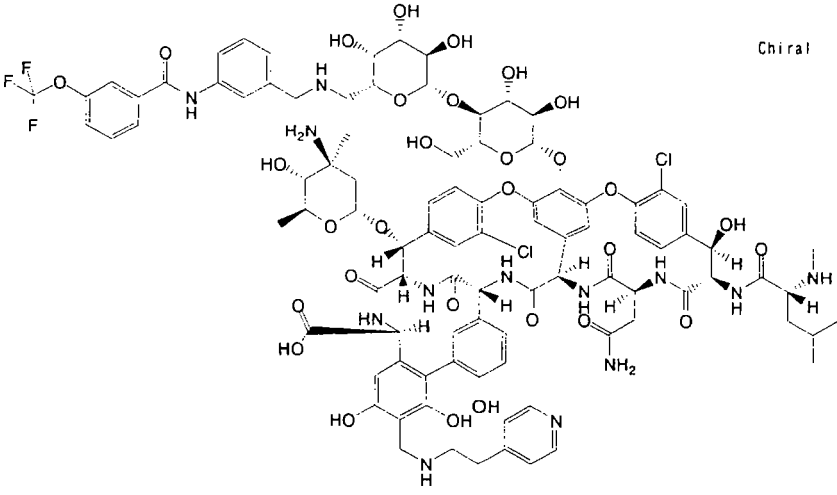
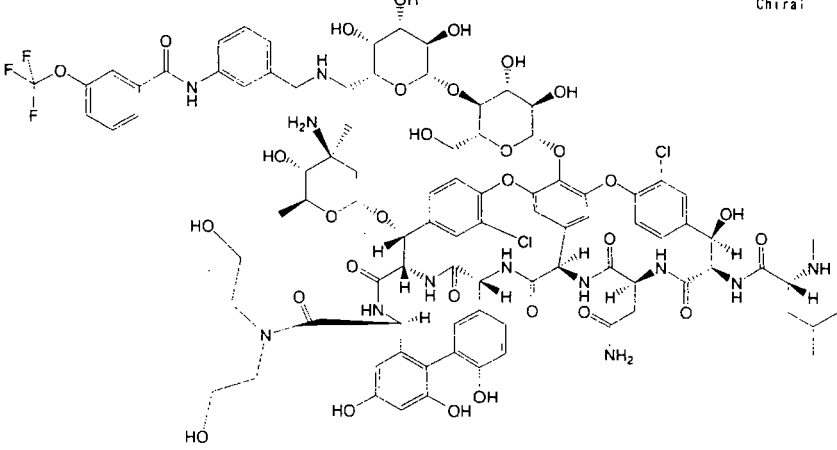
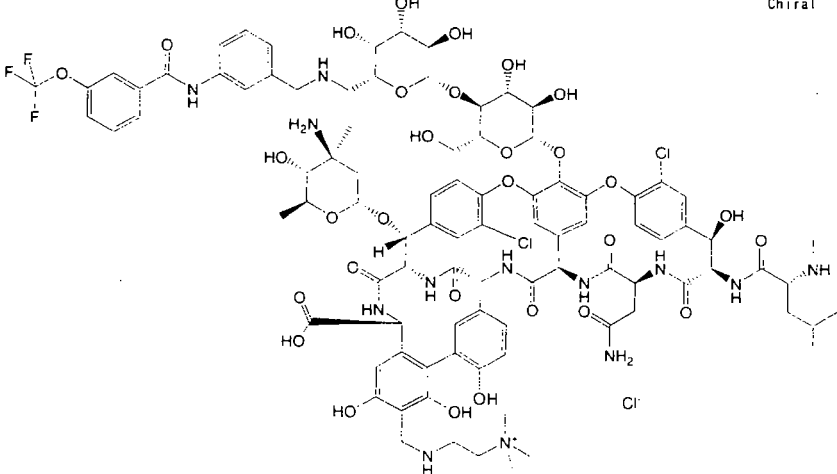
[0106]

[Table 18]

Example	Structure	Mass Spectrometry	Elementary analysis
22	 Chiral	$[M+1]^+$ =1975	Calculated value for $C_{90}H_{103}Cl_{12}F_3N_{12}O_{31}$ $10.9H_{2}O \cdot 3HCl$ C: 47.36%, H: 5.64%, N: 7.36%, Cl: 7.77%, F: 2.50% Measured value C: 47.37%, H: 5.58%, N: 7.37%, Cl: 7.80%, F: 2.42%
23	 Chiral	$[M+1]^+$ =1944	Calculated value for $C_{89}H_{102}Cl_{12}F_3N_{12}O_{29}$ $11.7H_{2}O \cdot 3.3HCl$ C: 46.95%, H: 5.70%, N: 8.00%, Cl: 8.25%, F: 2.50% Measured value C: 46.93%, H: 5.54%, N: 8.03%, Cl: 8.31%, F: 2.45%
24	 Chiral	$[M+1]^+$ =2019	Calculated value for $C_{92}H_{107}Cl_{12}F_3N_{12}O_{32}$ $13.9H_{2}O \cdot 3.5HCl$ C: 46.06%, H: 5.81%, N: 7.01%, Cl: 8.13%, F: 2.38% Measured value C: 46.04%, H: 5.73%, N: 7.14%, Cl: 8.08%, F: 2.30%

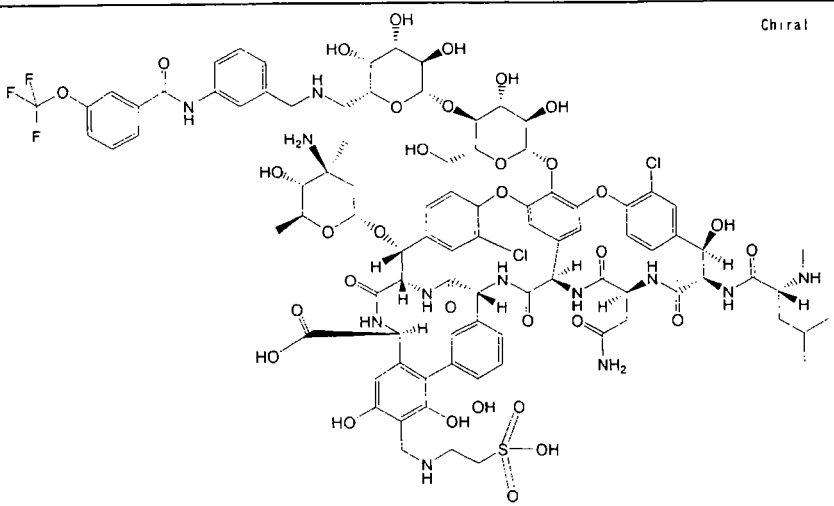
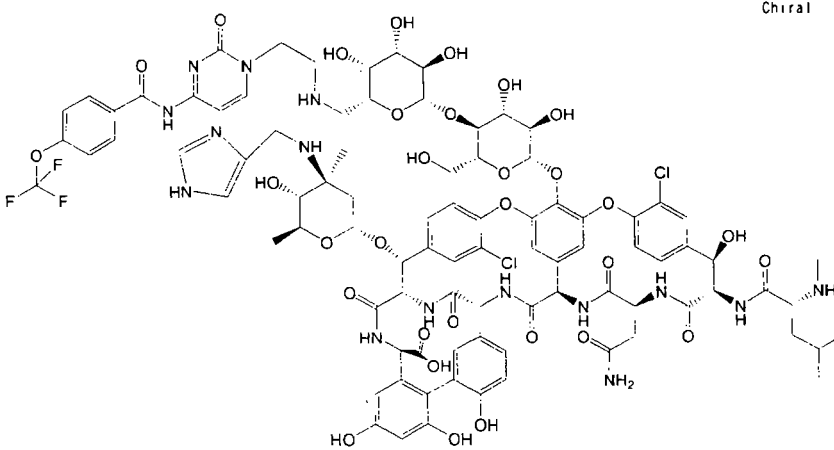
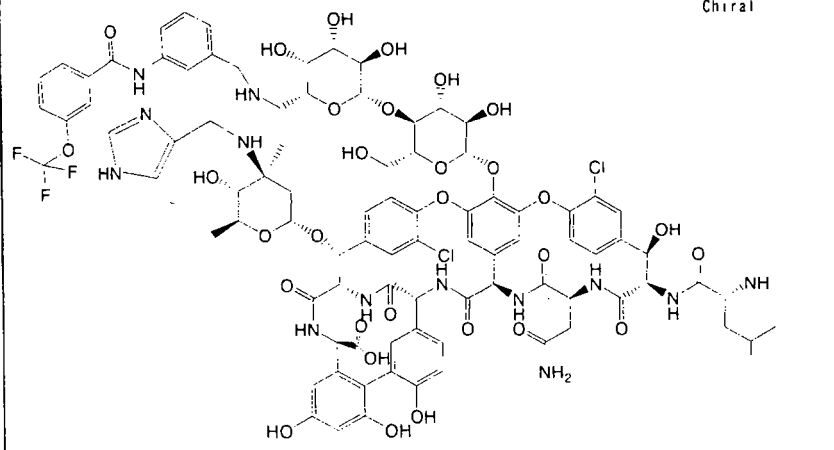
[0107]

[Table 19]

Example	Structure	MW [M+1]	Elementary analysis
25	 Chiral	[M+1] =2036	Calculated value for C₉₅H₁₀₆Cl₂F 3N₁₃O₃₀ · 14.4H₂O · 4.3HCl C: 46.5%. H: 5.71%. N: 7.42%. Cl: 9.10%. F: 2.32% Measured value C: 46.44%. H: 5.55%. N: 7.48%. Cl: 9.06%. F: 2.26%
26	 Chiral	[M+1] =1989	Calculated value for C₉₁H₁₀₅Cl₂F 3N₁₂O₃₁ · 11.9H₂O · 2.7HCl C: 47.45%. H: 5.75%. N: 7.30%. Cl: 7.23%. F: 2.47% Measured value C: 47.44%. H: 5.74%. N: 7.44%. Cl: 7.25%. F: 2.28%
27	 Chiral	M= C ₁ +Cl [C] =2017	Calculated value for C₉₃H₁₁₁Cl₂F 3N₁₃O₃₀ · Cl · 13.9H₂O · 3.6HCl C: 45.85%. H: 5.89%. N: 7.17%. Cl: 9.61%. F: 2.34% Measured value C: 45.84%. H: 5.53%. N: 7.43%. Cl: 9.55%. F: 2.77%

[0108]

[Table 20]

Example	Structure	Mass Spectrometry	Elementary analysis
28		[M+1] ⁺ =2039	Calculated value for C ₉₀ H ₁₀₃ Cl ₂ F ₃ N ₁₂ O ₃₃ S · 13.5H ₂ O · 2.7HCl C: 45.37%, H: 5.61%, N: 7.05%, Cl: 6.99%, F: 2.39%, S: 1.35% Measured value C: 45.33%, H: 5.47%, N: 7.02%, Cl: 6.99%, F: 2.37%, S: 1.36%
29		[M+1] ⁺ =2014	Calculated value for C ₉₀ H ₁₀₀ Cl ₂ F ₃ N ₁₅ O ₃₁ · 13.7H ₂ O · 4.2HCl C: 44.75%, H: 5.49%, N: 8.70%, Cl: 9.10%, F: 2.36% Measured value C: 44.70%, H: 5.55%, N: 8.89%, Cl: 9.10%, F: 2.25%
30		[M+1] ⁺ =1982	Calculated value for C ₉₁ H ₁₀₀ Cl ₂ F ₃ N ₁₃ O ₃₀ · 13.1H ₂ O · 3.7HCl C: 46.42%, H: 5.56%, N: 7.73%, Cl: 8.58%, F: 2.42% Measured value C: 46.41%, H: 5.58%, N: 7.81%, Cl: 8.54%, F: 2.29%

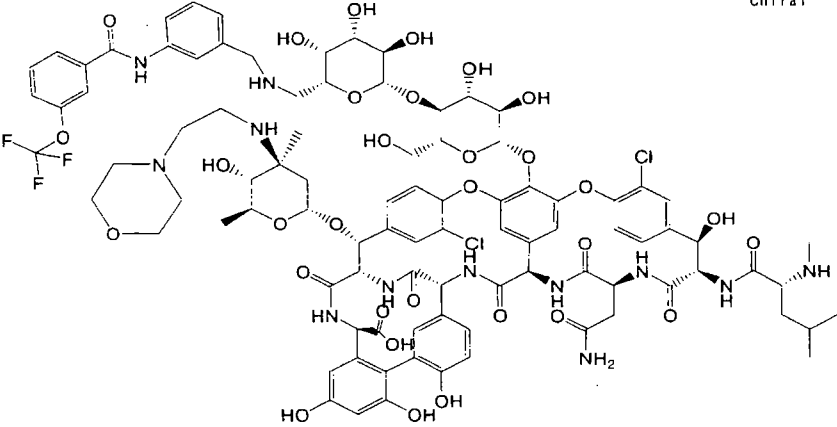
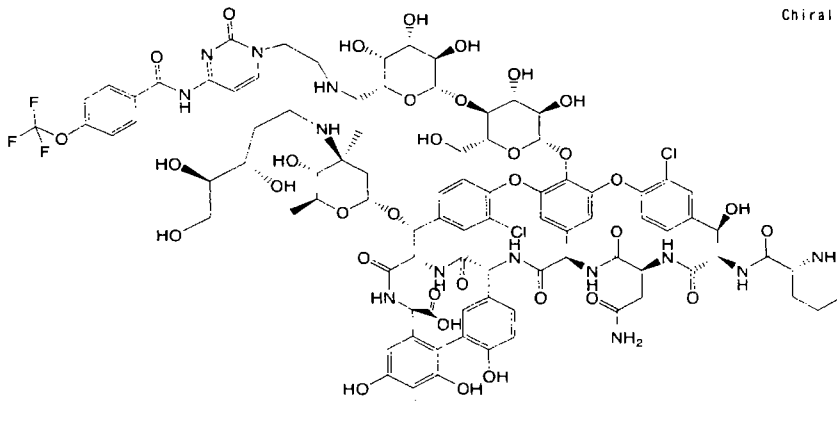
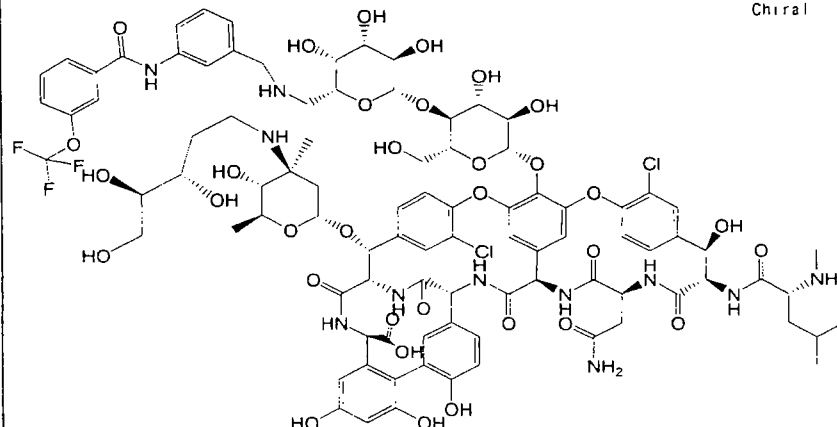
[0109]

[Table 21]

Example	Structure	Mass Spectrometry	Elementary analysis
31	Chiral	[M+1] =1993	Calculated value for C₉₃H₁₀₁Cl₁₂F₃N₁₂O₃₀ · 12.2H₂O · 3.2HCl C: 47.91% H: 5.56% N: 7.21% Cl: 7.91% F: 2.44% Measured value C: 47.92% H: 5.54% N: 7.33% Cl: 7.95% F: 2.31%
32	Chiral	[M+1] =2025	Calculated value for C₉₂H₁₀₁Cl₁₂F₃N₁₄O₃₁ · 13.2H₂O · 3.5HCl C: 46.19% H: 5.52% N: 8.20% Cl: 8.15% F: 2.38% Measured value C: 46.15% H: 5.53% N: 8.47% Cl: 8.15% F: 2.40%
33	Chiral	[M+1] =2047	Calculated value for C₉₂H₁₀₇Cl₁₂F₃N₁₄O₃₂ · 12.7H₂O · 3.7HCl C: 45.80% H: 5.69% N: 8.13% Cl: 8.38% F: 2.36% Measured value C: 45.77% H: 5.72% N: 8.27% Cl: 8.36% F: 2.33%

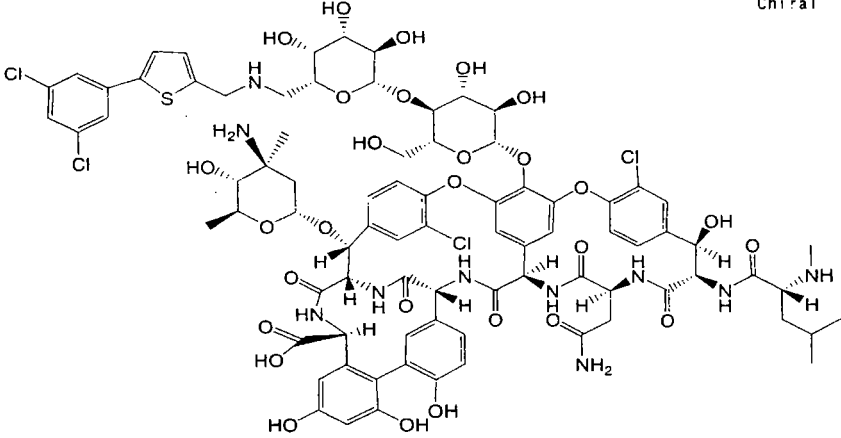
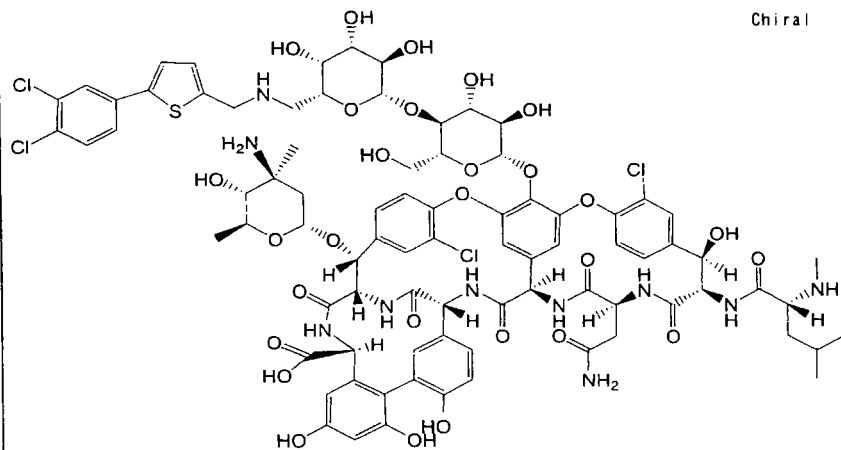
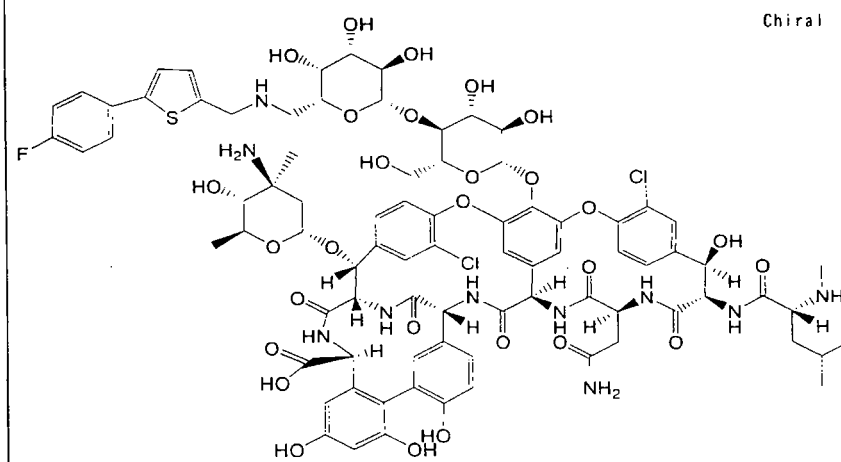
[0110]

[Table 22]

Example	Structure	M _n (MS) [M+1] ⁺	Elementary analysis
34	 Chiral	[M+1] ⁺ =2015	Calculated value for C₉₃H₁₀₇Cl₂F₃N₁₂O₃₁ · 11H₂O · 3.3HCl C: 47.83%, H: 5.71%, N: 7.20%, Cl: 8.05%, F: 2.44% Measured value C: 47.83%, H: 5.84%, N: 7.24%, Cl: 8.04%, F: 2.29%
35	 Chiral	[M+1] ⁺ =2052	Calculated value for C₉₁H₁₀₆Cl₂F₃N₁₃O₃₄ · 11.8H₂O · 2.9HCl C: 46.08%, H: 5.63%, N: 7.68%, Cl: 7.32%, F: 2.40% Measured value C: 45.91%, H: 5.58%, N: 8.58%, Cl: 7.30%, F: 2.50%
36	 Chiral	[M+1] ⁺ =2020	Calculated value for C₉₂H₁₀₆Cl₂F₃N₁₁O₃₃ · 11.8H₂O · 3.2HCl C: 47.00%, H: 5.69%, N: 6.55%, Cl: 7.84%, F: 2.42% Measured value C: 46.99%, H: 5.63%, N: 6.62%, Cl: 7.84%, F: 2.28%

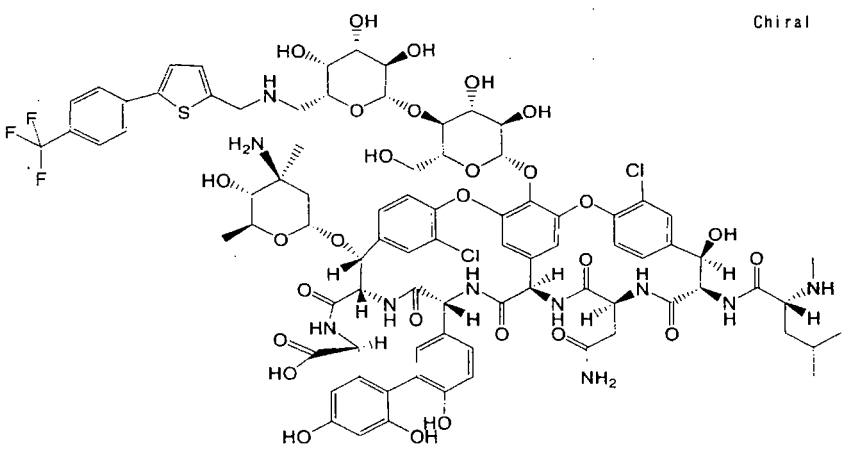
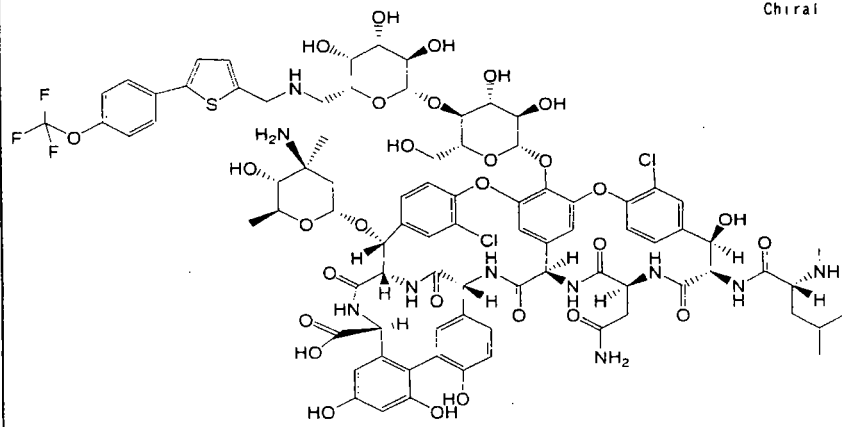
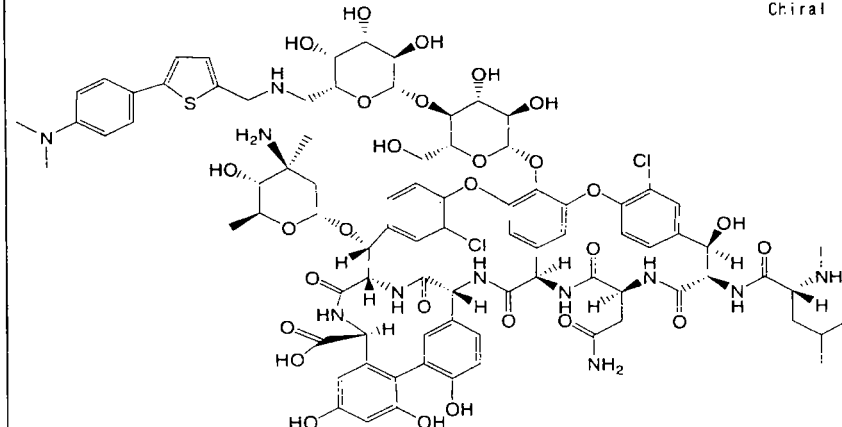
[0111]

[Table 23]

Example	Structure	Mass spectrometry	Elementary analysis
37	Chiral 	[M+1] =1849	Calculated value for C₈₃H₉₂Cl₄N₁ O₀₂₈S· 19.4H₂O· 4.1HCl C: 42.41%, H: 5.78%, N: 5.96%, Cl: 12.22%, S: 1.36% Measured value C: 42.38%, H: 5.35%, N: 6.15%, Cl: 12.24%, S: 1.30%
38	Chiral 	[M+1] =1849	Calculated value for C₈₃H₉₂Cl₄N₁ O₀₂₈S· 20.9H₂O· 4.4HCl C: 41.74%, H: 5.83%, N: 5.86%, Cl: 12.47%, S: 1.31% Measured value C: 41.68%, H: 5.26%, N: 6.04%, Cl: 12.36%, S: 1.23%
39	Chiral 	[M+1] =1799	Calculated value for C₈₃H₉₃Cl₂FN O₁₀₀₂₈S· 14.1H₂O· 3.6HCl C: 45.60%, H: 5.75%, N: 6.41%, Cl: 9.08%, F: 0.87%, S: 1.47% Measured value C: 45.61%, H: 5.82%, N: 6.49%, Cl: 9.06%, F: 0.94%, S: 1.44%

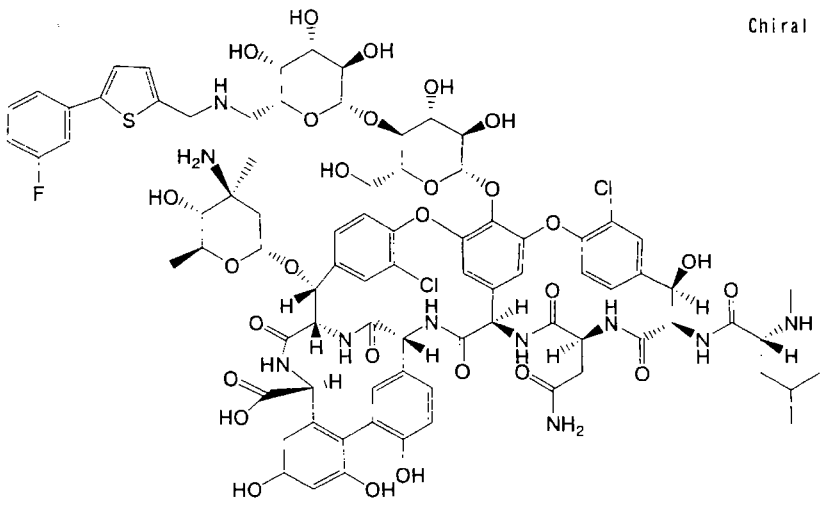
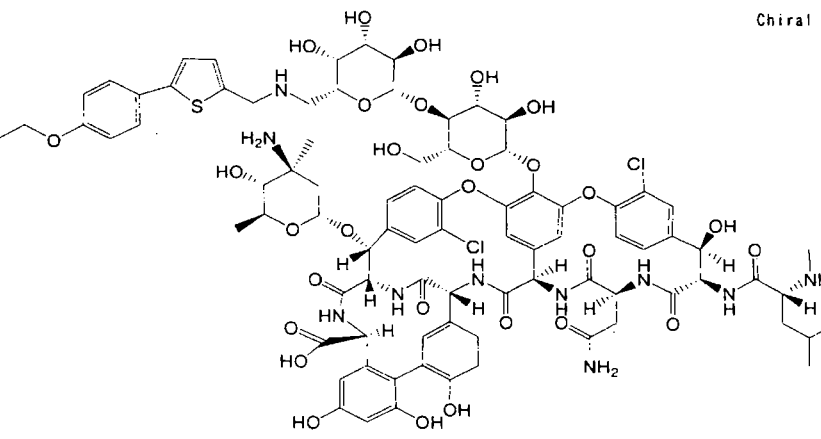
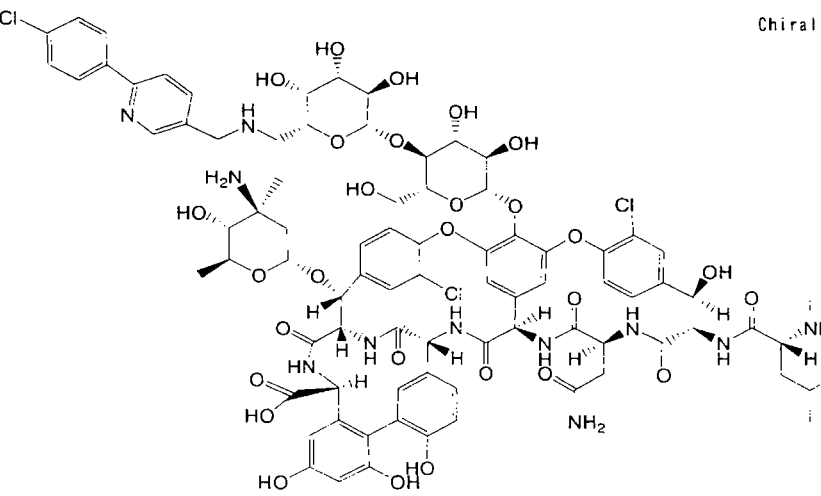
[0112]

[Table 24]

Example	Structure	Mass Spectrometry	Elementary analysis
40	 Chiral	[M+1] ⁺ =1849	Calculated value for C₈₄H₉₃Cl₂F₃N₁₀O₂₈·20.4H₂O·4.5HCl C: 42.35%, H: 5.85%, N: 5.88%, Cl: 9.67%, F: 2.39%, S: 1.35% Measured value C: 42.31%, H: 5.88%, N: 5.99%, Cl: 9.63%, F: 2.23%, S: 1.26%
41	 Chiral	[M+1] ⁺ =1865	Calculated value for C₈₄H₉₃Cl₂F₃N₁₀O₂₉·13.7H₂O·4.2HCl C: 44.51%, H: 5.54%, N: 6.18%, Cl: 9.70%, F: 2.51%, S: 1.41% Measured value C: 44.55%, H: 5.47%, N: 6.27%, Cl: 9.63%, F: 2.23%, S: 1.26%
42	 Chiral	[M+1] ⁺ =1824	Calculated value for C₈₅H₉₉Cl₂N₁₁O₂₈·15.2H₂O·5.1HCl C: 44.67%, H: 5.93%, N: 6.74%, Cl: 11.01%, S: 1.40% Measured value C: 44.58%, H: 5.43%, N: 6.90%, Cl: 11.00%, S: 1.30%

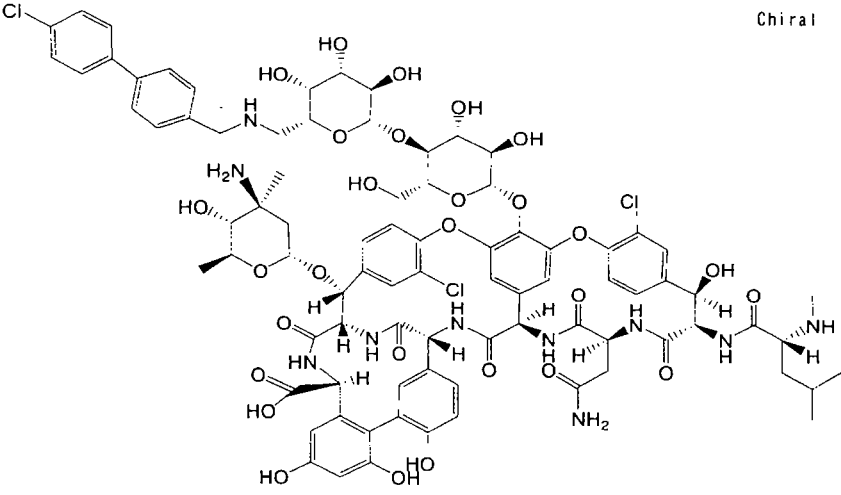
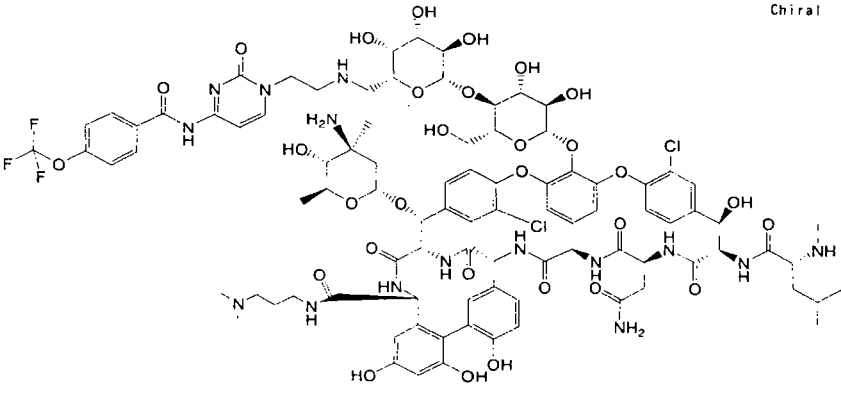
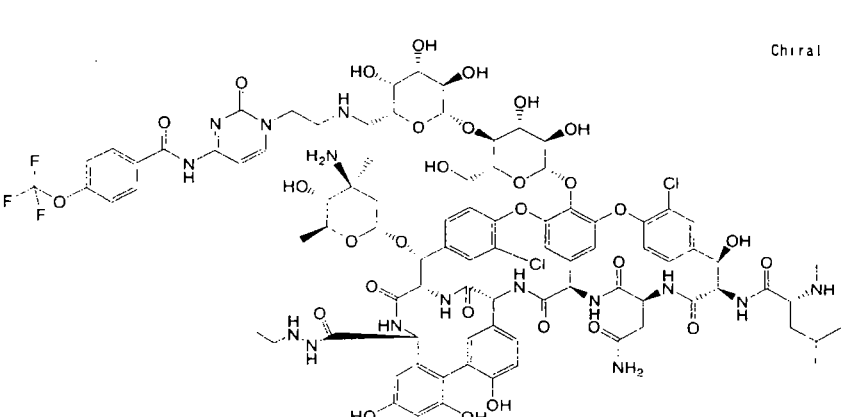
[0113]

[Table 25]

Example	Structure	Mass [M+1] ⁺	Elementary analysis
43	 Chiral	[M+1] ⁺ =1799	Calculated value for C₃₃H₉₃C₁₂FN 10028S· 10.7H₂O· 3.1HCl C: 47.33%, H: 5.62%, N: 6.65%, Cl: 9.58%, F: 0.90%, S: 1.52% Measured value C: 47.26%, H: 5.12%, N: 6.63%, Cl: 8.58%, F: 0.96%, S: 1.49%
44	 Chiral	[M+1] ⁺ =1825	Calculated value for C₃₅H₉₈C₁₂N₁ 0029S· 10H₂O· 3.2HCl C: 48.08%, H: 5.75%, N: 6.60%, Cl: 8.68%, S: 1.51% Measured value C: 48.03%, H: 5.68%, N: 6.81%, Cl: 8.64%, S: 1.42%
45	 Chiral	[M+1] ⁺ =1810	Calculated value for C₃₄H₉₄C₁₃N₁ 1028S· 13.3H₂O· 2.6HCl C: 47.00%, H: 5.79%, N: 7.18%, Cl: 9.25% Measured value C: 46.95%, H: 5.54%, N: 7.31%, Cl: 9.23%

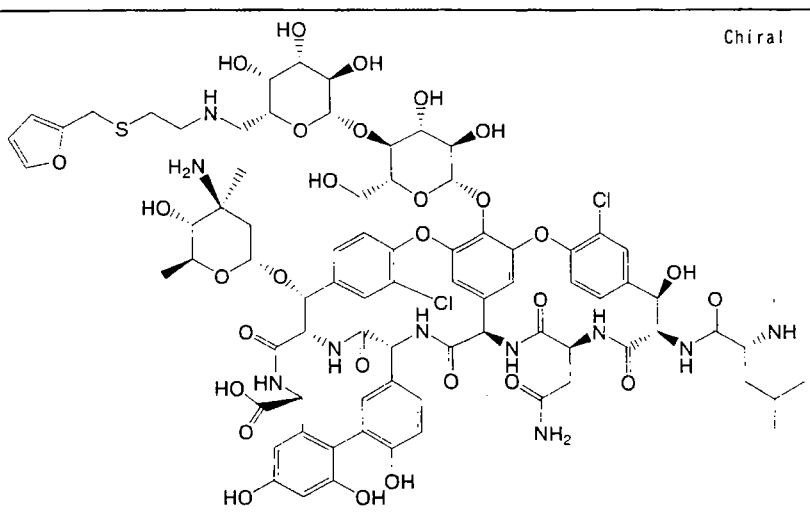
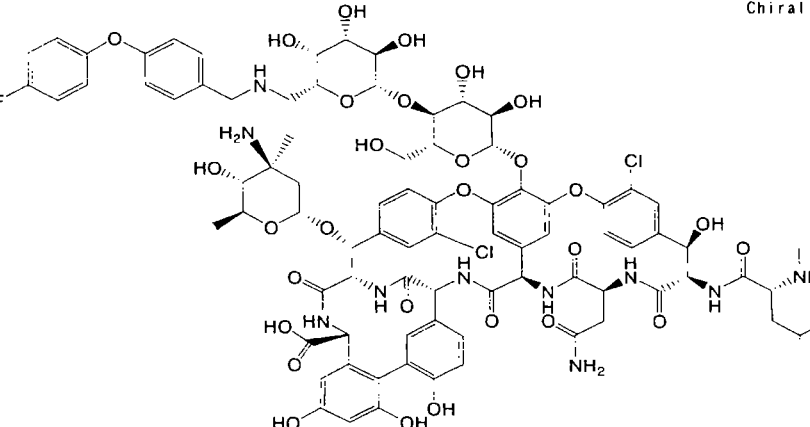
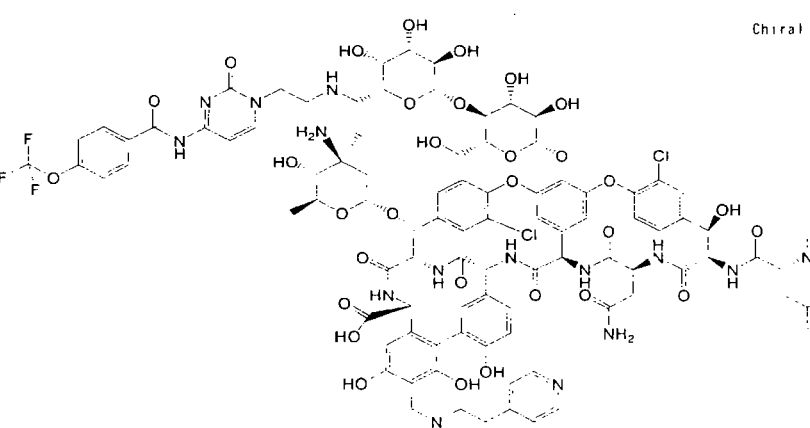
[0114]

[Table 26]

Example	Structure	Mass Spectrometry	Elementary analysis
46	 Chiral	[M+1] ⁺ =1809	Calculated value for C₈₅H₉₅Cl₃N₁₁O₂₈ · 12.4H₂O · 2.6HCl C: 47.95%, H: 5.79%, N: 6.58%, Cl: 9.32% Measured value C: 47.89%, H: 5.62%, N: 6.73%, Cl: 9.33%
47	 Chiral	[M+1] ⁺ =2018	Calculated value for C₉₁H₁₀₈Cl₂F₃N₁₁O₃₀ · 12.7H₂O · 4.3HCl C: 45.44%, H: 5.77%, N: 8.73%, Cl: 9.29%, F: 2.37% Measured value C: 45.42%, H: 5.55%, N: 8.77%, Cl: 9.32%, F: 2.30%
48	 Chiral	[M+1] ⁺ =1976	Calculated value for C₈₈H₁₀₂Cl₂F₃N₁₁O₃₀ · 10.2H₂O · 3.3HCl C: 46.32%, H: 5.55%, N: 9.21%, Cl: 8.23%, F: 2.50% Measured value C: 46.32%, H: 5.48%, N: 9.32%, Cl: 8.22%, F: 2.10%

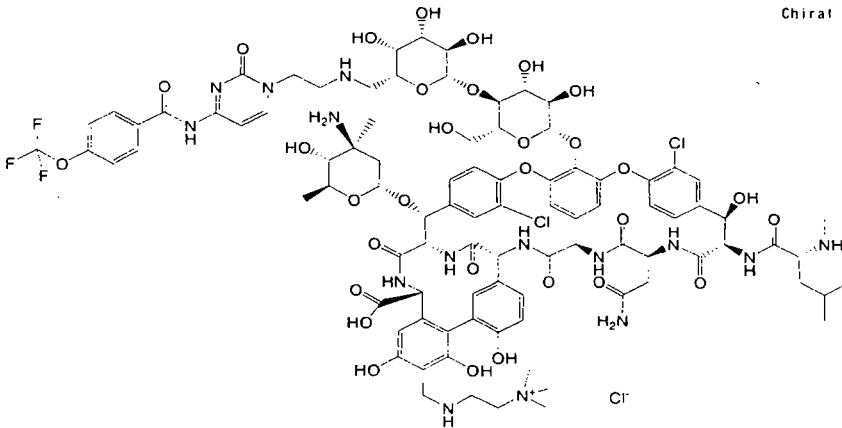
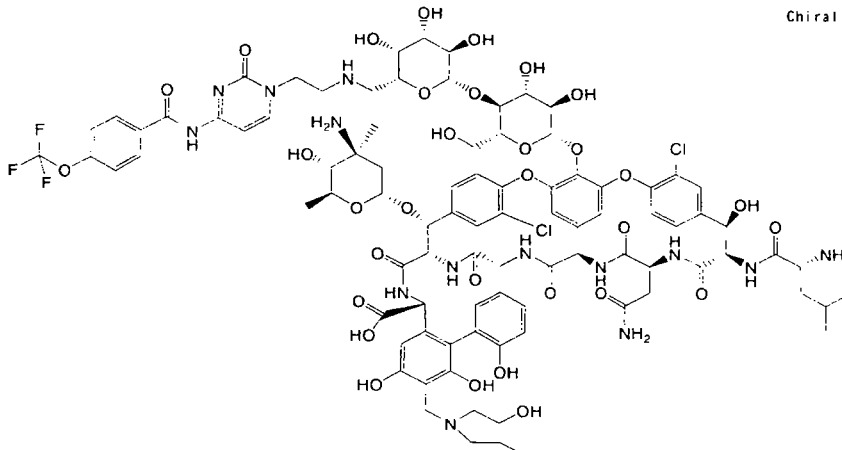
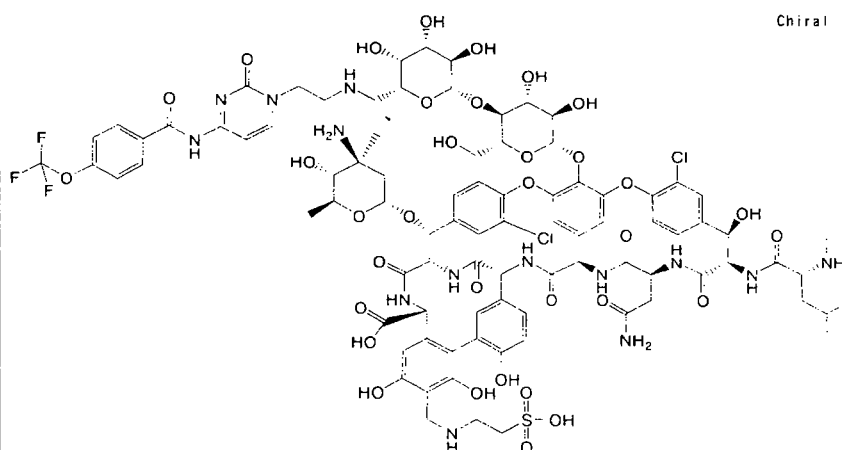
[0115]

[Table 27]

Example	Structure	M _w M ₀ (m ₀)	Elementary analysis
49	Chiral 	[M+1] =1749	Calculated value for C₇₉H₉₄Cl₂N₁ O₀₂₉S • 14.0H₂O • 3.1HCl C: 44.84%. H: 5.96%. N: 6.62%. Cl: 8.55%. S: 1.52%. Measured value C: 44.81%. H: 5.91%. N: 6.77%. Cl: 8.59%. S: 1.45%.
50	Chiral 	[M+1] =1809	Calculated value for C₈₅H₉₅Cl₂N₂ O₀₂₉S • 12.3H₂O • 3.1HCl C: 47.59%. H: 5.77%. N: 6.53%. Cl: 8.43%. F: 0.89%. Measured value C: 47.58%. H: 5.73%. N: 6.72%. Cl: 8.43%. F: 0.98%.
51	Chiral 	[M+1] =2068	Calculated value for C₉₄H₁₀₆Cl₂F N₀₃₁O • 16.2H₂O • 5.6HCl C: 44.09%. H: 5.66%. N: 8.19%. Cl: 10.50%. F: 2.22%. Measured value C: 43.97%. H: 5.67%. N: 8.32%. Cl: 10.45%. F: 2.13%.

[0116]

[Table 28]

Example	Structure	Mass Spectrometry	Elementary analysis
52	 Chiral	M= $[C+Cl]$ =2048	Calculated value for $C_{92}H_{111}Cl_{12}F_3N_{15}O_{31}$ Cl: 10.14% F: 2.26% Measured value C: 43.88% H: 5.86% N: 8.42% Cl: 10.11% F: 2.16%
53	 Chiral	M= $[M+1]$ =2051	Calculated value for $C_{91}H_{107}Cl_{12}F_3N_{14}O_{33}$ Cl: 8.55% F: 2.29% Measured value C: 43.79% H: 5.49% N: 8.52% Cl: 8.61% F: 2.10%
54	 Chiral	M= $[M+1]$ =2071	Calculated value for $C_{89}H_{103}Cl_{12}F_3N_{14}O_{34}S$ Cl: 6.82% F: 2.28% S: 1.28% Measured value C: 42.77% H: 5.59% N: 8.45% Cl: 6.75% F: 2.21% S: 1.23%

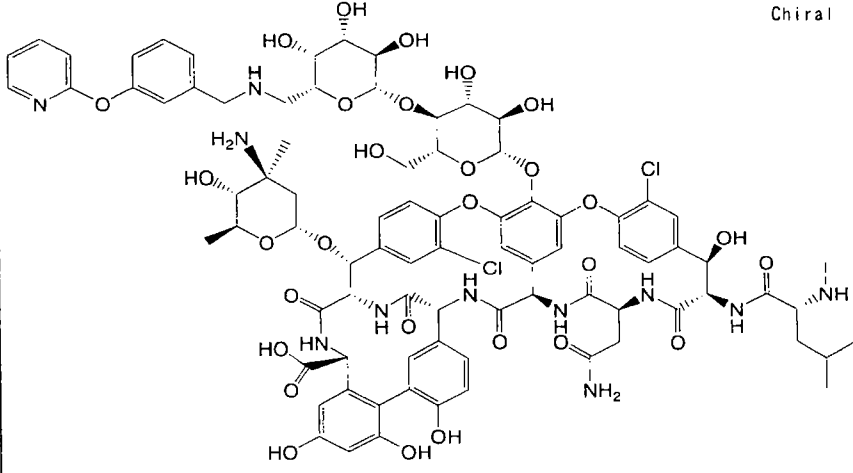
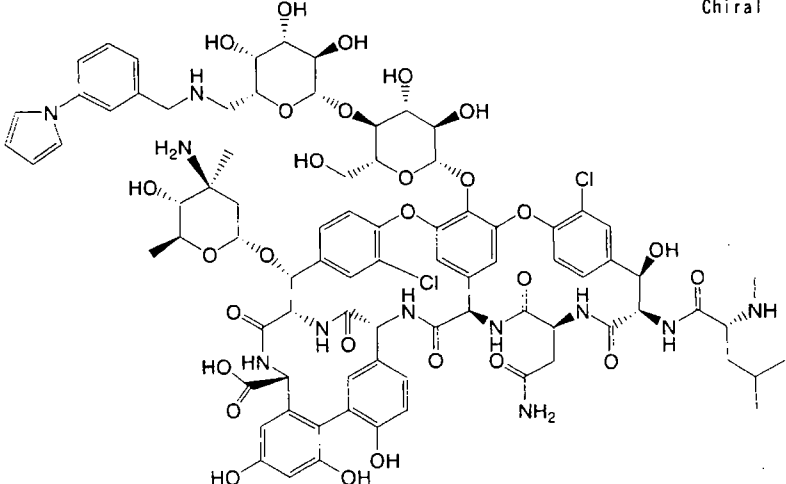
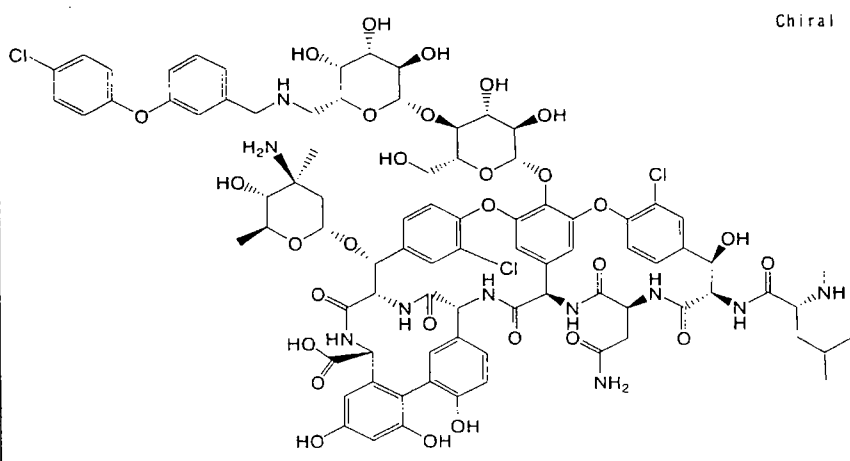
[0117]

[Table 29]

Example	Structure	Molecular Weight	Elementary analysis
55	Chiral	[M+1] ⁺ =1783	Calculated value for C₈₀H₉₁Cl₂F₃N₁₀O₂₉ · 16.0H₂O · 2.9HCl C: 44.11%, H: 5.83%, N: 6.43%, Cl: 7.97%, F: 2.62% Measured value C: 44.08%, H: 5.66%, N: 6.51%, Cl: 7.93%, F: 2.70%
56	Chiral	[M+1] ⁺ =1811	Calculated value for C₈₅H₁₀₄Cl₂N₁₂O₂₈ · 17.8H₂O · 4.5HCl C: 44.44%, H: 6.32%, N: 7.32%, Cl: 10.03% Measured value C: 44.43%, H: 6.23%, N: 7.43%, Cl: 9.98%
57	Chiral	[M+1] ⁺ =1806	Calculated value for C₈₂H₁₀₁Cl₂N₁₀O₂₈ · 15.0H₂O · 4.3HCl C: 44.07%, H: 6.10%, N: 6.89%, Cl: 9.99%, S: 1.43% Measured value C: 44.09%, H: 6.00%, N: 6.99%, Cl: 9.96%, S: 1.32%

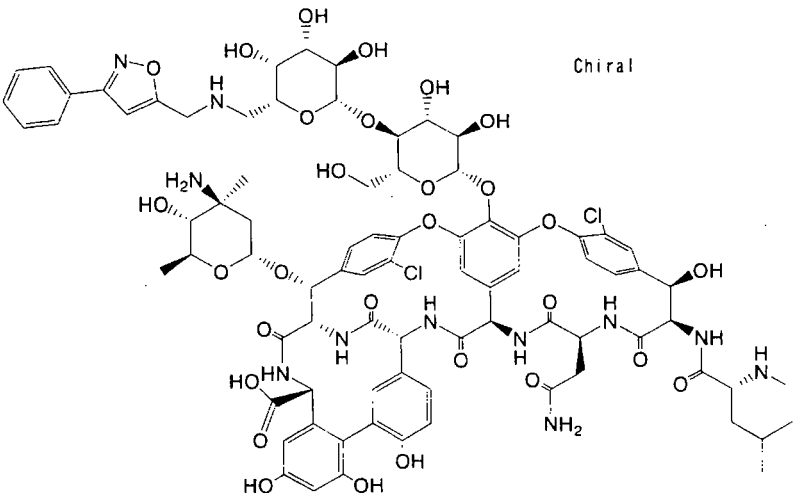
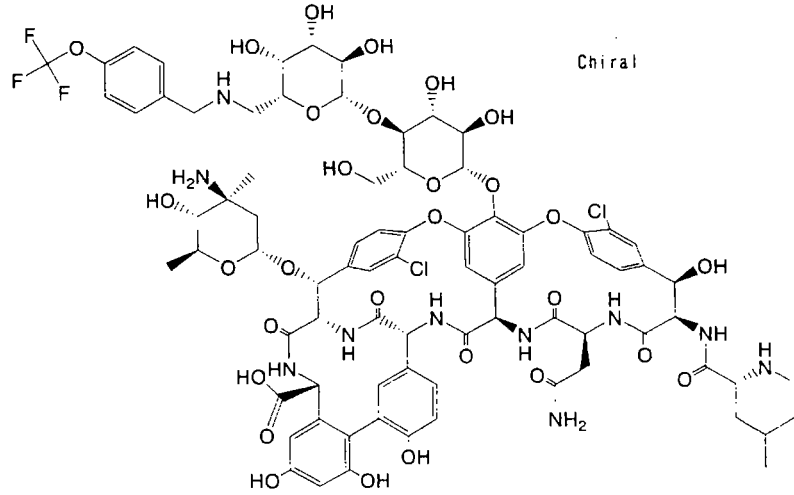
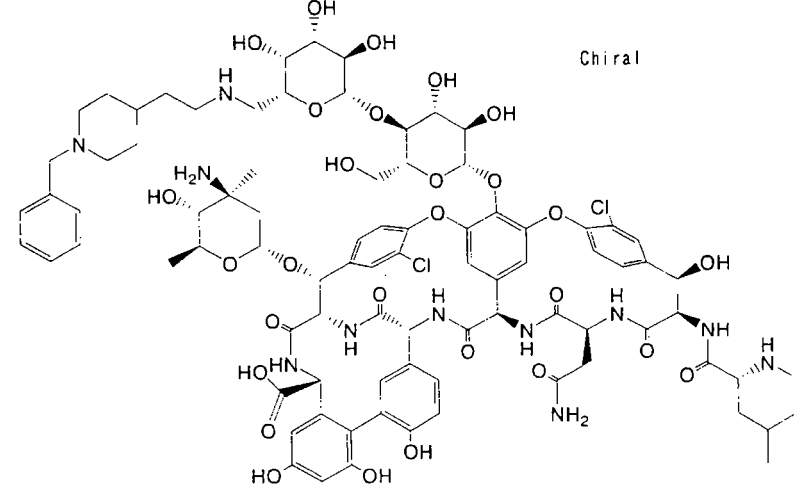
[0118]

[Table 30]

Example	Structure	M _n Spectrometry	Elementary analysis
58	Chiral 	[M+1] =1792	Calculated value for C₈₄H₉₅Cl₂N₁ 1029 • 14.1H₂O • 3.3HCl C: 46.54%. H: 5.88%. N: 7.11%. Cl: 8.67% Measured value C: 46.49%. H: 5.78%. N: 7.23%. Cl: 8.65%
59	Chiral 	[M+1] =1764	Calculated value for C₈₃H₉₅Cl₂N₁ 1028 • 15.1H₂O • 3.4HCl C: 46.12%. H: 6.00%. N: 7.13%. Cl: 8.86% Measured value C: 46.13%. H: 6.00%. N: 7.23%. Cl: 8.86%
60	Chiral 	[M+1] =1825	Calculated value for C₈₅H₉₅Cl₃N₁ 1029 • 14.0H₂O • 3.4HCl C: 46.34%. H: 5.78%. N: 6.36%. Cl: 10.30% Measured value C: 46.35%. H: 5.67%. N: 6.45%. Cl: 10.29%

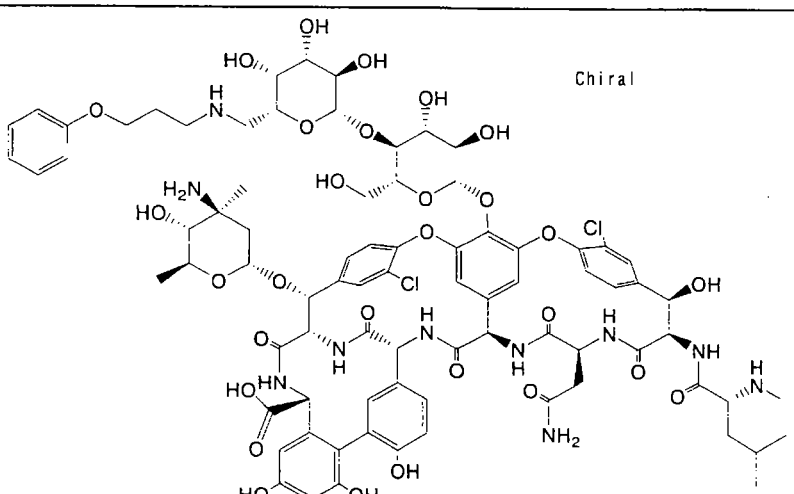
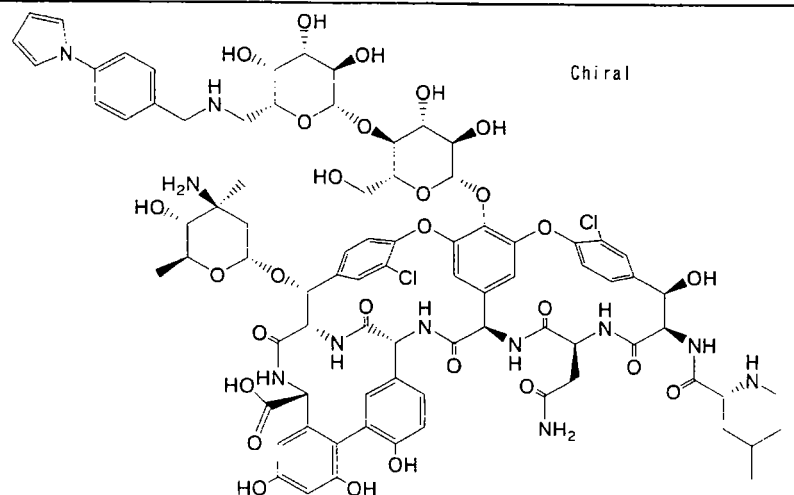
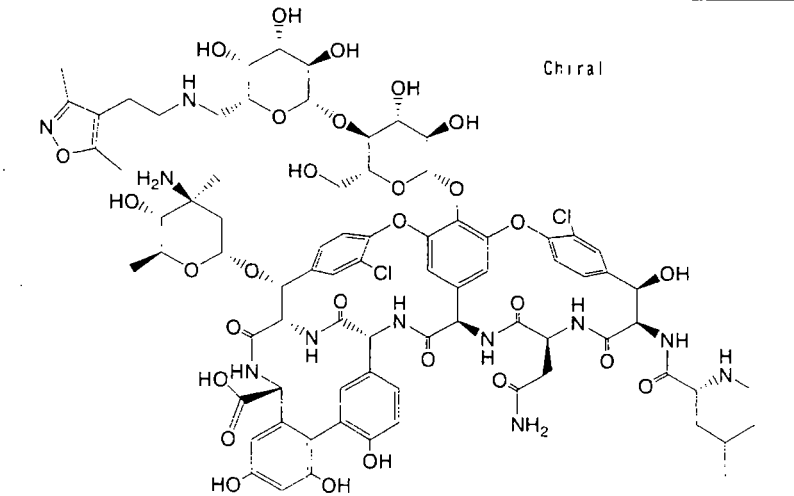
[0119]

[Table 31]

Example	Structure	Mass Spectrometry	Elementary analysis
61	 Chiral	[M+1] ⁺ =1766	Calculated value for C₈₂H₉₃Cl₂N₁O₂₉ · 3.2HCl · 10.9H₂O C: 47.34% H: 5.72% N: 7.41% Cl: 8.86% Measured value C: 47.32% H: 5.62% N: 7.60% Cl: 8.81%
62	 Chiral	[M+1] ⁺ =1783	Calculated value for C₈₀H₉₁Cl₂F₃N₁O₂₉ · 3.1HCl · 10.6H₂O C: 46.01% H: 5.56% N: 6.71% Cl: 8.66% F: 2.73% Measured value C: 45.94% H: 5.44% N: 6.87% Cl: 8.60% F: 3.35%
63	 Chiral	[M+1] ⁺ =1810	Calculated value for C₈₆H₁₀₅Cl₂N₁O₂₈ · 3.8HCl · 12.6H₂O C: 47.44% H: 6.20% N: 7.08% Cl: 9.44% Measured value C: 47.39% H: 6.03% N: 7.21% Cl: 9.34%

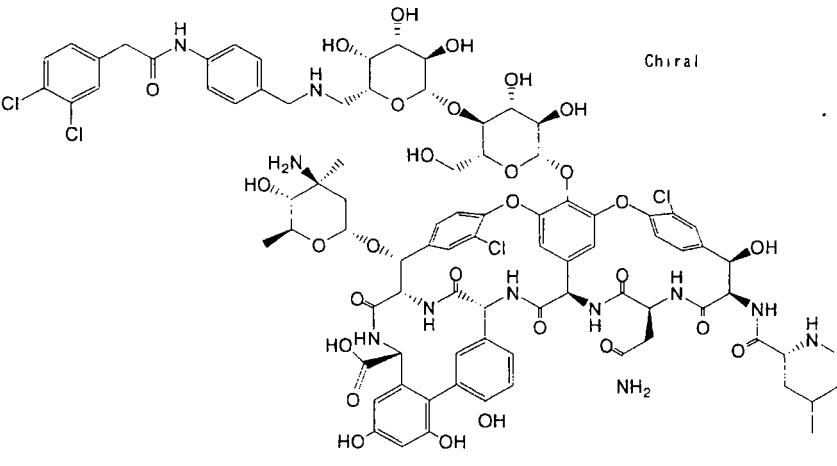
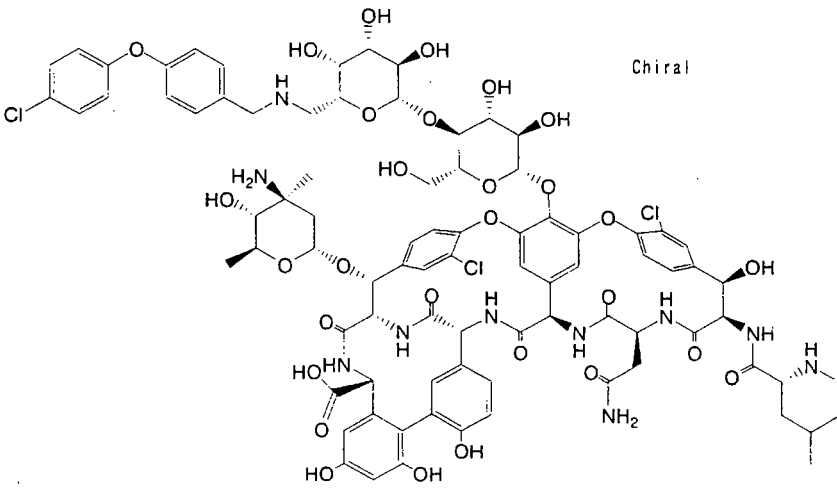
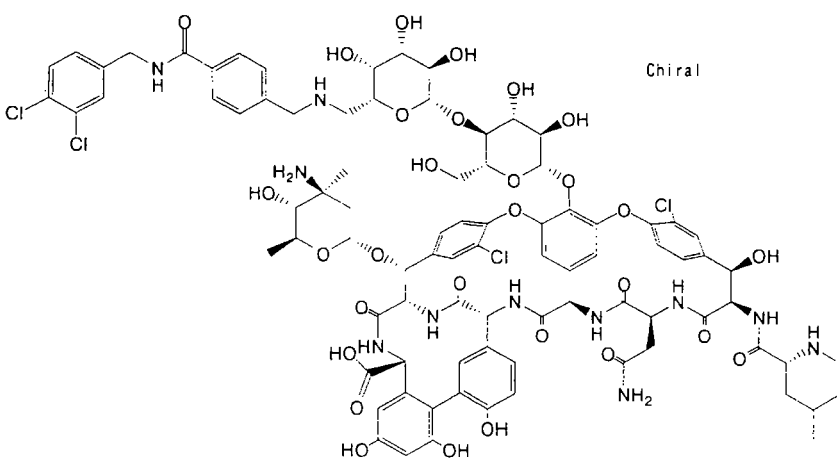
[0120]

[Table 32]

Example	Structure	Mass Structure	Elementary analysis
64	 Chiral	[M+1] =1743	Calculated value for C₈₁H₉₆Cl₂N₁ O₀₂₉ · 2.8HCl · 10.5H₂O C: 47.79% H: 5.93% N: 6.88% Cl: 8.36% Measured value C: 47.82% H: 5.83% N: 6.74% Cl: 8.30%
65	 Chiral	[M+1] =1764	Calculated value for C₈₃H₉₅Cl₂N₁ O₁₀₂₈ · 3.1HCl · 11.2H₂O C: 47.92% H: 5.84% N: 7.41% Cl: 8.69% Measured value C: 47.94% H: 5.85% N: 7.64% Cl: 8.66%
66	 Chiral	[M+1] =1732	Calculated value for C₇₉H₉₅Cl₂N₁ O₁₀₂₉ · 2.6HCl · 11.8H₂O C: 46.49% H: 5.99% N: 7.55% Cl: 7.99% Measured value C: 46.48% H: 5.93% N: 7.60% Cl: 7.99%

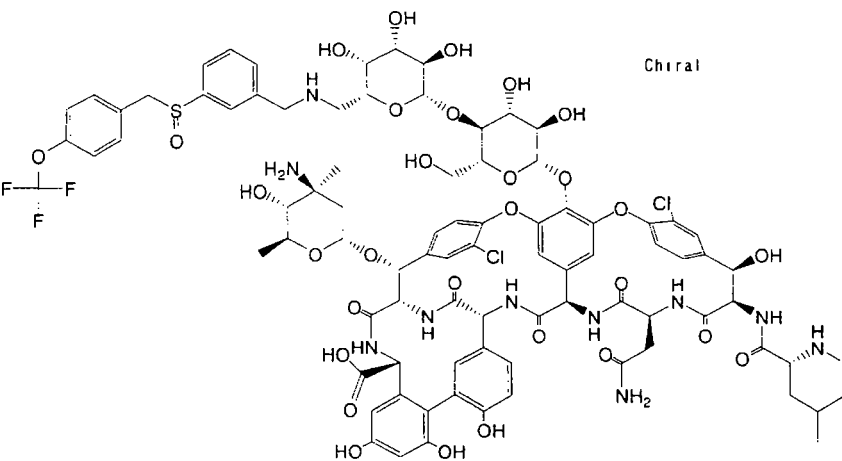
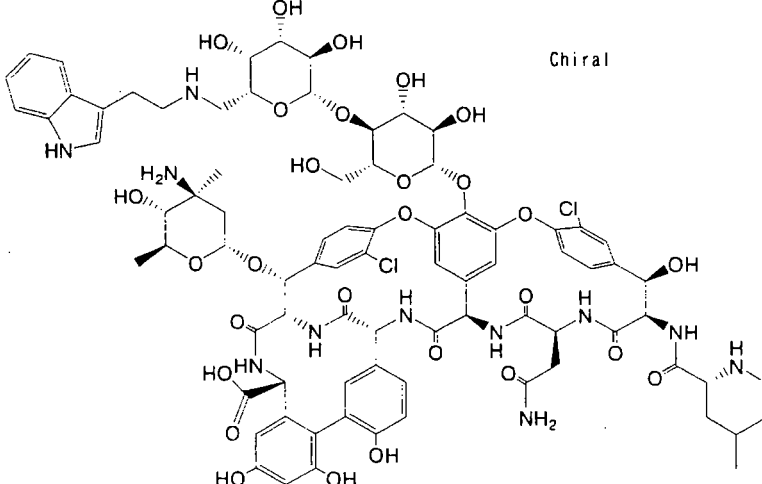
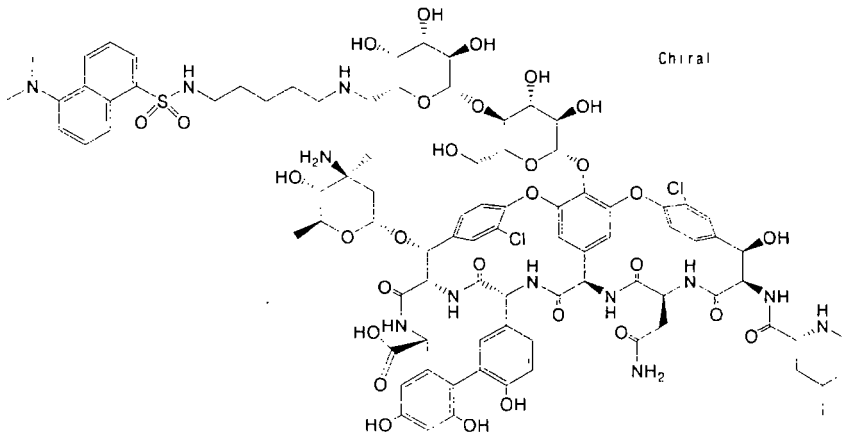
[0121]

[Table 33]

Exemplar	Structure	Mass [M+1] ⁺	Elementary analysis
67	 Chiral	[M+1] ⁺ =1900	Calculated value for C₈₇H₉₇Cl₄N₁ 1029 + 2.8HCl + 12.0H₂O C: 47.05% H: 5.62% N: 6.94% Cl: 10.86% Measured value C: 47.03% H: 5.57% N: 7.22% Cl: 10.79%
68	 Chiral	[M+1] ⁺ =1825	Calculated value for C₈₅H₉₅Cl₃N₁ 1009 + 2.7HCl + 12.3H₂O C: 47.55% H: 5.74% N: 6.52% Cl: 9.41% Measured value C: 47.51% H: 5.65% N: 6.59% Cl: 9.44%
69	 Chiral	[M+1] ⁺ =1900	Calculated value for C₈₇H₉₇Cl₄N₁ 1029 + 3.1HCl + 11.7H₂O C: 46.93% H: 5.59% N: 6.92% Cl: 11.31% Measured value C: 46.91% H: 5.51% N: 6.99% Cl: 11.28%

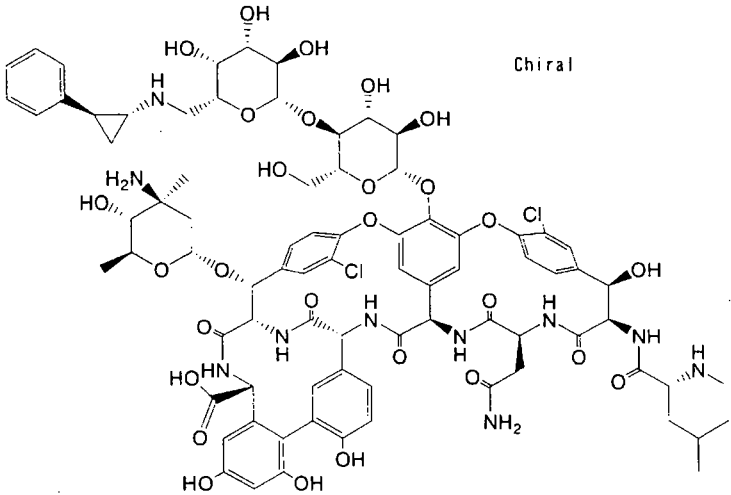
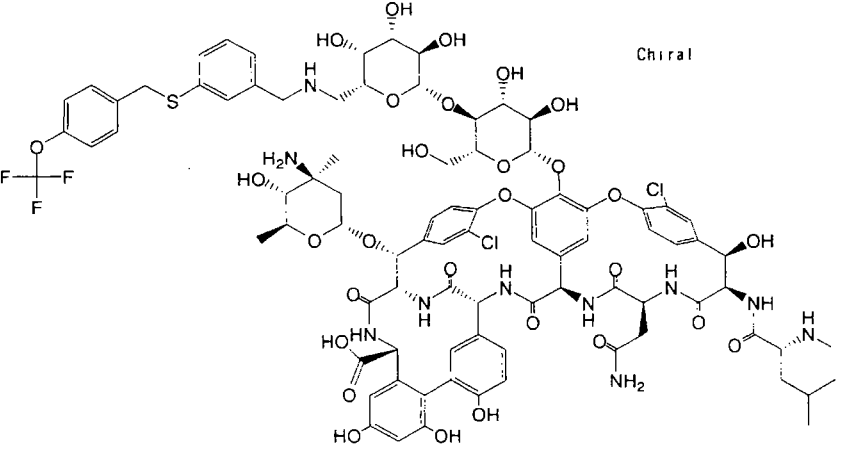
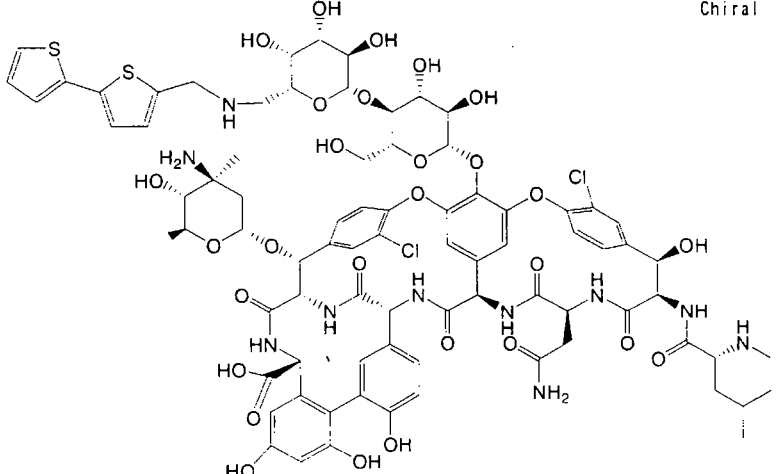
[0122]

[Table 34]

Exempl	Structure	Mass Spectrometry	Elementary analysis
70	 Chiral	[M+1] ⁺ =1921	Calculated value for C₈₇H₉₇Cl₂F₃N₁₀O₃₀S • 3.1HCl • 12.2H₂O C: 46.33%, H: 5.56%, N: 6.21%, Cl: 8.02%, F: 2.53%, S: 1.42% Measured value C: 46.34%, H: 5.47%, N: 6.29%, Cl: 7.96%, F: 2.39%, S: 1.38%
71	 Chiral	[M+1] ⁺ =1752	Calculated value for C₈₂H₉₅Cl₂N₁₁O₂₈ • 3.2HCl • 11.2H₂O C: 47.53%, H: 5.87%, N: 7.44%, Cl: 8.90% Measured value C: 47.50%, H: 5.95%, N: 7.56%, Cl: 8.84%
72	 Chiral	[M+1] ⁺ =1927	Calculated value for C₈₉H₁₀₈Cl₂N₁₂O₃₀S • 4.4HCl • 11.2H₂O C: 46.66%, H: 5.93%, N: 7.34%, Cl: 9.90%, S: 1.40% Measured value C: 46.61%, H: 6.00%, N: 7.59%, Cl: 9.93%, S: 2.07%

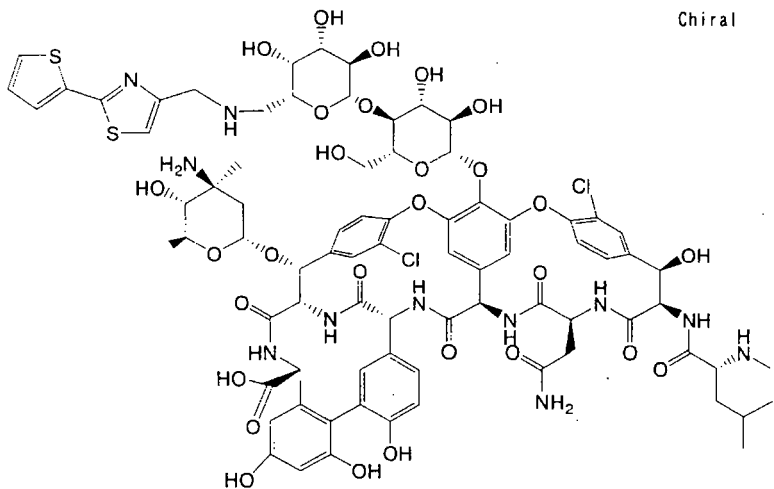
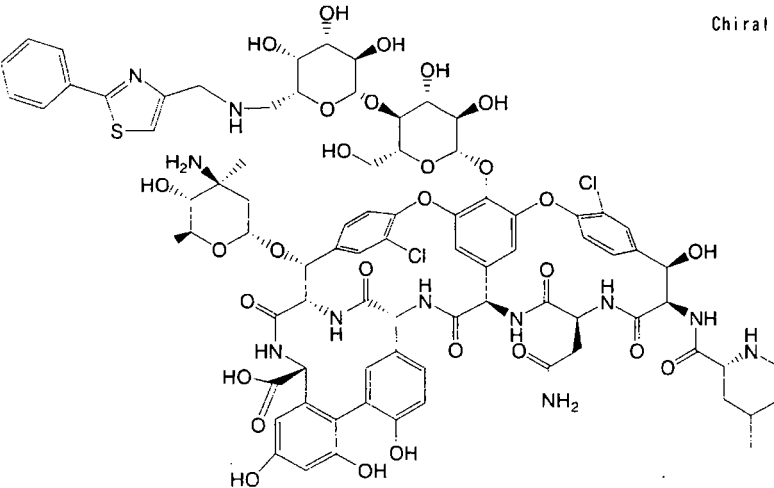
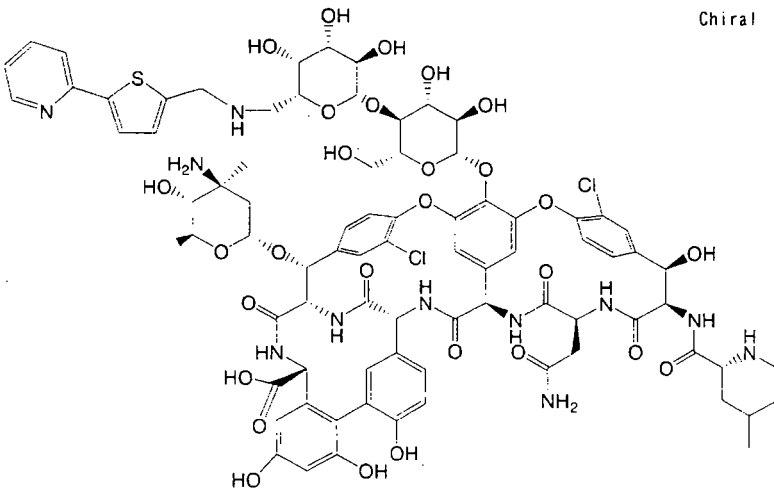
[0123]

[Table 35]

Example	Structure	Mass Spectrometry	Elementary analysis
73	 Chiral	[M+1]⁺ =1725	Calculated value for C₈₁H₉₄Cl₂N₁O₂₈ · 3.1HCl · 12.8H₂O C: 46.99%, H: 5.97%, N: 6.77%, Cl: 8.73% Measured value C: 46.97%, H: 5.90%, N: 6.88%, Cl: 8.79%
74	 Chiral	[M+1]⁺ =1905	Calculated value for C₈₇H₉₇Cl₂F₃N₁O₂₉ · 3.1HCl · 11.3H₂O C: 47.00%, H: 5.56%, N: 6.30%, Cl: 8.13%, F: 2.56%, S: 1.44% Measured value C: 47.05%, H: 5.49%, N: 6.33%, Cl: 8.06%, F: 2.46%, S: 1.37%
75	 Chiral	[M+1]⁺ =1787	Calculated value for C₈₁H₉₂Cl₂N₁O₂₈ · 12.8H₂O · 2.6HCl C: 46.02%, H: 5.73%, N: 6.63%, Cl: 7.71%, S: 3.03% Measured value C: 46.02%, H: 5.58%, N: 6.76%, Cl: 7.71%, S: 2.94%

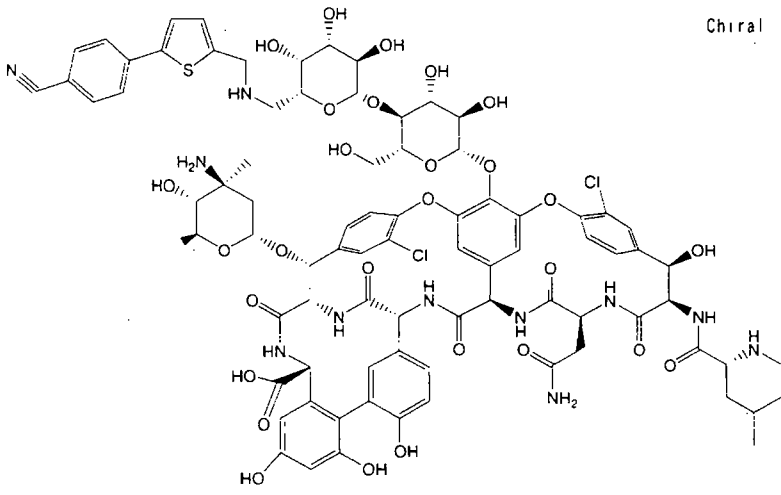
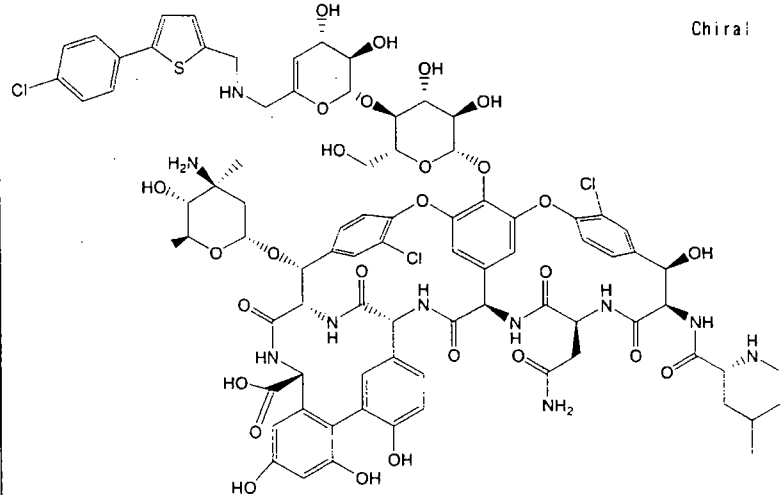
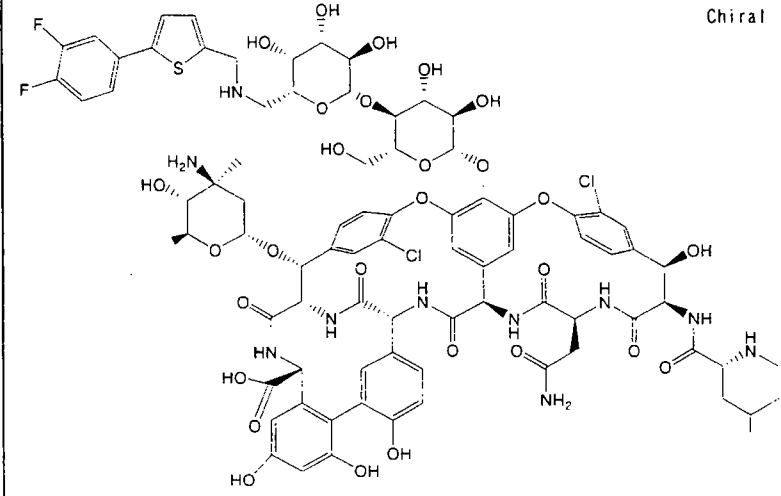
[0124]

[Table 36]

Example	Structure	Mass [M+1] ⁺	Elementary analysis
76	Chiral 	[M+1] ⁺ =1788	Calculated value for C₈₀H₉₁Cl₂N₁₁ O₂₈S₂· 12.1H₂O· 3.1HCl C: 45.31% H: 5.62% N: 7.27% Cl: 8.53% S: 3.02% Measured value C: 45.27% H: 5.35% N: 7.39% Cl: 8.47% S: 3.16%
77	Chiral 	[M+1] ⁺ =1782	Calculated value for C₈₂H₉₃Cl₂N₁₁ O₂₈S· 12.9H₂O· 2.3HCl C: 46.50% H: 5.79% N: 7.27% Cl: 8.03% S: 1.51% Measured value C: 46.48% H: 5.70% N: 7.40% Cl: 8.03% S: 1.48%
78	Chiral 	[M+1] ⁺ =1782	Calculated value for C₈₂H₉₃Cl₂N₁₁ O₂₈S· 14.3H₂O· 3.5HCl C: 45.41% H: 5.81% N: 7.10% Cl: 8.99% S: 1.48% Measured value C: 45.33% H: 5.60% N: 7.19% Cl: 9.01% S: 1.43%

[0125]

[Table 37]

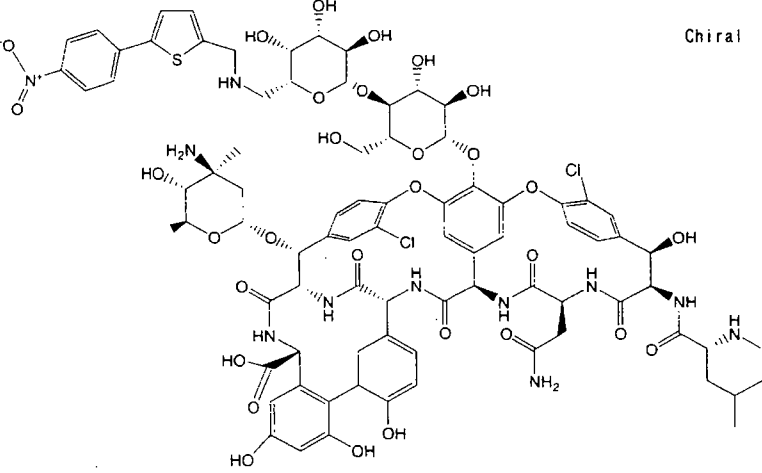
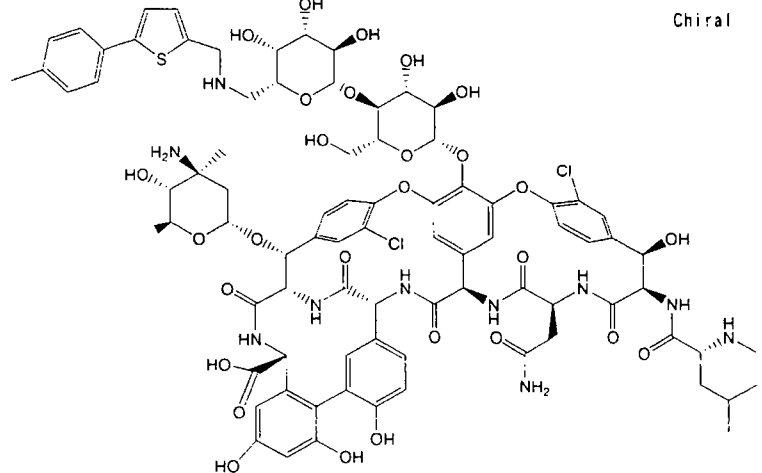
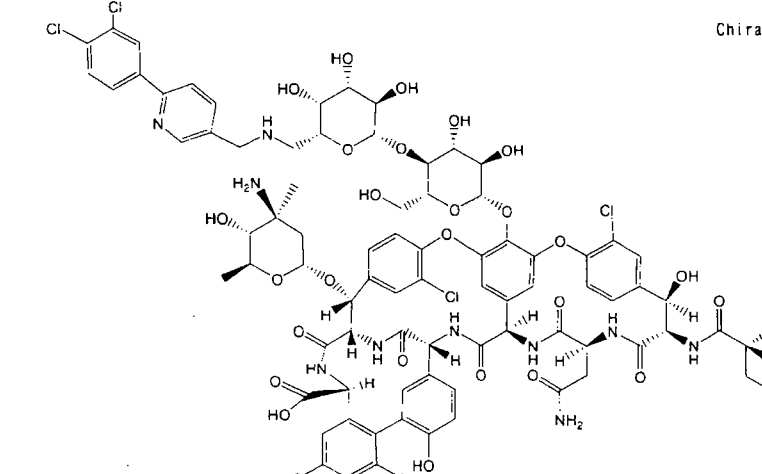
Example	Structure	Mass Spectrometry	Elementary analysis
79	Chiral 	$[M+1]^+$ =1806	Calculated value for C₈₄H₉₃C₁₂N₁O₂₈S· (H₂O) 12.4· (HCl) 2.3 C: 47.70%, H: 5.72%, N: 7.29%, Cl: 7.21%, S: 1.52% Measured value C: 47.71%, H: 5.59%, N: 7.35%, Cl: 7.23%, S: 1.37%
80	Chiral 	$[M+1]^+$ =1797	Calculated value for C₈₃H₉₁C₁₃N₁O₂₇S· (H₂O) 10· (HCl) 3.2 C: 47.56%, H: 5.49%, N: 6.68%, Cl: 10.49%, S: 1.53% Measured value C: 47.55%, H: 5.40%, N: 6.81%, Cl: 10.51%, S: 1.39%
81	Chiral 	$[M+1]^+$ =1817	Calculated value for C₈₃H₉₂C₁₂F₂N₁O₂₈S· (H₂O) 12· (HCl) 3.2 C: 46.33%, H: 5.58%, N: 6.51%, Cl: 8.57%, F: 1.77%, S: 1.49% Measured value C: 46.30%, H: 5.43%, N: 6.62%, Cl: 8.50%, F: 1.74%, S: 1.42%

[Table 38]

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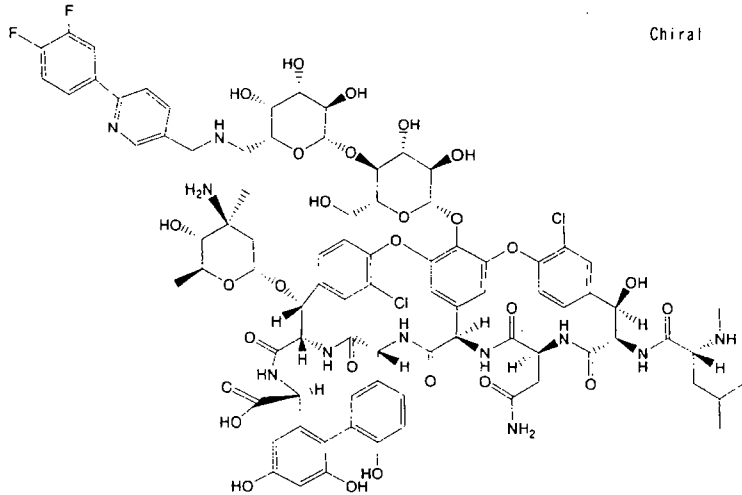
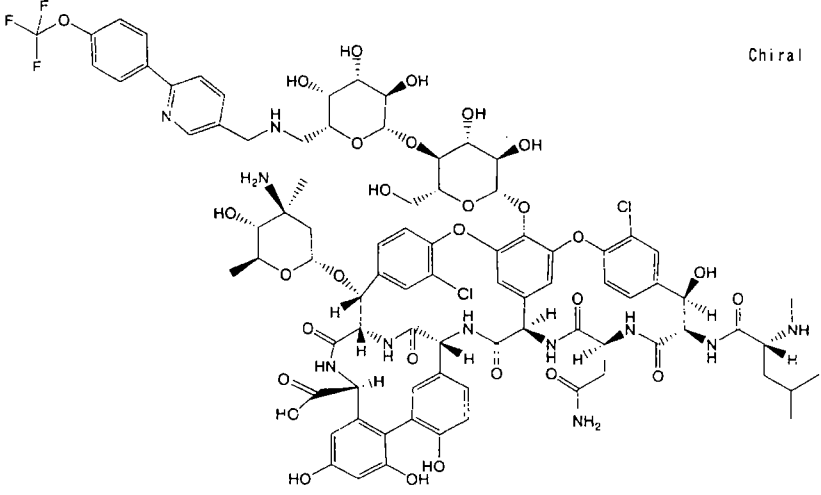
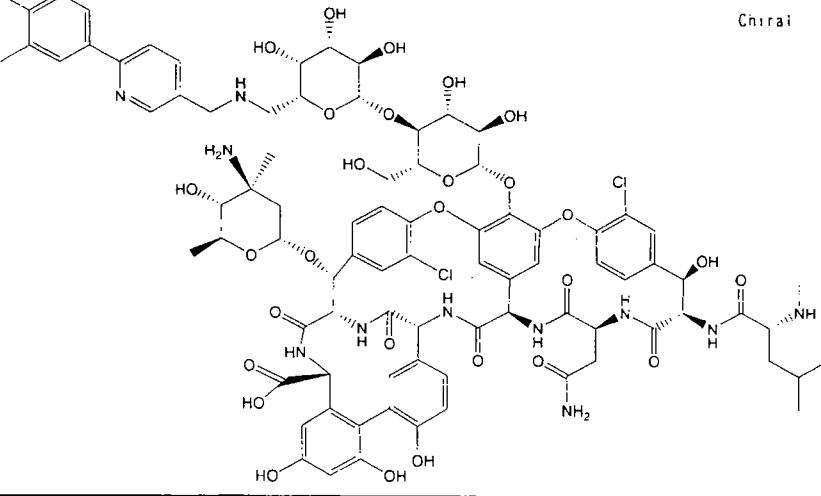
[0127]

[Table 39]

Example	Structure	Mass Spectrometry	Elementary analysis
85	 Chiral	[M+1] ⁺ =1826	Calculated value for C₈₃H₉₃Cl₂N₁O₁₀S⁺ (H₂O) 11.3 (HCl) 2.4 C: 47.05%, H: 5.61%, N: 7.27%, Cl: 7.36%, S: 1.51% Measured value C: 47.03%, H: 5.53%, N: 7.42%, Cl: 7.34%, S: 1.40%
86	 Chiral	[M+1] ⁺ =1795	Calculated value for C₈₃H₉₆Cl₂N₁O₁₀S⁺ (H₂O) 12.4 (HCl) 2.8 C: 47.54%, H: 5.87%, N: 6.60%, Cl: 8.02%, S: 1.51% Measured value C: 47.51%, H: 5.62%, N: 6.65%, Cl: 7.98%, S: 1.42%
87	 Chiral	[M+1] ⁺ =1844	Calculated value for C₈₄H₉₃Cl₂N₁O₁₀S⁺ (H₂O) 17 (HCl) 2.9 C: 44.67%, H: 5.80%, N: 6.82%, Cl: 10.83% Measured value C: 44.69%, H: 5.87%, N: 6.89%, Cl: 10.82%

[0128]

[Table 40]

Example	Structure	Mass Spectrometry	Elementary analysis
88	Chiral 	[M+1] ⁺ =1812	Calculated value for C₈₄H₉₃C₁₂F₂N₁₁O₂₈·(H₂O)_{16.5}·(HCl)_{2.6} C: 45.74%, H: 5.88%, N: 6.99%, Cl: 7.39%, F: 1.72% Measured value C: 45.73%, H: 5.82%, N: 7.05%, Cl: 7.36%, F: 1.62%
89	Chiral 	[M+1] ⁺ =1860	Calculated value for C₈₅H₉₄C₁₂F₃N₁₁O₂₉·(H₂O)_{17.4}·(HCl)₄ C: 43.99%, H: 5.77%, N: 6.64%, Cl: 9.17%, F: 2.46% Measured value C: 43.96%, H: 5.69%, N: 6.80%, Cl: 9.16%, F: 2.38%
90	Chiral 	[M+1] ⁺ =1801	Calculated value for C₈₆H₉₉C₁₂N₁₁O₂₈·(H₂O)_{15.4}·(HCl)_{4.2} C: 46.19%, H: 6.04%, N: 6.89%, Cl: 9.83% Measured value C: 46.20%, H: 5.83%, N: 6.98%, Cl: 9.76%

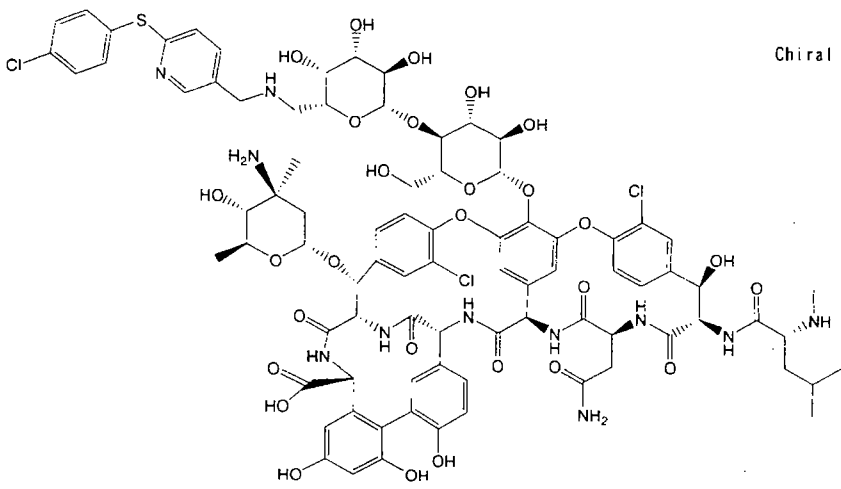
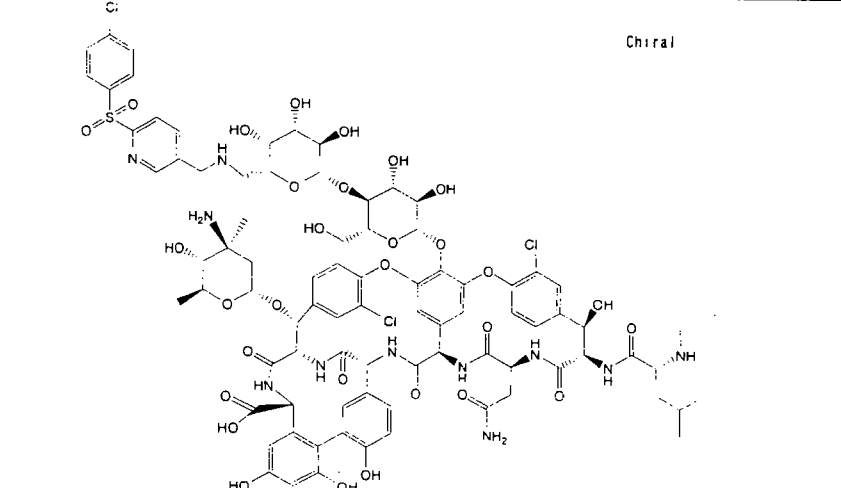
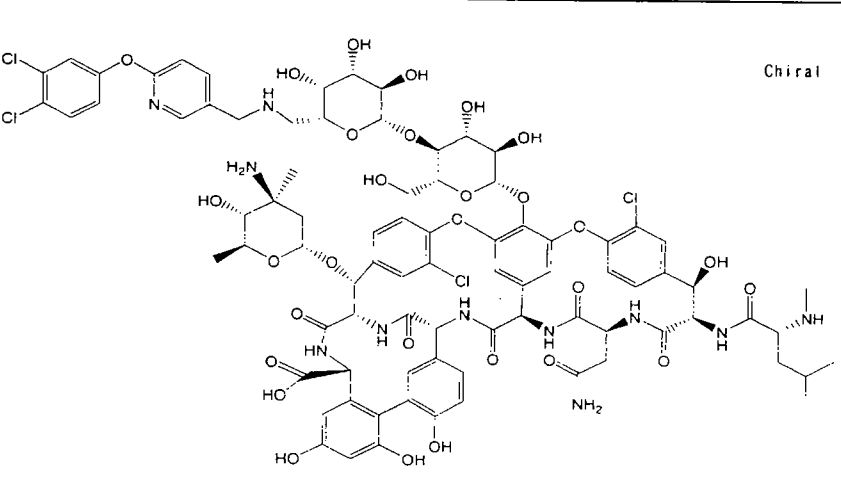
[0129]

[Table 41]

Example	Structure	Mass Spectrum, m/z	Elementary analysis
91	Chemical structure of compound 91, labeled "Chiral". The structure features a complex polycyclic core with multiple hydroxyl groups, a fluorophenyl group, a pyrazole ring, and a long chain containing amide and urea linkages. Stereochemistry is indicated with wedges and dashes.	[M+1] =1785	Calculated value for $C_{84}H_{91}Cl_2FN$ 12029 (H₂O) 15 (HCl) 2.6 C: 45.22% H: 5.79% N: 7.81% Cl: 7.58% F: 0.88% Measured value C: 45.23% H: 5.87% N: 7.80% Cl: 7.61% F: 0.87%
92	Chemical structure of compound 92, labeled "Chiral". The structure is similar to 91 but with a different side chain, featuring a 4-chlorophenyl group and a pyridine ring. Stereochemistry is indicated with wedges and dashes.	[M+1] =1828	Calculated value for $C_{84}H_{93}Cl_3FN$ 11028 (H₂O) 13.3 (HCl) 3 C: 46.30% H: 5.67% N: 7.07% Cl: 9.76% F: 0.87% Measured value C: 46.27% H: 5.63% N: 7.21% Cl: 9.69% F: 0.77%
93	Chemical structure of compound 93, labeled "Chiral". The structure is similar to 91 but with a different side chain, featuring a 4-fluorophenyl group and a pyridine ring. Stereochemistry is indicated with wedges and dashes.	[M+1] =1820	Calculated value for $C_{86}H_{96}Cl_2FN$ 11028 (H₂O) 14.6 (HCl) 2.7 C: 47.31% H: 5.91% N: 7.06% Cl: 7.63% F: 0.87% Measured value C: 47.26% H: 5.83% N: 7.17% Cl: 7.69% F: 0.77%

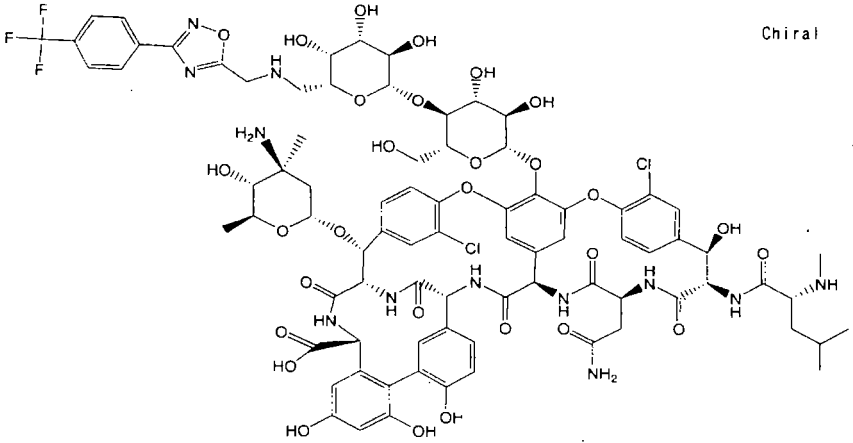
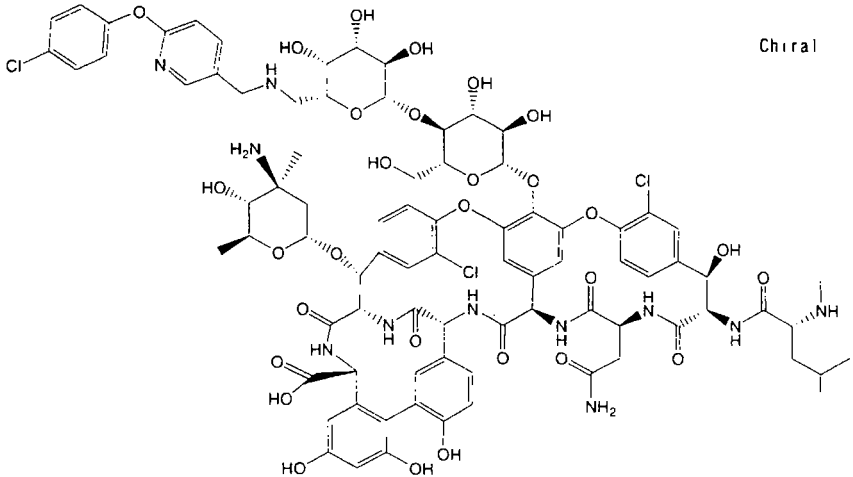
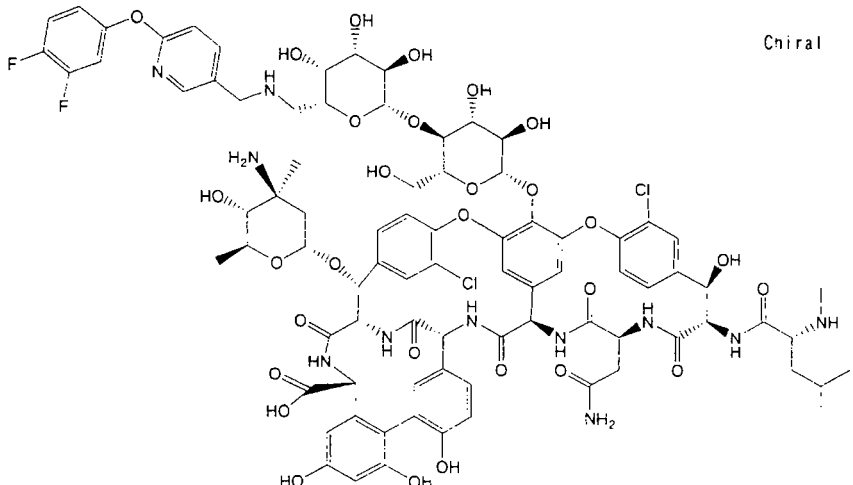
[0130]

[Table 42]

Example	Structure	Mass Spectrometry	Elementary analysis
94	 Chiral	[M+1] ⁺ =1842	Calculated value for C₈₄H₉₄Cl₃N₁O₂₈S· (H₂O) 14.4· (HCl) 2.6 C: 45.89%, H: 5.75%, N: 7.01%, Cl: 9.03%, S: 1.46% Measured value C: 45.84%, H: 5.63%, N: 7.14%, Cl: 9.05%, S: 1.51%
95	 Chiral	[M+1] ⁺ =1874	Calculated value for C₈₄H₉₄Cl₃N₁O₃₀S· (H₂O) 14.5· (HCl) 3.2 C: 44.76%, H: 5.64%, N: 6.81%, Cl: 9.75%, S: 1.42% Measured value C: 44.69%, H: 5.51%, N: 6.97%, Cl: 9.69%, S: 1.43%
96	 Chiral	[M+1] ⁺ =1860	Calculated value for C₈₄H₉₃Cl₃N₁O₂₉S· (H₂O) 13.5· (HCl) 3 C: 45.55%, H: 5.60%, N: 6.96%, Cl: 11.20% Measured value C: 45.53%, H: 5.50%, N: 7.15%, Cl: 11.14%

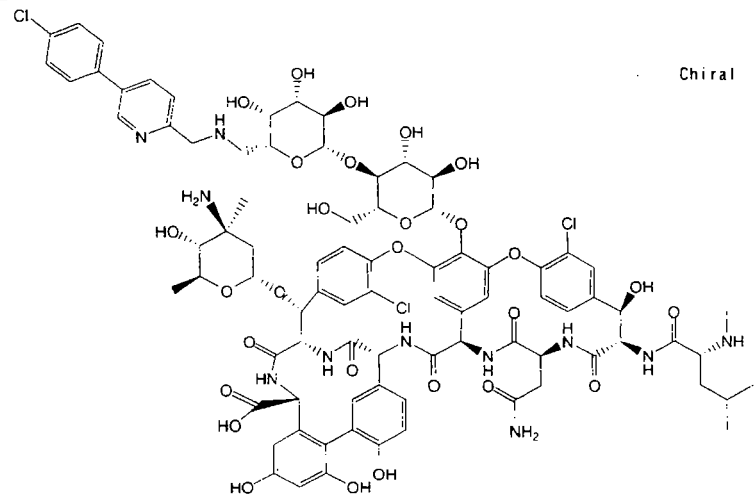
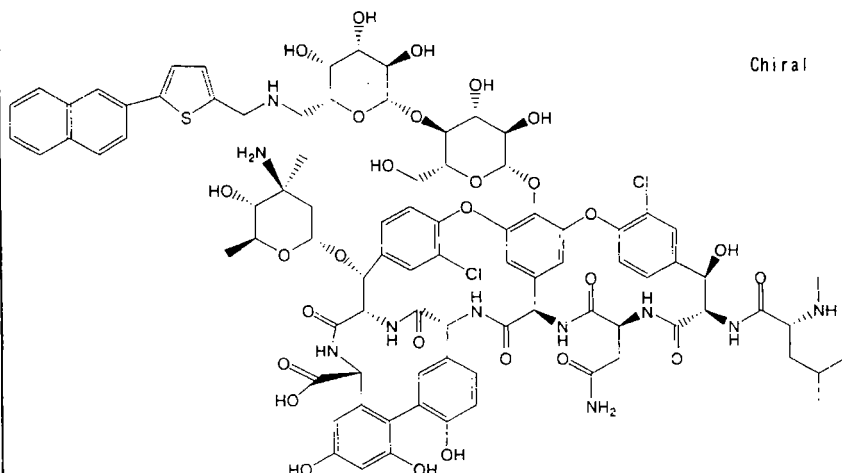
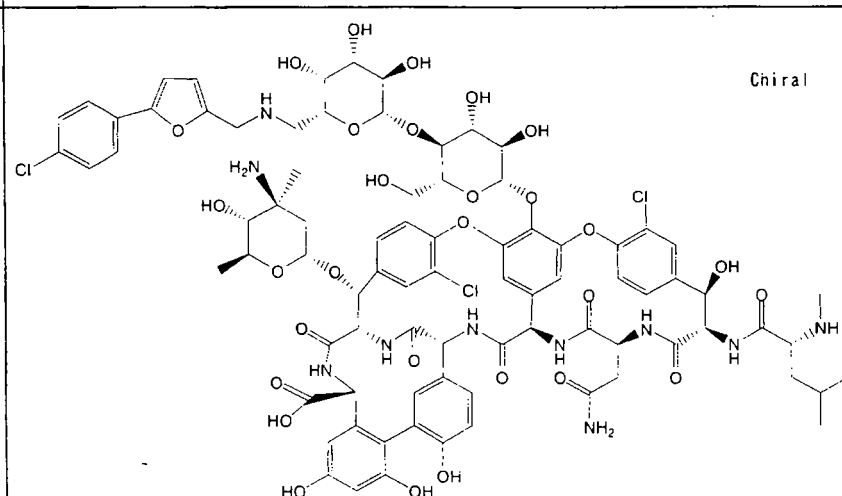
[0131]

[Table 43]

Example	Structure	Mass Spectrometry	Elementary analysis
97	 Chiral	$[M+1]^+$ =1835	Calculated value for $C_{82}H_{91}Cl_{12}F_3N_{12}O_{29}$ (H₂O) 13.7 (HCl) 2.9 C: 44.99% H: 5.59% N: 7.68% Cl: 7.94% F: 2.60% Measured value C: 45.13% H: 5.69% N: 7.71% Cl: 7.99% F: 2.30%
98	 Chiral	$[M+1]^+$ =1826	Calculated value for $C_{84}H_{94}Cl_{13}N_{11}O_{29}$ (H₂O) 11.3 (HCl) 3.7 C: 45.43% H: 5.73% N: 6.94% Cl: 10.70% Measured value C: 45.34% H: 5.68% N: 7.15% Cl: 10.75%
99	 Chiral	$[M+1]^+$ =1828	Calculated value for $C_{84}H_{93}Cl_{12}F_2N_{11}O_{29}$ (H₂O) 13.5 (HCl) 3.3 C: 46.00% H: 5.67% N: 7.03% Cl: 8.57% F: 1.73% Measured value C: 45.98% H: 5.62% N: 7.13% Cl: 8.59% F: 1.49%

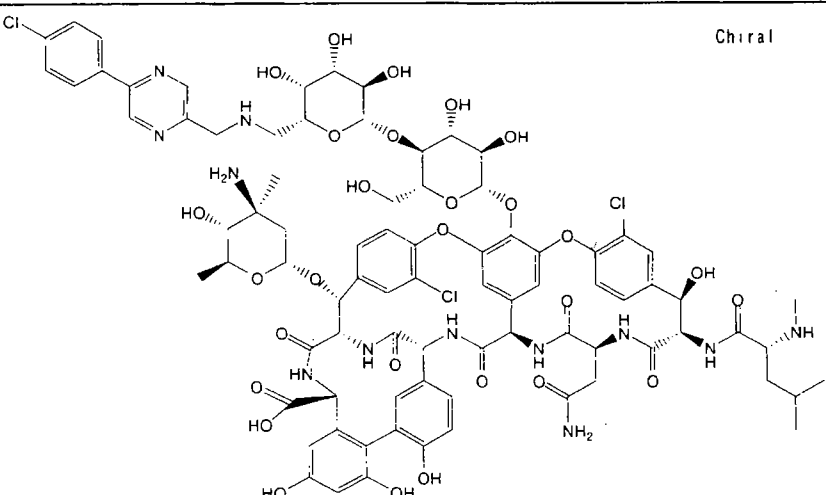
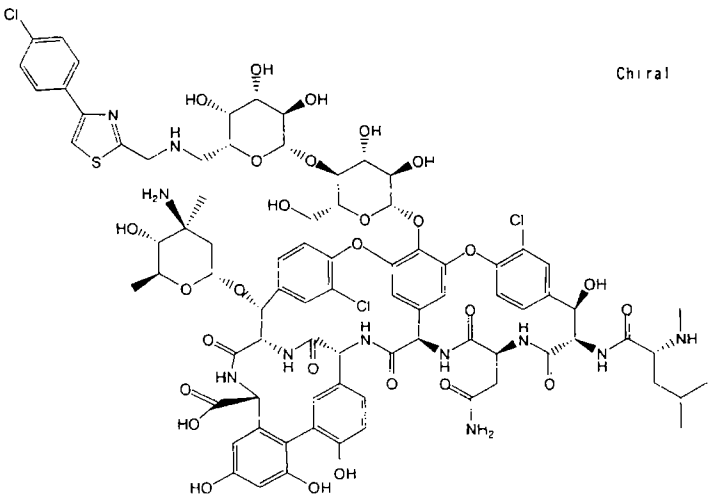
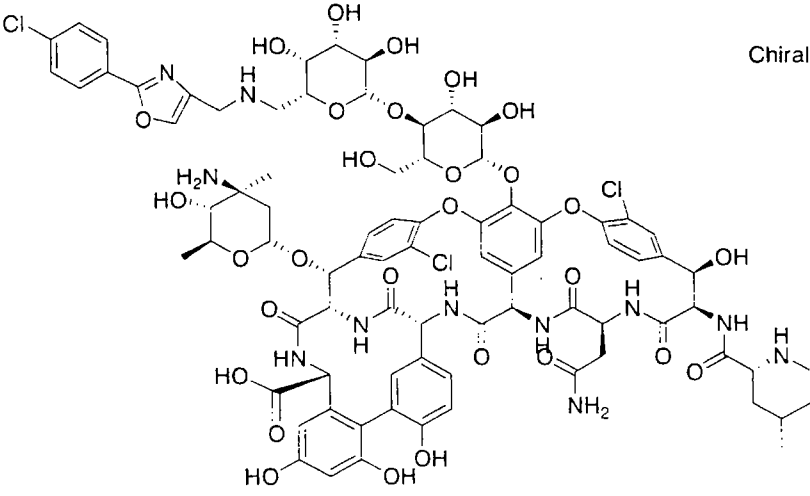
[0132]

[Table 44]

Example	Structure	Mass spectrometry	Elementary analysis
100	 Chiral	[M+1] =1810	Calculated value for C₈₄H₉₄Cl₃N₁ 1028· (H₂O) 14· (HCl) 3.5 C: 46.03%. H: 5.77%. N: 7.03%. Cl: 10.51% Measured value C: 45.96%. H: 5.53%. N: 7.12%. Cl: 10.47%
101	 Chiral	[M+1] =1831	Calculated value for C₈₇H₉₆Cl₂N₁ 0028S· 21.7 (H₂O)· 3.5 (HCl) C: 44.50%. H: 6.15%. N: 5.70%. Cl: 8.30%. S: 1.30% Measured value C: 44.44%. H: 6.13%. N: 5.96%. Cl: 8.29%. S: 1.36%
102	 Chiral	[M+1] =1799	Calculated value for C₈₃H₉₃Cl₃N₁ 0029· 18.4 (H₂O)· 3.4 (HCl) C: 44.37%. H: 5.87%. N: 5.91%. Cl: 10.1% Measured value C: 44.18%. H: 5.95%. N: 6.21%. Cl: 10.06%

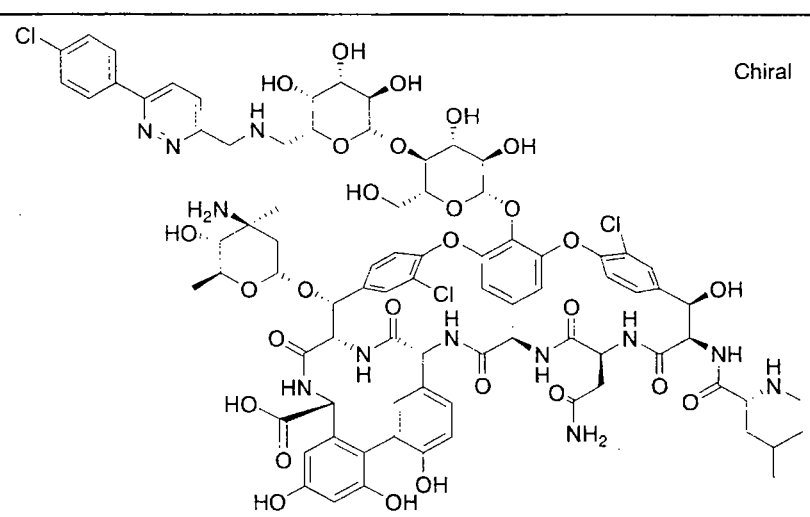
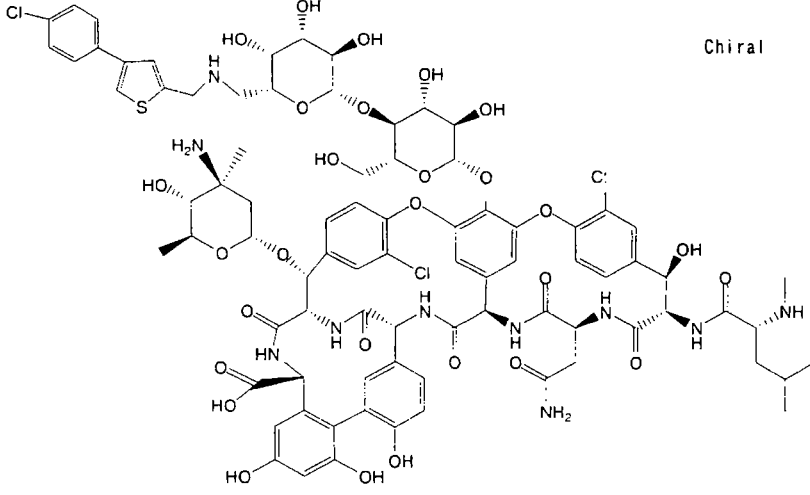
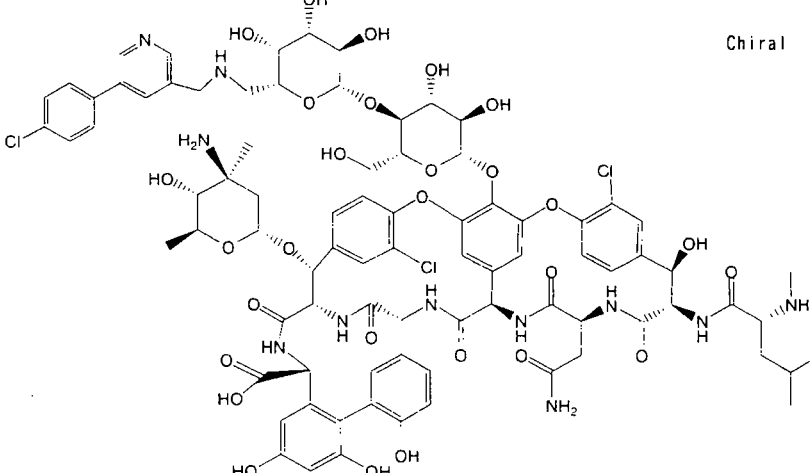
[0133]

[Table 45]

Example	Structure	Mass Spectrum (m/z)	Elementary analysis
103	 Chiral	[M+1] ⁺ =1811	Calculated value for C₈₃H₉₃Cl₃N₁ 2028 19.0 (H₂O) · 2.8 (HCl) C: 44.26%, H: 5.98%, N: 7.16%, Cl: 9.15% Measured value C: 44.16%, H: 5.97%, N: 7.45%, Cl: 9.11%
104	 Chiral	[M+1] ⁺ =1816	Calculated value for C₈₂H₉₂Cl₃N₁ 1028S 19.6 (H₂O) · 3.4 (HCl) C: 42.96%, H: 6.06%, N: 6.56%, Cl: 9.88%, S: 1.49% Measured value C: 42.91%, H: 5.91%, N: 6.71%, Cl: 9.89%, S: 1.40%
105	 Chiral	[M+1] ⁺ =1800	

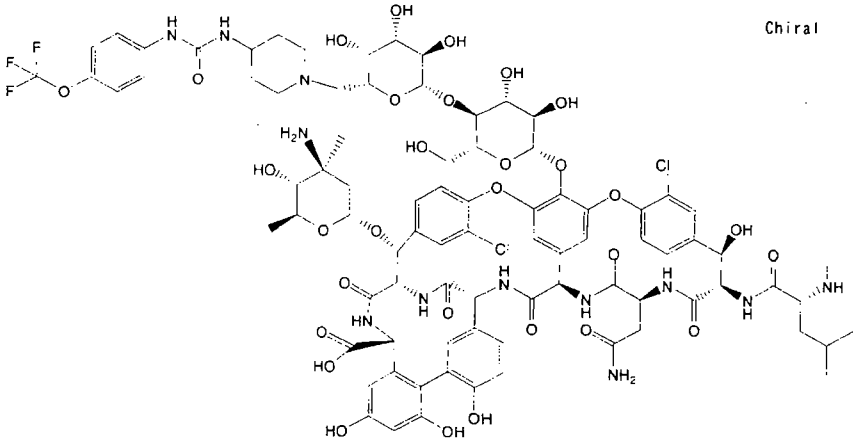
[0134]

[Table 46]

Example	Structure	Mass Synthesis	Elementary analysis
106	 Chiral	[M+1] ⁺ =1811	
107	 Chiral	[M+1] ⁺ =1815	Calculated value for C83H93ClN1 O028S· (H2O) 13.1· (HCl) 3.0 C: 46.10% H: 5.70% N: 6.48% Cl: 9.84% S: 1.48% Measured value C: 46.06% H: 5.70% N: 6.56% Cl: 9.88% S: 1.41%
108	 Chiral	[M+1] ⁺ =1811	Calculated value for C84H94ClN1 O028· (H2O) 15.2· (HCl) 3.6 C: 45.50% H: 5.82% N: 6.95% Cl: 10.55% Measured value C: 45.48% H: 5.82% N: 7.06% Cl: 10.59%

[0135]

[Table 47]

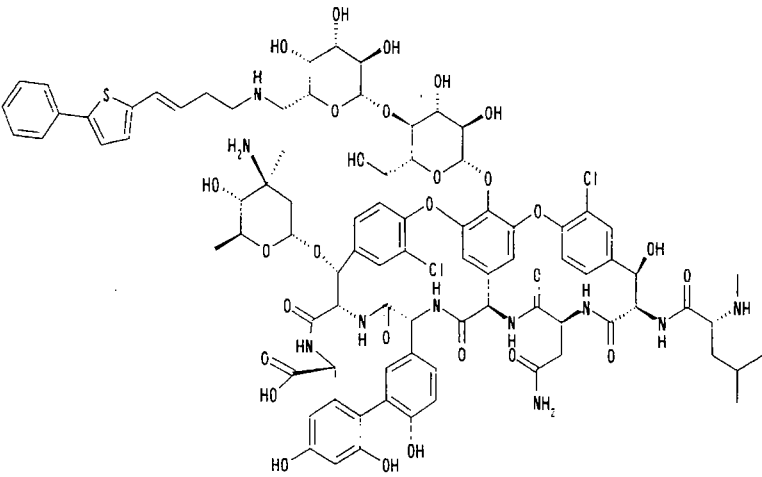
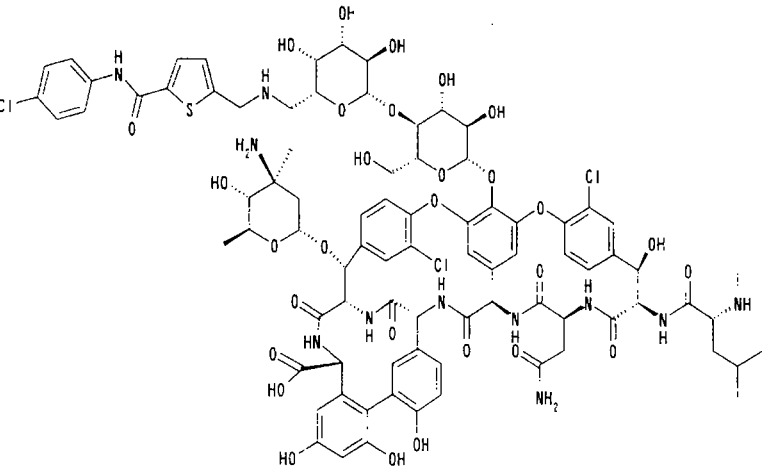
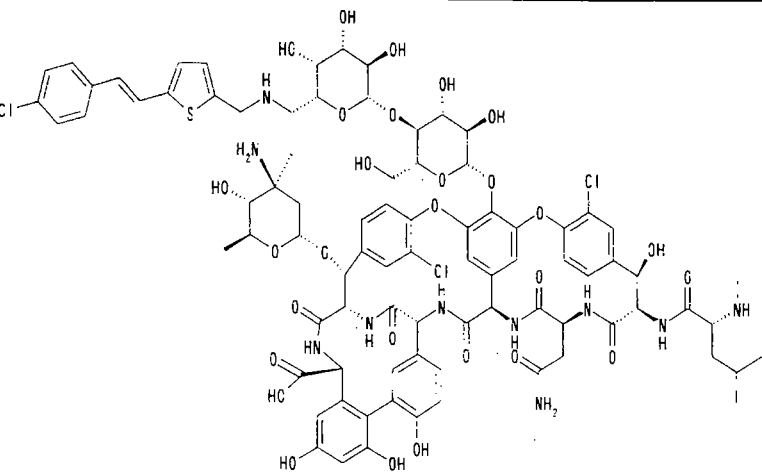
Example	Structure	Mass Signature	Elementary analysis
109	 Chiral	[M+1] ⁺ =1896	Calculated value for C₈₅H₉₉C₁₂F₃ N₁₂O₃₀· (H₂O) 13.6· (HCl) 2.9 C: 45.43%, H: 5.79%, N: 7.48%, Cl: 7.73%, F: 2.54% Measured value C: 45.38%, H: 5.72%, N: 7.92%, Cl: 7.76%, F: 2.96%

[Table 48]

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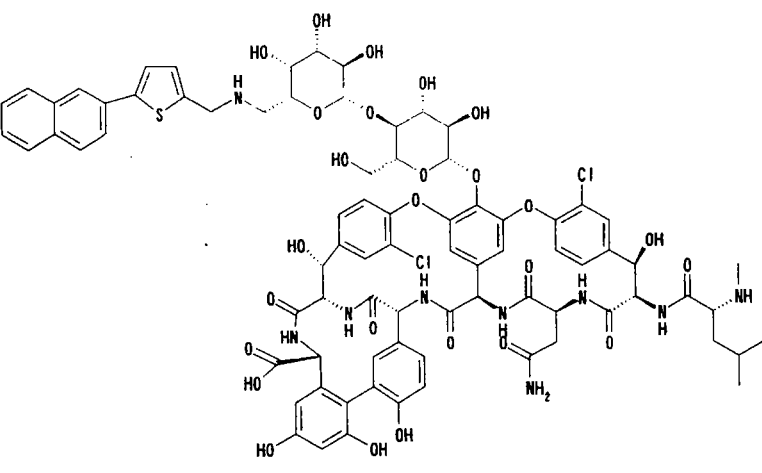
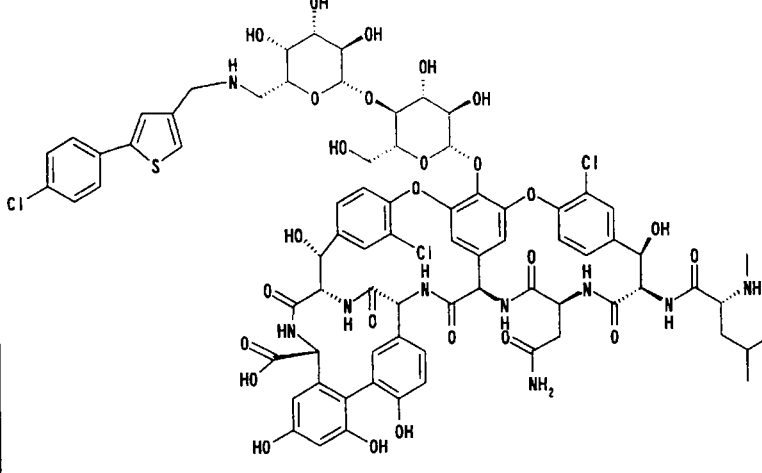
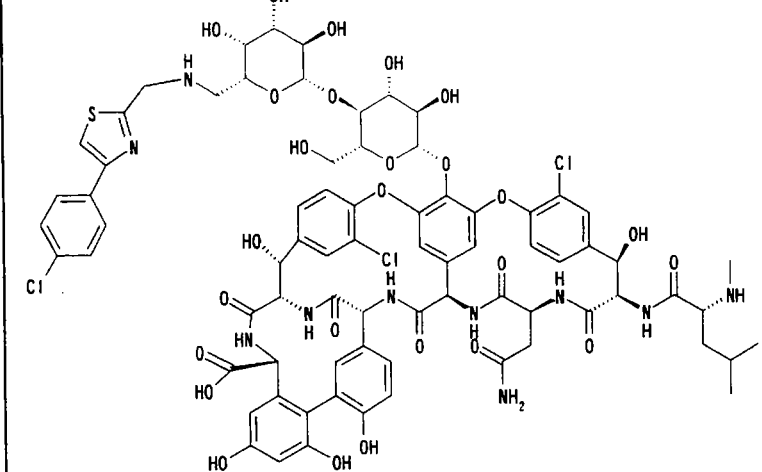
[0137]

[Table 49]

Example	Structure	Mass Spectrometry	Elementary analysis
113		Chiral	Calculated value for C₈₆H₉₈Cl₂N₁₀O₂₈S·(H₂O)_{15.5}·(HCl)_{2.9}: C: 46.79%, H: 6.02%, N: 6.34%, Cl: 7.87%, S: 1.45% Measured value: C: 46.74%, H: 5.75%, N: 6.27%, Cl: 7.80%, S: 1.37%
114		Chiral	Calculated value for C₈₄H₉₄Cl₃N₁₁O₂₉S·(H₂O)_{18.3}·(HCl)_{3.3}·(CH₃CN)_{0.6}: C: 43.83%, H: 5.86%, N: 6.96%, Cl: 9.57%, S: 1.37% Measured value: C: 43.76%, H: 5.59%, N: 7.03%, Cl: 9.59%, S: 1.32%
115		Chiral	Calculated value for C₈₅H₉₅Cl₃N₁₀O₂₈S·(H₂O)_{20.1}·(HCl)_{4.8}·(CH₃CN)_{0.6}: C: 43.05%, H: 5.94%, N: 6.17%, Cl: 11.50%, S: 1.33% Measured value: C: 42.76%, H: 5.64%, N: 6.33%, Cl: 11.49%, S: 1.31%

[0138]

[Table 50]

Example	Structure	Mass Spectrometry	Elementary analysis
116	 Chiral	$[M+1]^+ = 1688$	Calculated value for $C_{80}H_{83}Cl_{12}N_{9}O_{26}S \cdot (H_2O)_{13.6} \cdot (HCl)_{2.1}$: C: 47.78%, H: 5.63%, N: 6.27%, Cl: 7.23%, S: 1.59% Measured value: C: 47.77%, H: 5.58%, N: 6.39%, Cl: 7.18%, S: 1.53%
117	 Chiral	$[M+1]^+ = 1672$	Calculated value for $C_{76}H_{80}Cl_{13}N_{9}O_{26}S \cdot (H_2O)_{11.6} \cdot (HCl)_{1.4}$: C: 47.20%, H: 5.45%, N: 6.52%, Cl: 8.07%, S: 1.66% Measured value: C: 47.13%, H: 5.36%, N: 6.59%, Cl: 8.13%, S: 1.62%
118	 Chiral	$[M+1]^+ = 1673$	Calculated value for $C_{75}H_{79}Cl_{13}N_{10}O_{26}S \cdot (H_2O)_{11.2} \cdot (HCl)_{1.9}$: C: 46.29%, H: 5.35%, N: 7.2%, Cl: 8.93%, S: 1.65% Measured value: C: 46.07%, H: 5.20%, N: 7.27%, Cl: 8.84%, S: 1.46%

[0139]

[Table 51]

Example	Structure	Mass Spectrometry	Elementary analysis
119	Chiral	$[M+1]^+$ = 1668	Calculated value for C₇₆H₈₀Cl₃N₁₁O₂₆·(H₂O)_{10.2}·(HCl)_{2.6}: C: 46.85%, H: 5.33%, N: 7.91%, Cl: 10.19% Measured value C: 46.81%, H: 5.33%, N: 8.27%, Cl: 10.16%
120	Chiral	$[M+1]^+$ = 1668	Calculated value for C₇₆H₈₀Cl₃N₁₁O₂₆·(H₂O)_{13.1}·(HCl)_{1.8}: C: 46.30%, H: 5.52%, N: 7.82%, Cl: 8.63% Measured value C: 46.27%, H: 5.41%, N: 7.88%, Cl: 8.66%
121	Chiral	$[M+1]^+$ = 1856	Calculated value for C₈₅H₉₆Cl₃N₁₁O₂₈·(H₂O)_{18.7}·(HCl)_{3.1}: C: 44.23%, H: 5.96%, N: 6.68%, Cl: 9.37%, S: 1.39% Measured value C: 44.22%, H: 5.76%, N: 6.59%, Cl: 9.32%, S: 1.34%

As a typical example of processes for producing these compounds, processes for producing compounds of Example 13, Example 30, Example 80, Example 117 and Example 121 will be exemplified below.

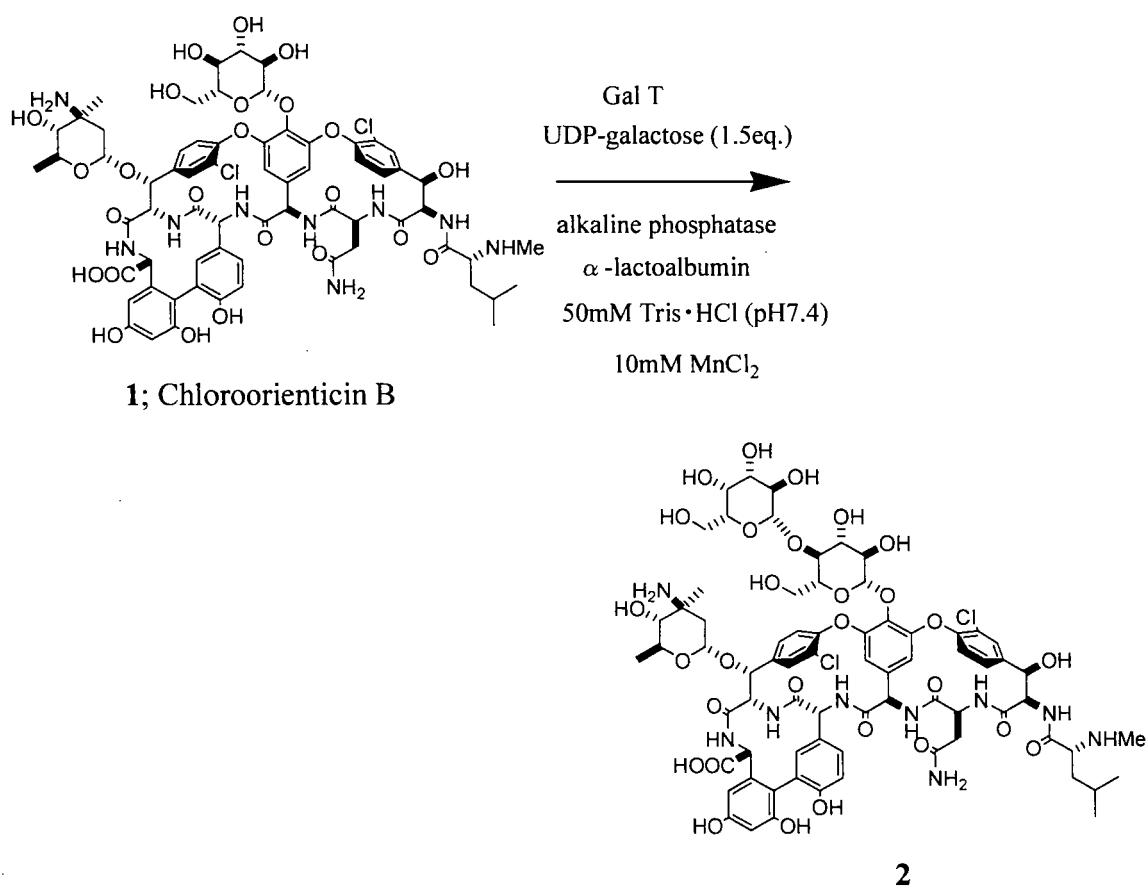
Other Example compounds can be produced by the same methods as follows.

Example 13

[0140]

First step: Production of intermediate compound 2

[Chemical formula 76]



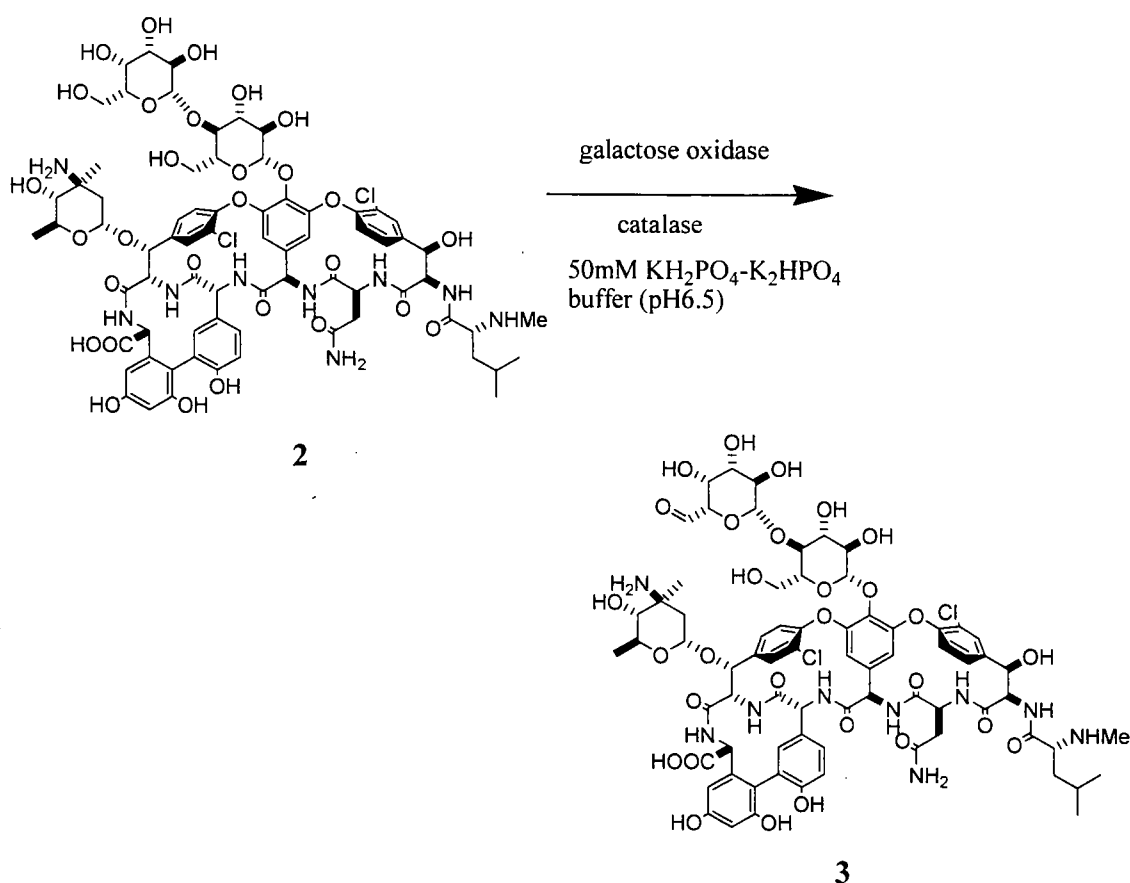
Chloroorienticin B (compound 1) (100 mg, 0.069 mmol) was dissolved in 5 mL of 50 mM Tris·HCl buffer (pH 7.4) containing 25 mM MnCl₂. 30 U

of alkaline phosphatase (P6774 manufactured by Sigma), 3 mg of α -lactalbumin, 63 mg (0.1 mmol) of UDP-galactose, and 3 U of cow milk-derived β 1,4 galactosyltransferase (G5507 manufactured by Sigma) were sequentially added, and the mixture was stirred at 30°C for 15 hours. The reaction mixture was purified by reverse phase column chromatography to obtain 90 mg (yield 81%) of compound 2 as a colorless solid.

[0141]

Second step: Production of intermediate compound 3

[Chemical formula 77]



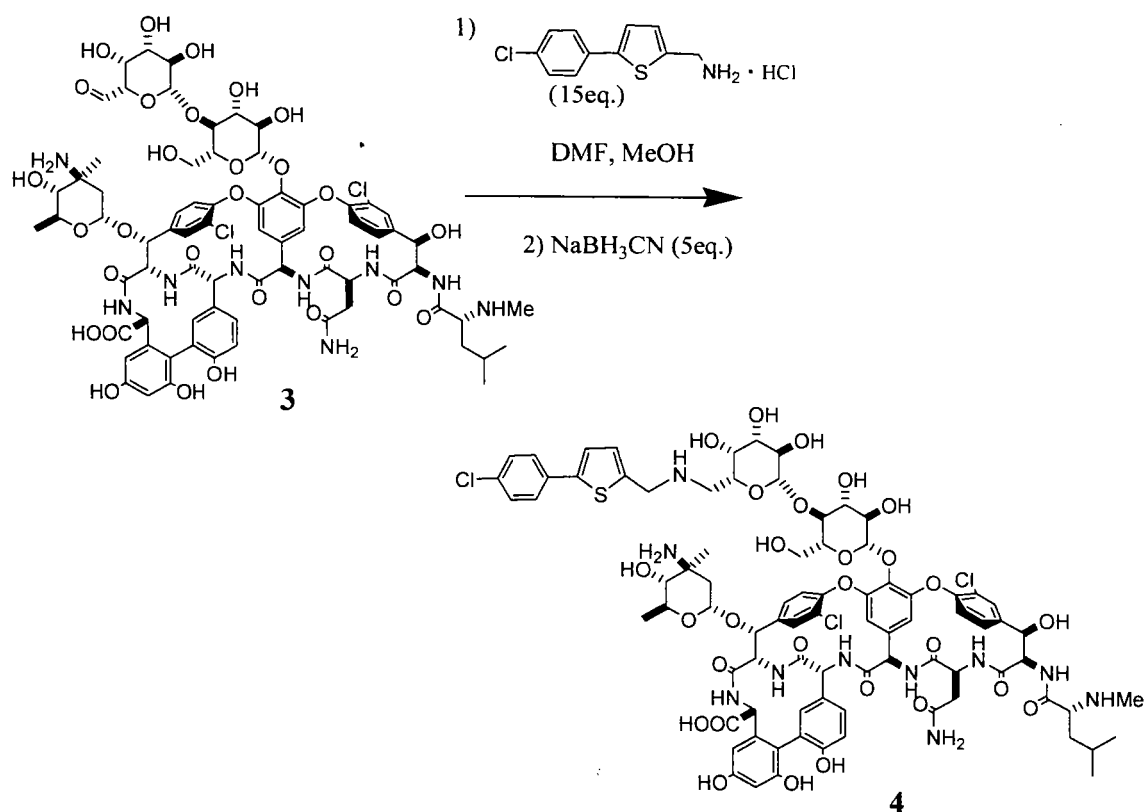
The compound 2 obtained in the first step (30 mg, 0.019 mmol) was dissolved in 3 mL of a 50 mM KH_2PO_4 - K_2HPO_4 buffer (pH 6.5). 3000 U of

catalase (C30 manufactured by Sigma), and 300 U of Dactylium dendroides-derived galactose oxidase (15996 manufactured by MP Biomedicals) were sequentially added and the mixture was stirred at 30°C for 24 hours. The reaction mixture was purified by reverse phase column chromatography to obtain 25 mg (yield 83%) of compound 3 as a white powder.

[0142]

Third step: Production of objective compound 4

[Chemical formula 78]



(5-(4-Chlorophenyl)thiophen-2-yl)methanamine hydrochloride (359 mg, 1.4 mmol) was dissolved in a mixed solvent of 30 mL of dimethylformamide and 30 mL of methanol. The compound 3 obtained in

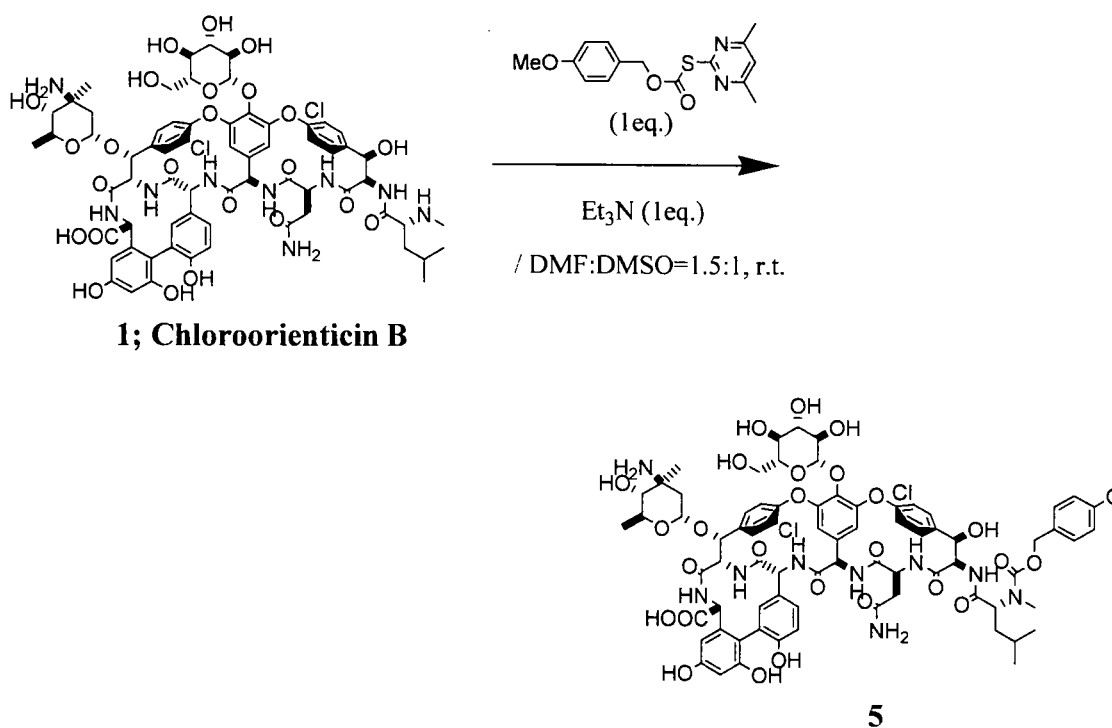
the second step (150 mg, 0.093 mmol) was added, and the mixture was stirred at room temperature for 2 hours. Sodium cyanoborohydride (29 mg, 0.46 mmol) was added, and the mixtures was stirred at 70°C for 2 hours. The reaction solution was poured into diethyl ether, the produced precipitate was collected by filtration, and the resulting crude solid was washed with 5% aqueous sodium chloride solution to remove unreacted sodium cyanoborohydrate. The resulting crude solid was purified by reverse phase column chromatography to obtain 78 mg (yield 46%) of compound 4 as a colorless solid.

Example 30

[0143]

First step: Production of Intermediate compound 5

[Chemical formula 79]

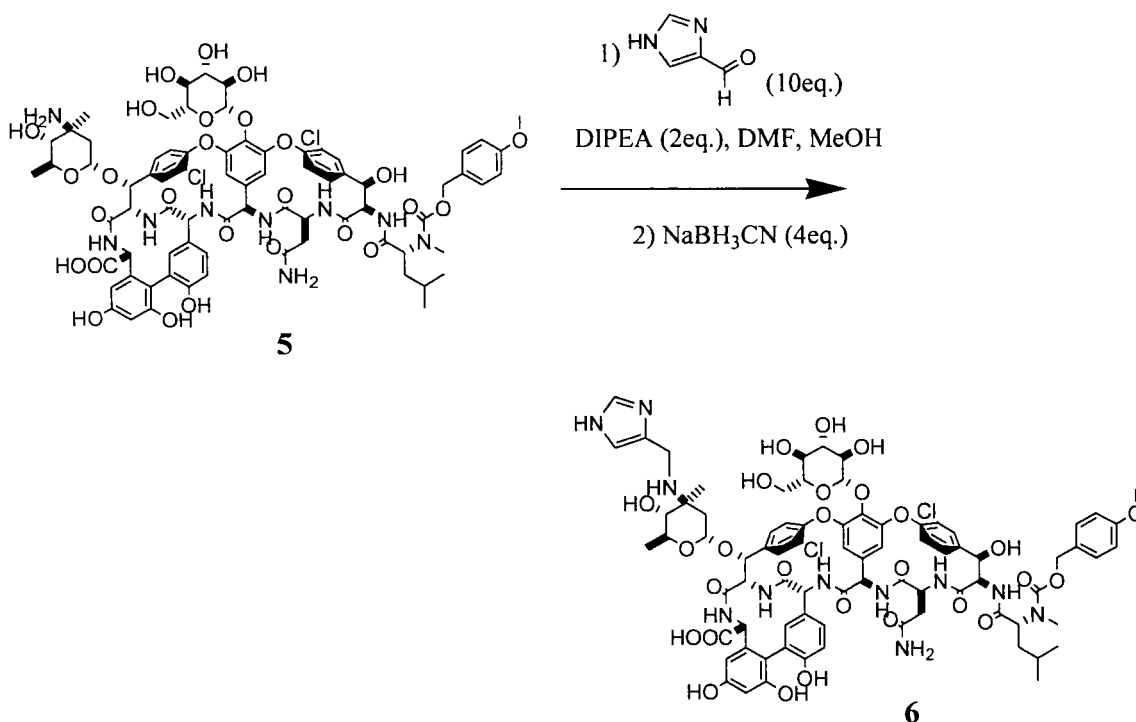


Under nitrogen gas stream, 20 g (12.4 mmol) of chloroorienticin B (compound 1) was dissolved in a mixed solvent of 150 mL of dimethylformamide and 1000 mL of dimethyl sulfoxide. Triethylamine (1.8 mL, 12.9 mmol) was added dropwise at room temperature, 3.93 g (12.9 mmol) of thiocarbonic acid (4,6-dimethyl-pyrimidin-2-yl)ester (4-methoxybenzyl) ester was added, and the mixture was stirred at room temperature for 45 hours. The reaction solution was concentrated under reduced pressure, and the remaining solution was poured into 1 L of cooled 5% aqueous sodium chloride solution. 1N hydrochloric acid was added to adjust to pH=3, and the mixture was stirred for 1 hour under ice-cooling. The produced precipitate was collected by filtration, dried, dissolved again in 100 mL of dimethyl sulfoxide, and poured into 1 L of cooled 5% aqueous sodium chloride solution. 1N hydrochloric acid was added to adjust to pH=3, and the mixture was stirred for 1 hour under ice-cooling. The produced precipitate was collected by filtration, washed with distilled water, and dried at room temperature for 3 days. The resulting crude solid was suspended in 400 mL of ethyl acetate, and stirred at room temperature for 2 hours, and the precipitate was collected by filtration, and dried to obtain 22.8 g (HPLC purity 89%) of compound 5 as a pale flesh-colored solid.

[0144]

Second step: Production of intermediate compound 6

[Chemical formula 80]

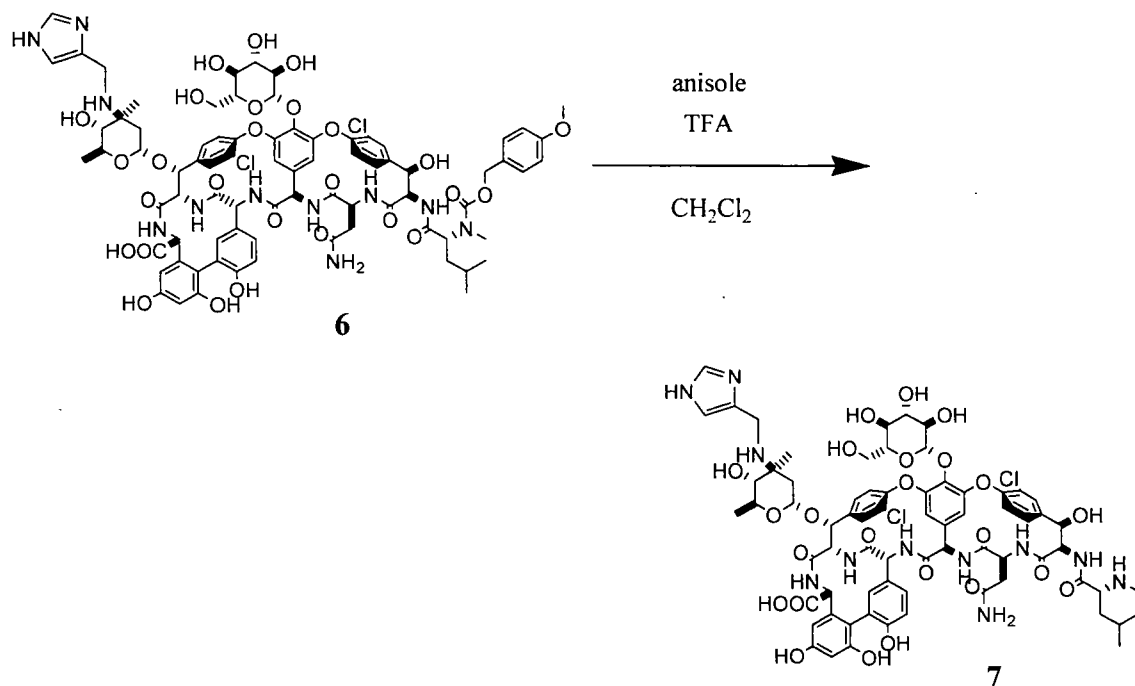


The compound **5** obtained in the first step (1 g, 0.62 mmol) was dissolved in a mixed solvent of 31 mL of dimethylformamide and 31 mL of methanol. 4-Formylimidazole (596 mg, 6.2 mmol), and 0.22 mL (1.24 mmol) of diisopropylethylamine were added sequentially, and the mixture was stirred at 70°C for 2 hours. After the reaction mixture was cooled to room temperature, 156 mg (2.5 mmol) of sodium cyanoborohydride was added, and the mixture was stirred at 70°C for 3 hours. Methanol in the reaction solution was distilled under reduced pressure, and the remaining solution was poured into cooled 10% aqueous sodium chloride solution. The produced precipitate was collected by filtration, and the resulting crude solid was washed with 5% aqueous sodium chloride solution to remove unreacted sodium cyanoborohydride. The washed solid was dried to obtain 869 mg (HPLC purity 73%, yield 60%) as a crude solid of compound **6**.

[0145]

Third step: Production of intermediate compound 7

[Chemical formula 81]

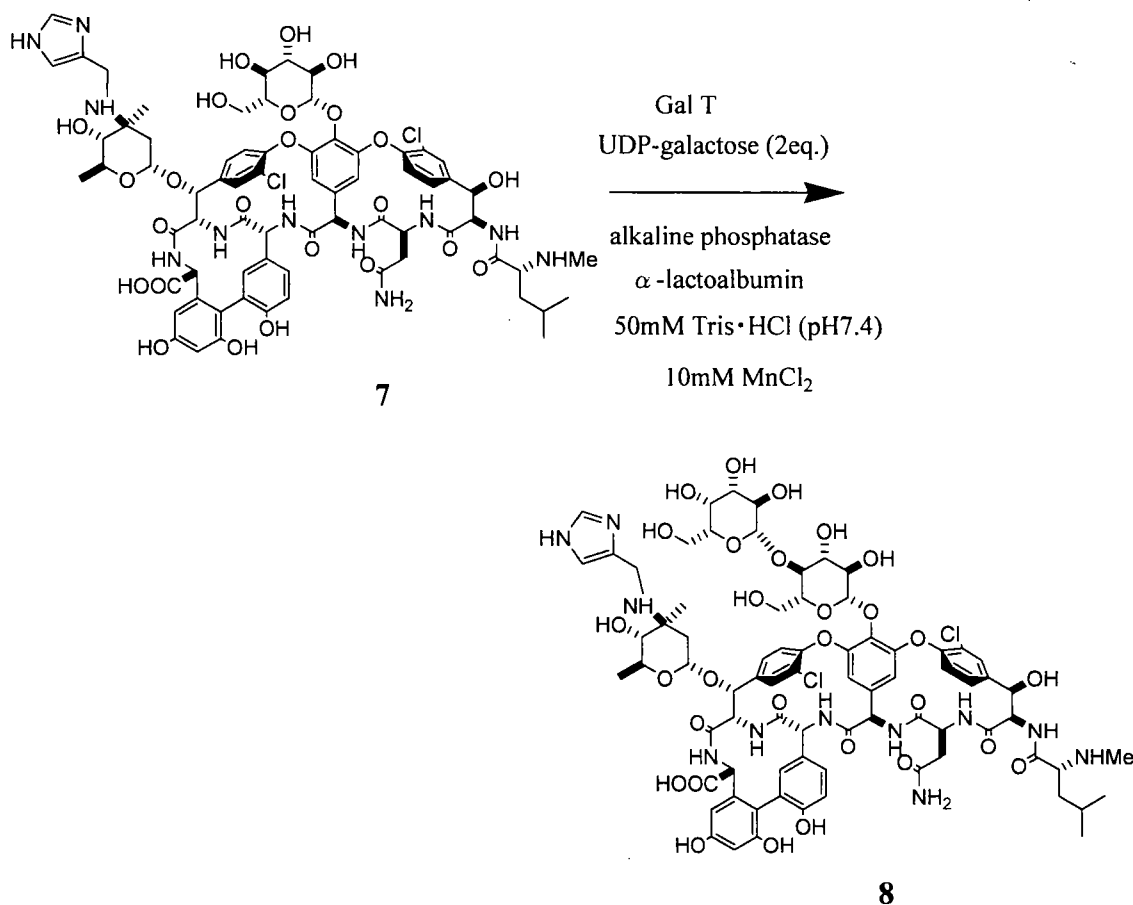


The crude solid of compound 6 obtained in the second step (869 mg, HPLC purity 73%, 0.375 mmol) was dissolved in 26 mL of dichloromethane, and the solution was cooled under ice-cooling. Anisole (1.4 mL) and 1.26 mL of trifluoroacetic acid were sequentially added dropwise, and the mixture was stirred for 2 hours under ice-cooling. The reaction solution was poured into ethyl acetate, the produced precipitate was collected by filtration, and the resulting crude solid was further washed with ethyl acetate. The washed solid was purified by reverse phase column chromatography to obtain 556 mg (yield 97%) of compound 7 as a colorless solid.

[0146]

Fourth step: Production of intermediate compound 8

[Chemical formula 82]



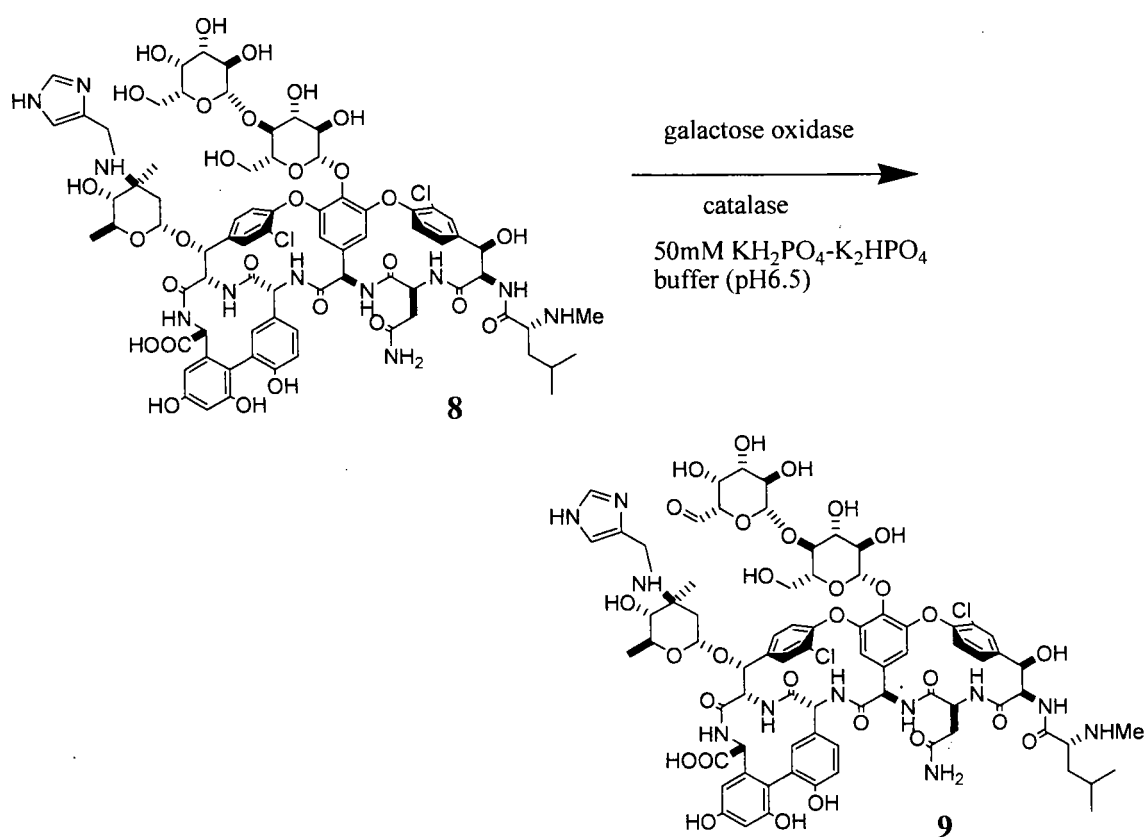
The compound 7 obtained in the third step (556 mg, 0.363 mmol) was dissolved in 37 mL of 50 mM Tris-HCl buffer (pH 7.4) containing 10 mM MnCl_2 . 180 U of alkaline phosphatase (P6774 manufactured by Sigma), 18 mg of α -lactoalbumin, 443 mg (0.73 mmol) of UDP-galactose, and 18 U of human-derived β 1,4 galactosyltransferase (BGT401 manufactured by TOYOBO CO., LTD.) were sequentially added, and the mixture was stirred at 30°C for 24 hours. The reaction mixture was loaded on a column filled with Diaion HP-20, and the column was washed with distilled water, and eluted with 50% aqueous acetonitrile solution containing 0.1% trifluoroacetic acid. The eluate was concentrated under reduced pressure, and the

remaining aqueous solution was lyophilized to obtain 541 mg (yield 88%) of compound 8 as a colorless solid.

[0147]

Fifth step: Production of intermediate compound 9

[Chemical formula 83]



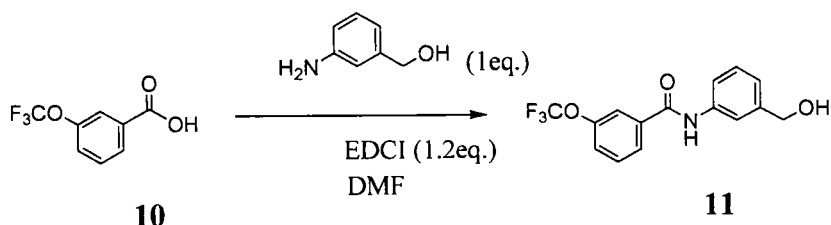
The compound 8 obtained by the fourth step (541 mg, 0.32 mmol) was dissolved in 95 mL of 50 mM KH_2PO_4 - K_2HPO_4 buffer (pH 6.5). 500 KU of catalase (C30 manufactured by Sigma), and 5 KU of Dactylium dendroides-derived galactose oxidase (15996 manufactured by MP Biomedicals) were sequentially added, and the mixture was stirred for 25°C for 48 hours. The reaction mixture was loaded on column filled with Diaion

HP-20, and the column was washed with distilled water, and eluted with 30% aqueous acetonitrile solution containing 0.1% trifluoroacetic acid. The eluate was concentrated under reduced pressure, and the remaining aqueous solution was lyophilized to obtain 470 mg (yield 87%) of compound 9 as a colorless solid.

[0148]

Sixth step: Production of intermediate compound 11

[Chemical formula 84]

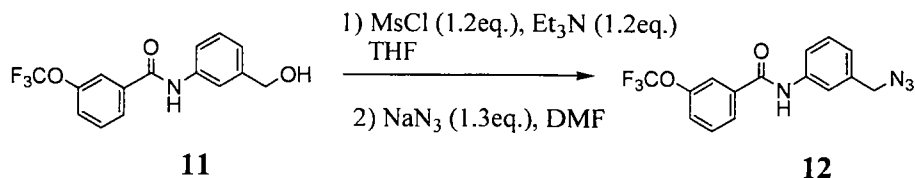


3-Trifluoromethoxybenzoic acid (compound 10) (3.58 g, 17.4 mmol), and 2.14 g (17.4 mmol) of 3-aminobenzyl alcohol were dissolved in 87 mL of dimethylformamide. N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (4 g, 20.9 mmol) was added, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into distilled water, this was extracted with ethyl acetate, and the extract was washed sequentially with 2N hydrochloric acid, aqueous saturated sodium bicarbonate solution, and aqueous saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. After the desiccant was filtered, the filtrate was distilled under reduced pressure to obtain 3.94 g (yield 73%) of compound 11 as a colorless solid.

[0149]

Seventh step: Production of intermediate compound 12

[Chemical formula 85]

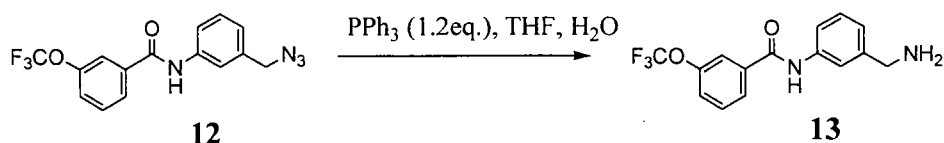


The compound 11 obtained in the sixth step (3.94 g, 12.7 mmol) was dissolved in 64 mL of tetrahydrofuran. Triethylamine (2.13 mL, 15.2 mmol), and 1.18 mL (15.2 mmol) of methanesulfonyl chloride were sequentially added dropwise, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into distilled water, and extracted with ethyl acetate, and the extract was washed with an aqueous saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. After the desiccant was filtered, the filtrate was distilled under reduced pressure to obtain solid, which was dissolved in 64 mL of dimethylformamide. Sodium azide (1.07 g, 16.5 mmol) was added, and the mixture was stirred at 40°C for 4 hours. The reaction mixture was poured into purified water, extracted with ethyl acetate, washed with aqueous saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The desiccant was filtered, and the filtrate was distilled under reduced pressure to obtain 4.1 g (yield 96%) of compound 12 as a colorless solid.

[0150]

Eighth step: Production of intermediate compound 13

[Chemical formula 86]

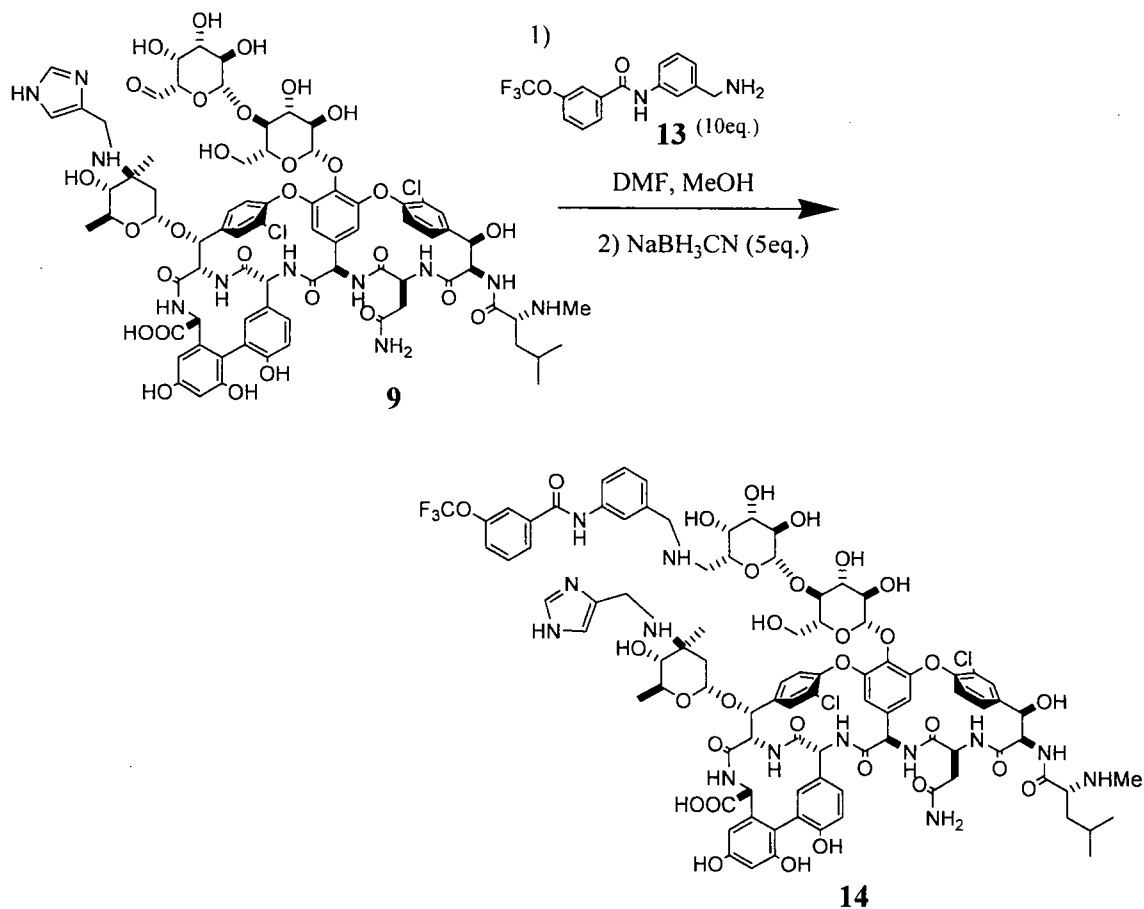


The compound 12 obtained in the seventh step (4.1 g, 12.2 mmol) was dissolved in mixed solvent of 45 mL of tetrahydrofuran and 15 mL of purified water. Triphenylphosphine (3.85 g, 14.6 mmol) was added, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was poured into 4N hydrochloric acid, and the aqueous solution was washed with ethyl acetate, and adjusted with a 2N sodium hydroxide aqueous solution to pH=12. The aqueous solution was extracted with ethyl acetate, and the extract was dried with anhydrous magnesium sulfate. After the desiccant was filtered, the filtrate was distilled under reduced pressure to obtain 2.89 g (yield 76%) of compound 13 as a colorless solid.

[0151]

Ninth step: Production of intermediate compound 14

[Chemical formula 87]



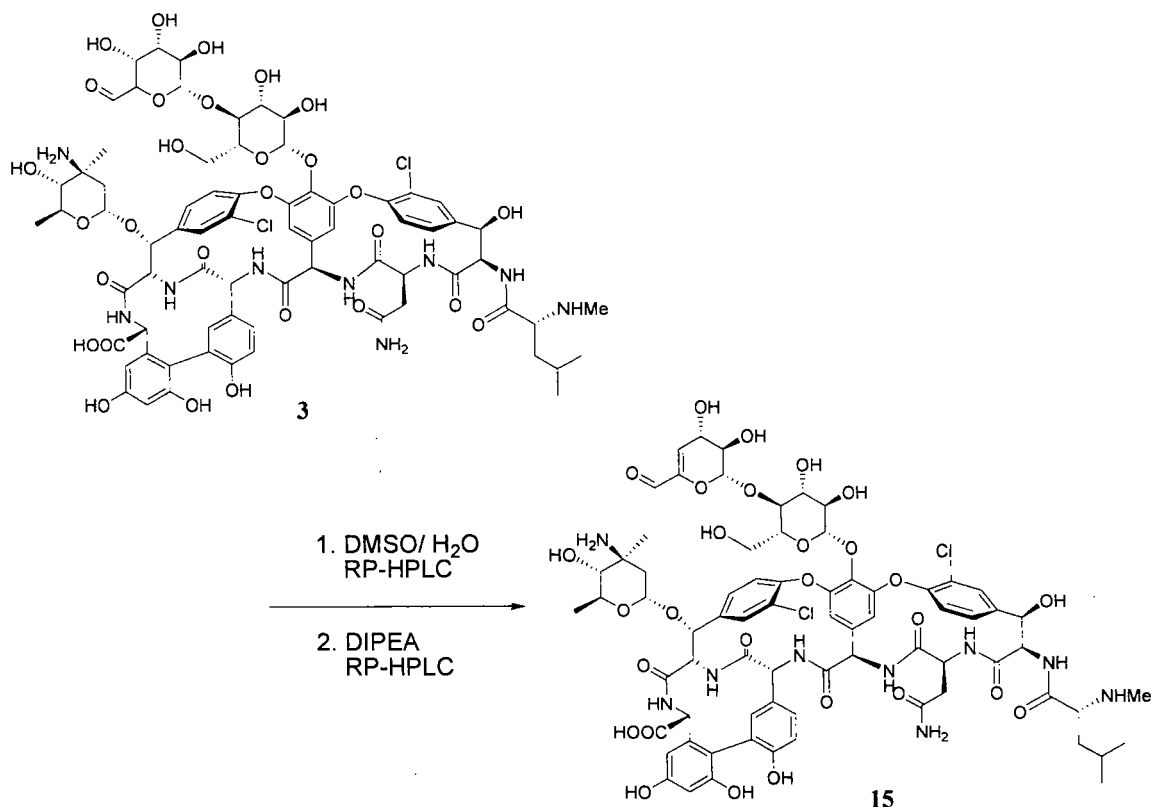
The compound **13** obtained in the eighth step (435 mg 1.4 mmol) was dissolved in mixed solvent of 20 mL of dimethylformamide and 60 mL of methanol. The compound **9** obtained in the fifth step (241 mg, 0.14 mmol) was added, and the mixture was stirred at room temperature for 3 hours. Sodium cyanoborohydride (45 mg, 0.72 mmol) was added, and the mixture was stirred at 70°C for 3 hours. The reaction solutions was poured into diethyl ether, the produced precipitate was collected by filtration, and the resulting crude solid was washed with 5% aqueous sodium chloride solution to remove unreacted sodium cyanoborohydride. The resulting crude solid was purified by reverses phase column chromatography to obtain 52 mg (yield 18%) of compound **14** as a colorless solid.

Example 80

[0152]

First step: Production of intermediate compound 15

[Chemical formula 88]



A compound 3 (547 mg, 0.34 mmol) which can be synthesized by the same procedure as that of Example 13 was dissolved in mixed solvent of 3 mL of dimethyl sulfoxide and 1 mL of water, and the solution was allowed to stand for 48 hours, and purified by reverse phase column chromatography to obtain crude purified compound 15 and unreacted compound 3.

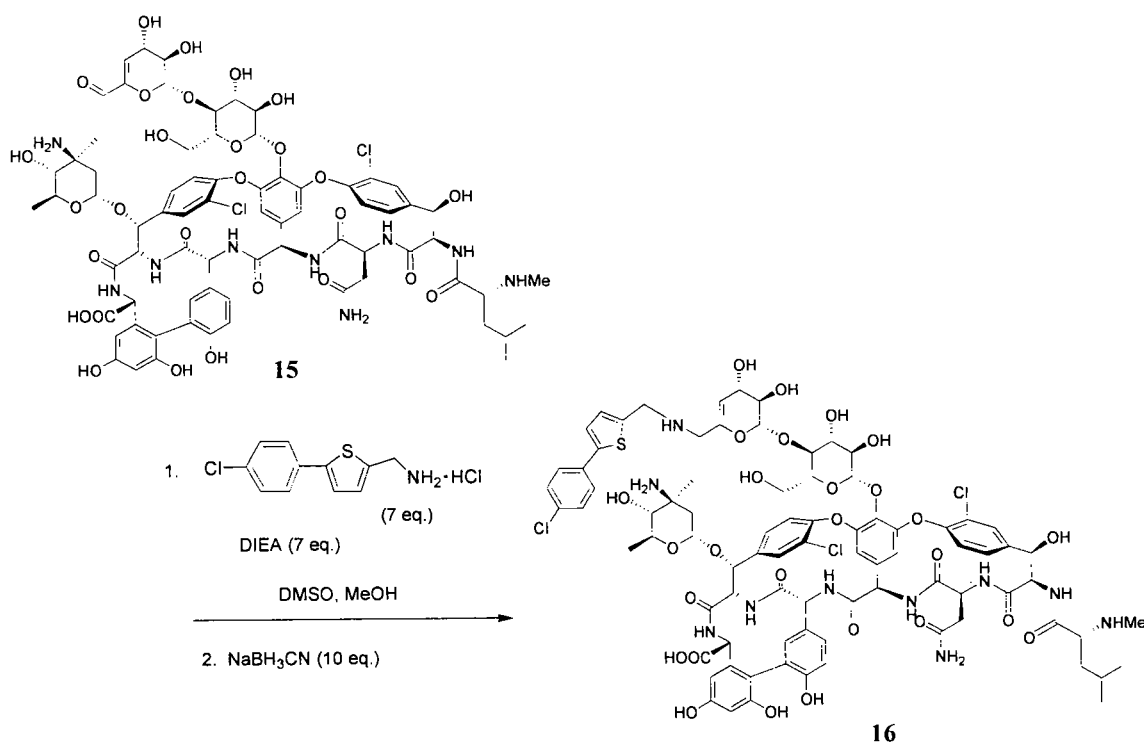
Subsequently, the unreacted compound 3 was dissolved in 3 mL of water, 0.3 mL of diisopropylethylamine was added and this was allowed to stand for 8 hours, and purified by reverse phase column chromatography to

obtain crude purified compound 15. The resulting crude purified compounds 15 were combined, and purified again by reverse phase column chromatography to obtain 189 mg (yield 35%) of compound 15 as a white powder.

[0153]

Second step: Production of objective compound 16

[Chemical formula 89]



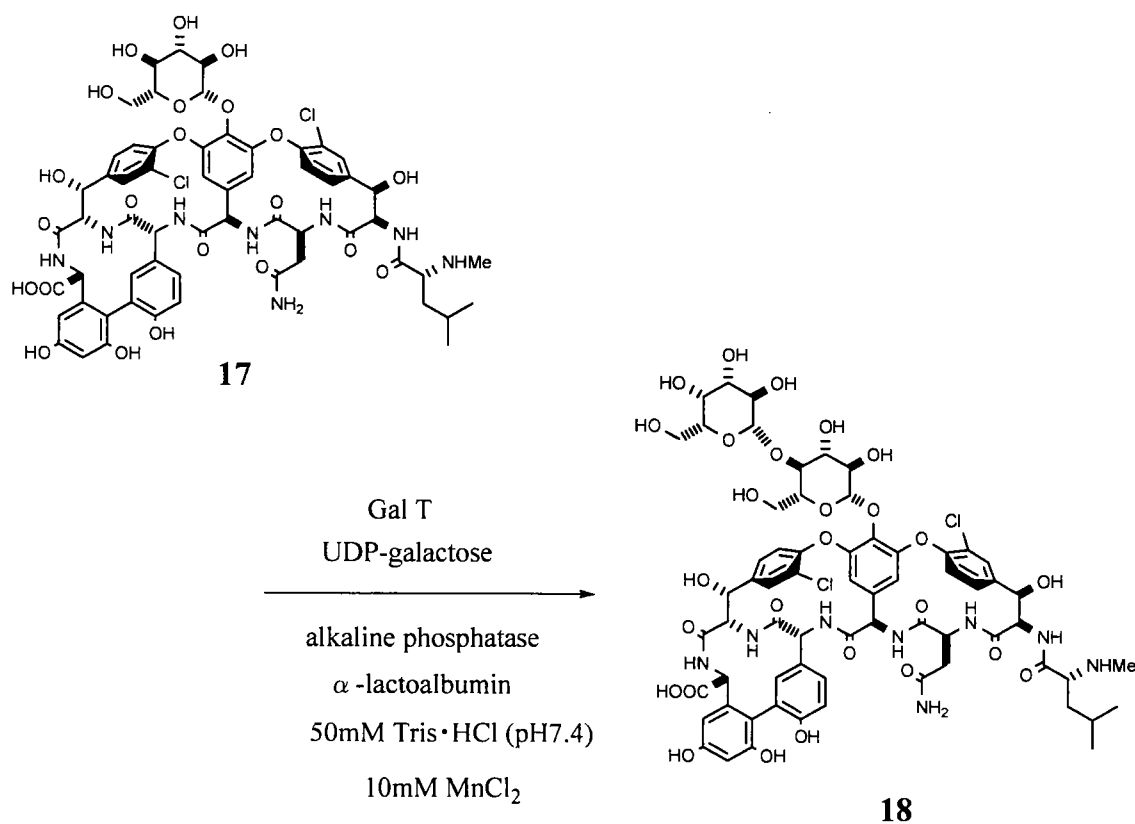
The compound 15 (248 mg, 0.156 mmol) was dissolved in mixed solvent of 7.2 mL of dimethyl sulfoxide and 7.2 mL of methanol, 273 mg (1.05 mmol) of (5-(4-chlorophenyl)thiophen-2-yl)methanamine hydrochloride and diisopropylamine (1.05 mmol) were added, and mixture was stirred at room temperature for 1.5 hours. Then, 94 mg (1.50 mmol) of sodium cyanoborohydride was added, and the mixture was stirred at 70°C for 2

stirred at 45°C for 1 hour. The precipitated solid was purified by HP20SS reverse phase column chromatography to obtain 16.5 g (yield 37.5%) of compound 17 as a colorless solid.

[0155]

Second step: Production of intermediate compound 18

[Chemical formula 91]

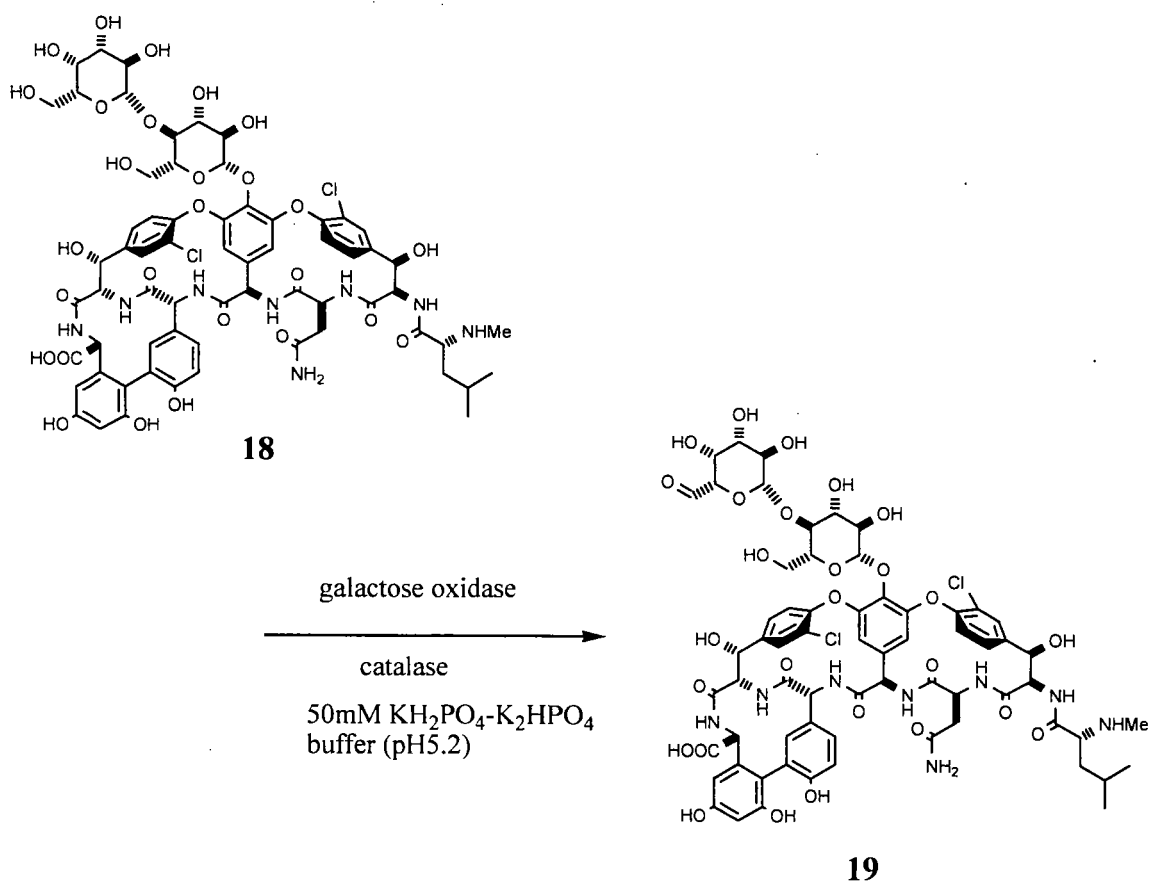


The compound 17 (40 mg, 0.031 mmol) was reacted by the same procedure as that of Example 13 to obtain 25 mg (yield 55.6%) of compound 18 as a colorless solid.

[0156]

Third step: Production of intermediate compound 19

[Chemical formula 92]

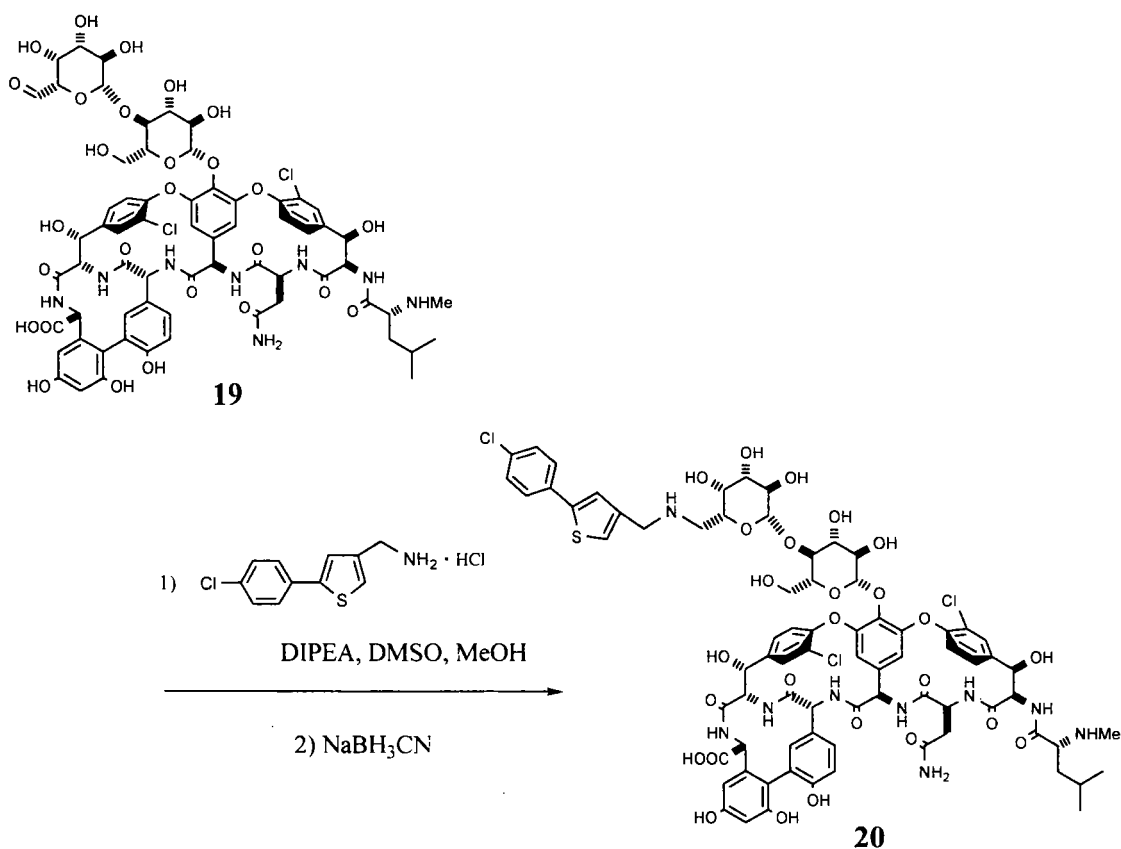


The compound 18 (300 mg, 0.204 mmol) was dissolved in 90 mL of 50 mM $\text{KH}_2\text{PO}_4\text{-K}_2\text{HPO}_4$ buffer (pH 5.2). Catalase, and Dactylium dendroides-derived galactose oxidase were sequentially added, and the mixture was stirred at 30°C for 24 hours. The reaction mixture was purified by HP20SS reverse phase column chromatography to obtain 262 mg (yield 87%) of compound 19 as a white powder.

[0157]

Fourth step: Production of objective compound 20

[Chemical formula 93]



The compound 19 (350 mg, 0.24 mmol) was dissolved in mixed solvent of 10 mL of dimethyl sulfoxide and 10 mL of methanol. To this solution were added 435 mg (1.7 mmol) of (5-(4-chlorophenyl) thiophen-3-yl) methanamine hydrochloride, and 0.29 mL (1.7 mmol) of diisopropylethylamine, and the mixture was stirred at room temperature for 2 hours. Sodium cyanoborohydride (167 mg, 2.4 mmol) was added, and the mixture was stirred at 70°C for 1 hour. After methanol in the reaction solution was distilled off under reduced pressure, the remaining solution was poured into ethyl acetate, then the produced precipitate was collected by filtration, and the resulting crude solid was rinsed with 10% aqueous sodium chloride solution. The resulting crude solid was purified by reverse phase

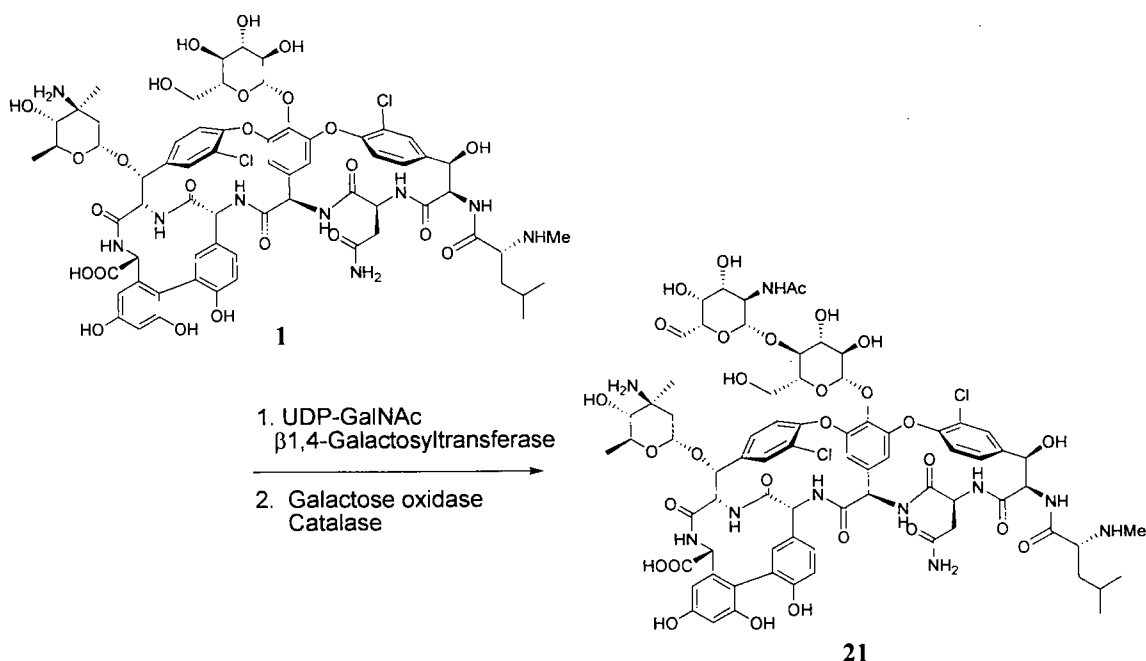
column chromatography to obtain 115 mg (yield 29%) of compound 20 as a colorless solid.

Synthesis Example 121

[0158]

First step: Production of intermediate compound 21

[Chemical formula 94]

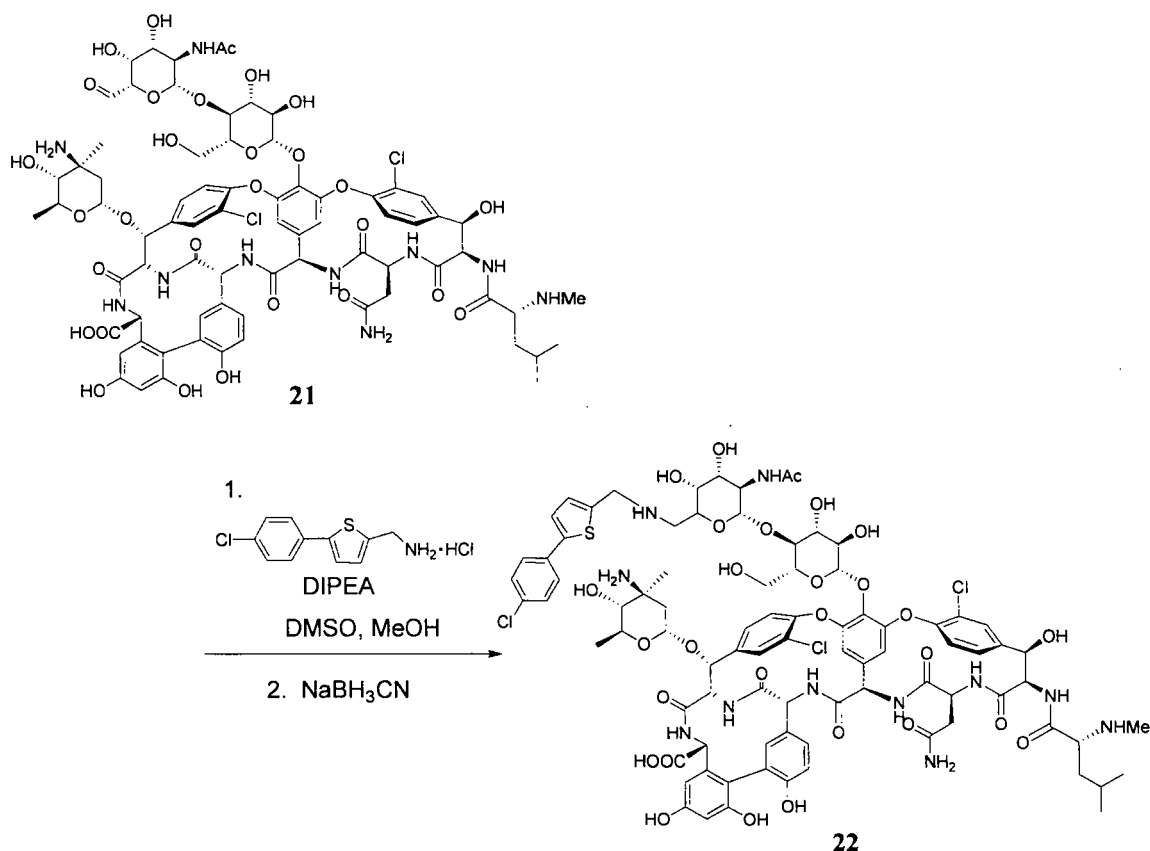


Synthesis was performed according to the same procedure like Example 13, and 592 mg (HPLC purity 65%, yield 56%) of mixture containing compound 21 and unreacted compound 1 was obtained from 600 mg (0.41 mmol) of compound 1 as a raw material.

[0159]

Second step: Synthesis of objective compound 22

[Chemical formula 95]



Synthesis was performed according to the same procedure like Example 13, and 80.2 mg (0.043 mmol, yield 36%) of compound 22 as a white powder was obtained from 300 mg (HPLC purity 65%, 0.118 mmol) of mixture containing compound 21 as a raw material.

[0160]

Test Example 1

In vitro measurement of antibacterial activity

(Test method)

Some of the present compounds were measured for a minimum growth inhibition concentration (MIC) by a small amount of liquid dilution method using a cation-adjusted Muller Hinton liquid medium well-known to

a person skilled in the art.

(Result)

The present compounds exhibited the high antibacterial activity against various bacterium including vancomycin-resistant bacterium. Particularly, compounds of Examples 1, 5, 6, 10, 11, 13, 30, 31, 43, 45, 50, 65, 69, 75, 82, 83, 85 and 88 had MIC: 2 to 4 µg/ml against *E. faecalis* SR7914 which is vancomycin-resistant *Enterococcus* (VRE VanA), and MIC: 1 to 4 µg/ml (vancomycin is >64 µg/ml) against *E. faecium* SR7940, and exhibited the remarkably higher activity than the existing drugs.

[0161]

Preparation Example

Following Preparation Examples 1 to 8 are illustrative, and are not meant to limit the scope of the invention at all. The term “active ingredient” means the present compound, a tautomer thereof, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof.

[0162]

Preparation Example 1

A hard gelatin capsule is produced using the following ingredients :

	Dose (mg/capsule)
Active ingredient	250
Starch (dry)	200
Magnesium stearate	10
Total	460 mg

[0163]

Preparation Example 2

A tablet is produced using the following ingredients:

	Dose (mg/tablet)
Active ingredient	250
Cellulose (microcrystalline)	400
Silicon dioxide (fumed)	10
Stearic acid	5
Total	665 mg

Ingredients are mixed, and compressed into a tablet of a weight of 665 mg.

[0164]

Preparation Example 3

An aerosol solution containing the following ingredients is produced:

	Weight
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (chlorodifluoromethane)	74.00
Total	100.00

An active ingredient and ethanol are mixed, this mixture is added to a part of a propellant 22, and this is cooled to -30°C, and then is transferred to a filling apparatus. Then, a required amount is supplied to a stainless steel container, and this is diluted with a remaining propellant. A valve unit is attached to a container.

[0165]

Preparation Example 4

A tablet containing 60 mg of an active ingredient is produced as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (10% solution in water)	4 mg
Sodium carboxymethylstarch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

An active ingredient, starch and cellulose are applied to a sieve of No. 45 mesh U.S., and are mixed well. An aqueous solution containing polyvinylpyrrolidone is mixed with the resulting powder and, then, the mixture is passed through a No. 14 mesh U.S. sieve. The thus obtained granule is dried at 50°C, and passed through a No. 18 mesh U.S. sieve. Sodium carboxymethylstarch, magnesium stearate and talc which have been passed through a No. 60 mesh U.S. sieve in advance are added to this granule, and these are mixed, and compressed with a tableting machine to obtain a tablet of a weight of 150 mg.

[0166]

Preparation Example 5

A capsule containing 80 mg of an active ingredient is produced as follows:

Active ingredient:	80 mg
--------------------	-------

Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

An active ingredient, starch, cellulose and magnesium stearate are mixed, and passed through a No. 45 mesh U.S. sieve, and each 200 mg is filled into hard gelatin capsule.

[0167]

Preparation Example 6

A suppository containing 225 mg of an active ingredient is produced as follows:

Active ingredient	225 mg
Saturated fatty acid glyceride	2000 mg
Total	2225 mg

An active ingredient is passed through a No. 60 mesh U.S. sieve, and is suspended in saturated fatty acid glyceride which has been heated requisition minimally and melted in advance. Then, this mixture is placed into a mold of apparently 2 g, and is cooled.

[0168]

Preparation Example 7

A suspension containing 50 mg of an active ingredient is produced as follows:

Active ingredient	50 mg
Sodium carboxymethylcellulose	50 mg
Syrup	1.25 ml

Benzoic acid solution	0.10 ml
Perfume	q.v.
Pigment	q.v.
Purified water ad.	5 ml

An active ingredient is applied to a sieve of No. 45 mesh U.S., and is mixed with sodium carboxymethylcellulose and a syrup to obtain a smooth paste. A benzoic acid solution and a perfume are diluted with a part or water and the mixture is stirred. Then, water is added at a sufficient amount to a required volume.

[0169]

Preparation Example 8

A preparation for intravenous injection is produced as follows:

Active ingredient	100 mg
Saturated fatty acid glyceride	1000 ml

A solution of the ingredients is usually intravenously administered to a patient at a rate of 1 ml per 1 minute.

[Industrial Applicability]

[0170]

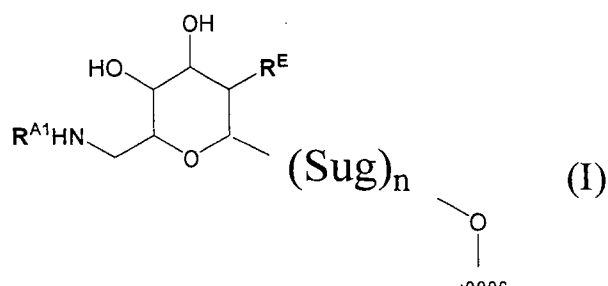
The glycopeptide derivative of the present invention, a pharmaceutically acceptable salt thereof and a solvate thereof are useful in medical treatment and exhibit the pharmacological activity including the antibacterial activity. The compound of the present invention is useful in treating infection caused by, particularly, meticillin-resistant *Staphylococcus aureus*. In addition, this compound is useful for treating infection with

Enterococcus including vancomycin-resistant *Enterococcus* (VRE). As an example of such a disease, there is serious staphylococcus infection, for example, staphylococcus endocarditis and staphylococcus sepsis.

CLAIMS

[Claim 1] A glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof, which is characterized in that a sugar residue (I) represented by the formula:

[Chemical Formula 1]



wherein

n is an integer of 1 to 5;

Sugs are each independently a monosaccharide, (Sug)_n is a divalent sugar residue formed by binding same or different 1 to 5 monosaccharides;

R^{A1} is optionally substituted lower alkyl, optionally substituted lower alkenyl, or optionally substituted cycloalkyl; and

R^E is OH or NHAc (Ac is acetyl);

is bound to an aromatic ring of the fourth amino acid residue in a glycopeptide skeleton.

[Claim 2] The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 1, wherein the monosaccharide is selected from the group consisting of glucose, galactose,

fructose, fucose, mannose, rhamnose, galactosamine, glucosamine, N-acetylgalactosamine, N-acetylglucosamine, vancosamine, epi-vancosamine, glucuronic acid, sialic acid, deoxyglucose, and deoxygalactose.

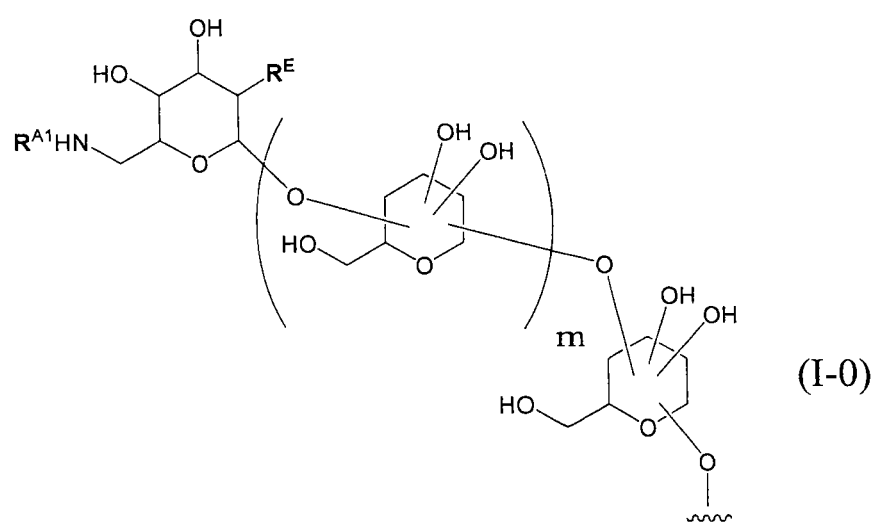
[Claim 3] The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 1, wherein the monosaccharide is glucose.

[Claim 4] The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of claims 1 to 3, wherein n is 1 or 2.

[Claim 5] The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 1, wherein the monosaccharide is glucose; and n is 1 or 2.

[Claim 6] The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 1, wherein the sugar residue (I) is a sugar residue (I-0) represented by the formula:

[Chemical Formula 2]



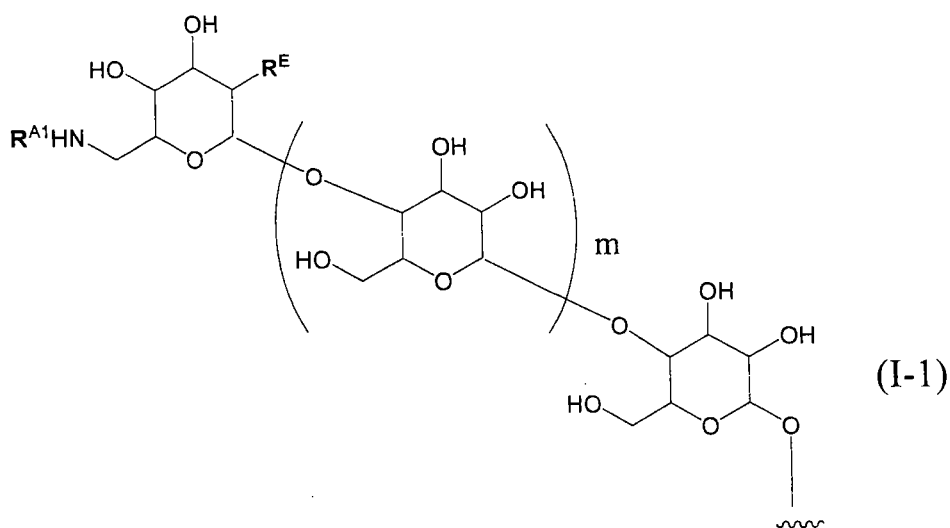
wherein

m is an integer of 0 to 4; and

R^{A1} and R^E are each as defined in claim 1.

[Claim 7] The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 1, wherein the sugar residue (I) is a sugar residue (I-1) represented by the formula:

[Chemical formula 3]



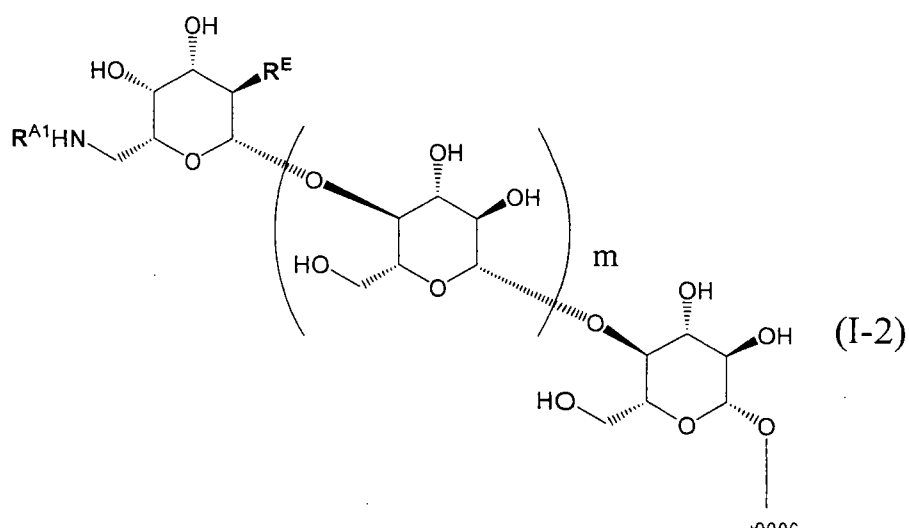
wherein

m is an integer of 0 to 4; and

R^{A1} and R^E are each as defined in claim 1.

[Claim 8] The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 1, wherein the sugar residue (I) is a sugar residue (I-2) represented by the formula:

[Chemical formula 4]



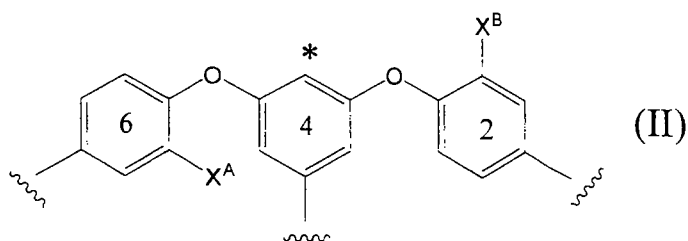
wherein

m is an integer of 0 to 4; and

R^{A1} and R^E are each as defined in claim 1.

[Claim 9] The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of claims 1 to 8, wherein the compound has a partial structure (II) represented by the formula:

[Chemical formula 5]

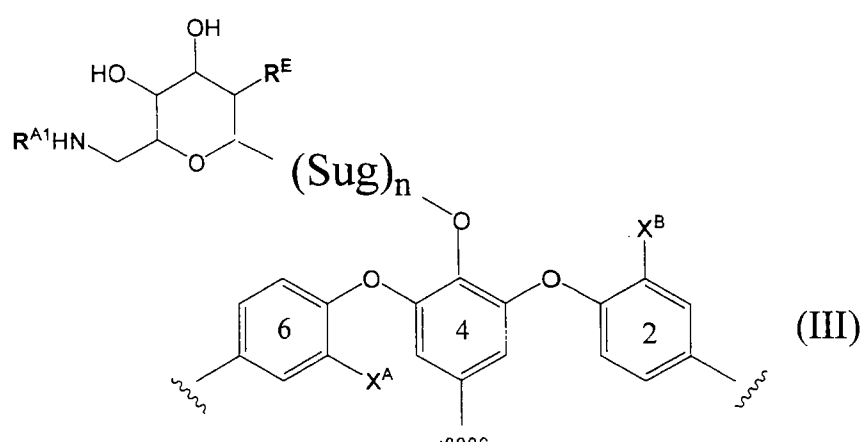


wherein the ring 2, the ring 4 and the ring 6 represent aromatic rings of the second, fourth and sixth amino acid residues of a glycopeptide antibiotic,

respectively; X^A and X^B each represent independently hydrogen or halogen; and * represents a binding position with a sugar residue.

[Claim 10] The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 1, wherein the compound has a partial structure (III) represented by the formula:

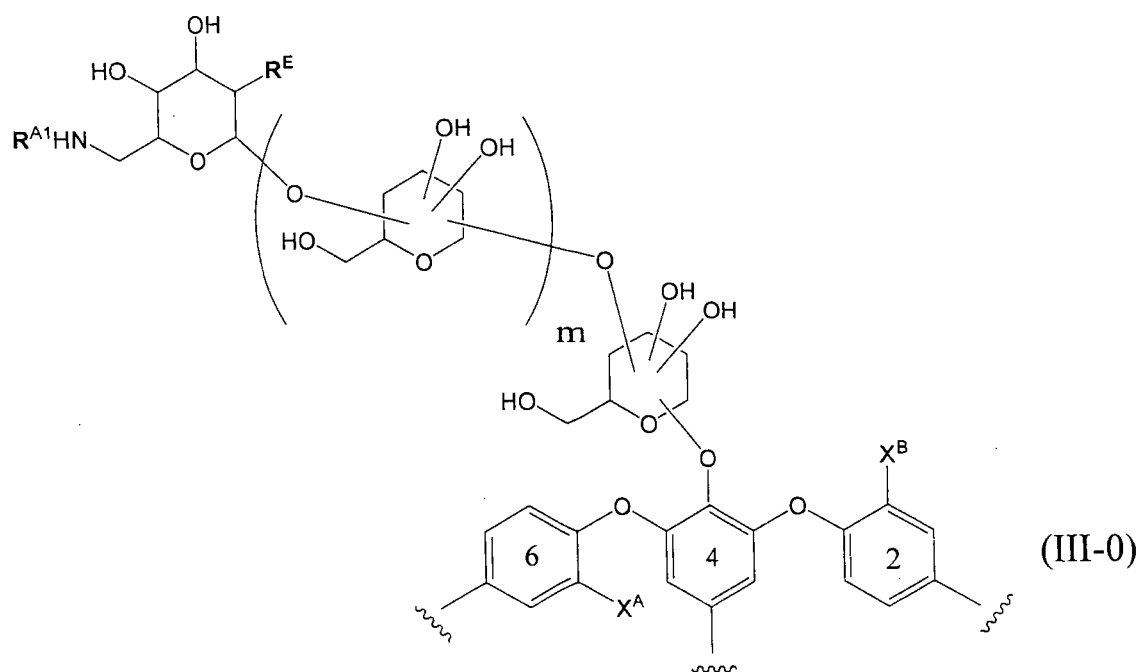
[Chemical formula 6]



wherein the ring 2, the ring 4 and the ring 6 represent aromatic rings of the second, fourth and sixth amino acid residues of a glycopeptide antibiotic, respectively; X^A and X^B each represent independently hydrogen or halogen; and other symbols are each as defined in claim 1.

[Claim 11] The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 10, wherein the partial structure (III) is a partial structure (III-0) represented by the formula:

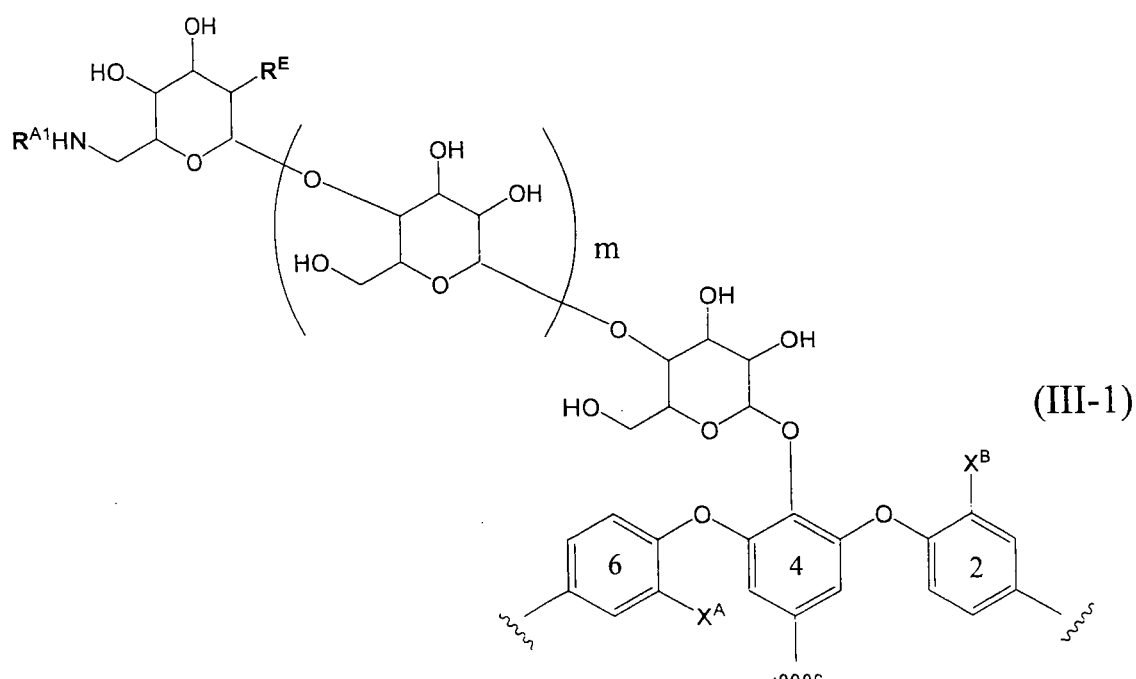
[Chemical formula 7]



wherein the ring 2, the ring 4 and the ring 6 represent aromatic rings of the second, fourth and sixth amino acid residues of a glycopeptide antibiotic; X^A and X^B each represent independently hydrogen or halogen; m is an integer of 0 to 4; and R^{A1} and R^E are each as defined in claim 1.

[Claim 12] The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 10, wherein the partial structure (III) is a partial structure (III-1) represented by the formula:

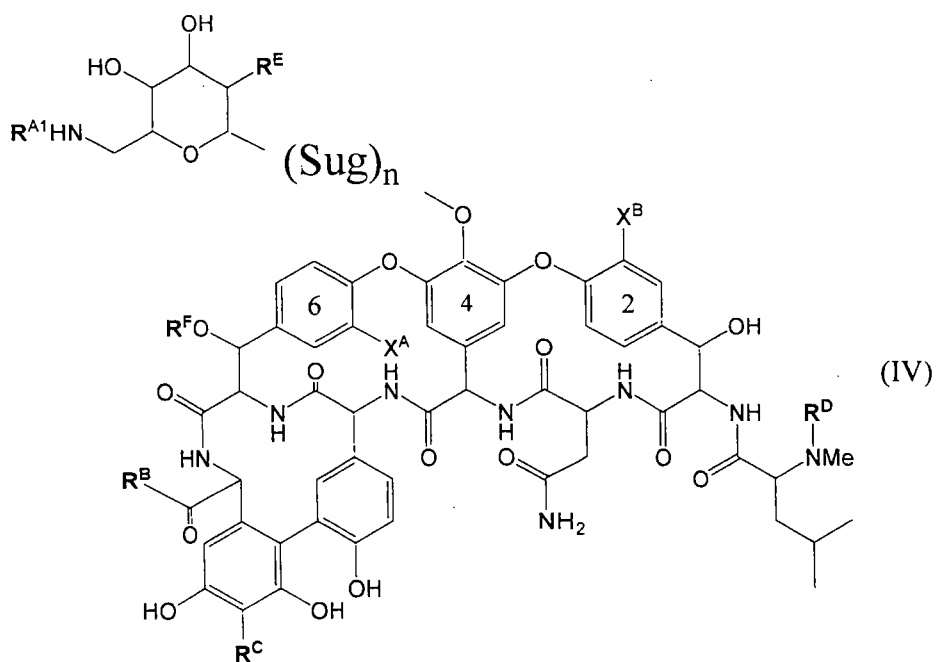
[Chemical formula 8]



wherein the ring 2, the ring 4 and the ring 6 represent aromatic rings of the second, fourth and sixth amino acid residue of a glycopeptides antibiotic, respectively; X^A and X^B each represents independently hydrogen or halogen; m is an integer of 0 to 4; and R^{A1} and R^E are each as defined in claim 1.

[Claim 13] The glycopeptide compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 10, wherein the partial structure (III) is a partial structure (III-2) represented by the formula:

[Chemical formula 9]



wherein

R^F is hydrogen or a sugar residue;

R^B is $\cdot\text{OH}$, $\cdot\text{NR}^5\text{R}^{5'}$ (wherein R^5 and $R^{5'}$ each are independently hydrogen, optionally substituted lower alkyl, optionally substituted lower alkyloxy, or optionally substituted amino or amino acid residue) or --OR^6 (wherein R^6 is optionally substituted lower alkyl (a hetero atom group may intervene in the lower alkyl part));

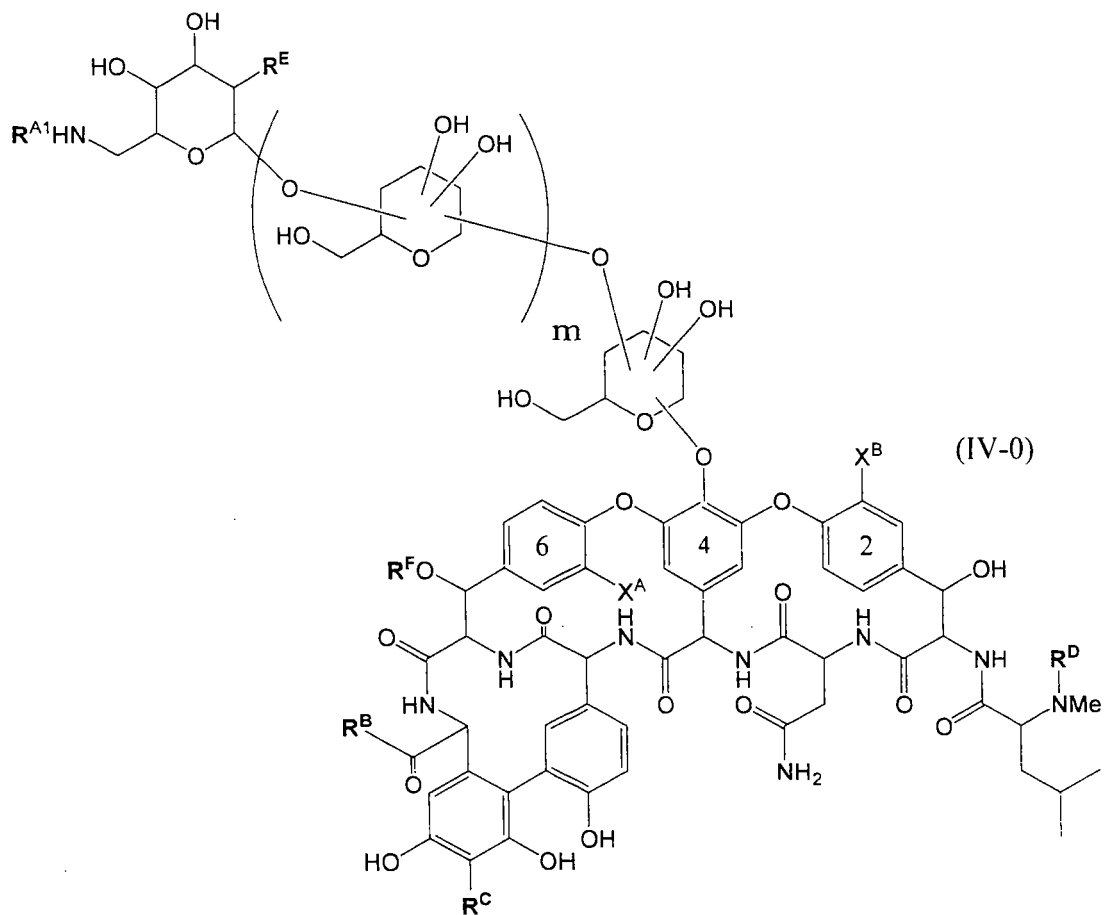
R^C is hydrogen or optionally substituted alkyl (a hetero atom group may intervene in the lower alkyl part);

R^D is hydrogen or lower alkyl; and

other symbols are each as defined in claim 1.

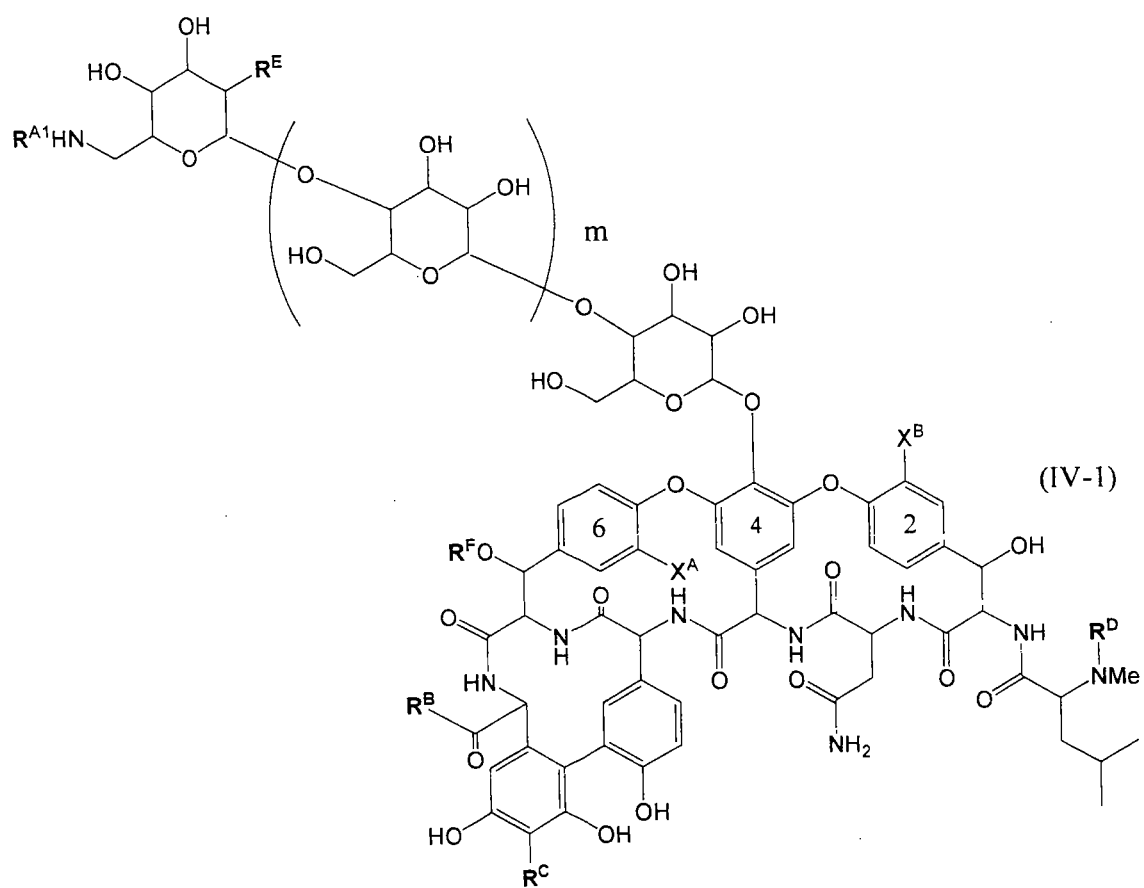
[Claim 16] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 15, wherein the compound is represented

[Chemical formula 11]



other symbols are each as defined in claim 15.

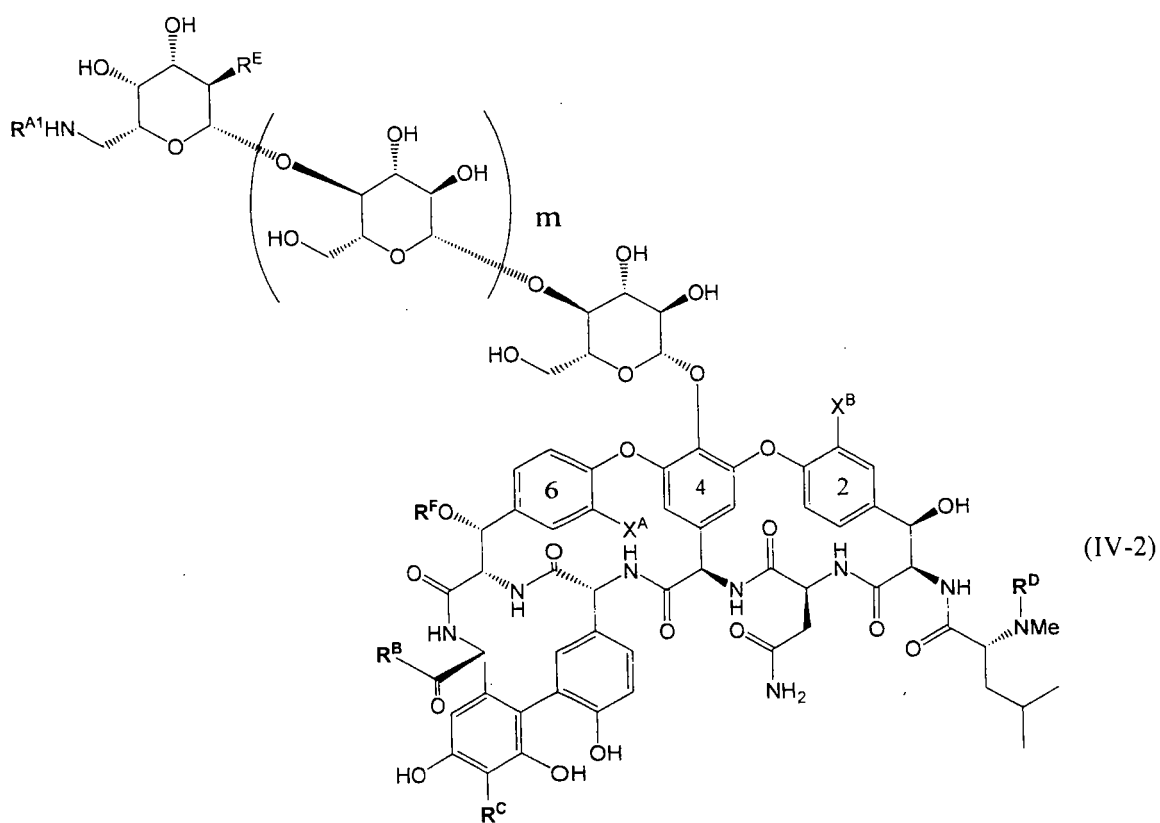
[Chemical formula 12]



wherein respective symbols are each as defined in claim 16.

[Claim 18] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 16, wherein the compound is represented by the formula:

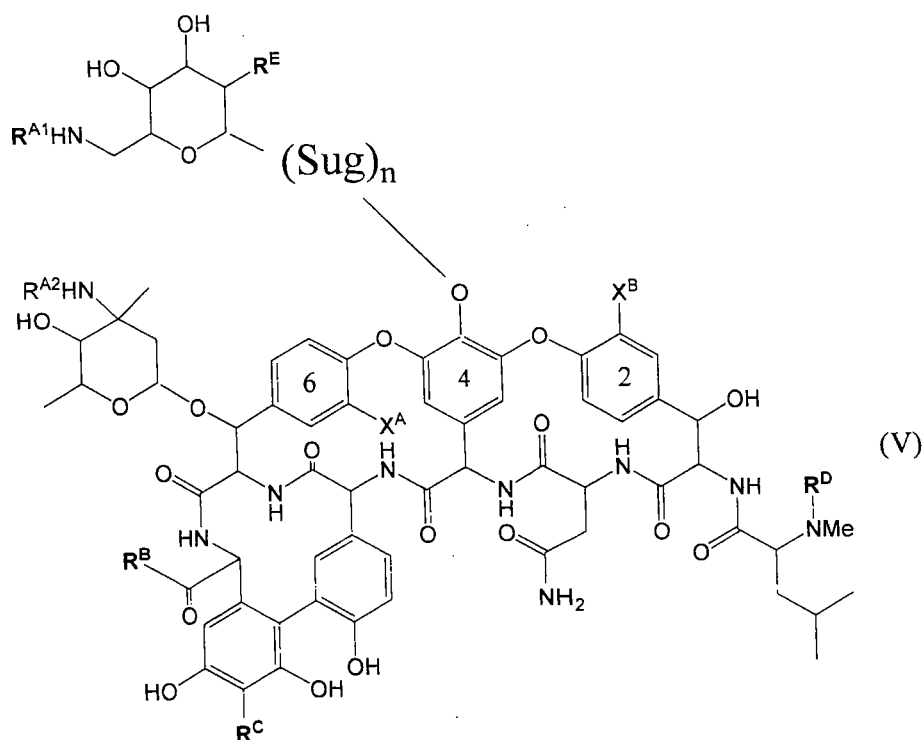
[Chemical formula 13]



wherein respective symbols are each as defined in claim 16.

[Claim 19] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 1, wherein the compound is represented by the formula:

[Chemical formula 14]



wherein

R^{A2} is hydrogen or optionally substituted lower alkyl;

R^B is $-OH$, $-NR^5R^{5'}$ (wherein R^5 and $R^{5'}$ each are independently hydrogen, optionally substituted lower alkyl, optionally substituted lower alkyloxy, optionally substituted amino or amino sugar residue) or $-OR^6$ (wherein R^6 is optionally substituted lower alkyl (a hetero atom group may intervene in the lower alkyl part));

R^C is hydrogen or optionally substituted lower alkyl (a hetero atom group may intervene in the lower alkyl part);

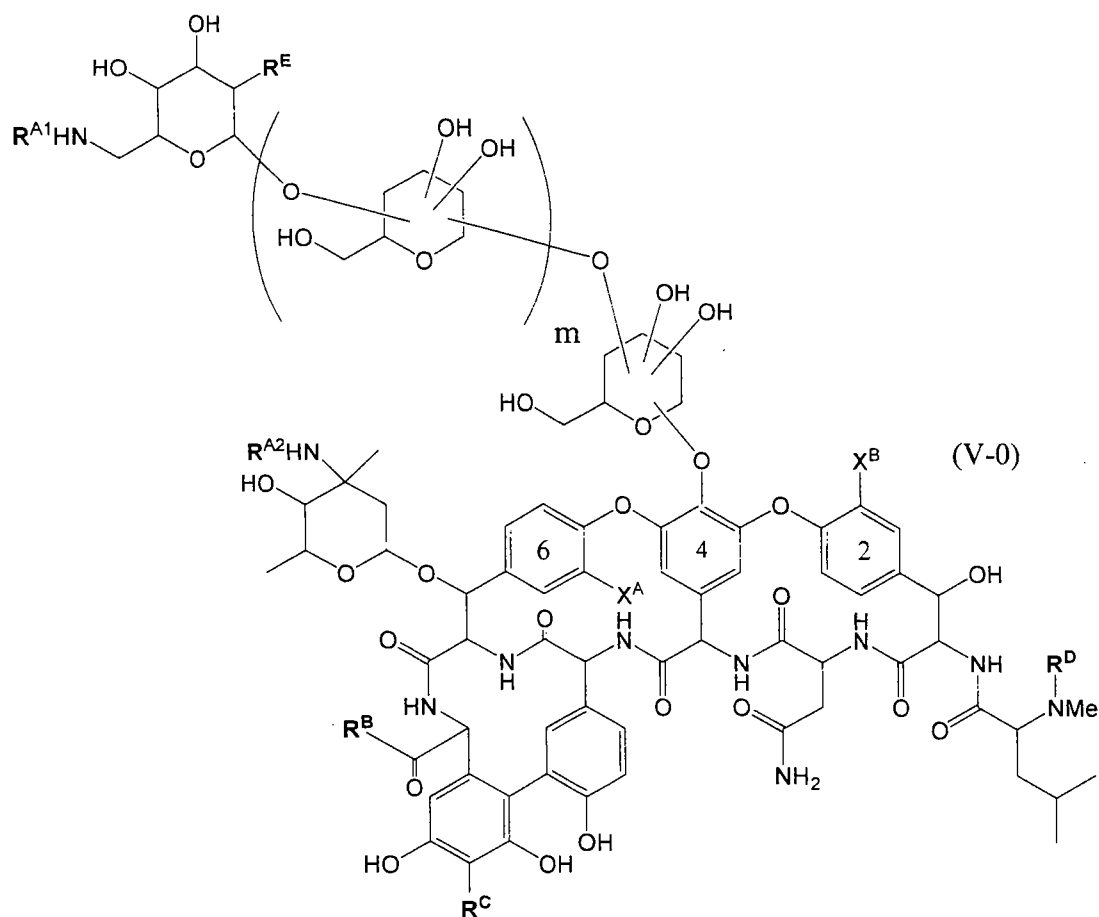
R^D is hydrogen or lower alkyl;

X^A and X^B each are independently hydrogen or halogen; and

other symbols are each as defined in claim 1.

[Claim 20] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 19, wherein the compound is represented by the formula:

[Chemical formula 15]



wherein

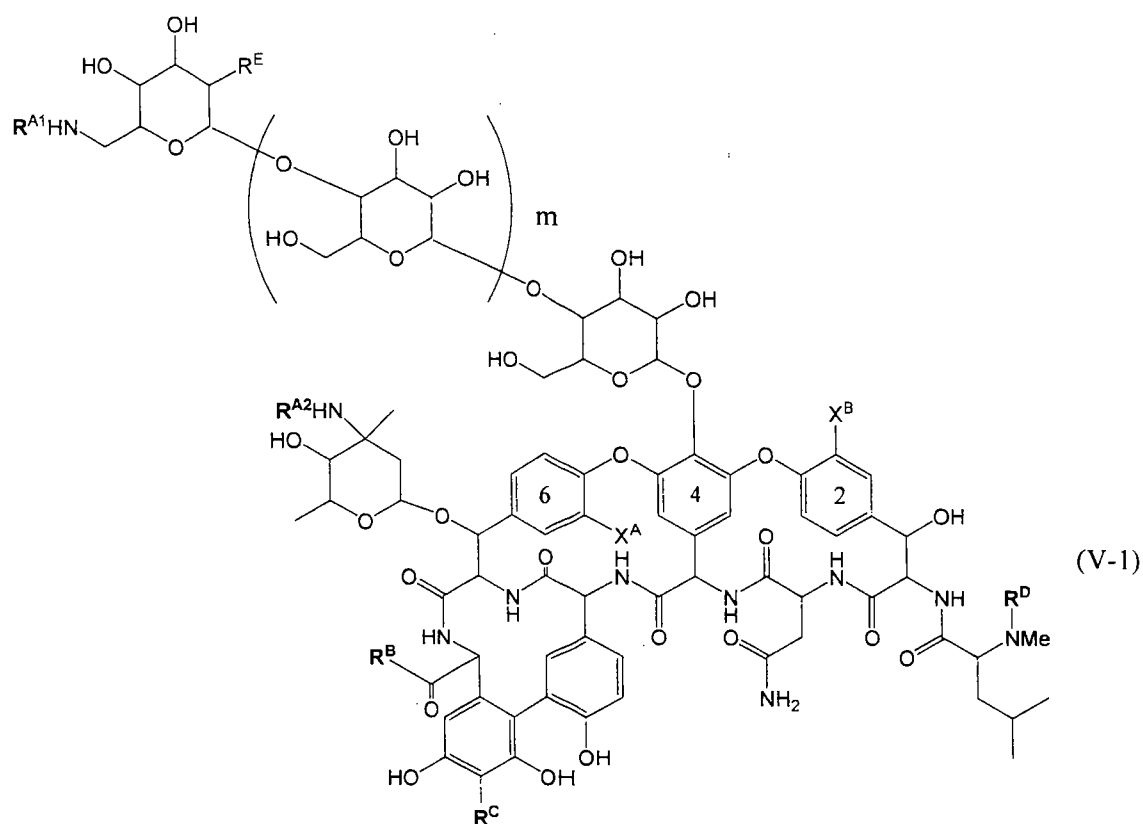
m is an integer of 0 to 4; and

other symbols are each as defined in claim 19.

[Claim 21] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 20, wherein the compound is represented

by the formula:

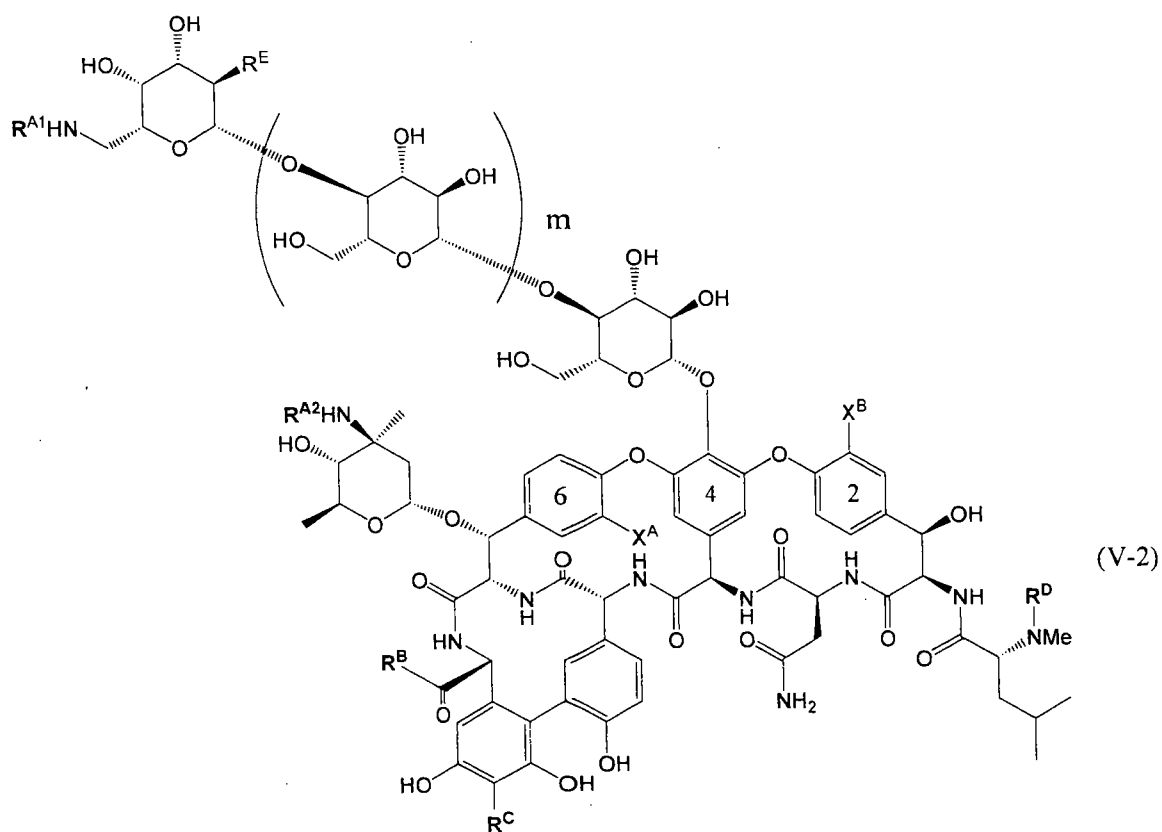
[Chemical formula 16]



wherein respective symbols are each as defined in claim 20.

[Claim 22] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 20, wherein the compound is represented by the formula:

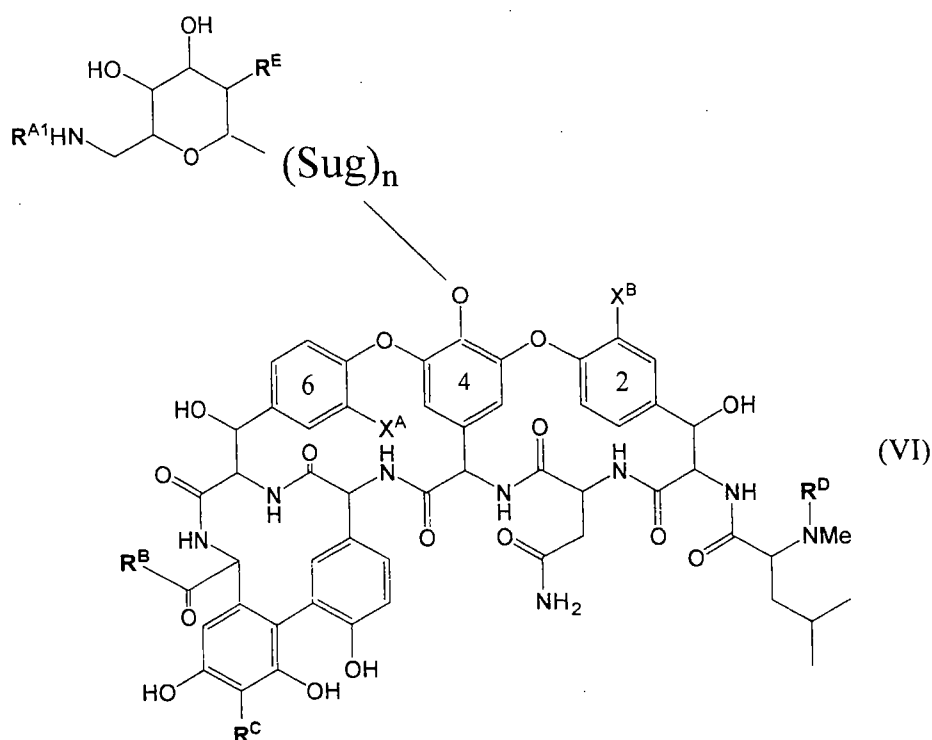
[Chemical formula 17]



wherein respective symbols are each as defined in claim 20.

[Claim 23] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 1, wherein the compound is represented by the formula:

[Chemical formula 18]



wherein

R^B is $-OH$, $-NR^5R^{5'}$ (wherein R^5 and $R^{5'}$ each are independently hydrogen, optionally substituted alkyl, optionally substituted alkyloxy, or optionally substituted amino or amino sugar residue) or $-OR^6$ (wherein R^6 is optionally substituted alkyl (a hetero atom group may intervene in the alkyl part));

R^C is hydrogen or optionally substituted alkyl (a hetero atom group may intervene in the alkyl part);

R^D is hydrogen or lower alkyl;

X^A and X^B each are independently hydrogen or halogen; and

other symbols are each as defined in claim 1.

[Claim 24] The compound, a pharmaceutically acceptable salt thereof, or

[Chemical formula 19]



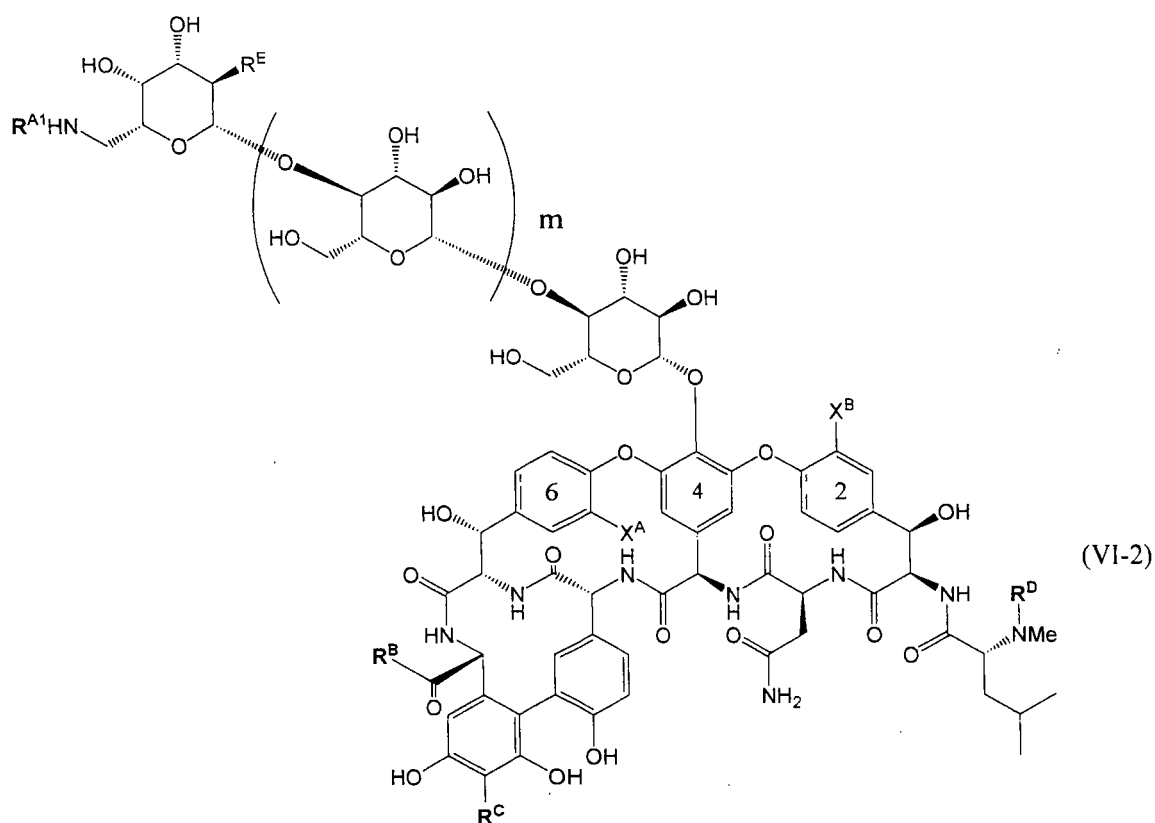
other symbols are each as defined in claim 23.

- 215 -

Chemical structure (VI-1) is a complex molecule. It features a repeating unit in parentheses, labeled 'm', which consists of a pyranose ring with hydroxyl groups and a substituent R^E. This unit is linked via an ether bond to a pyranose ring with hydroxyl groups and a substituent R^{A1}HN. The structure also includes a substituted benzene ring with a hydroxyl group, a substituent R^C, and a substituent R^B. The benzene ring is connected to a chain of amide and ester groups, which includes a substituent R^D and a substituent X^B. The structure is labeled (VI-1).

[Claim 26] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 24, wherein the compound is represented by the formula:

- 216 -



wherein respective symbols are each as defined in claim 24.

[Claim 27] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of claims 6 to 8, 11 to 13, 16 to 18, 20 to 22, and 24 to 26, wherein m is 0 or 1.

[Claim 28] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of claims 1 to 27, wherein R^E is OH.

[Claim 29] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of claims 1 to 28, wherein each substituents in optionally substituted lower alkyl, optionally substituted

lower alkenyl, or optionally substituted cycloalkyl, of R^{A1} are selected from the following Substituent group A.

Substituent group A: optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, optionally substituted aralkylthio, optionally substituted heteroaralkylthio, optionally substituted cycloalkyl, optionally substituted lower alkyloxy, optionally substituted aralkyloxy, optionally substituted aryloxy, optionally substituted arylsulfonylamino, and optionally substituted amino

[Claim 30] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 29, wherein each substituents of “optionally substituted” groups in Substituent group A of claim 29 are selected from the following Substituent group B.

Substituent group B: optionally substituted arylaminocarbonylamino, optionally substituted arylaminocarbonyl, optionally substituted arylcarbonyl, optionally substituted arylcarbonylamino, optionally substituted arylcarbonylaminoalkyl, oxo, halogen, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthio, optionally substituted arylamino, optionally substituted arylaminoalkyl, optionally substituted arylaminocarbonylalkyl, optionally substituted arylsulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted amino, optionally substituted aralkylcarbonylamino, optionally substituted aralkylamino, optionally substituted aralkylaminocarbonyl, optionally substituted aralkylsulfinyl, optionally substituted arylsulfonylamino, optionally substituted

arylamino sulfonyl, optionally substituted aralkylthio, halo lower alkyl, lower alkyloxy, lower alkylamino, halo lower alkyloxy, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylthio, optionally substituted aryl lower alkenyl, optionally substituted heteroaryl lower alkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkyloxy, optionally substituted cycloalkylthio, optionally substituted cycloalkylaminocarbonyl, optionally substituted cycloalkyl lower alkenyl, optionally substituted cycloalkylsulfonyl, optionally substituted cycloalkylaminocarbonylamino, optionally substituted cycloalkylaminoalkyl, optionally substituted cycloalkyl lower alkylamino, optionally substituted cycloalkylamino, optionally substituted cycloalkyl lower alkyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonylamino, optionally substituted cycloalkylcarbonylamino, optionally substituted cycloalkylcarbonylaminoalkyl, optionally substituted cycloalkyl lower alkylaminocarbonyl, optionally substituted cycloalkylsulfonylamino, optionally substituted cycloalkylaminocarbonylalkyl, and optionally substituted cycloalkylaminosulfonyl

[Claim 31] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to claim 30, wherein each substituents of “optionally substituted” groups in Substituent group B of claim 30 are selected from the following Substituent group C.

Substituent group C: lower alkyl, lower alkyloxy, lower alkylsulfonyl, nitro, aralkyloxy, halogen, cyano, halo lower alkyl, halo lower alkyloxy, and di-lower alkylamino

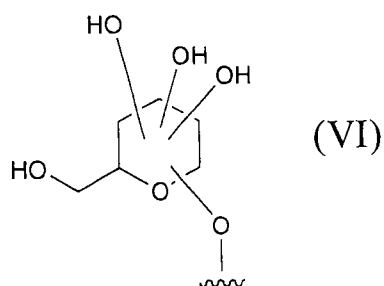
[Claim 32] The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of claims 15 to 31, wherein R^B is OH; R^C is H; and R^D is H.

[Claim 33] A process for producing the glycopeptide compound, a pharmaceutically acceptable salt thereof or a solvate thereof as defined in claim 6, comprising the following steps:

(step 1)

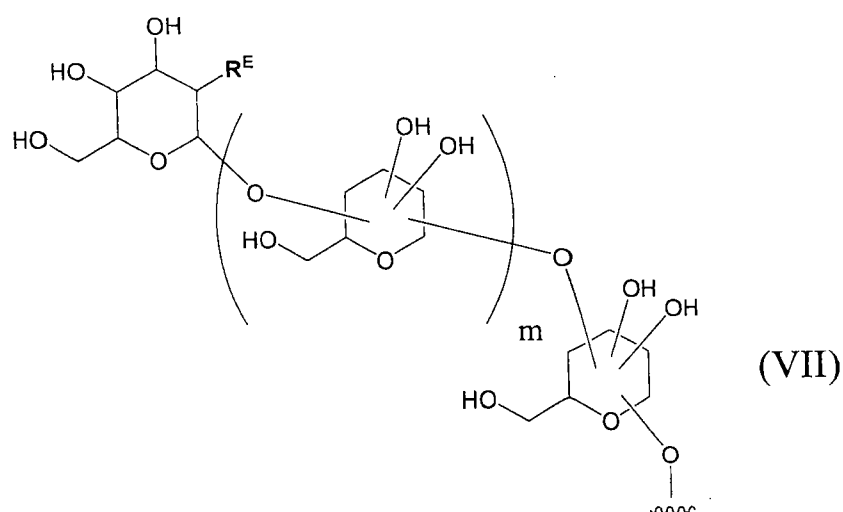
a step converting a sugar residue (VI) represented by the formula:

[Chemical formula 22]



into a group (VII) represented by the formula:

[Chemical formula 23]



wherein R^E is OH or NHAc; and m is an integer of 0 to 2;

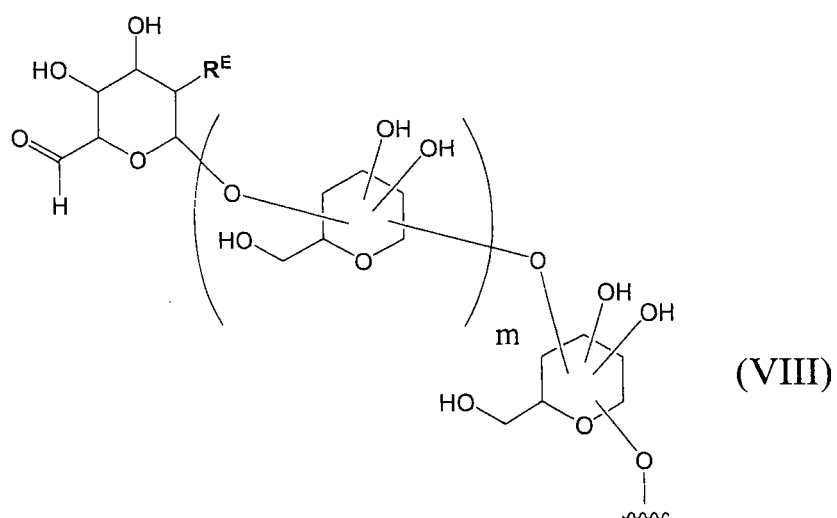
by performing $1+m$ (m is an integer of 0 to 2) times of glycosylating reaction in the presence of glycosyltransferase and a sugar donor using a glycopeptide compound, a salt thereof, or a solvate thereof as a raw material,

wherein an aromatic ring of a fourth amino acid residue is substituted with the sugar residue (VI);

(step 2)

a step converting the hydroxymethylene part in the sugar at the end of the group (VII) into a group (VIII) represented by the formula:

[Chemical formula 24]



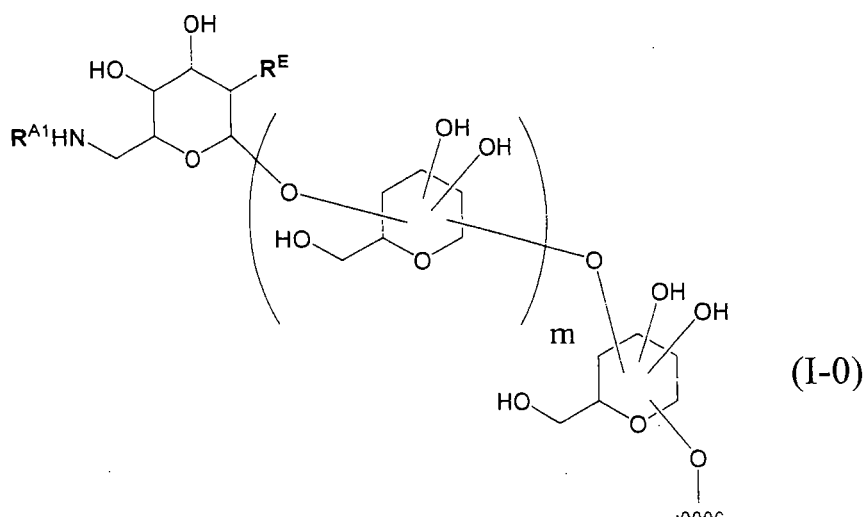
wherein respective symbols are as defined above;

by an oxidation reaction; and

(step 3)

a step converting the group (VIII) into a sugar residue (I-0) represented by the formula:

[Chemical formula 25]

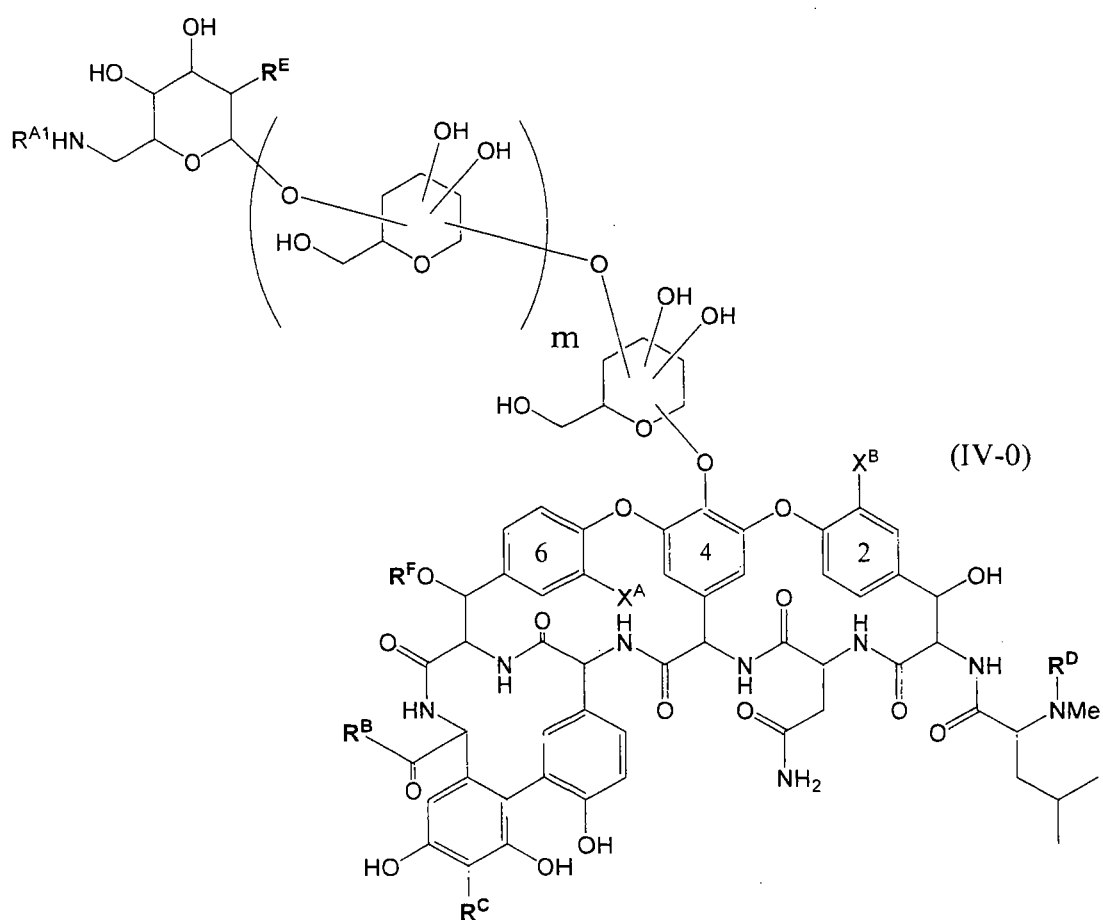


wherein respective symbols are as defined above;

by reductive amination reaction of the aldehyde group of the group (VIII) with a compound (A) represented by the formula $R^{A1}NH_2$.

[Claim 34] A process for producing the compound (IV-0), a pharmaceutically acceptable salt thereof or a solvate thereof as defined in claim 16 represented by the formula:

[Chemical formula 29]



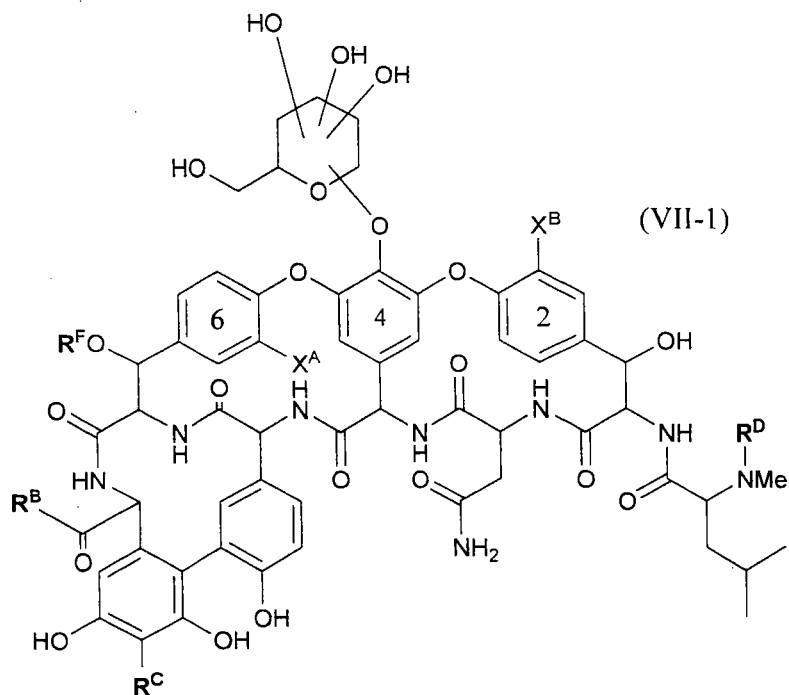
wherein respective symbols are as defined below,

comprising the following steps:

(step 1)

a step of reacting 1+m (m is an integer of 0 to 2) times of glycosylating reaction in the presence of glycosyltransferase and a sugar donor using a compound (VII-1) as a raw material, represented by the formula:

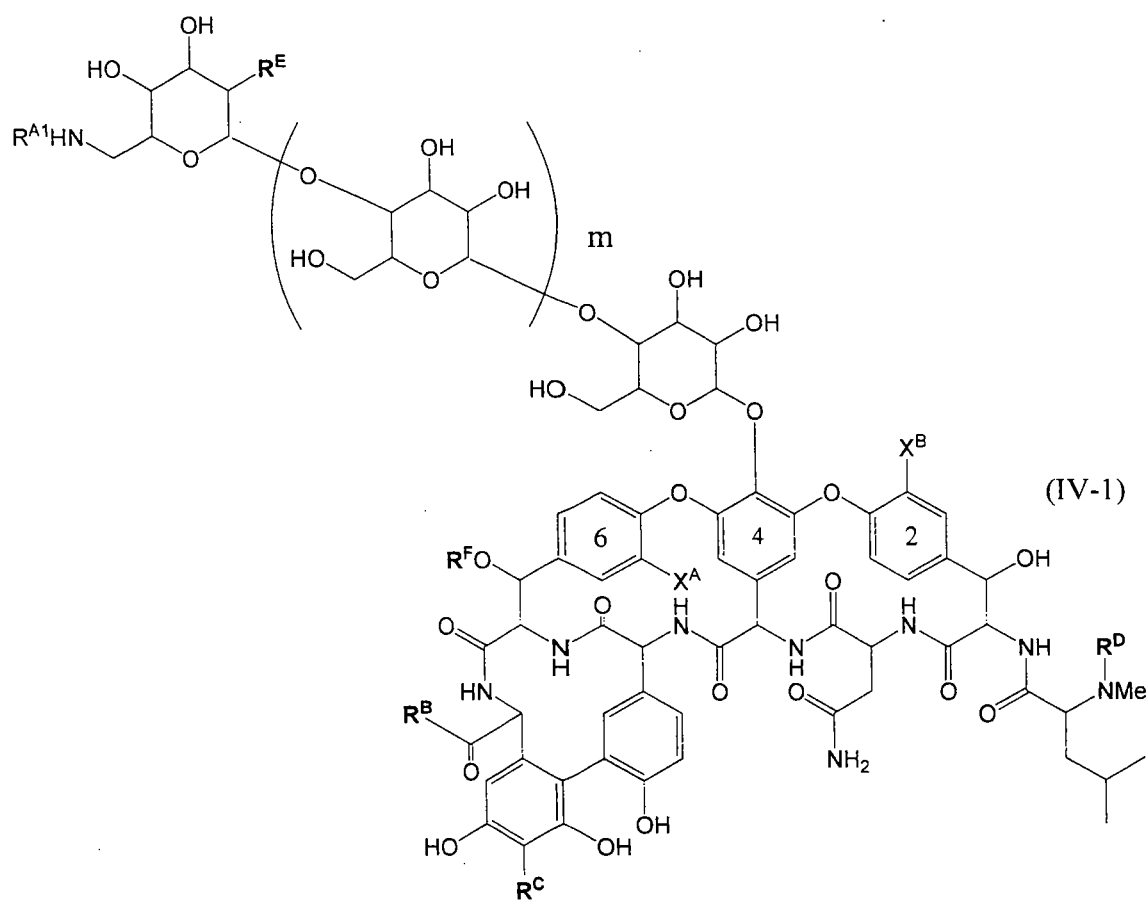
[Chemical formula 26]



wherein respective symbols are as defined in claim 15,

to obtain a compound (VIII-1), a salt thereof, or a solvate thereof represented by the formula:

[Chemical formula 27]



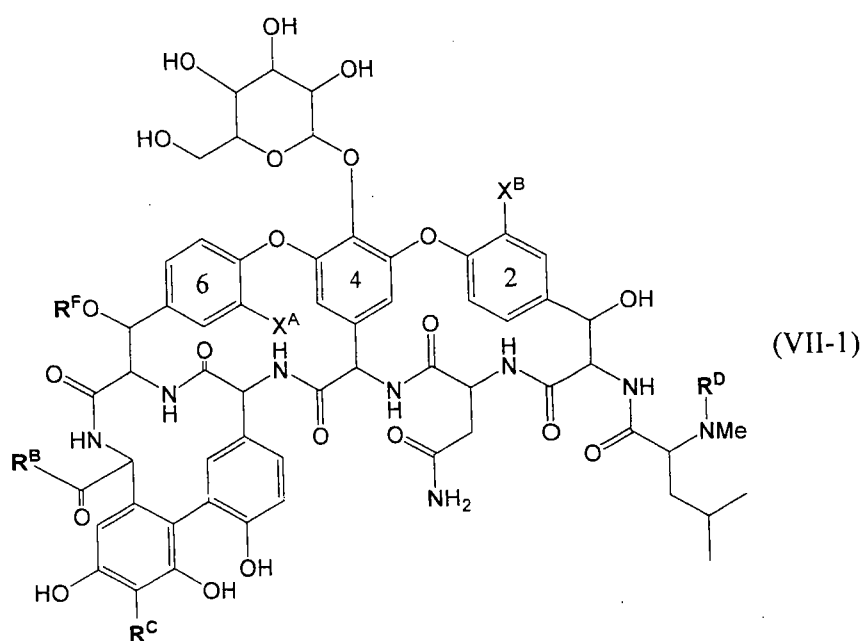
wherein respective symbols are as defined below,

comprising the following steps:

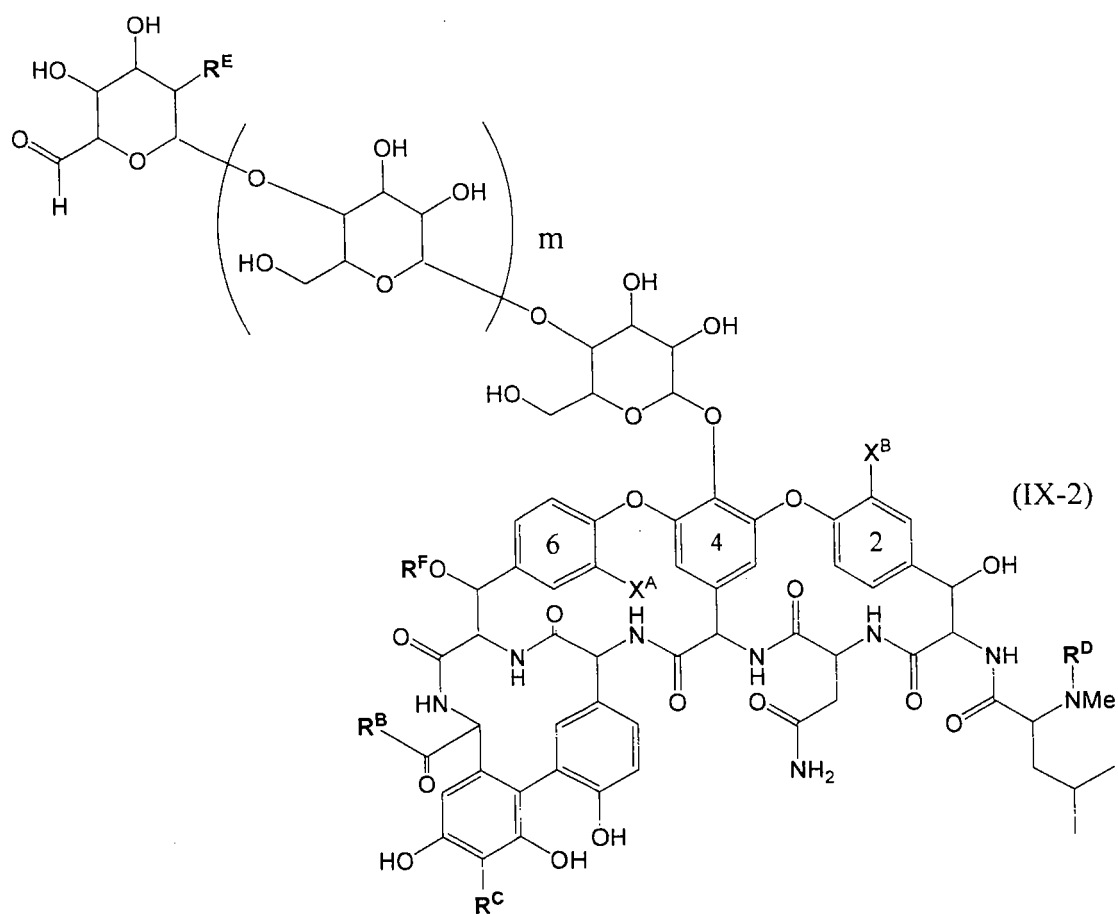
(step 1)

a step of reacting 1+m (m is an integer of 0 to 2) times of glycosylating reaction in the presence of glycosyltransferase and a sugar donor using a compound (VII-1) as a raw material represented by the formula:

[Chemical formula 30]



wherein respective symbols are as defined in claim 15,
to obtain a compound (VIII-2), a salt thereof, or a solvate thereof,
represented by the formula:
[Chemical formula 31]



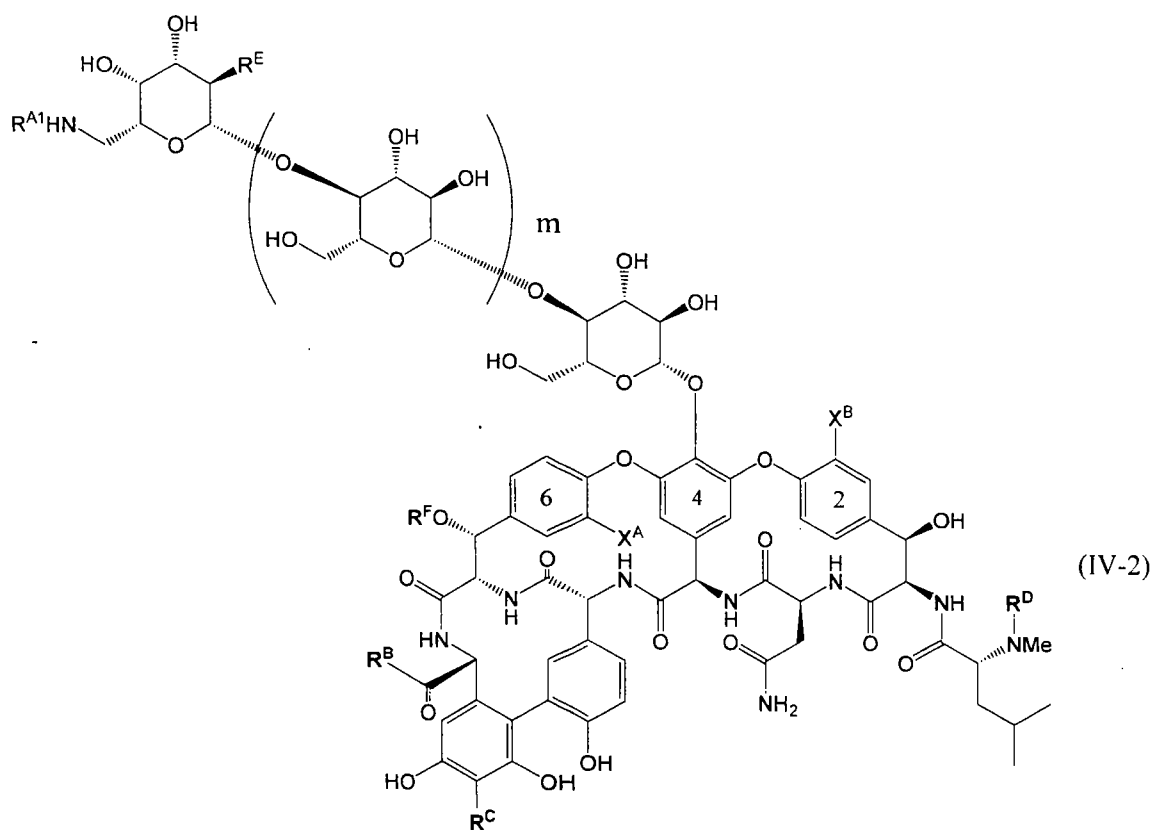
wherein respective symbols are as defined above, and

(step 3)

a step of subjecting the compound (IX-2), a salt thereof, or a solvate thereof to a reductive amination reaction with a compound (A) represented by the formula: $R^{A1}NH_2$.

[Clqim 36] A process for producing the compound (IV-2), a pharmaceutically acceptable salt thereof, or a solvate thereof, as defined in claim 18 represented by the formula:

[Chemical formula 37]



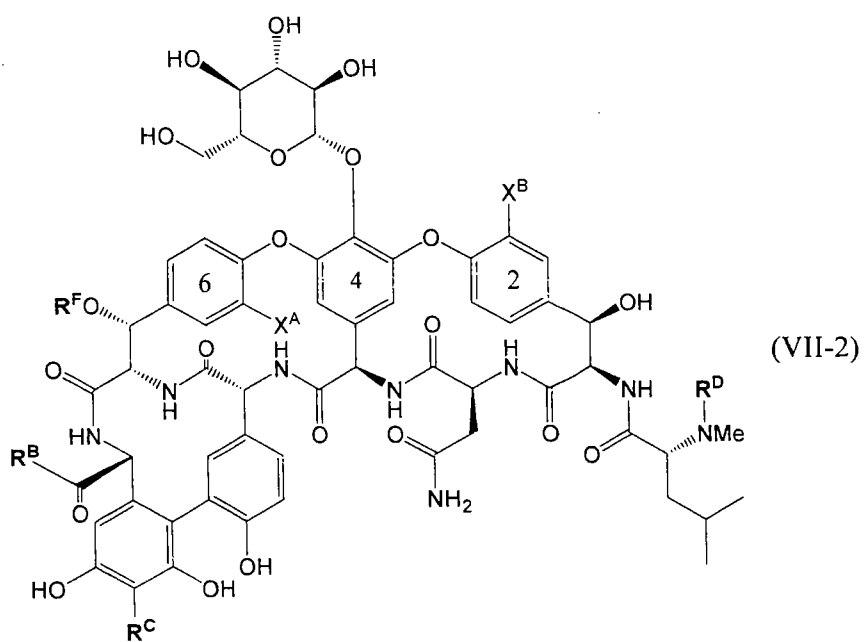
wherein respective symbols are as defined below,

comprising the following steps:

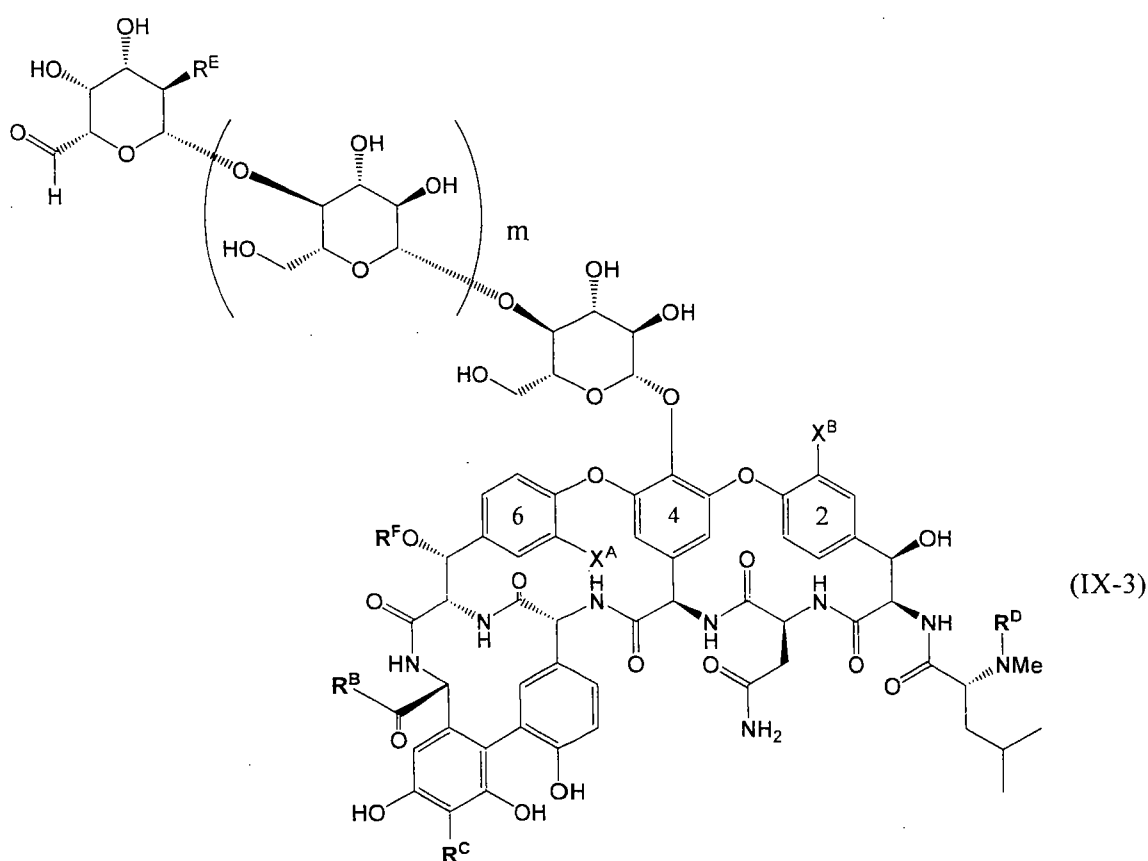
(step 1)

a step of reacting 1+m (m is an integer of 0 to 2) times of glycosylating reaction in the presence of glycosyltransferase and a sugar donor using a compound (VII-2) as a raw material represented by the formula:

[Chemical formula 34]



wherein respective symbols are as defined in claim 15,
to obtain a compound (VIII-3), a salt thereof, or a solvate thereof represented
by the formula:
[Chemical formula 35]



wherein respective symbols are as defined above,

and

(step 3)

a step of subjecting the compound (IX-3), a salt thereof, or a solvate thereof to a reductive amination reaction with a compound (A) represented by the formula: $R^{A1}NH_2$.

[Claim 37] The process according to any one of claims 33 to 36, wherein in the step 1, the glycosyltransferase is galactosyltransferase; a sugar of the sugar donor is the same or different 1 to 3 sugars selected from glucose, galactose, N-acetylgalactosamine, deoxyglucose, and deoxygalactose; and,

in the step 2, the oxidation reaction is performed with galactose oxidase.

[Claim 38] The process according to any one of claims 33 to 36, wherein in the step 1, the glycosyltransferase is galactosyltransferase; and, after addition of glucose by an optional first glycosylating reaction, galactose is further added by a second glycosylating reaction; and, in the step 2, the oxidation reaction is performed with galactose oxidase.

[Claim 39] The compound (VIII-1), a salt thereof, or a solvate thereof as defined in claim 34.

[Claim 40] The compound (IX-1), a salt thereof, or a solvate thereof as defined in claim 34.

[Claim 41] The compound as defined in any one of claims 1 to 32, 39 and 40, or a pharmaceutically acceptable salt thereof, or a solvate thereof.