

## DESCRIPTION

## POLYENE MACROLIDE DERIVATIVE

## TECHNICAL FIELD

[0 0 0 1]

The present invention relates to polyene macrolide derivatives. Especially, the present invention relates to polyene macrolide derivatives which are useful for treatment or prevention against fungal infection of human or animals.

## BACKGROUND ART

[0 0 0 2]

Amphotericin B is known as a drug having microbicidal effect by binding to ergosterol of cell membrane of fungi and forming ostium to membrane from long ago. Amphotericin B is used as formulation using deoxycholic acid or liposome due to its low water solubility and high toxicity. However, the formulation using deoxycholic acid is still high toxicity, so satisfactory administration and long-term treatment cannot be achieved. The formulation using liposome can greatly avoid possibility of hepatotoxicity and nephrotoxicity compared with the formulation using deoxycholic acid, but effective treatment is not still actually achieved because of decrease of drug efficacy (Non-patent Document 1, 2).

[0 0 0 3]

Therefore, chemical modification of amphotericin B has been tried for the improvement of its water solubility or the avoidance of its toxicity. For example, amphotericin B derivative having amide at 16th position (Patent Document 1, 3, 4, 5, 10) and ester derivative (Patent Document 2, 6, 7, 9, 11) are disclosed. In addition, amphotericin B derivatives having a modification at amino sugar part are disclosed as Patent Documents 1 to 4, 6 to 8, and 11. However, amphotericin B derivative having 16th position urea structure at is not disclosed in the above documents (Non-patent Document 3).

[0 0 0 4]

Moreover, amphotericin B derivatives having urea structure at 16th position wherein the end of urea is methyl, amino or carboxy are presented by Martin D Burke et al. at congress of American Chemical Society (ACS) on March 18, 2014 (Non-patent Document 4), and such the derivatives were disclosed in Patent Document 11 and released as scientific journal (Non-patent Document 5). It was suggested there that amphotericin B derivative having amino at the end part has lower nephrotoxicity than that of having carboxy at the end part.

## PRIOR ART REFERENCES

[Patent Document]

[0 0 0 5]

[Patent Document 1] WO 2007/096137

[Patent Document 2] WO 2001/051061

[Patent Document 3] WO 2001/009758

[Patent Document 4] WO 93/17034

[Patent Document 5] WO 96/32404

[Patent Document 6] WO 96/35701

[Patent Document 7] WO 99/51274

[Patent Document 8] WO 91/07421

[Patent Document 9] WO 2009/015541

[Patent Document 10] JP H55-157598

[Patent Document 11] WO 2015/054148

[Non-patent Document]

[0 0 0 6]

[Non-patent Document 1] Antimicrobial Agents and Chemotherapy (1998), 42(9), 2391-2398

[Non-patent Document 2] Clinical Infectious Diseases (2007), 44(10), 1289-1297

[Non-patent Document 3] Natural Product Reports (2010), 27, 1329-1349

[Non-patent Document 4] 247th ACS National Meeting & Exposition Web Abstracts

(<http://www.acs.org/content/acs/en/meetings/spring-2014/program.html>) ORGN 334

Non-toxic amphotericin B derivatization guided by a ligand-selective allosteric effects strategy

[Non-patent Document 5] Nature chemical biology published online 01 June 2015

## SUMMARY OF THE INVENTION

### PROBLEMS TO BE SOLVED BY THE INVENTION

[0 0 0 7]

The present invention is to provide amphotericin B derivatives having high antifungal activity against various fungi. Preferably, the present invention provides the derivatives having lower toxicity such as nephrotoxicity, hepatotoxicity and/or acute toxicity.

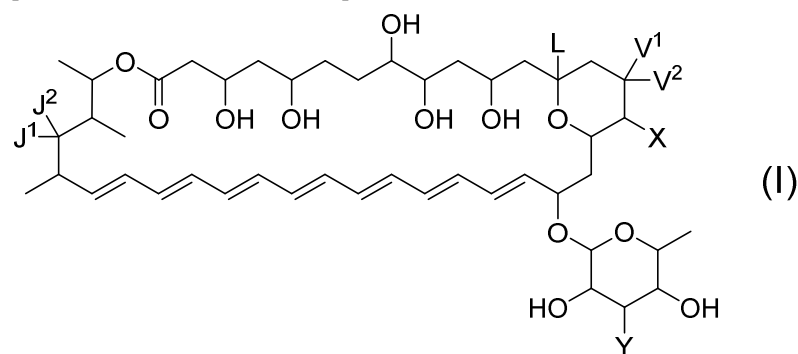
### MEANS FOR SOLVING THE PROBLEM

[0 0 0 8]

The present invention solves the above problems by modifying 16th position (X) and amino-position (Y) of sugar chain of amphotericin B, and the following invention has been accomplished.

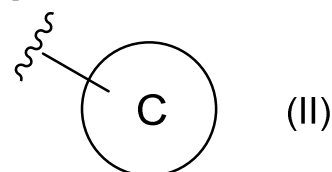
[1] A compound represented by formula (I):

[Chemical Formula 1]



wherein X is a group of formula:

[Chemical Formula 2]



, -N(R<sup>F</sup>)-CO-X<sup>1</sup>, hydroxyalkyl or a group of formula: -CO-NH(R<sup>X</sup>)

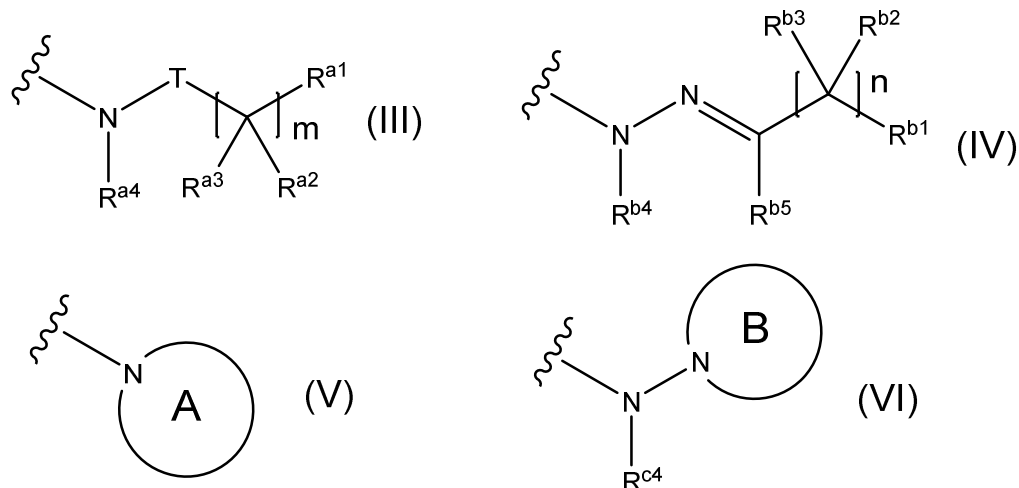
wherein  $R^X$  is substituted or unsubstituted non-aromatic heterocycloxyalkyl;

Ring C is substituted or unsubstituted aromatic carbocycle, substituted or unsubstituted non-aromatic carbocycle, substituted or unsubstituted aromatic heterocycle or substituted or unsubstituted non-aromatic heterocycle;

$R^F$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl; and

$X^1$  is any one of following groups:

[Chemical Formula 3]



$L$ ,  $J^1$  and  $V^1$  are each independently hydrogen, halogen, hydroxy, substituted or unsubstituted amino or substituted or unsubstituted alkyloxy;

$J^2$  and  $V^2$  are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl; or  $J^1$  and  $J^2$  and/or  $V^1$  and  $V^2$  may be taken together to form oxo;

$R^{a1}$  and  $R^{b1}$  are each independently, hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, formyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, sulfo, cyano, substituted or unsubstituted ureido, guanidino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkyl ammonium, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkenylsulfonyl, substituted or unsubstituted alkynylsulfonyl, substituted or unsubstituted alkylphosphonyl, substituted or unsubstituted dialkynylphosphonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkenylcarbonyloxy, substituted or unsubstituted alkynylcarbonyloxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocycloxy, substituted or unsubstituted non-aromatic carbocycloxy, substituted or unsubstituted aromatic heterocycloxy, substituted or unsubstituted non-aromatic heterocycloxy, substituted or unsubstituted aromatic carbocyclylcarbonyl, substituted or unsubstituted non-aromatic carbocyclylcarbonyl, substituted or unsubstituted aromatic heterocyclylcarbonyl, substituted or unsubstituted non-

aromatic heterocyclylcarbonyl, substituted or unsubstituted aromatic carbocyclylamino, substituted or unsubstituted non-aromatic carbocyclylamino, substituted or unsubstituted aromatic heterocyclylamino, substituted or unsubstituted non-aromatic heterocyclylamino, substituted or unsubstituted aromatic carbocyclylsulfonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted aromatic heterocyclylsulfonyl or substituted or unsubstituted non-aromatic heterocyclylsulfonyl;

$R^{a\ 2}$  and  $R^{b\ 2}$  are each independently hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkenylcarbonyloxy, substituted or unsubstituted alkynylcarbonyloxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxyalkyl, substituted or unsubstituted non-aromatic heterocyclyloxyalkenyl or substituted or unsubstituted non-aromatic heterocyclyloxyalkynyl;

$R^{a\ 3}$  and  $R^{b\ 3}$  are each independently, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxyalkyl, substituted or unsubstituted non-aromatic heterocyclyloxyalkenyl or substituted or unsubstituted non-aromatic heterocyclyloxyalkynyl; or  $R^{a\ 2}$  and  $R^{a\ 3}$  and/or  $R^{b\ 2}$  and  $R^{b\ 3}$  are each independently may be taken together to form oxo, substituted or unsubstituted imino or thioxo, or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle or substituted or unsubstituted non-aromatic heterocycle;

$R^{a\ 4}$ ,  $R^{b\ 4}$  and  $R^{c\ 4}$  are each independently, hydrogen, hydroxy, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl or substituted or unsubstituted non-aromatic carbocyclyl;

$R^{b\ 5}$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;

Ring A and Ring B are each independently, substituted or unsubstituted nitrogen-containing aromatic heterocycle or substituted or unsubstituted nitrogen-containing non-aromatic heterocycle;

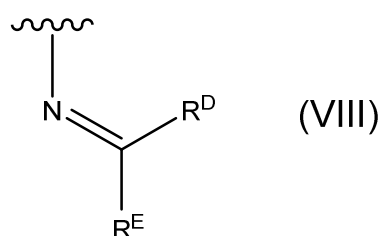
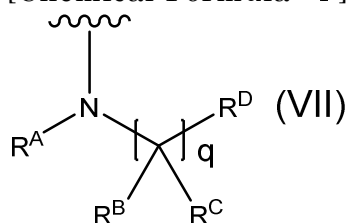
T is a bond,  $-N(R^{a\ 5})-$  or  $-O-$ ;

$R^{a\ 5}$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl or substituted or unsubstituted alkynylcarbonyl;

m and n are each independently an integer of 0 to 10;

Y is any one of following groups

[Chemical Formula 4]



$R^A$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;

$R^B$  and  $R^C$  are each independently hydrogen, hydroxy, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;

or  $R^B$  and  $R^C$  may be taken together to form oxo, substituted or unsubstituted imino or thioxo, or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle or substituted or unsubstituted non-aromatic heterocycle;

$R^D$  is hydrogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, substituted or unsubstituted amidino, substituted or unsubstituted guanidino, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl or substituted or unsubstituted non-aromatic heterocyclyl;

$R^E$  is hydrogen, hydroxy or substituted or unsubstituted amino;

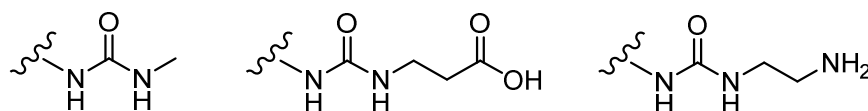
$q$  is an integer of 0 to 10;

provided that the following compounds are excluded:

(i) The compounds which  $X$  is  $-\text{CH}_2-\text{OH}$ ; and  $Y$  is  $-\text{NH}_2$ ;

(ii) The compounds which  $X$  is either of following groups; and  $Y$  is any one of  $-\text{NH}_2$ ; a group of formula:

[Chemical Formula 5]

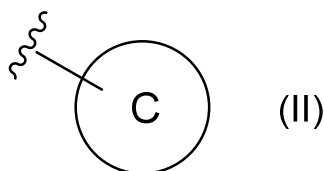


or a pharmaceutically acceptable salt thereof.

[2] The compound or its pharmaceutically acceptable salt according to the above item [1],

wherein  $X$  is

[Chemical Formula 6]



or  $-\text{N}(\text{R}^F)-\text{CO}-\text{X}^1$ .

[3] The compound or its pharmaceutically acceptable salt according to the above item [1] or [2], wherein  $J^1$ ,  $L$  and  $V^1$  are hydroxy; and  $J^2$  and  $V^2$  are hydrogen.

[4] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein  $X$  is a group of formula:  $-\text{N}(\text{R}^F)-\text{CO}-\text{X}^1$ ;  $\text{X}^1$  is a group

represented by formula (III); and T is a bond.

[5] The compound or its pharmaceutically acceptable salt according to the above item [4], wherein  $R^{a1}$  is halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted aromatic heterocyclamino, substituted or unsubstituted non-aromatic heterocyclamino, substituted or unsubstituted alkylammonium, carbamoyl, sulfamoyl, sulfo, cyano, substituted or unsubstituted ureido, guanidino, substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocycloxy, substituted or unsubstituted alkylphosphonyl, substituted sulfamoyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl or substituted or unsubstituted non-aromatic heterocyclyl;

wherein said substituted or unsubstituted amino is selected from unsubstituted amino, hydroxyamino, sulfamoylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkylsulfonylamino, substituted or unsubstituted non-aromatic carbocyclylcarbonylamino, substituted or unsubstituted aromatic carbocyclylcarbonylamino, substituted or unsubstituted aromatic heterocyclylcarbonylamino and substituted or unsubstituted non-aromatic heterocyclylcarbonylamino;

wherein said substituted or unsubstituted ureido is selected from ureido, substituted or unsubstituted alkylureido, substituted or unsubstituted aromatic heterocyclylureido and substituted or unsubstituted aromatic heterocyclylureido; and

wherein said substituted sulfamoyl is substituted or unsubstituted aromatic heterocyclylsulfamoyl.

[6] The compound or its pharmaceutically acceptable salt according to the above item [4] or [5], wherein  $R^{a2}$  are each independently hydrogen, halogen, hydroxy, carboxy, amino, carbamoyl, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic heterocycloxyalkyl or substituted or unsubstituted alkylcarbonyl;

$R^{a3}$  are each independently, hydrogen, halogen, substituted or unsubstituted alkyl or substituted or unsubstituted non-aromatic heterocycloxyalkyl; or  $R^{a2}$  and  $R^{a3}$  may be taken together to form oxo, or may be taken together with neighboring atoms to form non-aromatic carbocycle or non-aromatic heterocycle.

[7] The compound or its pharmaceutically acceptable salt according to any one of the above items [4] to [6], wherein  $R^{a4}$  is hydrogen, hydroxy, amino, substituted or unsubstituted alkyl or substituted or unsubstituted non-aromatic carbocyclyl.

[8] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3] wherein X is a group of formula:  $-N(R^F)-CO-X^1$ ;  $X^1$  is a group represented by formula (III); and T is  $-N(R^{a5})-$  or  $-O-$ .

[9] The compound or its pharmaceutically acceptable salt according to the above item [8], wherein  $R^{a1}$  is hydroxy, carboxy, substituted amino, substituted or unsubstituted aromatic heterocyclamino, formyl, carbamoyl, cyano, guanidino, substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocycloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted aromatic heterocyclylsulfonyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, or substituted ureido;

wherein said substituted amino is hydroxyamino or substituted or

unsubstituted alkylamino; and

wherein said substituted ureido is substituted or unsubstituted aromatic heterocyclureido.

[10] The compound or its pharmaceutically acceptable salt according to the above item [8] or [9], wherein  $R^{a2}$  are each independently hydrogen, hydroxy or substituted or unsubstituted alkyl;

$R^{a3}$  are each independently hydrogen or substituted or unsubstituted alkyl; or  $R^{a2}$  and  $R^{a3}$  may be taken together to form oxo or thioxo, or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle.

[11] The compound or its pharmaceutically acceptable salt according to any one of the above items [8] to [10], wherein  $R^{a2}$  is hydrogen.

[12] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein X is a group of formula:  $-N(R^F)-CO-X^1$ ; and  $X^1$  is a group represented by formula (IV).

[13] The compound or its pharmaceutically acceptable salt according to the above item [12], wherein  $R^{b1}$  is hydroxy.

[14] The compound or its pharmaceutically acceptable salt according to the above item [12] or [13], wherein n is 1 or 2;  $R^{b2}$  are each independently hydrogen or hydroxy; and  $R^{b3}$  is hydrogen.

[15] The compound or its pharmaceutically acceptable salt according to any one of the above items [12] to [14], wherein  $R^{b4}$  is hydrogen; and  $R^{b3}$  is hydrogen or substituted or unsubstituted alkyl.

[16] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein X is  $-N(R^F)-CO-X^1$ ; and  $X^1$  is a group represented by formula (V).

[17] The compound according to the above item [16], wherein ring A is substituted or unsubstituted nitrogen-containing non-aromatic heterocycle.

[18] The compound according to any one of the above items [1] to [3], wherein X is a group of formula:  $-N(R^F)-CO-X^1$ ; and  $X^1$  is a group represented by formula (VI).

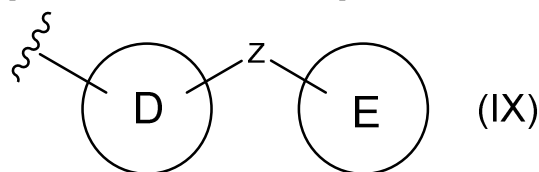
[19] The compound or its pharmaceutically acceptable salt according to the above item [18], wherein ring B is substituted or unsubstituted nitrogen-containing non-aromatic heterocycle.

[20] The compound or its pharmaceutically acceptable salt according to the above item [18] or [19], wherein  $R^{c4}$  is hydrogen.

[21] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [20], wherein  $R^F$  is hydrogen.

[22] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein X is a group represented by formula (II); and said group is represent by formula:

[Chemical Formula 7]



ring D and ring E are each independently substituted or unsubstituted aromatic carbocycle, substituted or unsubstituted non-aromatic carbocycle, substituted or unsubstituted aromatic heterocycle or substituted or unsubstituted

non-aromatic heterocycle; and Z is a bond, alkylene, -O-, -S- or -N(H)-.

[23] The compound or its pharmaceutically acceptable salt according to the above item [22], wherein ring D is substituted or unsubstituted aromatic heterocycle; and ring E is substituted or unsubstituted aromatic carbocycle or substituted or unsubstituted aromatic heterocycle.

[24] The compound or its pharmaceutically acceptable salt according to the above item [22] or [23], wherein Z is a bond.

[25] The compound or its pharmaceutically acceptable salt according to any one of the above items [22] to [24], wherein the substituent(s) on ring E is/are alkylamino.

[26] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [25], wherein R<sup>A</sup> are each independently hydrogen or substituted or unsubstituted alkyl; R<sup>B</sup> are each independently hydrogen or hydroxy or substituted or unsubstituted amino; R<sup>C</sup> are each independently hydrogen or hydroxy or substituted or unsubstituted amino; or R<sup>B</sup> and R<sup>C</sup> may be taken together to form oxo, substituted or unsubstituted imino, hydroxyimino or cyanoimino; R<sup>D</sup> is hydrogen, hydroxy, carboxy, substituted or unsubstituted amino, carbamoyl, guanidine, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl or substituted or unsubstituted non-aromatic heterocyclyl;

R<sup>E</sup> is amino;

wherein said substituted or unsubstituted amino is unsubstituted amino or substituted or unsubstituted alkylamino;

wherein said substituted or unsubstituted imino is unsubstituted imino, hydroxyimino or cyanoimino.

[27] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [25], wherein Y is NH<sub>2</sub>.

[28] The compound or its pharmaceutically acceptable salt according to the above item [1], wherein X is hydroxyalkyl; and q is an integer of 0 to 10.

[29] The compound according to the above item [1], wherein X is a group of formula: -CO-NH(R<sup>X</sup>), and wherein R<sup>X</sup> is substituted or unsubstituted non-aromatic heterocycloxyalkyl.

[30] The compound or its pharmaceutically acceptable salt according to the above item [3], wherein X is a group of formula: -N(R<sup>F</sup>)-CO-X<sup>1</sup>, wherein X<sup>1</sup> is a group represented by formula (II);

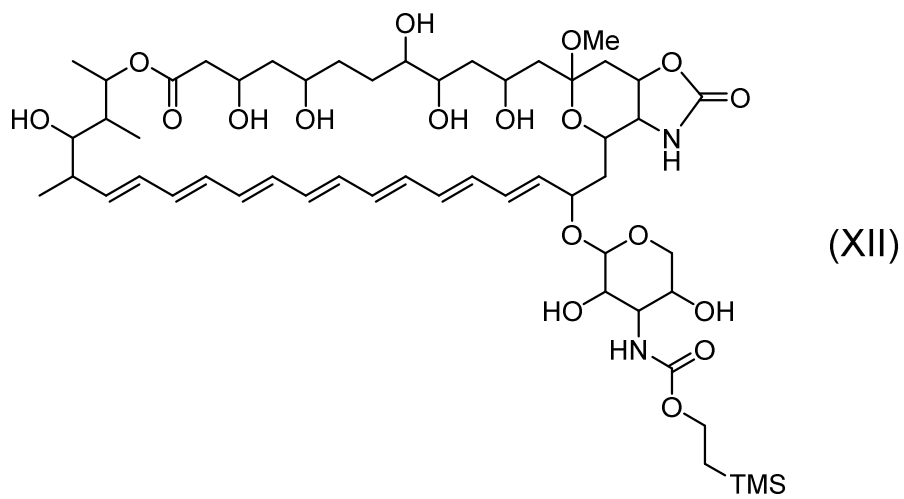
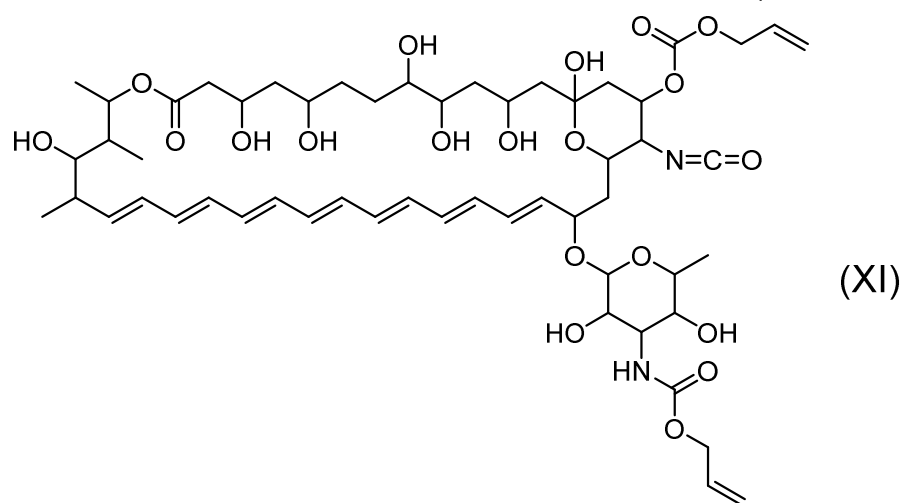
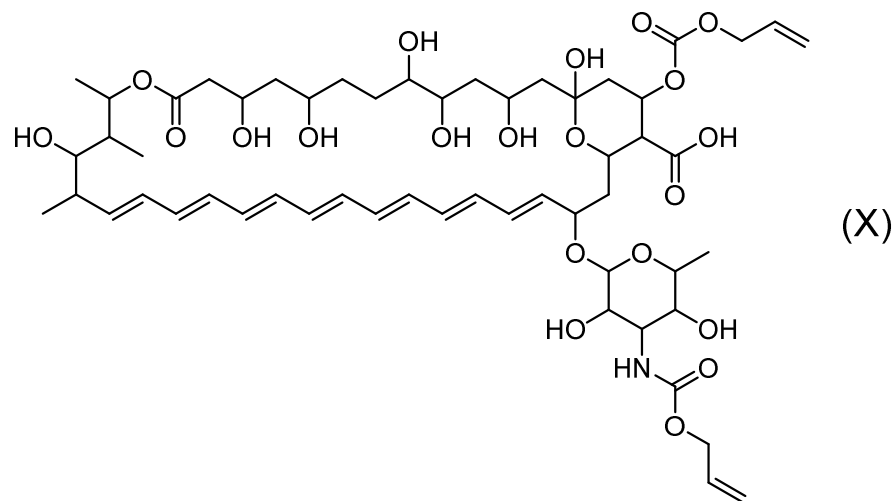
T is -N(H)-; R<sup>a 1</sup> is carboxy, carbamoyl or substituted amino; R<sup>a 2</sup> is each independently hydrogen or hydroxy; R<sup>a 3</sup> and R<sup>a 4</sup> are hydrogen; m is 2; and Y is NH<sub>2</sub>.

[31] A pharmaceutical composition containing the compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [30].

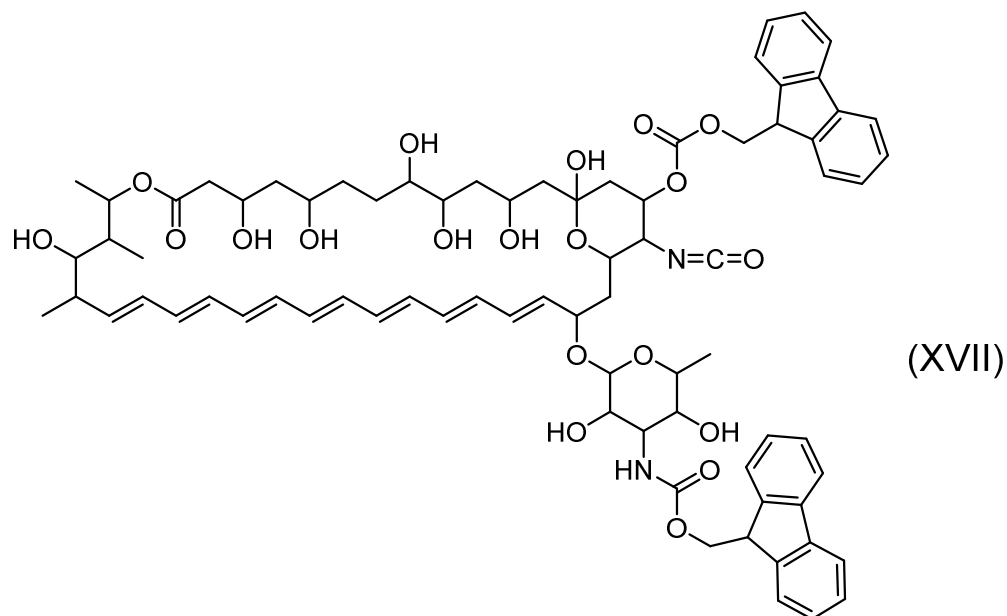
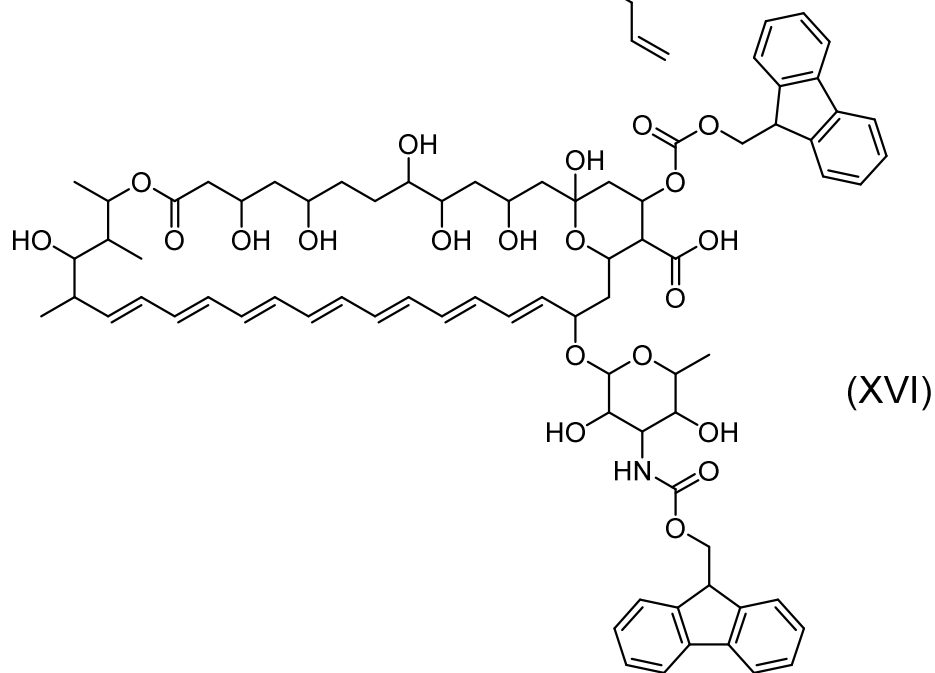
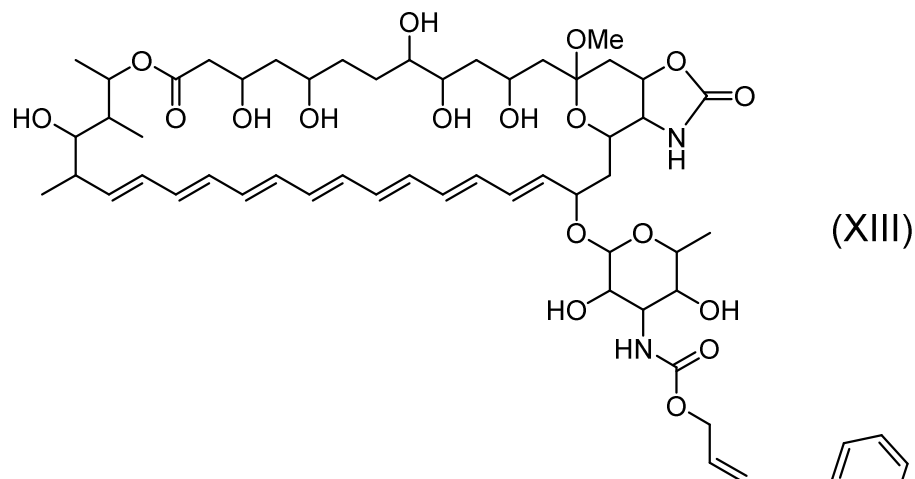
[32] A pharmaceutical composition of the above item [31] having antifungal activity.

[33] A compound represented by any one of formula (X), (XI), (XII), (XIII), (XVI) or (XVII):

[Chemical Formula 8]



[Chemical Formula 9]



or its pharmaceutically acceptable salt.

[34] A process for the preparation of the compound according to any one of the above items [1] to [30], wherein X is a group of formula:  $-N(R^F)-CO-X^1$ , which is characterized in using the compound or its pharmaceutically acceptable salt

according to the above item [33].

[35] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein said substituted or unsubstituted amino is selected from amino, hydroxyamino, sulfamoylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkylsulfonylamino, substituted or unsubstituted aromatic carbocyclylcarbonylamino, substituted or unsubstituted non-aromatic carbocyclylcarbonylamino, substituted or unsubstituted aromatic heterocyclylcarbonylamino or substituted or unsubstituted non-aromatic heterocyclylcarbonylamino.

[36] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein said substituted or unsubstituted carbamoyl is unsubstituted carbamoyl or substituted or unsubstituted alkylcarbamoyl.

[37] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein said substituted or unsubstituted sulfamoyl is selected from unsubstituted sulfamoyl, substituted or unsubstituted alkylsulfamoyl, substituted or unsubstituted aromatic carbocyclylsulfamoyl, substituted or unsubstituted non-aromatic carbocyclylsulfamoyl, substituted or unsubstituted aromatic heterocyclylsulfamoyl or substituted or unsubstituted non-aromatic heterocyclylsulfamoyl.

[38] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein said substituted or unsubstituted ureido is selected from unsubstituted ureido, substituted or unsubstituted alkylureido, substituted or unsubstituted aromatic carbocyclylureido, substituted or unsubstituted non-aromatic carbocyclylureido, substituted or unsubstituted aromatic heterocyclylureido or substituted or unsubstituted non-aromatic heterocyclylureido.

[39] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein said substituted or unsubstituted alkyloxy is selected from substituted or unsubstituted aromatic carbocyclylalkyloxy, substituted or unsubstituted non-aromatic carbocyclylalkyloxy, substituted or unsubstituted aromatic heterocyclylalkyloxy or substituted or unsubstituted non-aromatic heterocyclylalkyloxy.

[40] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein said substituted or unsubstituted alkylsulfonyl is selected from unsubstituted alkylsulfonyl, substituted or unsubstituted aromatic carbocyclylalkylsulfonyl, substituted or unsubstituted non-aromatic carbocyclylalkylsulfonyl, substituted or unsubstituted aromatic heterocyclylalkylsulfonyl or substituted or unsubstituted non-aromatic heterocyclylalkylsulfonyl.

[41] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein said substituted or unsubstituted alkylcarbonyloxy is selected from unsubstituted alkylcarbonyloxy, substituted or unsubstituted aromatic carbocyclylalkylcarbonyloxy, substituted or unsubstituted non-aromatic carbocyclylalkylcarbonyloxy, substituted or unsubstituted aromatic heterocyclylalkylcarbonyloxy or substituted or unsubstituted non-aromatic heterocyclylalkylcarbonyloxy.

[42] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein said substituted or unsubstituted aromatic carbocyclyl is selected from unsubstituted aromatic carbocyclyl or substituted or unsubstituted alkylaminoaromatic carbocyclyl.

[43] The compound or its pharmaceutically acceptable salt according to any one of

the above items [1] to [3], wherein said substituted or unsubstituted non-aromatic carbocyclyl is selected from unsubstituted non-aromatic carbocyclyl or substituted or unsubstituted alkylaminonon-aromatic carbocyclyl.

[44] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein said substituted or unsubstituted aromatic heterocyclyl is selected from unsubstituted aromatic heterocyclyl or substituted or unsubstituted alkylaminoaromatic heterocyclyl.

[45] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [3], wherein said substituted or unsubstituted non-aromatic heterocyclyl is selected from unsubstituted non-aromatic heterocyclyl or substituted or unsubstituted alkylaminonon-aromatic heterocyclyl.

[46] The compound or its pharmaceutically acceptable salt according to any one of the above items [4] to [11], wherein m is an integer of 0 to 6.

[47] The compound or its pharmaceutically acceptable salt according to any one of the above items [12] to [15], wherein n is an integer of 0 to 6.

[48] A method for treating a fungal infection, which comprises administering the effective doses for anti fungal of the compound according to any one of the above items [1] to [30] to human or animals.

[49] The compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [30], for use in a medical treatment.

[50] The use of the compound or its pharmaceutically acceptable salt according to any one of the above items [1] to [30], for the manufacture of a medicament for treating or preventing a fungal infection.

## EFFECT OF THE INVENTION

[0 0 0 9]

The compound of the present invention has antifungal activity against fungi. Moreover, the compound of the present invention has utility as a medicament, and it has preferably excellent effects of all or portion of the following points.

- a) Low possibility of nephrotoxicity
- b) Low possibility of hepatotoxicity
- c) Low possibility of acute toxicity
- d) High water solubility
- e) Low possibility of hemolytic toxicity
- f) Low possibility of cytotoxicity

Also, the present invention provides useful intermediates useful for preparing antifungal agent efficiently. Compound (I) can be easily prepared by using the intermediates in high yield and by short-step.

## EMBODIMENTS FOR CARRYING OUT THE INVENTION

[0 0 1 0]

Terms used in this description are explained below. Each term, unless otherwise indicated, has the same meaning when it is used alone or together with other terms.

The term of “consisting of” means having only components.

The term of “comprising” means not restricting with components and not excluding undescribed factors.

[0 0 1 1]

The term “halogen” includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. A fluorine atom and a chlorine atom are especially preferable.

[0 0 1 2]

The term "alkyl" includes a C1 to C15, preferably C1 to C10, more preferably C1 to C6 and further preferably C1 to C4 linear or branched hydrocarbon group. Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, n-heptyl, isoheptyl, n-octyl, isooctyl, n-nonyl, n-decyl and the like.

A preferred embodiment of "alkyl" is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or n-pentyl. A more preferred embodiment is methyl, ethyl, n-propyl, isopropyl or tert-butyl.

[0 0 1 3]

The term "hydroxyalkyl" means a group wherein one or more hydrogen atom(s) of "alkyl" described above are replaced with hydroxy. Examples include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 1,2-hydroxyethyl and the like.

A preferred embodiment of "hydroxyalkyl" is hydroxymethyl, hydroxyethyl.

[0 0 1 4]

The term "haloalkyl" means a group wherein one or more "halogen" described above is bonded to the above "alkyl". Examples include monofluoromethyl, monofluoroethyl, monofluoropropyl, 2,2,3,3,3-pentafluoropropyl, monochloromethyl, trifluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 1,2-dibromoethyl, 1,1,1-trifluoropropan-2-yl and the like.

A preferred embodiment of "haloalkyl" is trifluoromethyl or trichloromethyl.

[0 0 1 5]

The term "alkenyl" includes a C2 to C15, preferably a C2 to C10, more preferably a C2 to C6 and further preferably a C2 to C4 linear or branched hydrocarbon group having one or more double bond(s) at any position(s). Examples include vinyl, allyl, propenyl, isopropenyl, butenyl, isobutenyl, prenyl, butadienyl, pentenyl, isopentenyl, pentadienyl, hexenyl, isohexenyl, hexadienyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, pentadecenyl and the like.

A preferred embodiment of "alkenyl" is vinyl, allyl, propenyl, isopropenyl or butenyl.

[0 0 1 6]

The term "alkynyl" includes a C2 to C10, preferably a C2 to C8, more preferably a C2 to C6 and further preferably a C2 to C4 linear or branched hydrocarbon group having one or more triple bond(s) at any position(s). Furthermore, it may have double bond(s) at any position(s). Examples include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl and the like.

A preferred embodiment of "alkynyl" is ethynyl, propynyl, butynyl or pentynyl.

[0 0 1 7]

The term "alkylene" includes a C1 to C15, preferably a C1 to C10, more preferably a C1 to C6 and further preferably a C1 to C4 linear or branched bivalent hydrocarbon group. Examples include methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene and the like.

[0 0 1 8]

The term "aromatic carbocycle" means a cyclic aromatic hydrocarbon which is monocycle or polycycle having two or more rings. Examples include benzene, naphthalene, anthracene, phenanthrene and the like.

A preferred embodiment of "aromatic carbocycle" is benzene.

[0 0 1 9]

The term “aromatic carbocyclyl” means a monovalent group derived from “aromatic carbocycle” described above. Examples include phenyl, naphthyl, anthryl, phenanthryl and the like.

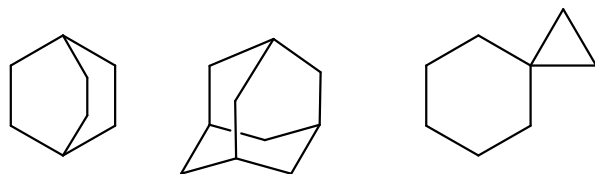
A preferred embodiment of “aromatic carbocyclyl” is phenyl.

[0 0 2 0]

The term “non-aromatic carbocycle” means a cyclic saturated hydrocarbon or a cyclic unsaturated non-aromatic hydrocarbon, which is monocycle or polycycle having two or more rings. Examples of the “non-aromatic carbocycle”, which is polycycle having two or more rings, include a fused ring wherein a non-aromatic carbocycle, which is monocycle or polycycle having two or more rings, is fused with a ring of the above “aromatic carbocycle”.

In addition, examples of the “non-aromatic carbocycle” also include a group having a bridge or a spiro ring as follows:

[Chemical Formula 1 0]



The non-aromatic carbocycle which is monocycle is preferably C3 to C16, more preferably C3 to C12 and further preferably C3 to C8 carbocycle. Examples include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene, cyclohexadiene and the like.

Examples of non-aromatic carbocycle, which is polycycle having two or more rings, include indane, indene, asenafuchine, tetrahydronaphthalene, fluorene and the like.

[0 0 2 1]

The term “non-aromatic carbocyclyl” means a monovalent group derived from “non-aromatic carbocycle” described above.

The non-aromatic carbocyclyl which is monocyclic is preferably C3 to C16, more preferably C3 to C12 and further preferably C3 to C8 carbocyclyl. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclohexadienyl and the like.

Examples of non-aromatic carbocyclyl, which is polycyclic having two or more rings, include indanyl, indenyl, acenaphthyl, tetrahydronaphthyl, fluorenyl and the like.

[0 0 2 2]

The term “aromatic heterocycle” means an aromatic cycle, which is monocycle or polycycle having two or more rings, containing one or more of heteroatom(s) selected independently from O, S and N. Examples of “aromatic heterocycle”, which is polycycle having two or more rings, include a fused ring group wherein an aromatic heterocycle, which is monocycle or polycycle having two or more rings, is fused with a ring of the above “aromatic carbocycle”.

The aromatic heterocycle, which is monocycle, is preferably a 5- to 8-membered and more preferably 5- to 6-membered ring. Examples include pyrroline, imidazoline, pyrazoline, pyridine, pyridazine, pyrimidine, pyrazine, triazole, triazine,

tetrazolin, furan, isoxazole, oxazole, oxadiazole, isothiazole, thiazole, thiadiazole and the like.

Examples of aromatic heterocycle, which is bicyclic, include indoline, isoindoline, indazoline, indorizidine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, naphthyridine, purine, pteridine, benzimidazole, benzisoxazole, benzoxazole, benzimidazole, oxadiazole, benzisothiazole, benzothiazole, benzothiadiazo, benzofuran, isobenzofuran, benzotriazole, imidazopyridine, triazolopyridine, imidazothiazole, pyridinopyridazole, oxazolopyridine, thiazolopyridine and the like.

Examples of aromatic heterocycle, which is polycycle having three or more rings, include carbazole, acridine, xanthene, phenothiazine, phenoxathiine, phenoxazine, dibenzofuran and the like.

[0 0 2 3]

The term "aromatic heterocyclyl" means a monovalent group derived from "aromatic heterocycle" described above.

The aromatic heterocyclyl, which is monocyclic, is preferably a 5- to 8-membered and more preferably 5- to 6-membered ring. Examples include pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazolyl, triazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, oxazolyl, oxadiazolyl, isothiazolyl, thiazolyl, thiadiazolyl and the like.

Examples of aromatic heterocyclyl, which is bicyclic, include indolyl, isoindolyl, indazolyl, indolizyl, quinolyl, isoquinolyl, cinnolyl, phthalazyl, quinazolyl, naphthyridyl, quinoxalyl, purinyl, pteridinyl, benzimidazolyl, benzisoxazolyl, benzoxazolyl, benzoxadiazolyl, benzisothiazolyl, benzothiazolyl, benzothiadiazo, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, imidazopyridyl, triazolopyridyl, imidazothiazolyl, pyrazinopyridazinyl, oxazolopyridyl, thiazolopyridyl and the like.

Examples of aromatic heterocyclyl, which is polycyclic having three or more rings, include carbazolyl, acridinyl, xanthenyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, dibenzofuryl and the like.

[0 0 2 4]

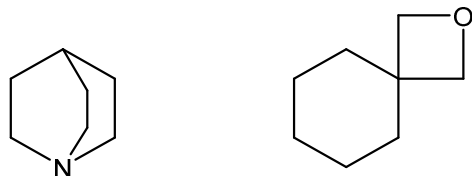
The term "nitrogen-containing aromatic heterocycle" means an aromatic heterocycle, which is monocycle or polycycle having two or more rings, containing one or more nitrogen atom(s) furthermore may have one or more heteroatom(s) selected independently from O and/or S. The "nitrogen-containing aromatic heterocycle" is preferably "aromatic heterocycle" containing nitrogen atom(s) in the ring(s) of "aromatic heterocycle" exemplified above.

[0 0 2 5]

The term "non-aromatic heterocycle" means a non-aromatic cycle, which is monocycle or polycycle having two or more rings, containing one or more heteroatom(s) selected independently from O, S and N. Examples of "non-aromatic heterocycle", which is polycycle having two or more rings, include a fused ring wherein a non-aromatic heterocycle, which is monocycle or polycycle having two or more ring(s), is fused with a ring of the above "aromatic carbocycle", "non-aromatic carbocycle" and/or "aromatic heterocycle".

In addition, examples of the "non-aromatic heterocyclyl" also include a group having a bridge or a group to form a spiro ring as follows:

[Chemical Formula 1 1]



The non-aromatic heterocycle, which is monocycle, is preferably a 3- to 16-membered and more preferably 3- to 12-membered ring and further more preferably 3- to 8-membered ring. Examples include dioxane, thiirane, oxirane, oxetane, oxathiolane, azetidine, thiazolidine, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, thiomorpholine, dihydropyridine, tetrahydropyridine, tetrahydrofuran, tetrahydropyran, dihydrothiazole, tetrahydroisothiazole, dihydrooxazine, hexahydroazepine, tetrahydrodiazepine, tetrahydropyridazine, hexahydropyrimidine, dioxolane, dioxazine, aziridine, dioxolane, oxepane, thiolane, thiazine and the like.

Examples of non-aromatic heterocycle, which is polycycle having two or more rings, include indoline, isoindoline, chromane, isochromane and the like.

[0 0 2 6]

The term “non-aromatic heterocyclyl” means a monovalent group derived from “non-aromatic heterocycle” described above.

The non-aromatic heterocyclyl, which is monocyclic, is preferably a 3- to 16-membered and more preferably 3- to 12-membered ring and further more preferably 3- to 8-membered ring. Examples include dioxanyl, thiiranyl, oxiranyl, oxetanyl, oxathiolanyl, azetidiny, thianyl, thiazolidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, dihydropyridyl, tetrahydropyridyl, tetrahydrofuryl, tetrahydropyranyl, dihydrothiazolyl, tetrahydrothiazolyl, tetrahydroisothiazolyl, dihydrooxazinyl, hexahydroazepinyl, tetrahydrodiazepinyl, tetrahydropyridazinyl, hexahydropyrimidinyl, dioxolanyl, dioxazinyl, aziridinyl, dioxolyl, oxepanyl, thiolanyl, thiinyl, thiazinyl and the like.

Examples of non-aromatic heterocyclyl, which is polycyclic having two or more rings, include indolinyl, isoindolinyl, chromanyl, isochromanyl and the like.

[0 0 2 7]

The term “nitrogen-containing non-aromatic heterocycle” means a non-aromatic heterocycle, which is monocycle or polycycle having two or more rings, containing one or more nitrogen atom(s) furthermore may have one or more heteroatom(s) selected independently from O and/or S. The nitrogen-containing non-aromatic heterocycle, which is monocycle, is preferably a 3- to 16-membered and more preferably 3- to 12-membered ring and further more preferably 3- to 8-membered ring. Examples include azetidine, thiazolidine, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, thiomorpholine, dihydropyridine, tetrahydropyridine, dihydrothiazole, tetrahydrothiazole, tetrahydroisothiazole, dihydrooxazine, hexahydroazepine, tetrahydrodiazepine, tetrahydropyridazine, hexahydropyrimidine, dioxazine, aziridine, thiazine, 1,4-diazepane, 1,4,7,10,13-pentaoxa-16-azacyclooctadecane, 1,4,7,10-tetraoxa-13-azacyclopentadecane and the like. Especially preferably, 1,4-diazepane, 1,4,7,10,13-pentaoxa-16-azacyclooctadecane, 1,4,7,10-tetraoxa-13-azacyclopentadecane, piperazine, morpholine, piperidine, pyrrolidine, thiazolidine, azetidine, pyrroline.

[0 0 2 8]

The term “aromatic carbocyclyloxy” means a group wherein “aromatic carbocycle” is bonded to an oxygen atom. Examples include phenyloxy, naphthyloxy and the like.

The term “non-aromatic carbocyclyloxy” means a group wherein “non-aromatic carbocycle” is bonded to an oxygen atom. Examples include cyclopropyloxy, cyclohexyloxy, cyclohexenyloxy and the like.

The term “aromatic heterocyclyloxy” means a group wherein “aromatic heterocycle” is bonded to an oxygen atom. Examples include pyridyloxy, oxazolyloxy and the like.

The term “non-aromatic heterocyclyloxy” means a group wherein “non-aromatic heterocycle” is bonded to an oxygen atom. Examples include piperidinyloxy, tetrahydrofuryloxy and the like.

[0 0 2 9]

The term “aromatic carbocyclylcarbonyl” means a group wherein “aromatic carbocycle” is bonded to carbonyl group. Examples include phenylcarbonyl, naphthylcarbonyl and the like.

The term “non-aromatic carbocyclylcarbonyl” means a group wherein “non-aromatic carbocycle” is bonded to carbonyl group. Examples include cyclopropylcarbonyl, cyclohexylcarbonyl, cyclohexenylcarbonyl and the like.

The term “aromatic heterocyclylcarbonyl” means a group wherein “aromatic heterocycle” is bonded to carbonyl group. Examples include pyridylcarbonyl, oxazolylcarbonyl, pyrazinecarbonyl and the like.

The term “non-aromatic heterocyclylcarbonyl” means a group wherein “non-aromatic heterocycle” is bonded to carbonyl group. Examples include piperidinylcarbonyl, tetrahydrofurylcarbonyl and the like.

[0 0 3 0]

The term “aromatic carbocyclylamino” means a group wherein the above “aromatic carbocycle” is replaced with one or two hydrogen atom(s) bonded to a nitrogen atom of an amino group. These two aromatic carbocycle may be the same or different. Examples include phenylamino, naphthylamino, diphenylamino and the like.

The term “non-aromatic carbocyclylamino” means a group wherein the above “non-aromatic carbocycle” is replaced with one or two hydrogen atom(s) bonded to a nitrogen atom of an amino group. These two non-aromatic carbocycle may be the same or different.

The term “aromatic heterocyclylamino” means a group wherein the above “aromatic heterocycle” is replaced with one or two hydrogen atom(s) bonded to a nitrogen atom of an amino group. These two aromatic heterocycle may be the same or different. Examples include pyridylamino, pyridazinylamino and the like.

The term “non-aromatic heterocyclylamino” means a group wherein the above “non-aromatic heterocycle” is replaced with one or two hydrogen atom(s) bonded to a nitrogen atom of an amino group. These two non-aromatic heterocycle may be the same or different.

[0 0 3 1]

The term “aromatic carbocyclylsulfonyl” means a group wherein “aromatic carbocycle” is bonded to sulfonyl group. Examples include phenylsulfonyl, naphthylsulfonyl and the like.

The term “non-aromatic carbocyclylsulfonyl” means a group wherein “non-aromatic carbocycle” is bonded to sulfonyl group. Examples include cyclopropylsulfonyl, cyclohexylsulfonyl, cyclohexenylsulfonyl and the like.

The term “aromatic heterocyclylsulfonyl” means a group wherein “aromatic heterocycle” is bonded to sulfonyl group. Examples include pyridylsulfonyl, oxazolylsulfonyl and the like.

The term “non-aromatic heterocyclylsulfonyl” means a group wherein “non-aromatic heterocycle” is bonded to sulfonyl group. Examples include piperidinylsulfonyl, tetrahydrofurylsulfonyl and the like.  
[0 0 3 2]

The term “aromatic carbocyclylcarbonylamino” means a group wherein the above “aromatic carbocyclylcarbonyl” is replaced with one or two hydrogen atom(s) bonded to a nitrogen atom of an amino group. These two aromatic carbocyclyl may be the same or different. Examples include phenylcarbonylamino, naphthylcarbonylamino, di(phenylcarbonyl)amino and the like.

The term “non-aromatic carbocyclylcarbonylamino” means a group wherein the above “non-aromatic carbocyclylcarbonylamino” is replaced with one or two hydrogen atom(s) bonded to a nitrogen atom of an amino group. These two non-aromatic carbocyclyl may be the same or different. Examples include cyclopropylcarbonylamino, cyclohexylcarbonylamino, cyclohexylcarbonylamino and the like.

The term “aromatic heterocyclylcarbonylamino” means a group wherein the above “aromatic heterocyclylcarbonyl” is replaced with one or two hydrogen atom(s) bonded to a nitrogen atom of an amino group. These two aromatic heterocyclyl may be the same or different. Examples include pyridylcarbonylamino, oxazolylcarbonylamino, pyrazinecarbonylamino and the like.

The term “non-aromatic heterocyclylcarbonylamino” means a group wherein the above “non-aromatic heterocyclylcarbonyl” is replaced with one or two hydrogen atom(s) bonded to a nitrogen atom of an amino group. These two non-aromatic heterocyclyl may be the same or different. Examples include piperidinylcarbonylamino, tetrahydrofurylcarbonylamino and the like.  
[0 0 3 3]

The term “aromatic carbocyclylsulfamoyl” means a group wherein “aromatic carbocycle” is bonded to sulfamoyl group. Examples include phenylsulfamoyl, naphthylsulfamoyl and the like.

The term “non-aromatic carbocyclylsulfamoyl” means a group wherein “non-aromatic carbocycle” is bonded to sulfamoyl group. Examples include cyclopropylsulfamoyl, cyclohexylsulfamoyl and the like.

The term “aromatic heterocyclylsulfamoyl” means a group wherein “aromatic heterocycle” is bonded to sulfamoyl group. Examples include pyridylsulfamoyl, pyrazinesulfamoyl and the like.

The term “non-aromatic heterocyclylsulfamoyl” means a group wherein “non-aromatic heterocycle” is bonded to sulfamoyl group. Examples include piperidinylsulfamoyl, piperazinylsulfamoyl, pyrrolidinylsulfamoyl, tetrahydrofurylsulfamoyl and the like.  
[0 0 3 4]

The term “aromatic carbocyclylureido” means a group wherein the above “aromatic carbocycle” is replaced with one or two hydrogen atom(s) bonded to a nitrogen atom of an ureido group. These two aromatic carbocycle may be the same or different.

The term “non-aromatic carbocyclylureido” means a group wherein the above “non-aromatic carbocycle” is replaced with one or two hydrogen atom(s) bonded to a nitrogen atom of an ureido group. These two non-aromatic carbocycle may be the

same or different.

The term “aromatic heterocyclureido” means a group wherein the above “aromatic heterocycle” is replaced with one or two hydrogen atom(s) bonded to a nitrogen atom of an ureido group. These two aromatic heterocycle may be the same or different.

The term “non-aromatic heterocyclureido” means a group wherein the above “non-aromatic heterocycle” is replaced with one or two hydrogen atom(s) bonded to a nitrogen atom of an ureido group. These two non-aromatic heterocycle may be the same or different.

[0 0 3 5]

The term “alkylamino” means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of an amino group are replaced with one or two “alkyl” described above. These two alkyl groups may be the same or different. Examples include monomethylamino, monoethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino and the like.

[0 0 3 6]

The term “hydroxyamino” means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of an amino group are replaced with one or two hydroxy. Examples include monohydroxyamino, dihydroxyamino.

[0 0 3 7]

The term “sulfamoylamino” means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of an amino group are replaced with one or two sulfamoyl. Examples include monosulfamoylamino, disulfamoylamino.

[0 0 3 8]

The term “alkylammonium” means a group wherein one, two or three hydrogen atom(s) attached to a nitrogen atom of an ammonium group are replaced with one, two or three “alkyl” described above. These two or three alkyl groups may be the same or different. Examples include monomethylammonium, monoethylammonium, dimethylammonium, diethylammonium, triethylammonium, triethylammonium, N-methyl-N-ethyl-N-isopropylammonium and the like.

[0 0 3 9]

The term “alkylureido” means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of an ureido group are replaced with one or two “alkyl” described above. These two alkyl groups may be the same or different. Examples include monomethylureido, monoethylureido, dimethylureido, diethylureido, N-methyl-N-ethylureido and the like.

[0 0 4 0]

The term “alkylcarbamoyl” means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of a carbamoyl group are replaced with one or two “alkyl” described above. These two alkyl groups may be the same or different. Examples include monomethylcarbamoyl, monoethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, N-methyl-N-ethylcarbamoyl and the like.

[0 0 4 1]

The term “alkylsulfamoyl” means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of a sulfamoyl group are replaced with one or two “alkyl” described above. These two alkyl groups may be the same or different. Examples include monomethylsulfamoyl, monoethylsulfamoyl, dimethylsulfamoyl, diethylsulfamoyl, N-methyl-N-ethylsulfamoyl and the like.

[0 0 4 2]

The term “alkylphosphonyl” means a group wherein one or two hydrogen

atom(s) attached to a nitrogen atom of a phosphonyl group are replaced with one or two “alkyl” described above. These two alkyl groups may be the same or different. Examples include monomethylphosphonyl, monoethylphosphonyl, dimethylphosphonyl, diethylphosphonyl, N-methyl-N-ethylphosphonyl and the like.  
[ 0 0 4 3 ]

The term “aromatic carbocyclalkyl” means an alkyl substituted with one or more “aromatic carbocycl” described above. Examples include benzyl, phenethyl, phenylpropyl, benzhydryl, trityl, naphthylmethyl and the like.

The term “non-aromatic carbocyclalkyl” means an alkyl substituted with one or more “non-aromatic carbocycl” described above. The “non-aromatic carbocyclalkyl” also includes “non-aromatic carbocyclalkyl” wherein the alkyl part is substituted with the above “aromatic carbocycl”. Examples include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl and the like.

The term “aromatic heterocyclalkyl” means an alkyl substituted with one or more “aromatic heterocycl” described above. The “aromatic heterocyclalkyl” also includes “aromatic heterocyclalkyl” wherein the alkyl part is substituted with the above “aromatic carbocycl” and/or “non-aromatic carbocycl”. Examples include pyridylmethyl, furanylmethyl, imidazolylmethyl, indolylmethyl, benzothiophenylmethyl, oxazolylmethyl, isoxazolylmethyl, thiazolylmethyl, isothiazolylmethyl, pyrazolylmethyl, isopyrazolylmethyl, pyrrolidinylmethyl, benzoxazolylmethyl and the like.

The term “non-aromatic heterocyclalkyl” means an alkyl substituted with one or more “non-aromatic heterocycl” described above. The “non-aromatic heterocyclalkyl” also includes “non-aromatic heterocyclalkyl” wherein the alkyl part is substituted with the above “aromatic carbocycl”, “non-aromatic carbocycl” and/or “aromatic heterocycl”. Examples include tetrahydropyranylmethyl, morpholinylethyl, piperidinylmethyl, piperazinylmethyl and the like.  
[ 0 0 4 4 ]

The term “aromatic carbocyclalkyloxy” means a group wherein a hydrogen atom of hydroxy is replaced with “aromatic carbocyclalkyl” described above.

The term “non-aromatic carbocyclalkyloxy” means a group wherein a hydrogen atom of hydroxy is replaced with “non-aromatic carbocyclalkyl” described above.

The term “aromatic heterocyclalkyloxy” means a group wherein a hydrogen atom of hydroxy is replaced with “aromatic heterocyclalkyl” described above.

The term “non-aromatic heterocyclalkyloxy” means a group wherein a hydrogen atom of hydroxy is replaced with “non-aromatic heterocyclalkyl” described above.

The term “aromatic carbocyclalkylsulfonyl” means a group wherein a hydrogen atom of sulfonyl group is replaced with “aromatic carbocyclalkyl” described above.

The term “non-aromatic carbocyclalkylsulfonyl” means a group wherein a hydrogen atom of sulfonyl group is replaced with “non-aromatic carbocyclalkyl” described above.

The term “aromatic heterocyclalkylsulfonyl” means a group wherein a hydrogen atom of sulfonyl group is replaced with “aromatic heterocyclalkyl” described above.

The term “non-aromatic heterocyclalkylsulfonyl” means a group wherein a hydrogen atom of sulfonyl group is replaced with “non-aromatic heterocyclalkyl”

described above.

[0 0 4 5]

The alkyl part of “alkyloxy”, “alkylsulfonyl”, “alkylphosphonyl”, “alkyloxyalkyl”, “alkyloxycarbonyl”, “alkylcarbonyl”, “alkylcarbonyloxy”, “alkylimino”, “alkylsulfonyl”, “hydroxyalkyloxy”, “hydroxyalkylamino”, “carboxyalkyl”, “carbamoylealkyl”, “haloalkyloxy” or “alkylsulfonylamino” is also same as the above “alkyl”.

[0 0 4 6]

The alkenyl part of “alkenyloxy”, “alkenyloxycarbonyl”, “alkenylcarbonyl”, “alkenylcarbonyloxy”, “alkenylsulfonyl”, “alkenylimino” or “carboxyalkenyl” is also same as the above “alkenyl”.

[0 0 4 7]

The alkynyl part of “alkynyloxy”, “alkynyloxycarbonyl”, “alkynylcarbonyl”, “alkynylcarbonyloxy”, “alkynylsulfonyl” or “alkynylimino” is also same as the above “alkynyl”.

[0 0 4 8]

The alkyl part of “aromatic carbocyclalkyloxy”, “non-aromatic carbocyclalkyloxy”, “aromatic heterocyclalkyloxy”, “non-aromatic heterocyclalkyloxy”, “aromatic carbocyclalkyloxycarbonyl”, “non-aromatic carbocyclalkyloxycarbonyl”, “aromatic heterocyclalkyloxycarbonyl”, “non-aromatic heterocyclalkyloxycarbonyl”, “aromatic carbocyclalkylcarbonyl”, “non-aromatic carbocyclalkylcarbonyl”, “aromatic heterocyclalkylcarbonyl”, “non-aromatic heterocyclalkylcarbonyl”, “aromatic carbocyclalkylcarbonyloxy”, “non-aromatic carbocyclalkylcarbonyloxy”, “aromatic heterocyclalkylcarbonyloxy”, “non-aromatic heterocyclalkylcarbonyloxy”, “aromatic carbocyclalkylamino”, “non-aromatic carbocyclalkylamino”, “aromatic heterocyclalkylamino”, “non-aromatic heterocyclalkylamino”, “aromatic carbocyclalkylsulfonyl”, “non-aromatic carbocyclalkylsulfonyl”, “aromatic heterocyclalkylsulfonyl”, “non-aromatic heterocyclalkylsulfonyl”, “aromatic carbocyclalkoxyalkyl”, “non-aromatic carbocyclalkoxyalkyl”, “aromatic heterocyclalkoxyalkyl” and “non-aromatic heterocyclalkoxyalkyl” is also same as the above “alkyl”.

[0 0 4 9]

The alkenyl part of “aromatic carbocyclalkenyl”, “non-aromatic carbocyclalkenyl”, “aromatic heterocyclalkenyl”, “non-aromatic heterocyclalkenyl”, “aromatic carbocyclalkenyloxy”, “non-aromatic carbocyclalkenyloxy”, “aromatic heterocyclalkenyloxy”, “non-aromatic heterocyclalkenyloxy”, “aromatic carbocyclalkenyloxyalkenyl”, “non-aromatic carbocyclalkenyloxyalkenyl”, “aromatic heterocyclalkenyloxyalkenyl”, “non-aromatic heterocyclalkenyloxyalkenyl”, “aromatic carbocyclalkenyloxycarbonyl”, “non-aromatic carbocyclalkenyloxycarbonyl”, “aromatic heterocyclalkenyloxycarbonyl”, “non-aromatic heterocyclalkenyloxycarbonyl”, “aromatic carbocyclalkenylcarbonyl”, “non-aromatic carbocyclalkenylcarbonyl”, “aromatic heterocyclalkenylcarbonyl”, “non-aromatic heterocyclalkenylcarbonyl”, “aromatic carbocyclalkenylcarbonyloxy”, “non-aromatic carbocyclalkenylcarbonyloxy”, “aromatic heterocyclalkenylcarbonyloxy”, “non-aromatic heterocyclalkenylcarbonyloxy”, “aromatic carbocyclalkenylamino”, “non-aromatic carbocyclalkenylamino”, “aromatic heterocyclalkenylamino”, “non-aromatic heterocyclalkenylamino”, “aromatic carbocyclalkenylsulfonyl”, “non-aromatic carbocyclalkenylsulfonyl”, “aromatic heterocyclalkenylsulfonyl”, “non-aromatic heterocyclalkenylsulfonyl”, “aromatic carbocyclalkoxyalkenyl”, “non-

aromatic carbocyclyloxyalkenyl”, “aromatic heterocyclyloxyalkenyl” and “non-aromatic heterocyclyloxyalkenyl” is also same as the above “alkenyl”.

[0 0 5 0]

The alkynyl part of “aromatic carbocyclylalkynyl”, “non-aromatic carbocyclylalkynyl”, “aromatic heterocyclylalkynyl”, “non-aromatic heterocyclylalkynyl”, “aromatic carbocyclylalkynyloxy”, “non-aromatic carbocyclylalkynyloxy”, “aromatic heterocyclylalkynyloxy”, “non-aromatic heterocyclylalkynyloxy”, “aromatic carbocyclylalkynyloxyalkynyl”, “non-aromatic carbocyclylalkynyloxyalkynyl”, “aromatic heterocyclylalkynyloxyalkynyl”, “non-aromatic heterocyclylalkynyloxyalkynyl”, “aromatic carbocyclylalkynyloxycarbonyl”, “non-aromatic carbocyclylalkynyloxycarbonyl”, “aromatic heterocyclylalkynyloxycarbonyl”, “non-aromatic heterocyclylalkynyloxycarbonyl”, “aromatic carbocyclylalkynylcarbonyl”, “non-aromatic carbocyclylalkynylcarbonyl”, “aromatic heterocyclylalkynylcarbonyl”, “non-aromatic heterocyclylalkynylcarbonyl”, “aromatic carbocyclylalkynylcarbonyloxy”, “non-aromatic carbocyclylalkynylcarbonyloxy”, “aromatic heterocyclylalkynylcarbonyloxy”, “non-aromatic heterocyclylalkynylcarbonyloxy”, “aromatic carbocyclylalkynylamino”, “non-aromatic carbocyclylalkynylamino”, “aromatic heterocyclylalkynylamino”, “non-aromatic heterocyclylalkynylamino”, “aromatic carbocyclylalkynylsulfonyl”, “non-aromatic carbocyclylalkynylsulfonyl”, “aromatic heterocyclylalkynylsulfonyl”, “non-aromatic heterocyclylalkynylsulfonyl”, “aromatic carbocyclyloxyalkynyl”, “non-aromatic carbocyclyloxyalkynyl”, “aromatic heterocyclyloxyalkynyl” and “non-aromatic heterocyclyloxyalkynyl” is also same as the above “alkynyl”.

[0 0 5 1]

The aromatic carbocyclyl part of “aromatic carbocyclylalkyloxy”, “aromatic carbocyclylalkyloxycarbonyl”, “aromatic carbocyclylalkylcarbonyl”, “aromatic carbocyclylalkylcarbonyloxy”, “aromatic carbocyclylalkylamino”, “aromatic carbocyclylalkylsulfonyl”, “aromatic carbocyclyloxyalkyl”, “aromatic carbocyclylalkenyl”, “aromatic carbocyclylalkenyloxy”, “aromatic carbocyclylalkenyloxyalkenyl”, “aromatic carbocyclylalkenyloxycarbonyl”, “aromatic carbocyclylalkenylcarbonyl”, “aromatic carbocyclylalkenylcarbonyloxy”, “aromatic carbocyclylalkenylamino”, “aromatic carbocyclylalkenylsulfonyl”, “aromatic carbocyclyloxyalkenyl”, “aromatic carbocyclylalkynyl”, “aromatic carbocyclylalkynyloxy”, “aromatic carbocyclylalkynyloxyalkynyl”, “aromatic carbocyclylalkynyloxycarbonyl”, “aromatic carbocyclylalkynylcarbonyl”, “aromatic carbocyclylalkynylcarbonyloxy”, “aromatic carbocyclylalkynylamino”, “aromatic carbocyclylalkynylsulfonyl” and “aromatic carbocyclyloxyalkynyl” is also same as the above “aromatic carbocyclyl”.

[0 0 5 2]

The non-aromatic carbocyclyl part of “non-aromatic carbocyclylalkyloxy”, “non-aromatic carbocyclylalkyloxycarbonyl”, “non-aromatic carbocyclylalkylcarbonyl”, “non-aromatic carbocyclylalkylcarbonyloxy”, “non-aromatic carbocyclylalkylamino”, “non-aromatic carbocyclylalkylsulfonyl”, “non-aromatic carbocyclyloxyalkyl”, “non-aromatic carbocyclylalkenyl”, “non-aromatic carbocyclylalkenyloxy”, “non-aromatic carbocyclylalkenyloxyalkenyl”, “non-aromatic carbocyclylalkenyloxycarbonyl”, “non-aromatic carbocyclylalkenylcarbonyl”, “non-aromatic carbocyclylalkenylcarbonyloxy”, “non-aromatic carbocyclylalkenylamino”, “non-aromatic carbocyclylalkenylsulfonyl”, “non-aromatic carbocyclyloxyalkenyl”, “non-aromatic carbocyclylalkynyl”, “non-aromatic carbocyclylalkynyloxy”, “non-aromatic carbocyclylalkynyloxyalkynyl”, “non-aromatic carbocyclylalkynyloxycarbonyl”, “non-aromatic carbocyclylalkynylcarbonyl”,

“non-aromatic carbocyclylalkynylcarbonyloxy”, “non-aromatic carbocyclylalkynylamino”, “non-aromatic carbocyclylalkynylsulfonyl” and “non-aromatic carbocyclylalkynyl” is also same as the above “non-aromatic carbocyclyl”.  
[0 0 5 3]

The aromatic heterocyclyl part of “aromatic heterocyclylalkyloxy”, “aromatic heterocyclylalkyloxycarbonyl”, “aromatic heterocyclylalkylcarbonyl”, “aromatic heterocyclylalkylcarbonyloxy”, “aromatic heterocyclylalkylamino”, “aromatic heterocyclylalkylsulfonyl”, “aromatic heterocyclylalkyl”, “aromatic heterocyclylalkenyl”, “aromatic heterocyclylalkenylloxy”, “aromatic heterocyclylalkenylloxyalkenyl”, “aromatic heterocyclylalkenylloxycarbonyl”, “aromatic heterocyclylalkenylcarbonyl”, “aromatic heterocyclylalkenylcarbonyloxy”, “aromatic heterocyclylalkenylamino”, “aromatic heterocyclylalkenylsulfonyl”, “aromatic heterocyclylalkenyl”, “aromatic heterocyclylalkynyl”, “aromatic heterocyclylalkynylloxy”, “aromatic heterocyclylalkynylloxyalkynyl”, “aromatic heterocyclylalkynylloxycarbonyl”, “aromatic heterocyclylalkynylcarbonyl”, “aromatic heterocyclylalkynylcarbonyloxy”, “aromatic heterocyclylalkynylamino”, “aromatic heterocyclylalkynylsulfonyl” and “aromatic heterocyclylalkynyl” is also same as the above “aromatic heterocyclyl”.  
[0 0 5 4]

The non-aromatic heterocyclyl part of “non-aromatic heterocyclylalkyloxy”, “non-aromatic heterocyclylalkyloxycarbonyl”, “non-aromatic heterocyclylalkylcarbonyl”, “non-aromatic heterocyclylalkylcarbonyloxy”, “non-aromatic heterocyclylalkylamino”, “non-aromatic heterocyclylalkylsulfonyl”, “non-aromatic heterocyclylalkyl”, “non-aromatic heterocyclylalkenyl”, “non-aromatic heterocyclylalkenylloxy”, “non-aromatic heterocyclylalkenylloxyalkenyl”, “non-aromatic heterocyclylalkenylloxycarbonyl”, “non-aromatic heterocyclylalkenylcarbonyl”, “non-aromatic heterocyclylalkenylcarbonyloxy”, “non-aromatic heterocyclylalkenylamino”, “non-aromatic heterocyclylalkenylsulfonyl”, “non-aromatic heterocyclylalkenyl”, “non-aromatic heterocyclylalkynyl”, “non-aromatic heterocyclylalkynylloxy”, “non-aromatic heterocyclylalkynylloxyalkynyl”, “non-aromatic heterocyclylalkynylloxycarbonyl”, “non-aromatic heterocyclylalkynylcarbonyl”, “non-aromatic heterocyclylalkynylcarbonyloxy”, “non-aromatic heterocyclylalkynylamino”, “non-aromatic heterocyclylalkynylsulfonyl” and “non-aromatic heterocyclylalkynyl” is also same as the above “non-aromatic heterocyclyl”.  
[0 0 5 5]

The term “alkylamino aromatic carbocyclyl”, “alkylamino non- aromatic carbocyclyl”, “alkylamino aromatic heterocyclyl” and “alkylamino non- aromatic heterocyclyl” means above “aromatic carbocyclyl”, “non- aromatic carbocyclyl”, “aromatic heterocyclyl” or “non- aromatic heterocyclyl” substituted one or more above “alkylamino”.  
[0 0 5 6]

Examples of the substituents of “substituted or unsubstituted amino”, “substituted or unsubstituted carbamoyl”, “substituted or unsubstituted sulfamoyl”, “substituted or unsubstituted ureido”, “substituted or unsubstituted amidino” and “substituted or unsubstituted guanidino” include same or different one or two group(s) selected from hydroxy, sulfamoyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkenylsulfonyl,

substituted or unsubstituted alkynylsulfonyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclylcarbonyl, substituted or unsubstituted non-aromatic carbocyclylcarbonyl, substituted or unsubstituted aromatic heterocyclylcarbonyl, substituted or unsubstituted non-aromatic heterocyclylcarbonyl, substituted or unsubstituted aromatic carbocyclylsulfonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted aromatic heterocyclylsulfonyl, substituted or unsubstituted non-aromatic heterocyclylsulfonyl.

Especially preferably, same or different one or two group(s) selected from hydroxy, sulfamoyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted aromatic carbocyclylcarbonyl, substituted or unsubstituted non-aromatic carbocyclylcarbonyl, substituted or unsubstituted aromatic heterocyclylcarbonyl, substituted or unsubstituted non-aromatic heterocyclylcarbonyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl and substituted or unsubstituted non-aromatic heterocyclyl are exemplified.

More preferably, same or different one or two group(s) selected from alkyl, hydroxy, hydroxyalkyl, alkylsulfonyl, alkylphosphonyl, sulfamoyl, aromatic carbocyclyl, non-aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocyclylcarbonyl, non-aromatic carbocyclylcarbonyl, aromatic heterocyclylcarbonyl and non-aromatic heterocyclylcarbonyl are exemplified.  
[0 0 5 7]

Examples of the substituents of “substituted or unsubstituted alkylamino” include the substituents of above “substituted or unsubstituted alkyl”. Preferably, halogen, hydroxy, carboxy, alkyloxycarbonyl, amino, alkylamino, carbamoyl, alkylimino, aromatic carbocyclyl, non-aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, alkyloxyaromatic carbocyclyl, alkyloxynon-aromatic carbocyclyl, alkyloxyaromatic heterocyclyl and alkyloxynon-aromatic heterocyclyl are exemplified. One or more, preferably 1 to 4 same or different substituent(s) may be had at any position(s).  
[0 0 5 8]

Examples of the substituents of “aromatic carbocyclyl”, “non-aromatic carbocyclyl”, “aromatic heterocyclyl” and “non-aromatic heterocyclyl” of “substituted aromatic carbocyclyl”, “substituted non-aromatic carbocyclyl”, “substituted aromatic heterocyclyl”, “substituted non-aromatic heterocyclyl”, “substituted aromatic carbocyclyl”, “substituted non-aromatic carbocyclyl”, “substituted aromatic heterocyclyl”, “substituted non-aromatic heterocyclyl”, “substituted aromatic carbocycloxy”, “substituted non-aromatic carbocycloxy”, “substituted aromatic heterocycloxy”, “substituted non-aromatic heterocycloxy”, “substituted aromatic carbocyclylcarbonyl”, “substituted non-aromatic carbocyclylcarbonyl”, “substituted aromatic heterocyclylcarbonyl”, “substituted non-aromatic heterocyclylcarbonyl”, “substituted aromatic carbocyclylamino”, “substituted non-aromatic carbocyclylamino”, “substituted aromatic heterocyclylamino”, “substituted non-aromatic heterocyclylamino”, “substituted aromatic carbocyclylsulfonyl”, “substituted non-aromatic carbocyclylsulfonyl”, “substituted aromatic heterocyclylsulfonyl”, “substituted non-aromatic heterocyclylsulfonyl”, “substituted non-aromatic heterocycloxyalkyl”, “substituted non-aromatic heterocycloxyalkenyl”,

“substituted non-aromatic heterocycloxyalkynyl”, “substituted nitrogen-containing aromatic heterocyclyl”, “substituted nitrogen-containing non-aromatic heterocyclyl”, “substituted aromatic carbocyclylcarbonylamino”, “substituted non-aromatic carbocyclylcarbonylamino”, “substituted aromatic heterocyclylcarbonylamino”, “substituted non-aromatic heterocyclylcarbonylamino”, “substituted aromatic carbocyclylsulfamoyl”, “substituted non-aromatic carbocyclylsulfamoyl”, “substituted aromatic heterocyclylsulfamoyl”, “substituted non-aromatic heterocyclylsulfamoyl”, “substituted aromatic carbocyclylureido”, “substituted non-aromatic carbocyclylureido”, “substituted aromatic heterocyclylureido”, “substituted non-aromatic heterocyclylureido”, “substituted aromatic carbocyclylalkyloxy”, “substituted non-aromatic carbocyclylalkyloxy”, “substituted aromatic heterocyclylalkyloxy”, “substituted non-aromatic heterocyclylalkyloxy”, “substituted aromatic carbocyclylalkylsulfonyl”, “substituted non-aromatic carbocyclylalkylsulfonyl”, “substituted aromatic heterocyclylalkylsulfonyl”, “substituted non-aromatic heterocyclylalkylsulfonyl”, “substituted aromatic carbocyclylalkylcarbonyloxy”, “substituted non-aromatic carbocyclylalkylcarbonyloxy”, “substituted aromatic heterocyclylalkylcarbonyloxy”, “substituted non-aromatic heterocyclylalkylcarbonyloxy”, “substituted alkylaminoaromatic carbocyclyl”, “substituted alkylaminonon-aromatic carbocyclyl”, “substituted alkylaminoaromatic heterocyclyl” and “substituted alkylaminonon-aromatic heterocyclyl” include halogen, cyano, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, carbamoylalkyl, haloalkenyl, hydroxyalkenyl, carbamoylalkenyl, carboxyalkyl, carboxyalkenyl, alkylcarbonyl, hydroxy, carboxy, oxo, thioxo, imino, alkylimino, alkyloxycarbonyl, amino, alkylamino(monoalkylamino, dialkylamino), hydroxyalkylamino, hydroxyalkyloxy, carbamoyl, sulfamoyl, alkylsulfonyl, alkyloxy, alkenylsulfonyl, alkenyloxy, amidino, aromatic carbocyclylalkyl, non-aromatic carbocyclylalkyl, aromatic heterocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic carbocyclyloxyalkyl, non-aromatic carbocyclyloxyalkyl, aromatic heterocyclyloxyalkyl, non-aromatic carbocyclyloxyalkyl, aromatic carbocyclyl, non-aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocyclyl substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino, non-aromatic carbocyclyl substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino, aromatic heterocyclyl substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino, non-aromatic heterocyclyl substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino, aromatic carbocyclylalkyloxy, non-aromatic carbocyclylalkyloxy, aromatic heterocyclylalkyloxy, non-aromatic heterocyclylalkyloxy, aromatic carbocyclylalkyloxy substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino, non-aromatic carbocyclylalkyloxy substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino, aromatic heterocyclylalkyloxy substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino, non-aromatic heterocyclylalkyloxy substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino, aromatic carbocyclyloxy, non-aromatic carbocyclyloxy, aromatic heterocyclyloxy, non-aromatic heterocyclyloxy,

aromatic carbocycloxy substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino,  
 non-aromatic carbocycloxy substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino,  
 aromatic heterocycloxy substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino,  
 non-aromatic heterocycloxy substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino.

Preferably, halogen, alkyl, haloalkyl, hydroxyalkyl, carbamoylalkyl, carboxyalkenyl, hydroxy, carboxy, oxo, alkyloxycarbonyl, amino, alkylamino, hydroxyalkylamino, carbamoyl, sulfamoyl, alkylsulfonyl, alkyloxy, amidino, aromatic carbocyclylalkyl, non-aromatic carbocyclylalkyl, aromatic heterocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic carbocycloxyalkyl, non-aromatic carbocycloxyalkyl, aromatic heterocycloxyalkyl, non-aromatic carbocycloxyalkyl, aromatic carbocyclyl, non-aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocyclyl substituted with halogen, alkyl, alkyloxy and/or amino, non-aromatic carbocyclyl substituted with halogen, alkyl, alkyloxy and/or amino, aromatic heterocyclyl substituted with halogen, alkyl, alkyloxy and/or amino, non-aromatic heterocyclyl substituted with halogen, alkyl, alkyloxy and/or amino, aromatic carbocyclylalkyloxy, non-aromatic carbocyclylalkyloxy, aromatic heterocyclylalkyloxy, non-aromatic heterocyclylalkyloxy, aromatic carbocyclylalkyloxy substituted with haloalkyl, non-aromatic carbocyclylalkyloxy substituted with haloalkyl, aromatic heterocyclylalkyloxy substituted with haloalkyl, non-aromatic heterocyclylalkyloxy substituted with haloalkyl, aromatic carbocycloxy, non-aromatic carbocycloxy, aromatic heterocycloxy, non-aromatic heterocycloxy, aromatic carbocycloxy substituted with hydroxy and/or hydroxyalkyl, non-aromatic carbocycloxy substituted with hydroxy or hydroxyalkyl, aromatic heterocycloxy substituted with hydroxy or hydroxyalkyl, non-aromatic heterocycloxy substituted with hydroxy or hydroxyalkyl are exemplified. One or more, preferably 1 to 4 same or different substituent(s) may be had at any position(s).  
 [0 0 5 9]

Examples of the substituents of "alkyl", "alkenyl" and "alkynyl" of "substituted alkyl", "substituted alkenyl", "substituted alkynyl", "substituted alkyloxy", "substituted alkenyloxy", "substituted alkynyloxy", "substituted alkylcarbonyl", "substituted alkenylcarbonyl", "substituted alkynylcarbonyl", "substituted alkylammonium", "substituted alkylsulfonyl", "substituted alkenylsulfonyl", "substituted alkynylsulfonyl", "substituted alkylphosphonyl", "substituted alkenylphosphonyl", "substituted alkynylphosphonyl", "substituted alkylcarbonyloxy", "substituted alkenylcarbonyloxy", "substituted alkynylcarbonyloxy", "substituted alkyloxycarbonyl", "substituted alkenyloxycarbonyl", "substituted alkynyloxycarbonyl", "substituted non-aromatic heterocycloxyalkyl", "substituted non-aromatic heterocycloxyalkenyl", "substituted non-aromatic heterocycloxyalkynyl", "substituted alkylamino", "substituted alkylsulfonamino", "substituted alkylcarbamoyl", "substituted alkylsulfamoyl", "substituted alkylureido", "substituted aromatic carbocyclylalkyloxy", "substituted non-aromatic carbocyclylalkyloxy", "substituted aromatic heterocyclylalkyloxy", "substituted non-aromatic heterocyclylalkyloxy", "substituted aromatic carbocyclylalkylsulfonyl",

“substituted non-aromatic carbocyclylalkylsulfonyl”, “substituted aromatic heterocyclylalkylsulfonyl”, “substituted non-aromatic heterocyclylalkylsulfonyl”, “substituted aromatic carbocyclylalkylcarbonyloxy”, “substituted non-aromatic carbocyclylalkylcarbonyloxy”, “substituted aromatic heterocyclylalkylcarbonyloxy”, “substituted non-aromatic heterocyclylalkylcarbonyloxy”, “substituted alkylaminoaromatic carbocyclyl”, “substituted alkylaminonon-aromatic carbocyclyl”, “substituted alkylaminoaromatic heterocyclyl” and “substituted alkylaminonon-aromatic heterocyclyl” include halogen, cyano, hydroxy, carboxy, amino, alkylamino(monoalkylamino, dialkylamino), alkyloxy, haloalkyloxy, alkenyloxy, hydroxyalkyloxy, alkyloxycarbonyl, alkylsulfonyl, alkenylsulfonyl, carbamoyl, alkylimino, aromatic carbocyclyl, non-aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocyclyl substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino, non-aromatic carbocyclyl substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino, aromatic heterocyclyl substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino, non-aromatic heterocyclyl substituted with halogen, cyano, hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy and/or amino.

Preferably, halogen, hydroxy, carboxy, amino, alkylamino, alkyloxy, hydroxyalkyloxy, alkyloxycarbonyl, alkylsulfonyl, carbamoyl, alkylimino, aromatic carbocyclyl, non-aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, alkyloxyaromatic carbocyclyl, alkyloxynon-aromatic carbocyclyl, alkyloxyaromatic heterocyclyl and alkyloxynon-aromatic heterocyclyl are exemplified.

Especially preferably, hydroxy, carboxy, amino, alkylamino, alkyloxy, hydroxyalkyloxy, alkyloxycarbonyl, alkylsulfonyl, aromatic carbocyclyl, non-aromatic carbocyclyl, aromatic heterocyclyl and non-aromatic heterocyclyl are exemplified. One or more, preferably 1 to 4 same or different substituent(s) may be had at any position(s).

[0 0 6 0]

The “substituted aromatic carbocyclylalkyl”, “substituted aromatic carbocyclyloxyalkyl”, “substituted aromatic carbocyclylalkyloxy”, “substituted aromatic carbocyclylalkyloxycarbonyl”, “substituted aromatic carbocyclylalkylcarbonyl”, “substituted aromatic carbocyclylalkylcarbonyloxy”, “substituted aromatic carbocyclylalkylamino” and “substituted aromatic carbocyclylalkylsulfonyl” means the part of “aromatic carbocyclyl” and/or above “alkyl” are substituted.

[0 0 6 1]

The “substituted non-aromatic carbocyclylalkyl”, “substituted non-aromatic carbocyclyloxyalkyl”, “substituted non-aromatic carbocyclylalkyloxy”, “substituted non-aromatic carbocyclylalkyloxycarbonyl”, “substituted non-aromatic carbocyclylalkylcarbonyl”, “substituted non-aromatic carbocyclylalkylcarbonyloxy”, “substituted non-aromatic carbocyclylalkylamino” and “substituted non-aromatic carbocyclylalkylsulfonyl” means the part of above “non-aromatic carbocyclyl” and/or above “alkyl” are substituted.

[0 0 6 2]

The “substituted aromatic heterocyclylalkyl”, “substituted aromatic heterocyclyloxyalkyl”, “substituted aromatic heterocyclylalkyloxy”, “substituted aromatic heterocyclylalkyloxycarbonyl”, “substituted aromatic

heterocyclalkylcarbonyl”, “substituted aromatic heterocyclalkylcarbonyloxy”, “substituted aromatic heterocyclalkylamino” and “substituted aromatic heterocyclalkylsulfonyl” means the part of above “aromatic heterocycl” and/or above “alkyl” are substituted.

[0 0 6 3]

The “substituted non-aromatic heterocyclalkyl”, “substituted non-aromatic heterocyclalkoxy”, “substituted non-aromatic heterocyclalkyloxy”, “substituted non-aromatic heterocyclalkyloxycarbonyl”, “substituted non-aromatic heterocyclalkylcarbonyl”, “substituted non-aromatic heterocyclalkylcarbonyloxy”, “substituted non-aromatic heterocyclalkylamino” and “substituted or unsubstituted non-aromatic heterocyclalkylsulfonyl” means the part of above “non-aromatic heterocycl” and/or above “alkyl” are substituted.

[0 0 6 4]

The “substituted non-aromatic heterocyclalkenyl” and “substituted non-aromatic heterocyclalkynyl” means the part of above “non-aromatic heterocycl”, above “alkenyl” and/or above “alkynyl” are substituted.

[0 0 6 5]

Examples of “substituted or unsubstituted amino” include unsubstituted amino, hydroxyamino, sulfamoylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkylsulfonylamino, substituted or unsubstituted carboxyamino, substituted or unsubstituted aromatic carbocyclamino, substituted or unsubstituted non-aromatic carbocyclamino, substituted or unsubstituted aromatic heterocyclamino, substituted or unsubstituted non-aromatic heterocyclamino, substituted or unsubstituted aromatic carbocyclcarbonylamino, substituted or unsubstituted non-aromatic carbocyclcarbonylamino, substituted or unsubstituted aromatic heterocyclcarbonylamino, substituted or unsubstituted non-aromatic heterocyclcarbonylamino and the like.

[0 0 6 6]

Examples of “substituted or unsubstituted alkyloxy” include unsubstituted alkyloxy, substituted or unsubstituted aromatic carbocyclalkyloxy, substituted or unsubstituted non-aromatic carbocyclalkyloxy, substituted or unsubstituted aromatic heterocyclalkyloxy, substituted or unsubstituted non-aromatic heterocyclalkyloxy and the like.

[0 0 6 7]

Examples of “substituted or unsubstituted alkylsulfonyl” include unsubstituted alkylsulfonyl, substituted or unsubstituted aromatic carbocyclalkylsulfonyl, substituted or unsubstituted non-aromatic carbocyclalkylsulfonyl, substituted or unsubstituted aromatic heterocyclalkylsulfonyl, substituted or unsubstituted non-aromatic heterocyclalkylsulfonyl and the like.

[0 0 6 8]

Examples of “substituted or unsubstituted alkylcarbonyloxy” include unsubstituted alkylcarbonyloxy, substituted or unsubstituted aromatic carbocyclalkylcarbonyloxy, substituted or unsubstituted non-aromatic carbocyclalkylcarbonyloxy, substituted or unsubstituted aromatic heterocyclalkylcarbonyloxy, substituted or unsubstituted non-aromatic heterocyclalkylcarbonyloxy and the like.

[0 0 6 9]

Examples of “substituted or unsubstituted aromatic carbocycl” include unsubstituted aromatic carbocycl, substituted or unsubstituted alkylaminoaromatic carbocycl and the like.

[0 0 7 0]

Examples of “substituted or unsubstituted non-aromatic carbocyclyl” include unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted alkylaminonon-aromatic carbocyclyl and the like.

[0 0 7 1]

Examples of “substituted or unsubstituted aromatic heterocyclyl” include unsubstituted aromatic heterocyclyl, substituted or unsubstituted alkylaminoaromatic heterocyclyl and the like.

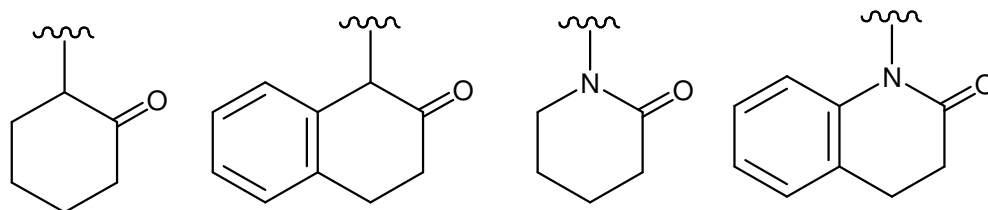
[0 0 7 2]

Examples of “substituted or unsubstituted non-aromatic heterocyclyl” include unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted alkylaminonon-aromatic heterocyclyl and the like.

[0 0 7 3]

Additionally, “substituted or unsubstituted non-aromatic carbocyclyl” and “substituted or unsubstituted non-aromatic heterocyclyl” may be substituted with “oxo”. In this case, it means a group wherein two hydrogen atoms on a carbon atom are substituted as below.

[Chemical Formula 1 2]



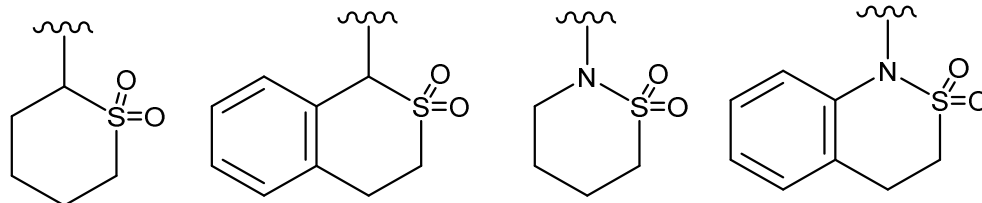
[0 0 7 4]

The non-aromatic carbocycle or non-aromatic heterocycle part of the above “substituted or unsubstituted non-aromatic carbocyclyloxy”, “substituted or unsubstituted non-aromatic heterocyclyloxy”, “substituted or unsubstituted non-aromatic carbocyclylamino”, “substituted or unsubstituted non-aromatic heterocyclylamino”, “substituted or unsubstituted non-aromatic carbocyclylcarbonyl”, “substituted or unsubstituted non-aromatic heterocyclylcarbonyl”, “substituted or unsubstituted non-aromatic carbocyclylcarbonylamino”, “substituted or unsubstituted non-aromatic heterocyclylcarbonylamino”, “substituted or unsubstituted non-aromatic carbocyclyloxycarbonyl”, “substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl”, “substituted or unsubstituted non-aromatic carbocyclylsulfamoyl”, “substituted or unsubstituted non-aromatic heterocyclylsulfamoyl”, “substituted or unsubstituted non-aromatic carbocyclylsulfonyl”, “substituted or unsubstituted non-aromatic heterocyclylsulfonyl”, “substituted or unsubstituted non-aromatic carbocyclylsulfamoyl”, “substituted or unsubstituted non-aromatic heterocyclylsulfamoyl”, “substituted or unsubstituted non-aromatic carbocyclylureido” and “substituted or unsubstituted non-aromatic heterocyclylureido” may be substituted with “oxo” as above.

[0 0 7 5]

Additionally, when “substituted or unsubstituted non-aromatic heterocyclyl” have a sulfur atom in ring, such sulfur atom may be substituted with “dioxo”. In this case, it means a group wherein four hydrogen atoms on a sulfur atom are substituted as below.

[Chemical Formula 1 3]



[0 0 7 6]

The non-aromatic carbocycle or non-aromatic heterocycle part of the above “substituted or unsubstituted non-aromatic carbocycloxy”, “substituted or unsubstituted non-aromatic heterocycloxy”, “substituted or unsubstituted non-aromatic carbocyclamino”, “substituted or unsubstituted non-aromatic heterocyclamino”, “substituted or unsubstituted non-aromatic carbocyclcarbonyl”, “substituted or unsubstituted non-aromatic heterocyclcarbonyl”, “substituted or unsubstituted non-aromatic carbocyclcarbonylamino”, “substituted or unsubstituted non-aromatic heterocyclcarbonylamino”, “substituted or unsubstituted non-aromatic carbocycloxy carbonyl”, “substituted or unsubstituted non-aromatic heterocycloxy carbonyl”, “substituted or unsubstituted non-aromatic carbocyclsulfamoyl”, “substituted or unsubstituted non-aromatic heterocyclsulfamoyl”, “substituted or unsubstituted non-aromatic carbocyclsulfonyl”, “substituted or unsubstituted non-aromatic heterocyclsulfonyl”, “substituted or unsubstituted non-aromatic carbocyclsulfamoyl”, “substituted or unsubstituted non-aromatic heterocyclsulfamoyl”, “substituted or unsubstituted non-aromatic carbocyclureido” and “substituted or unsubstituted non-aromatic heterocyclureido” may be substituted with “sulfonyl” as above.

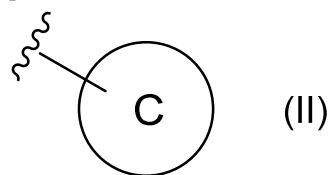
[0 0 7 7]

Preferred embodiments for the compound of formula (I) disclose below.

[0 0 7 8]

X is a group of formula:

[Chemical Formula 1 4]



, a group of formula:  $-N(R^F)-CO-X^1$ , hydroxyalkyl, or a group of formula:  $-CO-NH(R^X)$  wherein  $R^X$  is substituted or unsubstituted non-aromatic heterocycloxyalkyl.

X is preferably, a group of formula:  $-N(R^F)-CO-X^1$ , hydroxyalkyl or a group of formula:  $-CO-NH(R^X)$

wherein  $R^X$  is substituted or unsubstituted non-aromatic heterocycloxyalkyl.

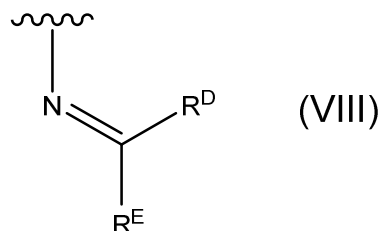
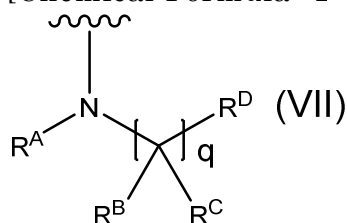
X is more preferably, a group of formula:  $-N(R^F)-CO-X^1$  or hydroxyalkyl.

X is especially preferably, a group of formula:  $-N(R^F)-CO-X^1$ .

[0 0 7 9]

When X is hydroxyalkyl, Y is any one of following groups:

[Chemical Formula 1 5]



Then q is an integer of 1 to 10.

[0 0 8 0]

J<sup>1</sup> is hydrogen, halogen, hydroxy, substituted or unsubstituted amino or substituted or unsubstituted alkyloxy.

J<sup>1</sup> is preferably, hydroxy, substituted or unsubstituted amino or substituted or unsubstituted alkyloxy.

J<sup>1</sup> is more preferably, hydroxy.

When J<sup>1</sup> is a substituted group, a preferable substituent on said substituted group is selected from alkyl, hydroxy, hydroxyalkyl and the like.

[0 0 8 1]

J<sup>2</sup> is preferably, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl.

J<sup>2</sup> is more preferably, hydrogen or substituted or unsubstituted alkyl.

J<sup>2</sup> is further preferably, hydrogen.

When J<sup>2</sup> is a substituted group, a preferable substituent on said substituted group is selected from alkyl, hydroxy, hydroxyalkyl and the like.

[0 0 8 2]

J<sup>1</sup> and J<sup>2</sup> may be taken together to form oxo.

[0 0 8 3]

L is hydrogen, halogen, hydroxy, substituted or unsubstituted amino or substituted or unsubstituted alkyloxy.

L is more preferably, hydroxy, substituted or unsubstituted amino or substituted or unsubstituted alkyloxy.

L is further preferably, hydroxy.

When L is a substituted group, a preferable substituent on said substituted group is selected from alkyl, hydroxy, hydroxyalkyl and the like.

[0 0 8 4]

V<sup>1</sup> is hydrogen, halogen, hydroxy, substituted or unsubstituted amino or substituted or unsubstituted alkyloxy.

V<sup>1</sup> is more preferably, hydroxy, substituted or unsubstituted amino or substituted or unsubstituted alkyloxy.

V<sup>1</sup> is further preferably, hydroxy.

When V<sup>1</sup> is a substituted group, a preferable substituent on said substituted group is selected from alkyl, hydroxy, hydroxyalkyl and the like.

[0 0 8 5]

V<sup>2</sup> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl.

V<sup>2</sup> is more preferably, hydrogen or substituted or unsubstituted alkyl.

V<sup>2</sup> is further preferably, hydrogen.

When V<sup>2</sup> is a substituted group, a preferable substituent on said substituted group is selected from alkyl, hydroxy, hydroxyalkyl and the like.

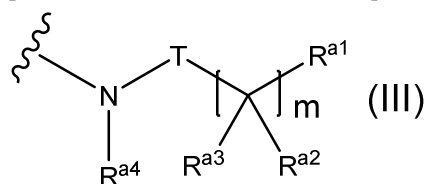
[0 0 8 6]

V<sup>1</sup> and V<sup>2</sup> may be taken together to form oxo.

[0 0 8 7]

A group represented by formula (III) of X<sup>1</sup> group is explained as follows:

[Chemical Formula 1 6]



[0 0 8 8]

T is a bond, -N(R<sup>a5</sup>)- or -O-.

T is preferably, a bond or -N(R<sup>a5</sup>)-.

T is more preferably, -N(R<sup>a5</sup>)-.

[0 0 8 9]

When T is a bond, preferable embodiment is following.

[0 0 9 0]

R<sup>a1</sup> is hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, formyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, sulfo, cyano, substituted or unsubstituted ureido, guanidino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkylammonium, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkenylsulfonyl, substituted or unsubstituted alkynylsulfonyl, substituted or unsubstituted alkylphosphonyl, substituted or unsubstituted alkenylphosphonyl, substituted or unsubstituted alkynylphosphonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkenylcarbonyloxy, substituted or unsubstituted alkynylcarbonyloxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocycliloxy, substituted or unsubstituted non-aromatic carbocycliloxy, substituted or unsubstituted aromatic heterocycliloxy, substituted or unsubstituted non-aromatic heterocycliloxy, substituted or unsubstituted aromatic carbocyclylcarbonyl, substituted or unsubstituted non-aromatic carbocyclylcarbonyl, substituted or unsubstituted aromatic heterocyclylcarbonyl, substituted or unsubstituted non-aromatic heterocyclylcarbonyl, substituted or unsubstituted aromatic carbocyclylamino, substituted or unsubstituted non-aromatic carbocyclylamino, substituted or unsubstituted aromatic heterocyclylamino, substituted or unsubstituted non-aromatic heterocyclylamino, substituted or unsubstituted aromatic carbocyclylsulfonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted aromatic heterocyclylsulfonyl or substituted or unsubstituted non-aromatic heterocyclylsulfonyl.

R<sup>a1</sup> is preferably, hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or

unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, sulfo, cyano, substituted or unsubstituted ureido, guanidino, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkylammonium, substituted or unsubstituted alkylphosphonyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocycloxyloxy or substituted or unsubstituted aromatic heterocyclylamino.

$R^{a1}$  is more preferably, hydrogen, hydroxy, carboxy, amino, substituted or unsubstituted alkylamino, substituted or unsubstituted carbamoyl, cyano, substituted or unsubstituted ureido, substituted or unsubstituted alkylammonium, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl.

When  $R^{a1}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or hydroxy or non-aromatic heterocycloxyloxy optionally substituted with hydroxyalkyl.

When  $R^{a1}$  is a substituted group, a more preferable substituent on said substituted group is selected from unsubstituted alkyl, unsubstituted haloalkyl, amino, hydroxy, carboxy, unsubstituted hydroxyalkyl, unsubstituted carbamoylalkyl, unsubstituted alkyloxy, unsubstituted alkyloxycarbonyl, carbamoyl, unsubstituted alkylamino, hydroxyamino, unsubstituted hydroxyalkylamino, unsubstituted alkylimino, sulfamoyl, unsubstituted alkylsulfonyl, cyano, unsubstituted aromatic carbocyclyl, unsubstituted aromatic heterocyclyl, unsubstituted alkylaromatic heterocyclyl, unsubstituted alkyloxyaromatic carbocyclyl, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl, aromatic carbocyclyl optionally substituted with halogen or aromatic heterocyclyl optionally substituted with amino.

When  $R^{a1}$  is a substituted group, an especially preferable substituent on said substituted group is selected from hydroxy or unsubstituted hydroxyalkylamino.  
[ 0 0 9 1 ]

$R^{a2}$  is each independently, hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkenylcarbonyloxy, substituted or unsubstituted alkynylcarbonyloxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted non-aromatic heterocycloxyalkyl,

substituted or unsubstituted non-aromatic heterocycloxyalkenyl or substituted or unsubstituted non-aromatic heterocycloxyalkynyl.

$R^{a2}$  is preferably, each independently, hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkyloxycarbonyl, or substituted or unsubstituted non-aromatic heterocycloxyalkyl.

$R^{a2}$  is more preferably, each independently, hydrogen, hydroxy, carboxy, substituted or unsubstituted amino or substituted or unsubstituted alkyl.

When  $R^{a2}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 0 9 2]

$R^{a3}$  is each independently, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted non-aromatic heterocycloxyalkyl, substituted or unsubstituted non-aromatic heterocycloxyalkenyl or substituted or unsubstituted non-aromatic heterocycloxyalkynyl.

$R^{a3}$  is preferably, each independently, hydrogen, halogen, substituted or unsubstituted alkyl or substituted or unsubstituted non-aromatic heterocycloxyalkyl.

$R^{a3}$  is more preferably, hydrogen.

When  $R^{a3}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 0 9 3]

$R^{a2}$  and  $R^{a3}$  may be each independently, taken together to form oxo, substituted or unsubstituted imino or thioxo, or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle or substituted or unsubstituted non-aromatic heterocycle.

$R^{a2}$  and  $R^{a3}$  may be each independently, taken together to form oxo, or thioxo,

or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle or substituted or unsubstituted non-aromatic heterocycle.

$R^{a2}$  and  $R^{a3}$  may be each independently, taken together to form oxo, may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle or substituted or unsubstituted non-aromatic heterocycle.  
[0 0 9 4]

$R^{a4}$  is hydrogen, hydroxy, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl or substituted or unsubstituted non-aromatic carbocyclyl.

$R^{a4}$  is preferably, hydrogen, hydroxy, substituted or unsubstituted amino, substituted or unsubstituted alkyl or substituted or unsubstituted non-aromatic carbocyclyl.

$R^{a4}$  is more preferably, hydrogen or hydroxy.

When  $R^{a4}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocyclyloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocyclyloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 0 9 5]

Especially preferable combination of ( $R^{a1}$ ,  $R^{a2}$ ,  $R^{a3}$ ,  $R^{a4}$ , m) is following:  
(hydrogen, -, -, hydrogen, 0), (hydrogen, hydrogen, hydrogen, hydroxy, 1), (hydrogen, hydrogen, hydrogen, hydroxy, 2), (hydrogen, hydrogen, hydrogen, hydroxy, 3), (hydrogen, substituted or unsubstituted alkyl, hydrogen, hydrogen, 1), (hydrogen, substituted or unsubstituted alkyl, hydrogen, hydrogen, 2), (hydrogen, substituted or unsubstituted alkyl, hydrogen, hydrogen, 3), (hydrogen, substituted or unsubstituted alkyl, hydrogen, hydrogen, 4), (hydrogen, substituted or unsubstituted alkyl, hydrogen, hydrogen, 5), (hydrogen, substituted or unsubstituted alkyl, hydrogen, hydroxy, 1), (hydrogen, substituted or unsubstituted alkyl, hydrogen, hydroxy, 2), (hydrogen, carboxy, hydroxy, hydrogen, 1), (hydrogen, carboxy, hydroxy, hydrogen, 2), (hydrogen, carboxy, hydroxy, hydrogen, 3), (halogen, -, -, hydrogen, 0), (halogen, hydrogen, hydrogen, hydrogen, 1), (halogen, hydrogen, hydrogen, hydrogen, 2), (halogen, hydrogen, hydrogen, hydrogen, 3), (halogen, halogen, halogen, hydrogen, 1), (halogen, halogen, halogen, hydrogen, 2), (hydroxy, -, -, hydrogen, 0), (hydroxy, hydrogen, hydrogen, hydrogen, 1), (hydroxy, hydrogen, hydrogen, hydrogen, 2), (hydroxy, hydrogen, hydrogen, hydrogen, 3), (hydroxy, hydrogen, hydrogen, hydrogen, 4), (hydroxy, hydrogen, hydrogen, hydrogen, 5), (hydroxy, hydrogen, hydrogen, hydrogen, 6), (hydroxy, hydroxy, hydrogen, hydrogen, 1), (hydroxy, hydroxy, hydrogen, hydrogen, 2), (hydroxy, hydroxy, hydrogen, hydrogen, 3), (hydroxy, hydroxy, hydrogen, hydrogen, 4), (hydroxy, hydroxy, hydrogen, hydroxy, 1), (hydroxy, hydroxy, hydrogen, hydroxy, 2), (hydroxy, hydroxy, hydrogen, hydroxy, 3), (hydroxy,

[illegible]

[illegible]

[illegible]

(substituted or unsubstituted aromatic heterocyclureido, -, -, hydrogen, 0), (substituted or unsubstituted aromatic heterocyclureido, hydrogen, hydrogen, hydrogen, 1) or (substituted or unsubstituted aromatic heterocyclureido, hydrogen, hydrogen, hydrogen, 2).

[0 0 9 6]

When T is  $-N(R^{a5})-$ , preferable embodiment is following.

[0 0 9 7]

$R^{a1}$  is hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, formyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, sulfo, cyano, substituted or unsubstituted ureido, guanidino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkylammonium, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkenylsulfonyl, substituted or unsubstituted alkynylsulfonyl, substituted or unsubstituted alkylphosphonyl, substituted or unsubstituted alkenylphosphonyl, substituted or unsubstituted alkynylphosphonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkenylcarbonyloxy, substituted or unsubstituted alkynylcarbonyloxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocycliloxy, substituted or unsubstituted non-aromatic carbocycliloxy, substituted or unsubstituted aromatic heterocycliloxy, substituted or unsubstituted non-aromatic heterocycliloxy, substituted or unsubstituted aromatic carbocyclylcarbonyl, substituted or unsubstituted non-aromatic carbocyclylcarbonyl, substituted or unsubstituted aromatic heterocyclylcarbonyl, substituted or unsubstituted non-aromatic heterocyclylcarbonyl, substituted or unsubstituted aromatic carbocyclylamino, substituted or unsubstituted non-aromatic carbocyclylamino, substituted or unsubstituted aromatic heterocyclylamino, substituted or unsubstituted non-aromatic heterocyclylamino, substituted or unsubstituted aromatic carbocyclylsulfonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted aromatic heterocyclylsulfonyl or substituted or unsubstituted non-aromatic heterocyclylsulfonyl.

$R^{a1}$  is preferably, hydrogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, formyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted ureido, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclylamino, substituted or unsubstituted aromatic heterocyclylamino or substituted or unsubstituted aromatic heterocyclylsulfonyl.

$R^{a1}$  is more preferably, hydrogen, hydroxy, carboxy, substituted or unsubstituted alkylamino, formyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted ureido, substituted or unsubstituted alkylsulfonyl,

substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl or substituted or unsubstituted aromatic heterocyclylsulfonyl.

$R^{a1}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

When  $R^{a1}$  is a substituted group, a more preferable substituent on said substituted group is selected from halogen, haloalkyl, hydroxy, amino, carbamoyl or unsubstituted non-aromatic heterocyclyl.

When  $R^{a1}$  is a substituted group, an especially preferable substituent on said substituted group is hydroxy.  
[0 0 9 8]

$R^{a2}$  is each independently, hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkenylcarbonyloxy, substituted or unsubstituted alkynylcarbonyloxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted non-aromatic heterocycloxyalkyl, substituted or unsubstituted non-aromatic heterocycloxyalkenyl or substituted or unsubstituted non-aromatic heterocycloxyalkynyl.

$R^{a2}$  is preferably, each independently, hydrogen, or substituted or unsubstituted alkyl.

When  $R^{a2}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.  
[0 0 9 9]

$R^{a3}$  is each independently, hydrogen, halogen, substituted or unsubstituted

alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted non-aromatic heterocycloxyalkyl, substituted or unsubstituted non-aromatic heterocycloxyalkenyl or substituted or unsubstituted non-aromatic heterocycloxyalkynyl.

$R^{a3}$  is preferably, hydrogen.

When  $R^{a3}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 0 0]

$R^{a2}$  and  $R^{a3}$  may be each independently, taken together to form oxo, substituted or unsubstituted imino or thioxo, or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle or substituted or unsubstituted non-aromatic heterocycle.

$R^{a2}$  and  $R^{a3}$  may be each independently, taken together to form oxo, or thioxo, or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle.

$R^{a2}$  and  $R^{a3}$  may be each independently, more preferably, each independently, taken together to form oxo or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle.

[0 1 0 1]

$R^{a4}$  is hydrogen, hydroxy, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl or substituted or unsubstituted non-aromatic carbocyclyl.

$R^{a4}$  is more preferably, hydrogen.

When  $R^{a4}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 0 2]

R<sup>a</sup> 5 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl or substituted or unsubstituted alkynylcarbonyl.

R<sup>a 5</sup> is preferably, hydrogen or substituted or unsubstituted alkyl.

When R<sup>a 5</sup> is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocyclyloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocyclyloxy optionally substituted with hydroxy or hydroxyalkyl.

$$\begin{bmatrix} 0 & 1 & 0 & 3 \end{bmatrix}$$

Especially preferable combination of ( $R^{a\ 1}$ ,  $R^{a\ 2}$ ,  $R^{a\ 3}$ ,  $R^{a\ 4}$ , m) is following:  
(hydrogen, -, -, hydrogen, hydrogen, 0), (hydrogen, hydrogen, hydrogen, hydrogen,  
hydrogen, 1), (hydrogen, hydrogen, hydrogen, hydrogen, hydrogen, 2), (hydrogen,  
hydrogen, hydrogen, hydrogen, hydrogen, 3), (hydrogen, hydrogen, hydrogen,  
hydrogen, hydrogen, 4), (hydrogen, hydrogen, hydrogen, hydrogen, alkyl, 1),  
(hydrogen, substituted or unsubstituted alkyl, hydrogen, hydrogen, hydrogen, 1),  
(hydrogen, substituted or unsubstituted alkyl, hydrogen, hydrogen, hydrogen, 2),  
(hydrogen, substituted or unsubstituted alkyl, hydrogen, hydrogen, hydrogen, 3),  
(hydrogen, substituted or unsubstituted alkyl, hydrogen, hydrogen, hydrogen, 4),  
(hydrogen, substituted or unsubstituted alkyl, hydrogen, hydrogen, hydrogen, 5),  
(hydroxy, -, -, hydrogen, hydrogen, 0), (hydroxy, hydrogen, hydrogen, hydrogen,  
hydrogen, 1), (hydroxy, hydrogen, hydrogen, hydrogen, hydrogen, 2), (hydroxy,  
hydrogen, hydrogen, hydrogen, hydrogen, 3), (hydroxy, hydrogen, hydrogen,  
hydrogen, hydrogen, 4), (hydroxy, hydrogen, hydrogen, hydrogen, hydrogen, 5),  
(hydroxy, hydrogen, hydrogen, hydrogen, hydrogen, 6), (hydroxy, hydroxy, hydrogen,  
hydrogen, hydrogen, 1), (hydroxy, hydroxy, hydrogen, hydrogen, hydrogen, 2),  
(hydroxy, hydroxy, hydrogen, hydrogen, hydrogen, 3), (hydroxy, hydroxy, hydrogen,  
hydrogen, hydrogen, 4), (hydroxy, hydroxy, hydrogen, hydrogen, hydrogen, 5),  
(hydroxy, hydroxy, hydrogen, hydrogen, hydrogen, 6), (hydroxy, hydroxy, hydrogen,  
hydrogen, substituted or unsubstituted alkyl, 1), (hydroxy, hydroxy, hydrogen,  
hydrogen, substituted or unsubstituted alkyl, 2), (hydroxy, hydroxy, hydrogen,  
hydrogen, substituted or unsubstituted alkyl, 3), (hydroxy, hydroxy, substituted or  
unsubstituted alkyl, hydrogen, hydrogen, 1), (hydroxy, hydroxy, substituted or  
unsubstituted alkyl, hydrogen, hydrogen, 2), (hydroxy, hydroxy, substituted or  
unsubstituted alkyl, hydrogen, hydrogen, 3), (hydroxy, hydroxy, substituted or  
unsubstituted alkyl, hydrogen, hydrogen, 4), (hydroxy, substituted or unsubstituted  
hydroxyalkyl, hydrogen, hydrogen, hydrogen, 1), (hydroxy, substituted or  
unsubstituted hydroxyalkyl, hydrogen, hydrogen, hydrogen, 2), (hydroxy, substituted  
or unsubstituted hydroxyalkyl, hydrogen, hydrogen, hydrogen, 3), (hydroxy,  
substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted alkyl,  
hydrogen, hydrogen, 1), (hydroxy, substituted or unsubstituted hydroxyalkyl,  
substituted or unsubstituted alkyl, hydrogen, hydrogen, 2), (hydroxy, substituted or

[illegible]

unsubstituted non-aromatic heterocycloxy, substituted or unsubstituted non-aromatic heterocycloxyalkyl, substituted or unsubstituted non-aromatic heterocycloxyalkyl, hydrogen, hydrogen, 2), (substituted or unsubstituted aromatic carbocyclamino, hydrogen, hydrogen, hydrogen, hydrogen, 1), (substituted or unsubstituted aromatic heterocyclamino, -, -, hydrogen, hydrogen, 0), (substituted or unsubstituted aromatic heterocyclamino, hydrogen, hydrogen, hydrogen, hydrogen, 1), (substituted or unsubstituted aromatic heterocyclamino, hydrogen, hydrogen, hydrogen, hydrogen, 2), (substituted or unsubstituted aromatic heterocyclsulfonyl, -, -, hydrogen, hydrogen, 0), (substituted or unsubstituted aromatic heterocyclureido, -, -, hydrogen, hydrogen, 0), (substituted or unsubstituted aromatic heterocyclureido, hydrogen, hydrogen, hydrogen, hydrogen, 1), (substituted or unsubstituted aromatic heterocyclureido, hydrogen, hydrogen, hydrogen, hydrogen, 2) or (substituted or unsubstituted aromatic heterocyclsulfonyl, -, -, hydrogen, hydrogen, 0).

[0 1 0 4]

When T is -O-, preferable embodiment is following.

[0 1 0 5]

R<sup>a1</sup> is hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, formyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, sulfo, cyano, substituted or unsubstituted ureido, guanidino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkylammonium, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkenylsulfonyl, substituted or unsubstituted alkynylsulfonyl, substituted or unsubstituted alkylphosphonyl, substituted or unsubstituted alkenylphosphonyl, substituted or unsubstituted alkynylphosphonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkenylcarbonyloxy, substituted or unsubstituted alkynylcarbonyloxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted aromatic carbocycl, substituted or unsubstituted non-aromatic carbocycl, substituted or unsubstituted aromatic heterocycl, substituted or unsubstituted non-aromatic heterocycl, substituted or unsubstituted aromatic carbocycloxy, substituted or unsubstituted non-aromatic carbocycloxy, substituted or unsubstituted aromatic heterocycloxy, substituted or unsubstituted non-aromatic heterocycloxy, substituted or unsubstituted aromatic carbocyclcarbonyl, substituted or unsubstituted non-aromatic carbocyclcarbonyl, substituted or unsubstituted aromatic heterocyclcarbonyl, substituted or unsubstituted non-aromatic heterocyclcarbonyl, substituted or unsubstituted aromatic carbocyclsulfonyl, substituted or unsubstituted non-aromatic carbocyclsulfonyl, substituted or unsubstituted aromatic heterocyclsulfonyl or substituted or unsubstituted non-aromatic heterocyclsulfonyl.

R<sup>a1</sup> is preferably, hydrogen, hydroxy, carboxy, substituted or unsubstituted alkylamino, cyano, guanidino, substituted or unsubstituted alkyloxy, substituted or unsubstituted aromatic carbocycl, substituted or unsubstituted non-aromatic carbocycl, substituted or unsubstituted aromatic heterocycl, substituted or unsubstituted non-aromatic heterocycl or substituted or unsubstituted non-

aromatic heterocycloxy.

$R^{a1}$  is more preferably, hydrogen, hydroxy, carboxy, guanidino, substituted or unsubstituted aromatic heterocyclyl or substituted or unsubstituted non-aromatic heterocyclyl.

When  $R^{a1}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

When  $R^{a1}$  is a substituted group, a more preferable substituent on said substituted group is selected from preferable substituents is hydroxy, amino or unsubstituted hydroxyalkyl.

[0 1 0 6]

$R^{a2}$  is each independently, hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkenylcarbonyloxy, substituted or unsubstituted alkynylcarbonyloxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted non-aromatic heterocycloxyalkyl, substituted or unsubstituted non-aromatic heterocycloxyalkenyl or substituted or unsubstituted non-aromatic heterocycloxyalkynyl.

$R^{a2}$  is preferably, each independently, hydrogen, hydroxy or substituted or unsubstituted hydroxyalkyl.

$R^{a2}$  is more preferably, each independently, hydrogen or substituted or unsubstituted hydroxyalkyl.

When  $R^{a2}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 0 7]

$R^{a3}$  is each independently, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted non-aromatic heterocycloxyalkyl, substituted or unsubstituted non-aromatic heterocycloxyalkenyl or substituted or unsubstituted non-aromatic heterocycloxyalkynyl.

$R^{a3}$  is preferably, hydrogen.

When  $R^{a3}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 0 8]

$R^{a2}$  and  $R^{a3}$  may be each independently, taken together to form oxo, substituted or unsubstituted imino or thioxo, or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle or substituted or unsubstituted non-aromatic heterocycle.

$R^{a2}$  and  $R^{a3}$  may be each independently, taken together to form oxo.

[0 1 0 9]

$R^{a4}$  is hydrogen, hydroxy, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl or substituted or unsubstituted non-aromatic carbocyclyl.

$R^{a4}$  is preferably, hydrogen or substituted or unsubstituted alkyl.

When  $R^{a4}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 1 0]

Especially preferable combination of ( $R^{a1}$ ,  $R^{a2}$ ,  $R^{a3}$ ,  $R^{a4}$ , m) is following: (hydrogen, -, -, hydrogen, 0), (hydrogen, hydrogen, hydrogen, hydrogen, 1), (hydrogen, hydrogen, hydrogen, hydrogen, 2), (hydrogen, hydrogen, hydrogen, hydrogen, 3), (hydrogen, hydrogen, hydrogen, hydrogen, 4), (hydroxy, -, -, hydrogen, 0), (hydroxy,

hydrogen, hydrogen, hydrogen, 1), (hydroxy, hydrogen, hydrogen, hydrogen, 2), (hydroxy, hydrogen, hydrogen, hydrogen, 3), (hydroxy, hydrogen, hydrogen, hydrogen, 4), (hydroxy, hydrogen, hydrogen, hydrogen, 5), (hydroxy, hydrogen, hydrogen, hydrogen, 6), (hydroxy, hydroxy, hydrogen, hydrogen, 1), (hydroxy, hydroxy, hydrogen, hydrogen, 2), (hydroxy, hydroxy, hydrogen, hydrogen, 3), (hydroxy, hydroxy, hydrogen, hydrogen, 4), (hydroxy, hydroxy, hydrogen, hydrogen, 5), (hydroxy, hydroxy, hydrogen, hydrogen, 6), (hydroxy, substituted or unsubstitutedhydroxyalkyl, hydrogen, hydrogen, 1), (hydroxy, substituted or unsubstitutedhydroxyalkyl, hydrogen, hydrogen, 2), (hydroxy, substituted or unsubstitutedhydroxyalkyl, hydrogen, hydrogen, 3), (cyano, hydroxy, hydrogen, hydrogen, 1), (cyano, hydroxy, hydrogen, hydrogen, 2), (cyano, hydroxy, hydrogen, hydrogen, 3), (guanidino, -, -, hydrogen, 0), (guanidino, hydrogen, hydrogen, hydrogen, 1), (guanidino, hydrogen, hydrogen, hydrogen, 2), (substituted or unsubstitutedalkylamino, -, -, hydrogen, 0), (substituted or unsubstitutedalkylamino, hydrogen, hydrogen, hydrogen, 1), (substituted or unsubstitutedalkylamino, hydrogen, hydrogen, hydrogen, 2), (substituted or unsubstitutedalkylamino, hydrogen, hydrogen, hydrogen, 3), (substituted or unsubstitutedalkyloxy, -, -, hydrogen, 0), (substituted or unsubstitutedalkyloxy, hydrogen, hydrogen, hydrogen, 1), (substituted or unsubstitutedalkyloxy, hydrogen, hydrogen, hydrogen, 2), (substituted or unsubstitutedalkyloxy, hydrogen, hydrogen, hydrogen, 3), (substituted or unsubstitutedalkyloxy, hydrogen, hydrogen, hydrogen, 4), (substituted or unsubstitutedaromatic heterocyclyl, -, -, hydrogen, 0), (substituted or unsubstitutedaromatic heterocyclyl, hydrogen, hydrogen, hydrogen, 1), (substituted or unsubstitutedaromatic heterocyclyl, hydrogen, hydrogen, hydrogen, 2), (substituted or unsubstitutedaromatic heterocyclyl, hydrogen, hydrogen, hydrogen, 3), (substituted or unsubstitutednon-aromatic heterocyclyl, -, -, hydrogen, 0), (substituted or unsubstitutednon-aromatic heterocyclyl, hydrogen, hydrogen, hydrogen, 1) or (substituted or unsubstitutednon-aromatic heterocyclyl, hydrogen, hydrogen, hydrogen, 2).

[ 0 1 1 1 ]

m is an integer of 0~10.

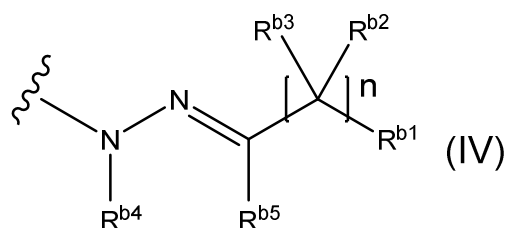
m is preferably, an integer of 0~6.

m is more preferably, an integer of 0~4.

[ 0 1 1 2 ]

A group represented by formula (IV) of X<sup>1</sup> group is described as follows:

[Chemical Formula 1 7 ]



[ 0 1 1 3 ]

R<sup>b1</sup> is hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, folmyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, sulfo, cyano, substituted or unsubstituted ureido, guanidino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or

unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkylammonium, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkenylsulfonyl, substituted or unsubstituted alkynylsulfonyl, substituted or unsubstituted alkylphosphonyl, substituted or unsubstituted alkenylphosphonyl, substituted or unsubstituted alkynylphosphonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkenylcarbonyloxy, substituted or unsubstituted alkynylcarbonyloxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyloxy, substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted aromatic heterocyclyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, substituted or unsubstituted aromatic carbocyclylcarbonyl, substituted or unsubstituted non-aromatic carbocyclylcarbonyl, substituted or unsubstituted aromatic heterocyclylcarbonyl, substituted or unsubstituted non-aromatic heterocyclylcarbonyl, substituted or unsubstituted aromatic carbocyclylsulfonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted aromatic heterocyclylsulfonyl or substituted or unsubstituted non-aromatic heterocyclylsulfonyl.

$R^{b1}$  is preferably, hydroxy.

When  $R^{b1}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocyclyloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocyclyloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 1 4]

$R^{b2}$  is each independently, hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkenylcarbonyloxy, substituted or unsubstituted alkynylcarbonyloxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxyalkyl, substituted or unsubstituted non-aromatic heterocyclyloxyalkenyl or substituted or unsubstituted non-aromatic heterocyclyloxyalkynyl.

$R^{b2}$  is preferably, each independently, hydrogen or hydroxy.

When  $R^{b2}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocyclyloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocyclyloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 1 5]

$R^{b3}$  is each independently, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxyalkyl, substituted or unsubstituted non-aromatic heterocyclyloxyalkenyl or substituted or unsubstituted non-aromatic heterocyclyloxyalkynyl.

$R^{b3}$  is preferably, hydrogen.

When  $R^{b3}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocyclyloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocyclyloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 1 6]

$R^{b2}$  and  $R^{b3}$  may be each independently, taken together to form oxo, substituted or unsubstituted imino or thioxo, or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle or substituted or unsubstituted non-aromatic heterocycle.

[0 1 1 7]

$R^{b4}$  is hydrogen, hydroxy, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl or substituted or unsubstituted non-aromatic carbocyclyl.

$R^{b4}$  is preferably, hydrogen.

When  $R^{b4}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl,

aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 1 8]

$R^{b5}$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl.

$R^{b5}$  is preferably, hydrogen or substituted or unsubstituted alkyl.

When  $R^{b5}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 1 9]

n is preferably, an integer of 0~10.

n is more preferably, an integer of 0~6.

n is further preferably, an integer of 0~2.

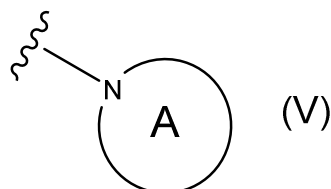
[0 1 2 0]

Especially preferable combination of ( $R^{b1}$ ,  $R^{b2}$ ,  $R^{b3}$ ,  $R^{b4}$ ,  $R^{b5}$ , m) is following: (hydroxy, hydroxy, hydrogen, hydrogen, hydrogen, 1), (hydroxy, hydroxy, hydrogen, hydrogen, hydrogen, 2), (hydroxy, hydroxy, hydrogen, hydrogen, hydrogen, 3), (hydroxy, hydroxy, hydrogen, hydrogen, hydrogen, 4), (hydroxy, hydroxy, hydrogen, hydrogen, hydrogen, 5), (hydroxy, hydroxy, hydrogen, hydrogen, hydrogen, 6), (hydroxy, hydrogen, hydrogen, hydrogen, substituted or unsubstituted hydroxyalkyl, 1) or (hydroxy, hydrogen, hydrogen, hydrogen, substituted or unsubstituted hydroxyalkyl, 2).

[0 1 2 1]

A group represented by formula (V) of  $X^1$  group is described as follows:

[Chemical Formula 1 8]



[0 1 2 2]

A ring is substituted or unsubstituted nitrogen-containing aromatic heterocycle or substituted or unsubstituted nitrogen-containing non-aromatic heterocycle.

A ring is preferably, 3- to 16-membered, more preferably 3- to 12-membered, further preferably 3- to 8-membered, substituted or unsubstituted nitrogen-

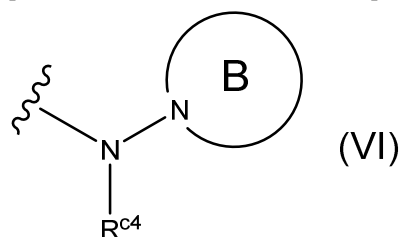
containing non-aromatic heterocycle.

When A ring is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxyloxy optionally substituted with hydroxy or hydroxyalkyl.

When A ring is a substituted group, a more preferable substituent on said substituted group is selected from hydroxy, carboxy, unsubstituted carboxyalkenyl, unsubstituted hydroxyalkyl, unsubstituted alkylamino, unsubstituted hydroxyalkylamino, carbamoyl, unsubstituted aromatic carbocyclyl, unsubstituted aromatic carbocyclylalkyl, unsubstituted non-aromatic heterocyclylalkyl, unsubstituted aromatic carbocycloxyalkyl or hydroxy or non-aromatic heterocycloxyloxy optionally substituted with hydroxyalkyl.

When A ring is a substituted group, a especially preferable substituent on said substituted group is selected from hydroxy, carboxy, hydroxyalkylamino or non-aromatic heterocycloxyloxy optionally substituted with hydroxy or hydroxyalkyl.  
[ 0 1 2 3 ]

A group represented by formula (VI) of X<sup>1</sup> group is described as follows:  
[Chemical Formula 1 9 ]



[ 0 1 2 4 ]

B ring is preferably, substituted or unsubstituted nitrogen-containing aromatic heterocycle or substituted or unsubstituted nitrogen-containing non-aromatic heterocycle.

B ring is preferably, 3- to 16-membered, more preferably 3- to 12-membered, further preferably 3- to 8-membered, substituted or unsubstituted nitrogen-containing non-aromatic heterocycle.

When B ring is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted

with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycliloxy optionally substituted with hydroxy or hydroxyalkyl.

When B ring is a substituted group, a more preferable substituent on said substituted group is selected from unsubstituted alkyl or hydroxyalkyl.

[0 1 2 5]

$R^{c4}$  is preferably, hydrogen, hydroxy, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl or substituted or unsubstituted non-aromatic carbocyclyl.

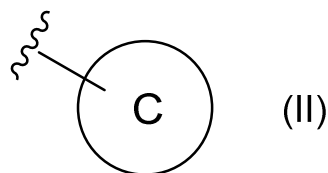
$R^{c4}$  is more preferably, hydrogen.

When  $R^{c4}$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycliloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycliloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 2 6]

A group represented by formula (II) of X group is described as follows:

[Chemical Formula 2 0]



[0 1 2 7]

C ring is preferably, substituted or unsubstituted aromatic carbocycle, substituted or unsubstituted non-aromatic carbocycle, substituted or unsubstituted aromatic heterocycle or substituted or unsubstituted non-aromatic heterocycle.

C ring is preferably, 5- or 6-membered substituted or unsubstituted aromatic heterocycle.

When C ring is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycliloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic

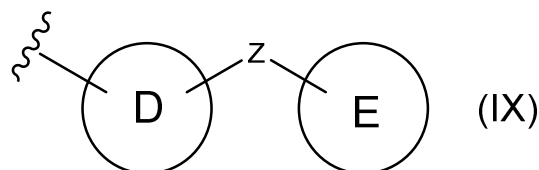
heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

When C ring is a substituted group, a more preferable substituent on said substituted group is selected from unsubstituted aromatic carbocyclyl or unsubstituted aromatic heterocyclyl.

[0 1 2 8]

A group represented by formula (IX) of X group is described as follows:

[Chemical Formula 2 1]



[0 1 2 9]

D ring is preferably, substituted or unsubstituted aromatic carbocycle, substituted or unsubstituted non-aromatic carbocycle, substituted or unsubstituted aromatic heterocycle or substituted or unsubstituted non-aromatic heterocycle.

D ring is more preferably, 5- or 6-membered unsubstituted aromatic heterocycle.

When D ring is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 3 0]

E ring is preferably, substituted or unsubstituted aromatic carbocycle, substituted or unsubstituted non-aromatic carbocycle, substituted or unsubstituted aromatic heterocycle or substituted or unsubstituted non-aromatic heterocycle.

E ring is more preferably, 5- or 6-membered substituted or unsubstituted aromatic carbocycle or substituted or unsubstituted aromatic heterocycle.

When E ring is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

When E ring is a substituted group, a more preferable substituent on said

substituted group is selected from unsubstituted alkylamino.

[ 0 1 3 1 ]

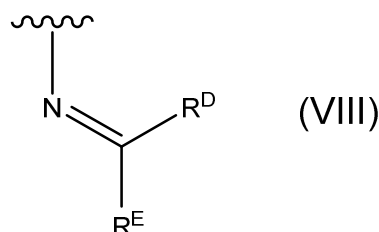
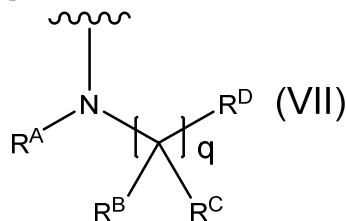
Z is preferably, a bond, alkylene, -O-, -S- or -N(H)-.

Z is more preferably, a bond.

[ 0 1 3 2 ]

A group represented by formula (VII) and formula (VIII) of Y group is described as follows:

[Chemical Formula 2 2]



[ 0 1 3 3 ]

R<sup>A</sup> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl.

R<sup>A</sup> is preferably, hydrogen or substituted or unsubstituted alkyl.

R<sup>A</sup> is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[ 0 1 3 4 ]

R<sup>B</sup> is each independently, hydrogen, hydroxy, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl.

R<sup>B</sup> is preferably, hydrogen, hydroxy or substituted or unsubstituted amino.

When R<sup>B</sup> is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[ 0 1 3 5 ]

R<sup>C</sup> is each independently, hydrogen, hydroxy, substituted or unsubstituted

amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl.

$R^C$  is preferably, hydrogen.

When  $R^C$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

[0 1 3 6]

$R^B$  and  $R^C$  may be preferably, each independently, taken together to form oxo, substituted or unsubstituted imino or thioxo, or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle or substituted or unsubstituted non-aromatic heterocycle.

$R^B$  and  $R^C$  may be more preferably, each independently, taken together to form oxo, unsubstituted imino, cyanoimino or hydroxyimino.

[0 1 3 7]

$R^D$  is preferably, hydrogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted carbamoyl, substituted or unsubstituted amidino, substituted or unsubstituted guanidino, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl or substituted or unsubstituted non-aromatic heterocyclyl.

$R^D$  is more preferably, hydrogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted carbamoyl, guanidino, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl or substituted or unsubstituted non-aromatic heterocyclyl.

When  $R^D$  is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocycloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocycloxy optionally substituted with hydroxy or hydroxyalkyl.

When  $R^D$  is a substituted group, a more preferable substituent on said substituted group is selected from alkyl, hydroxy, amino, alkylamino or amidino.

[0 1 3 8]

$q$  is preferably, an integer of 0~10.

q is more preferably, an integer of 0~6.

[ 0 1 3 9 ]

R<sup>E</sup> is preferably, hydrogen, hydroxy or substituted or unsubstituted amino.

R<sup>E</sup> is more preferably, substituted or unsubstituted amino.

When R<sup>E</sup> is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocyclyloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocyclyloxy optionally substituted with hydroxy or hydroxyalkyl.

[ 0 1 4 0 ]

R<sup>F</sup> is preferably, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl.

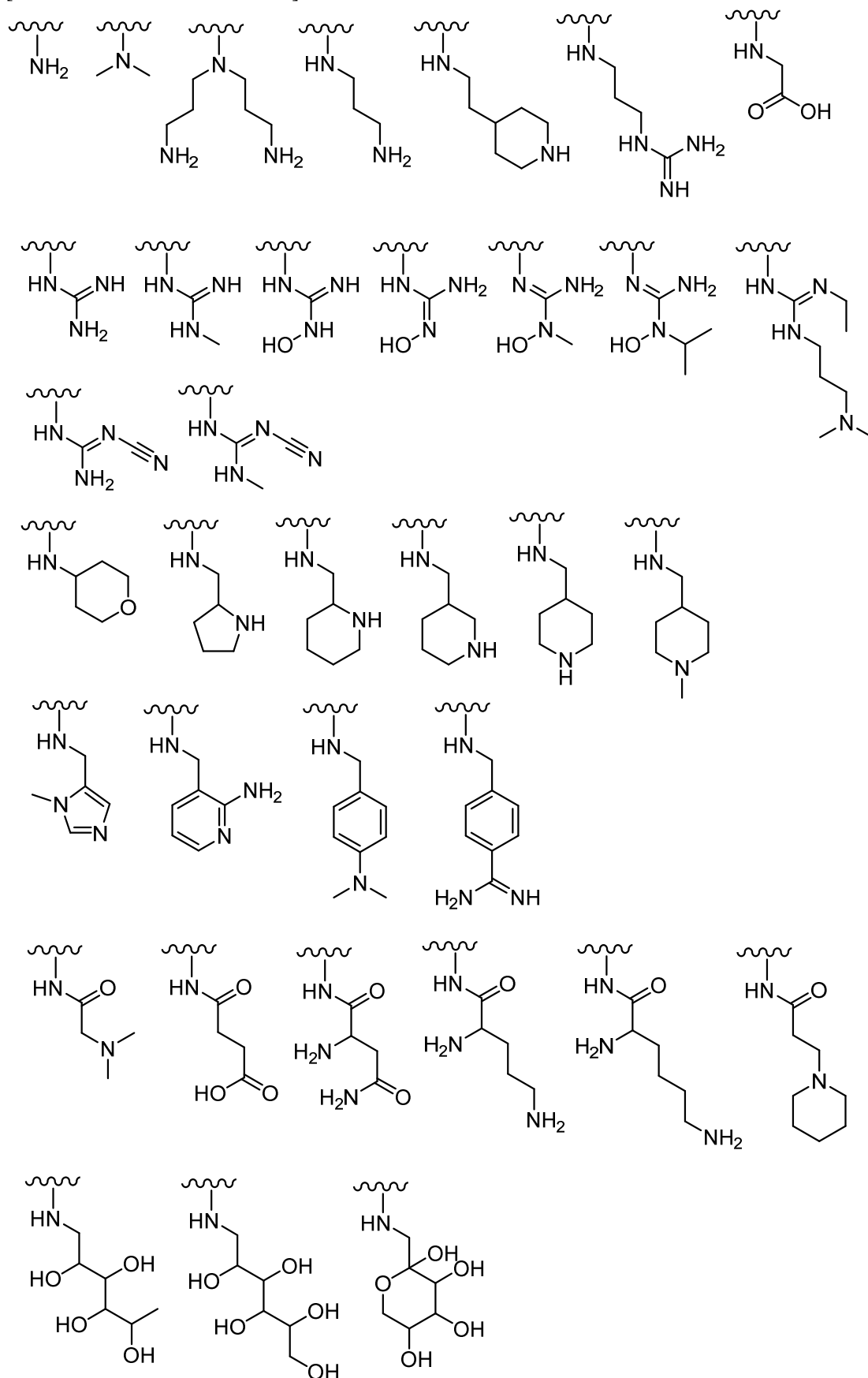
R<sup>F</sup> is more preferably, hydrogen.

When R<sup>F</sup> is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, carboxy, carboxyalkyl, carboxyalkenyl, amino, carbamoyl, carbamoylalkyl, cyano, sulfamoyl, amidino, alkyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyloxy, alkyloxy, alkylcarbonyl, alkylamino, alkylsulfonyl, alkylimino, alkyloxycarbonyl, aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocyclyloxyalkyl, aromatic carbocyclylalkyl, non-aromatic heterocyclylalkyl, aromatic heterocyclyl optionally substituted with alkyl, aromatic carbocyclyl optionally substituted with alkyloxy, aromatic heterocyclyl optionally substituted with amino, aromatic carbocyclyl optionally substituted with halogen, aromatic carbocyclylalkyloxy optionally substituted with haloalkyl or non-aromatic heterocyclyloxy optionally substituted with hydroxy or hydroxyalkyl.

[ 0 1 4 1 ]

Y includes, for example, following groups:

[Chemical Formula 23]



[0 1 4 2]

The compounds of formula (I) have antifungal activity and low possibility of nephrotoxicity by having structure preferably, T is a bond or  $-\text{N}(\text{R}^{\text{a}5})-$ .

[0 1 4 3]

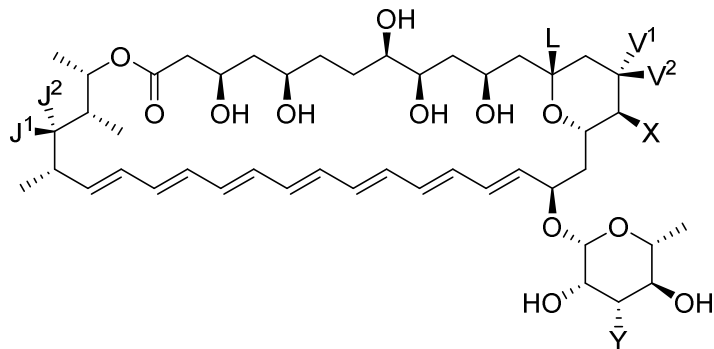
The other characteristics of the compounds of formula (I) have low possibility of nephrotoxicity by having structure  $R^{a1}$  or  $R^{b1}$  is carboxy.

[0 1 4 4]

The compounds of formula (I) are not limited to specific isomers but include all possible isomers (e.g., keto-enol isomers, imine-enamine isomers, diastereoisomers, enantiomers, rotamers or the like), racemates or mixtures thereof.

[0 1 4 5]

The compounds of formula (I) are preferably following structure.  
[Chemical Formula 2 4]



[0 1 4 6]

One or more hydrogen, carbon and/or other atoms in the compounds of formula (I) may be replaced with isotopes of hydrogen, carbon and/or other atoms respectively. Examples of isotopes include hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, iodine and chlorine, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{11}\text{C}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ ,  $^{123}\text{I}$  and  $^{36}\text{Cl}$  respectively. The compounds of formula (I) include compounds replaced with these isotopes. The compounds replaced with the above isotopes are useful as medicines and include all of radiolabeled compounds of the compound of formula (I). A “method of radiolabeling” in the manufacture of the “radiolabeled compounds” is encompassed by the present invention, and the “radiolabeled compounds” are useful for studies on metabolized drug pharmacokinetics, studies on binding assay and/or diagnostic tools.

[0 1 4 7]

A radiolabeled compound of formula (I) can be prepared using well-known methods in this field of the invention. For example, a tritium-labeled compound of formula (I) can be prepared by introducing a tritium to a certain compound of formula (I), through a catalytic dehalogenation reaction using a tritium. This method comprises reacting with an appropriately-halogenated precursor of the compound of formula (I) with tritium gas in the presence of an appropriate catalyst, such as Pd/C, and in the presence or absent of a base. The other appropriate method of preparing a tritium-labeled compound can be referred to “Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A), Chapter 6 (1987)”. A  $^{14}\text{C}$ -labeled compound can be prepared by using a raw material having  $^{14}\text{C}$ .

[0 1 4 8]

The pharmaceutically acceptable salts of the compounds of formula (I) include, for example, salts with alkaline metal (e.g., lithium, sodium, potassium or the like), alkaline earth metal (e.g., calcium, barium or the like), magnesium, transition metal (e.g., zinc, iron or the like), ammonia, organic bases (e.g., trimethylamine, triethylamine, dicyclohexylamine, ethanamine, diethanolamine, triethanolamine,

meglumine, ethylenediamine, pyridine, picoline, quinoline or the like) or amino acids, or salts with inorganic acids (e.g., hydrochloric acid, sulfuric acid, nitric acid, carbonic acid, hydrobromic acid, phosphoric acid, hydroiodic acid or the like) or organic acids (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, citric acid, lactic acid, tartaric acid, oxalic acid, maleic acid, fumaric acid, mandelic acid, glutaric acid, malic acid, benzoic acid, phthalic acid, ascorbic acid, benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid or the like). Especially, salts with hydrochloric acid, sulfuric acid, phosphoric acid, tartaric acid, methanesulfonic acid and the like are included. These salts can be formed by the usual methods.

[0 1 4 9]

The compounds of formula (I) of the present invention or its pharmaceutically acceptable salts may form solvates (e.g., hydrates or the like) and/or crystal polymorphs. The present invention encompasses those various solvates and crystal polymorphs. "Solvates" may be those wherein any numbers of solvent molecules (e.g., water molecules or the like) are coordinated with the compounds of formula (I). When the compounds of formula (I) or its pharmaceutically acceptable salts are allowed to stand in the atmosphere, the compounds may absorb water, resulting in attachment of adsorbed water or formation of hydrates. Recrystallization of the compounds of formula (I) or its pharmaceutically acceptable salts may produce crystal polymorphs.

[0 1 5 0]

The compounds of formula (I) of the present invention or its pharmaceutically acceptable salts may form prodrugs. The present invention also encompasses such various prodrugs. Prodrugs are derivatives of the compounds of the present invention that have chemically or metabolically degradable groups, and compounds that are converted to the pharmaceutically active compounds of the present invention through solvolysis or under physiological conditions in vivo. Prodrugs include compounds that are converted to the compounds of formula (I) through enzymatic oxidation, reduction, hydrolysis or the like under physiological conditions in vivo, compounds that are converted to the compounds of formula (I) through hydrolysis by gastric acid etc., and the like. Methods for selecting and preparing suitable prodrug derivatives are described in, for example, "Design of Prodrugs, Elsevier, Amsterdam, 1985". Prodrugs themselves may have some activity.

[0 1 5 1]

When the compounds of formula (I) or its pharmaceutically acceptable salts have hydroxyl group(s), prodrugs include acyloxy derivatives and sulfonyloxy derivatives that are prepared by, for example, reacting compounds having hydroxyl group(s) with suitable acyl halide, suitable acid anhydride, suitable sulfonyl chloride, suitable sulfonyl anhydride or mixed anhydride, or with a condensing agent. For example, they include  $\text{CH}_3\text{COO}^-$ ,  $\text{C}_2\text{H}_5\text{COO}^-$ ,  $\text{tert-BuCOO}^-$ ,  $\text{C}_{15}\text{H}_{31}\text{COO}^-$ ,  $\text{PhCOO}^-$ ,  $(\text{m-NaOOCPh})\text{COO}^-$ ,  $\text{NaOOCCH}_2\text{CH}_2\text{COO}^-$ ,  $\text{CH}_3\text{CH}(\text{NH}_2)\text{COO}^-$ ,  $\text{CH}_2\text{N}(\text{CH}_3)_2\text{COO}^-$ ,  $\text{CH}_3\text{SO}_3^-$ ,  $\text{CH}_3\text{CH}_2\text{SO}_3^-$ ,  $\text{CF}_3\text{SO}_3^-$ ,  $\text{CH}_2\text{FSO}_3^-$ ,  $\text{CF}_3\text{CH}_2\text{SO}_3^-$ ,  $\text{p-CH}_3\text{O-PhSO}_3^-$ ,  $\text{PhSO}_3^-$  and  $\text{p-CH}_3\text{PhSO}_3^-$ .

[0 1 5 2]

A pharmaceutical composition of the present invention can be administered orally or parenterally. Methods for parenteral administration include dermal, subcutaneous, intravenous, intraarterial, intramuscular, intraperitoneal, transmucosal, inhalation, transnasal, ophthalmic, inner ear or vaginal administration and the like.

[ 0 1 5 3 ]

In case of oral administration, any forms, which are usually used, such as oral solid formulations (e.g., tablets, powders, granules, capsules, pills, films or the like), oral liquid formulations (e.g., suspension, emulsion, elixir, syrup, lemonade, spirit, aromatic water, extract, decoction, tincture or the like) and the like may be prepared according to the usual method and administered. The tablets can be sugar-coated tablets, film-coated tablets, enteric-coating tablets, sustained-release tablets, troche tablets, sublingual tablets, buccal tablets, chewable tablets or orally disintegrated tablets. Powders and granules can be dry syrups. Capsules can be soft capsules, micro capsules or sustained-release capsules.

[ 0 1 5 4 ]

In case of parenteral administration, any forms, which are usually used, such as injections, drips, external preparations (e.g., ophthalmic drops, nasal drops, ear drops, aerosols, inhalations, lotion, infusion, liniment, mouthwash, enema, ointment, plaster, jelly, cream, patch, cataplasm, external powder, suppository or the like) and the like can be preferably administered. Injections can be emulsions whose type is O/W, W/O, O/W/O, W/O/W or the like.

[ 0 1 5 5 ]

The pharmaceutical composition may be manufactured by mixing an effective amount of the compound of the present invention with various pharmaceutical additives suitable for the formulation, such as excipients, binders, moistening agents, disintegrants, lubricants, diluents and the like. Furthermore, the pharmaceutical composition can be for pediatric patients, geriatric patients, serious cases or operations by appropriately changing the effective amount of the compound of the present invention, formulation and/or various pharmaceutical additives. The pediatric pharmaceutical compositions are preferably administered to patients under 12 or 15 years old. In addition, the pediatric pharmaceutical compositions can be administered to patients who are under 27 days old after the birth, 28 days to 23 months old after the birth, 2 to 11 years old, 12 to 16 years old, or 18 years old. The geriatric pharmaceutical compositions are preferably administered to patients who are 65 years old or over.

[ 0 1 5 6 ]

Although the dosage of a pharmaceutical composition of the present invention should be determined in consideration of the patient's age and body weight, the type and degree of diseases, the administration route and the like, a usual oral dosage is 0.05 to 100 and preferably 0.1 to 10 mg/kg/day. For parenteral administration, although the dosage highly varies with administration routes, a usual dosage is 0.005 to 10 and preferably 0.01 to 1 mg/kg/day. The dosage may be administered in one to several divisions per day.

[ 0 1 5 7 ]

The compounds of formula (I) is useful as therapeutic agent for fungal infection such as fungemia, fungal respiratory disease, fungal meningitis, disseminated mycosis by *Aspergillus* genus, *Candida* genus, *Cryptococcus* genus, *Mucor* genus, *Absidia* genus, *Rhizopus* genus, *Rhizomucor* genus, *Cladosporium* genus, *Cladophialophora* genus, *Fonsecaea* genus, *Phialophora* genus, *Exophiala* genus, *Coccidioides* genus, *Histoplasma* genus or *Blastomyces* genus.

[ 0 1 5 8 ]

(Synthetic methods for the compounds of the present invention)

For example, the compounds of formula (I) of the present invention can be prepared by the general synthetic methods described below. The methods for

extraction, purification and the like may be carried out by using the usual method for the experiments of organic chemistry. Since chemical modification of J<sup>1</sup>, J<sup>2</sup>, V<sup>1</sup>, V<sup>2</sup> and L had been performed in amphotericin B derivative, these can be referred.

Commercial reagents can be used as starting materials, or starting materials can be synthesized by referring to the known methods in this field.

[0 1 5 9]

In this description, meaning of each abbreviation is as follows:

Alloc: Allyloxycarbonyl

Alloc-OSu: Allyl n-succinimidyl carbonate

Alloc-Cl: Allyloxycarbonylchloride

AMB: Amphotericin B

Boc: tert-Butoxycarbonyl

CSA: 10-Camphorsulfonic acid

TBS: tert-Butyldimethylsilyl

DEAD: Diethyl azodicarboxylate

DMAD: Dimethyl azodicarboxylate

DMSO: Dimethyl sulfoxide

DIEA: N,N-Diisopropylethylamine

DMF: N,N-Dimethylformamide

DMA: N,N-Dimethylacetamide

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

NMP: N-methylpyrrolidone

Fmoc: 9-Fluorenylmethyloxycarbonyl

Teoc: 2-(Trimethylsilyl)ethoxymethyl chloride

TBAF: Tetrabutylammonium fluoride

TFA: Trifluoroacetic acid

HATU: O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium

Hexafluorophosphate

Pd(PPh<sub>3</sub>)<sub>4</sub>: Tetrakis(triphenylphosphine)palladium(0)

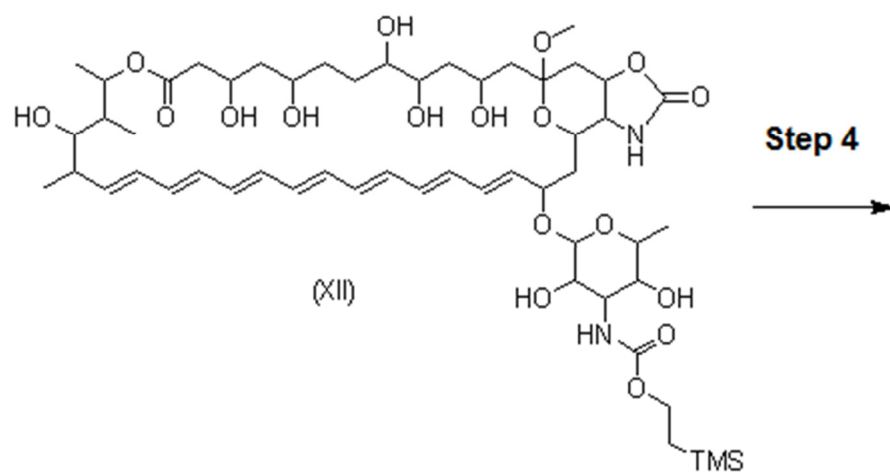
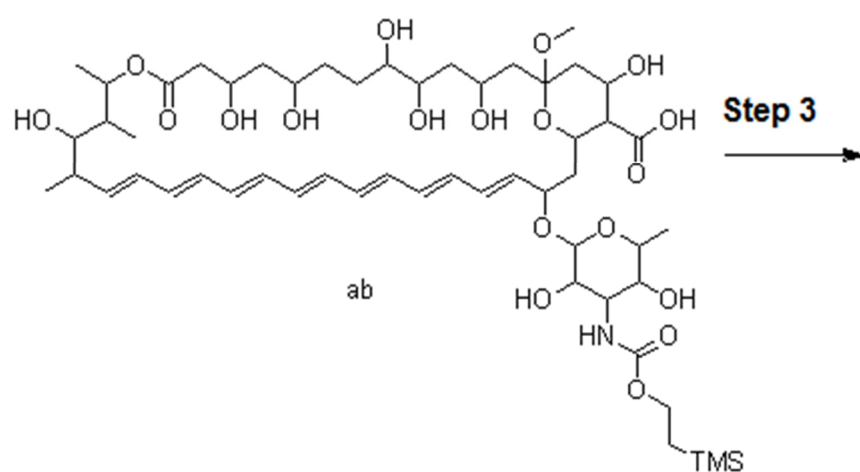
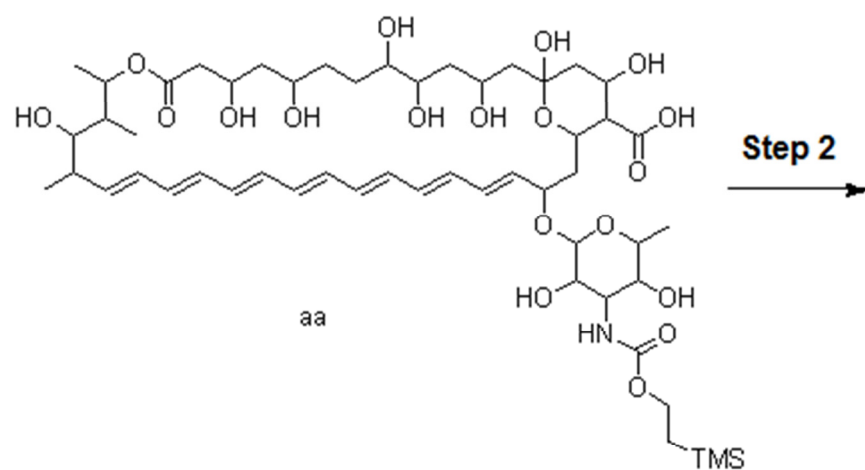
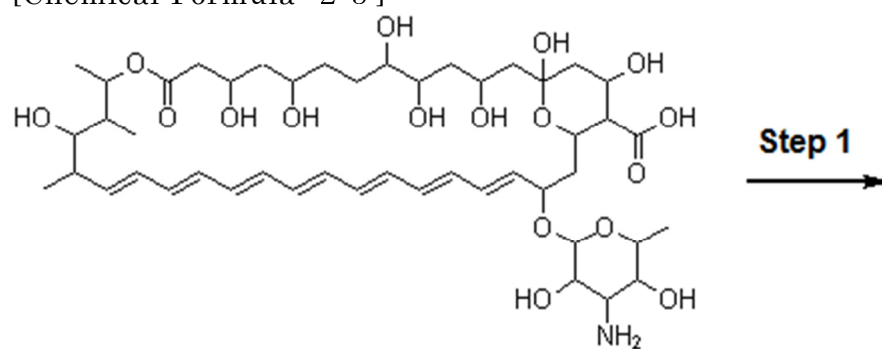
PPTS: Pyridinium p-Toluenesulfonate

PyBOP: (1H-Benzotriazole-1-yloxy)tripyrrolizinophosphonium hexafluorophosphate

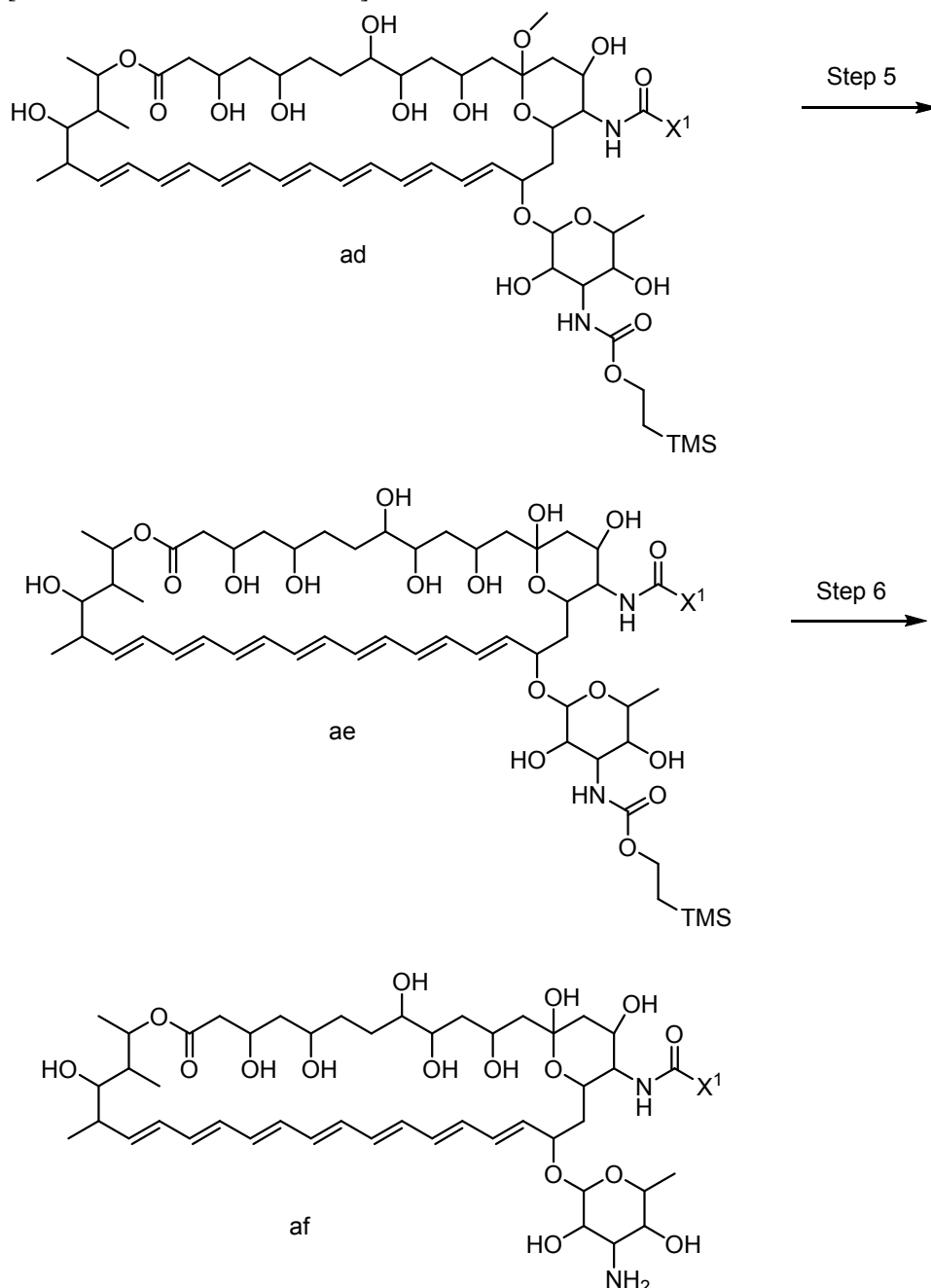
[0 1 6 0]

(General synthetic method 1-1)

[Chemical Formula 25]



## [Chemical Formula 26]



## Step 1

The compound aa can be synthesized by the reaction which tertiary amine such as triethylamine, DIEA, pyridine and the like and N-[2-(trimethylsilyl)-ethoxycarbonyloxy]succinimide are added dropwise to the commercially available amphptericin B in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof for 0.5 to 24 hours, preferably 1 to 5 hours at 20 to 30 °C.

## Step 2

The compound ab can be synthesized by the reaction which camphorsulfonic acid is added to the compound aa under ice cooling in the solvent such as tetrahydrofuran, ether and the like or solvent mixture thereof including methanol for 10 minutes to 6 hours, preferably 30 minutes to 3 hours at -30 to 10 °C, preferably -15 to 0 °C.

## Step 3

The compound (XII) can be synthesized by the reaction which tertiary amine such as triethylamine, DIEA, pyridine and the like and diphenylphosphoryl azide are reacted to the compound ab in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof for 0.5 to 2 hours at 20 to 30 °C, further for 1 to 6 hours, preferably 3 to 4 hours at 40 to 70 °C, preferably 40 to 60 °C.

#### Step 4

The compound ad can be synthesized by the reaction which the compound having amino group represented as X<sup>1</sup> such as primary amines, secondary amines, hydrazine, substituted hydrazine, alkoxy amine, amino acid and the like which is commercially available or can be synthesized according to the known methods is added to the compound (XII) in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof for 0.1 to 24 hours, preferably 1 to 12 hours at 20 to 70 °C, preferably 20 to 40 °C.

#### Step 5

The compound ae can be synthesized by the reaction which water is added, and PPTS is added to the compound ad in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof for 0.1 to 24 hours, preferably 1 to 6 hours at 20 to 40 °C, preferably 20 to 30 °C.

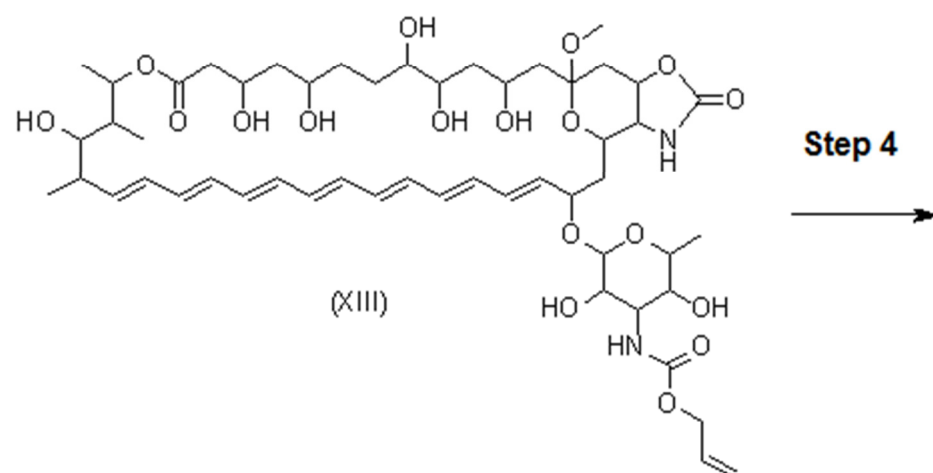
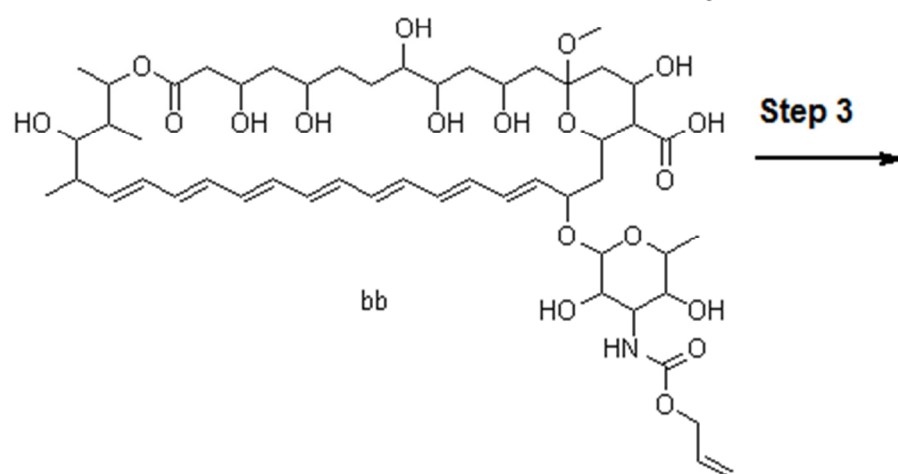
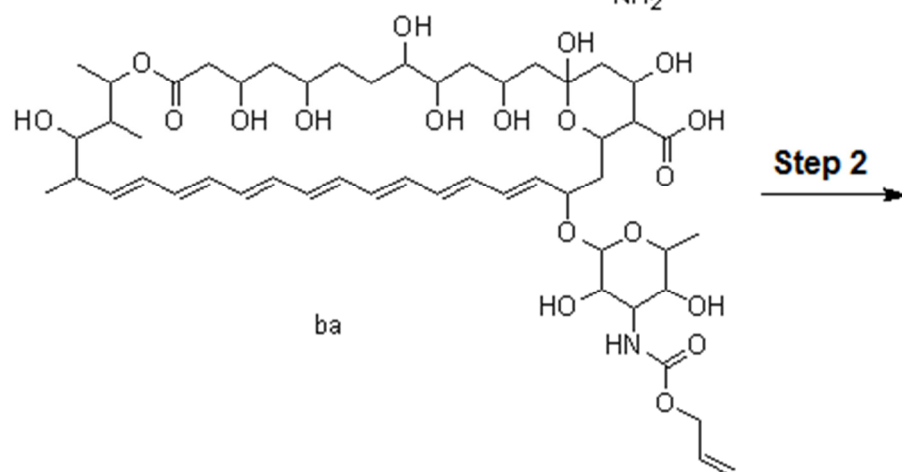
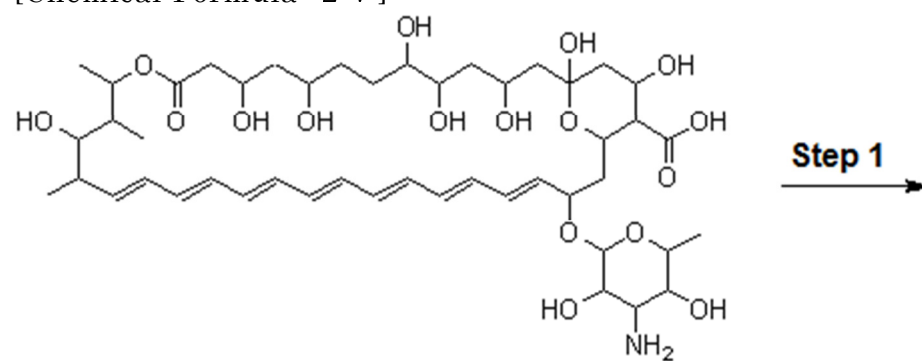
#### Step 6

The compound af can be synthesized by the commonly known deprotect reaction of carbamate protecting group of compound ae in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof.

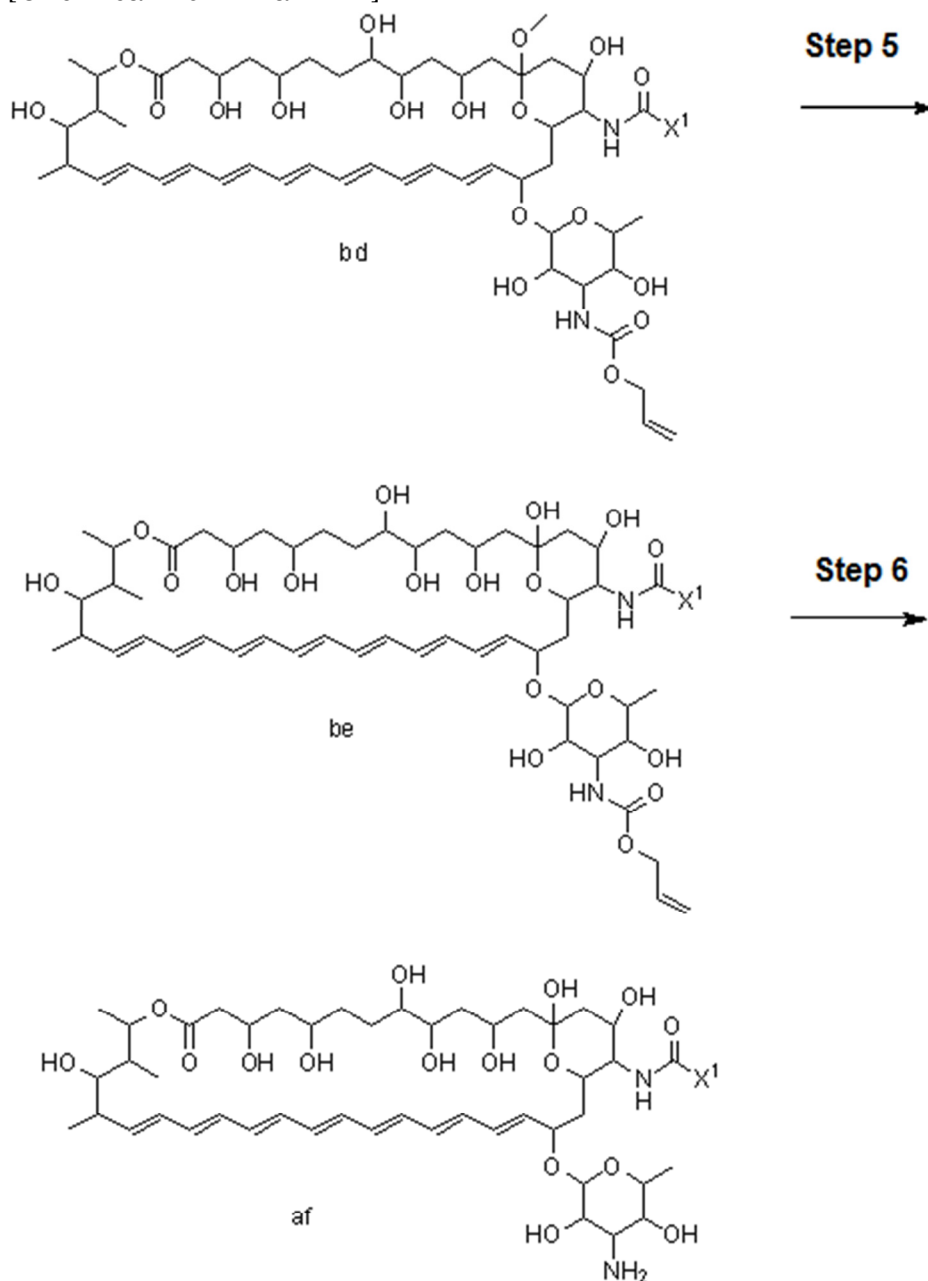
[ 0 1 6 1 ]

(General synthetic method 1-2)

[Chemical Formula 27]



[Chemical Formula 28]

**Step 1**

The compound ba can be synthesized by the reaction which tertiary amine such as triethylamine, DIEA, pyridine and the like and N-(Allyloxycarbonyloxy)succinimide are added dropwise to the commercially available amphotericin B in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof for 0.5 to 24 hours, preferably 1 to 5 hours at 20 to 30 °C.

**Step 2**

The compound bb can be synthesized by the reaction which camphorsulfonic acid is added to the compound ba under ice cooling in the solvent such as tetrahydrofuran, ether and the like or solvent mixture thereof including methanol for 10 minutes to 6 hours, preferably 30 minutes to 3 hours at -30 to 10 °C, preferably -15 to 0 °C.

## Step 3

The compound (XIII) can be synthesized by the reaction which tertiary amine such as triethylamine, DIEA, pyridine and the like and diphenylphosphoryl azide are reacted to the compound bb in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof for 0.5 to 2 hours at 20 to 30 °C, further for 1 to 6 hours, preferably 3 to 4 hours at 40 to 70 °C, preferably 40 to 60 °C.

## Step 4

The compound bd can be synthesized by the reaction which the compound having amino group represented as X<sup>1</sup> such as primary amines, secondary amines, hydrazine, substituted hydrazine, alkoxy amine, amino acid and the like which is commercially available or can be synthesized according to the known methods is added to the compound (XIII) in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof for 0.1 to 24 hours, preferably 1 to 12 hours at 20 to 70 °C, preferably 20 to 40 °C.

## Step 5

The compound be can be synthesized by the reaction which water is added, and PPTS is added to the compound bd in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof for 0.1 to 24 hours, preferably 1 to 6 hours at 20 to 40 °C, preferably 20 to 30 °C.

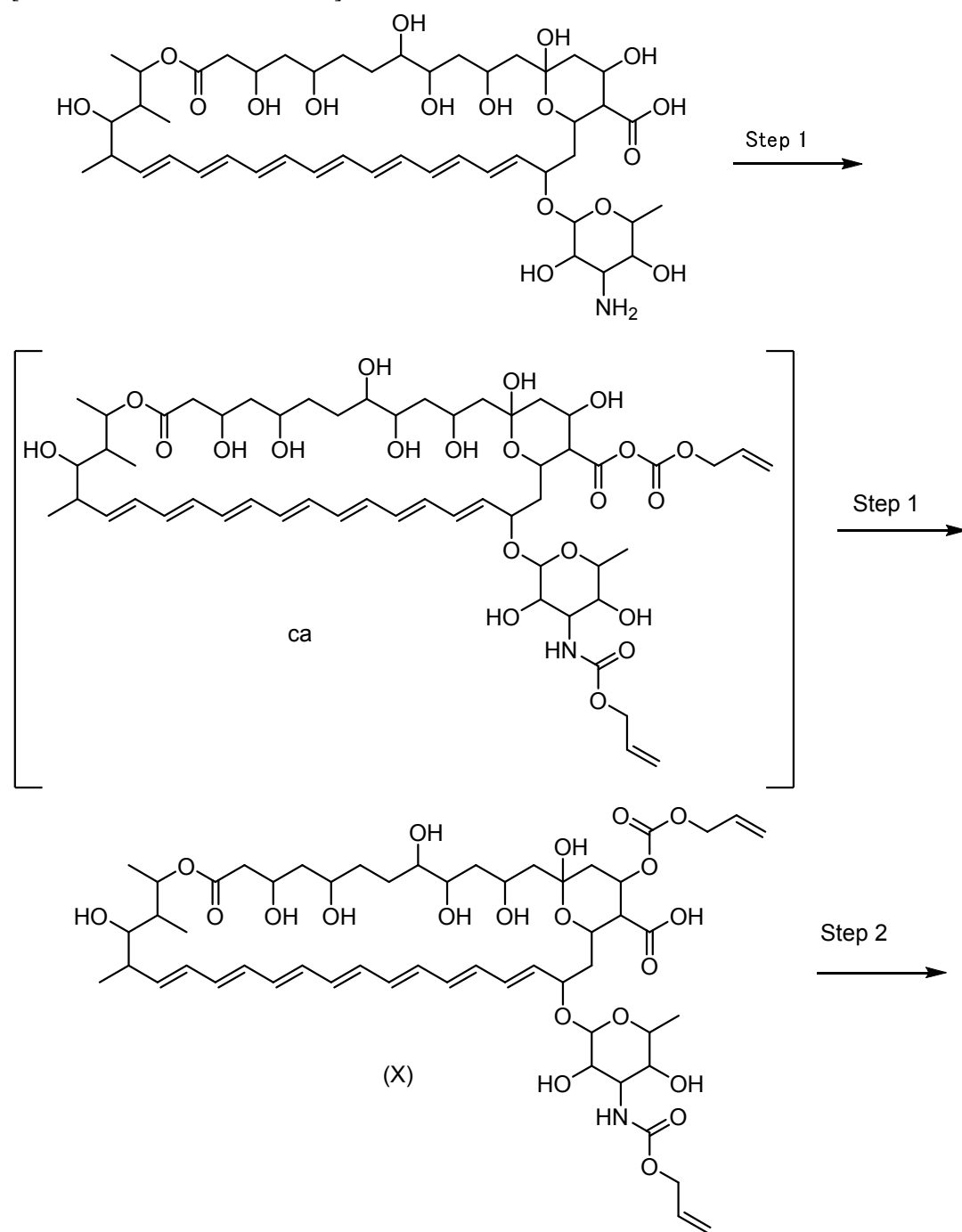
## Step 6

The compound af can be synthesized by the commonly known deprotect reaction of carbamate protecting group of the compound be in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof.

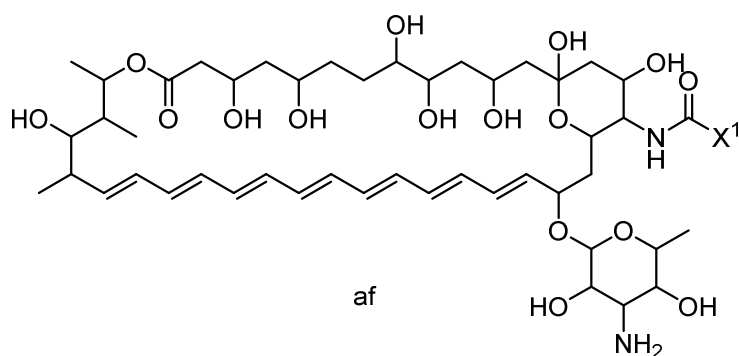
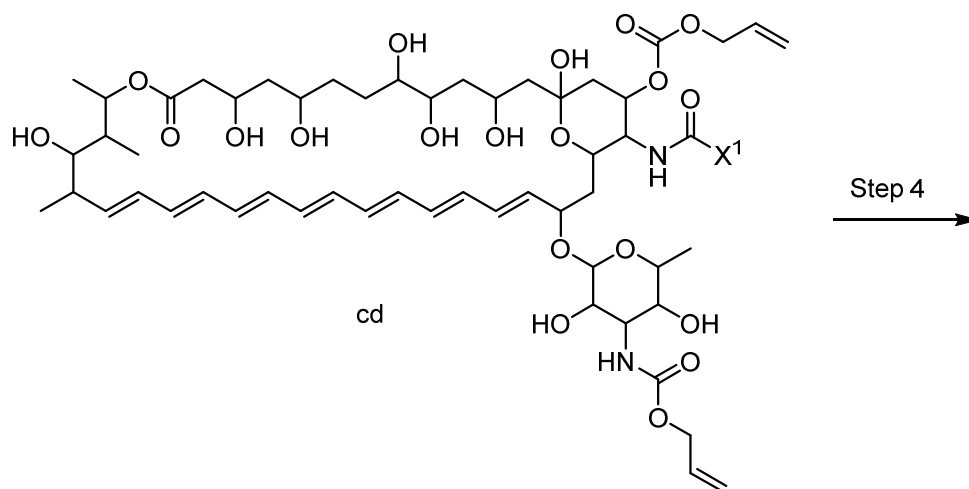
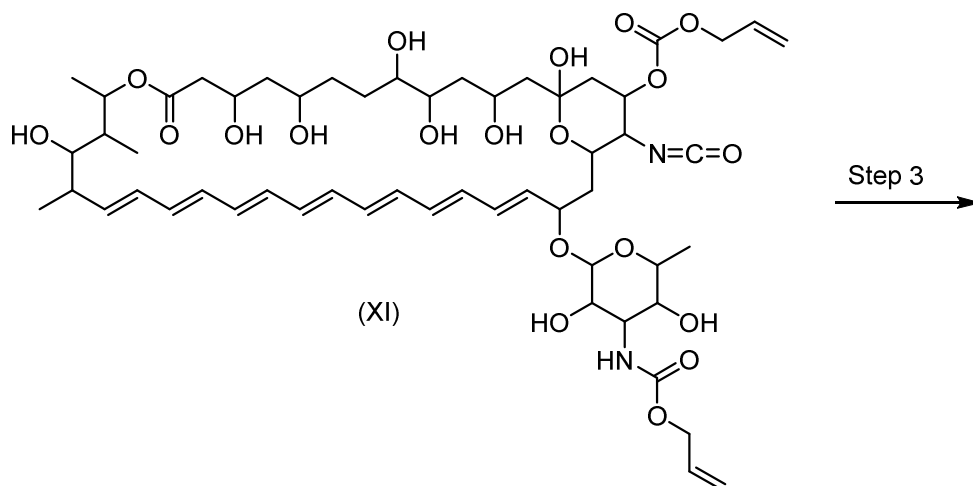
[ 0 1 6 2 ]

(General synthetic method 1-3)

[Chemical Formula 29]



[Chemical Formula 30]



## Step 1

Tertiary amine such as triethylamine, DIEA, pyridine and the like and allyloxycarbonyl chloride are added dropwise to the commercially available amphotericin B in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or its solvent mixture for 0.5 to 6 hours, preferably 2 to 3 hours at 0 to 20 °C, preferably 0 to 4 °C in the reaction mixture. Thereby, the anhydride intermediate ca can be synthesized.

The compound (X) can be synthesized by the intramolecular rearrangement of Alloc group with heating to 20 to 40 °C, preferably 20 to 30 °C for 0.5 to 6 hours, preferably 2 to 4 hours.

## Step 2

Tertiary amine such as triethylamine, DIEA, pyridine and the like and diphenylphosphoryl azide are reacted to the compound (X) in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof at 20 to 30 °C for 0.5 to 2 hours, further at 40 to 60 °C for 1 to 6 hours, preferably 2 to 4 hours. Thereby, the compound (XI) can be synthesized.

The compound (XI) can also be used as one-pot reaction of step 3 without purification.

## Step 3

The compound having amino group such as primary amines, secondary amines, hydrazine, substituted hydrazine, alkoxy amine, amino acid and the like which is commercially available or can be synthesized according to the known methods is added to the compound (XI) in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof at -20 to 50 °C, preferably 20 to 40 °C for 0.1 hours to 4 days, preferably 1 to 12 hours. Thereby, the compound cd can be synthesized.

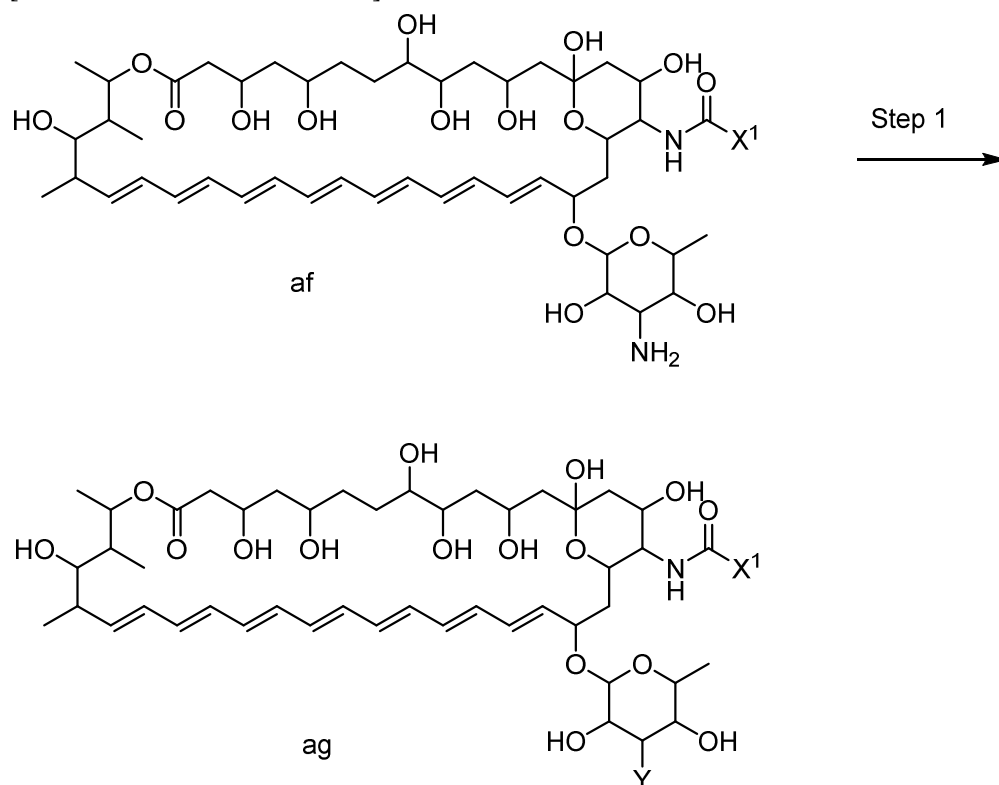
## Step 4

The compound af can be synthesized by the commonly known deprotect reaction of protecting group such as allyloxycarbonyl group of the compound cd in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof.

[ 0 1 6 3 ]

(General synthetic method 2)

[Chemical Formula 3 1 ]



## Step 1

The compound ag can be synthesized by the reaction which the compound having amino group such as primary amines, secondary amines, hydrazine, substituted hydrazine, alkoxy amine, amino acid and the like which is commercially available or can be synthesized according to the known methods is added to the

compound af in the solvent such as DMF, DIEA, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof at -20 to 50 °C, preferably 20 to 40 °C for 0.1 hours to 4 days, preferably 1 to 12 hours.

[0 1 6 4]

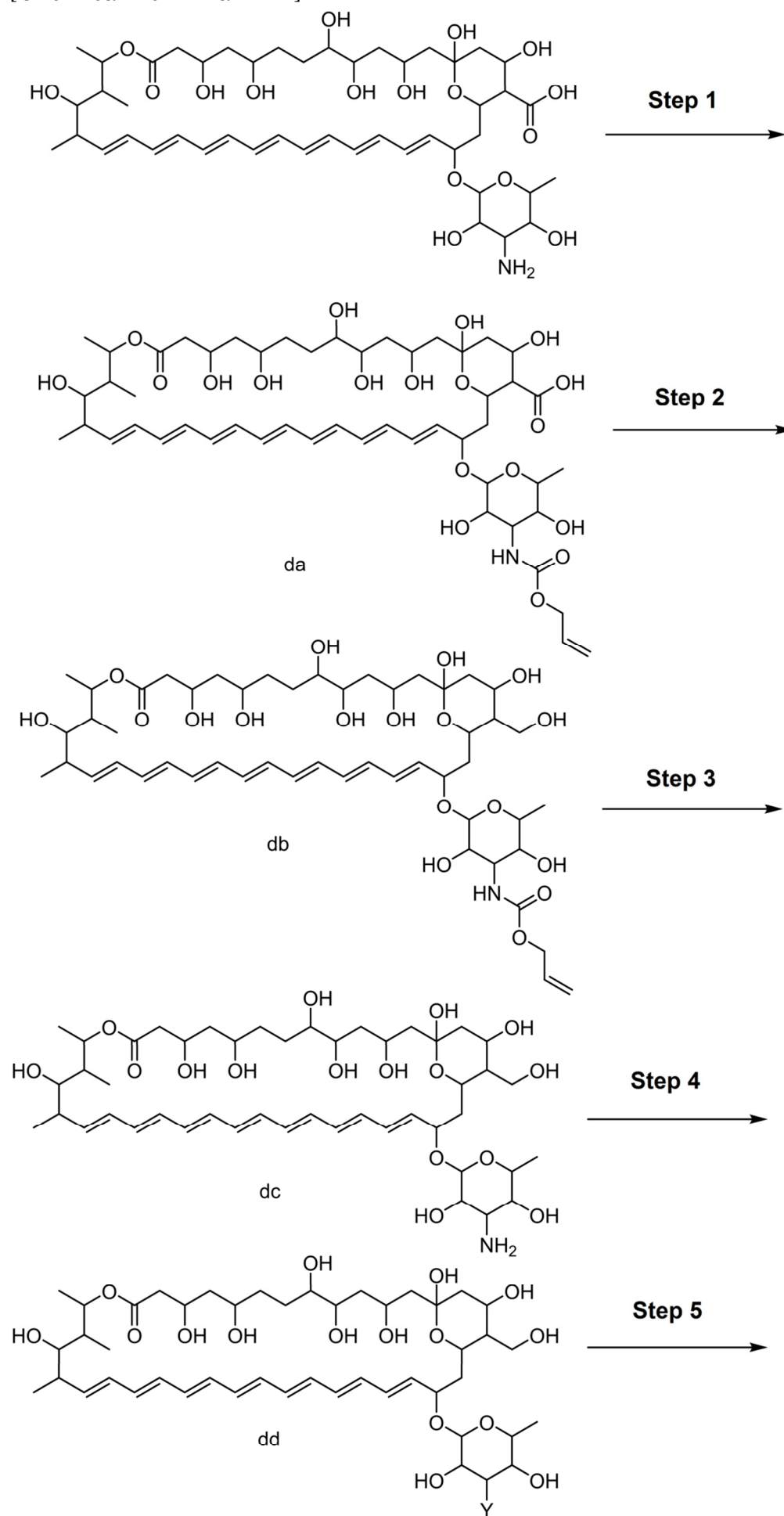
As above, the compound (I) having X represented  $-N(R^F)-CO-X^1$  can be synthesized by using the intermediate of the present invention (X), (XI), (XII) or (XIII) easily, with high yield, with short steps. Various compound (I) can be synthesized from the obtained compound (I) by chemical modifying hydroxy part or sugar chain part and the like of core structure according to the known reaction.

the compound (I) represented as X is formula (II) can also be synthesized by inducing from carboxy group or isocyanate group.

[0 1 6 5]

(General synthetic method 3)

[Chemical Formula 3 2]



## Step 1

The compound da can be synthesized by the reaction which tertiary amine such as triethylamine, DIEA, pyridine and the like and allyloxycarbonyl chloride or allyloxycarbonyl chloride succinimidediester are added dropwise to the commercially available amphptericin B in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof at 20 to 40 °C, preferably 20 to 30 °C for 0.5 to 6 hours, preferably 2 to 4 hours at.

## Step 2

The active ester is synthesized by the reacting the compound da with tertiary amine such as triethylamine, DIEA, pyridine and the like and phosphonium condensing agent such as PyBOP, BOP, BrOP, PyBrBOP and the like in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof at 0 to 20 °C, preferably 0 to 10 °C for 0.5 to 4 hours, preferably 0.5 to 1 hours. After that, the compound db can be synthesized by the reaction which sodium borohydride or boron reducing agent equivalents thereof is added, and reacted at 0 to 20 °C, preferably 0 to 10 °C for 0.5 to 4 hours, preferably 0.5 to 1 hours.

## Step 3

The compound dc can be synthesized by the commonly known deprotect reaction of allyloxycarbonyl group of the compound db in the solvent such as DMF, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof.

## Step 4

The compound dd can be synthesized by the reaction which the compound having amino group such as primary amines, secondary amines, hydrazine, substituted hydrazine, alkoxy amine, amino acid and the like which is commercially available or can be synthesized according to the known methods is added to the compound dc in the solvent such as DMF, DIEA, DMA, NMP, dichloromethane, tetrahydrofuran, acetonitrile and the like or solvent mixture thereof at -20 to 50 °C, preferably 20 to 40 °C for 0.1 hours to 4 days, preferably 1 to 12 hours.

## EXAMPLES

[0 1 6 6]

The present invention will be described in more detail with reference to, but not limited to, the following Examples, Reference Examples and Test Examples.

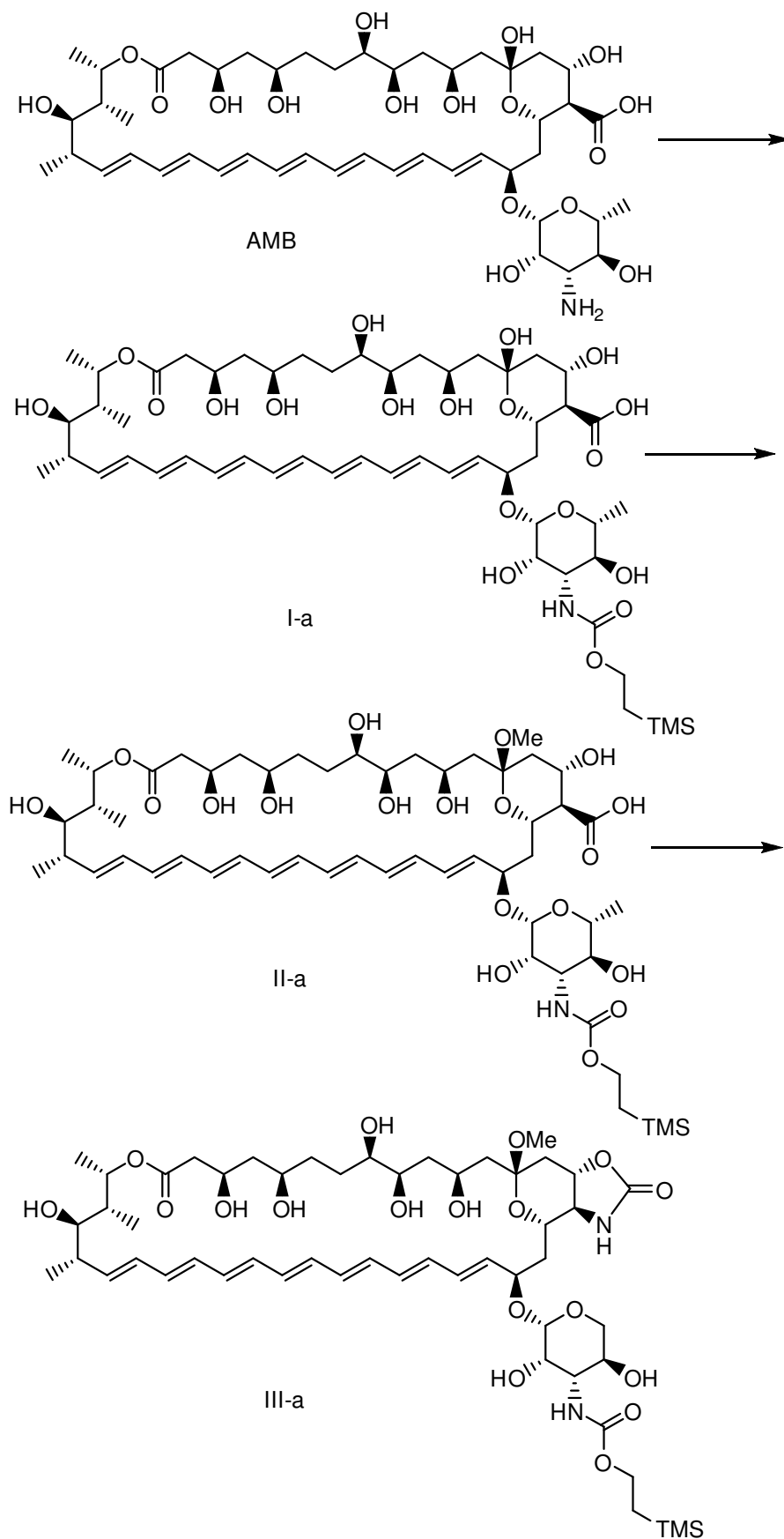
[0 1 6 7]

NMR analysis of each example was performed by 300 MHz using DMSO-d<sub>6</sub> or CDCl<sub>3</sub>.

[0 1 6 8]

Reference Example 1: Synthesis of Compound III-a

[Chemical Formula 3 3]



### Step 1 Synthesis of Compound I-a

Amphotericin B (5g, 5.41mmol) was dissolved in DMF (25mL) and added triethylamine (10mL, 72.1mmol) and N-[2-(trimethylsilyl)-

ethoxycarbonyloxy]succinimide (3.51g, 13.5mmol), and the mixture was stirred for an hour at room temperature. Diisopropyl ether and acetonitrile were added, and the resulting solids were filtered. Compound I-a (7.11g) was obtained as crude by evaporating in vacuo.

[M+Na]<sup>+</sup>= 1090

#### Step 2 Synthesis of Compound II-a

Compound I-a (2g, 1.87mmol) was dissolved in methanol (20mL), and stirred for 10 minutes in an ice-water bath. Camphorsulfonic acid (0.609g, 2.62mmol) was added and stirred for an hour in an ice-water bath. Methanol was removed by evaporating in vacuo, and the residue was resolved in a little methanol. The obtained methanol solution was added dropwise to diisopropyl ether (500mL) to give Compound II-a (1.8g, 89%).

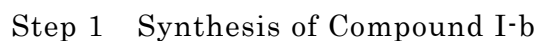
#### Step 3 Synthesis of Compound III-a

Compound II-a (1.8g, 1.66mmol) was dissolved in DMF (10mL) and added diphenylphosphoryl azide (1.075mL, 4.99mmol) and trimethylamine (1.2mL, 8.32mmol), and the mixture was stirred for an hour at room temperature, moreover, 3 hours at 40 °C. The reaction mixture was powderized by adding dropwise to the solvent mixture of diisopropyl ether and methanol. The resulting residue was filtrated to give Compound III-a (1.37g, 76%).

[M+Na]= 1101

[0 1 6 9]

#### Reference Example 2: Synthesis of Compound III-b



Amphotericin B (10.07g, 10.9mmol) was dissolved into N-methylpyrrolidone (50mL) and methanol (50mL) and added N,N-diisopropylethylamine (5.7mL, 32.7mmol) and Alloc-OSu (2.6g, 13.1mmol), and the mixture was stirred for 2 hours 30 minutes at room temperature. The reaction mixture was added to diisopropyl

ether/methanol (10/1, 550mL) and stirred strongly. The deposited powder was filtrated. The obtained solids was washed with isopropylether and evaporated in vacuo to give Compound I-b (11.58g) as crude. The retention time of Compound I-b was 10.4 minutes by HPLC analysis (methanol/distilled water containing 0.1% PIC-B7= gradient from 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm). The retention time of raw material amphotericin B was 8.6 minutes under the same condition.

[M+Na]<sup>+</sup>= 1032.5

#### Step 2 Synthesis of Compound II-b

Compound I-b (9.8g, 7.78mmol) was dissolved into tetrahydrofuran (150mL) and methanol (150mL) and cooled to 0 °C. Camphorsulfonic acid (1.5g, 6.45mmol) was added in an ice-water bath, and the mixture was stirred for 2 hours 30 minutes. Triethylamine (1.12mL, 6.45mmol) was added, and reaction was quenched. The mixture was evaporated in vacuo to 50mL by rotatory evaporator. The concentrated solution was added dropwise to diethylether/hexane (1/1, 1L) with stirring. The obtained solids were filtrated to give Compound II-b (yellow powder, 12.48g). The retention time of Compound II-b was 8.5 minutes by HPLC analysis (methanol/distilled water containing 0.1% PIC-B7= gradient from 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm).

#### Step 3 Synthesis of Compound III-b

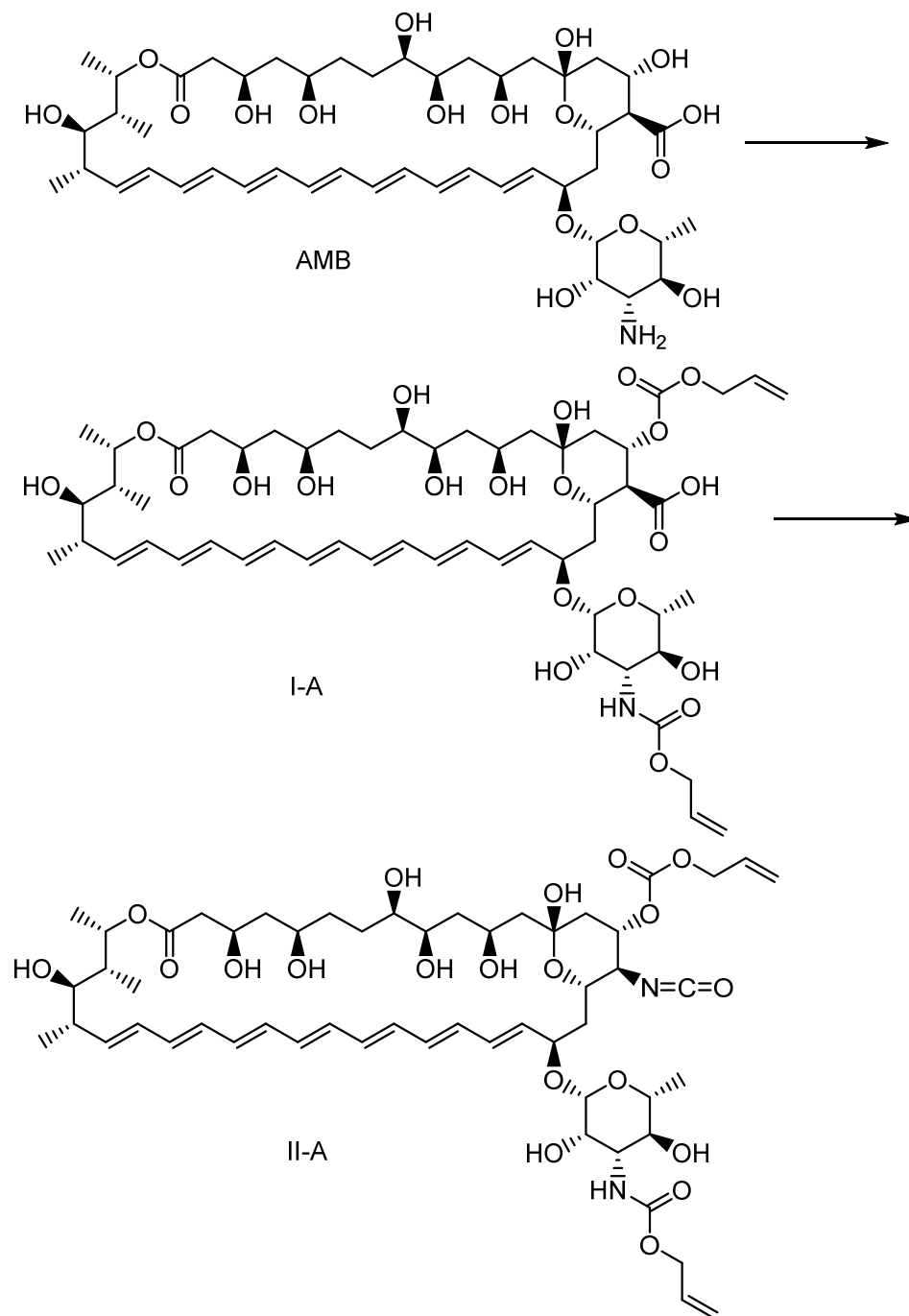
Compound II-b (7.17g, 7.01mmol) was dissolved into DMF (36mL) and added DIEA (7.35mL, 42.1mmol) and diphenylphosphoryl azide (4.52mL, 21.4mmol), and the mixture was stirred for an hour at room temperature, moreover, stirred 3 hours at 50 °C. The reaction mixture was added dropwise to the solvent mixture of diisopropyl ether and methanol (10/1, 525mL) to give powder. The obtained solids were filtrated to give Compound III-b (4.85g, 87%). The retention time was 8.1 minutes by HPLC analysis (methanol/distilled water containing 0.1% PIC-B7= gradient from 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm).

[M+Na]<sup>+</sup>=1041.4

[0 1 7 0]

Reference Example 3-1: Synthesis of Compound I-A and Compound II-A

[Chemical Formula 3 5]



### Step 1 Synthesis of Compound I-A

Amphotericin B (5g, 5.41mmol) was dissolved in DMF (50mL), followed by the addition of DIEA (10mL, 27.1mmol). Allyloxycarbonyl chloride (3.51g, 13.5mmol) was added dropwise at 4°C or below under control, and the mixture was stirred for 2 hours 50 minutes in an ice-water bath. After heating to room temperature, the mixture was stirred for 4 hours. The mixture was added dropwise to the solvent mixture of diisopropyl ether/methanol (4/1, 500mL). After the mixture was incubated at room temperature, the obtained solids were filtrated to give Compound I-A (5.85g). The retention time was 12.4 minutes by HPLC analysis (methanol/distilled water containing 0.1% PIC-B7= gradient from 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm).

[M+H]<sup>+</sup> = 1093.9

### Step 2 Synthesis of Compound II-A

Compound I-A (5.28g, 4.83mmol) was dissolved into DMA (25mL), followed by the addition of DIEA (1.26mL, 7.25mmol). Diphenylphosphoryl azide (1.56mL, 7.25mmol) was added, and the mixture was stirred for 2 hours 20 minutes at room temperature and further stirred for 2 hours at 50°C. After cooling to room temperature, the reaction mixture was diluted with acetonitrile (25mL) and added diisopropyl ether (350mL). The obtained solids was filtrated to give Compound II-A (5.01g) as yellow powder. The retention time was 12.5 minutes by HPLC analysis (methanol/distilled water containing 0.1% PIC-B7= gradient from 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm).

Infrared absorption spectrometry (IR spectrum): 2141.85 ( $\text{cm}^{-1}$ )

Elementary analysis:  $(\text{C}_{55}\text{H}_{80}\text{N}_2\text{O}_{20})(\text{C}_3\text{H}_7\text{NO})_{3.5}(\text{H}_2\text{O})_1$

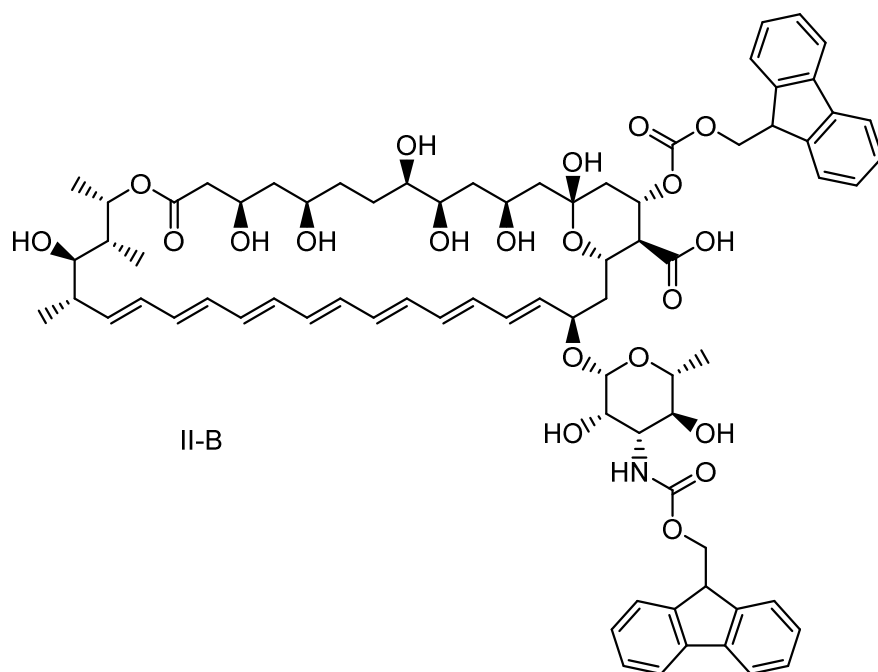
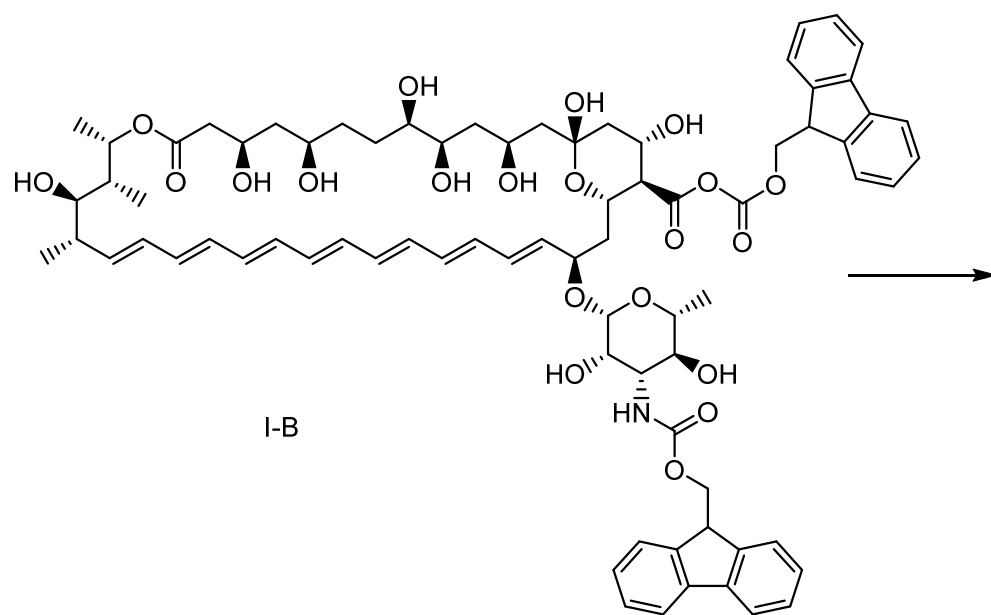
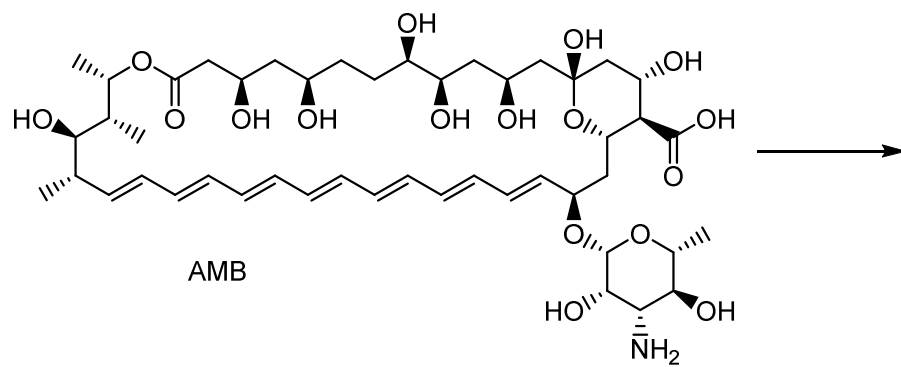
Calculated value: C 57.72; H 7.88; N 5.65 (%)

Actual value: C 57.81; H 7.31; N 6.03 (%)

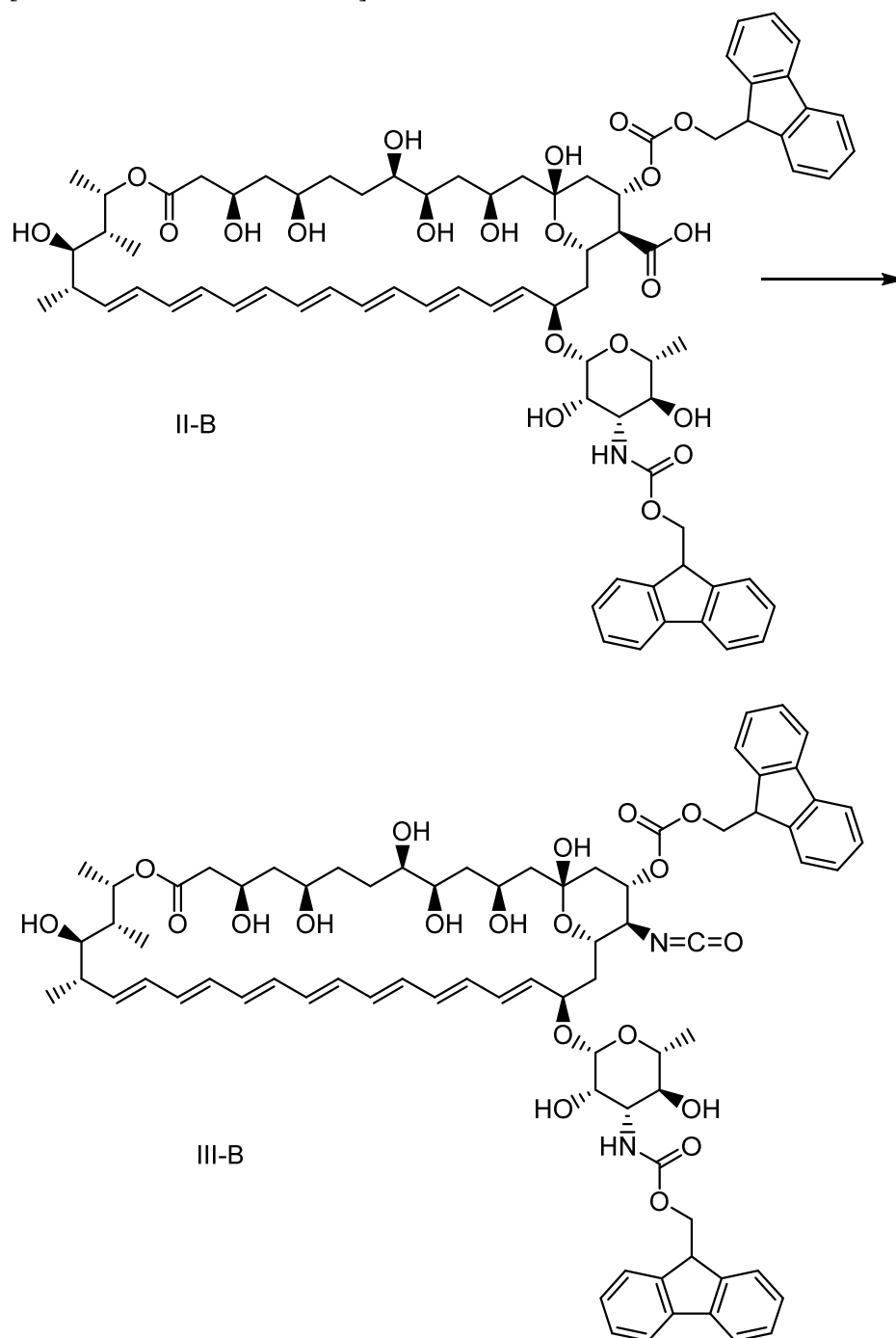
[0 1 7 1]

Reference Example 3-2: Synthesis of Compound I-B, Compound II-B and Compound III-B

[Chemical Formula 3 6]



[Chemical Formula 3 7]



### Step 1 Synthesis of Compound I-B

Amphotericin B (10.00g, 10.82mmol) was dissolved into DMA (78mL), followed by the addition of DIEA (2.53g, 19.58mmol). 9-Fluorenylmethoxycarbonylchloride (5.32g, 20.6mmol) was added carefully dropwise at 4°C or below under control in an ice-water bath. After heating to room temperature, the mixture was stirred for an hour 30 minutes. After the mixture was added to the solution mixture of acetonitrile (100mL) and DMA (3.6mL), diisopropyl ether (500mL) was added dropwise. The mixture was incubated at room temperature and filtrated to give crude Compound I-B (15.92g, 11.63mmol).

### Step 2 Synthesis of Compound II-B

Compound I-B (10.00g, 7.31mmol) was dissolved into DMA (50mL) and trimethylamine (0.506mL, 3.65mmol) was added. The mixture was stirred for an

hour 40 minutes at room temperature. After acetonitrile (50mL) was added, diisopropyl ether (500mL) was added dropwise. After incubating at room temperature, the obtained powder was filtrated to give crude Compound II-B (8.79g, 6.42mmol). The crude Compound II-B (4.50g, 3.29mmol) was purified by silica-gel column chromatography by using chloroform/methanol (89/11) to give Compound II-B (2.02g, 1.48mmol). The retention time was 16.7 minutes by HPLC analysis (acetonitrile/distilled water containing 0.1% formic acid= gradient from 20/80 to 90/10, flow speed 1ml/min, wavelength of detection= 385nm).

[M+Na]= 1392

### Step 3 Synthesis of Compound III-B

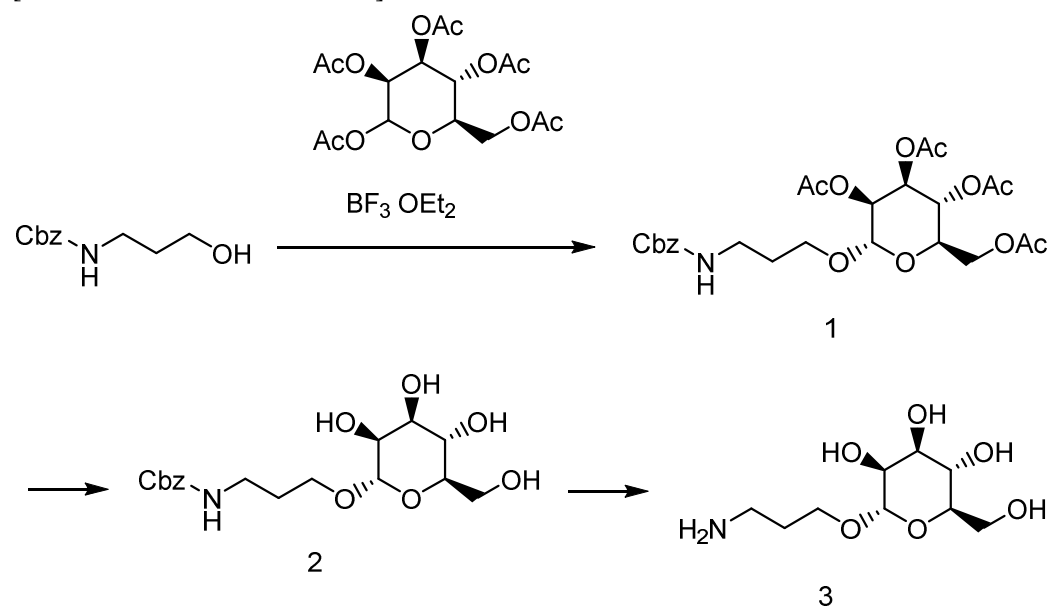
Compound II-B (1.50g, 1.10mmol) was dissolved into THF/DMA (1/4, 7.5mL), followed by the addition of DIEA (325.5 $\mu$ L, 1.86mmol). Diphenylphosphoryl azide (400.5  $\mu$ L, 1.86mmol) was added, and the mixture was stirred for an hour at room temperature, in addition, stirred for 9.5 hours at 40°C. After cooling to room temperature, acetonitrile (25mL) was added dropwise. After incubation at room temperature, the obtained powder was filtrated to give yellow powder Compound III-B (0.59g, 0.435mmol). The retention time was 17.2 minutes by HPLC analysis (methanol/distilled water containing 0.1% formic acid= gradient from 20/80 to 90/10, flow speed 1ml/min, wavelength of detection= 385nm).

Infrared absorption spectrometry (IR spectrum): 2143 or 2165 ( $\text{cm}^{-1}$ )

[0 1 7 2]

### Example 1: Synthesis of Compound I-1

[Chemical Formula 3 8]



### Step 1 Synthesis of Compound 1

Pentaacetylmannose (4g, 10.25mmol) and N-benzyloxycarbonyl-aminopropanol (4.29g, 20.49mmol) were dissolved into dichloromethane (20mL) and boron trifluoride diethyl ether complex (10.39mL, 82mmol) was added, and the mixture was stirred for 16 hours at room temperature. After the reaction was quenched by adding saturated sodium bicarbonate aqueous solution and 2mol/L sodium hydroxide solution, the reaction mixture was extracted with ethyl acetate, and the organic phase was washed with water and brine. The organic phase was dried over with magnesium sulfate and filtrated and concentrated. The resulted residue was purified by silica-gel column chromatography (hexane-ethyl acetate) to give Compound 1 (2.55g, 46%).

TLC: Rf= 0.3 (hexane/ethyl acetate= 1/1)

#### Step 2 Synthesis of Compound 2

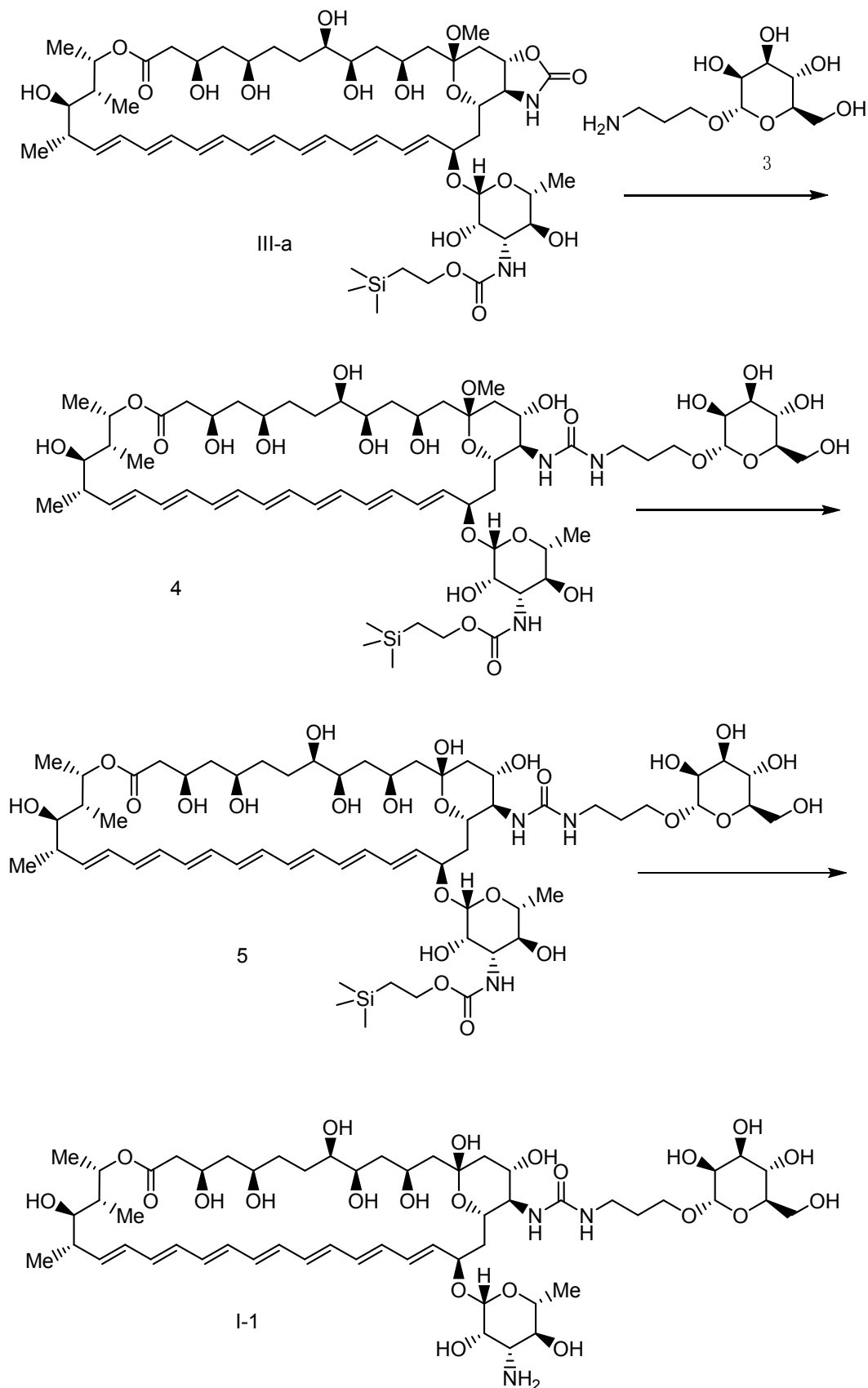
Compound 1 (2.55g, 4.73mmol) was dissolved into methanol (10mL), sodium methoxide (5.2mol/L, 1.8mL, 9.45mmol) was added, and the mixture was stirred for 20 minutes at room temperature. After disappearance of raw material, Dowex was added, and the mixture was filtrated and concentrated and purified by silica-gel column chromatography (ethyl acetate, methanol) to give Compound 2 (1.3g, 74%).

TLC: Rf= 0.2 (chloroform/mthanol= 4/1)

#### Step 3 Synthesis of Compound 3

Compound (1.3g, 3.5mmol) was dissolved into methanol (20mL) and 5% Pd·C (373mg, 0.175mmol) was added, and the mixture was stirred for 15 hours under 1 atm of hydrogen. The mixture was filtrated and concentrated to give 3-aminopropyl-β-D-mannopyranoside (Compound 3, 840mg). Crude Compound 3 was used to next reaction without purification.

[Chemical Formula 3 9]



#### Step 4 Synthesis of Compound I-1

Compound III-a (500mg, 0.463mmol) and 3-aminopropyl-β-D-mannopyranoside (Compound 3) (154mg, 0.649mmol) were dissolved into DMF (5mL) and DIEA (0.405mL, 2.32mmol) was added. The mixture was stirred for 2 hours at room

temperature, moreover, stirred for 2 days at 40°C, moreover, stirred for 6 hours at 55°C. After disappearance of raw material, diisopropyl ether was added to give powder. Crude Compound 4 (497mg) was obtained. Compound 4 (470mg, 0.357mmol) was dissolved to tetrahydrofuran (3mL), water (3mL) and DMF (0.3mL) and PPTS (269mg, 1.07mmol) was added, and the mixture was stirred for an hour at room temperature. Diisopropyl ether was added to be powder to give crude Compound 5 (465mg). The obtained Compound 5 (465mg, 0.357mmol) was dissolved into tetrahydrofuran (6mL) and DMF (3mL) and TBAF (1mol/L, 1.78mL) was added, and the mixture was stirred for 3 days at room temperature. The mixture was oilouted by adding diisopropyl ether and purified by silica-gel column chromatography (chloroform/methanol/water= 50/50/5 to 20/80/8). The obtained solids was dissolved into DMF (1mL) again, and diisopropyl ether was added to solidify. Compound I-1 (44mg, total yield 8%) was obtained.

LC/MS: 1158.6 [M+H]<sup>+</sup>

Elementary analysis: C<sub>56</sub>H<sub>91</sub>N<sub>3</sub>O<sub>22</sub>(C<sub>3</sub>H<sub>7</sub>N)<sub>0.9</sub>(H<sub>2</sub>O)<sub>7.1</sub>

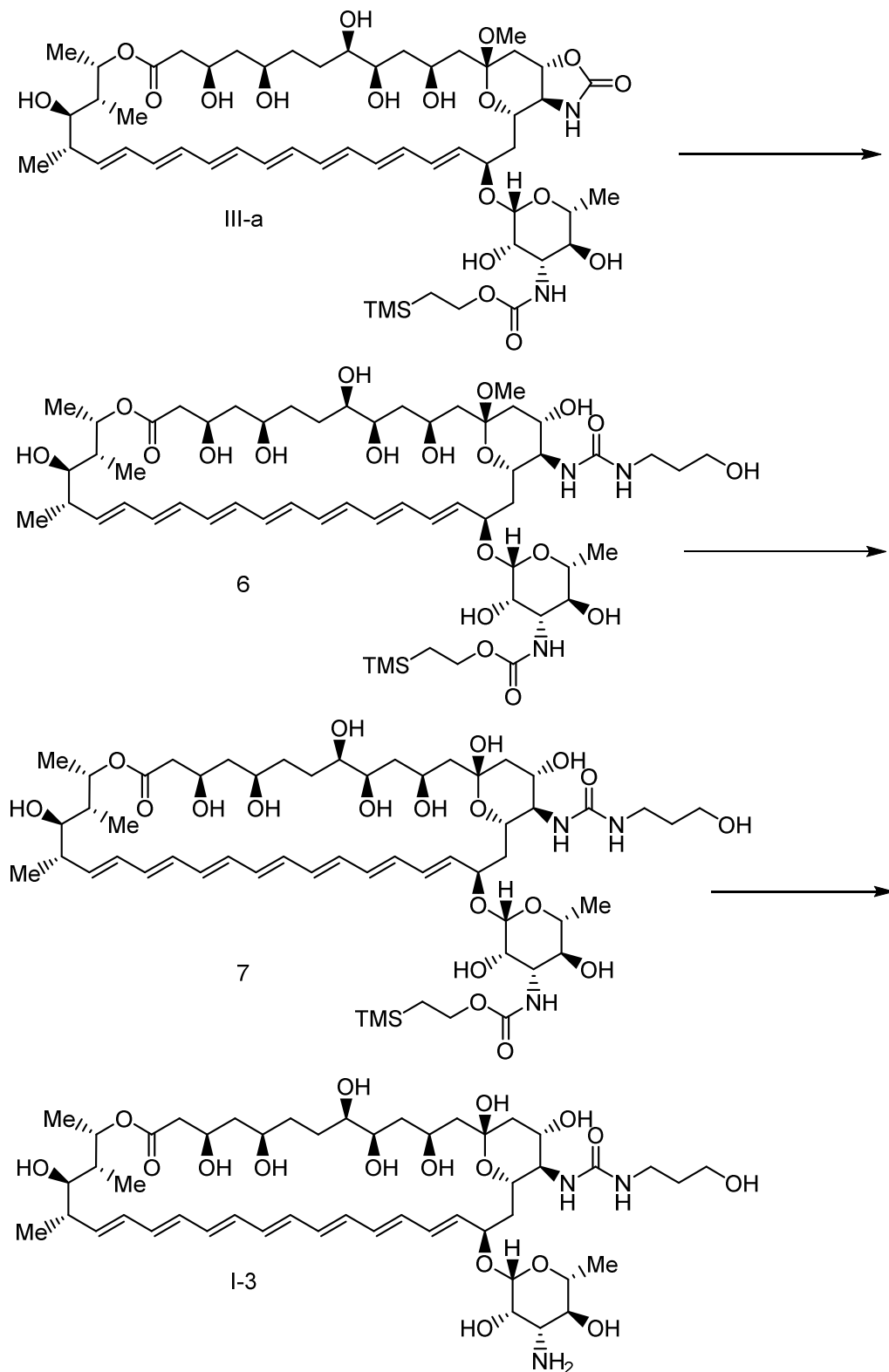
Calculated value: C 52.78; H 8.40; N 4.09 (%)

Actual value: C 52.71; H 8.40; N 4.08 (%)

[ 0 1 7 3 ]

Example 2: Synthesis of Compound I-3

## [Chemical Formula 40]



Compound III-a (420mg, 0.389mmol) was dissolved into DMF (5mL) and added 3-aminopropanol (175mg, 2.34mmol), and the mixture was stirred for 2 hours at room temperature. The mixture was oil-outed by adding diisopropylether to give crude Compound 6 (365mg). Compound 6 was dissolved into tetrahydrofuran (2mL), DMF (1mL) and water (0.5mL) and added PPTS (238mg, 0.948mmol), and the mixture was stirred for 2 hours at room temperature. Compound 7 (360mg) was obtained by adding diisopropylether to be powder. Compound 7 was dissolved into DMF (5mL)

and added TBAF (1mol/L, 3.16mL, 10 equivalent), and the mixture was stirred for overnight at roomtemperature. After the reaction mixture was oil-outed by adding diisopropylether, the mixture was purified by silica-gel column chromatography to give Compound I-3 (110mg, total yield 28%)

LC/MS: 996.9 [M+H]<sup>+</sup>

Elementary analysis: C<sub>50</sub>H<sub>81</sub>N<sub>3</sub>O<sub>17</sub>(C<sub>3</sub>H<sub>7</sub>NO)<sub>1</sub>(H<sub>2</sub>O)<sub>4.3</sub>

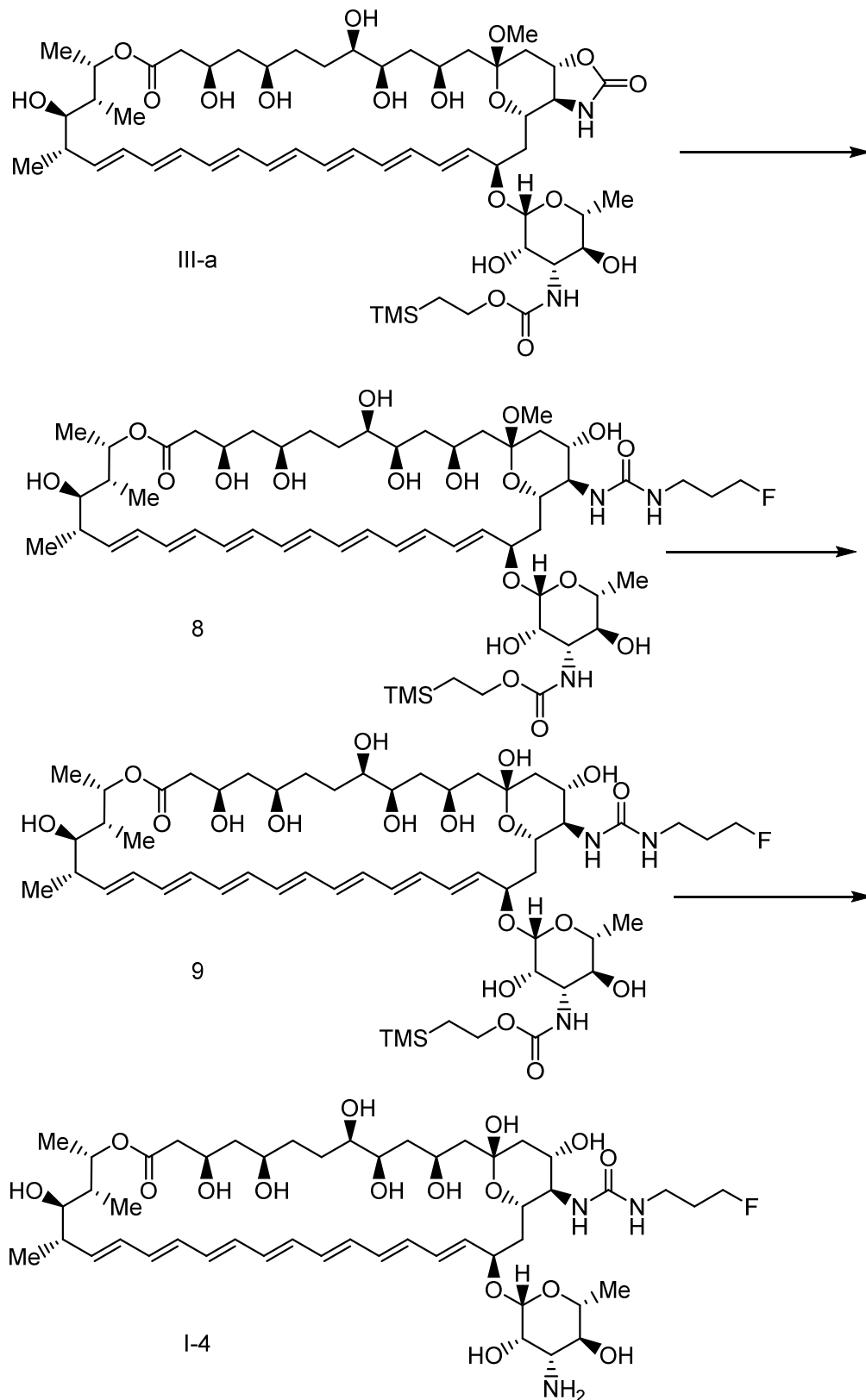
Calculated value: C 55.51; H 8.49; N 4.89 (%)

Actual value: C 55.53; H 8.61; N 4.98 (%)

[ 0 1 7 4 ]

Example 3: Synthesis of Compound I-4

[Chemical Formula 4-1]



Compound III-a (400mg, 0.371mmol) was dissolved into DMF (5mL) and added 3-fluoropropanpolamine hydrochloride (168mg, 1.48mmol) and trimethylamine (0.2mL, 1.48mmol), and the mixture was stirred for an hour at room temperature. Diisopropylethylamine (0.26mL, 1.48mmol) was added, and the mixture was stirred for 3 hours at room temperature. The crude Compound 8 (260mg, 0.225mmol) was obtained by adding diisopropylether to be oil-outed. Compound 8 (260mg,

0.225mmol) was dissolved into tetrahydrofuran (2mL), DMF (1mL) and water (0.5mL) and added PPTS (169mg, 0.674mmol), and the mixture was stirred for 2 hours at room temperature. The obtained Compound 9 by adding diisopropylether to be oil-outed was used to next reaction without purification. Compound 9 (257mg) was dissolved into DMF (3mL) and added TBAF (1mol/L, 2.2mL), and the mixture was stirred for 24 hours at room temperature. The mixture was oil-outed by adding diisopropylether and purified by silica-gel column chromatography to give Compound I-4 (54mg, total yield 15%).

LC/MS: 998.5 [M+H]<sup>+</sup>

Elementary analysis: (C<sub>50</sub>H<sub>80</sub>FN<sub>3</sub>O<sub>16</sub>)(C<sub>3</sub>H<sub>7</sub>NO)(H<sub>2</sub>O)<sub>3</sub>

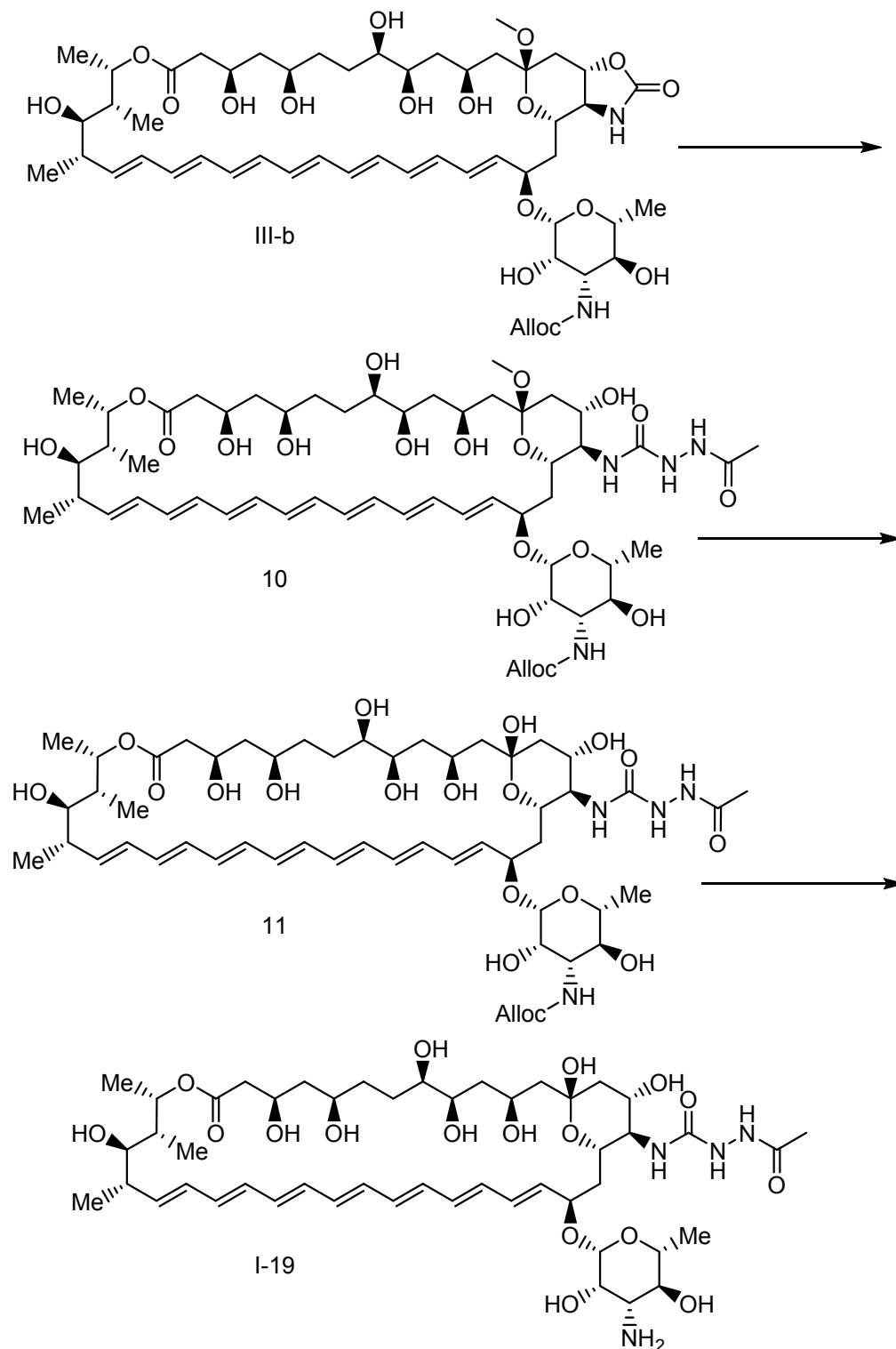
Calculated value: C 56.57; H 8.33; N 4.98; F 1.69 (%)

Actual value: C 56.20; H 8.64; N 4.94; F 2.16 (%)

[ 0 1 7 5 ]

Example 4: Synthesis of Compound I-19

[Chemical Formula 4 2]



Compound III-b (2g, 1.96mmol) was dissolved into DMA (20mL) and added DIEA (2mL, 11.7mmol) and acetohydrazide (0.58g, 7.85mmol), and the mixture was stirred for 12 hours at 70°C. After powderization by diisopropyl ether/methanol, the crude Compound 10 (1.79g) was filtrated. The crude Compound 10 was used to next reaction without purification. Compound 10 (1.79g, 1.64mmol) was dissolved into tetrahydrofuran (10mL), DMF (5mL) and water (1.25mL) and added PPTS (2.05g, 8.19mmol), and the mixture was stirred for an hour at room temperature. The reaction was quenched by trimethylamine (1.36mL, 9.82mmol). After concentration, the mixture was oil-outed by adding diisopropyl ether. The mixture was dissolved

into chloroform and methanol. After aminosilica-gel was added, the mixture was purified by silica-gel column chromatography (aminosilica-gel, chloroform/methanol/water= 80/20/2) to give Compound 11 (295mg, 17%). Compound 11 (295mg, 0.27mmol) was dissolved into DMF (3mL) and added morpholine (0.24mL, 2.7mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (93mg, 0.091mmol), and the mixture was stirred for 2 hours at room temperature. After powderization by adding diisopropyl ether/methanol (10/1), Compound I-19 (160mg, 59%) was obtained by silica-gel column chromatography (chloroform/methanol/water= from 90/10/1 to 40/60/6).

LC-MS:  $m/z$  995.5  $[\text{M}+\text{H}]^+$

Elementary analysis:  $(\text{C}_{49}\text{H}_{78}\text{N}_4\text{O}_{17})(\text{C}_3\text{H}_7\text{NO})(\text{H}_2\text{O})_{3.7}$

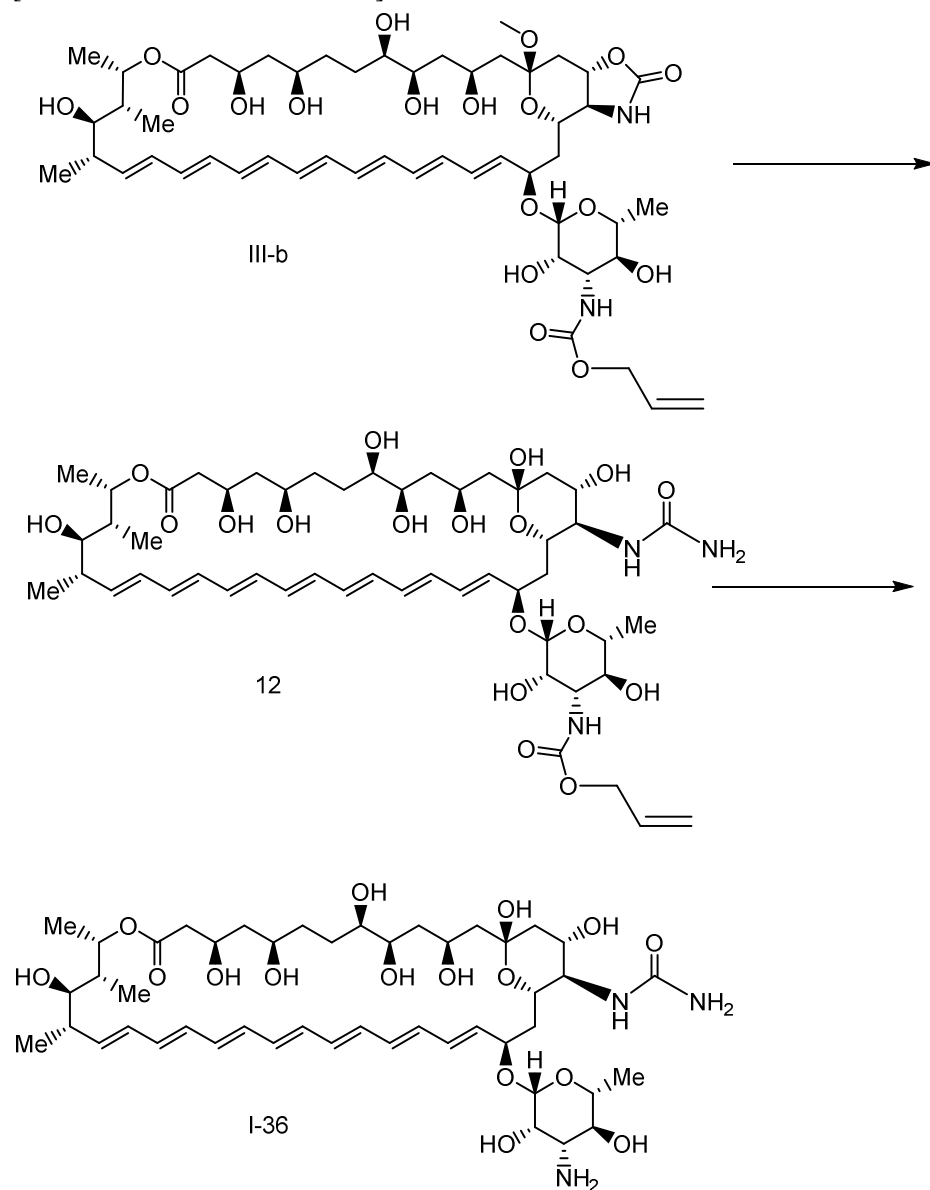
Calculated value: C 55.03; H 8.21; N 6.17 (%)

Actual value: C 54.97; H 8.15; N 6.53 (%)

[0 1 7 6]

### Example 5: Synthesis of Compound I-36

[Chemical Formula 4 3]



### Step 1

Compound III-b (3.08g, 1.87mmol) was dissolved into DMA (20mL) and added ammonia (2mol/L, methanol solution, 15mL, 30mmol), and the mixture was stirred

for 3 hours 20 minutes at room temperature. Furthermore, ammonia (2mol/L, methanol solution, 15mL, 30mmol) was added, and the mixture was stirred for 2 hours 30 minutes at 45 °C. Diisopropyl ether/methanol (10/1, 400mL) was added to the reaction mixture to give yellow powder (2.14g). The resulting powder was dissolved into tetrahydrofuran (10mL), DMF(5mL) and water (2.5mL) and added PPTS (0.778g, 3.1mmol), and the mixture was stirred for 5 hours at room temperature. The reaction mixture was quenched by adding trimethylamine (0.429mL, 3.1mmol). The reaction mixture was added to hexane/diethyl ether (1/1, 1L) to give crude Compound 12 (1.84g) by powderization. The retention time was 9.5 minutes by HPLC analysis (methanol/distilled water containing 0.1% PIC-B7= gradient from 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm).  
Step 2

Compound 12 (1.844g, 1.804mmol) was dissolved into DMF (11mL) and added DMF (11mL), morpholine (0.47mL, 0.54mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (104mg, 0.009mmol), and the mixture was stirred for 2 hours at room temperature. After powderization by adding diisopropyl ether, the mixture was purified by reverse-phase chromatography (HP20ss, hydrochloric acid aq (0.5mM)/acetonitrile= 100/0 to 70/30). After lyophilization, Compound I-36 (126mg, 8%) was obtained. The retention time was 6.7 minutes by HPLC analysis (methanol/distilled water containing 0.1% PIC-B7= gradient from 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm).

LC-MS: m/z 938.5 [M+H]<sup>+</sup>

Elementary analysis: (C<sub>47</sub>H<sub>75</sub>N<sub>3</sub>O<sub>16</sub>)(HCl)0.7(H<sub>2</sub>O)6

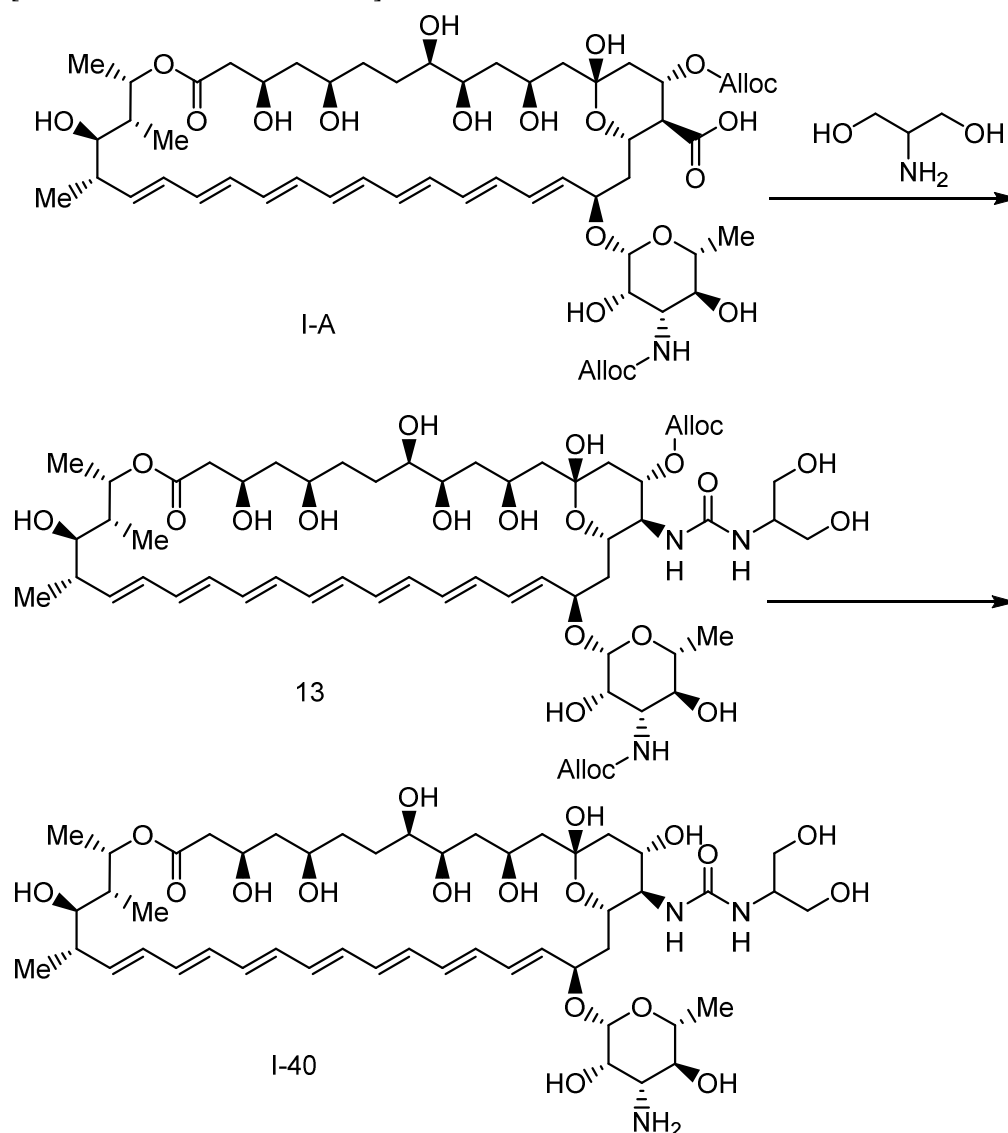
Calculated value: C 52.67; H 8.25; N 3.92; Cl 2.32

Actual value: C 52.97; H 8.01; N 4.01; Cl 2.62

[ 0 1 7 7 ]

Example 6: Synthesis of Compound I-40

[Chemical Formula 4 4]



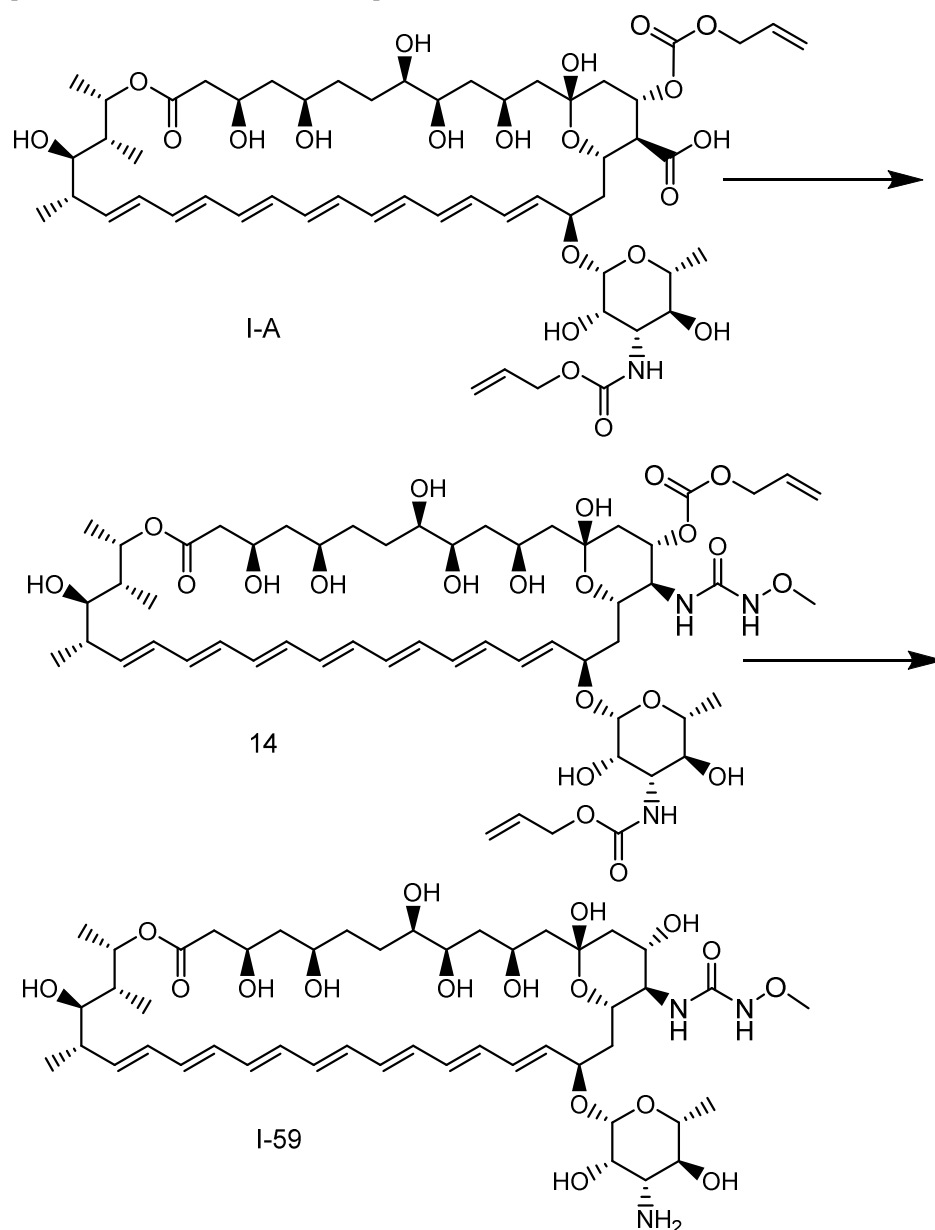
Compound I-A (1g, 0.916mmol) was dissolved into DMA (10mL) and added DIEA (0.24mL, 1.37mmol) and diphenylphosphoryl azide (0.295mL, 1.37mmol), and the mixture was stirred for 3 hours at room temperature. After conversion to acid azide, curtius rearrangement was carried out by stirring for 30 minutes at 50 °C. 2-aminopropane-1,3-diol (250mg, 2.75mmol) was added and reacted against generated isocyanate in the reaction mixture, and the reaction mixture was stirred for 30 minutes. After the mixture was oil-outed by adding diisopropyl ether, the resulting residue was purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5 to 50/50/5) to give Compound 13 (180mg, 17%). Compound 13 (180mg, 0.152mmol) was dissolved into DMF (2mL) and added morpholine (0.13mL, 1.52mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (17mg, 0.015mmol), and the mixture was stirred for 40 minutes at room temperature. Furthermore, Pd(PPh<sub>3</sub>)<sub>4</sub> (17mg, 0.015mmol) was added, and the mixture was stirred for 20 minutes at room temperature. After powderization by adding diisopropyl ether/methanol (10/1), the mixture was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=90/10/1 to 50/50/5) to give Compound I-40 (76mg, 49%). LC-MS: 1012.4 [M+H]<sup>+</sup>, 1034.5 [M+Na]<sup>+</sup>  
 Elementary analysis: C<sub>50</sub>H<sub>81</sub>N<sub>3</sub>O<sub>18</sub>(C<sub>3</sub>H<sub>7</sub>NO)<sub>1.3</sub>(H<sub>2</sub>O)<sub>4.1</sub>  
 Calculated value: C 54.81; H 8.39; N 5.10 (%)

Actual value: C 54.85; H 8.34; N 5.08 (%)

[0 1 7 8]

### Example 7: Synthesis of Compound I-59

[Chemical Formula 4 5]



#### Step 1

Compound I-A (500mg, 0.458mmol) was dissolved into DMF (1.5mL) and added DIEA (0.096mL, 0.549mmol) and diphenylphosphoryl azide (0.118mL, 0.549mmol), and the mixture was stirred for 2 hours 10 minutes at room temperature, in addition, stirred for 40 minutes at 50°C. O-Methylhydroxylamine hydrochloride (76mg, 0.916mmol) and DIEA (0.19mL, 1.1mmol) were added, and the mixture was stirred for 80 minutes at 50°C. After the mixture was oil-outed by adding diisopropyl ether, the resulting residue was purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5 to 85/15/1.5, containing 0.2% triethylamine) to give Compound 14 (163mg, 17%).

LC-MS: 1158.5 [M+Na]<sup>+</sup>

#### Step 2

Compound 14 (163mg, 0.143mmol) was dissolved into tetrahydrofuran (4mL)

and added water (0.4mL). Morpholine (0.125mL, 1.435mmol) and  $\text{Pd(PPh}_3)_4$  (8mg, 0.007mmol) were added, and the mixture was stirred for 2 hours at room temperature. After concentration, the mixture was evaporated in vacuo. The resulting residue was purified by silica-gel column chromatography to give Compound I-59 (60mg, 43%).

LC-MS:  $m/z$  968.5  $[\text{M}+\text{H}]^+$

Elementary analysis:  $\text{C}_{48}\text{H}_{77}\text{N}_3\text{O}_{17}(\text{H}_2\text{O})_{3.5}$

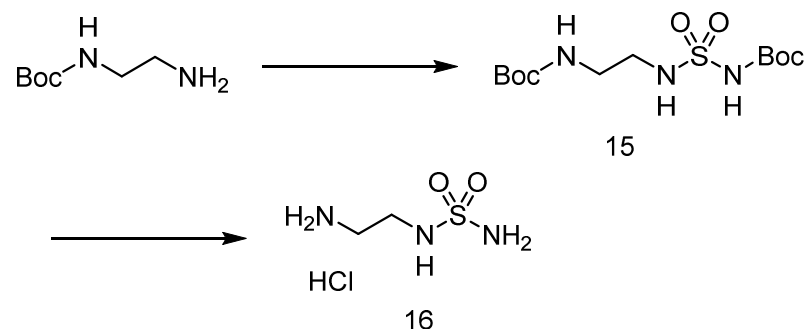
Calculated value: C 55.91; H 8.21; N 4.07 (%)

Actual value: C 55.95; H 8.13; N 4.21 (%)

[0 1 7 9]

Example 8: Synthesis of Compound I-65

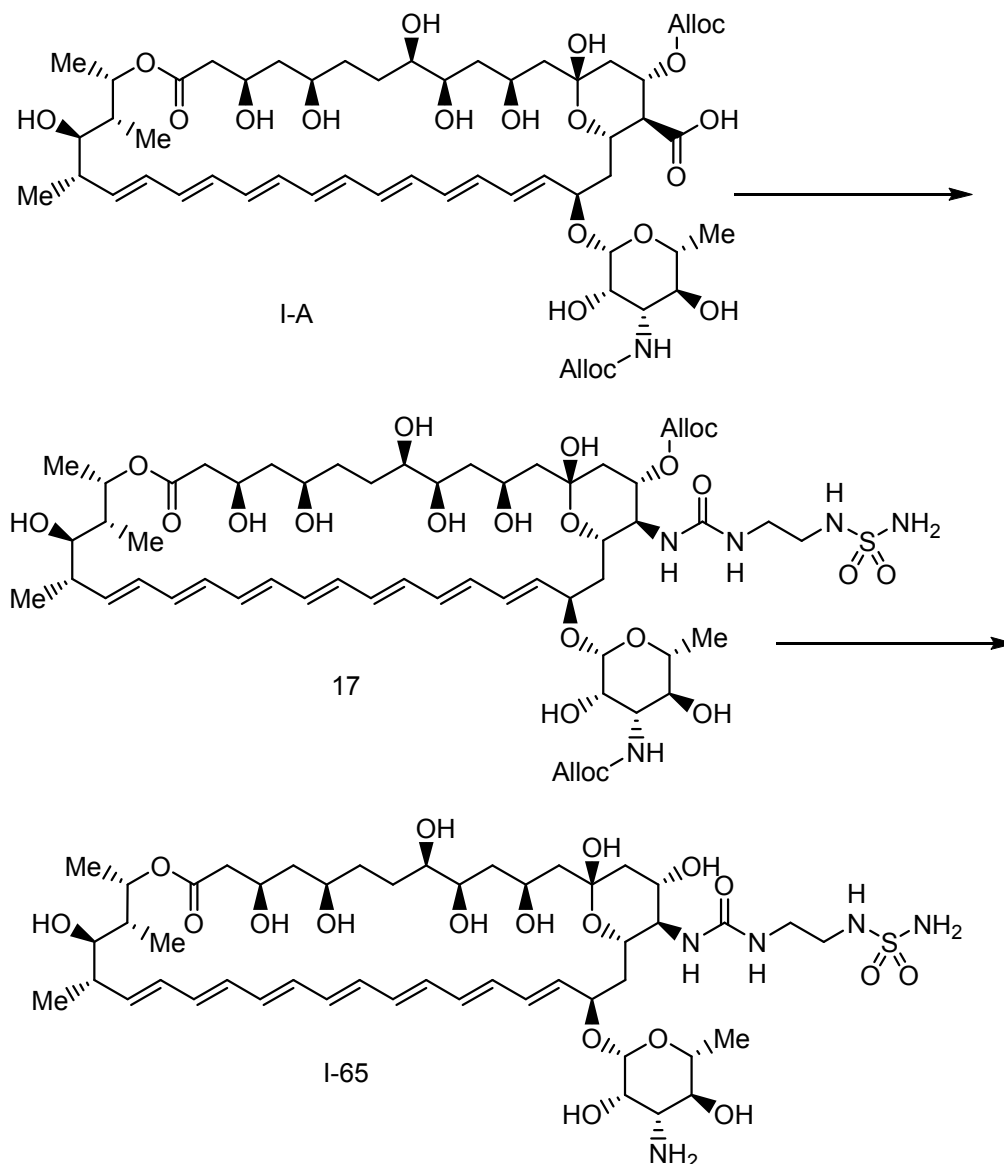
[Chemical Formula 4 6]



Tert-butanol (2.4mL, 24.9mmol) was dissolved into dichloromethane (20mL) and cooled to  $-15^{\circ}\text{C}$ . Chlorosulfonyl isocyanate (2.2mL, 24.9mmol) was added, and the mixture was stirred for 5 minutes at  $-15^{\circ}\text{C}$  as the solution A. The other side, tert-butyl 2-aminoethylcarbamate (2g, 12.5mmol) was dissolved into dichloromethane (20mL) and added triethylamine (1.7mL, 12.5mmol) and cooled to  $-30^{\circ}\text{C}$ . The solution A was added to the reaction mixture, the mixture was stirred for an hour at  $-15^{\circ}\text{C}$  by controlling inside temperature. After the reaction was quenched by saturated ammonium chloride aqueous solution, dichloromethane was removed by evaporating in vacuo, and the mixture was extracted by ethyl acetate. The organic phase was washed with brine and dried over with magnesium sulfate and filtrated. The mixture was condensed and filtrated to give Compound 15 (2.6g, 61%).

Compound 15 was dissolved into dichloromethane (20mL) and added hydrochloric acid-dioxane (4mol/L, 11.5mL, 46mmol), and the mixture was stirred for 4 hours at room temperature. The mixture was condensed to give Compound 16 (1.345g, 7.66mmol).

[Chemical Formula 4 7]



Compound I-A (2.5g, 2.289mmol) was dissolved into DMA (12mL) and added DIEA (0.6mL, 3.43mmol) and diphenylphosphoryl azide (0.74mL, 3.43mmol), and the mixture was stirred for an hour at room temperature, furthermore, stirred for an hour at 50°C. The solution of 2-sulfamoylaminoethylamine hydrochloride (Compound 16, 1.345g, 7.66mmol) and DIEA (1.6mL, 9.16mmol) in DMA was added to the mixture, and the mixture was stirred for 30 minutes at room temperature. The mixture was oil-outed by adding diisopropyl ether and purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5 to 80/20/2) to give Compound 17 (250mg, 9%). Compound 17 (250mg) was dissolved into DMF (3mL) and added morpholine (0.177mL, 2.03mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (24mg, 0.02mmol), and the mixture was stirred for an hour at room temperature. After powderization with diisopropyl ether/methanol (10/1), the resulted residue was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=70/30/3 to 50/50/5) to give Compound I-65 (216mg, 62%).

LC-MS:  $m/z$  1060.5  $[\text{M}+\text{H}]^+$ , 1082.5  $[\text{M}+\text{Na}]^+$

Elementary analysis:  $\text{C}_{49}\text{H}_{81}\text{N}_5\text{O}_{18}\text{S}(\text{H}_2\text{O})_{3.4}(\text{C}_3\text{H}_7\text{NO})_{0.4}$

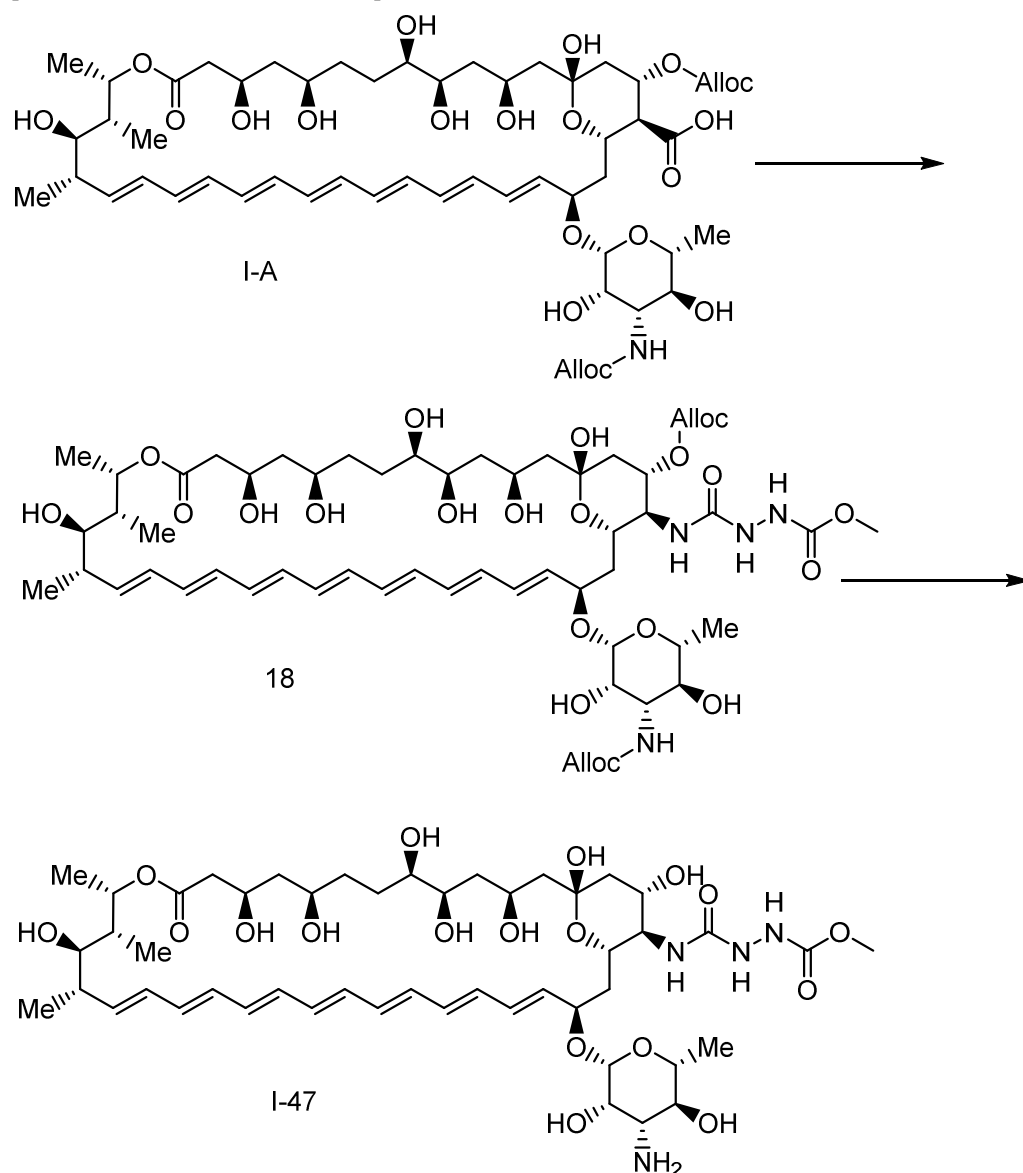
Calculated value: C 52.40; H 7.94; N 6.57; S 2.79 (%)

Actual value: C 52.40; H 7.82; N 6.60; S 2.63 (%)

[0 1 8 0]

## Example 9: Synthesis of Compound I-47

[Chemical Formula 4 8]



Compound I-A (1g, 0.916mmol) is dissolved into DMA (5mL) and added DIEA (0.24mL, 1.37mmol) and diphenylphosphoryl azide (0.295mL, 1.37mmol), and the mixture was stirred for 40 minutes at room temperature, furthermore, stirred for an hour at 50°C. Methoxycarbonylhydrazine (247mg, 2.75mmol) was added, and the mixture was stirred for 2 hours at room temperature. The mixture was oil-outed with diisopropyl ether and purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5 to 80/20/2) to give Compound 18 (311mg, 29%). Compound 18 (311mg, 0.264mmol) was dissolved into DMF (5mL) and added morpholine (0.46mL, 5.2mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (61mg, 0.052mmol), and the mixture was stirred for an hour at room temperature. After powderization with diisopropyl ether/methanol (10/1), the resulted residue was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=70/30/3 to 50/50/5) to give Compound I-47 (89mg, 33%).

LC-MS: m/z 1011.4 [M+H]<sup>+</sup>, 1033.4 [M+Na]<sup>+</sup>

Elementary analysis: (C<sub>49</sub>H<sub>78</sub>N<sub>4</sub>O<sub>18</sub>)(C<sub>3</sub>H<sub>7</sub>NO)(H<sub>2</sub>O)<sub>4</sub>

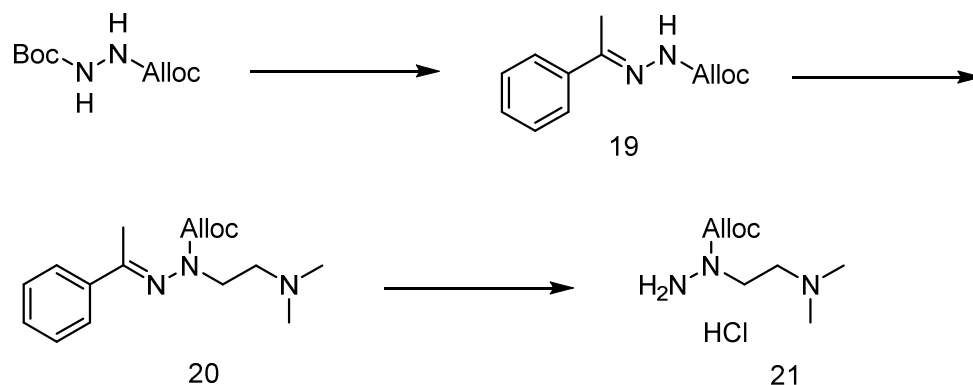
Calculated value: C 54.01; H 8.11; N 6.06 (%)

Actual value: C 54.00; H 8.02; N 6.22 (%)

[0 1 8 1]

### Example 10: Synthesis of Compound I-78

[Chemical Formula 4 9]



#### Step 1 Synthesis of Compound 19

1-Allyl 2-tert-butyl hydrazine-1,2-dicarboxylate (8.06g, 37.3mmol) was dissolved into dichloromethane (100mL) and added hydrochloride-dioxane (4mol/L, 28mL), the mixture was stirred for 4 hours at room temperature. The resulted precipitate was filtrated to give Alloc hydrazine hydrochloride (5.2g, 91%). The resulted Alloc hydrazine hydrochloride (4g, 26.2mmol) was dissolved into ethanol and added acetophenone (4.6mL, 39.3mmol), and the mixture was stirred for 6 hours under heat reflux. After evaporating in vacuo, ethyl acetate and water were added, and the mixture was extracted with ethyl acetate. After the organic phase was washed with saturated sodium hydrogen carbonate aqueous solution, the organic phase was dried out with magnesium sulfate and filtrated and condensed. The resulted solids were washed with hexane to give Compound 19 (3.2g, 56%).

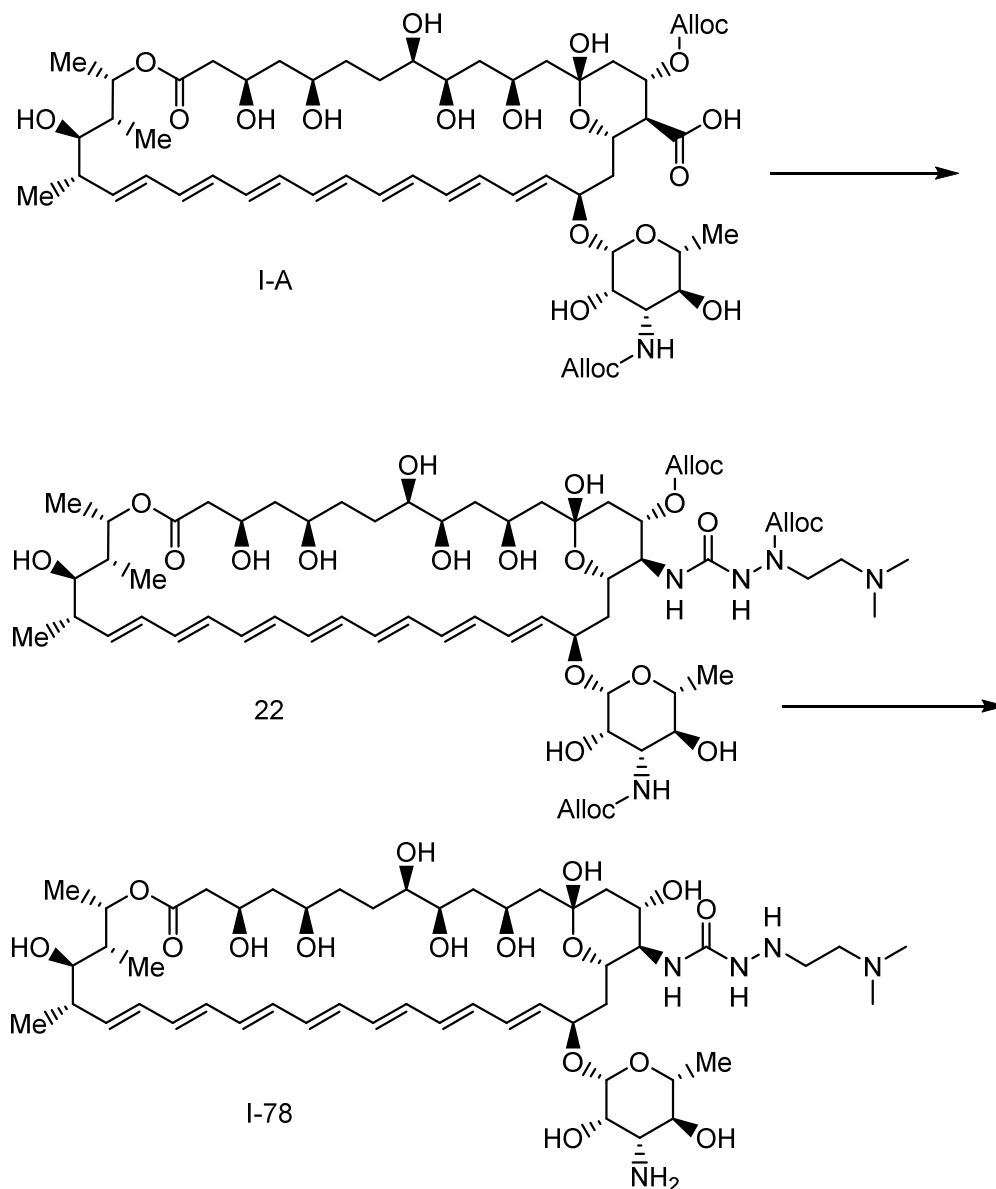
#### Step 2 Synthesis of Compound 20

Compound 19 (1.9g, 8.71mmol) was dissolved into tetrahydrofuran (40mL). After sodium hydride (60%, 3.48g, 87mmol) was added in an ice-water bath, 2-bromoethyldimethylamine (7.94g, 52.2mmol) was added, and the mixture was stirred for 6 days. After the reaction was quenched by adding water, the reaction was extranced with dichloromethane. After the organic phase was washed with brine, the organic phase was dried up with magnesium sulfate and filtrated and condensed. The resulted residue was purified by column chromatography to give Compound 20 (2.17g, 86%).

#### Step 3 Synthesis of Compound 21

Compound 20 (2.16g, 7.46mmol) was dissolved into dichloromethane (10mL) and methanol (2mL) and added hydrochloric acid-dioxane (4mol/L, 5.6mL). After the mixture was stirred, the mixture was condensed. After the resulted residue was dissolved into methanol, the mixture was oil-outed by adding diisopropyl ether to give crude Compound 21 (1.43g). The crude Compound 21 was used to next reaction without purification.

[Chemical Formula 50]



Compound I-A (2g, 1.83mmol) was dissolved into DMA (5mL) and added DIEA (0.48mL, 2.75mmol) and diphenylphosphoryl azide (0.591mL, 2.75mmol), the mixture was stirred for 2 hours 30 minutes at room temperature, furthermore, stirred with heat for 2 hours at 50°C. DIEA (1.92mL, 10.99mmol) and allyl 1-(2-(dimethylamino)ethyl)hydrazine-1-carboxylate hydrochloride 21 (1.43g, 5.49mmol) were added, and the mixture was stirred for 50 minutes at room temperature. The mixture was oil-outed by adding diisopropyl ether. The resulted gummy solids was purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5 to 80/20/2) to give Compound 22 (960mg, 41%). Compound 22 (960mg, 0.752mmol) was dissolved into DMF (10mL) and added morpholine (0.65mL, 7.52mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (87mg, 0.0075mmol), and the mixture was stirred for 90 minutes at room temperature. After powderization with diisopropyl ether, the resulted powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=70/30/3 to 20/80/8) to give Compound I-78 (156mg, 20%). LC-MS: m/z 1024.5 [M+H]<sup>+</sup>

Elementary analysis: C<sub>51</sub>H<sub>85</sub>N<sub>5</sub>O<sub>16</sub>(C<sub>3</sub>H<sub>7</sub>NO)<sub>0.7</sub>(H<sub>2</sub>O)<sub>3.4</sub>

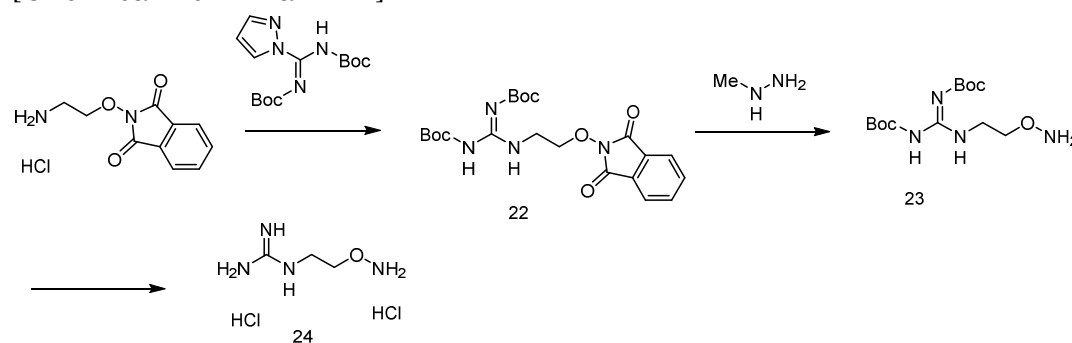
Calculated value: C 56.11; H 8.57; N 7.02 (%)

Actual value: C 56.12; H 8.45; N 7.02 (%)

[0 1 8 2]

### Example 11: Synthesis of Compound I-70

[Chemical Formula 5 1]



#### Step 1 Synthesis of Compound 22

2-(2-Aminoethoxy)isoindoline-1,3-dione hydrochloride (717mg, 2.95mmol) was dissolved into tetrahydrofuran (10mL) and added DIEA (0.542mL, 3.10mmol) and N,N'-Di-Boc-1H-pyrazole-1-carboxamidine (963mg, 3.10mmol), the mixture was stirred for 30 minutes at room temperature. After adding DMF (10mL), the mixture was stirred for 20 hours, further, stirred for 3 hours 40 minutes at 60°C. The reaction was quenched with saturated sodium bicarbonate aqueous solution, and the mixture was extracted with ethyl acetate. The organic phase was washed with water and brine, and dried up with sodium sulfate anhydrous and filtrated and condensed. The resulted residue was purified by silica-gel column chromatography (hexane/ethyl acetate=3/1) to give Compound 22 (856mg, 65%, white frothy solid).

TLC: Rf= 0.3 (hexane/ethyl acetate=3/1)

#### Step 2 Synthesis of Compound 23

Compound 22 (427mg, 0.952mmol) was dissolved into dichloromethane (5mL) and added methylhydrazine (0.053mL, 1.00mmol), and the mixture was stirred for 4 hours 40 minutes at room temperature. After the resulted white solids were removed by filtration, the resulted filtrate was condensed to give white oily liquid. The resulted liquid was purified by silica-gel column chromatography (hexane/ethyl acetate=3/1 to 1/1) to give Compound 23 (180mg, 59%, colorless and transparent liquid).

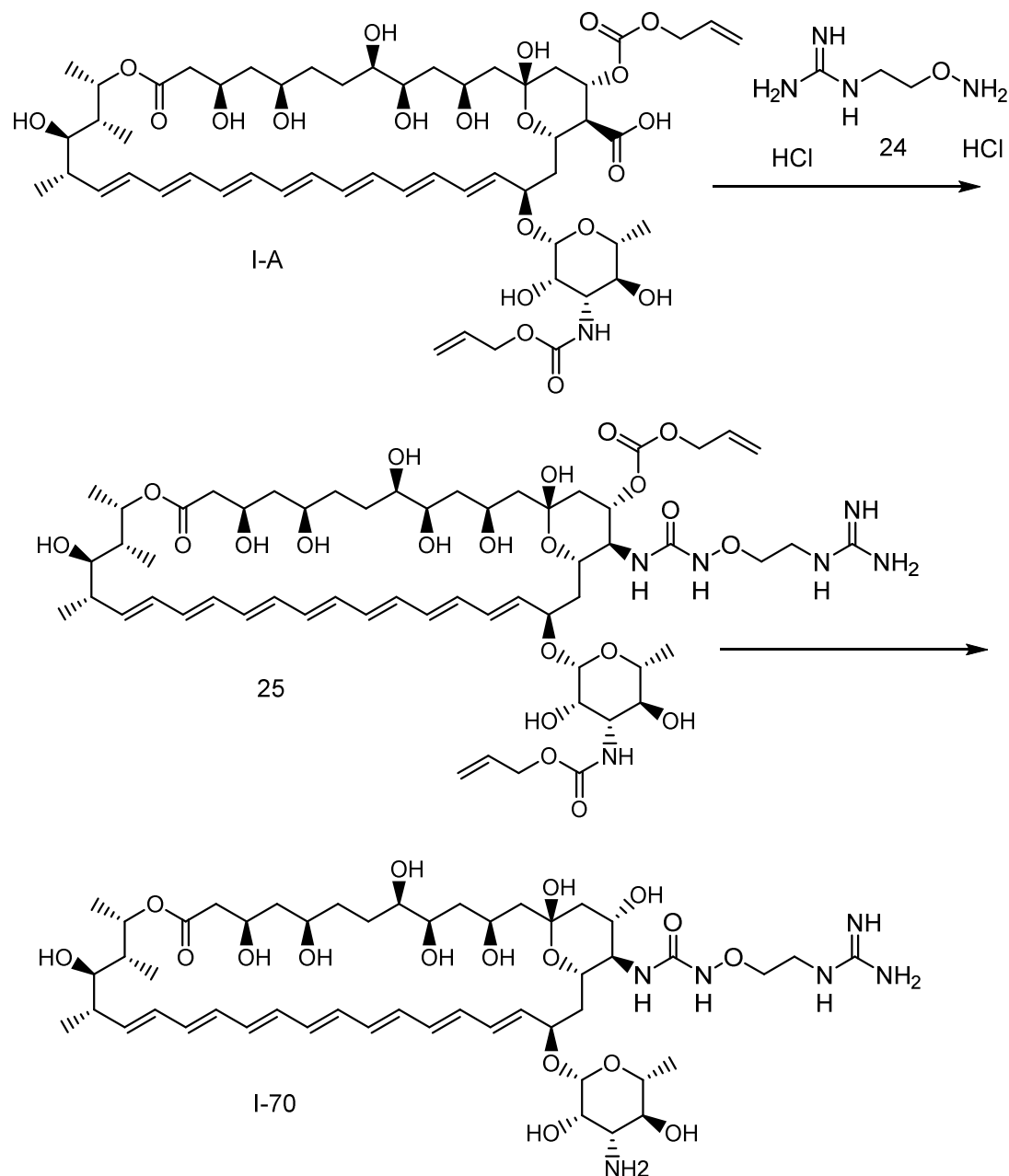
TLC: Rf=0.3 (hexane/ethyl acetate=1/1)

LC-MS: 319.4 [M+H]<sup>+</sup>

#### Step 3 Synthesis of Compound 24

Compound 23 (180mg, 0.565mmol) was dissolved into hydrochloric acid-dioxane (4mol/L, 1.4mL), and the mixture was stirred for an hour 40 minutes at room temperature. After confirming disappearance of raw materials by TLC, the solvent was removed by evaporating in vacuo. The resulted gummy solids were washed with hexane and dried up in vacuo to give Compound 24 (182mg). The compound 24 was used to next reaction without purification.

[Chemical Formula 5 2]



### Step 1 Synthesis of Compound 25

Compound I-A (500mg, 0.458mmol) was dissolved into DMF (2mL) and added DIEA (0.088mL, 0.504mmol) and diphenylphosphoryl azide (0.108mL, 0.504mmol), the mixture was stirred for 90 minutes at room temperature, further, stirred for 30 minutes at 50°C. DIEA (0.088mL, 0.504mmol) and 2-guanidinyloxyamine dihydrochloride (Compound 24, 163mg, 0.504mmol) were added, the mixture was stirred for an hour 40 minutes at 50°C. The mixture was oil-outed by adding diisopropyl ether and dried up by evaporating in vacuo. The resulted residue was purified by silica-gel column chromatography (chloroform/methanol/water=90/10/1 to 85/15/1.5) to give Compound 25(209mg, 38%).

LC-MS:  $m/z$  1208.6  $[M+H]^+$

### Step 2 Synthesis of Compound I-70

Compound 25 (200mg, 0.166mmol) was dissolved into DMF (5mL) and morpholine (0.10mL, 1.16mmol) and  $Pd(PPh_3)_4$  (19.1mg, 0.017mmol) were added, and the mixture was stirred for 2 hours at room temperature. After powderization with

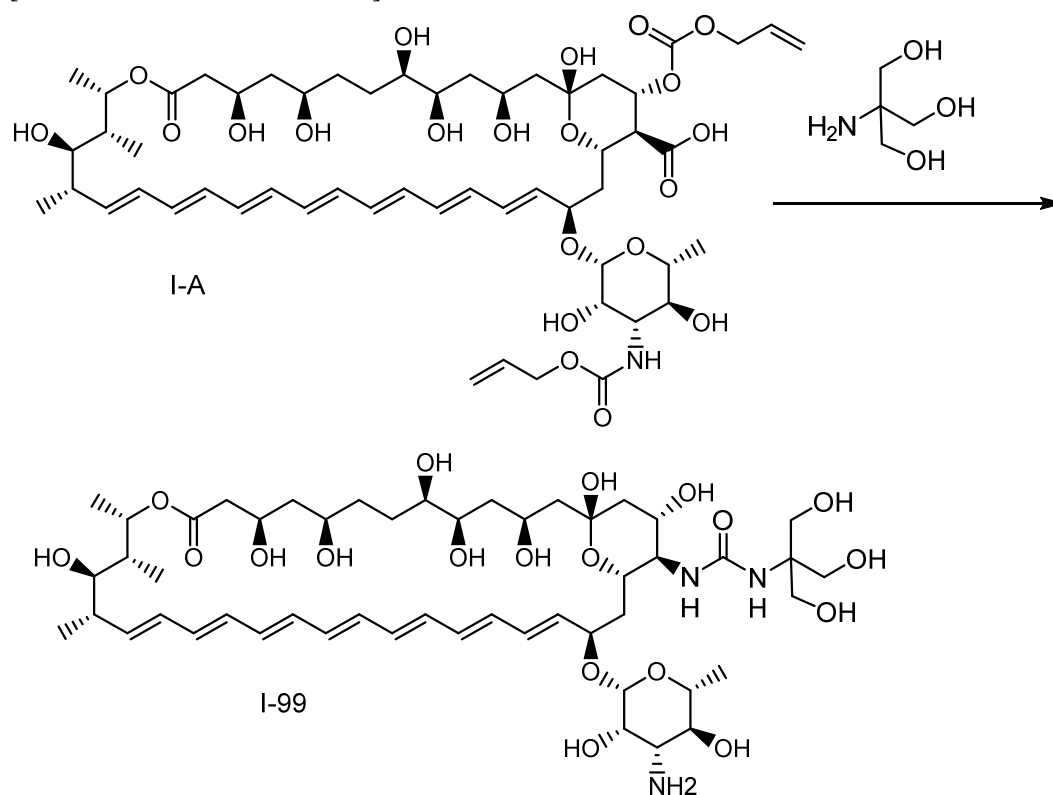
diisopropyl ether, the resulted residue was purified by reverse-phase chromatography (HP20ss, acetonitrile/aqueous solution containing 0.05% formic acid=10/90 to 30/70) to give Compound I-70 (37mg, 21%).

LC-MS:  $m/z$  1039.5  $[M+H]^+$

[0 1 8 3]

#### Example 12: Synthesis of Compound I-99

[Chemical Formula 5 3]



Compound I-A (1g, 0.916mmol) was dissolved into DMF (8mL) and added DIEA (0.24mL, 1.373mmol) and diphenylphosphoryl azide (0.295mL, 1.373mmol), and the mixture was stirred for 2 hours at room temperature. 2-amino-2-(hydroxymethyl)propane-1,3-diol (222mg, 1.831mmol) was added, and the mixture was stirred for 30 minutes at 50 °C. The mixture was oil-outed by adding diisopropyl ether, and the resulted residue was dried out by evaporating in vacuo. The resulted residue was purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3) to give yellow powder (262mg, 24%).

LC-MS:  $m/z$  1211.2  $[M+H]^+$

The resulted yellow powder was dissolved into DMF (5mL) and morpholine (0.19mL, 2.17mmol) and  $Pd(PPh_3)_4$  (25mg, 0.022mmol) were added, and the mixture was siterred for an hour at room temperature. After powderiation with diisopropyl ether, the resulted powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=60/40/4) to give Compound I-99 (110mg, 48%).

LC-MS:  $m/z$  1042.5  $[M+H]^+$

Elementary analysis:  $(C_{51}H_{83}N_3O_{19})(C_3H_7NO)0.9(H_2O)_2$

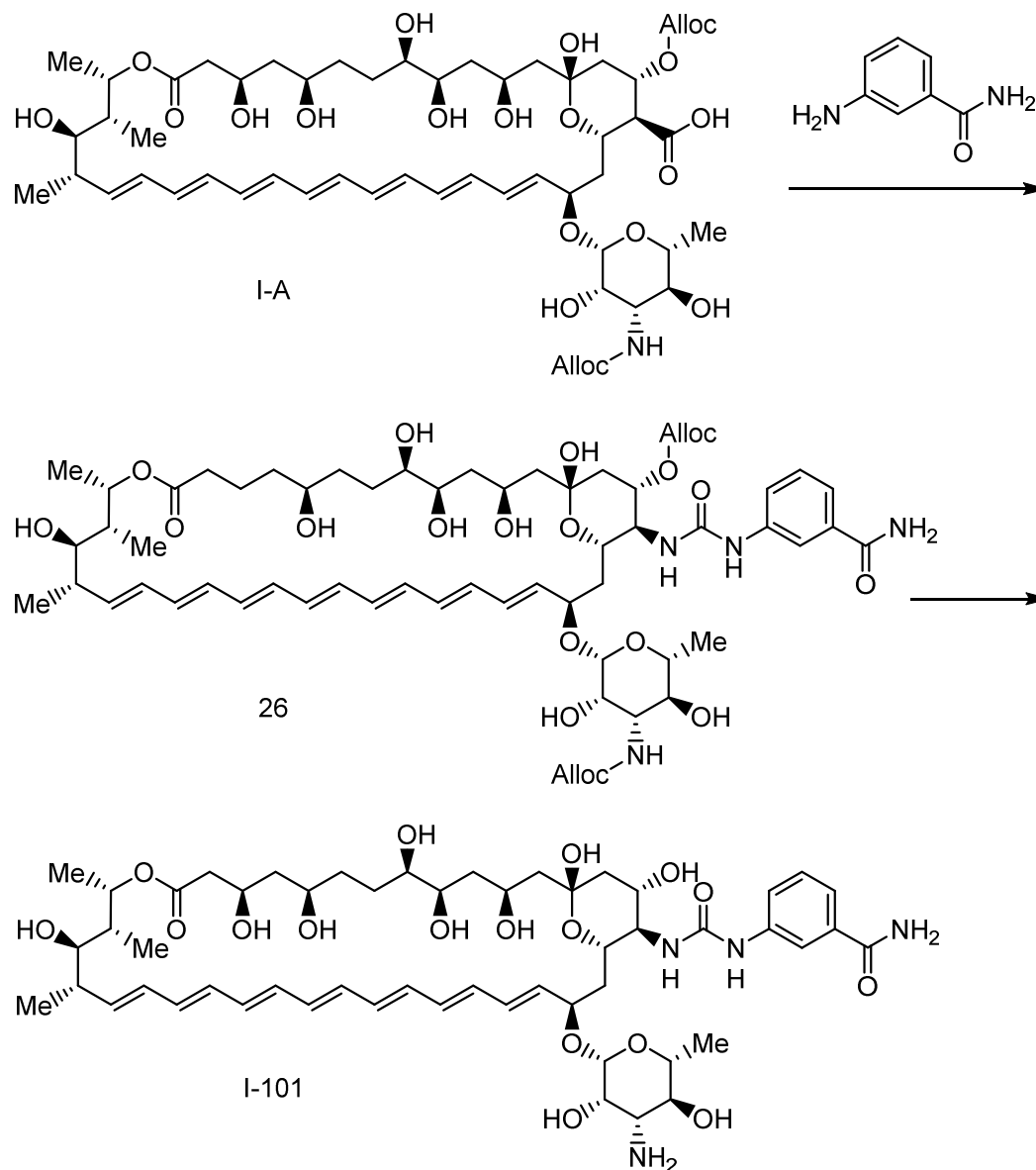
Calculated value: C 56.38; H 8.22; N 4.77 (%)

Actual value: C 56.16; H 8.22; N 5.08 (%)

[0 1 8 4]

#### Example 13: Synthesis of Compound I-101

[Chemical Formula 5 4]



Compound I-A (1g, 0.916mmol) was dissolved into DMA (5mL) and added DIEA (0.24mL, 1.37mmol) and diphenylphosphoryl azide (0.295mL, 1.37mmol), and the mixture was stirred for an hour at room temperature, further stirred for 2 hours at 50 °C. 3-Aminobenzamido (374mg, 2.753mmol) and Bis tributyltin oxide (0.465mL, 0.915mmol) were added, and the mixture was stirred for 2 hours. The resulted residue by decantation adding diisopropyl ether was purified by silica-gel column chromatography (CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O=80/20/2) to give Compound 26 (160mg, 14%). Compound 26 (160mg, 0.131mmol) was dissolved into DMF (5mL) and added morpholine (0.114mL, 1.31mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (15mg, 0.013mmol), and the mixture was stirred for 20 minutes at room temperature. After powderization by adding diisopropyl ether, the resulted powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=90/10/1 to 70/30/3) to give Compound I-101 (59mg, 43%).

LC/MS: m/z 1057.6 [M+H]<sup>+</sup>

Elementary analysis: C<sub>54</sub>H<sub>80</sub>N<sub>4</sub>O<sub>17</sub>(C<sub>3</sub>H<sub>7</sub>NO)<sub>0.4</sub>(H<sub>2</sub>O)<sub>3.7</sub>

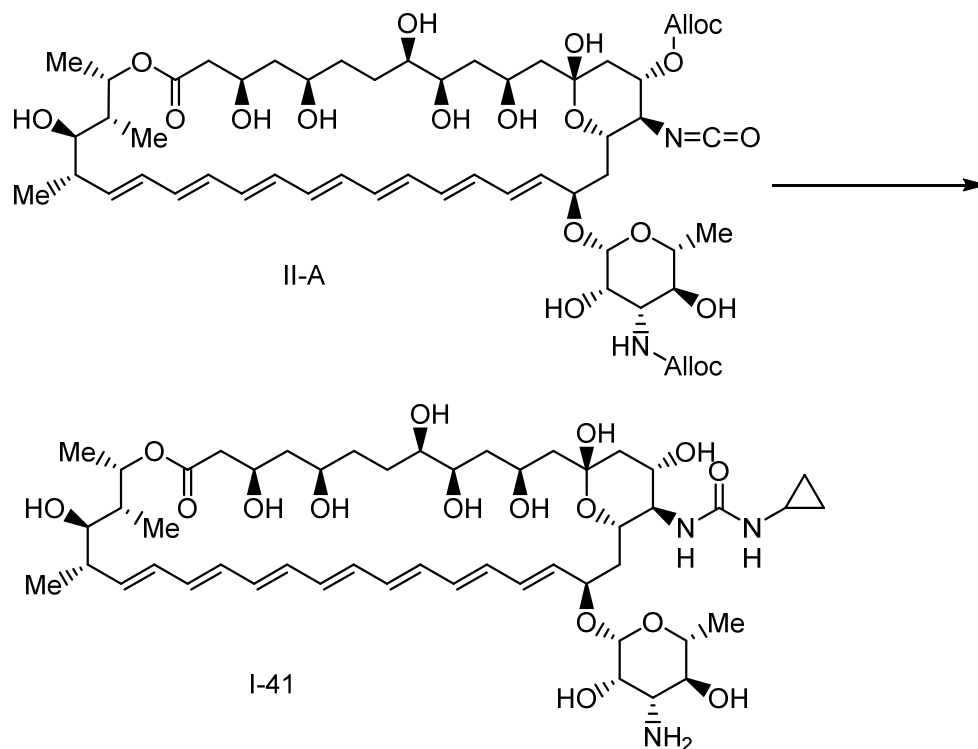
Calculated value: C 57.50; H 7.88; N 5.34 (%)

Actual value: C 57.46; H 7.83; N 5.37 (%)

[ 0 1 8 5 ]

## Example 14: Synthesis of Compound I-41

[Chemical Formula 5 5]



Compound II-A (3g, 2.75mmol) was dissolved into DMF (10mL) and added cyclopropanamine (157mg, 2.75mmol), the mixture was stirred for 2 hours at room temperature. The mixture was oil-outed with diisopropyl ether. The resulted residue was purified by silica-gel column chromatography (chloroform/methanol=70/30) to give Compound 14 (1g, 31%). Compound 14 (1g) was dissolved into DMF (5mL) and added morpholine (0.76mL, 8.72mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (50mg, 0.044mmol), the mixture was stirred for an hour at room temperature. After powderization by adding diisopropylether/methanol (10/1), the resulted powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=70/30/3 to 30/70/7) to give Compound I-41 (159mg, 19%). LC-MS:  $m/z$  978.3  $[\text{M}+\text{H}]$ , 1000.4  $[\text{M}+\text{Na}]$ +

Elementary analysis:  $\text{C}_{50}\text{H}_{79}\text{N}_3\text{O}_{16}(\text{C}_3\text{H}_7\text{NO})_{0.7}(\text{H}_2\text{O})_{2.2}$ ,  $[\text{C}_{52.1}\text{H}_{88.3}\text{N}_{3.7}\text{O}_{18.9}]$   
FW: 1068.97

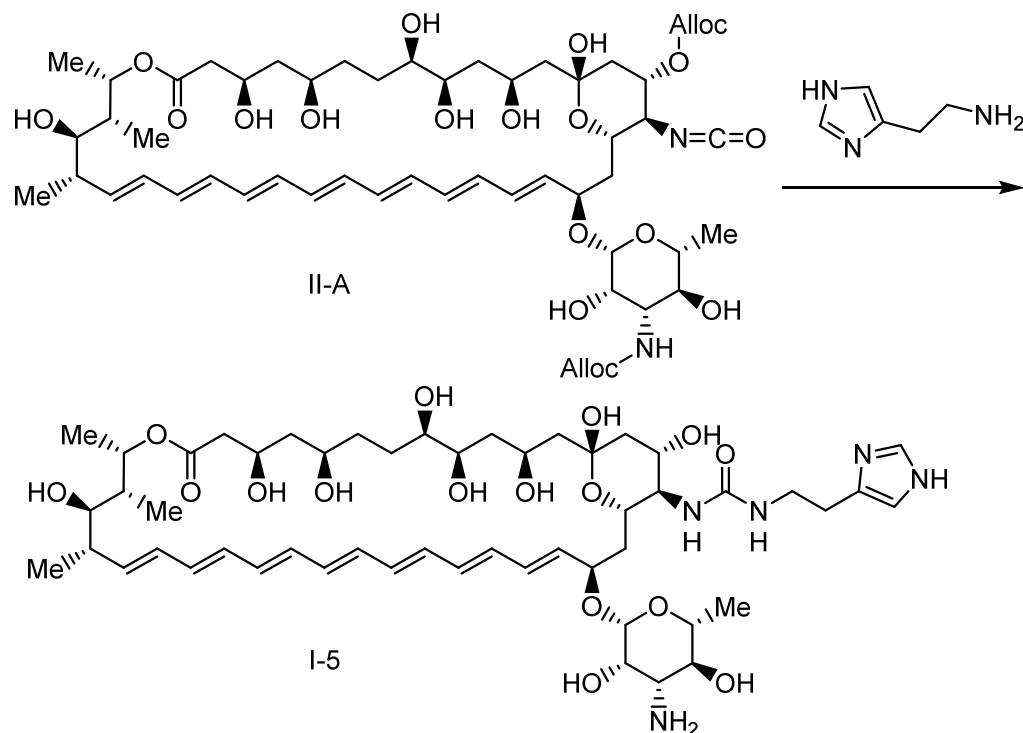
Calculated value: C 58.54; H 8.33; N 4.85 (%)

Actual value: C 58.52; H 8.25; N 4.83 (%)

[ 0 1 8 6 ]

## Example 15: Synthesis of Compound I-5

[Chemical Formula 5 6]



Compound II-A (6g, 5.5mmol) was dissolved into DMA and added histamine (918mg, 8.26mmol), and the mixture was stirred for a few hours at room temperature. After the mixture was oil-outed with diisopropyl ether, the resulted residue was purified by silica-gel column chromatography. The resulted powder (1.12g) was dissolved into DMA (8mL) and added morpholine (0.81mL, 9.3mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (54mg, 0.047mmol), and the mixture was stirred for 20 minutes under nitrogen atmosphere. After powderization, the resulted residue was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water) to give Compound I-5 (370mg, 6%).

LC-MS:  $m/z$  1032.5  $[\text{M}+\text{H}]^+$

Elementary analysis:  $\text{C}_{52}\text{H}_{81}\text{N}_5\text{O}_{16}(\text{C}_3\text{H}_7\text{NO})_{0.2}(\text{H}_2\text{O})_{2.5}$

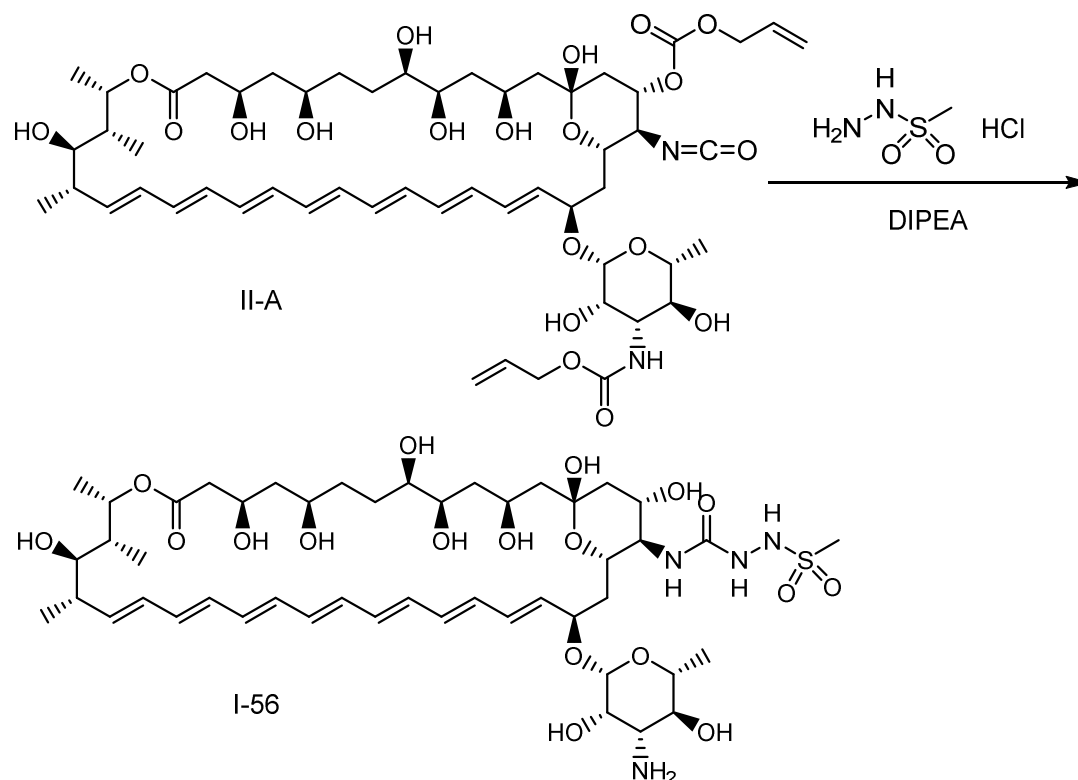
Calculated value: C 57.86; H 8.07; N 6.67 (%)

Actual value: C 57.87; H 8.07; N 6.71 (%)

[0 1 8 7]

Example 16: Synthesis of Compound I-56

[Chemical Formula 5 7]



Compound II-A (13.1g, 12.03mmol) was dissolved into DMF (65mL) and added methanesulfonylhydrazine hydrochloride (2.645g, 18.04mmol) and DIEA (6.3mL, 36.1mmol), and the mixture was stirred for 4 hours 25 minutes at room temperature. After the mixture was oil-outed with diisopropyl ether, the resulted residue was purified by silica-gel column chromatography (chloroform/methanol/water) to give yellow powder (1.05g, 0.875mmol). The yellow powder was dissolved into DMF (10mL) and added morpholine (0.53mL, 6.13mmol) and  $\text{Pd(PPh}_3)_4$  (51mg, 0.044mmol), and the mixture was stirred for 2 hours at room temperature. After the mixture was powderization with diisopropyl ether, the mixture was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=50/50/5) to give Compound I-56 (284mg, 0.062mmol).

LC-MS:  $m/z$  1031.5  $[\text{M}+\text{H}]^+$

Elementary analysis:  $\text{C}_{48}\text{H}_{78}\text{N}_4\text{O}_{18}\text{S} (\text{C}_3\text{H}_7\text{NO})_{0.1}(\text{H}_2\text{O})_{1.5}$

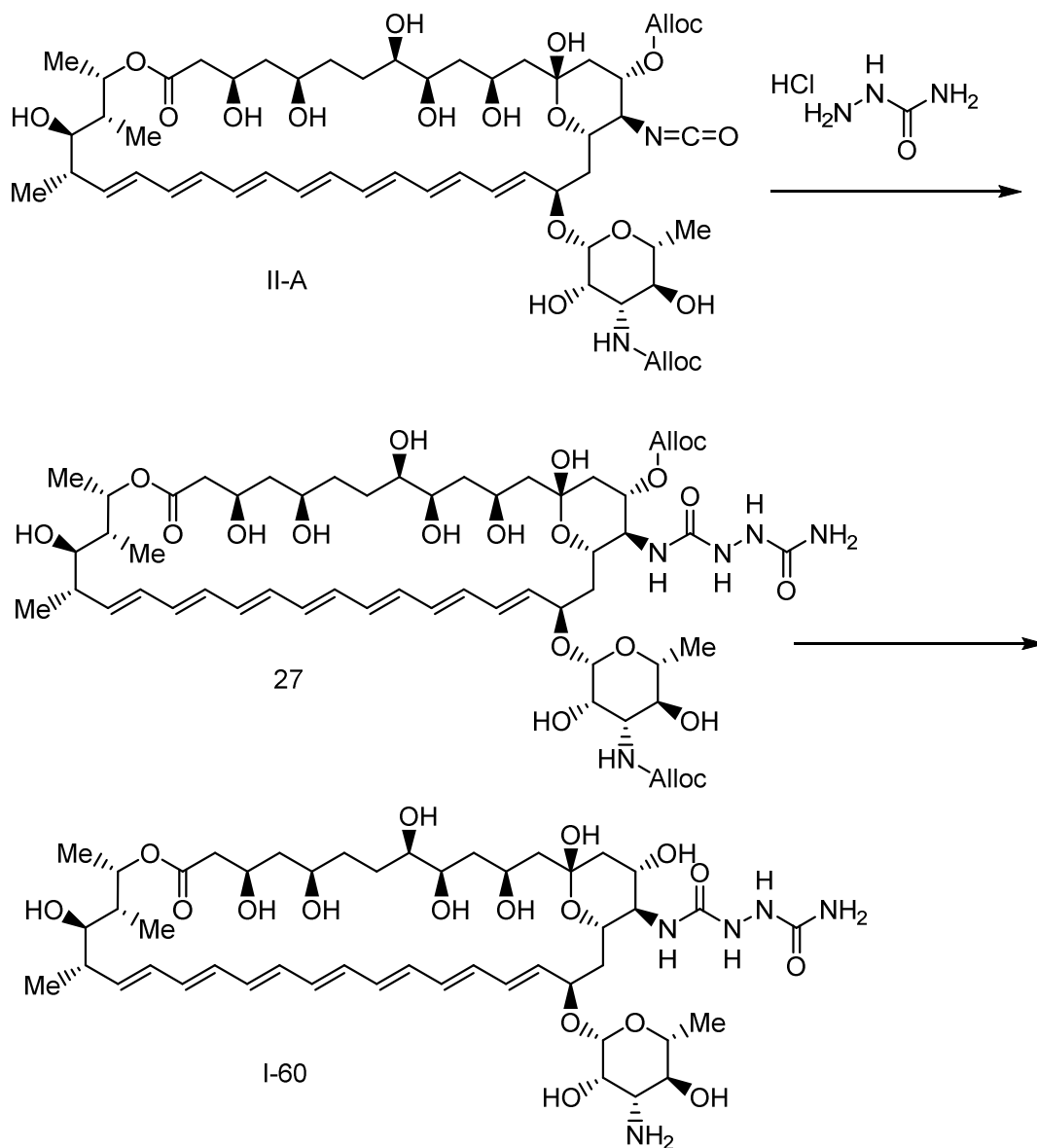
Calculated value: C 54.44; H 7.73; N 5.39 (%)

Actual value: C 54.46; H 7.69; N 5.37 (%)

[0 1 8 8]

Example 17: Synthesis of Compound I-60

[Chemical Formula 5 8]



Compound II-A (17.8g, 16.3mmol) was dissolved into DMA (54mL) and added DIEA (4.3mL, 24.5mmol) and hydrazinecarboxamide hydrochloride (1.82g, 16.3mmol), and the mixture was stirred for an hour at room temperature. After the mixture was oil-outed with diisopropyl ether, the resulted residue was purified by silica-gel column chromatography (chloroform/methanol=92/8 to 70/30) to give Compound 27 (5.56g, 19%). Compound 27 (5.56g, 4.78mmol) was dissolved into DMF (30mL) and added morpholine (2.5mL, 28.7mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (166mg, 0.143mmol), the mixture was stirred for 30 minutes at room temperature. After the mixture was powderization with diisopropyl ether/methanol (10/1), the mixture was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=70/30/3 to 50/50/5) to give Compound I-60 (1.85g, 4%).

LC/MS:m/z 996.5  $[\text{M}+\text{H}]^+$

Elementary analysis:  $\text{C}_{48}\text{H}_{77}\text{N}_5\text{O}_{17}(\text{H}_2\text{O})_{4.4}$ ,

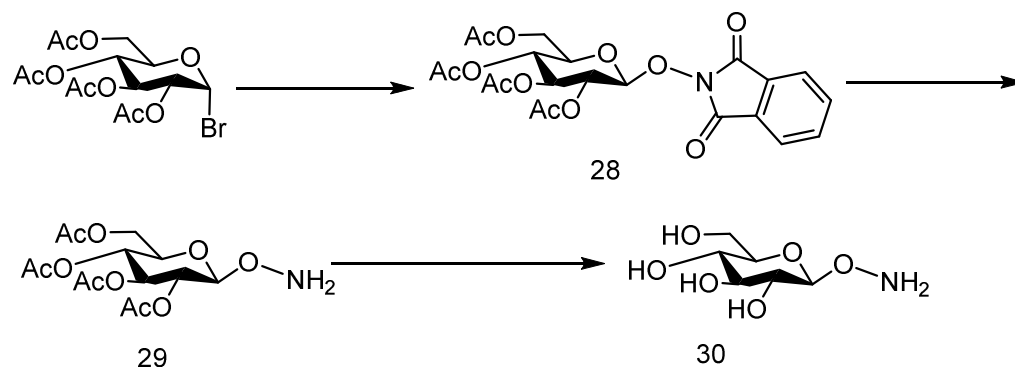
Calculated value: C 53.61; H 8.04; N 6.51 (%)

Actual value: C 53.60; H 8.07; N 6.59 (%)

[0 1 8 9]

Example 18: Synthesis of Compound I-74

[Chemical Formula 5 9]



### Step 1 Synthesis of Compound 28

2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosylbromide (5.346g, 13mmol) was dissolved into dichloromethane (100mL) and added tetrabutyl ammonium hydrogen sulfate (4.11g, 13mmol) and further added the solution N-hydroxyphthalimide (10.6g, 65mmol) dissolved into sodium carbonate aqueous solution (1mmol/L, 100mL). The mixture was stirred for 20 hours at room temperature. After the obtained organic phase by extracting with dichloromethane was washed with saturated sodium bicarbonate aqueous solution and burine, the mixture was dried up with sodium sulfate anhydrous and filtrated and condensed. The resulted residue was purified by silica-gel column chromatography (dichloromethane/ethyl acetate=9/1) to give 2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyloxypthalimide, Compound 28 (980mg, white foamy solids).

TLC: Rf= 0.5(dichloromethane/ethyl acetate=9/1)

### Step 2 Synthesis of Compound 29

Compound 28 (872mg, 1.767mmol) was dissolved into methanol (18mL) and added hydrazine monohydrate (0.086mL, 1.767mmol). After the mixture was stirred for 20 minutes at room temperature, the mixture was condensed. After ethyl acetate was added and impurities were removed, the filtrate was condensed. The resulted residue was purified by silica-gel column chromatography (hexane/ethyl acetate=1/2) to give 2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyloxyamine, Compound 29 (516mg, white foamy solids, 80%).

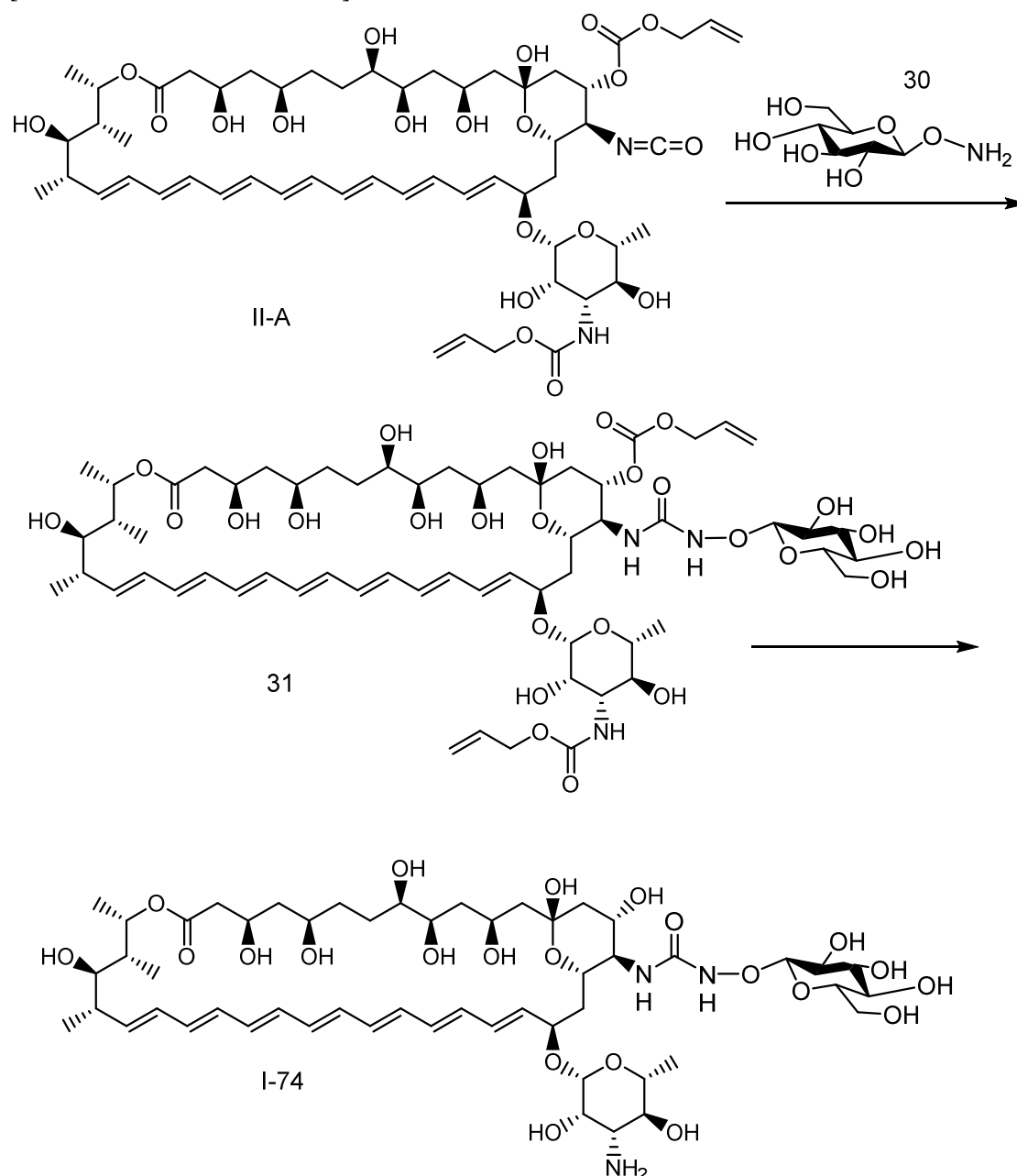
TLC: Rf= 0.4(hexane/ethyl acetate=1/2)

$^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 75MHz)  $\delta$ : 170.3, 169.8, 169.2, 169.1, 134.4, 123.7, 103.1, 72.7, 71.6, 69.5, 68.1, 61.6, 20.7, 20.6, 20.5.  $^1\text{H}$ -NMR( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 6.1-5.8 (br, 2H), 5.4-6.0 (m, 3H), 4.72 (d, 1H, J=8.1Hz), 4.4-4.0 (m, 2H), 3.8-3.6 (d, 1H), 2.1-2.0 (m, 12H).

### Step 3 Synthesis of Compound 30

Compound 29 (508mg, 1.398mmol) was dissolved into methanol (14mL) and added sodium methoxide (1mol/L, 0.22mL), and the mixture was stirred for 3 hours at 0 °C. Amberlite IR-120 was added and the reaction was quenched by neutralization. Water was added, and the mixture was filtrated. The resulted filtrate was condensed and lyphlized to give Compound 30 (229mg, light yellow solids, 80%).  $^1\text{H}$ -NMR( $\text{D}_2\text{O}$ , 300MHz)  $\delta$ : 7.58 (br, 2H), 4.21 (d, 1H, J=8.1Hz), 3.7-2.9 (m, 6H).

[Chemical Formula 60]



### Step 1 Synthesis of Compound 31

Compound II-A (10.5g, 9.64mmol) was dissolved into DMA (60mL), and DIEA (5.05mL, 28.9mmol) was added. Separately, the solution which β-glucose-1-oxyamine (Compound 30) (2.258g, 11.57mmol) was dissolved to water (10mL) and DMA (5mL) was prepared, and the prepared solution was added to the reaction mixture. The reaction mixture was stirred for an hour at room temperature, further stirred for 25 minutes at 40 °C. After the mixture was oil-outed with diisopropyl ether, the resulted residue was purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5 to 85/15/1.5) to give Compound 31 (2.43g, 19%). LC-MS: 1306.5 [M+H<sup>+</sup>]

### Step 2 Synthesis of Compound I-74

Compound 16 (2.43g, 1.892mmol) was dissolved into DMF (30mL) and added morpholine (1.65mL, 18.9mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (219mg, 0.189mmol), and the mixture was stirred for 3 hours at room temperature. After powderization by adding diisopropyl ether, the resulted powder was purified by silica-gel column

chromatography (chloroform/methanol/water=85/15/1.5 to 30/70/7). The obtained fractions was condensed and lyophilized to give Compound I-74 (818mg, 39%).

LC/MS:  $m/z$  1116.5  $[M+H]^+$

Elementary analysis:  $(C_{53}H_{85}N_3O_{22})(H_2O)_{2.3}$

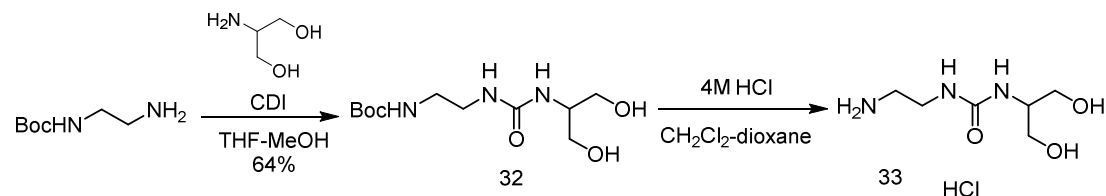
Calculated value: C 54.99; H 7.80; N 3.63 (%)

Actual value: C 55.01; H 7.88; N 3.48 (%)

[0 1 9 0]

Example 19: Synthesis of Compound I-164

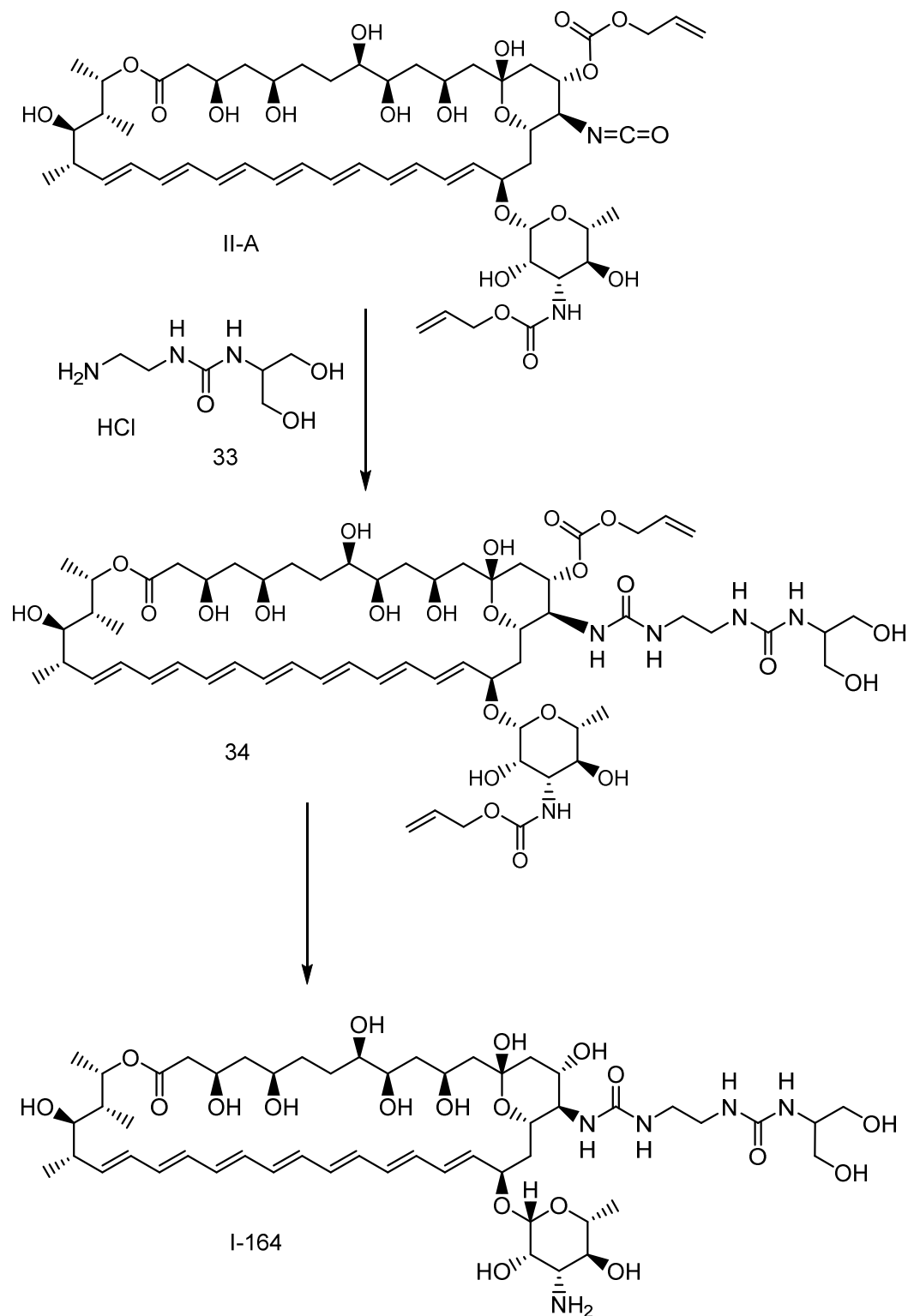
[Chemical Formula 6 1]



1,1'-Carbonyldiimidazole (1.316g, 8.11mmol) was dissolved into tetrahydrofuran (10mL). After tert-buthyl 2-aminoethylcarbamate (0.984mL, 6.24mmol) was added, the methanol (2mL) solution including 2-aminopropane-1,3-diol (0.569g, 6.24mmol) was added to the mixture, and the mixture was stirred for an hour at 50 °C, further stirred for an hour at 65 °C. After concentration, the mixture was purified by silica-gel column chromatography to give Compound 32 (1.1g, 64%). Compound 32 (1.1g, 3.97mmol) was dissolved into methanol (10mL) and added hydrochloric acid-dioxane (4mmol/L, 16mL), and the mixture was stirred for 2 hours. The mixture was condensed to give Compound 33 (1.09g). Compound 33 was used to next reaction without purification.

<sup>1</sup>H-NMR(D<sub>2</sub>O, 300MHz)δ:3.9-3.7 (m, 1H), 3.7-3.5 (m, 4H), 3.4-3.35(m, 2H),3.34(s, 2H), 3.15-3.05 (m, 2H).

[Chemical Formula 6 2]



Compound II-A (1.5g, 1.377mmol) was dissolved into DMF (5mL) and added DIEA (0.481mL, 2.75mmol) and 1-(2-aminoethyl)-3-(1,3-dihydroxypropane-2-yl)urea hydrochloride (Compound 33) (294mg, 1.377mmol), and the mixture was stirred for 30 minutes. After powderization by adding diisopropyl ether, the resulted powder was purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5 to 85/15/1.5) to give Compound 34 (450mg, 26%). Compound 34 (450mg, 0.355mmol) was dissolved into DMF (2.5mL) and added morpholine (0.31mL, 3.55mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (21mg, 0.018mmol), and the mixture was stirred for 40 minutes at room

Elementary analysis: C53H87N5O19(C3H7NO)0.5(H2O)2.4

Actual value: C 55.55; H 8.07; N 6.56 (%)

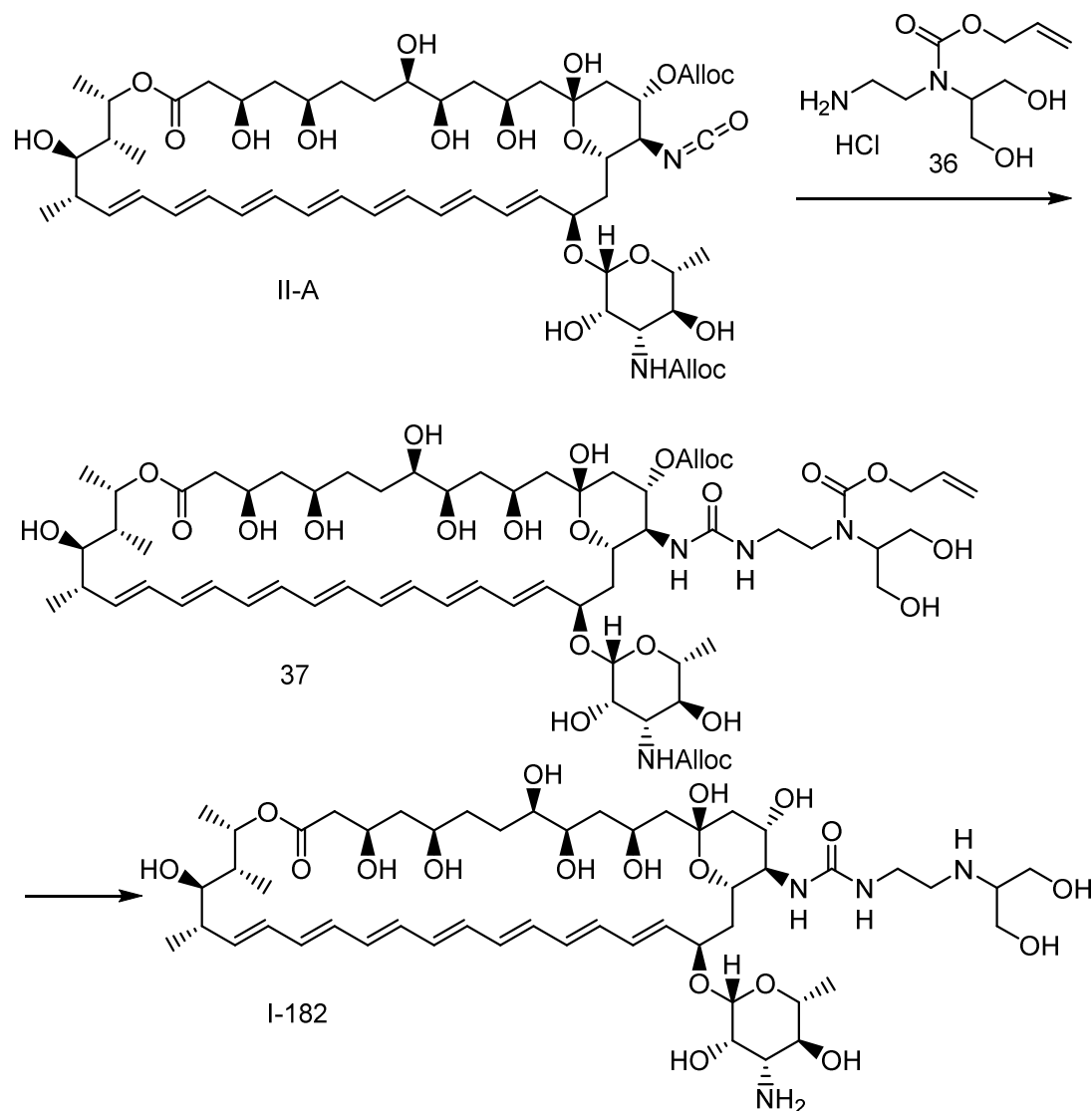
### Example 20: Synthesis of Compound I-182

2,2-dimethyl-1,3-dioxane-5-one (1g, 7.68mmol) was dissolved into dichloromethane (50mL) and added tert-buthyl 2-aminoethylcarbamate (1.354g, 8.45mmol) and sodium triacetoxyborohydride (2.117g, 9.99mmol), and the mixture was stirred for 2 hours 40 minutes at room temperature. N-(allyloxycarbonyloxy)succinimide (2.469g, 12.4mmol) and DIEA (6.71mL, 38.4mmol) was added, the mixture was stirred at room temperature. After water was added and the reaction was quenched, the mixture was extracted with dichloromethane. The resulted residue was purified by silica-gel column chromatography (hexane/ethyl acetate=50/50 to 10/90) to give Compound 35 (2.45g, colorless liquid, 89%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, 300MHz)δ:6.1-5.9 (m, 1H), 5.4-5.2 (m, 2H), 4.7-4.6 (m, 2H), 4.2-3.9 (m, 4H), 3.7-3.5(br, 2H), 3.4-3.3 (br, 2H), 1.5-1.3(m, 15H)

Compound 35 (2.45g, 6.84mmol) was dissolved into dichloromethane (30mL) and hydrochloric acid-dioxane (4mol/L, 10.25mL, 41mmol) was added, and the mixture was stirred for 4 hours at room temperature. The mixture was condensed to give Compound 36 (1.7g). Compound 36 was used to next reaction without purification.

[Chemical Formula 6 4]



Compound II-A (1g, 0.918mmol) was dissolved into DMF (5mL), and DIEA (0.64mmol) and Compound 36 (234mg, 0.918mmol) were added. The mixture was stirred for an hour at room temperature. After powderization by adding diisopropyl ether, the resulted powder was purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5) to give Compound 37 (240mg, 10%).

Compound 37 (240mg, 0.184mmol) was dissolved into DMF (3mL) and added morpholine (0.24mL, 2.75mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (11mg, 0.009mmol), and the mixture was stirred for 20 minutes at room temperature. After powderization by adding diisopropyl ether, the resulted powder was purified by silica-gel column chromatography (chloroform/methanol/water=50/5/5 to 20/80/8). The obtained fractions were condensed and lyophilized to give Compound I-182 (67mg, 26%).

LC/MS:  $m/z$  1055.6  $[\text{M}+\text{H}]^+$ , 1077.6  $[\text{M}+\text{Na}]^+$

Elementary analysis:  $\text{C}_{52}\text{H}_{86}\text{N}_4\text{O}_{18}(\text{H}_2\text{O})_{3.0}$

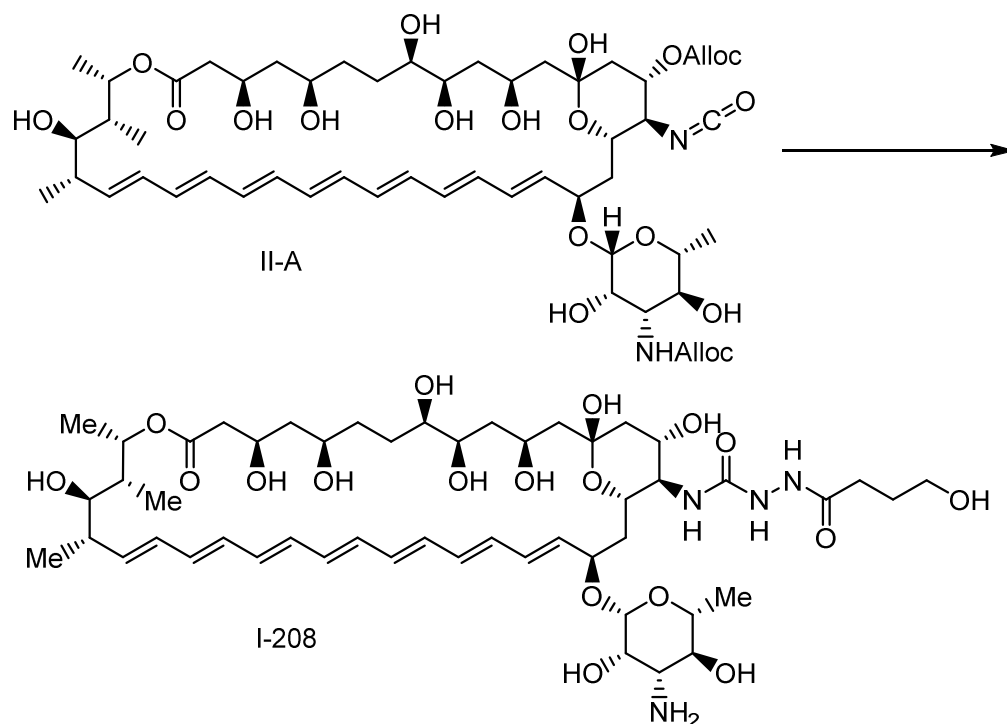
Calculated value: C 56.30; H 8.36; N 5.05 (%)

Actual value: C 56.35; H 8.36; N 4.84 (%)

[0 1 9 2]

Example 21: Synthesis of Compound I-208

[Chemical Formula 6 5]



Compound II-A (1.32g, 1.21mmol) was dissolved into DMA (5mL) and added DIEA (0.42mL, 2.42mmol) and 4-hydroxybutanehydrazide (143mg, 1.21mmol), and the mixture was stirred for an hour 20 minutes at room temperature. The mixture was purified by silica-gel column chromatography. The resulted solids (200mg, 0.166mmol) was dissolved into DMF (3mL) and added morpholine (0.144mL, 1.657mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (9.5mg, 0.0082mmol), and the mixture was stirred for 15 minutes at room temperature. The mixture was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=90/10/1 to 50/50/5) to give Compound I-208 (61mg, 5%).

LC/MS: m/z 1039.56 [M+H]<sup>+</sup>, 1061.6 [M+Na]<sup>+</sup>

Elementary analysis: C<sub>51</sub>H<sub>82</sub>N<sub>4</sub>O<sub>18</sub> (C<sub>3</sub>H<sub>7</sub>NO)<sub>0.3</sub>(H<sub>2</sub>O)<sub>5.9</sub>

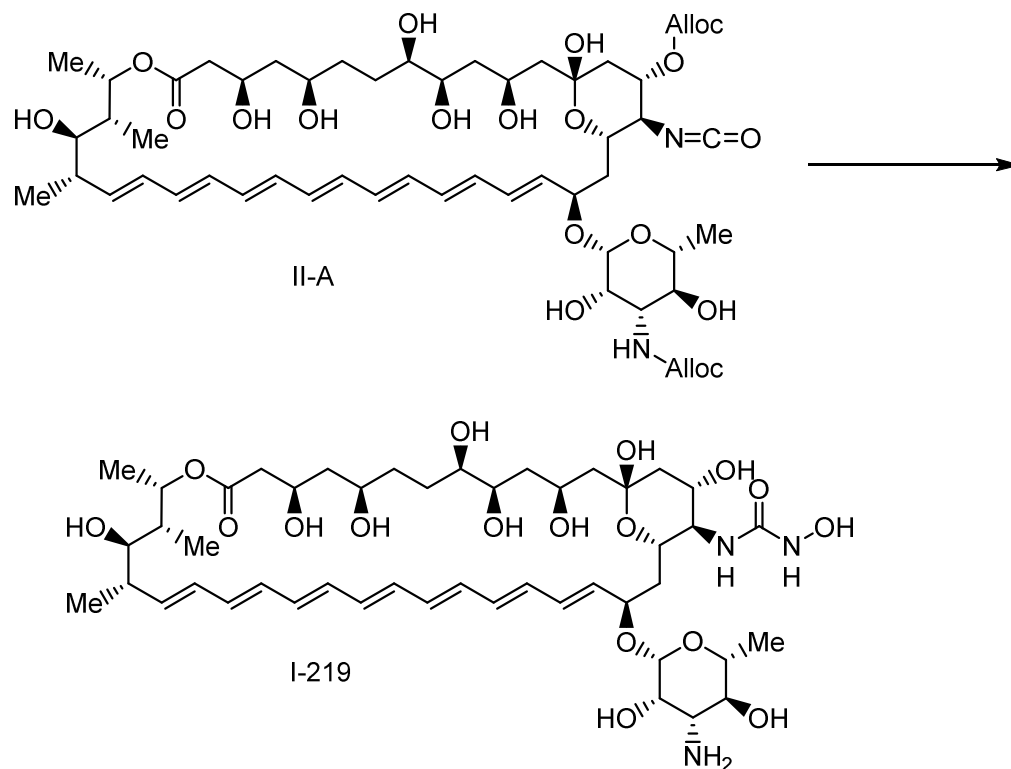
Calculated value: C 53.40; H 8.28; N 5.16 (%)

Actual value: C 53.43; H 8.15; N 5.21 (%)

[0 1 9 3]

Example 22: Synthesis of Compound I-219

[Chemical Formula 6 6]



Compound II-A (10g, 9.18mmol) was dissolved into DMF (25mL) and added DIEA (4.81mmol) and hydroxylamine hydrochloride (766mg, 11.02mmol), and the mixture was stirred for 40 minutes at room temperature. After powderization by adding diisopropyl ether, the resulted powder was purified by silica-gel column chromatography (chloroform/methanol=70/30) to give yellow powder (2.1g, 20%). The resulted powder was dissolved into DMF (10mL) and added morpholine (1.63mL, 18.71mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (216mg, 0.187mmol), and the mixture was stirred for 40 minutes at room temperature. After powderization by adding diisopropyl ether, the powder was purified by silica-gel column chromatography (chloroform/methanol=40/60 to 5/95) to give Compound I-219 (530mg, 30%).

LC/MS:  $m/z$  954.4  $[\text{M}+\text{H}]^+$ , 976.5  $[\text{M}+\text{Na}]^+$

Elementary analysis:  $\text{C}_{47}\text{H}_{75}\text{N}_3\text{O}_{17}(\text{C}_3\text{H}_7\text{NO})_{0.5}(\text{H}_2\text{O})_{2.8}$

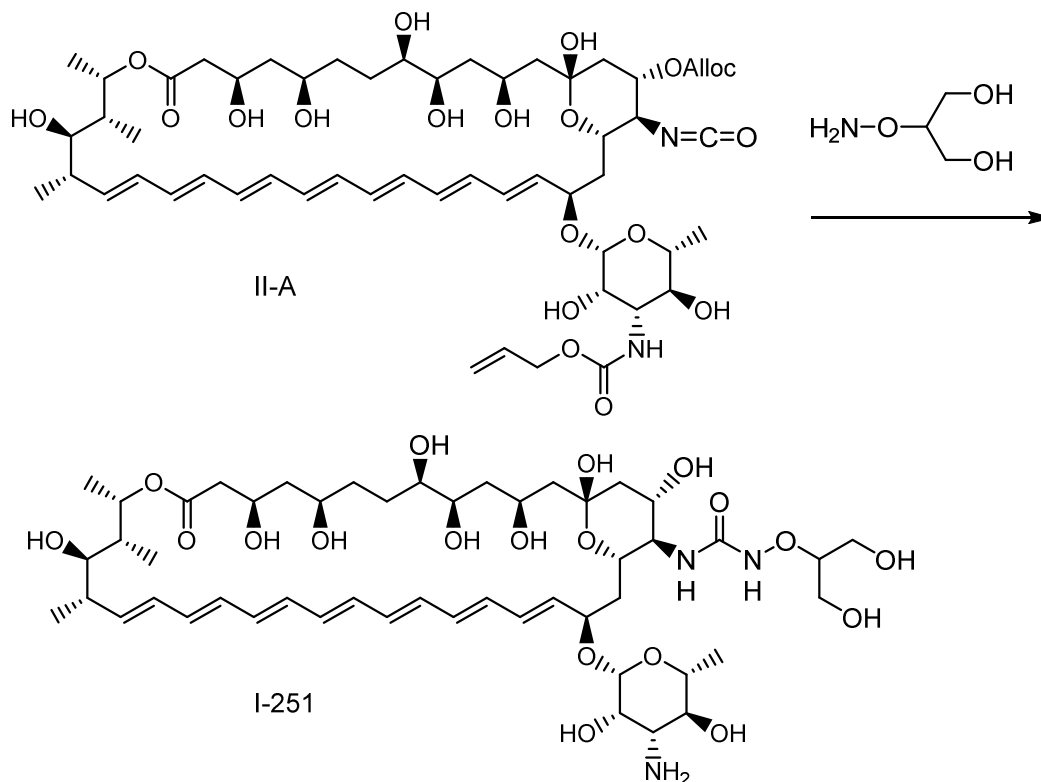
Calculated value: C 55.95(-0.02%); H 8.14 (-0.01%); N 4.71 (-0.03%); O 31.20 (%)

Actual value: C 55.93; H 8.13; N 4.68 (%)

[0 1 9 4]

Example 23: Synthesis of Compound I-251

[Chemical Formula 6 7]



Compound II-A (2.6g, 2.387mmol) was dissolved into DMA (10mL) and added 1-(hydroxymethyl)-2-hydroxy-ethoxyamine (811mg, 2.86mmol) and tributyltin oxide (1.46mL, 2.86mmol), the mixture was stirred at room temperature. After powderization by adding diisopropyl ether, the resulted powder was purified by silica-gel column chromatography. The obtained powder (250mg, 0.209mmol) was dissolved into NMP (3mL) and added morpholine (0.13mL, 1.46mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (24.1mg, 0.021mmol), and the mixture was stirred for 10 minutes at room temperature. After powderization by adding diisopropyl ether, the resulted powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol=90/10 to 70/30) to give Compound I-251 (114mg, 5%).

LC/MS:  $m/z$  1028.4  $[\text{M}+\text{H}]^+$ , 1050.4  $[\text{M}+\text{Na}]^+$

Elementary analysis:  $\text{C}_{50}\text{H}_{81}\text{N}_3\text{O}_{19}(\text{C}_3\text{H}_7\text{NO})_{2.9}(\text{H}_2\text{O})_{1.9}$

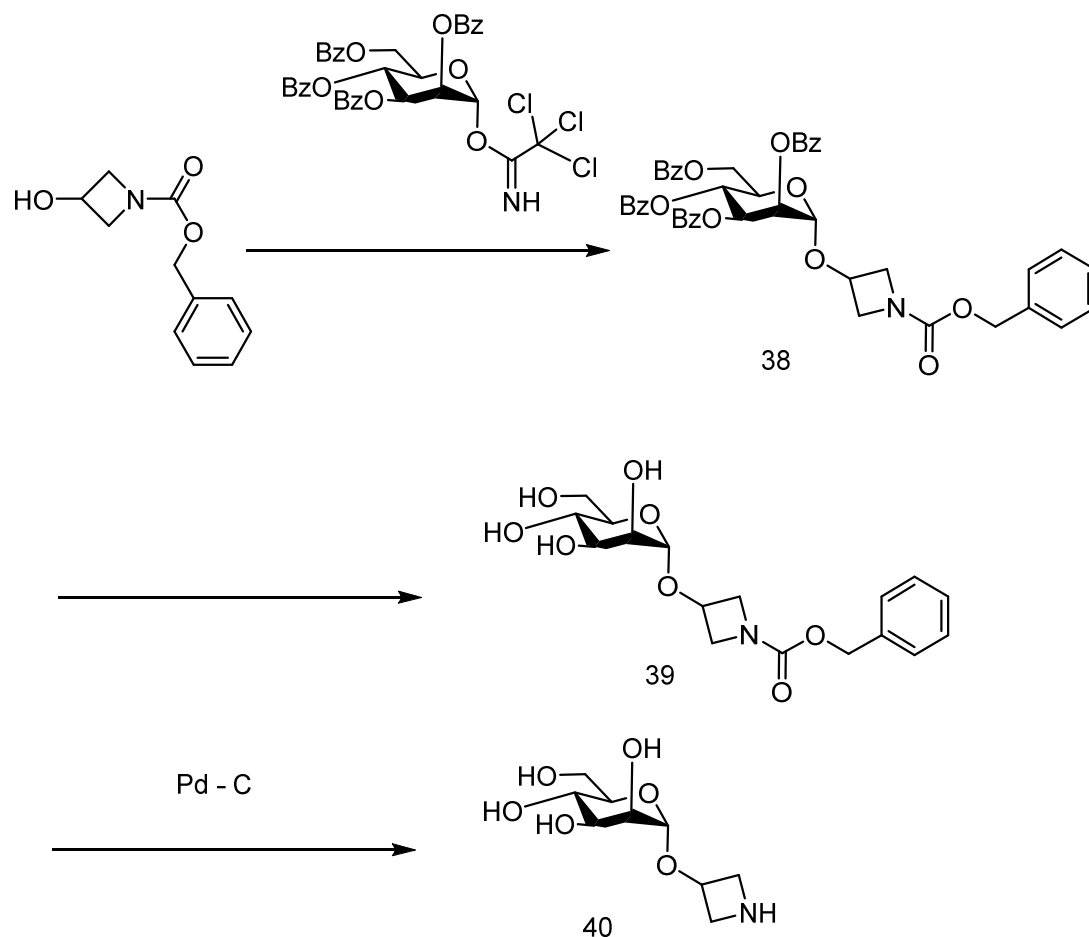
Calculated value: C 55.32; H 8.31; N 6.48 (%)

Actual value: C 55.30; H 8.30; N 6.90 (%)

[0 1 9 5]

Example 24: Synthesis of Compound I-303

[Chemical Formula 6 8]



### Step 1 Synthesis of Compound 38

2,3,4,6-tetra-O-benzyl-mannose-1-O-trichloroacetimidate (4.19g, 5.79mmol) and benzyl 3-hydroxyazetidine-1-carboxylate (1g, 4.83mmol) were dissolved into dichloromethane (15mL) and boron trifluoride diethyl ether complex (0.685mL, 5.79mmol) was added at -20 °C, and the mixture was stirred for 2 hours in an ice-water bath. After heating to room temperature, the reaction was quenched with saturated sodium bicarbonate aqueous solution, and the mixture was extracted with ethyl acetate. The mixture was purified by silica-gel column chromatography to give Compound 38 (2.84g, 74.9%).

TLC: R<sub>f</sub>=0.2(hexane/ethyl acetate=2/1)

LC-MS: 785 [M+H]<sup>+</sup>, 803 [M+Na]<sup>+</sup>

### Step 2 Synthesis of Compound 39

Compound 38 (2.71g, 3.45mmol) was dissolved into methanol (20mL) and tetrahydrofuran (20mL) and added sodium methoxide (1mol/L, 0.345mL) in an ice-water bath, and the mixture was stirred for 16 hours at room temperature. After the reaction was quenched by adding Amberlite (H)IRA, the mixture was filtrated, and the obtained filtrate was condensed. The obtained gummy condensed residue was triturated to give Compound 39 (1.017g, 79.8%) as white solid.

TLC: R<sub>f</sub>=0.3(chloroform/methanol=5/1)

<sup>1</sup>H-NMR(d<sub>2</sub>o)δ:7.37 (brs, 5H), 5.06 (s, 2H),4.82 (s, 1H), 4.57 (s, 1H), 4.20 (brs, 2H), 4.0-3.5 (br, 8H)

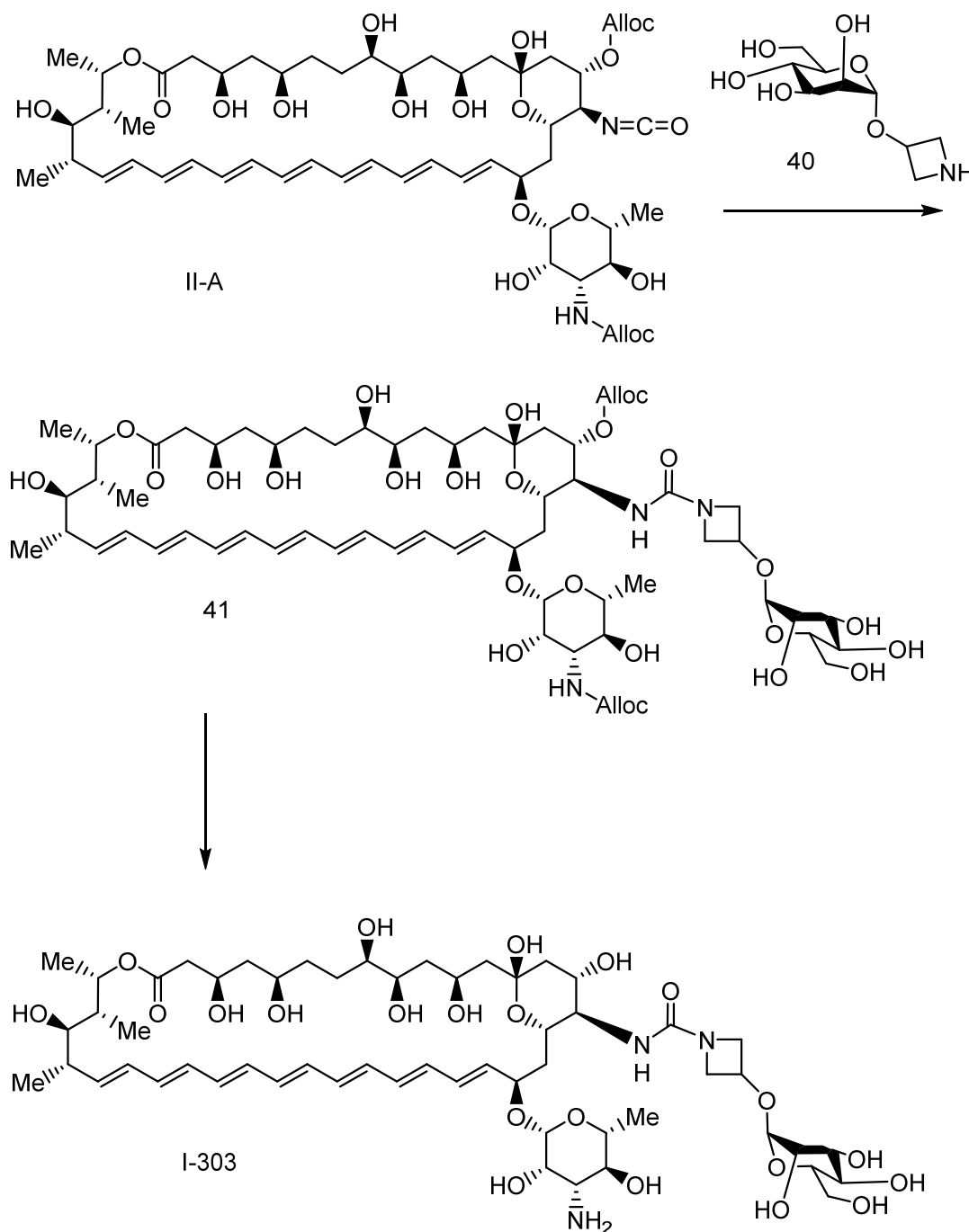
### Step 3 Synthesis of Compound 40

Compound 39 (1.01g, 2.73mmol) was dissolved into methanol (20mL) and added

10%Pd-C (200mg, 0.188mmol), and the mixture was stirred for 2 hours at room temperature under 1 atm hydrogen atmosphere. After confirmation of disappearance of material by TLC, the mixture was filtrated by Celite®. The obtained filtrate was condensed. The obtained residue was washed with hexane to give Compound 40 (597mg, 92.8%) as white solid.

LC-MS: 236 [M+H]<sup>+</sup>

[Chemical Formula 6 9]



#### Step 1 Synthesis of Compound 41

Compound II-A (2.284g, 2.097mmol) was dissolved into DMF (12mL) and added side chain amine 40 (0.592g, 2.52mmol) and DIEA (1.1mL, 6.29mmol), and the mixture was stirred for 2 hours 40 minutes at room temperature. After the mixture was oil-outed with diisopropyl ether, the resulted residue was purified by silica-gel column chromatography (chloroform/methanol=90/10 to 70/30) to give Compound 41 (1.15g, 41%).

LC/MS:  $m/z$  1324  $[M+H]^+$

## Step 2 Synthesis of Compound I-303

Compound 41 (1.15g, 0.865mmol) was dissolved into DMF (10mL) and added morpholine (1.05mL, 12.1mmol) and  $Pd(PPh_3)_4$  (200mg, 0.173mmol), and the mixture was stirred for 4 hours at room temperature. After powderization by adding diisopropyl ether, the resulted powder was purified by silica-gel column chromatography to give Compound I-303 (187mg, 18%).

LC-MS: 1156.5  $[M+H]^+$ , 1178.5  $[M+Na]^+$ .

Elementary analysis:  $(C_{56}H_{89}N_3O_{22})(H_2O)_4(C_3H_7NO)_{0.3}$ :

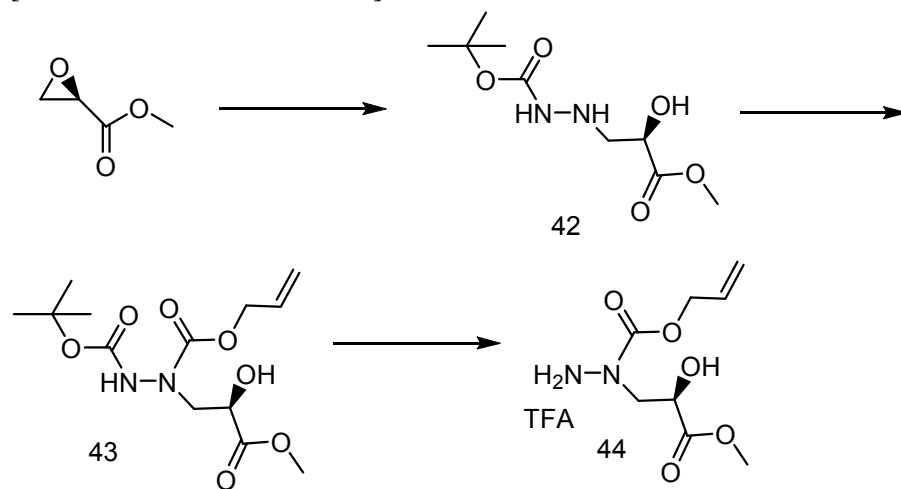
Calculated value: C 54.66; H 7.99; N 3.70 (%)

Actual value: C 54.63; H 7.91; N 3.94 (%)

[0 1 9 6]

## Example 25: Synthesis of Compound I-310

[Chemical Formula 7 0]



## Step 1 Synthesis of Compound 42

To a solution of tert-butoxycarbonylhydrazine (11.35g, 86mmol) in methanol (70mL) was added (R)-methyl oxirane-2-carboxylate (25.4g, 249mmol). The mixture was stirred for 24 hours at room temperature. After the reaction mixture was concentrated, the residue was purified by silica-gel column chromatography (hexane/ethyl acetate=9/1 to 1/1) to give Compound 42 (7.84g, white solid, 39%).

TLC:  $R_f$ =0.1 (hexane/ethyl acetate=1/1)

$^{13}C$ -NMR( $CDCl_3$ , 100MHz)  $\delta$ : 173.82, 157.36, 81.17, 68.92, 54.89, 52.49, 28.36, 14.21. ;

$^1H$ -NMR( $CDCl_3$ , 400MHz)  $\delta$ : 6.20 (brs, 1H), 4.30-4.20 (m, 1H), 3.78 (s, 3H), 3.25-3.10 (m, 2H), 1.48 (s, 9H).

## Step 2 Synthesis of Compound 43

To a solution of Compound 42 (7.84g, 33.5mmol) in dichloromethane (80mL) were added DIEA (7.6mL, 43.5mmol) and allyloxycarbonyl chloride (4.26mL, 40.2mmol). The mixture was stirred for an hour at room temperature. Water and ethyl acetate are added. After extracted with ethyl acetate, the organic phase was washed with water. The solution was dried with sodium sulfate anhydrous and filtrated and condensed. The resulted residue was purified by silica-gel column chromatography (hexane/ethyl acetate=1/1) to give Compound 43 (9.38g, colorless liquid, 88%).

TLC:  $R_f$ =0.3(hexane/ethyl acetate=1/1)

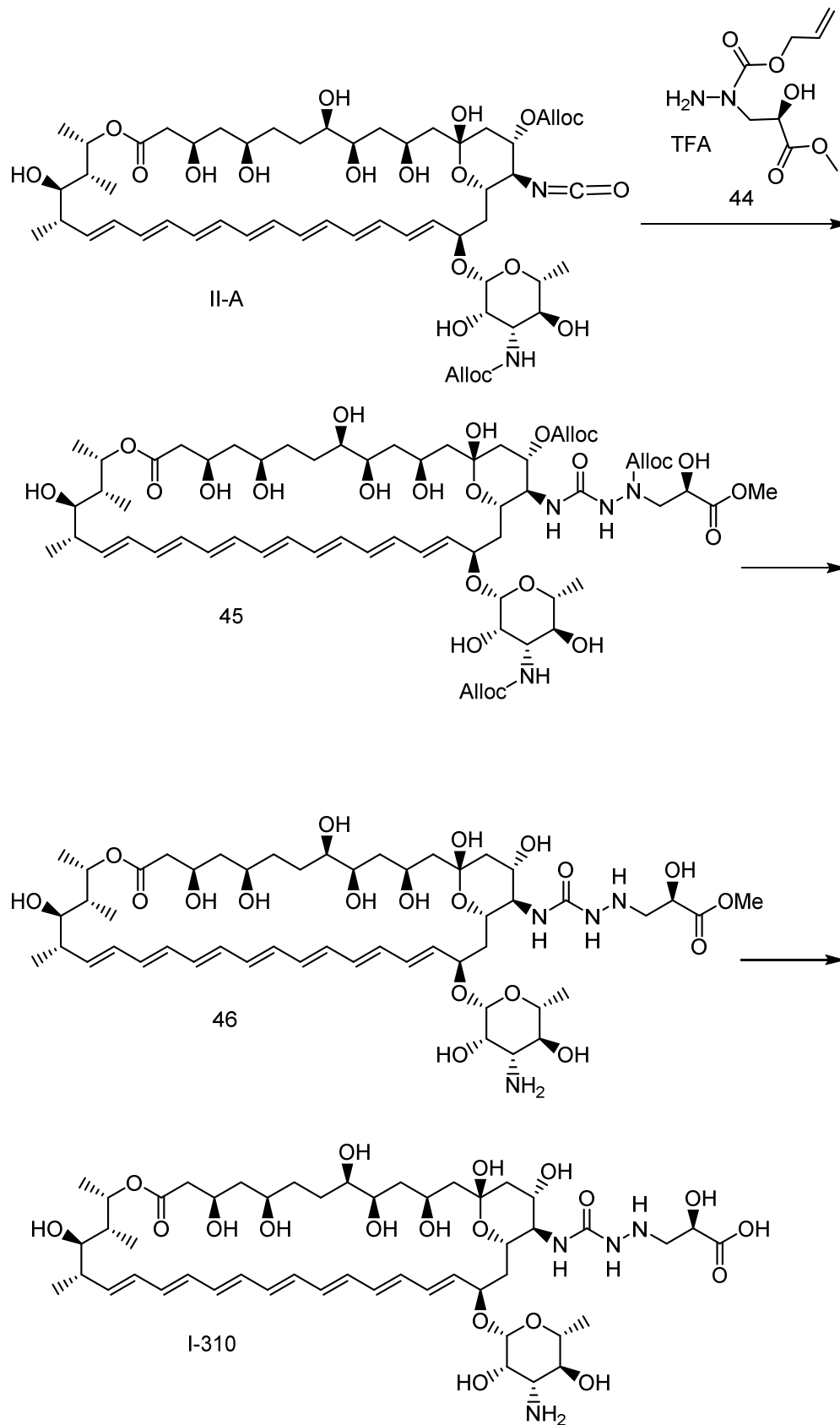
$^1H$ -NMR( $CDCl_3$ , 400MHz)  $\delta$ : 6.50 (brs, 1H), 5.9 (brs, 1H), 5.4-5.2 (m, 2H), 4.63 (brs, 2H), 4.43 (s, 1H), 4.40-3.8 (m, 3H), 3.79(s, 3H), 1.48(s, 9H). LC-MS:  $[M+H]^+=341.15$

### Step 3 Synthesis of Compound 44

To a solution of Compound 43 (9.38g, 29.5mmol) in dichloromethane (100mL) was added trifluoroacetic acid (22.7mL, 295mmol) in an ice-water bath. The mixture was stirred for 3 hours at room temperature. After condensed by rotatory evaporator, the mixture was condensed by adding toluene. The resulted residue was evaporated in vacuo to give Compound 44 (11.3g, gummy colorless liquid).

TLC: Rf=0.1 (hexane/ethyl acetate=1/1)

$^1\text{H-NMR}$ (D<sub>2</sub>O, 400MHz)  $\delta$ : 5.9-5.8 (m, 1H), 5.3-5.2 (m, 2H), 4.61 (m, 2H), 4.48 (m, 1H), 3.92(m, 2H), 3.65(s, 3H).  $^{13}\text{C-NMR}$  (D<sub>2</sub>O, 100MHz)  $\delta$ : 173.6, 162.8, 162.4, 131.5, 131.1, 119.0, 117.6, 114.7, 68.6, 68.4, 53.0, 52.9, 50.6.



### Step 1 Synthesis of Compound 45

To a solution of Compound II-A (9.27g, 8.51mmol) in DMF (40mL) were added DIEA (10.4mL, 59.6mmol), side chain amide Compound 44 (5.35g, 11.9mmol) and bis tributyltin oxide (0.867mmol, 1.70mmol). The mixture was stirred for 2 hours at room temperature. After cooling to 4 °C, the mixture was reacted for 4 days at 4 °C.

The reaction solution was suspended first, after 4 days, the solution became orange color. Diisopropyl ether (1L)/methanol (30mL) was added to the reaction mixture, and the mixture was stirred strongly. The obtained orange color solids were filtrated. The solids were purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5 to 90/10/1). The obtained fractions were condensed to give Compound 45 (6.82g, 5.22mmol, 61%) as orange color powder. The retention time of Compound 17 by HPLC analysis was 11.8 minutes (methanol/distilled water containing 0.1% PIC-B7= gradient from 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm).

LC-MS: m/z 1308.6 [M+H]<sup>+</sup>

#### Step 2 Synthesis of Compound 46

To a solution of Compound 45 (10.03g, 7.67mmol) in DMF (55mL) were added morpholine (4.68mL, 53.7mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.887g, 0.767mmol). The mixture was stirred for 40 minutes at room temperature under nitrogen atmosphere. The deposited solids by adding diisopropyl ether (900mL) was filtrated. The solids were purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3 to 5/95/5). The obtained fractions were condensed to give Compound 46 (4.45g, yellow powder, 55%) as orange color powder. The retention time of Compound 46 by HPLC analysis was 6.37 minutes (methanol/distilled water containing 0.1% PIC-B7= gradient from 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm). LC-MS: m/z 1055.6 [M+H]<sup>+</sup>

#### Step 3 Synthesis of Compound I-310

Tetrahydrofuran (210mL) and water (11mL) was added to Compound 46 (4.45g, 4.22mmol), and sodium hydroxide aqueous solution (0.5mol/L, 12.65mL, 6.33mmol) was added in an ice-water bath. The mixture was stirred for an hour at 0 °C. After the solution was neutralized by adding hydrochloric acid aqueous solution (0.5mol/L, 12.65mL, 6.33mmol) dropwise, the mixture was condensed by rotatory evaporator. After all tetrahydrofuran were removed, water was condensed to 30mL. The mixture was lyophilized to give Compound I-310 (5.87g). The retention time by HPLC analysis was 7.39 minutes (methanol/distilled water containing 0.1% PIC-B7= gradient from 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm). LC-MS: m/z 1041.6 [M+H]<sup>+</sup>

Elementary analysis: (C<sub>50</sub>H<sub>80</sub>N<sub>4</sub>O<sub>19</sub>)(NaCl)1.7(H<sub>2</sub>O)2.8

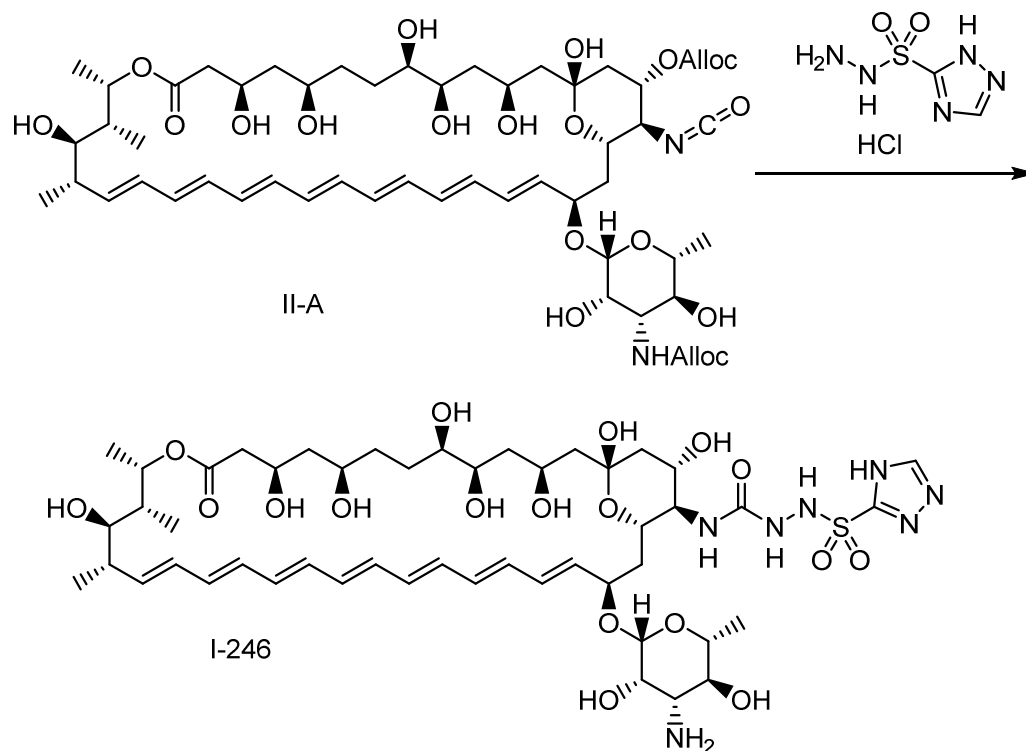
Calculated value: C 50.42; H 7.24; N 4.70; Na 3.28; Cl 5.06 (%)

Actual value: C 50.41; H 7.21; N 4.75; Na 3.05; Cl 5.51 (%)

[0 1 9 7]

#### Example 26: Synthesis of Compound I-246

[Chemical Formula 7 2]



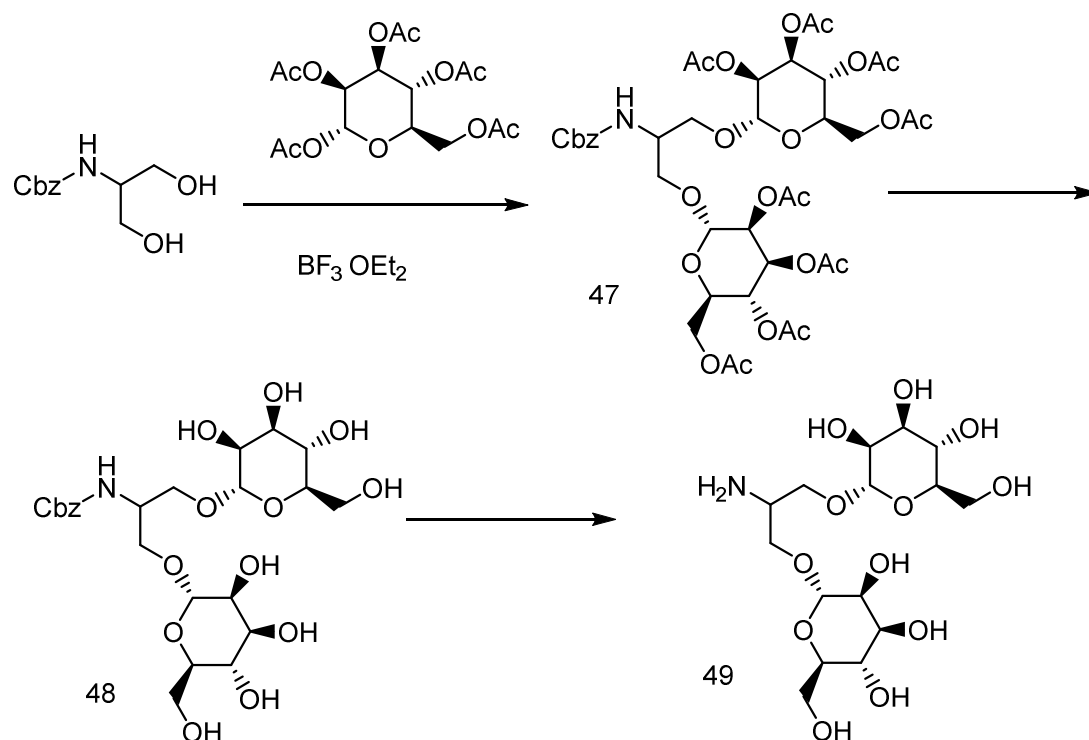
Compound II-A (2g, 1.836mmol) was dissolved into DMF (10mL), and DIEA (3.21mL, 18.36mmol) and 1H-1,2,4-triazole-5-sulfonylhydrazine hydrochloride (0.733g, 3.67mmol) were added. The mixture was stirred at 40 °C. After powderization by adding diisopropyl ether, the obtained solids were purified by silica-gel column chromatography to give oily solids (200mL). The solids were dissolved into DMF (2mL), and morpholine (0.139mL, 1.59mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (9.2mg, 0.008mmol) were added. The mixture was stirred for an hour at room temperature. After powderization by adding diisopropyl ether, the obtained powder was purified by silica-gel column chromatography to give Compound I-246 (21mg, 10%).

LC/MS: m/z 1084.4 [M+H]<sup>+</sup>

[0 1 9 8]

Example 27: Synthesis of Compound I-254

[Chemical Formula 7 3]



## Step 1

Benzyl 1,3-hydroxypropane-2-yl carbamate (4.72g, 21mmol) was dissolved into dichloromethane (310mL), and 8-D-mannopyranose 1,2,3,4,6-pentaacetate (24.5g, 62.9mmol) was added and was cooled in an ice-water bath. Boron trifluoride diethyl ether complex (8mL, 62.9mmol) was added dropwise. After the mixture was stirred for an hour, boron trifluoride diethyl ether complex (0.8mL, 6.29mmol) was added. The mixture was stirred at room temperature over night. After the reaction was quenched by saturated sodium bicarbonate aqueous solution, the mixture was extracted with chloroform (200mL) twice. The organic phase was washed with brine and dried up with sodium sulfate anhydrous and filtrated and condensed. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate) to give Compound 47 (3.45g, 18%).

TLC:  $R_f=0.4$  (hexane/ethyl acetate=1/2)

LC-MS: 886.5  $[\text{M}+\text{H}]^+$

## Step 2

Compound 47 (3.36g, 3.79mmol) was dissolved into methanol (30mL), and sodium methoxide (1mol/L, 3.79mL) was added in an ice-water bath. The mixture was stirred for an hour at  $0^\circ\text{C}$ , further stirred for an hour at room temperature. The mixture was neutralized by adding ion exchange resin of Amberlite IR-120B ( $\text{H}^+$  form) and filtrated and condensed to give Compound 48 (2.05g, 98%).

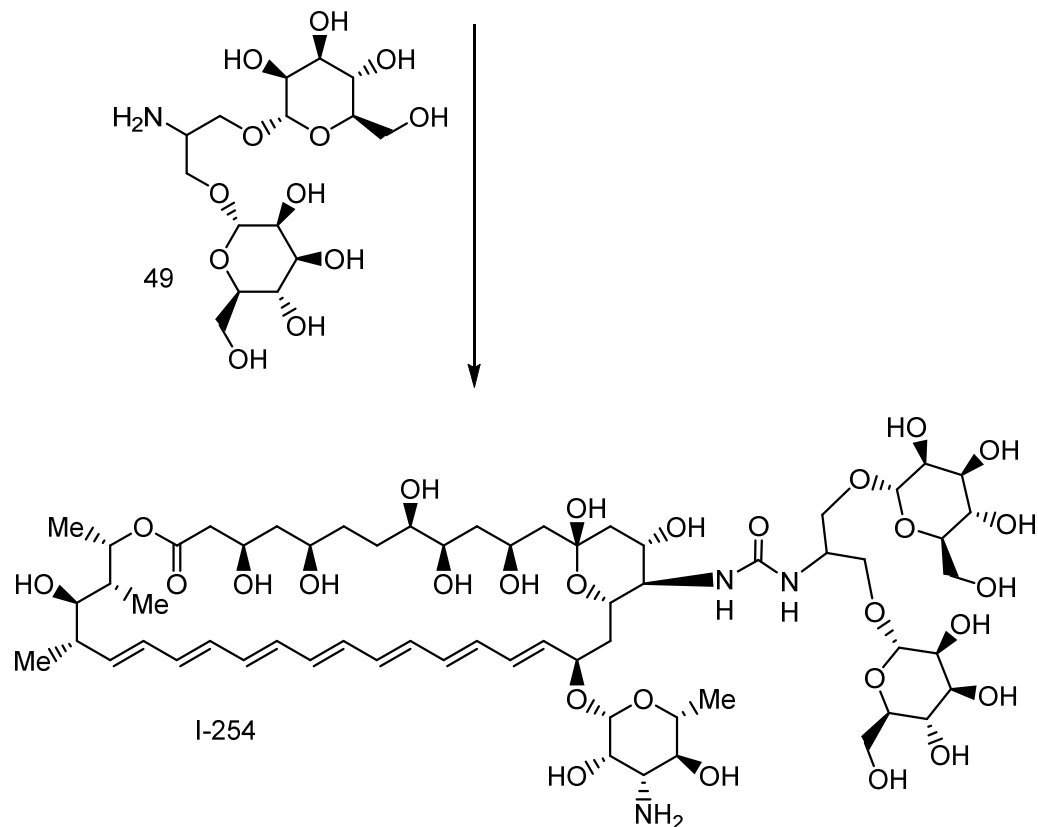
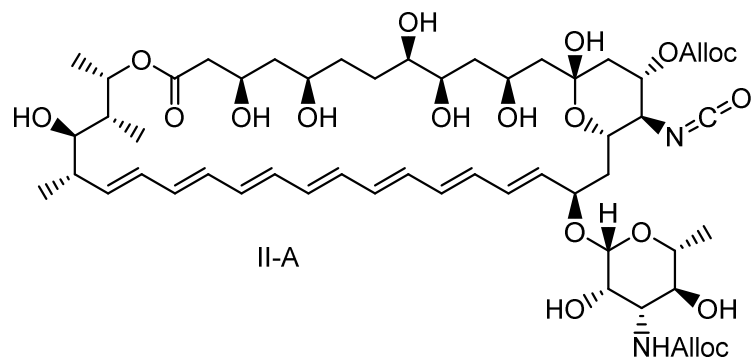
TLC:  $R_f=0.1$  (chloroform/methanol=4/1)

## Step 3

Compound 48 (2.05g, 3.73mmol) was dissolved into methanol (50mL), and 10% Pd-C (200mg, 0.188mmol) was added. The mixture was stirred under hydrogen atmosphere (1 atm). The reaction mixture was filtrated and condensed to give Compound 49 (1.62g). Compound 49 was used to next reaction without purification.

LC-MS: 416.1  $[\text{M}+\text{H}]^+$

[Chemical Formula 7 4]



Compound II-A (500mg, 0.459mmol) was dissolved into DMF (2mL), and DIEA (0.241mL, 1.38mmol) and 2-amino-1,3-propanediyl bis- $\alpha$ -D-mannopyranoside (Compound 49: 286mg, 0.689mmol) were added. The mixture was stirred for an hour at 40 °C. After powderization by adding diisopropyl ether, the obtained solids were purified by silica-gel column chromatography to give solids (220mg, 0.146mmol). The solids were dissolved into DMF (2mL), and morpholine (0.127mL, 1.462mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (51mg, 0.044mmol) were added. The mixture was stirred for an hour at room temperature. After powderization by adding diisopropyl ether, the obtained solids were purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=70/30/3 to 10/90/9) to give Compound I-254 (70mg, 12%). LC/MS:  $m/z$  1336.6  $[\text{M}+\text{H}]^+$

Elementary analysis:  $(\text{C}_{62}\text{H}_{101}\text{N}_3\text{O}_{28})(\text{H}_2\text{O})_{9.5}$

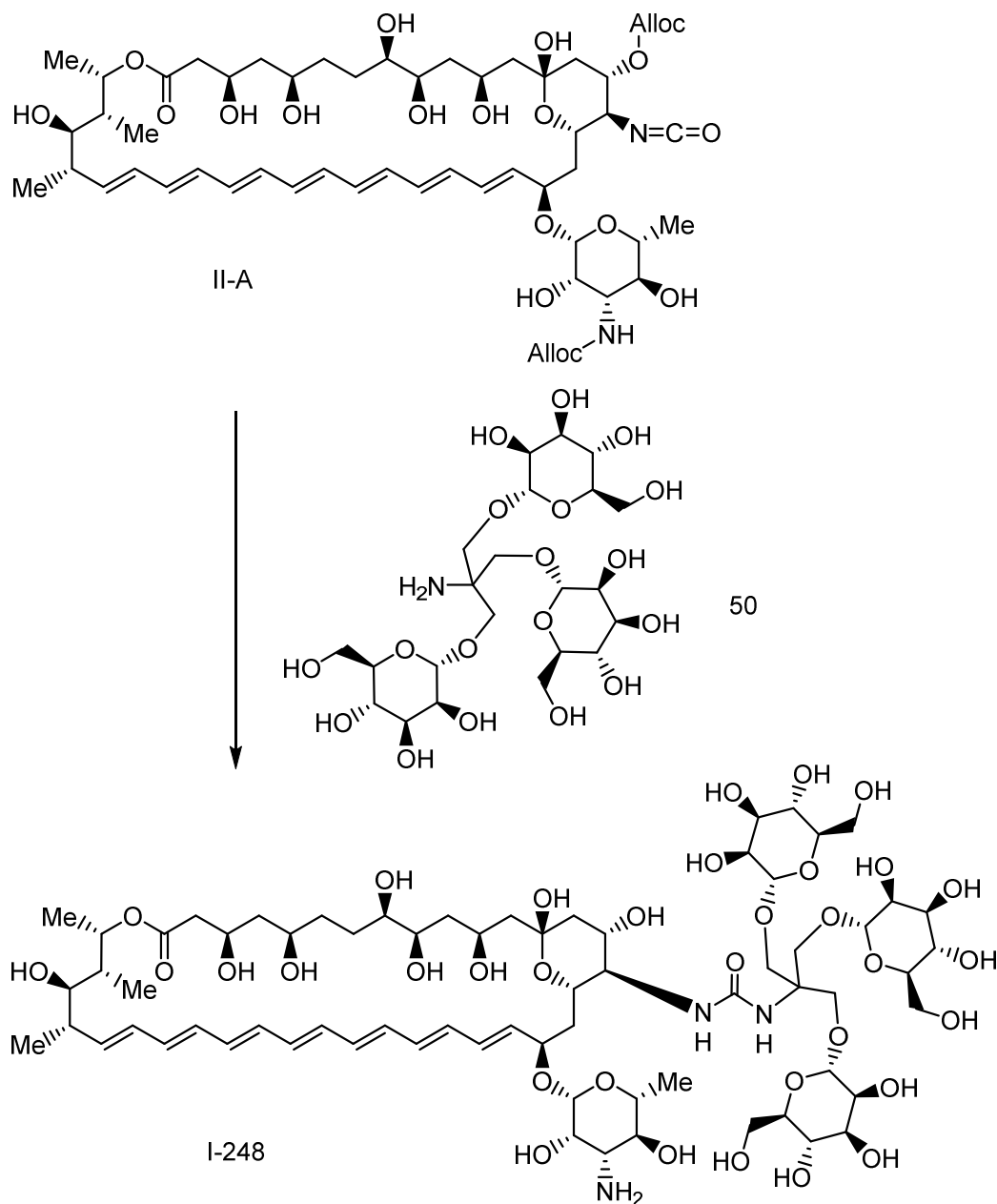
Calculated value: C 49.39; H 8.02; N 2.79 (%)

Actual value: C 49.29; H 7.55; N 4.75; Na 3.14 (%)

[0 1 9 9]

Example 27: Synthesis of Compound I-248

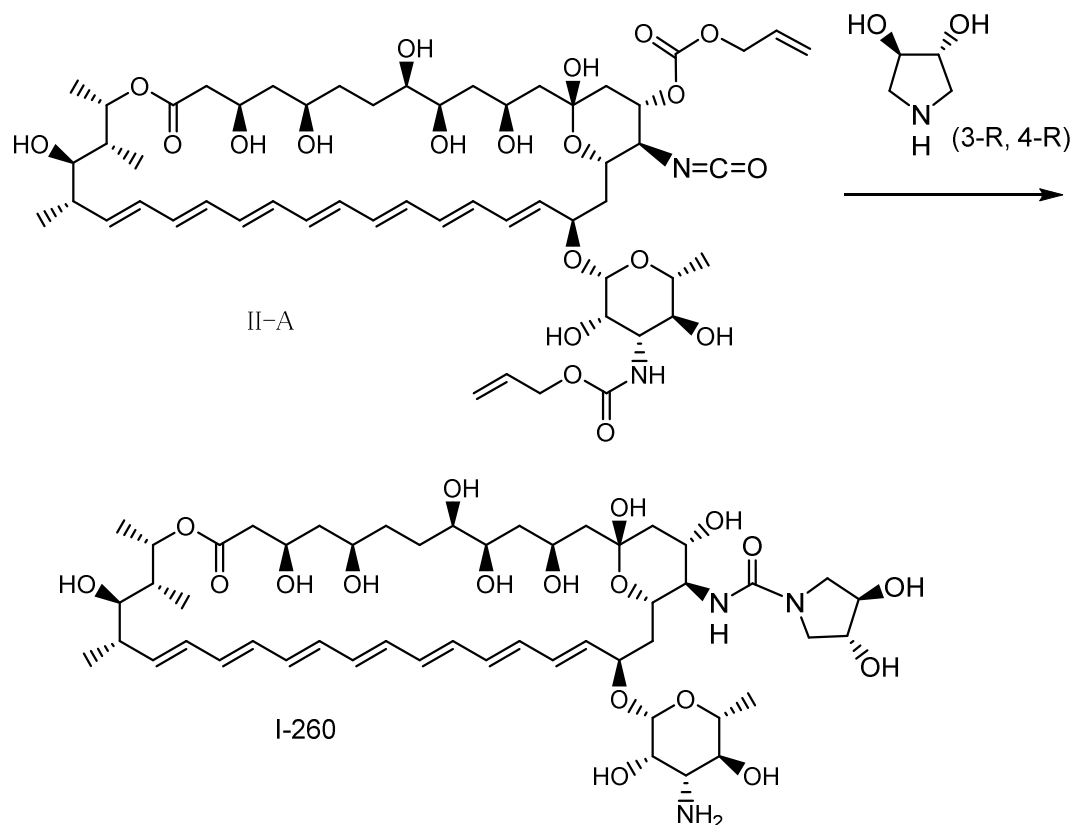
[Chemical Formula 7 5]



Compound II-A (240mg, 0.220mmol) was dissolved into DMF (2mL), and DIEA (0.115mL, 0.661mmol) and α-D-mannopyranoside, 2-amino-2-[(α-D-mannopyranosyloxy)methyl]-1,3-propanediyl, bis- (Compound 50: 201mg, 0.331mmol) were added. The mixture was stirred for 20 hours at room temperature. After powderization by adding diisopropyl ether, the obtained solids were purified by silica-gel column chromatography to give solids (30mg, 0.018mmol). The solids were dissolved into DMF (1mL), and morpholine (0.015mL, 0.177mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (10mg, 0.009mmol) were added. The mixture was stirred for an hour 15 minutes at room temperature. After powderization by adding diisopropyl ether, the powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=50/50/5 to 10/90/9) to give Compound I-248 (16mg, 5%).  
 LC/MS: m/z 1529.3 [M+H]<sup>+</sup>  
 [0 2 0 0]

Example 28: Synthesis of Compound I-260

[Chemical Formula 7 6]



Compound II-A (2g, 1.836mmol) was dissolved into DMF (10mL), and DIEA (1.28mL, 7.34mmol) and (3R,4R)-pyrrolidine-3,4-diol (227mg, 2.203mmol) were added. The mixture was stirred for 3 hours at room temperature. After powderization by adding diisopropyl ether, the obtained solids were purified by silica-gel column chromatography (chloroform/methanol/water=85/15/1.5) to give Compound 19 (379mg, 17%) as brown solids. Compound 19 (379mg, 0.318mmol) was dissolved into DMF (5mL), and morpholine (0.277mL, 3.18mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (18.4mg, 0.016mmol) were added. The mixture was stirred for an hour at room temperature. After powderization by adding diisopropyl ether, the obtained powder was purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3 to 10/90/9) to give Compound I-260 (195mg, 10%).

LC/MS: m/z 1024.5 [M+H]<sup>+</sup>, 1046.6, [M+Na]<sup>+</sup>

Elementary analysis: (C<sub>51</sub>H<sub>81</sub>N<sub>3</sub>O<sub>18</sub>)(H<sub>2</sub>O)<sub>3.9</sub>

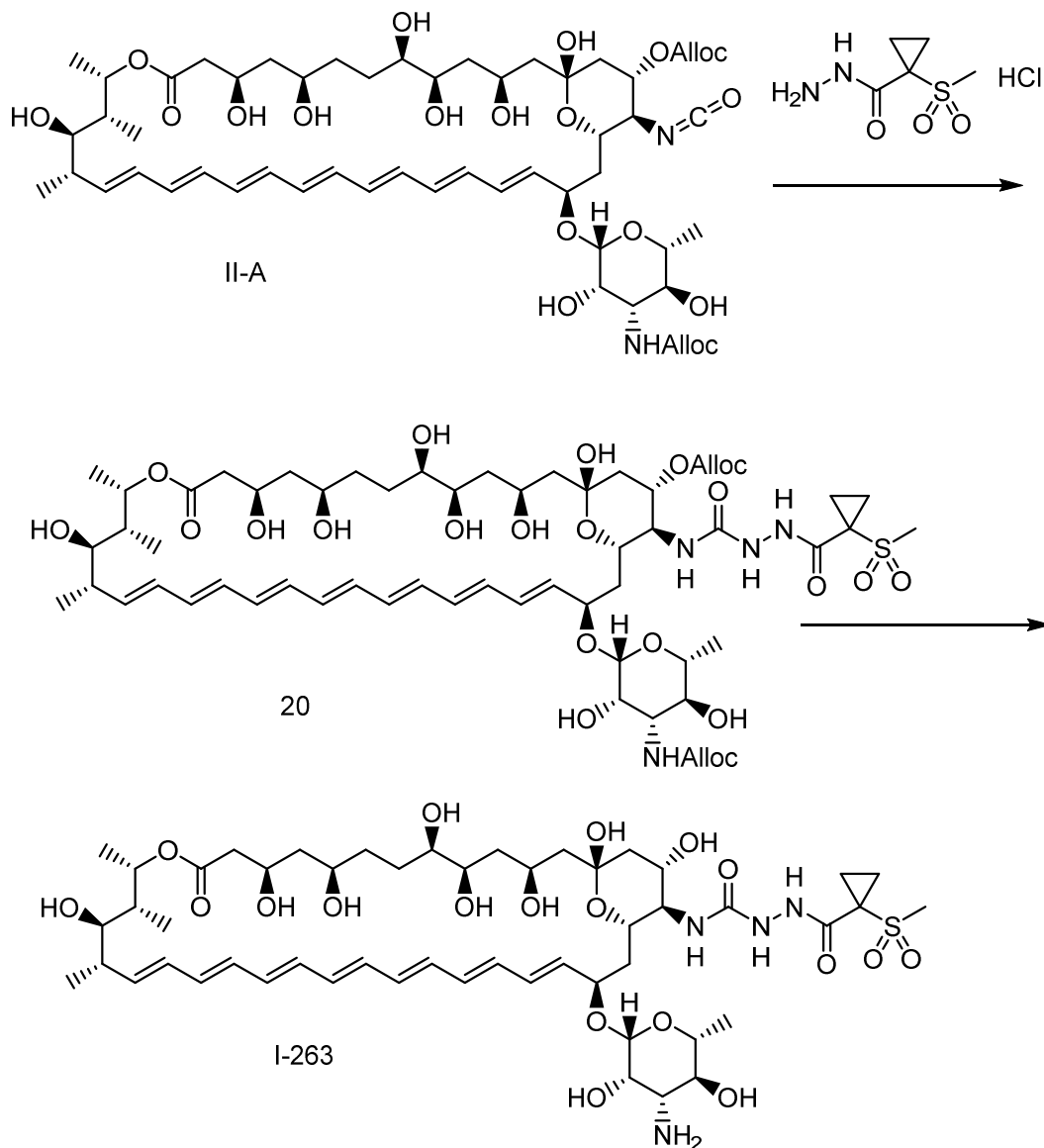
Calculated value: C 55.97; H 8.18; N 3.84 (%)

Actual value: C 55.98; H 8.25; N 3.97 (%)

[0 2 0 1]

Example 29: Synthesis of Compound I-263

[Chemical Formula 7 7]



Compound II-A (2g, 1.836mmol) was dissolved into DMF (10mL), and DIEA (1.6mL, 9.18mmol) and 1-(methanesulfonyl)cyclopropanecarbohydrazide hydrochloride (394mg, 1.836mmol) were added. The mixture was stirred at 40°C. After powderization by adding diisopropyl ether, the obtained solids were purified by silica-gel column chromatography to give Compound 20 (576mg, 25%) as brown solids. Compound 20 was dissolved into DMF (5mL), and morpholine (0.396mL, 4.54mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (26mg, 0.023mmol) were added. The mixture was stirred for an hour at room temperature. After powderization by adding diisopropyl ether, the obtained powder was purified by silica-gel column chromatography to give Compound I-263 (307mg, 58%).

LC/MS: m/z 1099.4 [M+H]<sup>+</sup>, 1121.5, [M+Na]<sup>+</sup>

Elementary analysis: C<sub>52</sub>H<sub>82</sub>N<sub>4</sub>O<sub>19</sub>S(C<sub>3</sub>H<sub>7</sub>NO)<sub>0.4</sub>(H<sub>2</sub>O)<sub>2.8</sub>

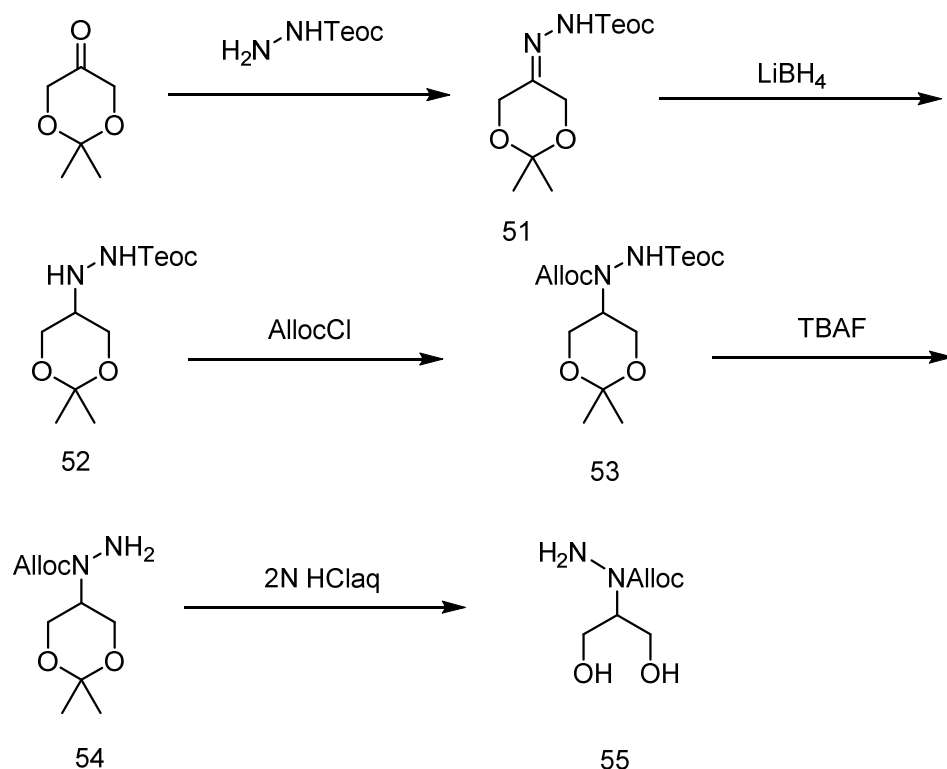
Calculated value: C 54.20; H 7.73; N 5.23; S 2.72 (%)

Actual value: C 54.22; H 7.68; N 5.23; S 2.76 (%)

[0 2 0 2]

Example 30: Synthesis of Compound I-272

[Chemical Formula 7 8]



## Step 1

2-Trimethylsilylethyloxycarbonylhydrazine (3.27g, 18.55mmol) and 2,2-dimethyl-1,3-dioxane-5-one (2.414g, 18.55mmol) were dissolved into methanol (20mL). After the mixture was stirred at room temperature, the mixture was condensed. The mixture was purified by silica-gel column chromatography (hexane/ethyl acetate=9/1) to give Compound 51 (4.46g, 83%) as white solids.  $^1\text{H-NMR}(\text{CDCl}_3, 400\text{MHz})\delta$ : 4.19 (m, 4H), 4.29 (t, 2H,  $J=12\text{ Hz}$ ), 1.26 (s, 6H), 1.05 (t, 2H,  $J=12\text{ Hz}$ ), 0.04 (s, 9H)

## Step 2

Compound 51 (4.46g, 15.5mmol) was dissolved into tetrahydrofuran (100mL), and  $\text{LiBH}_4$  (1.013g, 46.5mmol) and methanol (10mL) were added. After the mixture was stirred for 40 minutes at  $0^\circ\text{C}$ ,  $\text{LiBH}_4$  (1.013g, 46.5mmol) was added and further the mixture was stirred at room temperature. The reaction was quenched by water. After the mixture was extracted with ethyl acetate, the mixture was purified by silica-gel column chromatography to give Compound 52 (3.91g, 87%).

## Step 3

Compound 52 (3.91g, 13.46mmol) was dissolved into DMF (20mL), and DIEA (3.29mL, 18.85mmol) was added, and further allyl chloroformate (1.72mL, 16.16mmol) was added in an ice-water bath. The mixture was stirred at room temperature. The reaction was quenched by adding saturated sodium bicarbonate aqueous solution, and the mixture was extracted with ethyl acetate. The organic phase was washed with water five times and dried up with magnesium sulfate. The obtained residue was purified by silica-gel column chromatography (hexane/ethyl acetate= 4/1 to 3/2).

$^1\text{H-NMR}(\text{CDCl}_3, 400\text{MHz})\delta$ : 5.88 (m, 1H), 5.30 (d, 1H,  $J=16\text{Hz}$ ), 5.27 (m, 1H), 4.62 (s, 2H), 4.23 (m, 3H), 3.97 (br, 4H), 1.41 (s, 3H), 1.40 (s, 3H), 1.01 (t, 2H,  $J=8\text{Hz}$ ), 0.03 (s, 9H)

## Step 4

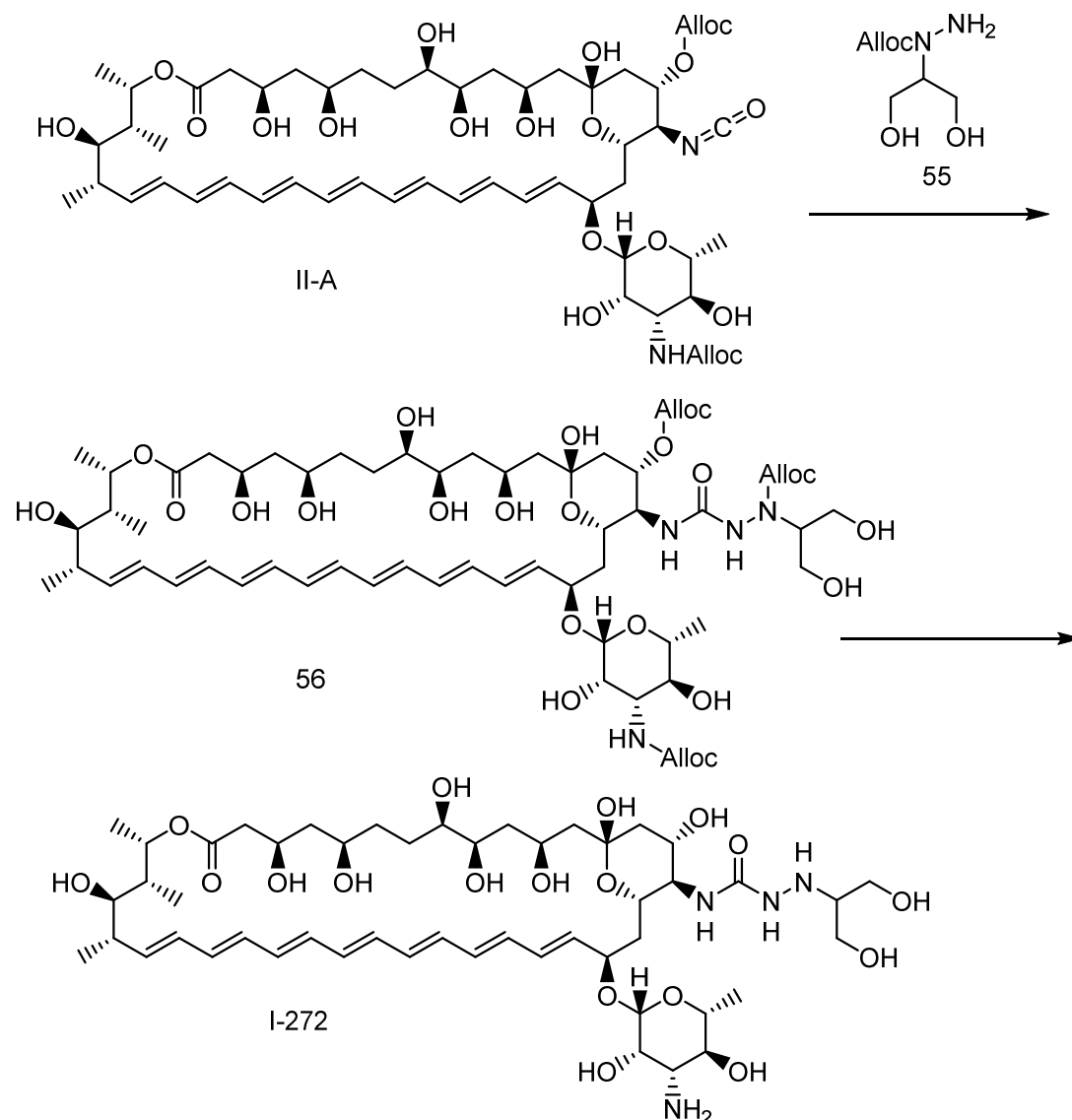
Compound 53 (1.73g, 4.62mmol) was dissolved into tetrahydrofuran (20mL), and tetrabutylammonium fluoride (1mol/L, 9.2mL, 9.2mmol) was added. The mixture was stirred for an hour at room temperature. The reaction was quenched with water, and the mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and dried up with sodium sulfate anhydrous. The residue was condensed to give crude Compound 54 (1.17g).

$\delta$ : 6.00-5.90 (m, 1H), 5.32 (d, 1H,  $J=16\text{Hz}$ ), 5.25(d, 1H,  $J=8\text{Hz}$ ), 4.62 (d, 2H,  $J=4\text{Hz}$ ), 4.23 (m, 1H), 4.13 (br, 2H), 3.84(br, 4H), 1.51(s, 3H), 1.41 (s, 3H).

#### Step 5

Compound 54 (1.17g, 5.08mmol) was dissolved into tetrahydrofuran (10mL), and 2 mol/L hydrochloric acid aqueous solution (5.08mL, 10.16mmol) was added. After the mixture was stirred at room temperature, the mixture was condensed. The resulted residue was dissolved into methanol and purified by silica-gel column chromatography (chloroform/methanol=1/1) to give Compound 55 (1.02g).

[Chemical Formula 7 9]



Compound II-A (3g, 2.75mmol) was dissolved into DMF (15mL), and Compound 55 (524mg, 2.75mmol) and DIEA (1.92mL, 11.02mmol) were added. The mixture was stirred at room temperature. After powderization by adding diisopropyl ether, the obtained residue was purified crudely by silica-gel column chromatography. The

obtained powder (Compound 56: 887mg) was dissolved into DMF (5mL), and morpholine (0.6mL, 6.93mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (40mg, 0.035mmol) were added. The mixture was stirred at room temperature under nitrogen atmosphere. The obtained solids by adding diisopropyl ether (900mL) were filtrated. The resulted residue was purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3 to 10/90/9). The obtained fractions were condensed to give Compound I-272 (213mg, 0.176mmol, yellow powder, 6%) as orange color powder.

LC/MS: m/z 1027.4 [M+H]<sup>+</sup>

Elementary analysis: C<sub>50</sub>H<sub>82</sub>N<sub>4</sub>O<sub>18</sub>(C<sub>3</sub>H<sub>7</sub>NO)<sub>0.5</sub>(H<sub>2</sub>O)<sub>2.4</sub>

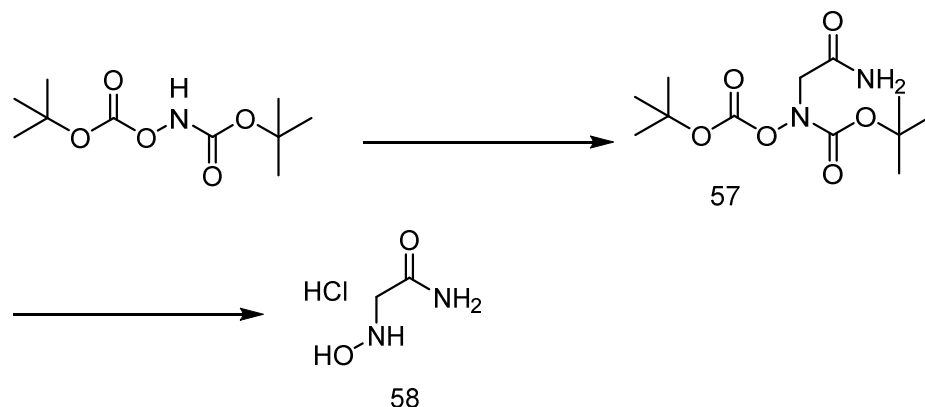
Calculated value: C 55.88 (0.02%); H 8.22 (-0.05%); N 5.69 (-0.02%) (%)

Actual value: C 55.90; H 8.17; N 5.67 (%)

[0 2 0 3]

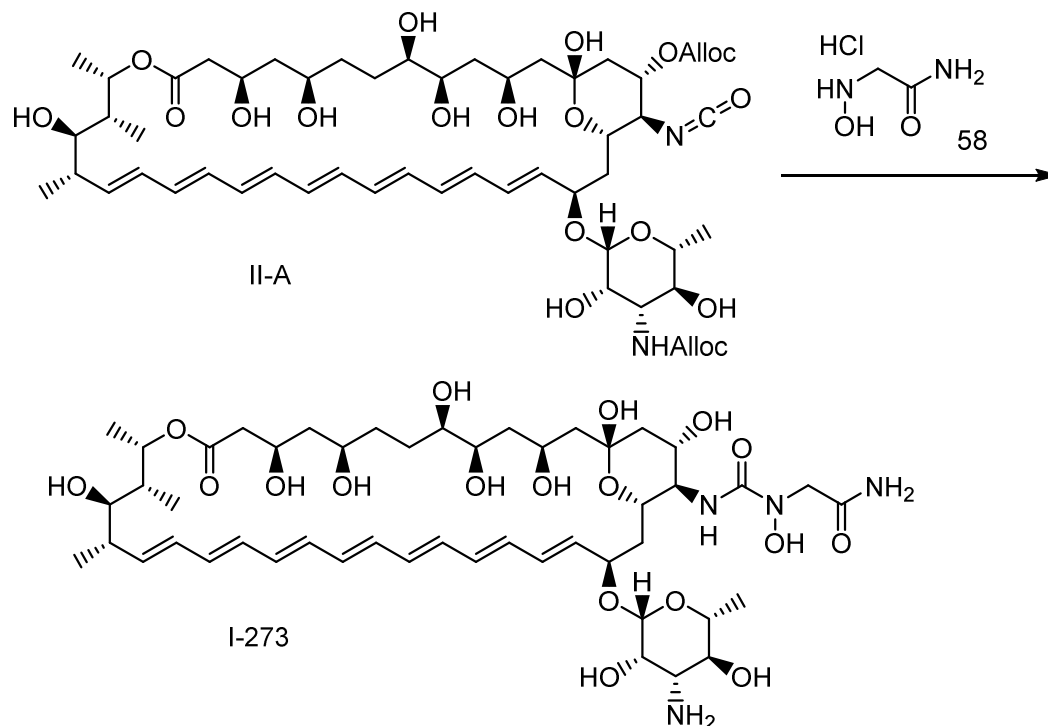
Example 31: Synthesis of Compound I-273

[Chemical Formula 8 0]



Tert-butyl tert-butyloxycarbonyloxycarbamate (1.91g, 8.19mmol) was dissolved into DMF (10mL), and 2-bromoacetamide (1.243g, 9.01mmol) and potassium carbonate (1.471g, 10.64mmol) were added. The mixture was stirred at room temperature. After the reaction was quenched with ethyl acetate, the mixture was purified by silica-gel column chromatography to give Compound 57 (898mg, 38%). Compound 57 was dissolved into dichloromethane (20mL), and hydrochloric acid-dioxane (4mol/L, 6.19mL, 24.75mmol) was added. After the mixture was stirred at room temperature, the mixture was condensed to give Compound 58 (391mg). Compound 58 was used to next reaction without purification.

[Chemical Formula 8 1]



2-Hydroxyamino acetate amide (Compound 58: 0.391g, 3.08mmol) was dissolved into DMF (15mL), and DIEA (1.924mL, 11.02mmol) was added. After the mixture was stirred at room temperature, Compound II-A (3g, 2.75mmol) was added. The mixture was stirred for 20 minutes at room temperature. After powderization by adding diisopropyl ether, the obtained residue was purified crudely by silica-gel column chromatography. The obtained solids(2,23g, 1.891mmol) were dissolved into DMF (4mL), morpholine (1.65mL, 18.91mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (109mg, 0.095mmol) were added. The mixture was stirred at room temperature under nitrogen atmosphere. After the resulting solids by adding diisopropyl ether were filtered, the solids were purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3 to 10/90/9) to give Compound I-273 (341mg, 16%) as yellow powder.

LC/MS: m/z 1011.4 [M+H]<sup>+</sup>

Elementary analysis: C<sub>49</sub>H<sub>78</sub>N<sub>4</sub>O<sub>18</sub>(C<sub>3</sub>H<sub>7</sub>NO)<sub>1.3</sub>(H<sub>2</sub>O)<sub>1.9</sub>

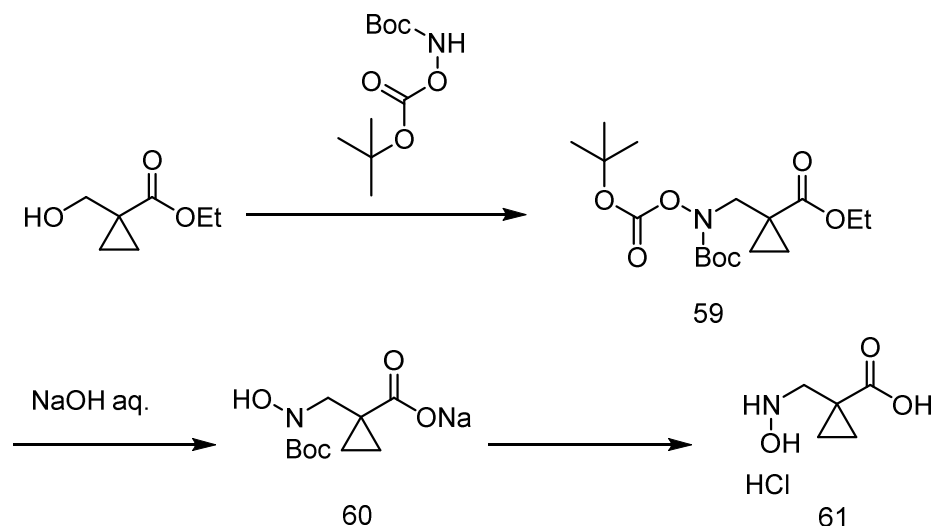
Calculated value: C 55.71 (0.02%); H 8.03 (-0.05%); N 6.51 (-0.02%) (%)

Actual value: C 55.73; H 7.98; N 6.49 (%)

[ 0 2 0 4 ]

Example 32: Synthesis of Compound I-281

[Chemical Formula 8 2]



## Step 1

Ethyl 1-(hydroxymethyl)cyclopropanecarboxylate (500mg, 3.47mmol) was dissolved into tetrahydrofuran (20mL), and tert-butyl tert-butyloxycarbonyloxycarbamate (0.971g, 4.16mmol) was added, and triphenylphosphine (1.364g, 5.20mmol) and DIAD (2.74mmol) were added in an ice-water bath. The mixture was stirred. After silica-gel was added, and the mixture was condensed, the residue was purified by silica-gel column chromatography to give Compound 59 (1.29g, 99%).

## Step 2

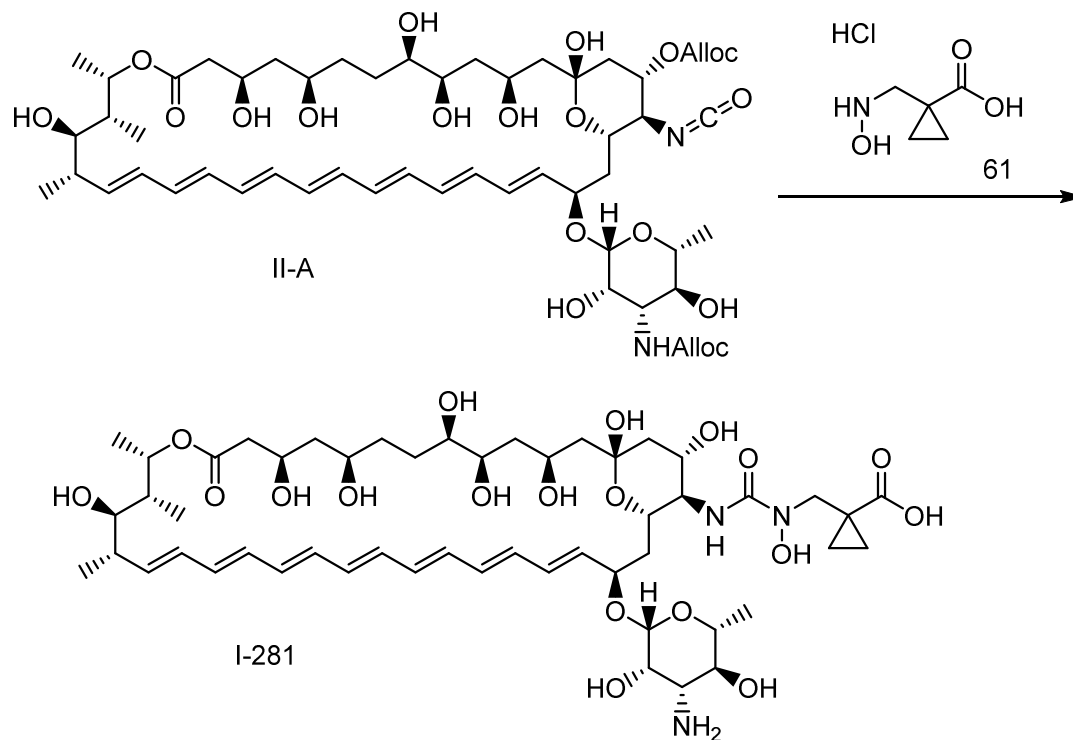
Compound 59 (1.29g, 3.61mmol) was dissolved into tetrahydrofuran (10mL), and 2mol/L sodium hydroxide aqueous solution (1.8mL, 3.61mmol) was added. The mixture was stirred under heat reflux. The mixture was reacted not only hydrolysis but also leaving carbonate reaction by cooling to room temperature. Ethanol was added, and the mixture was condensed and solidified to give Compound 60 (914mg). Compound 60 was used to next reaction without purification.

## Step 3

Compound 60 (914mg, 3.61mmol) was dissolved into dichloromethane (20mL), and hydrochloric acid-dioxane (4mol/L, 7.2mL) was added. After the mixture was stirred at room temperature, the mixture was condensed to give Compound 61 (615mg).

LC-MS: 132 [M+1]

[Chemical Formula 8 3]



Compound II-A (2g, 1.84mmol) was dissolved into DMF (10mL), and Compound 61 (615mg, 3.67mmol) and DIEA (1.6mL, 9.18mmol) were added. The mixture was stirred at room temperature. After powderization by adding diisopropyl ether, the obtained residue was purified crudely by silica-gel column chromatography. The obtained solids (753mg) were dissolved into DMF (5mL), and morpholine (0.54mL, 6.17mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (36mg, 0.031mmol) were added. The mixture was stirred at room temperature under nitrogen atmosphere. The resulted solids by adding diisopropyl ether were filtered. The resulted solids were purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3 to 10/90/9). The obtained fractions were condensed to give Compound I-281 (199mg, 28%) as orange color powder.

LC/MS:  $m/z$  1052.4  $[\text{M}+\text{H}]^+$

Elementary analysis:  $\text{C}_{52}\text{H}_{81}\text{N}_3\text{O}_{19}(\text{C}_3\text{H}_7\text{NO})_{1.3}(\text{H}_2\text{O})_{1.7}$

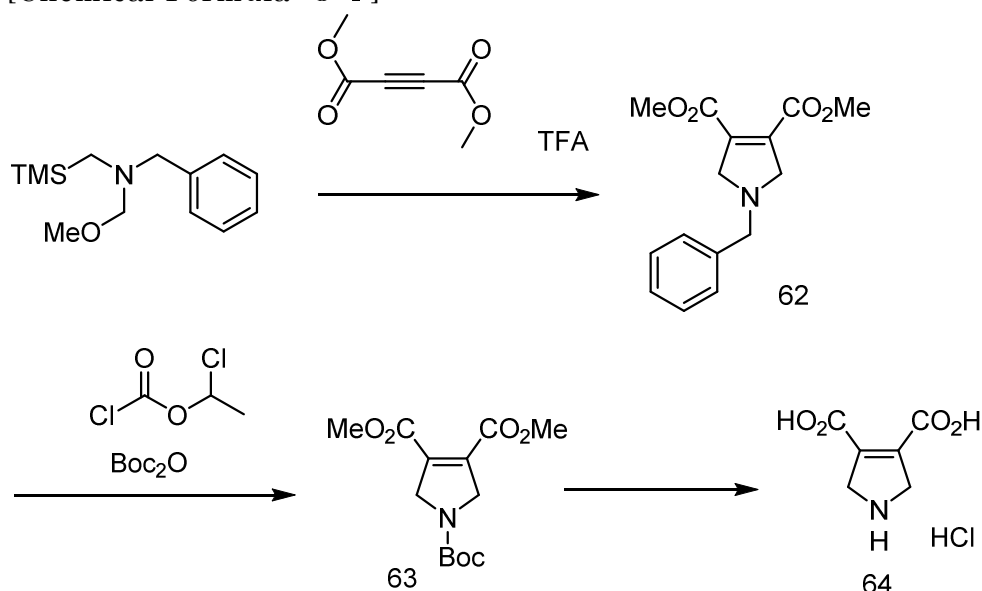
Calculated value: C 57.00; H 8.00; N 5.11 (%)

Actual value: C 57.01; H 8.01; N 5.17 (%)

[0 2 0 5]

Example 33: Synthesis of Compound I-292

[Chemical Formula 8 4]



## Step 1

N-Benzyl-N-(methoxymethyl)-N-trimethylsilylmethylamine (10g, 42.1mmol) was dissolved into dichloromethane (150mL), and Dimethyl acetylenedicarboxylate (7.18g, 50.5mmol) was added in an ice-water bath. The mixture was stirred. After trifluoroacetic acid (16.2mL, 211mmol) was added and stirred, the reaction was quenched with saturated sodium bicarbonate aqueous solution. After the mixture was extracted with dichloromethane, the organic phase was washed with brine and dried up with sodium sulfate anhydrous. The resulted residue was purified by silica-gel column chromatography (hexane/ethyl acetate=9/1 to 1/1) to give Compound 62 (5.87g, 51%) as yellow oil.

$^1\text{H-NMR}(\text{CDCl}_3, 400\text{MHz})\delta$ : 7.33-7.27 (m, 5H), 3.94(s, 2H), 3.82(s, 4H), 3.77 (s, 6H).

## Step 2

Compound 62 (5.36g, 19.5mmol) was dissolved into toluene (76mL), and 1-chloroethyl chloroformate (2.94mL, 27.3mmol) was added in an ice-water bath. The mixture was stirred under heat reflux. After confirmation of disappearance of materials by TLC, the obtained gel solid by evaporating was dissolved into methanol (7mL). The mixture was stirred under heat reflux to remove benzyl group. After cooling to room temperature,  $\text{Boc}_2\text{O}$  (9.04mL, 38.9mmol) and DIEA (6.8mL, 38.9mmol) were added. Methanol was removed by evaporating, and the mixture was extracted with ethyl acetate. The organic phase was washed with 0.2 mol/L hydrochloric acid aqueous solution and brine and dried up with sodium sulfate anhydrous. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate=7/3) to give Compound 63 (4.17g, 75%) as colorless oil.

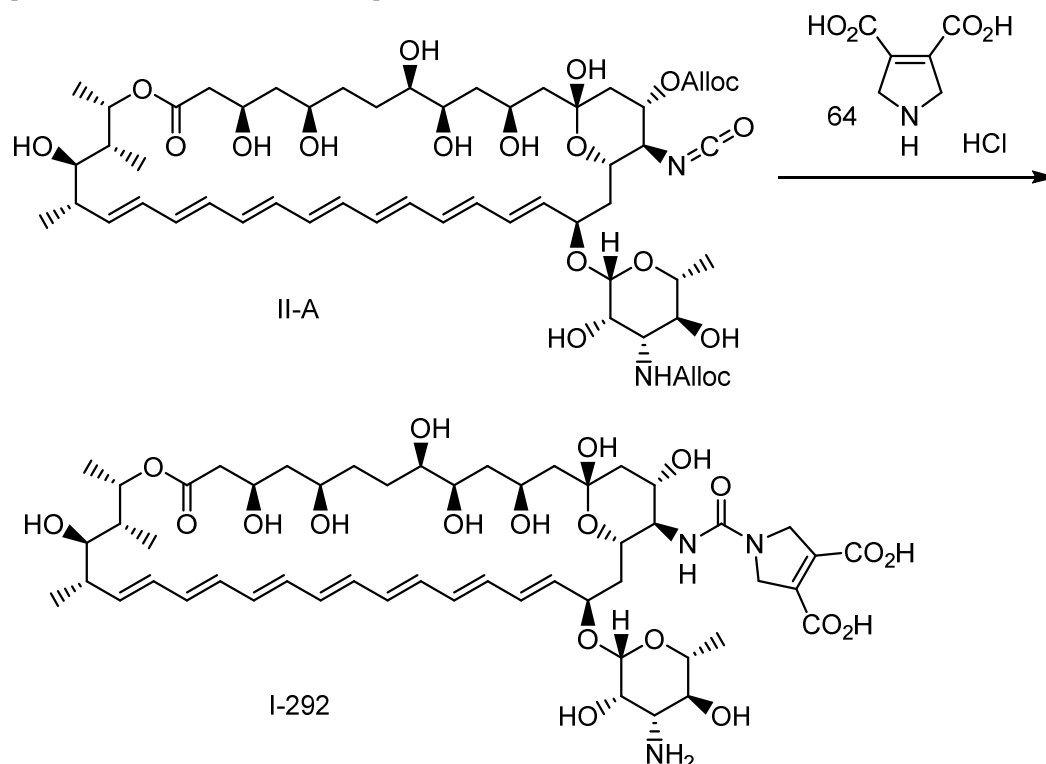
$^1\text{H-NMR}(\text{CDCl}_3, 400\text{MHz})\delta$ : 4.44 (d, 4H,  $J=12\text{Hz}$ ), 3.82(s, 6H), 1.48(s, 9H).

## Step 3

Compound 63 (917mg, 3.21mmol) was dissolved into tetrahydrofuran (10mL), and 2mol/L sodium hydroxide aqueous solution (4.82mL) was added. The mixture was stirred for 2 hours at room temperature. After the mixture was neutralized with 2mol/L hydrochloric acid aqueous solution (4.82mL) and condensed, the mixture was dissolved into dichloromethane (15mL). After hydrochloric acid-dioxane (4mol/L, 3.2mL) was added, and the mixture was stirred at room temperature, the mixture was condensed to give Compound 64 (600mg). Compound 64 was used to next reaction

without purification.

[Chemical Formula 8 5]



Compound 64 (355mg, 1.83mmol) was dissolved into DMF (10mL), and DIEA (0.321mL, 1.83mmol) and Compound II-A (2g, 1.84mmol) were added. The mixture was stirred for a few hours at room temperature. After powderization by adding diisopropyl ether, the obtained residue was purified crudely by silica-gel column chromatography. The obtained solids (1.47g) were dissolved into DMF (5mL), and morpholine (1.03mL, 11.8mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (68mg, 0.059mmol) were added. The mixture was stirred at room temperature under nitrogen atmosphere. The resulted solids by adding diisopropyl ether were filtrated. The solids were purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3 to 10/90/9). The obtained fractions were condensed to give Compound I-292 (13mg, yellow powder, 0.9%).

LC/MS: m/z 1078.5 [M+H]<sup>+</sup>

Elementary analysis: C<sub>53</sub>H<sub>79</sub>N<sub>3</sub>O<sub>20</sub>(C<sub>3</sub>H<sub>7</sub>NO)<sub>0.3</sub>(H<sub>2</sub>O)<sub>4.4</sub>

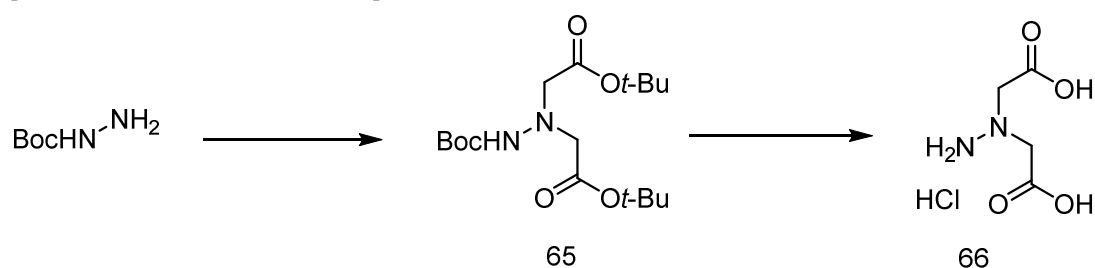
Calculated value: C 54.89; H 7.68; N 3.97 (%)

Actual value: C 54.90; H 7.49; N 3.97 (%)

[0 2 0 6]

Example 34: Synthesis of Compound I-309

[Chemical Formula 8 6]



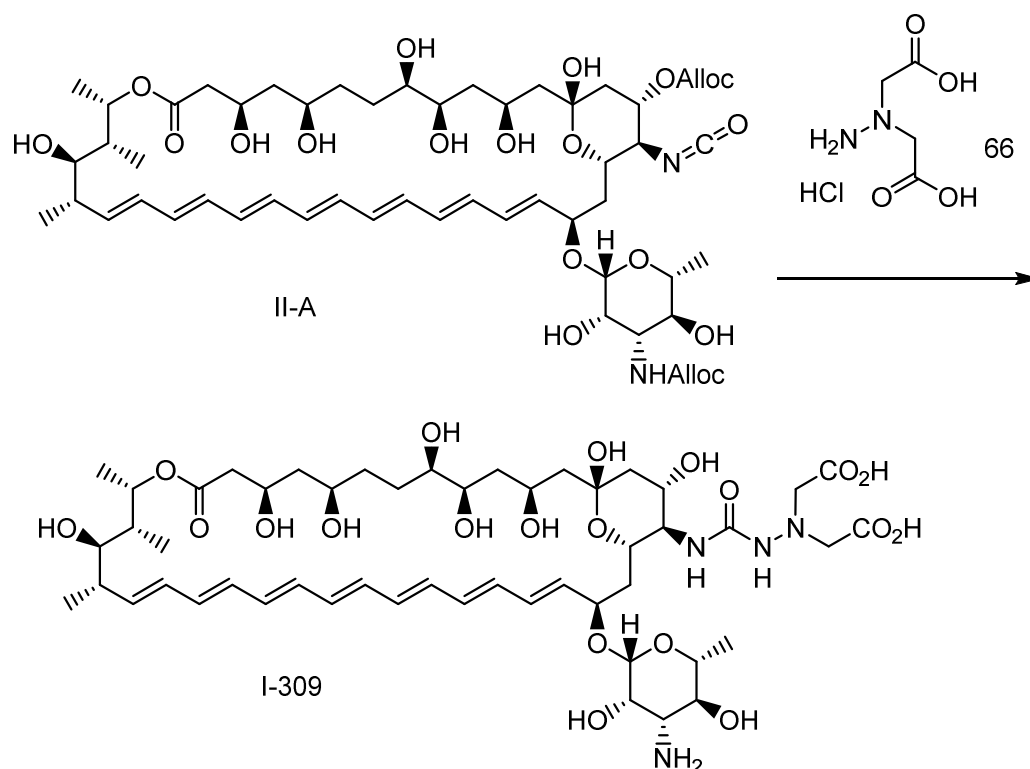
Step 1

Tert-butyl 2-bromoacetate (2.2mL, 15.1mmol) was dissolved into DMF (10mL), and DIEA (2.64mL, 15.1mmol) and tert-butyl hydrazine carboxylate (1g, 7.57mmol) were added. The mixture was stirred at room temperature. After water was added, the mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and dried up with sodium sulfate anhydrous. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate=1/1) to give Compound 65 (1.8g, 66%) as white solids.

#### Step 2

Compound 1 (1.8g, 4.99mmol) was dissolved into dichloromethane (20mL), and hydrochloric acid-dioxane (4mol/L, 5mL) was added. The mixture was stirred at room temperature and condensed to give Compound 66 (1.01g) as gummy solids. Compound 66 was used to next reaction without purification.

[Chemical Formula 8 7]



Compound II-A (2g, 1.84mmol) was dissolved into DMF (10mL), and DIEA (0.321mL, 1.84mmol) and Compound 66 (0.339g, 1.836mmol) were added. The mixture was stirred for 40 minutes at room temperature. After powderization by adding diisopropyl ether, the obtained residue was purified crudely by silica-gel column chromatography. The obtained solids (1.51g) were dissolved into DMF (6mL), and morpholine (1.06mL, 12.2mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (71mg, 0.061mmol) were added. The mixture was stirred for 20 minutes at room temperature under nitrogen atmosphere. The resulting solids by adding diisopropyl ether were filtered. The solids were purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3 to 10/90/9). The obtained fractions were condensed to give Compound I-309 (174mg, 7%) as orange powder. LC/MS: m/z 1069.4 [M+H]<sup>+</sup>

Elementary analysis: C<sub>51</sub>H<sub>80</sub>N<sub>4</sub>O<sub>20</sub>(C<sub>3</sub>H<sub>7</sub>NO)1.1(H<sub>2</sub>O)0.4(MeOH)1.7

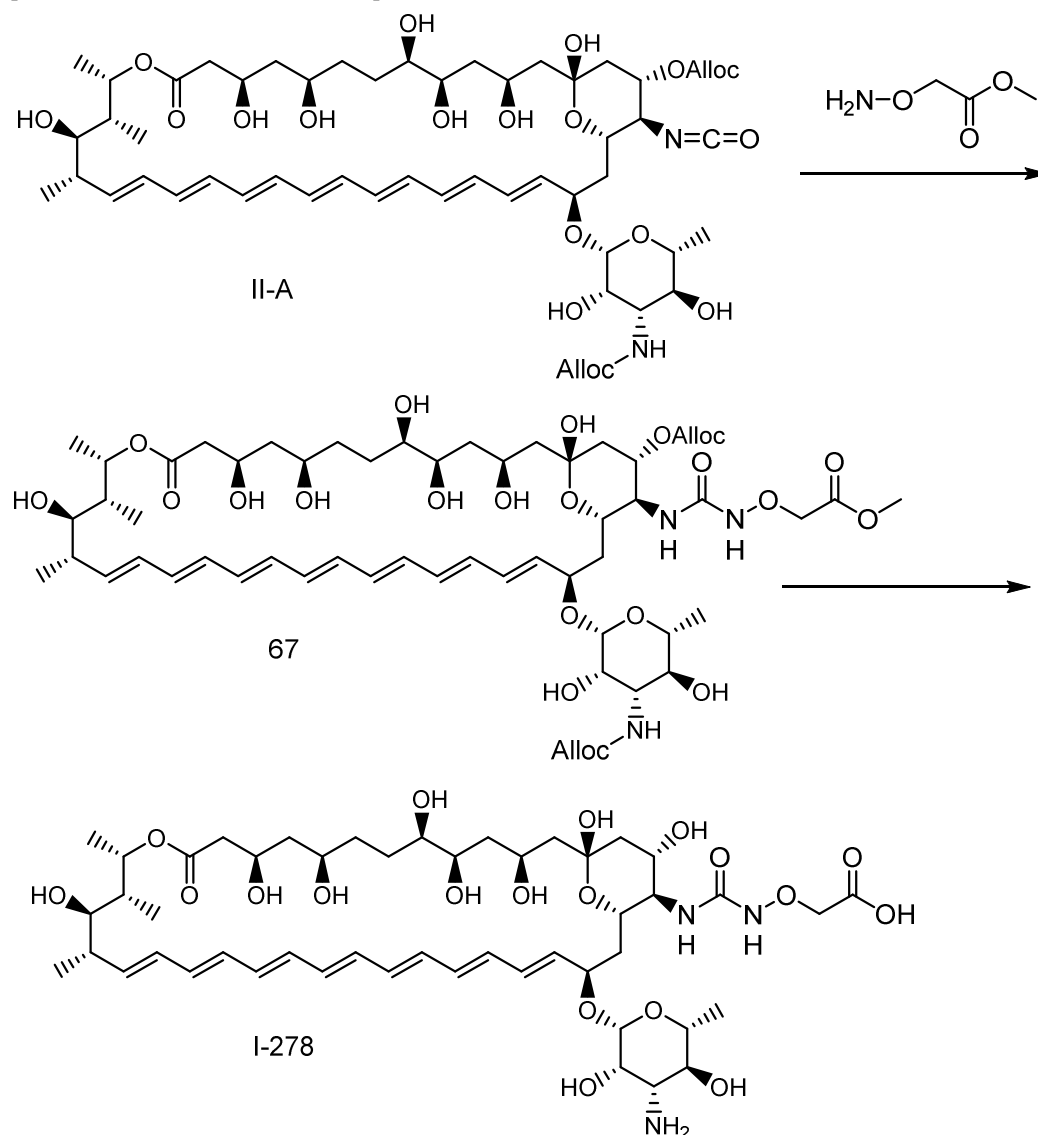
Calculated value: C 55.53 (-0.01%); H 7.93 (0.01%); N 5.90 (0.02%) (%)

Actual value: C 55.52; H 7.94; N 5.92 (%)

[0 2 0 7]

## Example 35: Synthesis of Compound I-278

[Chemical Formula 8 8]



## Step 1

Compound II-A (2g, 1.84mmol) was dissolved into DMF (10mL), and DIEA (1.6mL, 9.18mmol) and methylaminooxy acetate (347mg, 3.31mmol) were added. The mixture was stirred for an hour 20 minutes at room temperature. After water was added, the mixture was stirred for an hour 30 minutes at room temperature. After powderization by adding diisopropyl ether, the powder was purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5~85/15/1.5) to give yellow powder (Compound 67: 300mg, 13%). The retention time was 11.4 minutes by HPLC analysis (methanol/distilled water containing 0.1% PIC-B7= gradient 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm).

## Step 2

Compound 67 (300mg, 0.251mmol) was dissolved into DMF (5mL), and morpholine (0.22mL, 2.51mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (14.5mg, 0.013mmol) were added. The mixture was stirred for 45 minutes at room temperature under nitrogen atmosphere. The resulting solids by adding diisopropyl ether were filtered. The solids were purified by silica-gel column chromatography (chloroform/methanol/water=50/50/3 to 10/90/9). The obtained fractions were condensed to give orange powder (141mg, 0.137mmol). The powder was dissolved

into tetrahydrofuran (12mL) and methanol (6mL), and 2mol/L sodium hydroxide aqueous solution (0.21mL, 0.412mmol) was added. The mixture was stirred for an hour at room temperature. The mixture was neutralized with 2 mol/L hydrochloric acid aqueous solution and diluted with water. After organic solvent was condensed, the residue was lyophilized to give Compound I-278 (190mg, 55%). The retention time was 7.7 minutes by HPLC analysis (methanol/distilled water containing 0.1% PIC-B7=gradient 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm). LC/MS: 1012.3 [M+H]<sup>+</sup>

Elementary analysis: C<sub>49</sub>H<sub>77</sub>N<sub>3</sub>O<sub>19</sub>(H<sub>2</sub>O)<sub>6.1</sub>(NaCl)<sub>5</sub>

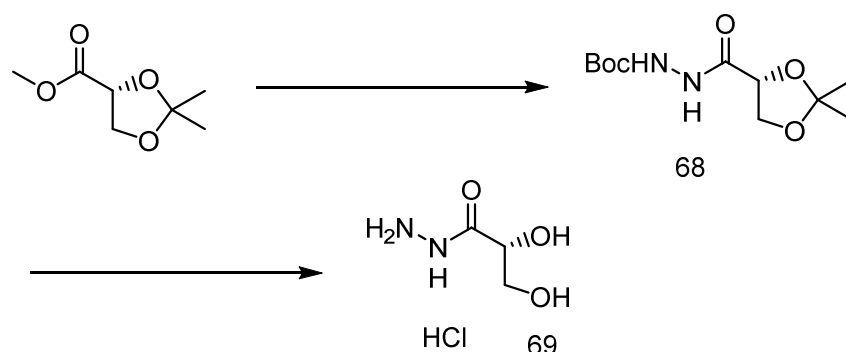
Calculated value: C 41.61; H 6.36; N 2.97 (%)

Actual value: C 41.64; H 6.65; N 3.34 (%)

[0 2 0 8]

Example 36: Synthesis of Compound I-223

[Chemical Formula 8 9]

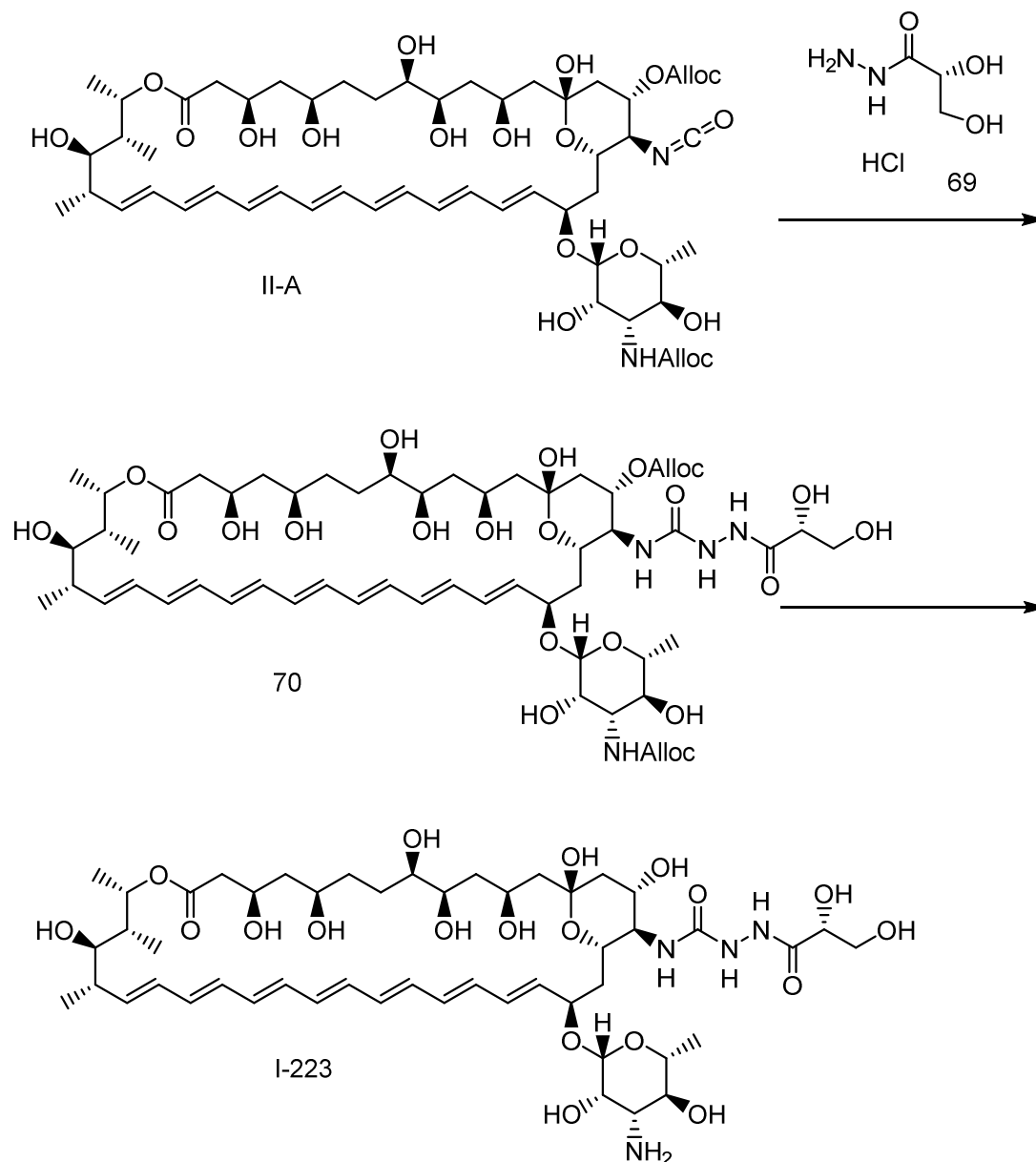


(R)-methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate (1g, 6.24mmol) was dissolved into methanol (10mL), and hydrazine monohydrate (0.303mL, 6.24mmol) was added. The mixture was stirred for 4 hours at room temperature. Boc<sub>2</sub>O (1.45mL, 6.24mmol) was added, and the mixture was stirred. After concentration, the mixture was purified by silica-gel column chromatography to give (R)-tert-butyl 2-(2,2-dimethyl-1,3-dioxolane-4-carbonyl)hydrazine carboxylate (Compound 68: 490mg, 30%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, 400MHz)δ: 8.13 (s, 1H), 6.44(br, 1H), 4.59 (m, 1H), 4.30(m, 1H), 4.18(m, 1H), 1.58(s, 3H), 1.48(s, 9H), 1.40(s, 3H)

Compound 68 was dissolved into dichloromethane (10mL), hydrochloric acid-dioxane (4mol/L, 1.883mL, 7.53mmol) was added. The mixture was stirred and condensed to give Compound 69. Compound 69 was used to next reaction without purification.

[Chemical Formula 9 0 ]



Compound II-A (1.961g, 1.8mmol) was dissolved into DMF, and DIEA (1.57mL, 9.00mmol) and Compound 69 (282mg, 1.8mmol) were added. The mixture was stirred at room temperature. After powderization by adding diisopropyl ether, the powder was purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5 to 85/15/1.5) to give Compound 70 (750mg, 34%). Compound 70 (750mg, 0.62mmol) was dissolved into DMF (4mL), and morpholine (0.54mL, 6.2mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (35.8mg, 0.031mmol) were added. The mixture was stirred for an hour at room temperature under nitrogen atmosphere. The resulting solids by adding diisopropyl ether were filtered and purified by silica-gel column chromatography (chloroform/methanol/water=50/50/3 to 10/90/9) to give Compound I-223 (104mg, 14%).

LC/MS: 1041.4 [M+H]<sup>+</sup>, 1063.5 [M+Na]<sup>+</sup>

Elementary analysis: C<sub>50</sub>H<sub>80</sub>N<sub>4</sub>O<sub>19</sub>(H<sub>2</sub>O)<sub>4.5</sub>

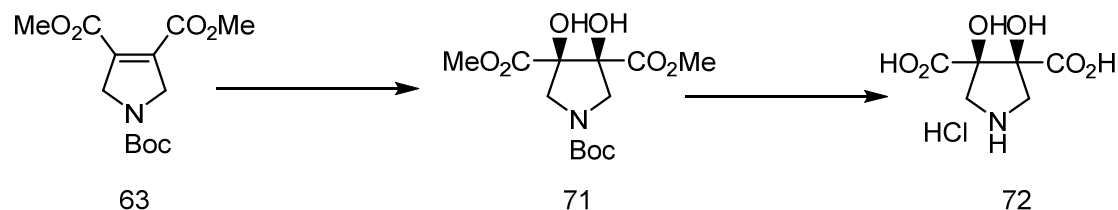
Calculated value: C 53.51; H 7.99; N 4.99 (%)

Actual value: C 53.53; H 7.73; N 4.86 (%)

[ 0 2 0 9 ]

## Example 37: Synthesis of Compound I-298

[Chemical Formula 9 1]



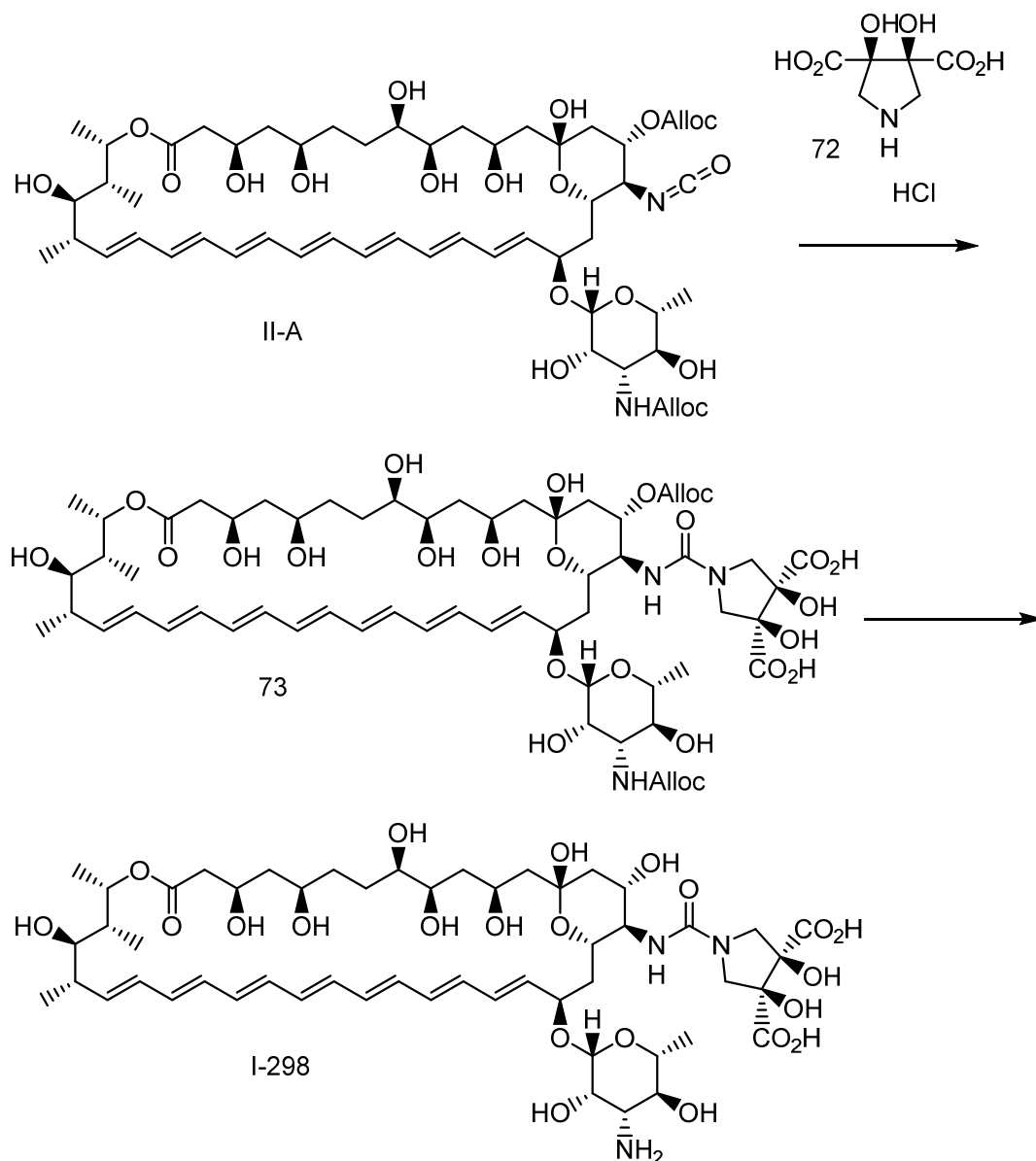
## Step 1

1-Tert-butyl 3,4-dimethyl 1H-pyrrole-1,3,4(2H,5H)-tricarboxylate (Compound 63: 1g, 3.51mmol) synthesized at Example 33 was dissolved into dioxane (10mL), and water (10mL) and Potassium Osmate(VI) Dihydrate (65mg, 0.175mmol) were added. The mixture was stirred in an ice-water bath. N-methylmorpholine N-oxide (616mg, 5.26mmol) was added, and the mixture was stirred. The reaction was quenched with 10% sodium hydrogen sulfite aqueous solution, and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and dried up with sodium sulfate anhydrous, and the resulted residue was purified by silica-gel column chromatography (hexane/ethyl acetate=1/1) to give Compound 71 (843mg, 75%). <sup>1</sup>H-NMR(CDCl<sub>3</sub>, 400MHz)δ:3.97 (d, 1H, J=8Hz), 3.90(d, 1H, J=8Hz), 3.79 (s,6H).3.72(d, 2H, J=8Hz), 3.62(d, 2H, J=12Hz), 1.49(s, 9H)

## Step 2

Compound 71 (743mg, 2.327mmol) was dissolved into tetrahydrofuran (10mL) and water (5mL), and 2mol/L sodium hydroxide aqueous solution (3.49mL, 6.98mmol) was added. The mixture was stirred for 2 hours at room temperature. The mixture was neutralized with 2mol/L hydrochloric acid aqueous solution and condensed. Dichloromethane (20mL) was added to the obtained residue, and hydrochloric acid-dioxane (4mol/L, 2.3mL) was added. After the mixture was stirred for at room temperature, the mixture was condensed to give Compound 72 (530mg) as gummy solids. Compound 72 was used to next reaction without purification.

[Chemical Formula 9 2]



Compound 72 (530mg, 2.33mmol) was dissolved into DMF (10mL), and DIEA (1.28mL, 7.34mmol) and Compound II-A (2g, 1.84mmol) were added. The mixture was stirred at room temperature. After powderization by adding diisopropyl ether, the resulted powder was purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5 to 85/15/1.5). The obtained powder 73 (706mg, 0.551mmol) was dissolved into DMF (3mL), and morpholine (0.48mL, 5.51mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (32mg, 0.028mmol) were added. The mixture was stirred at room temperature. The resulting solids by adding diisopropyl ether were filtered. The solids were purified by silica-gel column chromatography (chloroform/methanol/water=50/50/3 to 10/90/9) to give Compound I-298 (43mg, 7%).

LC/MS: 1112.4  $[\text{M} + \text{H}]^+$

Elementary analysis:  $\text{C}_{53}\text{H}_{81}\text{N}_3\text{O}_{22}(\text{C}_3\text{H}_7\text{NO})_{0.2}(\text{H}_2\text{O})_{4.2}$

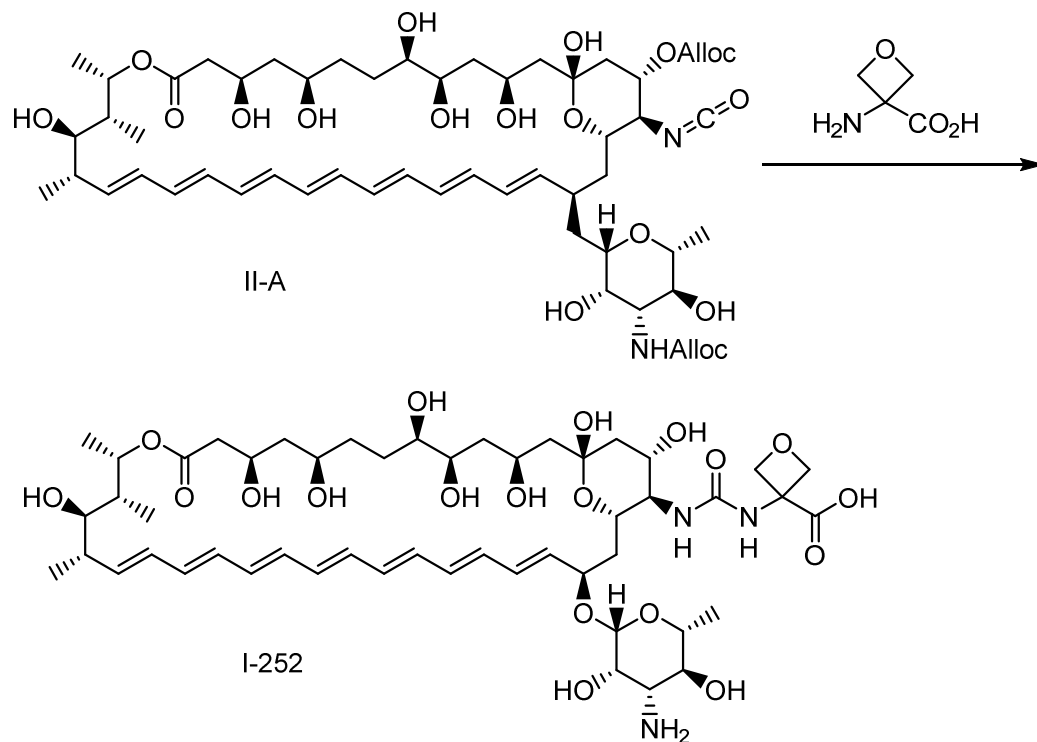
Calculated value: C 53.54; H 7.61; N 3.73 (%)

Actual value: C 53.55; H 7.54; N 3.80 (%)

[0 2 1 0]

Example 38: Synthesis of Compound I-252

[Chemical Formula 9 3]



Compound II-A (2g, 1.836mmol) was dissolved into DMF (10mL), and DIEA (1.6mL, 9.18mmol) and 3-aminooxetan-3-carboxylic acid (215mg, 1.836mmol) were added. The mixture was stirred at 40°C over night. After powderization by adding diisopropyl ether, the resulted powder was purified by silica-gel column chromatography. The obtained powder (695mg, 31%) was dissolved into DMF (5mL), and morpholine (0.50mL, 5.76mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (33mg, 0.029mmol) were added. The mixture was stirred for 15 minutes at room temperature under nitrogen atmosphere. The resulting solids by adding diisopropyl ether were filtered. The resulted solids were purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3 to 10/90/9) to give Compound I-252 (58.4mg, 8%). LC/MS: 1038.4[M+H]<sup>+</sup>

Elementary analysis: C<sub>51</sub>H<sub>79</sub>N<sub>3</sub>O<sub>19</sub>(C<sub>3</sub>H<sub>7</sub>NO)0.7(H<sub>2</sub>O)2.0(MeOH)1.8

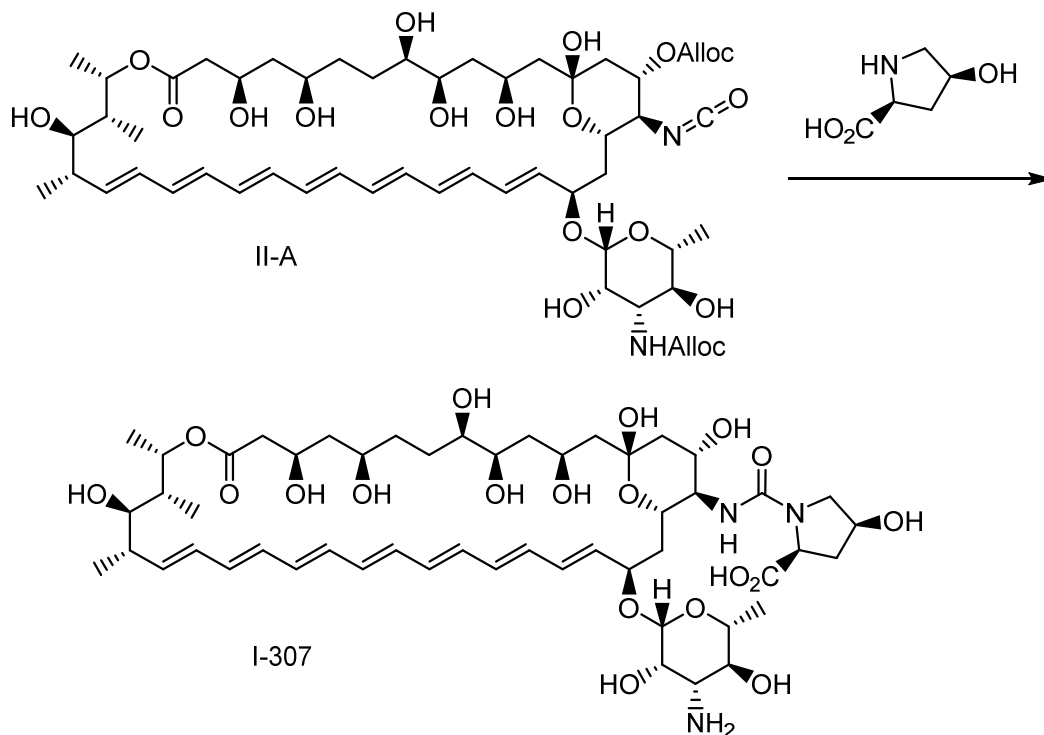
Calculated value: C 55.74; H 8.10; N 4.38 (%)

Actual value: C 55.72; H 8.04; N 4.36 (%)

[0 2 1 1]

Example 39: Synthesis of Compound I-307

[Chemical Formula 9 4]



Compound II-A (2g, 1.836mmol) was dissolved into DMF (10mL), and DIEA (1.283mL, 7.34mmol) and (2S,4S)-4-Hydroxypyrrolidine-2-carboxylic acid (241mg, 1.836mmol) were added. The mixture was stirred at 40°C over night. After powderization by adding diisopropyl ether, the obtained powder was purified by silica-gel column chromatography. The obtained powder (1g, 0.819mmol, 45%) was dissolved into DMF (5mL), and morpholine (0.71mL, 8.19mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (47mg, 0.041mmol) were added. The mixture was stirred for 15 minutes at room temperature. The resulting solids by adding diisopropyl ether were filtered. The resulted solids were purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3 to 10/90/9) to give Compound I-307 (124mg, 13%).

LC/MS: 1052.5 [M+H]<sup>+</sup>, 1074.5 [M+Na]<sup>+</sup>

Elementary analysis: C<sub>52</sub>H<sub>81</sub>N<sub>3</sub>O<sub>19</sub>(C<sub>3</sub>H<sub>7</sub>NO)<sub>0.8</sub>(H<sub>2</sub>O)<sub>1.8</sub>(MeOH)<sub>0.2</sub>

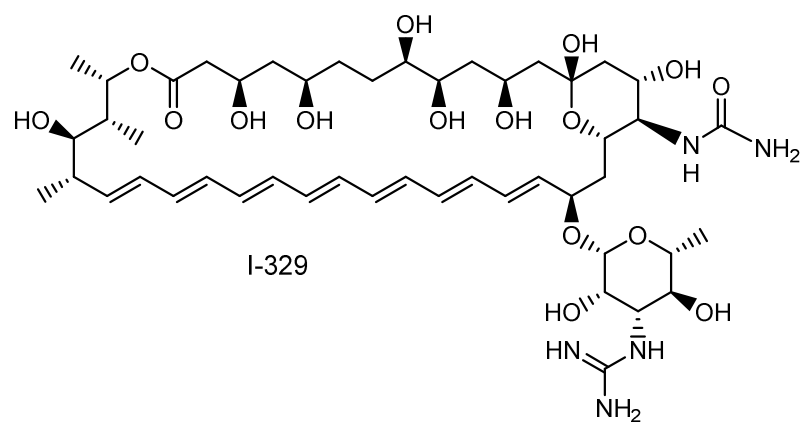
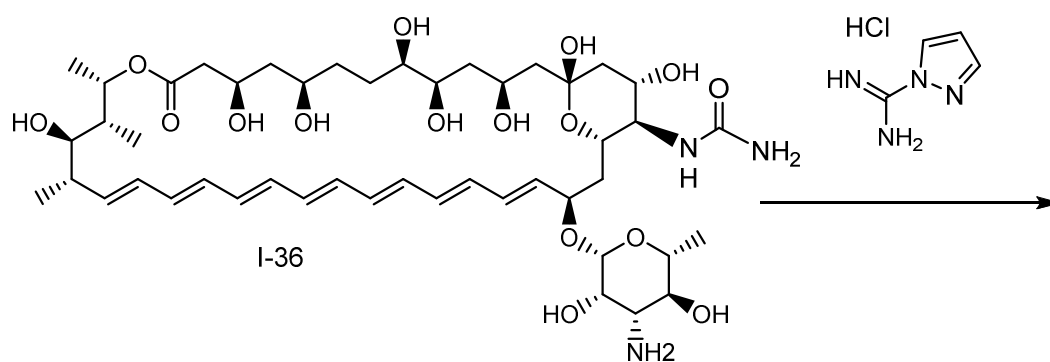
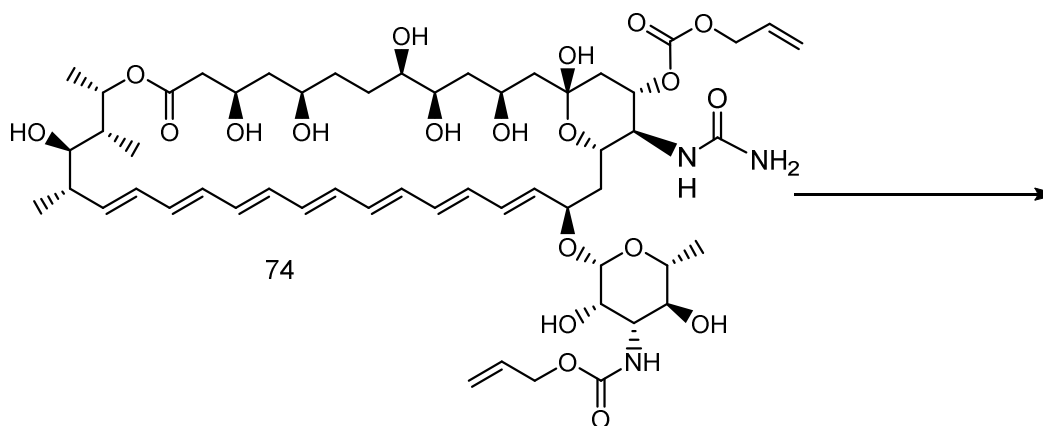
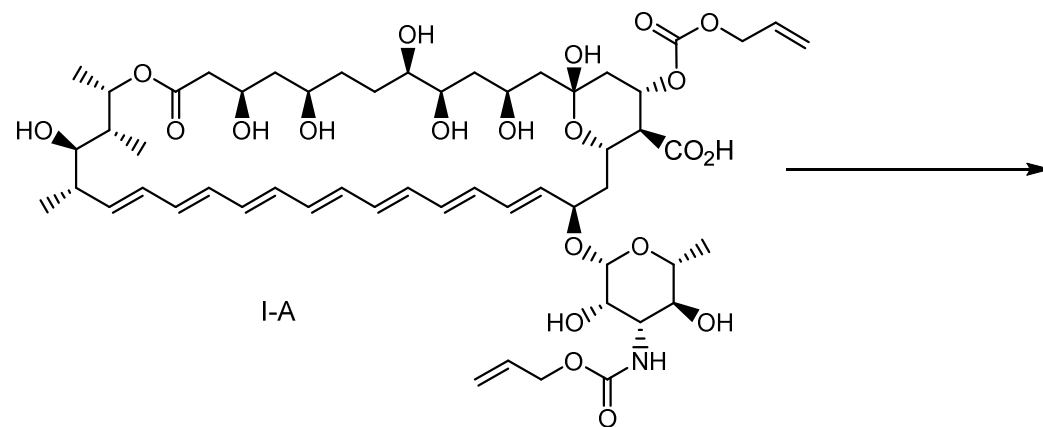
Calculated value: C 57.05; H 7.98; N 4.63 (%)

Actual value: C 57.06; H 7.97; N 4.60 (%)

[0 2 1 2]

Example 40: Synthesis of Compound I-329

[Chemical Formula 9 5]



## Step 1

Compound I-A (10.3g, 9.43mmol) was dissolved into DMF (50mL), and DIEA (2.47mmol) and diphenylphosphoryl azide (3.04mL, 14.1mmol) were added. The

mixture was stirred for 2 hours 30 minutes at room temperature further 90 minutes 50°C. Ammonia (7mol/L, methanol solution, 4mL) was added, and the mixture was stirred for 35 minutes at room temperature. After powderization by adding diisopropyl ether (600mL), the resulted powder was purified by silica-gel column chromatography (chloroform/methanol/water=10/1/0.1) to give Compound 74 (3.14g, 30%).

#### Step 2

Compound 74 (3.14g) was dissolved into DMF (15mL), and morpholine (1.73mL, 19.8mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (328mg, 0.284mmol) were added. The mixture was stirred for 90 minutes at room temperature under nitrogen atmosphere. The resulting solids by adding diisopropyl ether were filtered. The resulted residue was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=70/30/3 to 50/50/9) to give Compound I-36 (615mg, 23%). LC-MS: 938.9 [M+H]<sup>+</sup>

#### Step 3

Compound I-36 (614mg, 0.656mmol) was dissolved into DMF (10mL), and DIEA (0.572mL, 3.28mmol) and 1H-pyrazole-1-carboxyimide hydrochloride (480mg, 3.28mmol) were added. The mixture was stirred for 22 hours at room temperature. After powderization by adding diisopropyl ether, the obtained powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=70/30/3 to 30/70/7) to give Compound I-329 (262mg, 41%). LC-MS: 980.5[M+H]<sup>+</sup>

Elementary analysis: (C<sub>48</sub>H<sub>77</sub>N<sub>5</sub>O<sub>16</sub>)(C<sub>3</sub>H<sub>7</sub>NO)0.5(H<sub>2</sub>O)4.4

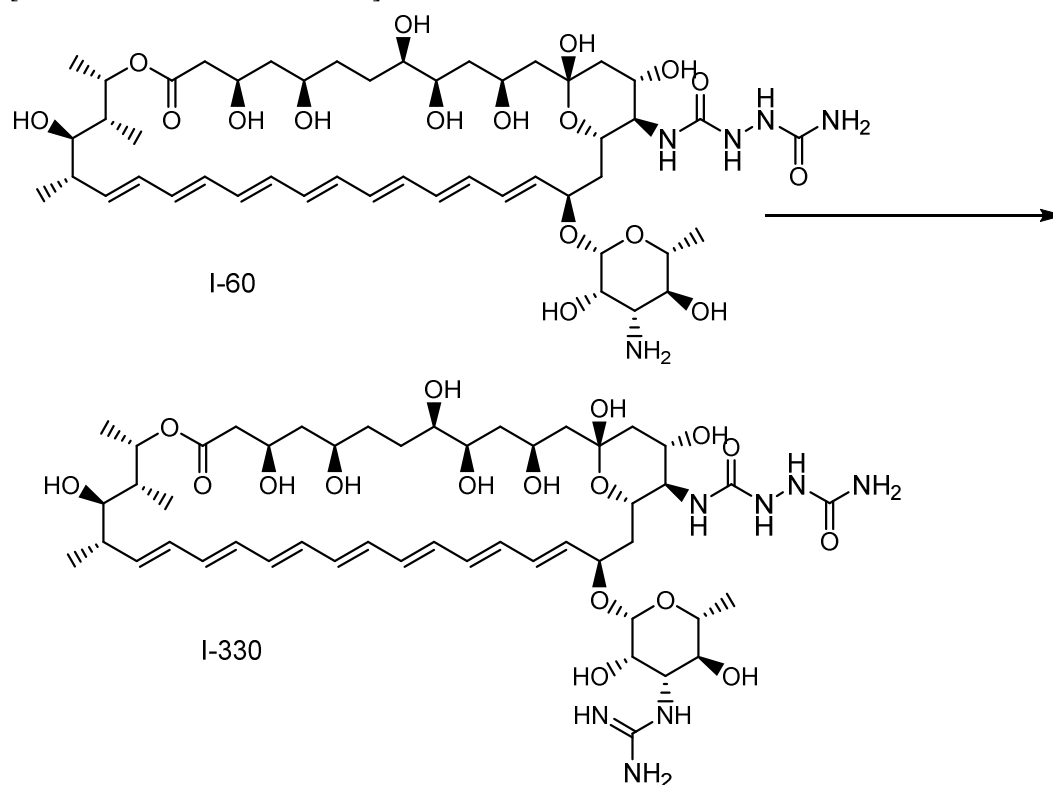
Calculated value: C 54.25; H 8.21; N 7.03 (%)

Actual value: C 54.26; H 7.97; N 7.32 (%)

[0 2 1 3]

#### Example 41: Synthesis of Compound I-330

[Chemical Formula 9 6]



Compound I-60 (200mg, 0.201mmol) was dissolved into DMF (1mL), and DIEA

(0.245mL, 1.41mmol) and 1H-pyrazole-1-carboxyimide hydrochloride (206mg, 1.41mmol) were added. The mixture was stirred for 24 hours at room temperature. After powderization by adding diisopropyl ether, the powder was purified by reverse-phase chromatography (HP20ss, 0.05% formic acid aqueous solution/acetonitrile=90/10 to 70/30). The obtained fractions were codensed and lyophilized to give Compound I-330 (119mg, 58%).

LC-MS: 1038.5[M+H]<sup>+</sup>

Elementary analysis: (C<sub>49</sub>H<sub>78</sub>N<sub>7</sub>O<sub>17</sub>)(HCO<sub>2</sub>H)0.5(C<sub>12</sub>H<sub>11</sub>O<sub>4</sub>P)0.3(H<sub>2</sub>O)7(HCl)0.1

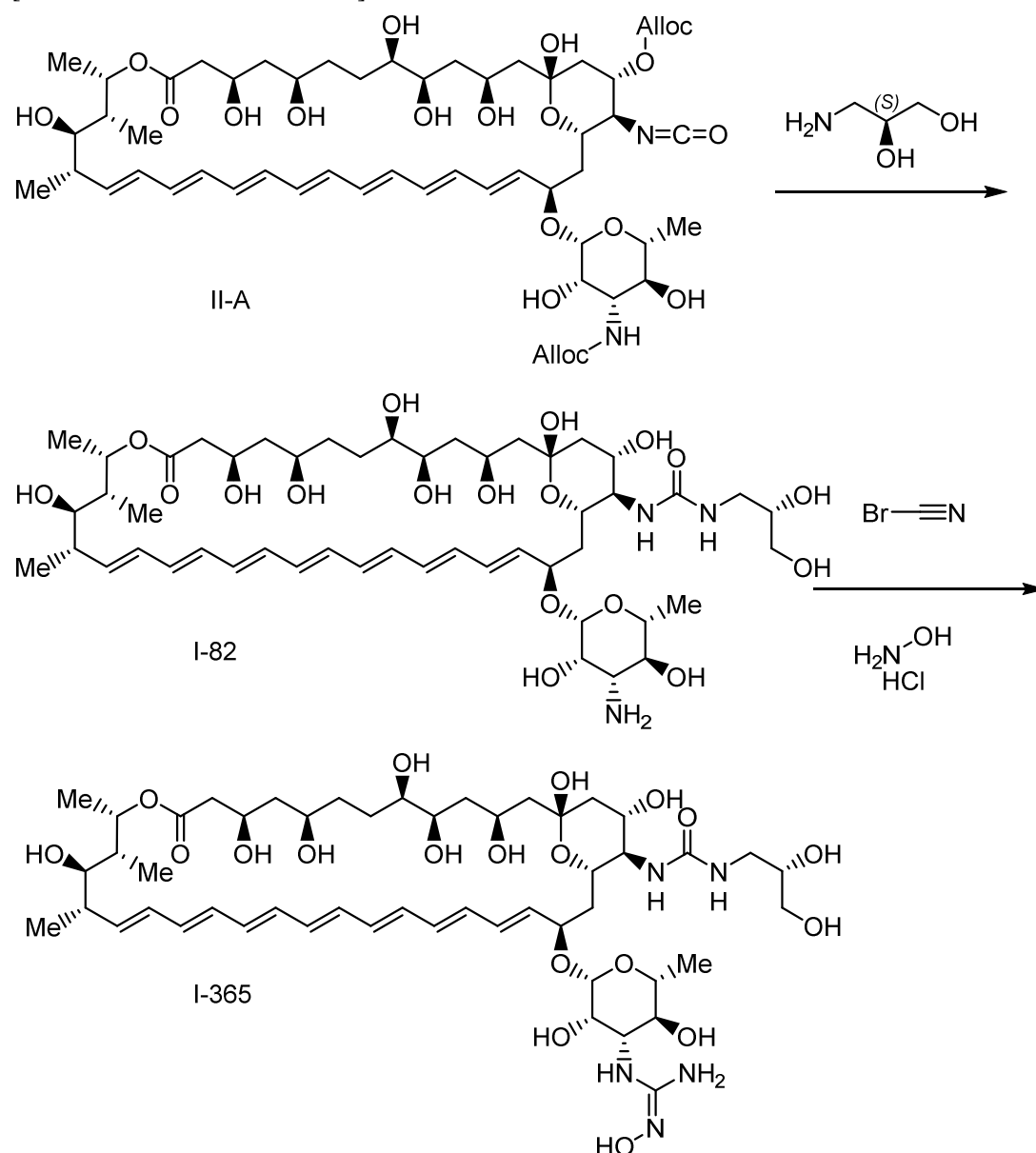
Calculated value: C 50.42; H 7.68; N 7.75 (%)

Actual value: C 50.58; H 7.51; N 7.55 (%)

[0 2 1 4]

Example 42: Synthesis of Compound I-365

[Chemical Formula 9 7]



#### Step 1

Compound II-A (15.7g, 14.41mmol) was dissolved into DMF (75mL), and DIEA (7.55mL, 43.2mmol) and (S)-3-aminopropane-1,2-diol (1.97g, 21.62mmol) were added. The mixture was stirred for 2 hours 30 minutes at room temperature. After powderization by adding diisopropyl ether, the resulted powder was purified by silica-

gel column chromatography to give powder (1.07g, 6%). The obtained powder was dissolved into DMF (10mL), and morpholine (0.553mL, 6.35mmol) and  $\text{Pd(PPh}_3)_4$  (52.4mg, 0.045mmol) were added. The mixture was stirred for 2 hours 30 minutes at room temperature under nitrogen atmosphere. The resulting solids by adding diisopropyl ether were filtered. The solids were purified by silica-gel column chromatography to give Compound I-82 (882mg, 6%).

LC-MS: 1012.4[M+H]<sup>+</sup>, 1034.4[M+Na]<sup>+</sup>

#### Step 2

Compound I-82 (365mg, 0.361mmol) was dissolved into DMF (3.6mL), and DIEA (0.157mL, 0.902mmol) and cyanicbromide (76mg, 0.721mmol) were added. The mixture was stirred for an hour 40 minutes at room temperature. DIEA (0.189mL, 1.082mmol) and hydroxylamine hydrochloride (75mg, 1.08mmol) were added, and the mixture was stirred for an hour 40 minutes. After powderization by adding diisopropyl ether, the powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=90/10/3 to 50/50/5) to give Compound I-365 (93mg, 24%).

LC-MS: 1071 [M+H]<sup>+</sup>

Elementary analysis:  $(\text{C}_{51}\text{H}_{83}\text{N}_5\text{O}_{19})(\text{C}_3\text{H}_7\text{NO})1.2(\text{H}_2\text{O})_4$

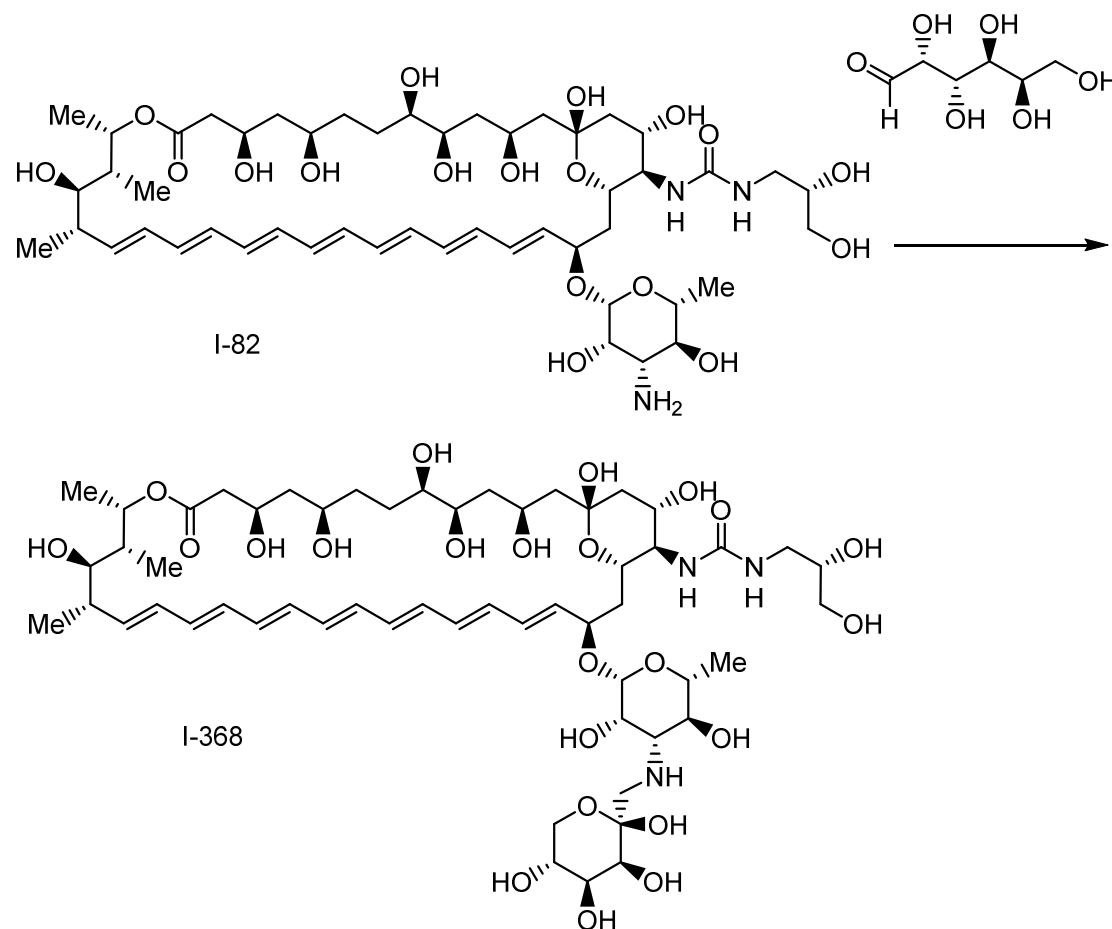
Calculated value: C 53.32; H 8.15; N 7.06 (%)

Actual value: C 53.59; H 7.94; N 7.40 (%)

[0 2 1 5]

#### Example 43: Synthesis of Compound I-368

[Chemical Formula 9 8]



Compound I-82 (200mg, 0.198mmol) was dissolved into DMF (1mL), and d-galactose (71mg, 0.395mmol) and acetic acid (0.113mL, 1.976mmol) were added. The

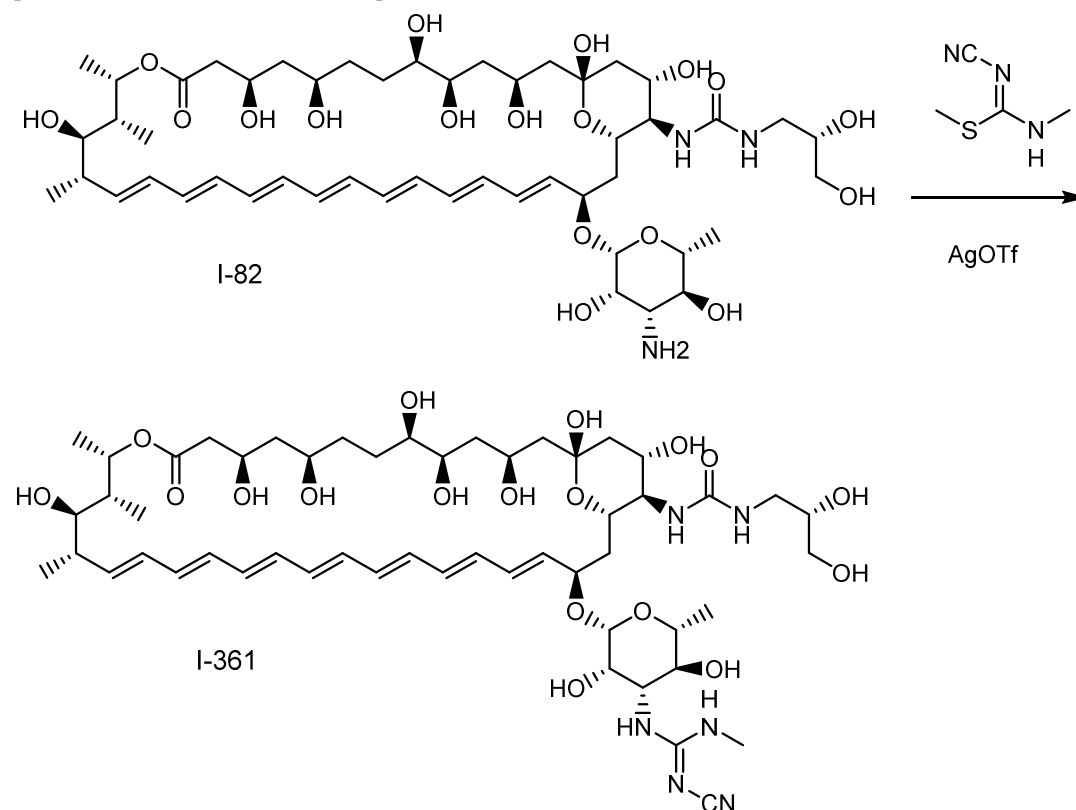
mixture was stirred for 2 hours 30 minutes at room temperature, further for 3 hours at 40°C. After powderization by adding diisopropyl ether, the powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=70/30/3) to give Compound I-368 (11mg, 5%).

LC-MS: 1174 [M+H]<sup>+</sup>

[0 2 1 6]

#### Example 44: Synthesis of Compound I-361

[Chemical Formula 9 9]



Compound I-82 (100mg, 0.099mmol) was dissolved into DMF (1mL), and (Z)-methyl N'-cyano-N-methylcarbamidethioate (15.32mg, 0.119mmol), DIEA (0.052mL, 0.296mmol) and Silver Trifluoromethanesulfonate (30mg, 0.119mmol) were added. The mixture was stirred for 2 hours at 0°C. (Z)-methyl N'-methylcarbamidethioate (15.32mg, 0.119mmol), Silver Trifluoromethanesulfonate (30mg, 0.119mmol) and DIEA (0.052mL, 0.296mmol) were added. The mixture was stirred for an hour 30 minutes at 0°C, further 3 hours at room temperature. After powderization by adding diisopropyl ether, the powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=95/5/0.5 to 50/50/5) to give Compound I-361 (27mg, 25%).

LC-MS: 1093.5 [M+H]<sup>+</sup>, 1115.5 [M+Na]<sup>+</sup>

Elementary analysis: C<sub>53</sub>H<sub>84</sub>N<sub>6</sub>O<sub>18</sub>(H<sub>2</sub>O)<sub>6.5</sub>(C<sub>6</sub>H<sub>14</sub>O)<sub>0.5</sub>

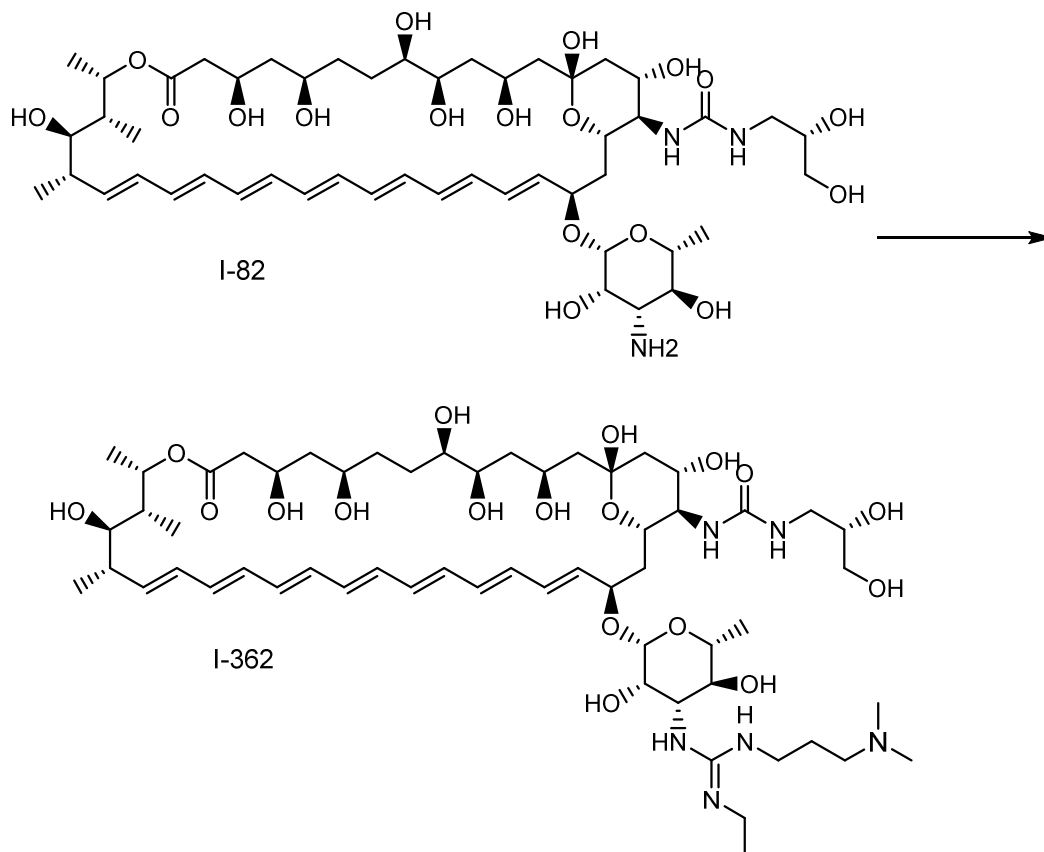
Calculated value: C 53.32; H 8.31; N 6.66 (%)

Actual value: C 53.45; H 7.86; N 6.36 (%)

[0 2 1 7]

#### Example 45: Synthesis of Compound I-362

[Chemical Formula 1 0 0]



Compound I-82 (98mg, 0.097mmol) was dissolved into DMF (1mL), and EDC HCl (27.8mg, 0.145mmol) and DMAP (1.183mg, 0.009mmol) were added. The mixture was stirred for 4 hours at room temperature. DMAP (5.3mg, 0.044mmol) was added, and the mixture was stirred for 19 hours at room temperature. DIEA (0.034mL, 0.194mmol), EDC HCl (37.1mg, 0.194mmol) and DIEA (0.034mL, 0.194mmol) were added, and the mixture was stirred for 23 hours at room temperature. After powderization by adding diisopropyl ether, the powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=50/50/5) to give Compound I-362 (45mg, 39%).

LC-MS: 1167.6 [M+H]<sup>+</sup>

Elementary analysis: C<sub>58</sub>H<sub>98</sub>N<sub>6</sub>O<sub>18</sub>(H<sub>2</sub>O)<sub>6</sub>

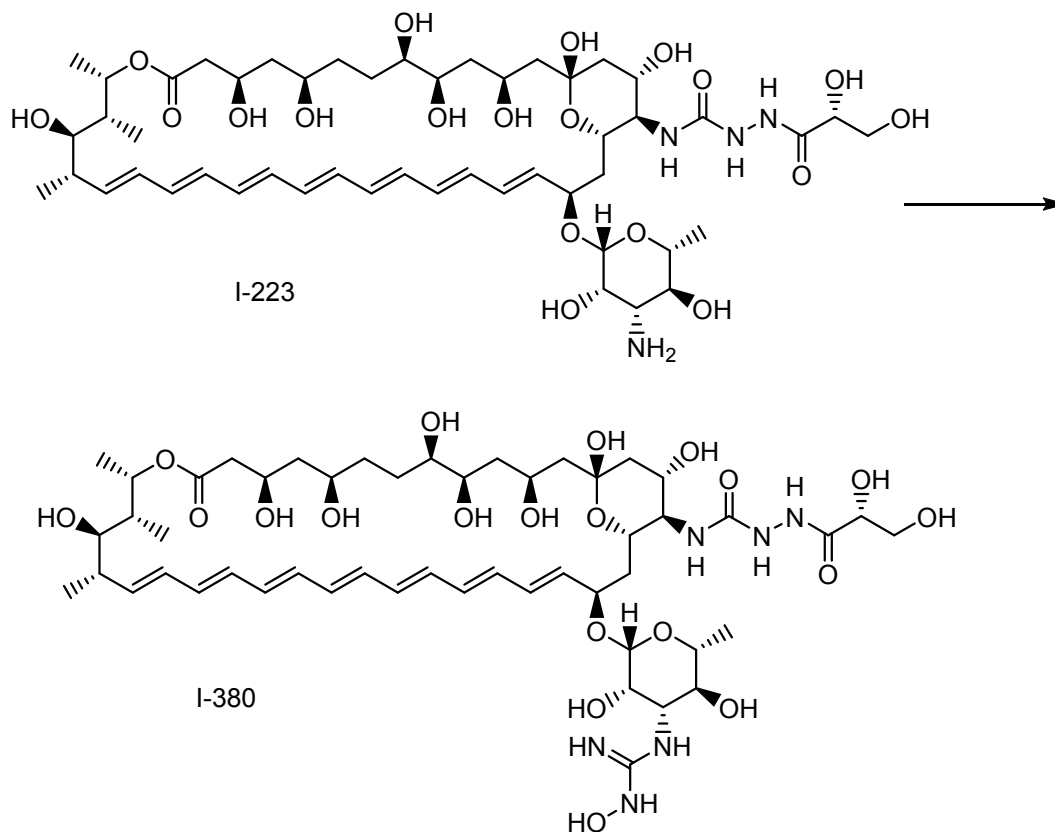
Calculated value: C 54.62; H 8.69; N 6.59 (%)

Actual value: C 54.79; H 8.16; N 6.31 (%)

[0 2 1 8]

Example 46: Synthesis of Compound I-380

[Chemical Formula 1 0 1]



Compound I-223 (121mg, 0.116mmol) was dissolved into DMF (3mL), and DIEA (0.20mL, 1.162mmol) and cyanicbromide (42mg, 0.397mmol) were added. The mixture was stirred for 50 minutes at room temperature. Hydroxylamine hydrochloride (41mg, 0.58mmol) was added, and the mixture was stirred for an hour. After powderization by adding diisopropyl ether, the powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=90/10/3 to 50/50/5) to give Compound I-380 (80mg, 54%).

LC-MS: 1099.5 [M+H]<sup>+</sup>, 1121.6 [M+Na]<sup>+</sup>

Elementary analysis: C<sub>51</sub>H<sub>82</sub>N<sub>6</sub>O<sub>20</sub>(C<sub>3</sub>H<sub>7</sub>NO)<sub>0.8</sub>(H<sub>2</sub>O)<sub>3.9</sub>

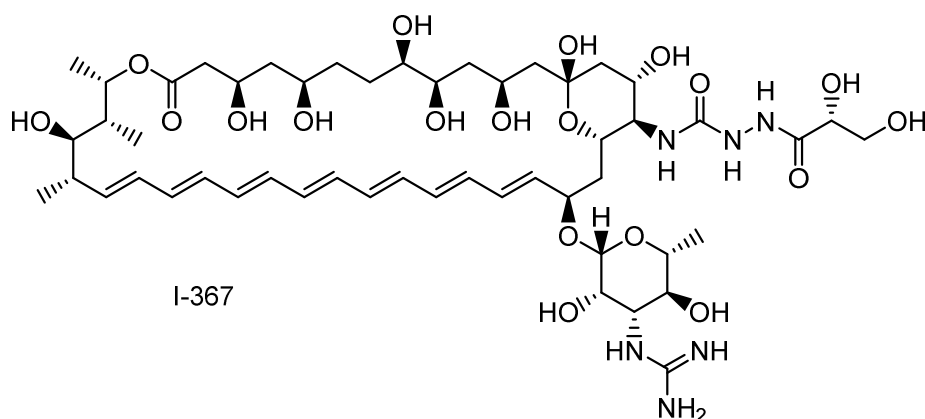
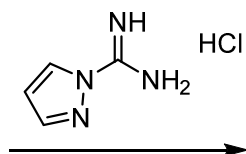
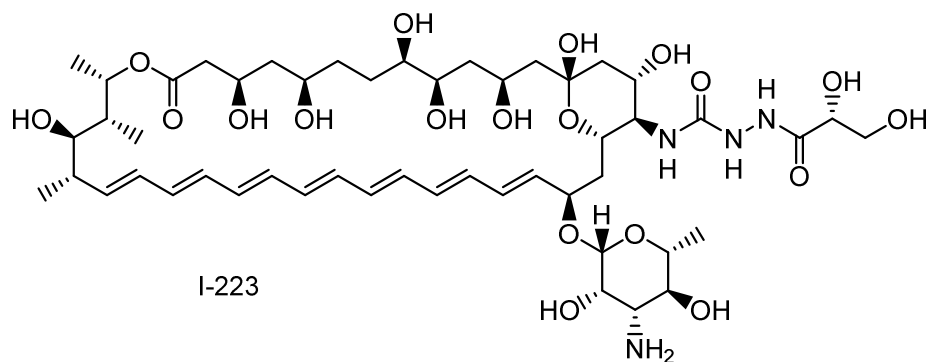
Calculated value: C 52.23; H 7.83; N 7.76 (%)

Actual value: C 52.17; H 7.55; N 7.76 (%)

[0 2 1 9]

Example 47: Synthesis of Compound I-367

[Chemical Formula 1 0 2]



Compound I-223 (108mg, 0.104mmol) was dissolved into DMF (2mL), and DIEA (0.127mL, 0.726mmol) and 1H-pyrazole-1-carboxyimide hydrochloride (106mg, 0.726mmol) were added. The mixture was stirred for 24 hours at room temperature. 1H-pyrazole-1-carboxyimide hydrochloride (106mg, 0.726mmol) was added, and the mixture was stirred for 24 hours at room temperature. After powderization by adding diisopropyl ether, the powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=70/30/3). The obtained fractions were condensed and lyophilized to give Compound I-367 (74mg, 59%).

LC-MS: 1083.3 [M+H]<sup>+</sup>

Elementary analysis: C<sub>51</sub>H<sub>82</sub>N<sub>6</sub>O<sub>19</sub>(C<sub>3</sub>H<sub>7</sub>NO)<sub>0.7</sub>(H<sub>2</sub>O)<sub>3.4</sub>(CHCl<sub>3</sub>)<sub>0.4</sub>

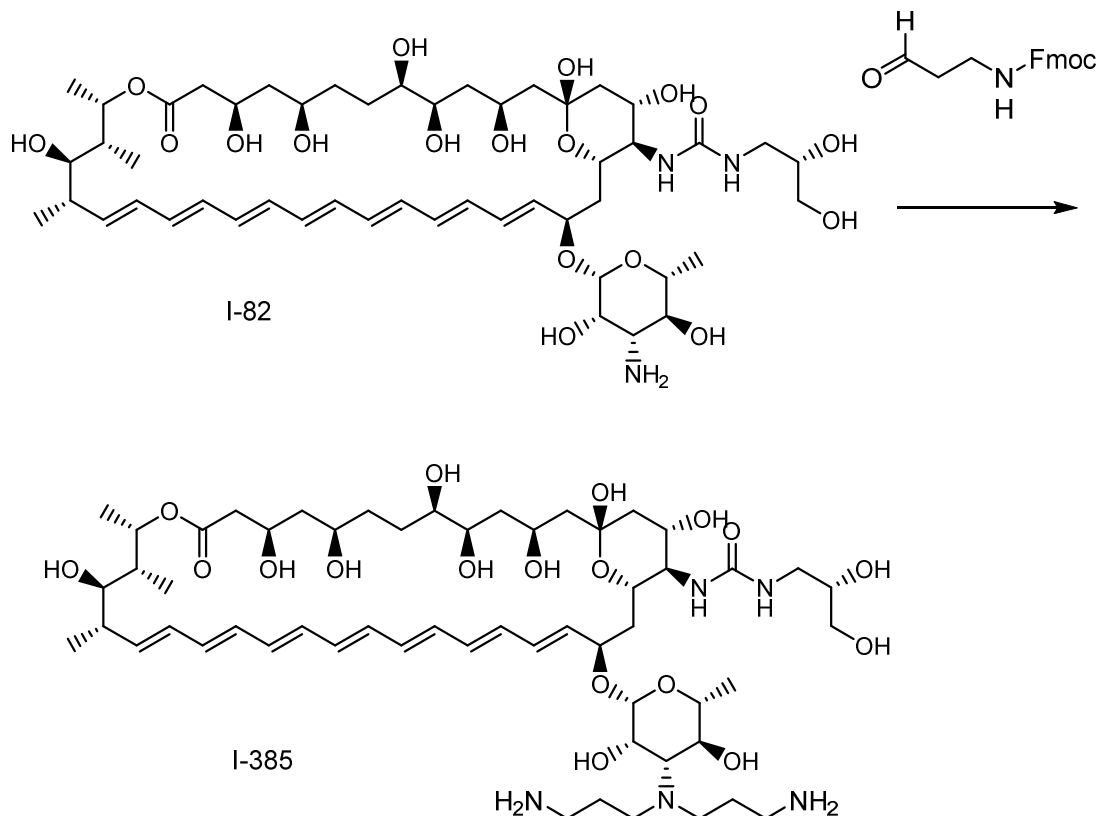
Calculated value: C 51.68; H 7.63; N 7.55 (%)

Actual value: C 51.64; H 7.60; N 7.61 (%)

[0 2 2 0]

Example 48: Synthesis of Compound I-385

[Chemical Formula 1 0 3]



Compound I-82 (1g, 0.998mmol) was dissolved into DMF (10mL), and 3-N-(fluorenylmethyloxycarbonyl)-3-aminopropionaldehyde (875mg, 2.96mmol) was added. After the mixture was stirred for 5 minutes at room temperature, sodium cyanoborohydride (186mg, 2.96mmol) and concentrated hydrochloric acid (0.165mL, 1.976mmol) were added. The mixture was stirred for 24 hours at room temperature. 3-N-(fluorenylmethyloxycarbonyl)-3-aminopropionaldehyde (292mg, 0.988mmol), sodium cyanoborohydride (93mg, 1.48mmol) and concentrated hydrochloric acid (0.041mL, 0.494mmol) were added, and the mixture was stirred for 24 hours. After powderization by adding diisopropyl ether, the powder was purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5 to 70/30/3). The obtained solids (261mg, 0.166mmol) were dissolved into DMF (2.5mL), and piperidine (0.082mL, 0.831mmol) was added. The mixture was stirred for 3 hours 50 minutes at room temperature. diisopropyl ether was added and filtrated, and the mixture was washed with diisopropyl ether to give Compound I-385 (178mg, 0.158mmol, 16%) as yellow solids. The retention time was 5.1 minutes by HPLC analysis (methanol/distilled water containing 0.1% PIC-B7= gradient 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm).

LC-MS: 1126.6[M+H]<sup>+</sup>

Elementary analysis: C<sub>56</sub>H<sub>95</sub>N<sub>5</sub>O<sub>18</sub> (H<sub>2</sub>O)<sub>3.5</sub>

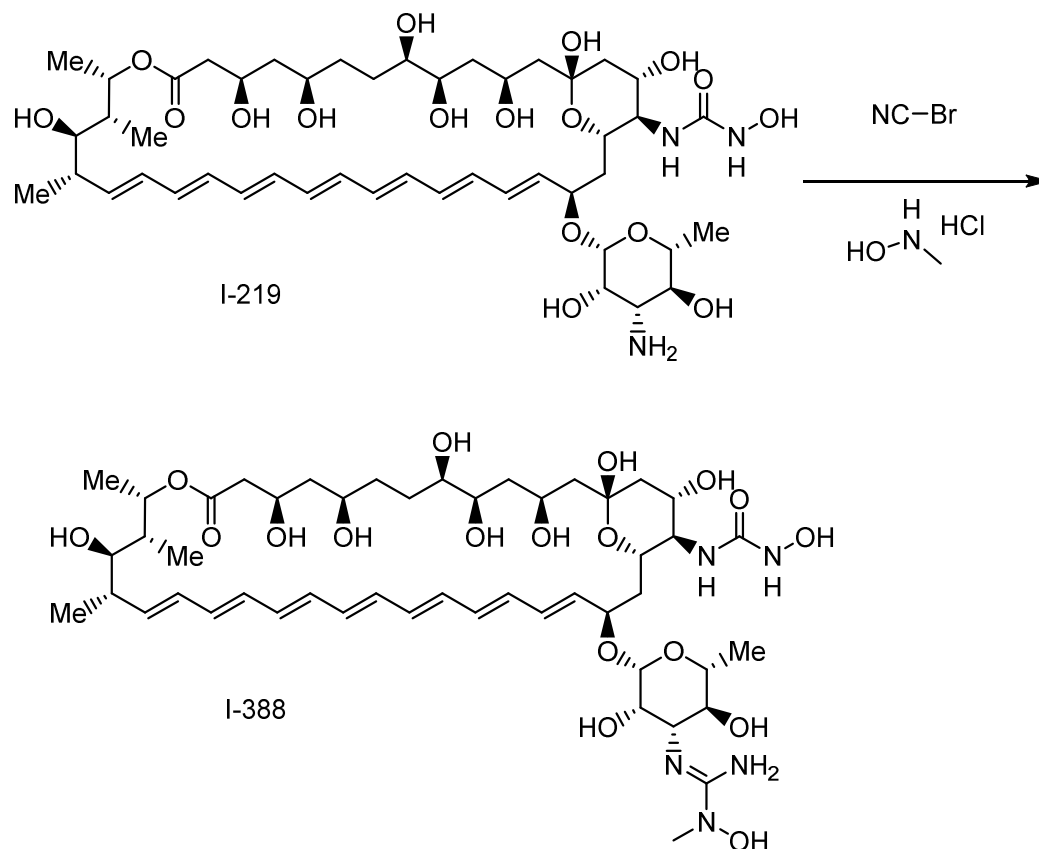
Calculated value: C 56.55; H 8.64; N 5.89 (%)

Actual value: C 56.76; H 8.31; N 5.75 (%)

[0 2 2 1]

Example 49: Synthesis of Compound I-388

[Chemical Formula 1 0 4]



Compound I-219 (150mg, 0.157mmol) was dissolved into DMF (5mL), and DIEA (0.165mM, 0.943mmol) and cyanicbromide (33mg, 0.31mmol) were added. The mixture was stirred for 55 minutes at room temperature. N-Methylhydroxylamine hydrochloride(26mg, 0.31mmol) was added, and the mixture was stirred for 21 hours at room temperature. After powderization by adding diisopropyl ether, the obtained powder was purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3 to 30/70/7) to give Compound I-388 (23mg, 27%).

LC-MS: 1026.5 [M+H]<sup>+</sup>, 1048.5 [M+Na]<sup>+</sup>

Elementary analysis: C<sub>49</sub>H<sub>79</sub>N<sub>5</sub>O<sub>18</sub>(C<sub>3</sub>H<sub>7</sub>NO)<sub>2</sub>(H<sub>2</sub>O)<sub>9.5</sub>

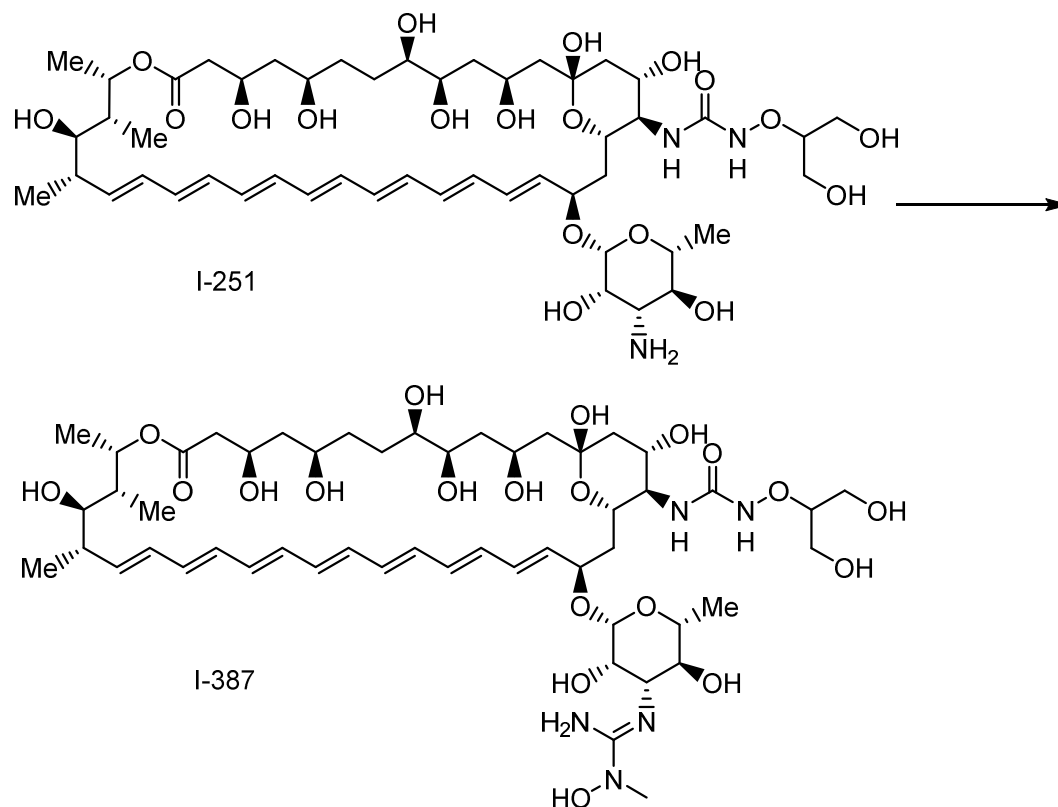
Calculated value: C 49.17; H 8.40; N 7.30 (%)

Actual value: C 49.00; H 7.30; N 7.49 (%)

[0 2 2 2]

Example 50: Synthesis of Compound I-387

[Chemical Formula 1 0 5]



Compound I-251 (110mg, 0.107mmol) was dissolved into DMF (5mL), and DIEA (0.112mL, 0.642mmol) and cyanicbromide (17mg, 0.16mmol) were added. The mixture was stirred for an hour 15 minutes at room temperature. N-Methylhydroxylamine hydrochloride (26.8mg, 0.32mmol) was added, and the mixture was stirred at room temperature overnight. After powderization by adding diisopropyl ether, the obtained powder was purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3 to 30/70/7) to give Compound I-387 (40mg, 34%).

LC-MS: 1100.5 [M+H]<sup>+</sup>, 1122.5 [M+Na]<sup>+</sup>

Elementary analysis: C<sub>52</sub>H<sub>85</sub>N<sub>5</sub>O<sub>20</sub> (C<sub>3</sub>H<sub>7</sub>NO)<sub>0.3</sub> (H<sub>2</sub>O)<sub>3.5</sub>

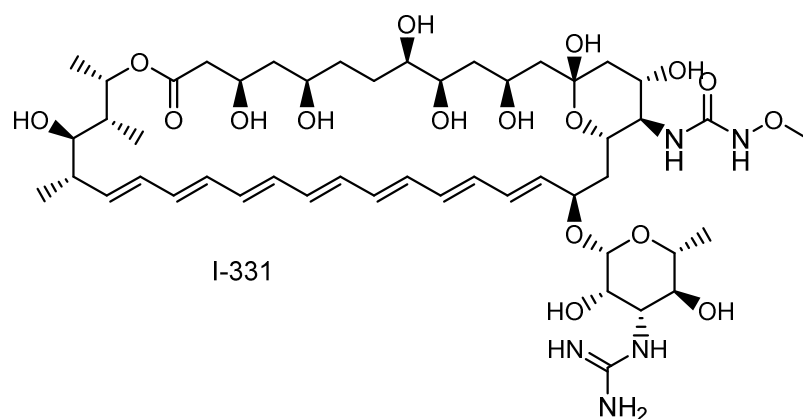
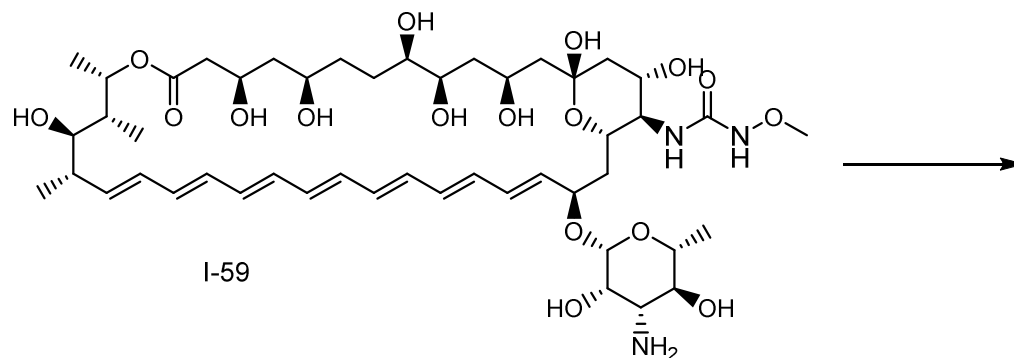
Calculated value: C 53.61; H 8.00; N 6.26 (%)

Actual value: C 53.65; H 7.94; N 6.24 (%)

[ 0 2 2 3 ]

Example 51: Synthesis of Compound I-331

[Chemical Formula 106]



Compound I-59 (250mg, 0.258mmol) and 1H-pyrazole-1-carboxyimidamide hydrochloride (265mg, 1.81mmol) were dissolved into DMF (1mL), and DIEA (0.316mL, 1.81mmol) was added. The mixture was stirred for 25 hours at room temperature. After powderization by adding diisopropyl ether, the obtained powder was purified by reverse-phase chromatography (HP20ss, acetonitrile/aqueous solution containing 0.05% formic acid=10/90 to 30/70). The obtained fractions were condensed and lyophilized to give Compound I-331 (154mg, 51%).

LC-MS: 1011.1 [M+H]<sup>+</sup>

Elementary analysis: (C<sub>49</sub>H<sub>79</sub>N<sub>5</sub>O<sub>17</sub>) (HCO<sub>2</sub>H)0.4 (H<sub>2</sub>O)7.3

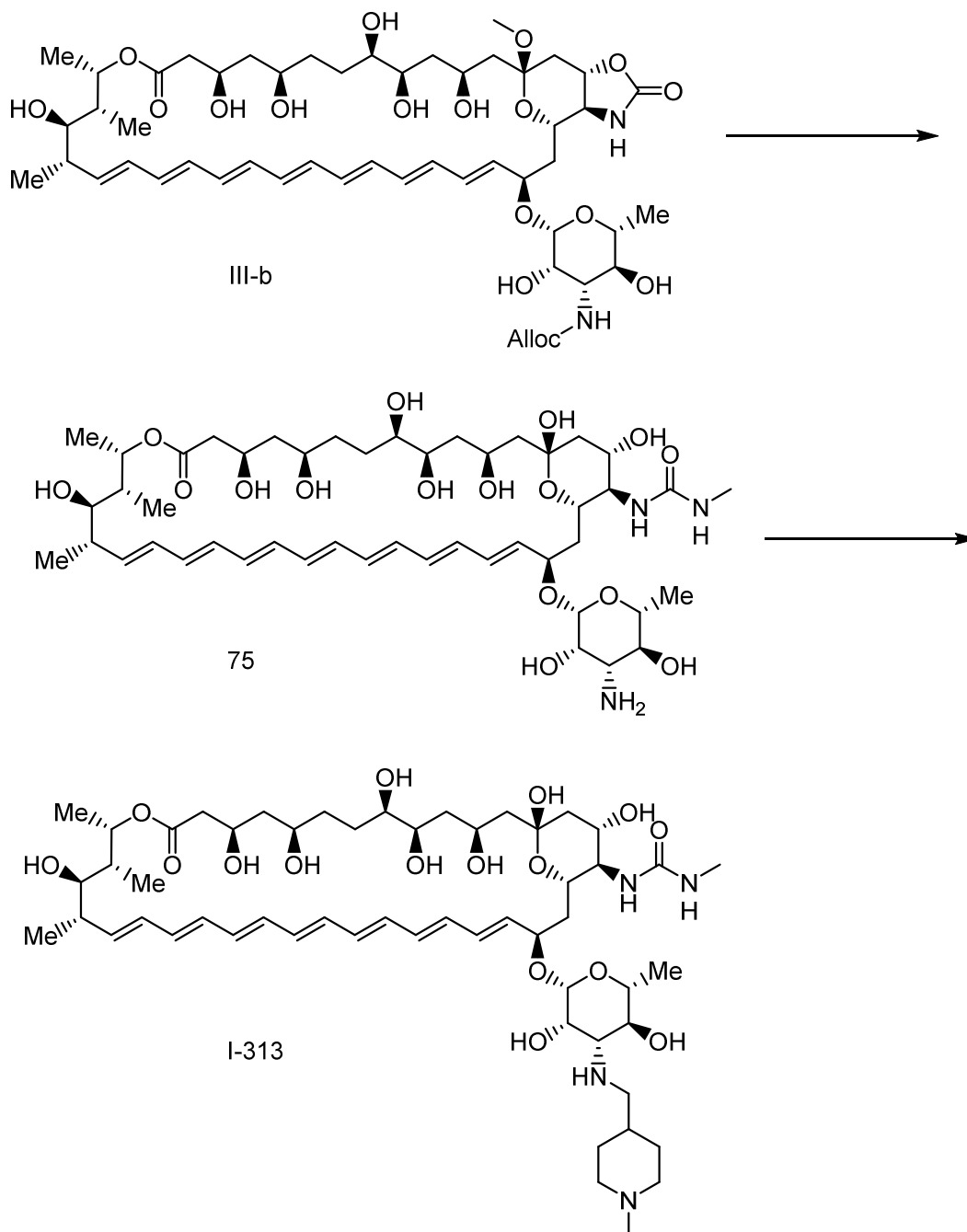
Calculated value: C 51.14; H 8.20; N 6.04 (%)

Actual value: C 51.10; H 7.81; N 6.13 (%)

[0 2 2 4]

Example 52: Synthesis of Compound I-313

[Chemical Formula 1 0 7]



## Step 1

Compound III-b (10g, 9.81mmol) was dissolved into DMA (30mL), and methylamine (30% ethanol solution, 2g, 19.6mmol) was added. The mixture was stirred for 2 hours at room temperature. After powderization by adding diisopropyl ether/methanol, the crude purified powder (8.8g) was obtained. Without purification, the crude powder was dissolved into DMF (4mL), tetrahydrofuran (16mL), water (2mL), and PPTS (8.42g, 33.5mmol) was added. The mixture was stirred for 3 hours at room temperature. Further, water (2mL) and PPTS (2.1mmol, 8.38mmol) were added, and the mixture was stirred for an hour. The reaction was quenched by adding triethylamine (11.6mL, 84mmol). After the mixture was condensed and oil-outed with diisopropyl ether, the obtained residue was purified by silica-gel column chromatography (chloroform/methanol/water=70/30/3) to give the objective substance (3.85g, 3.71mmol, 44%). The objective substance was dissolved

into DMF (20mL), and morpholine (3.2mL, 37.2mmol) was added. The mixture was degassed and replaced by nitrogen gas. Pd (PPh<sub>3</sub>)<sub>4</sub> (429mg, 0.37mmol) was added, and the mixture was stirred for 10 minutes at room temperature. After powderization by adding diisopropyl ether, the obtained powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=65/35/3.5) to give Compound 75 (1.1g, 31%).

LC-MS: 952.5 [M+H]<sup>+</sup>, 974.6 [M+Na]<sup>+</sup>

Elementary analysis: C<sub>48</sub>H<sub>77</sub>N<sub>3</sub>O<sub>16</sub>(C<sub>3</sub>H<sub>7</sub>NO)(H<sub>2</sub>O)<sub>2.4</sub>

Calculated value: C 57.33; H 8.38; N 5.24 (%)

Actual value: C 57.35; H 8.37; N 5.27 (%)

#### Step 2

Compound 75 (230mg, 0.242mmol) and 4-formyl-1-methylpiperidine hydrochloride (119mg, 0.725mmol) were added to DMF (2.4mL), and methanol (0.7mL), acetic acid (0.4mL) and NaBH<sub>3</sub>CN (76mg, 1.21mmol) were added. The mixture was stirred at room temperature overnight. The reaction was quenched by adding Amberlite IRA-743 (630mg). After the reaction mixture was filtrated, the mixutre was powderid by adding diisopropyl ether. The powder was purified by silica-gel column chromatography to give Compound I-313 (143mg, 55%).

LC-MS: 1064.2 [M+H]<sup>+</sup>

Elementary analysis: C<sub>55</sub>H<sub>90</sub>N<sub>4</sub>O<sub>16</sub>(H<sub>2</sub>O)<sub>6.2</sub>

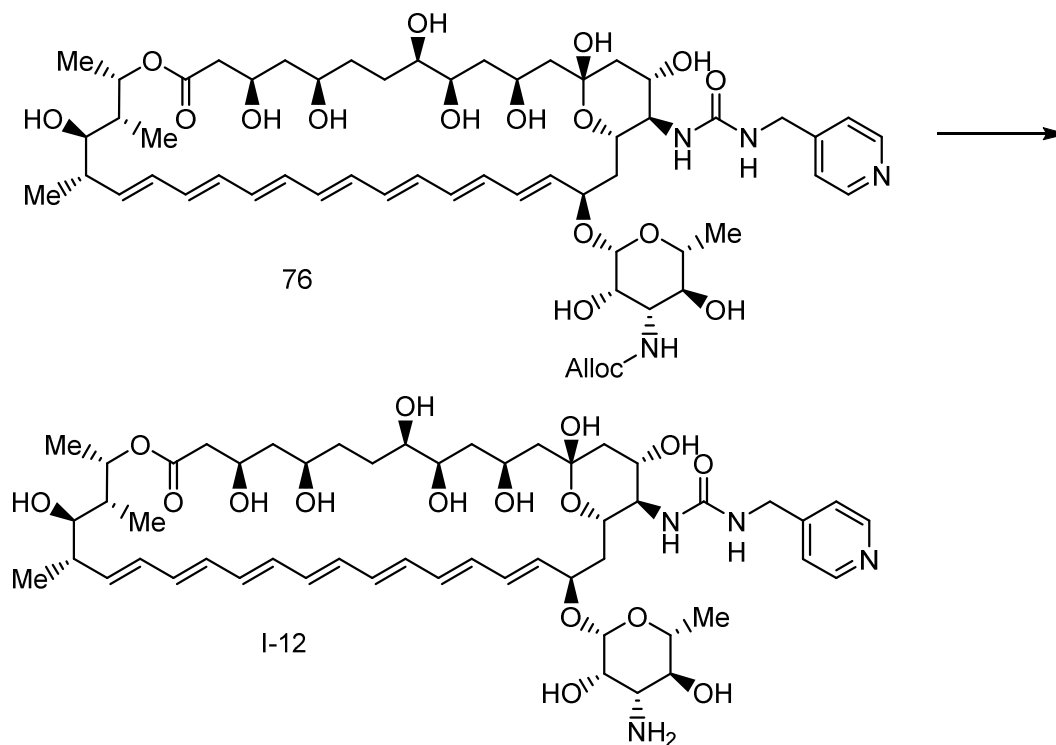
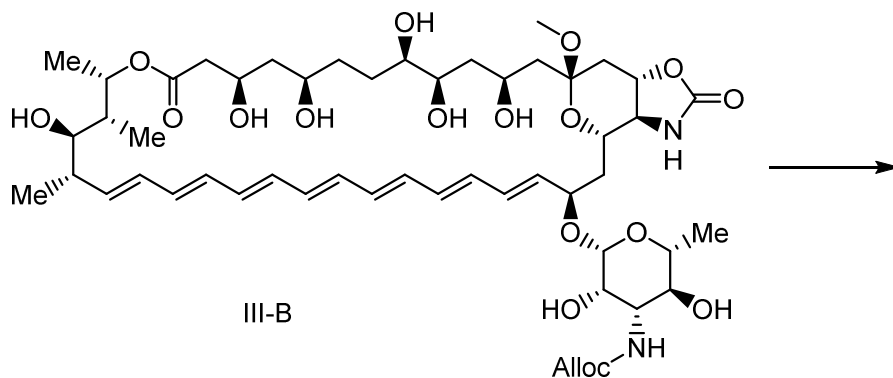
Calculated value: C 56.22; H 8.78; N 4.77 (%)

Actual value: C 56.03; H 8.48; N 5.02 (%)

[ 0 2 2 5 ]

Example 53: Synthesis of Compound I-12

[Chemical Formula 108]



### Step 1 Synthesis of Compound 76

Compound III-b (1g, 0.981mmol) was dissolved into DMF (10mL), and 2-(4-pyridyl)methylamine (0.299mL, 2.94mmol) was added. The mixture was stirred for 3.5 hours at room temperature. 2-(4-pyridyl)methylamine (0.299mL, 2.94mmol) was added, and the mixture was stirred for 23.5 hours at room temperature. Further, 2-(4-pyridyl)methylamine (0.299mL, 2.94mmol) was added, and the mixture was stirred for 3 hours at room temperature. After powderization by adding diisopropyl ether/acetonitrile, the solids were filtrated. The obtained solids (1.09g) were dissolved to tetrahydrofuran (4mL) and water (1mL). PPTS (740mg, 2.94mmol) was added, and the mixture was stirred for 5 hours at room temperature. After the mixture incubated at 4°C overnight, the mixture was stirred for 3 hours at room temperature. After the reaction was quenched by adding triethylamine (0.408mL, 2.94mmol), the mixture was condensed and oil-outed with diisopropyl ether/acetonitrile. After decantation of the obtained oil, the obtained oil was dissolved into chloroform/methanol. After the solvent was removed, the residue was dissolved into DMF. After powderization with diisopropyl ether/acetonitrile, the obtained solids were filtrated and washed with diisopropyl ether to give crude

Compound 76 (0.84g).

## Step 2 Synthesis of Compound I-12

Crude product of Compound 2 (0.84g) was dissolved into DMF (8mL), morpholine (0.131mL, 1.509mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (61mg, 0.053mmol) were added. After degassing and nitrogen purge, the mixture was stirred for 2 hours at room temperature. After the reaction mixture was powdered with diisopropyl ether/acetonitrile, the mixture was purified by reverse-phase chromatography (HP20ss, acetonitrile/0.5mmol/L hydrochloric acid aq) to give Compound I-12 (52.9mg, 6.8%).

Elementary analysis:  $\text{C}_{53}\text{H}_{80}\text{N}_4\text{O}_{16}(\text{HCl})0.17(\text{H}_2\text{O})3.4(\text{H}_2\text{SO}_4)0.27$

Calculated value: C 56.68; H 7.85; N 4.99; Cl 0.54; S 0.77 (%)

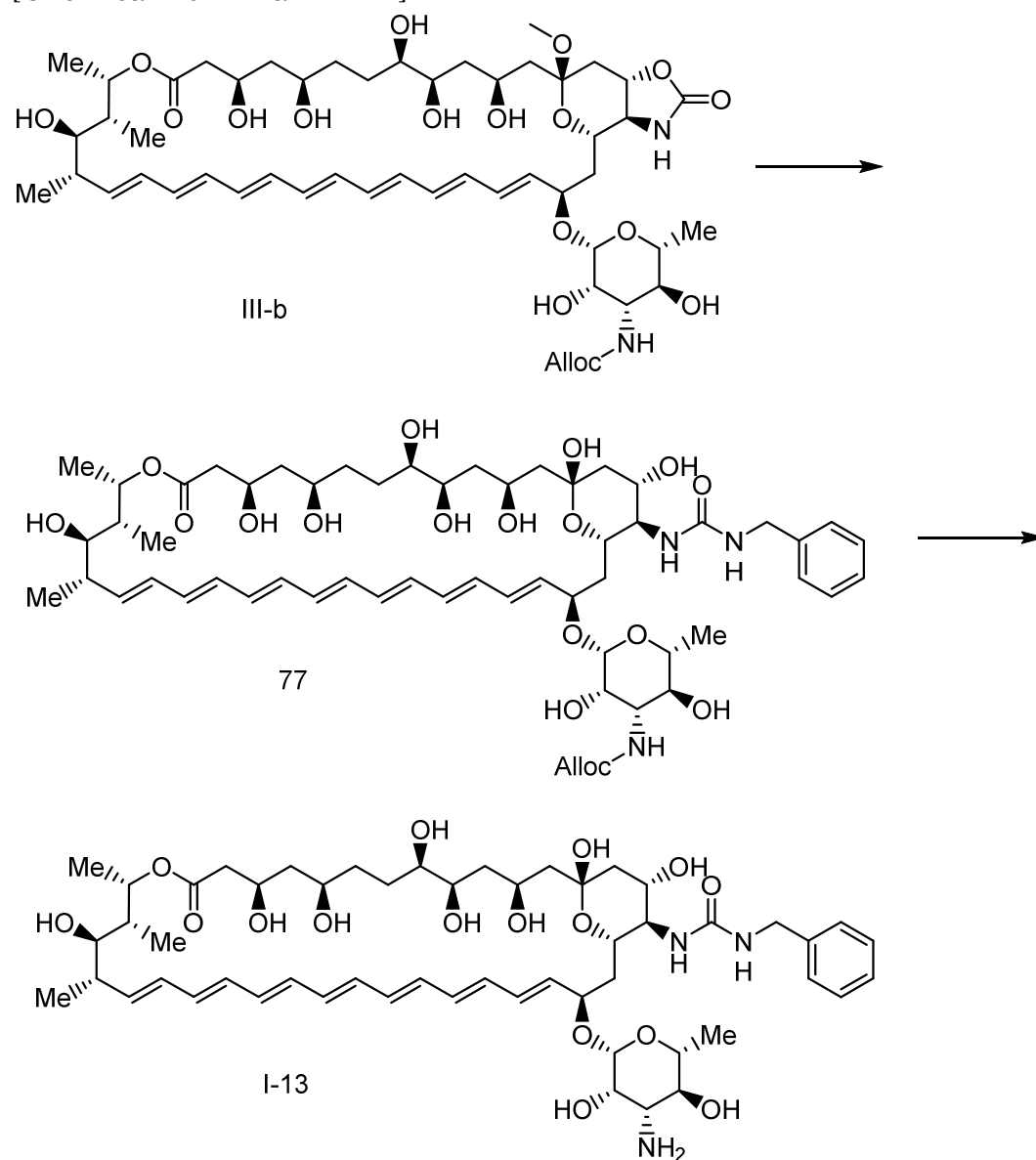
Actual value: C 56.73; H 7.51; N 4.85; Cl 0.54; S 0.78 (%)

MS(ESI) m/z: 1029.6(M+H+), 1051.6(M+Na+)

[0 2 2 6]

## Example 54: Synthesis of Compound I-13

[Chemical Formula 1 0 9]



## Step 1 Synthesis of Compound 77

Compound III-b (1g, 0.981mmol) was dissolved into DMF (10mL), and

benzylamine (0.322mL, 2.94mmol) was added. The mixture was stirred for 27 hours at room temperature. Benzylamine (0.215mL, 1.96mmol) was added, and the mixture was stirred for 3 hours at room temperature. After the reaction mixture was powdered with diisopropyl ether/acetonitrile, the mixture was purified by silica-gel column chromatography to give crude product (203mg). The obtained crude product (200mg) was dissolved into tetrahydrofuran (3mL) and water (0.75mL), and PPTS (66.9mg, 0.266mmol) was added. After the mixture was stirred for 2.5 hours at room temperature, the mixture was incubated at 4°C overnight. After that, the mixture was stirred for 3 hours at room temperature. After the reaction was quenched with triethylamine (0.039mL, 0.284mmol), the mixture was incubated at 4°C overnight. After powderization by adding diisopropyl ether/acetonitrile, the obtained solids were filtrated and washed with diisopropyl ether to give crude Compound 77 (0.195mg).

#### Step 2

Crude product of Compound 77 (193mg) was dissolved into N-methylpyrrolidone (10mL), the mixture was degassed and replaced by nitrogen gas. Morpholine (0.030mL, 0.347mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (14mg, 0.012mmol) were added, and the mixture was stirred for 1.5 hours at room temperature. After the reaction mixture was powdered with diisopropyl ether/acetonitrile, the powder was purified by silica-gel column chromatography (CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O) to give Compound I-13 (87.8mg, 49.2%).

Elementary analysis: C<sub>54</sub>H<sub>81</sub>N<sub>3</sub>O<sub>16</sub>(H<sub>2</sub>O)<sub>2.6</sub>(CHCl<sub>3</sub>)<sub>0.47</sub>(H<sub>2</sub>SO<sub>4</sub>)<sub>0.42</sub>

Calculated value: C 55.77; H 7.32; N 3.51; Cl 4.27; S 1.08 (%)

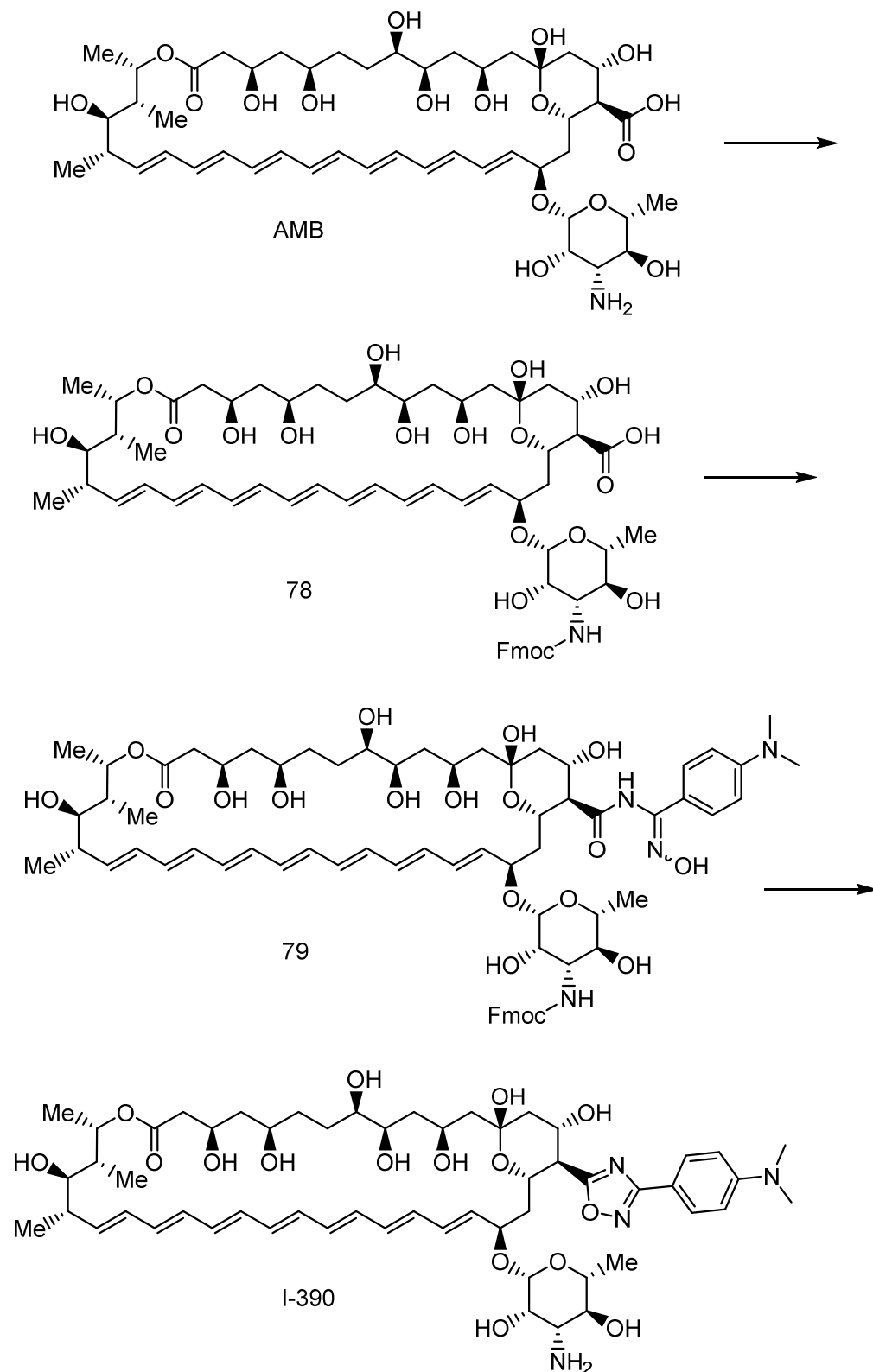
Actual value: C 55.80; H 7.52; N 3.58; Cl 4.26; S 1.15 (%)

MS(ESI) m/z: 1028.6(M+H<sup>+</sup>), 1050.6(M+Na<sup>+</sup>)

[ 0 2 2 7 ]

Example 55: Synthesis of Compound I-390

[Chemical Formula 1 1 0]



### Step 1 Synthesis of Compound 78

Amphotericin B (5g, 5.41mmol) was dissolved into DMF (100mL), and pyridine (1.31mL, 16.23mmol) and N-(9-Fluorenylmethoxycarbonyloxy)succinimide (3.65g, 10.82mmol) were added. The mixture was stirred for 3 hours at room temperature. After that, pyridine (0.873mL, 10.82mmol) and N-(9-Fluorenylmethoxycarbonyloxy)succinimide (1.83g, 5.41mmol) were added, and the mixture was stirred for 2 hours at room temperature. After powderization by adding

diisopropyl ether, the obtained solids were filtrated to give crude product of Compound 78 (6.42g).

#### Step 2 Synthesis of Compound I-390

Compound 78 (500mg) was dissolved into DMF (5mL), and PyBOP (681mg, 1.309mmol) and ethylisopropylamine (0.229mL, 1.309mmol) were added. The mixture was stirred for an hour at room temperature. (Z)-4-dimethylaminobenzamido oxime (313mg, 1.745mmol) was added, and the mixture was stirred for 5 hours at room temperature. After powderization by adding diisopropyl ether/acetonitrile, the obtained solids were filtrated and washed with diisopropyl ether to give crude Compound (545.6mg). The obtained crude Compound 79 (545.6mg) was dissolved into DMF (6mL), and molecular sieve 3Å was added. 1mol/L Tetrabutylammonium Fluoride tetrahydrofuran solution (0.625mL, 0.625mmol) was added, and the mixture was stirred for 8 hours at 45°C. After the reaction mixture was filtrated and dissolved materials were removed, the mixture was condensed. After powderization by adding diisopropyl ether/acetonitrile (6/1), the powder was purified by silica-gel column chromatography (CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O) to give Compound I-390 (94.2mg, 27.2%).

Elementary analysis: C<sub>56</sub>H<sub>82</sub>N<sub>4</sub>O<sub>16</sub>(H<sub>2</sub>O)<sub>3.2</sub>

Calculated value: C 59.79; H 7.92; N 4.98 (%)

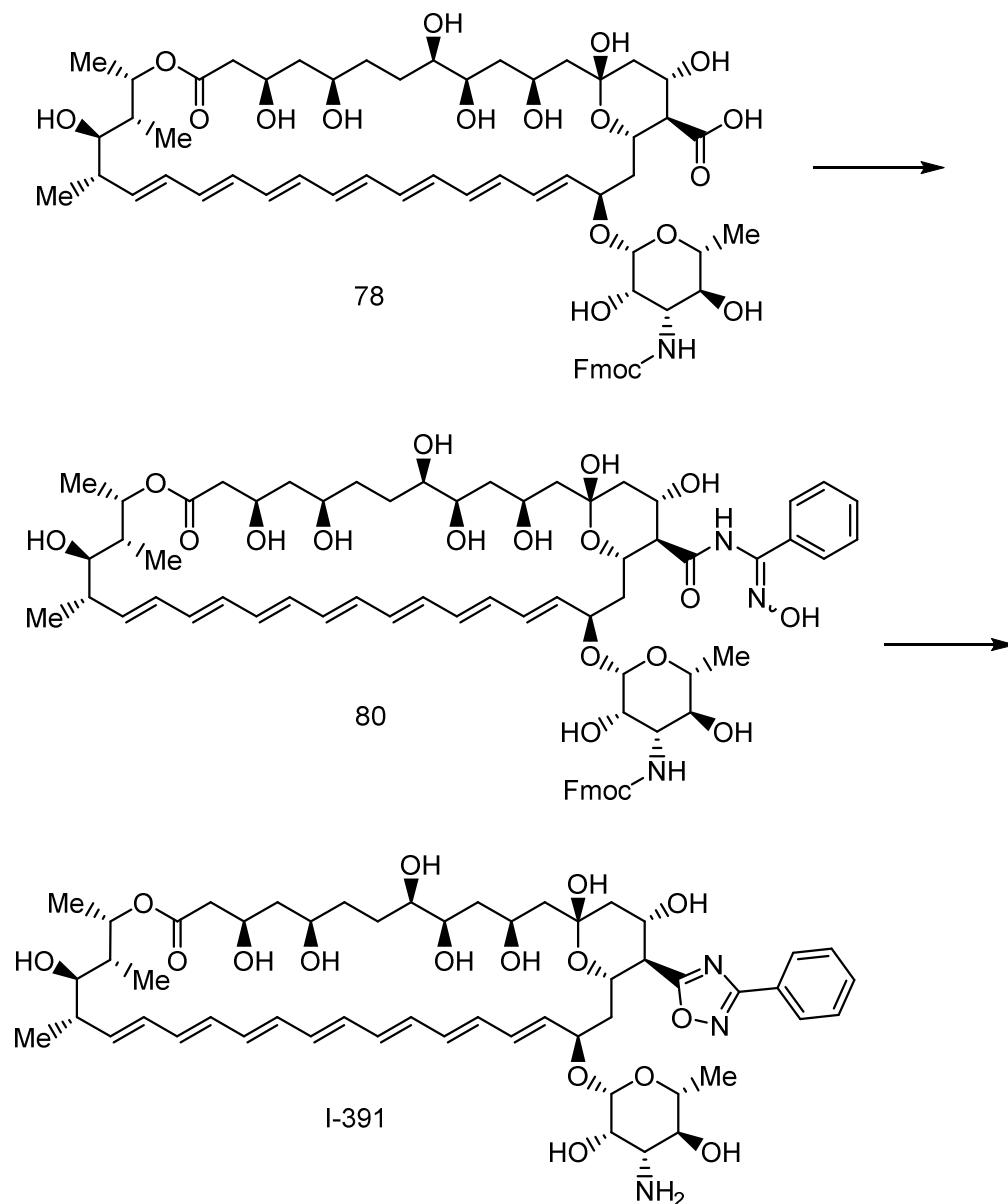
Actual value: C 59.75; H 7.73; N 4.90 (%)

MS(ESI) m/z: 1067.5(M+H<sup>+</sup>)

[ 0 2 2 8 ]

Example 56: Synthesis of Compound I-391

[Chemical Formula 1 1 1]



Compound 78 (500mg) synthesized as reference to Step 1 of Example 55 was dissolved in DMF (5mL), and PyBOP (681mg, 1.309mmol) and ethylisopropylamine (0.229mL, 1.309mmol) were added. The mixture was stirred for an hour at room temperature. (Z)-Benzamido oxime (178mg, 1.309mmol) was added, and the mixture was stirred for 5 hours at room temperature. After powderization by adding diisopropyl ether/acetonitrile, the obtained solids were filtrated and washed with diisopropyl ether to give crude Compound 80 (485.9mg). The crude Compound 80 (485.9mg) was dissolved into DMF (7mL), and molecular sieve 3Å was added. 1mol/L Tetrabutylammonium Fluoride tetrahydrofuran solution (0.460mL, 0.460mmol) was added, and the mixture was stirred for 8 hours at 45°C. After that, 1mol/L Tetrabutylammonium Fluoride tetrahydrofuran solution (0.115mL, 0.115mmol) was added, and the mixture was stirred for 8 hours at 40°C. After the reaction mixture was filtrated and dissolved materials were removed, the mixture was condensed. After powderization by adding diisopropyl ether/acetonitrile (6/1), the powder was purified by silica-gel column chromatography (CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O) to give Compound I-391 (85.6mg, 19.3%).

Elementary analysis: C<sub>54</sub>H<sub>77</sub>N<sub>3</sub>O<sub>16</sub>(H<sub>2</sub>O)<sub>2.3</sub>(CHCl<sub>3</sub>)<sub>0.4</sub>

Calculated value: C 58.68; H 7.42; N 3.77 (%)

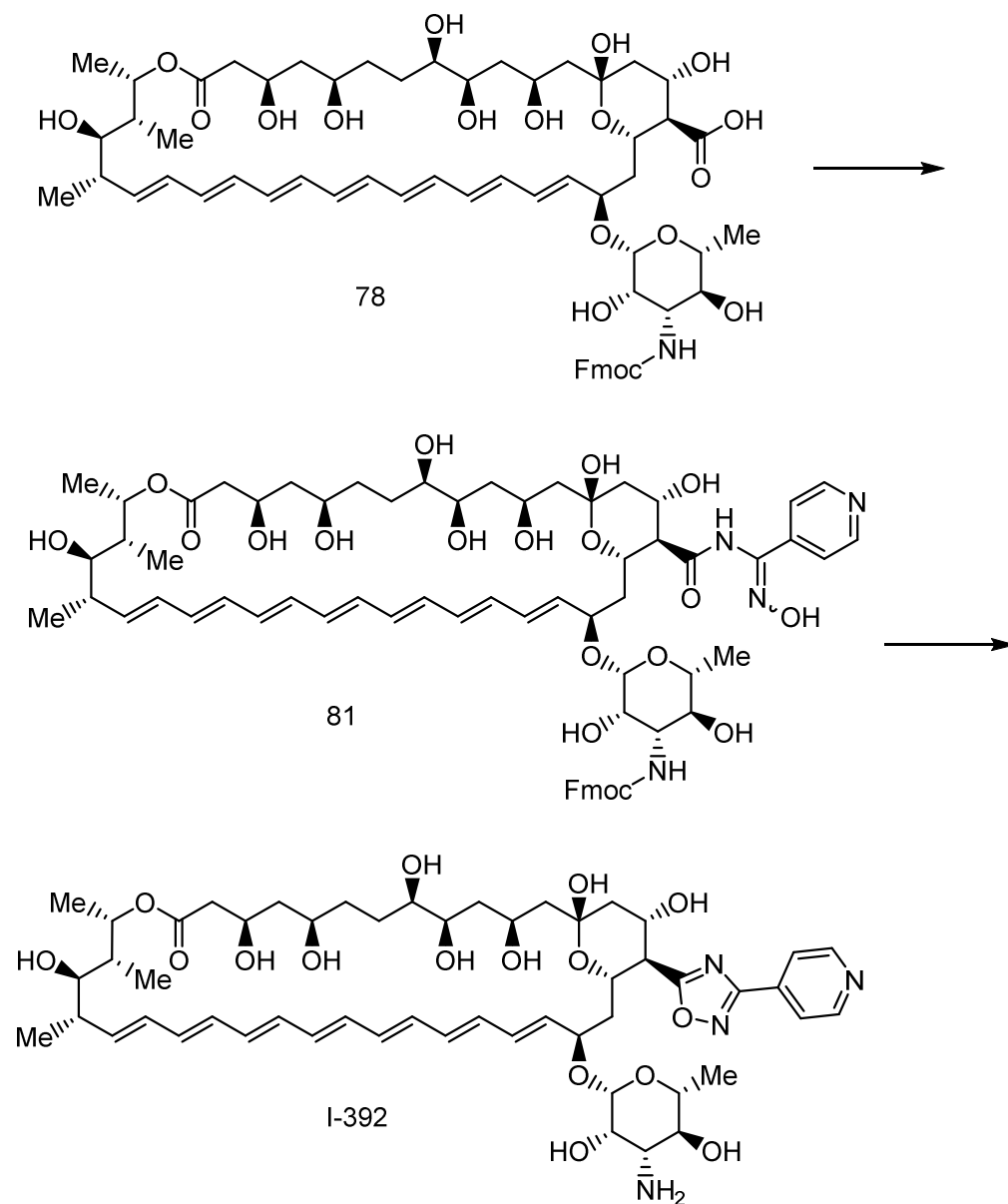
Actual value: C 58.67; H 7.42; N 3.85 (%)

MS(ESI)  $m/z$ : 1024.5(M+H<sup>+</sup>)

[0 2 2 9]

Example 57: Synthesis of Compound I-392

[Chemical Formula 1 1 2]



The crude Compound 78 (1g) synthesized as reference to Step 1 of Example 55 was DMF (10mL), and PyBOP (1.36g, 2.62mmol) and ethylisopropylamine (0.457mL, 2.62mmol) were added. The mixture was stirred for 4.5 hours at room temperature. After that, (Z)-4-pyridilamideoxime (479mg, 3.49mmol) was added, and the mixture was stirred for 3 days at room temperature. PyBOP (227mg, 0.436mmol) and ethylisopropylamine (0.076mL, 0.436mmol) were added, and the mixture was stirred for 3 hours at room temperature. After powderization by adding diisopropyl ether/acetonitrile, the obtained solids were filtrated and washed with diisopropyl ether to give crude Compound 81 (966.4mg). The crude Compound 81 (966mg) was dissolved into DMF (10mL), and molecular sieve 3Å was added. 1mol/L Tetrabutylammonium Fluoride tetrahydrofuran solution (1.145mL, 1.145mmol) was added, and the mixture was stirred for 8 hours at 45°C. After the reaction mixture

was filtrated and dissolved materials were removed, the mixture was condensed. After powderization by adding diisopropyl ether/acetonitrile (6/1), the powder was purified by silica-gel column chromatography ( $\text{CHCl}_3/\text{MeOH}/\text{H}_2\text{O}$ ) to give Compound I-392 (200.6mg, 23.4%).

Elementary analysis:  $\text{C}_{54}\text{H}_{77}\text{N}_3\text{O}_{16}(\text{H}_2\text{O})_{2.3}(\text{CHCl}_3)_{0.4}$

Calculated value: C 56.32; H 7.51; N 4.93; Cl 2.81 (%)

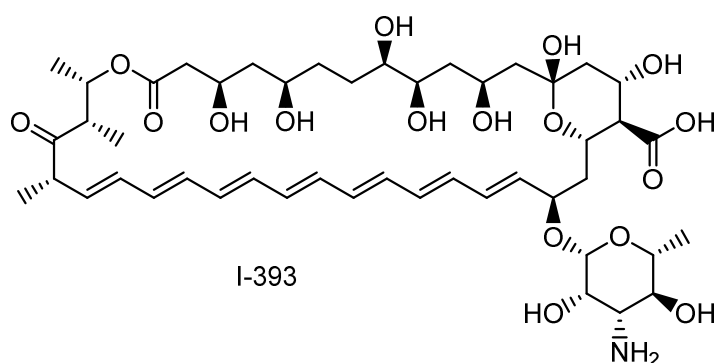
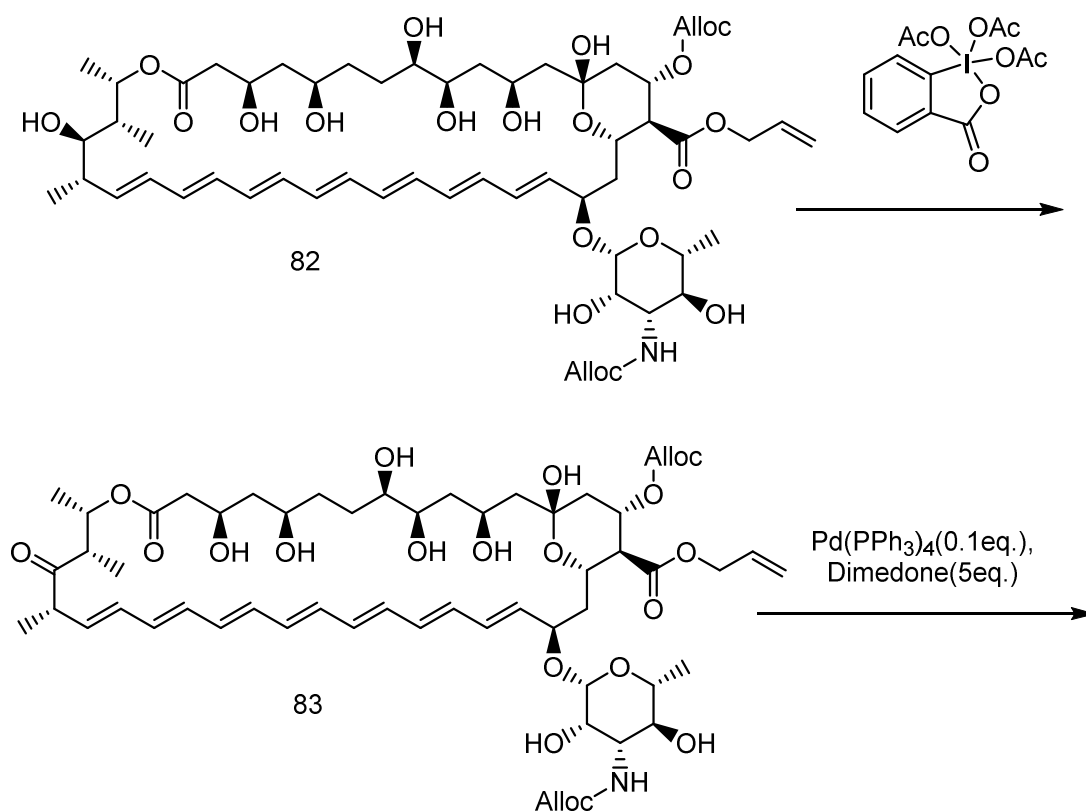
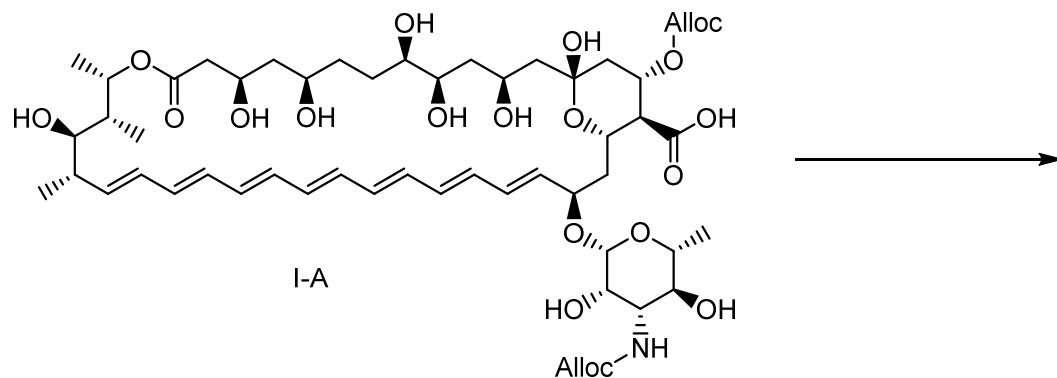
Actual value: C 56.28; H 7.51; N 5.07; Cl 2.75 (%)

MS(ESI)  $m/z$ : 1025.5(M+H<sup>+</sup>)

[ 0 2 3 0 ]

Example 58: Synthesis of Compound I-393

[Chemical Formula 1 1 3]



### Step 1 Synthesis of Compound 82

Compound I-A (1g, 0.916mmol) was dissolved into DMF (10mL), and DIEA (1.12mL, 6.41mmol) and Allyl Bromide (0.396mL, 4.58mmol) were added. After the mixture was stirred for 6 hours at room temperature, and DIEA (0.32mL, 1.83mmol) and Allyl Bromide (0.079mL, 0.916mmol) were added. The mixture was stirred for 2 hours at room temperature. The reaction mixture was added to diisopropyl ether/acetonitrile

(6/1, 200mL) and stirred to give solids by filtration. The obtained solids were purified by silica-gel column chromatography (chloroform/methanol/water=96/4/0.4) to give Compound 82 (277mg, 27%).

LC-MS: 1133.8 [M+H]<sup>+</sup>, 1114.9 [M+H-H<sub>2</sub>O]<sup>+</sup>

#### Step 2 Synthesis of Compound 83

Compound 82 (277mg, 0.245mmol) was dissolved into dichloromethane (8mL), and Dess-Martin Periodinane (Dess-Martin Reagent: 114mg, 0.269mmol) was added. The mixture was stirred for 1.5 hours at 0°C. Dess-Martin Periodinane (Dess-Martin Reagent: 21mg, 0.049mmol) was added, and the mixture was stirred for 2 hours at 0°C. The reaction mixture was diluted with saturated sodium bicarbonate aqueous solution, and extracted with dichloromethane (20mL) three times. After the organic phase was washed with water and brine, the organic phase was dried with sodium sulfate anhydrous. After the mixture was filtrated and condensed, the residue was purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5) to give Compound 83 (91mg, 33%).

LC-MS: 1112.8 [M+H-H<sub>2</sub>O]<sup>+</sup>

#### Step 3 Synthesis of Compound I-393

Compound 83 (90mg, 0.080mmol) was dissolved into tetrahydrofuran (1mL) and water (0.1mL), and dimedone (56mg, 0.398mmol) and Tetrakis (triphenylphosphine)palladium (0) (9.2mg, 0.008mmol) were added. The mixture was stirred for an hour at room temperature under nitrogen atmosphere. After the reaction mixture was filtrated and washed with tetrahydrofuran, corrected filtrate was condensed in vacuo. The residue was purified by reverse-phase chromatography (HP20ss, acetonitrile/water=95/5) to give 35-position ketone Compound I-393 (12mg, 17%).

LC-MS: m/z = 922.9 [M+H]<sup>+</sup>

Elementary analysis: (C<sub>47</sub>H<sub>71</sub>NO<sub>17</sub>)(H<sub>2</sub>O)<sub>3.8</sub>(CH<sub>3</sub>CN)<sub>0.2</sub>

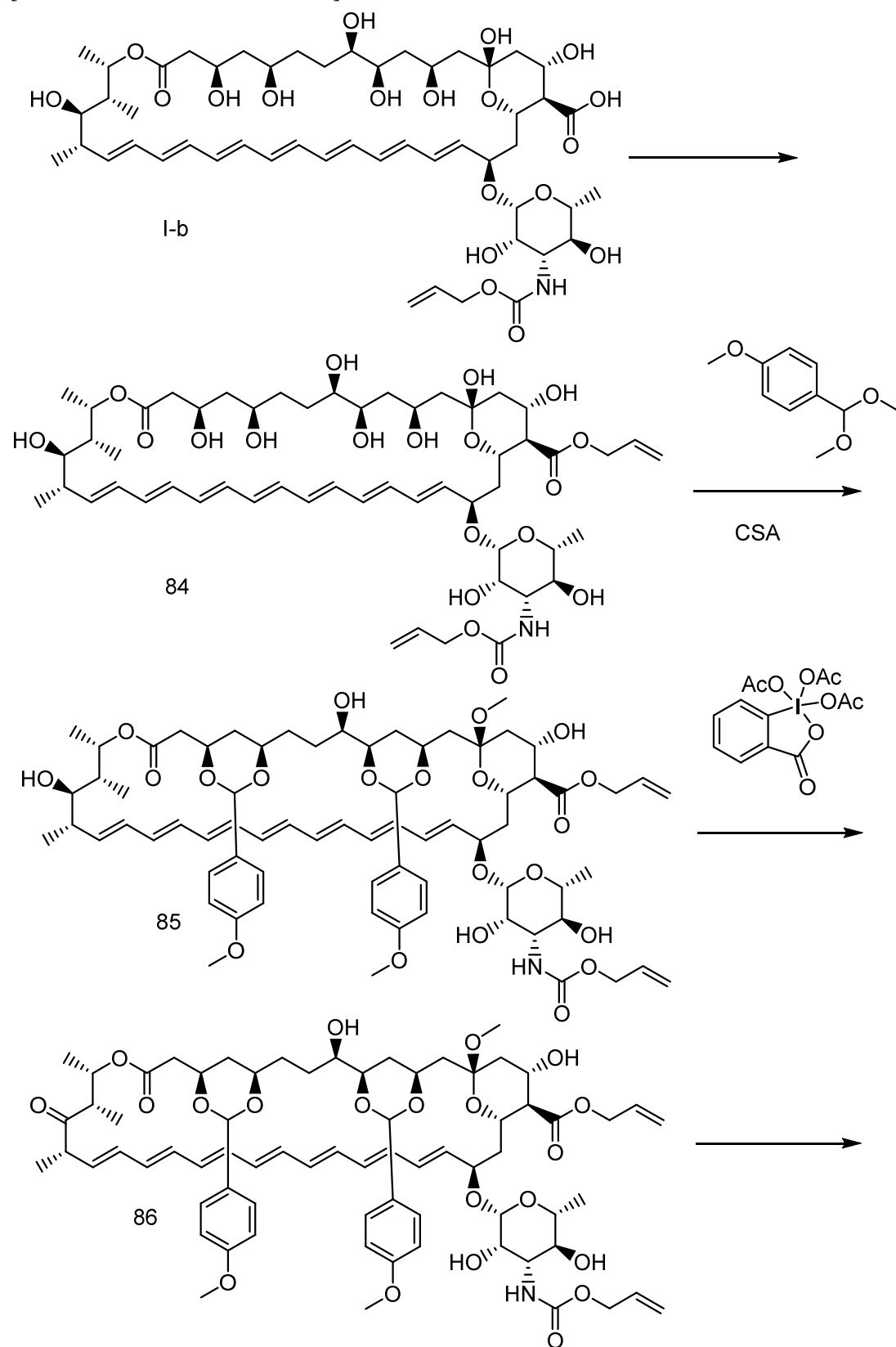
Calculated value: C 57.00; H 7.99; N 1.68 (%)

Actual value: C 57.06; H 7.85; N 2.00 (%)

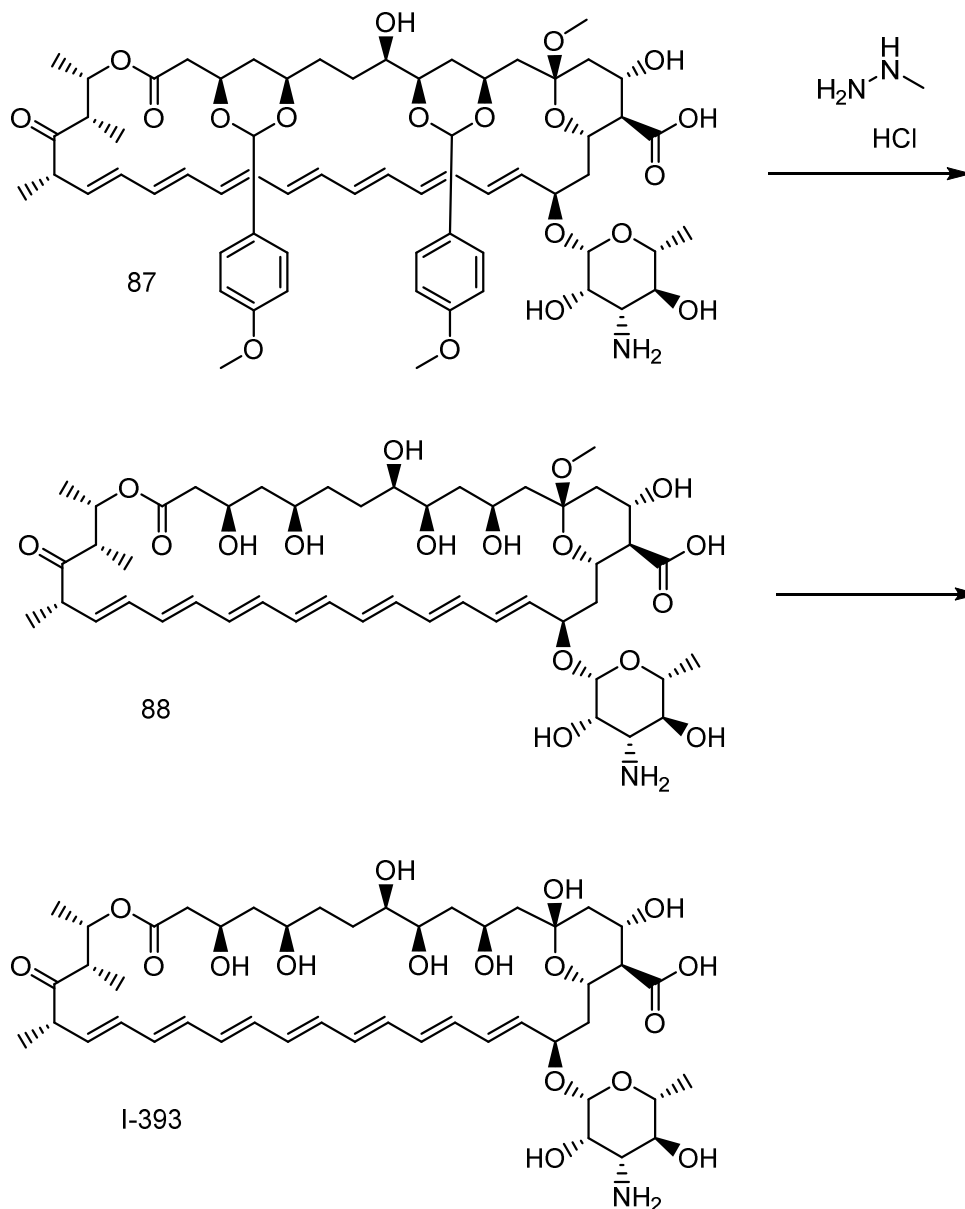
[ 0 2 3 1 ]

Example 59: Synthesis of Compound I-393

[Chemical Formula 1 1 4]



[Chemical Formula 1 1 5]



## Step 1

The intermediate I-b (16.3g, 16.23mmol) was dissolved into DMF (100mL), and allyl bromide (4.2mL, 48mmol) and DIEA (14mL, 81mmol) were added. The mixture was stirred for 5.5 hours at room temperature. allyl bromide (2.8mL, 32.5mmol) and DIEA (5.7mL, 32.5mmol) were added, and the mixture was stirred overnight. The reaction solution was powderized with diisopropyl ether (1.5L) to give Compound 85 (20.84g).

## Step 2

Compound 84 (10.48g, 10mmol) was suspended in methanol (100mL), and 1-(Dimethoxymethyl)-4-Methoxybenzene (9.2mL, 54mmol) and CSA (1.533g, 6.6mmol) were added. After The mixture was stirred for 1.5 hours at  $0^\circ\text{C}$ , the reaction was quenched with triethylamine (0.97mL, 7mmol). After concentration, the reaction mixture was diluted with ethyl acetate and filtrated. The obtained organic phase was washed with water. After the organic phase was dried up with magnesium sulfate anhydrous, the organic phase was condensed. The obtained residue was purified by silica-gel column chromatography (chloroform/methanol/water=99/1/0.1) to give yellow caramel-solids Compound 85 (5.14g, 39%).

LC-MS: 1299.2 [M+H]<sup>+</sup>

### Step 3

Compound 85 (5.1g, 3.93mmol) was dissolved into dichloromethane (70mL), and Dess-Martin Periodinane (1.89g, 4.32mmol) was added in an ice-water bath. The mixture was stirred for an hour 30 minutes. The reaction mixture was diluted with saturated sodium bicarbonate aqueous solution and extracted with dichloromethane. The organic phase was washed with brine and dried up with sodium sulfate anhydrous. The residue was purified by silica-gel column chromatography to give orange caramel-solids Compound 86 (2.16g, 42%). The presence of 35-position ketone was identified by <sup>13</sup>C NMR and HMBC.

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) δ 211.90 (35-C).

LC-MS: 1265.9 [M-CH<sub>2</sub>O+H]<sup>+</sup>, 1296.9 {M+H}<sup>+</sup>

### Step 4

Compound 86 (0.96g, 0.74mmol) was dissolved into tetrahydrofuran (15mL), and dimedone (519mg, 3.7mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (60mg, 0.052mmol) were added. The mixture was stirred for 90 minutes at room temperature under nitrogen atmosphere. The reaction mixture was condensed, and dissolved into DMF (5mL). The mixture was added dropwise to diisopropyl ether. The obtained solids were filtrated to give Compound 87 (887mg).

LC-MS: 1173.1 [M+H]<sup>+</sup>

### Step 5

Compound 87 (887mg, 0.757mmol) was dissolved into DMF (3mL), and hydrochloric acid-methanol (3.5mol/L, 2.6mL, 9mmol) was added. The mixture was stirred for an hour at 0°C. hydrochloric acid-methanol (3.5mol/L, 0.857mL, 3mmol) and methylhydrazine (0.128mL, 2.24mmol) were added, and the mixture was stirred for an hour at 0°C. The reaction was quenched with triethylamine (1.67mL, 12.1mmol) and added dropwise to diisopropyl ether to give Compound 88 (1.95g).

### Step 6

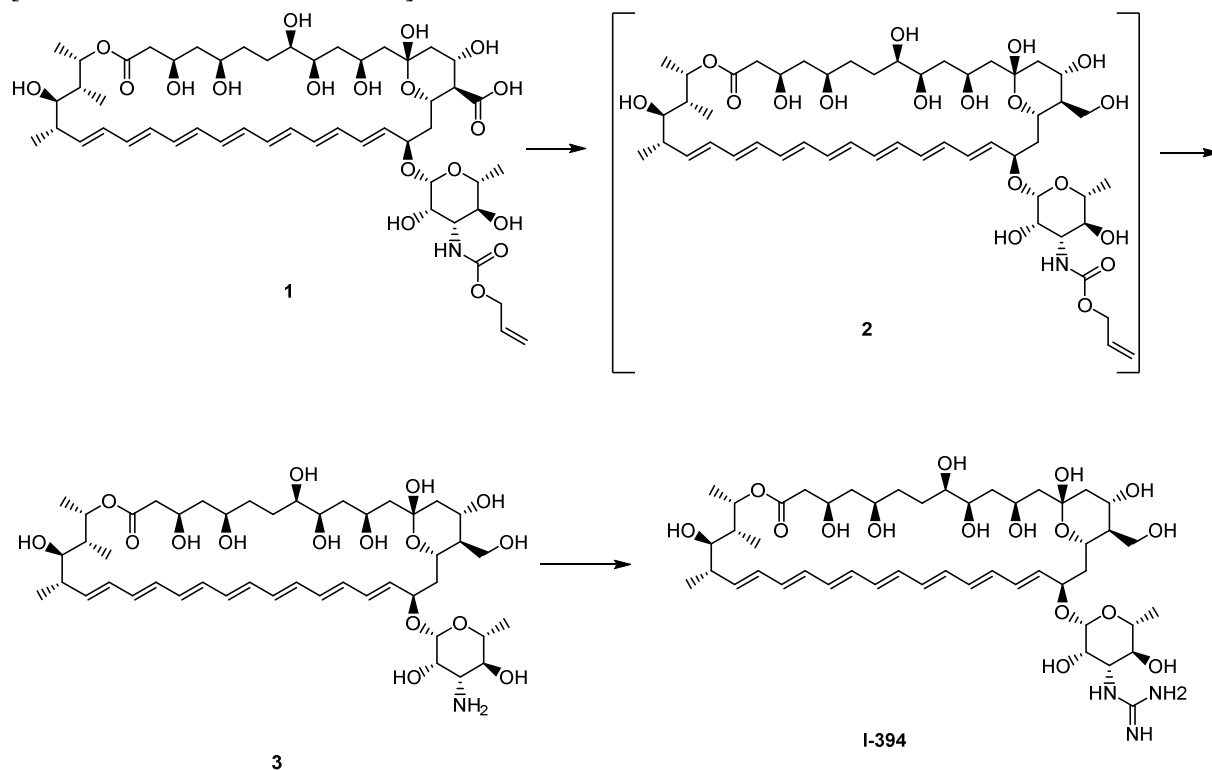
Compound 88 (709mg, 0.75mmol) was dissolved into DMF (8mL), and water (5mL) was added. The mixture was cooled. Concentrated hydrochloric acid (0.667mL, 8mmol) was added in an ice-water bath, and the mixture was stirred for 2 hours at 0°C. The reaction mixture was neutralized by adding triethylamine (1.15mL, 8.33mmol). After tetrahydrofuran was removed by concentration in vacuo, the mixture was poured to diisopropyl ether-methanol (800mL/30mL). The mixture was stirred for 10 minutes at room temperature. After filtration, the obtained solids were purified by reverse-phase chromatography (HP20ss, acetonitrile:water=20:80 to 35:65) to give Compound I-393 (46mg, 7%).

LC-MS: 922.9 [M+H]<sup>+</sup>

[0 2 3 2]

Example 60: Synthesis of Compound I-394

## [Chemical Formula 1 1 6]



## Step 1 Synthesis of Compound 3

Compound 1 (1g, 0.992mmol) was dissolved into NMP (7mL), and the mixture was cooled to 0°C. (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium Hexafluorophosphate (542mg, 1.042mmol) and DIEA (0.26mL, 1.49mmol) were added, and the mixture was stirred for 30 minutes at room temperature. Sodium borohydride (113mg, 2.98mmol) was added, and the mixture was stirred for an hour at room temperature. Further, sodium borohydride (75mg, 1.98mmol) was added, and the mixture was stirred for an hour at room temperature. Acetone and IRA743 resin (1g) were added, the mixture was stirred for an hour at room temperature. The mixture was filtrated by Celite®. The mixture was oil-outed by adding diisopropyl ether, and the residue was purified by silica-gel column chromatography (chloroform/methanol/water=95/5/0.5 to 80/20/2) to give Compound 2 (232mg, 24%). Compound 2 (232mg, 0.233mmol) was dissolved into NMP (3mL), and morpholine (0.142mL, 1.63mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (27mg, 0.023mmol) were added. The mixture was stirred for an hour at room temperature. After powderization by adding diisopropyl ether, the powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=70/30/3~70/30/5) to give Compound 3 (81mg, 38%).

LC-MS: m/z 910.5 [M+H]<sup>+</sup>, 932.5[M+Na]<sup>+</sup>

## Step 2 Synthesis of Compound I-394

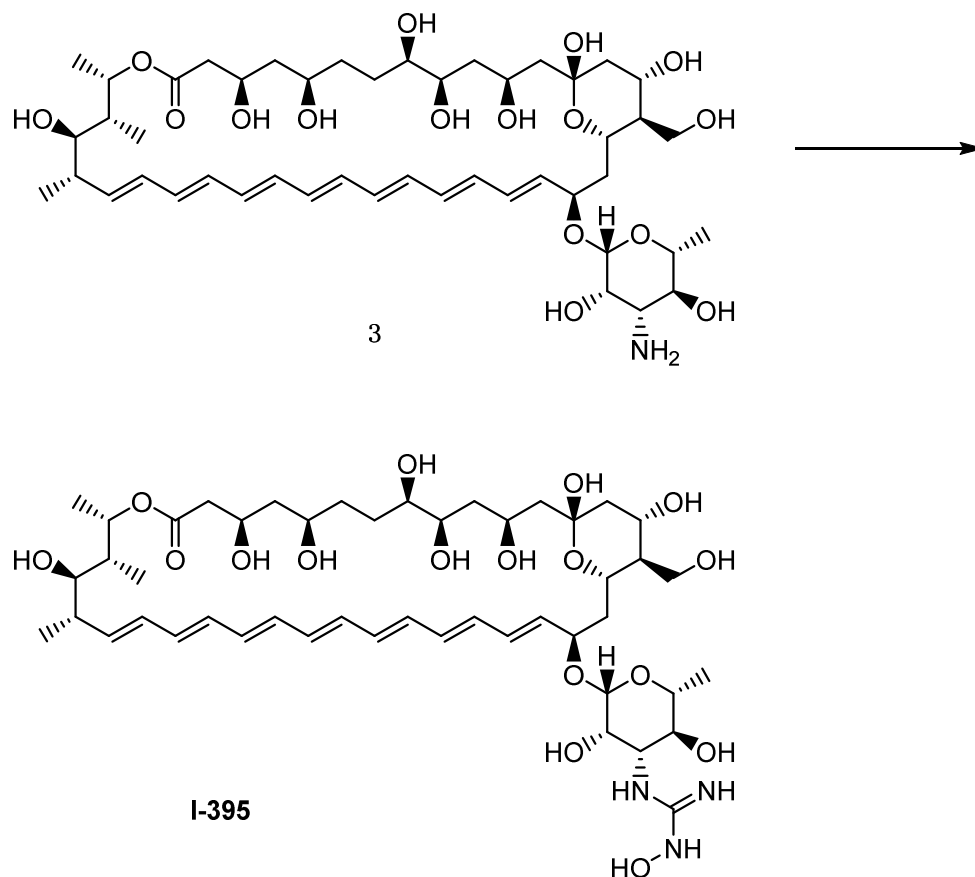
Compound 3 (200mg, 0.220mmol) was dissolved into DMF (2mL), and 1H-pyrazole-1-carboxyimidamide hydrochloride (169mg, 1.15mmol) and DIEA (0.269mL, 1.54mmol) were added. The mixture was stirred for 12 hours at room temperature. After powderization by adding diisopropyl ether, the obtained powder was purified by silica-gel column chromatography (amino silica-gel, chloroform/methanol/water=70/30/3~50/50/5) to give Compound I-394 (110mg, 53%).

LC-MS: m/z 952.8 [M+H]<sup>+</sup>

[0 2 3 3]

## Example 61: Synthesis of Compound I-395

[Chemical Formula 1 1 7]



## Synthesis of Compound I-395

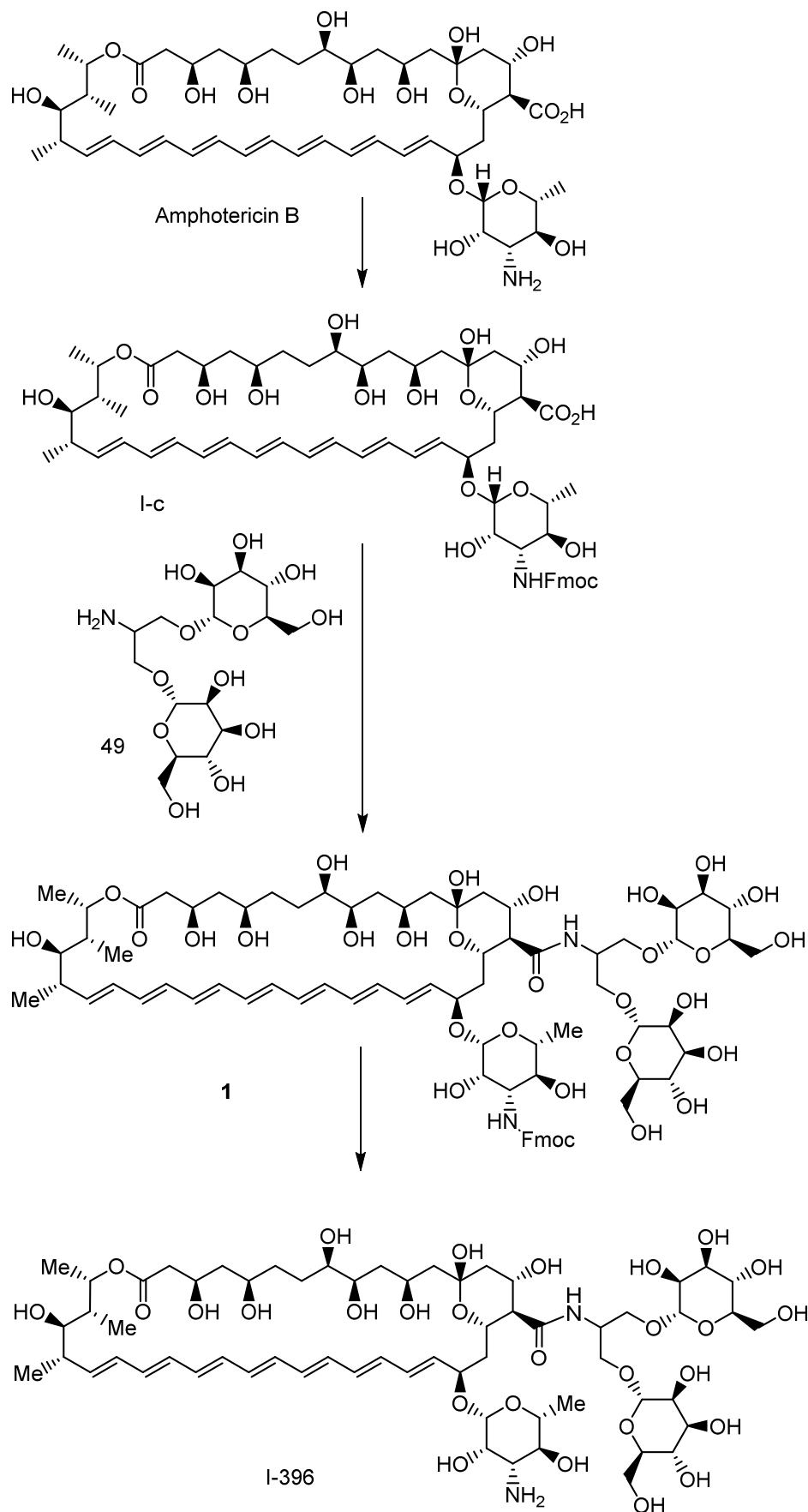
Compound 3 (100mg, 0.11mmol) was dissolved into DMF (1mL), and DIEA (0.096ml, 0.55mmol), cyanogen bromide (11.6mg, 0.11mmol) and Hydroxylamine Hydrochloride (7.64mg, 0.11mmol) were added at room temperature. After the mixture was stirred for 5 hours at room temperature, Hydroxylamine Hydrochloride (1.53mg, 0.022mmol) was added. After the mixture was stirred for 15 hours at room temperature, isopropyl ether was added to give solids. the obtained solids were purified by silica-gel column chromatography (chloroform/methanol/water=50/45/5) to give Compound I-395 (36mg, 27%).

LC-MS: m/z 968.5 [M+H]<sup>+</sup>

[0 2 3 4]

## Example 62: Synthesis of Compound I-396

## [Chemical Formula 1 1 8]



## Step 1 Synthesis of Compound I-c

Amphotericin B (10g, 9.74mmol) was dissolved into dimethylformamide (25mL) and methanol (25mL), and pyridine (9mL, 112mmol) and Fmoc-OSu (9.20g, 27.3mmol)

were added. The mixture was stirred for 12 hours at room temperature. The reaction solution was poured to isopropyl ether (1000mL) and stirred strongly. The obtained powder was filtrated. The obtained solids were washed with isopropyl ether and dried up in vacuo to give crude Compound I-c (14.27g). The retention time of Compound I-c was 13 minutes by HPLC analysis (methanol/distilled water containing 0.1% PIC-B7= gradient 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm). The retention time of raw material amphotericin B was 8.6 minutes under the same condition.

#### Step 2 Synthesis of Compound I-396

Compound I-c (2g, 1.745mmol) was dissolved into N,N-dimethylformamide (18mL), and PyBOP (2.72g, 5.23mmol) and N,N-diisopropylethylamine (1.52mL, 8.72mmol) were added. Compound 49 (1.087g, 2.62mmol) synthesized at example 27 was added, and the mixture was stirred for 5 hours at room temperature. The reaction mixture was poured to diisopropyl ether (300mL) and stirred strongly. The obtained powder was filtrated and purified by silica-gel column chromatography (chloroform:methanol containing 10% water=9:1~1:1~3:7) to give Compound 1 (1.95g, 72%). The retention time of Compound 1 was 9.5 minutes by HPLC analysis (methanol/distilled water containing 0.1% PIC-B7= gradient 70/30 to 100/0, flow speed 1ml/min, wavelength of detection= 385nm).

#### Step 3

Compound 1 (1.84g, 1.192mmol) was dissolved into N,N-dimethylformamide (10mL), and piperidine (1.18mL, 11.92mmol) was added. The mixture was stirred for an hour in an ice-water bath. The reaction mixture was poured to diisopropyl ether (300mL) and stirred strongly. The obtained powder was filtrated to give crude gummy solids (1.98g). The obtained solids were purified by reverse-phase chromatography (HP20ss, acetonitrile-water). The obtained fractions were condensed and lyophilized to give Compound I-396 (350mg, 23%).

m/z 1321.7 [M+H]<sup>+</sup>.

Elementary analysis: (C<sub>62</sub>H<sub>100</sub>N<sub>2</sub>O<sub>28</sub>)(H<sub>2</sub>O)<sub>8.9</sub>

Calculated value: C 50.25; H 8.01; N 1.89 (%)

Actual value: C 50.21; H 7.91; N 2.53 (%)

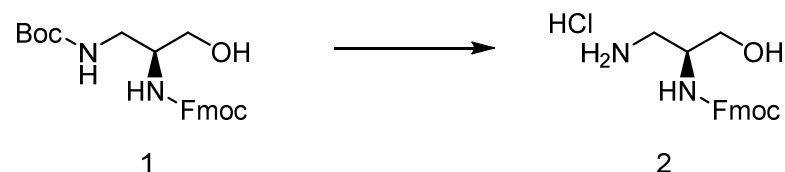
[0 2 3 5]

The synthesis example of the side chain is shown as follow.

[0 2 3 6]

Reference Example 4: Synthesis of Compound 2 (The side chain of Compound I-162)

[Chemical Formula 1 1 9]



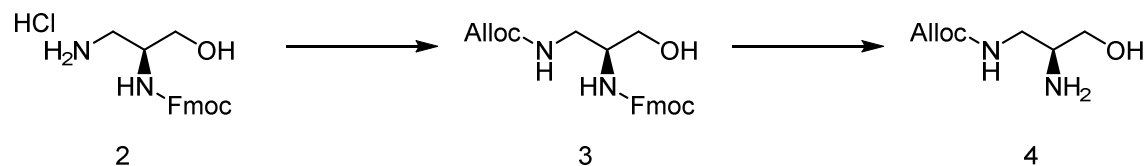
#### Step 1 Synthesis of Compound 2

Compound 1 (5.0g, 12.1mmol) was suspended in dichloromethane (50mL), and hydrochloric acid (4mol/L, dioxane solution, 6mL) was added. The mixture was stirred for an hour at room temperature. The resulted solids were filtrated and dried up to give Compound 2. Compound 2 was used to synthesis of Compound I-162 without purification.

[0 2 3 7]

Reference Example 5: Synthesis of Compound 4 (The side chain of Compound I-169)

[Chemical Formula 1 2 0]



### Step 1 Synthesis of Compound 3

Compound 2 obtained at Step 1 of example 1 and Compound 1 (1.0g, 2.87mmol) were dissolved into dichloromethane (10mL) and triethylamine (795mL, 5.73mmol), and Alloc-OSu (1.0g, 2.87mmol) was added. The mixture was stirred for 2.5 hours at room temperature. The solvent was removed by evaporating in vacuo and extracted by adding water to residue. After the organic phase was washed with saturated ammonium chloride aqueous solution and brine, the organic phase was dried up with magnesium sulfate anhydrous. The solvent was evaporated in vacuo, and the obtained residue was purified by silica-gel column chromatography (hexane/ethyl acetate) to give Compound 3 (760mg, 67%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

δ: 3.26-3.46 (m, 3H), 3.53-3.70 (m, 3H), 4.20 (t, J = 6.9 Hz, 1H), 4.40 (d, J = 6.9 Hz, 2H), 4.58 (d, J = 6.0 Hz, 2H), 5.05-5.09 (m, 1H), 5.10-5.34 (m, 3H), 5.90 (ddt, J = 17.0, 10.7, 5.8 Hz, 1H), 7.31 (t, J = 7.3 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.58 (d, J = 7.3 Hz, 2H), 7.76 (d, J = 7.3 Hz, 2H).

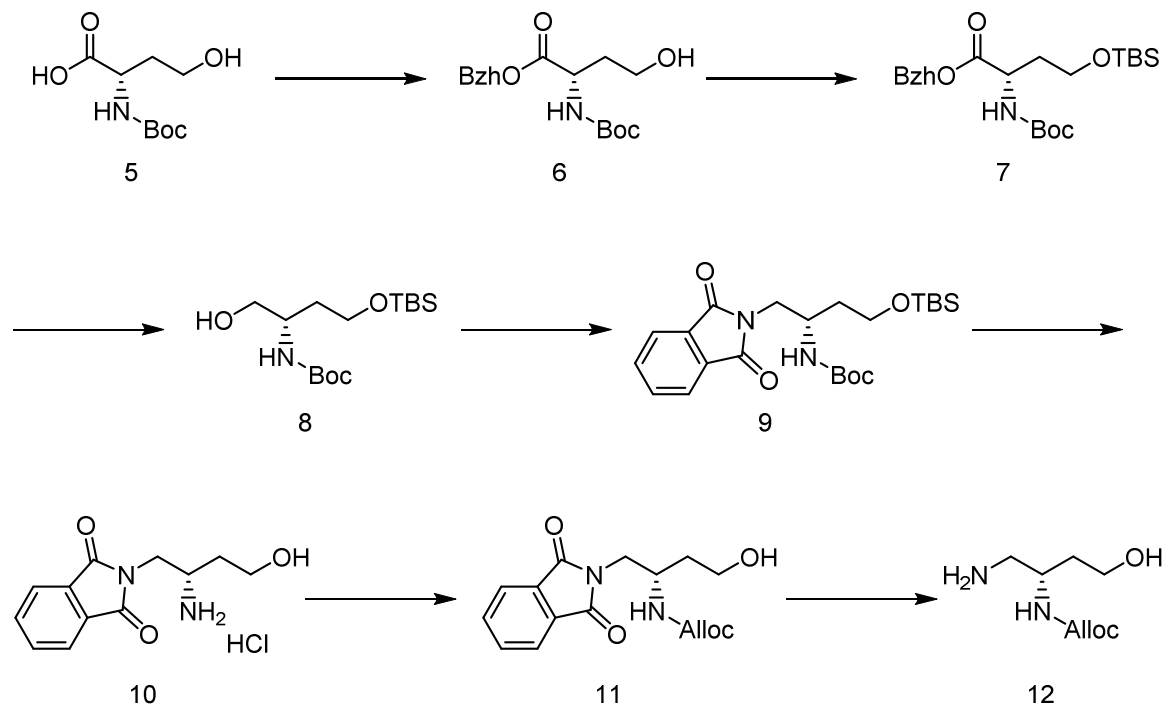
### Step 2 Synthesis of Compound 4

Compound 3 (790mg, 1.99mmol) was dissolved into dichloromethane (10mL), and piperidine (395mL, 3.99mmol) was added. The mixture was stirred for 3.5 hours at room temperature. After the solvent was evaporated in vacuo and dissolved into methanol, the solvent was oil-outed by adding isopropyl ether to remove solvent. This operation was repeated twice. Compound 4 was used to synthesis of Compound I-169 without purification.

[0 2 3 8]

Reference Example 6: Synthesis of Compound 12 (The side chain of Compound I-163)

[Chemical Formula 1 2 1]



### Step 1 Synthesis of Compound 6

Compound 5 (3.27g, 14.9mmol) was dissolved into tetrahydrofuran (15mL), and diphenyldiazomethane (3.48g, 17.9mmol) was added. The mixture was stirred at room temperature. The reaction mixture was condensed, and the obtained residue was purified by silica-gel column chromatography (hexane/ethyl acetate) to give Compound 6 (5.17g, 90%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

δ: 1.44 (s, 9H), 1.56-1.60 (m, 2H), 2.22-2.28 (m, 1H), 3.27-3.30 (m, 1H), 3.62-3.70 (m, 2H), 4.58-4.65 (m, 1H), 5.38 (d, J = 7.5 Hz, 1H), 6.90 (s, 1H), 7.27-7.36 (m, 10H).

### Step 2 Synthesis of Compound 7

Compound 6 (2.1g, 5.45mmol) was dissolved into N,N-dimethylformamide (5mL) and tetrahydrofuran (5mL), and imidazole (816mg, 12mmol) and TBS chloride (985mg, 6.54mmol) were added. The mixture was stirred for an hour at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. After the organic phase was washed with water and brine, the organic phase was dried up with magnesium sulfate anhydrous and evaporated in vacuo. The obtained residue was purified by silica-gel column chromatography (hexane/ethyl acetate) to give Compound 7 (2.4g, 88%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

δ: 0.03 (s, 3H), 0.05 (s, 3H), 0.90 (s, 9H), 1.49 (s, 9H), 1.95-2.19 (m, 2H), 3.55-3.64 (m, 1H), 3.66-3.74 (m, 1H), 4.52-4.60 (m, 1H), 5.84 (d, J = 7.0 Hz, 1H), 6.95 (s, 1H), 7.32-7.41 (m, 10H).

### Step 3 Synthesis of Compound 8

Compound 7 (2.45g, 4.9mmol) was dissolved into tetrahydrofuran (20mL) and methanol (10mL), and the mixture was cooled to 0°C. Lithium triethylborohydride (12mL, 2mol/L solution, 23.9mmol) was added dropwise, and the mixture was stirred for 30 minutes at room temperature. Water was added to the mixture, and the mixture was extracted with ethyl acetate. After the organic phase was washed with water and brine, the organic phase was dried up with magnesium sulfate anhydrous

and evaporated in vacuo. The obtained residue was purified by silica-gel column chromatography (hexane/ethyl acetate) to give Compound 8 (2.4g, 88%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

δ: 0.08 (s, 6H), 0.91 (s, 9H), 1.44 (s, 9H), 1.63-1.76 (m, 1H), 1.79-1.89 (m, 1H), 3.40-3.48 (m, 1H), 3.58-3.69 (m, 2H), 3.70-3.81 (m, 3H), 5.40-5.50 (m, 1H).

#### Step 4 Synthesis of Compound 9

Compound 8 (3.71g, 11.6mmol) was dissolved into tetrahydrofuran (20mL), and phthalimide (2.05g, 13.9mmol), triphenylphosphine (3.65g, 13.9mmol) and DMAD (5.16mL, 13.9mmol, 2.7mol/L solution) were added. The mixture was stirred at room temperature. Saturated sodium bicarbonate aqueous solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. After the organic phase was washed with water and brine, the organic phase was dried up with magnesium sulfate anhydrous and evaporated in vacuo. The obtained residue was purified by silica-gel column chromatography (hexane/ethyl acetate) to give Compound 9 (4.68g, 90%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

δ: 0.07 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.22 (s, 9H), 1.63-1.71 (m, 1H), 1.80-1.93 (m, 1H), 3.70-3.86 (m, 4H), 4.08-4.17 (m, 1H), 5.12 (d, J = 8.0 Hz, 1H), 7.66-7.72 (m, 2H), 7.80-7.86 (m, 2H).

#### Step 5 Synthesis of Compound 11

Compound 9 (2.23g, 4.97mmol) was dissolved into dichloromethane (15mL) and methanol (1mL), and hydrochloric acid (4mol/L dioxane solution, 5mL) was added. The mixture was stirred for 2 hours at room temperature. The resulted solids were filtrated to give Compound 10. Compound 10 was used to next reaction without purification. Compound 10 was dissolved into dichloromethane (10mL), and Alloc-OSu (1.11g, 5.6mmol) and triethylamine (1.55mL, 11.1mmol) were added. The mixture was stirred for 30 minutes at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. After the organic phase was washed with water and brine, the organic phase was dried up with magnesium sulfate anhydrous and evaporated in vacuo. The obtained residue was purified by silica-gel column chromatography (hexane/ethyl acetate) to give Compound 11 (1.47g, 99%).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ: 1.50-1.70 (m, 2H), 3.34-3.50 (m, 2H), 3.52-3.66 (m, 2H), 3.86-3.97 (m, 1H), 4.20-4.37 (m, 2H), 4.44 (t, J = 5.0 Hz, 1H), 5.03 (dq, J = 10.4, 1.5 Hz, 1H), 5.14 (dd, J = 17.3, 1.5 Hz, 1H), 5.71 (ddt, J = 17.3, 10.4, 5.5 Hz, 1H), 7.08 (d, J = 8.9 Hz, 1H), 7.80-7.88 (m, 4H).

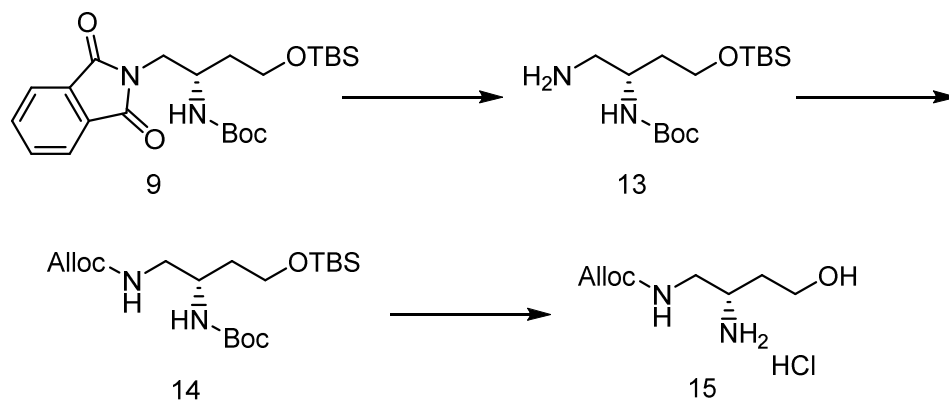
#### Step 6 Synthesis of Compound 12

Compound 11 (1.47g, 4.62mmol) was dissolved into ethanol (10mL), and hydrazine hydrate (337mL, 6.93mmol) was added. The mixture was stirred for 6 hours at 80°C. The reaction mixture was filtrated and condensed to give Compound 12. Compound 12 was used to synthesis of Compound I-163 without purification.

[ 0 2 3 9 ]

Reference Example 7: Synthesis of Compound 15 (The side chain of Compound I-168)

[Chemical Formula 1 2 2]



### Step 1 Synthesis of Compound 14

Compound 9 (2.46g, 5.48mmol) was dissolved into ethanol (20mL), and hydrazine hydrate (533mL, 11mmol) was added. The mixture was stirred for 4 hours at 80°C. The reaction mixture was filtrated and condensed to give Compound 13. The obtained Compound 13 was dissolved into dichloromethane (10mL), and Alloc-OSu (1.68g, 8.4mmol) and DIEA (0.98mL, 5.62mmol) were added. The mixture was stirred for 20 hours at room temperature. The reaction mixture was condensed. Water was added to the mixutre, and the mixure was extracted with ethyl acetate. After the organic phase was washed with water and brine, the organic phase was dried up with magnesium sulfate anhydrous and evaporated in vacuo. The obtained residue was purified by silica-gel column chromatography (hexane/ethyl acetate) to give Compound 14 (1.75g, 77%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

δ: 0.06 (s, 6H), 0.90 (s, 9H), 1.43 (s, 9H), 1.59-1.70 (m, 1H), 1.72-1.85 (m, 1H), 3.20-3.31 (m, 1H), 3.31-3.41 (m, 1H), 3.65-3.83 (m, 4H), 4.55 (d, J = 5.5 Hz, 2H), 5.19 (dd, J = 10.4, 1.0 Hz, 1H), 5.29 (dd, J = 17.2, 1.0 Hz, 1H), 5.35-5.43 (m, 1H), 5.90 (ddt, J = 17.2, 10.4, 5.5 Hz, 1H).

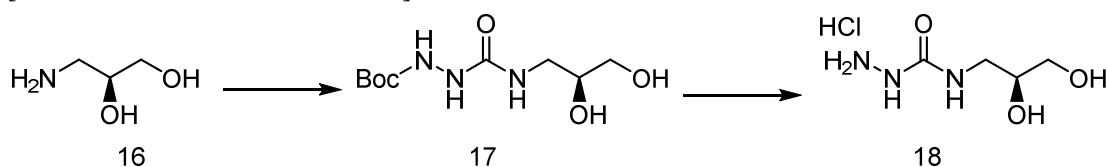
### Step 2 Synthesis of Compound 15

Compound 14 (1.75g, 4.35mmol) was dissolved into dichloromethane (10mL) and methanol (1mL), and hydrochloric acid (4mol/L dioxane solution, 2.2mL) was added. The mixture was stirred for an hour at room temperature. The reaction mixture was condensed to give Compound 15. Compound 15 was used to systhesis of Compound I-168 without purification.

[0 2 4 0]

Reference Example 8: Synthesis of Compound 18 (The side chain of Compound I-225)

[Chemical Formula 1 2 3]



### Step 1 Synthesis of Compound 17

Boc hydrazine (2.1g, 15.9mmol) was dissolved into tetrahydrofuran (20mL). After the mixture was cooled to 0°C, pyridine (4.1mL, 50.8mmol) and p-nitrophenyl chloroformate (3.52g, 17.5mmol) were added. The mixture was stirred for 1.5 hours at 0°C. After that, Compound 16 (1.88g, 20.7mmol) and DIEA (3.61mL, 20.7mmol)

were added, and the mixture was stirred for an hour at room temperature. The solvent was removed in vacuo, and the obtained residue was purified by silica-gel column chromatography (chloroform/methanol) to give Compound 17 (2.9g, 73%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

$\delta$ : 1.38 (s, 9H), 2.90-2.98 (m, 1H), 3.10-3.51 (m, 4H), 4.54 (t, J = 5.7 Hz, 1H), 4.77 (d, J = 4.5 Hz, 1H), 6.14-6.19 (m, 1H), 7.72 (s, 1H), 8.51 (s, 1H).

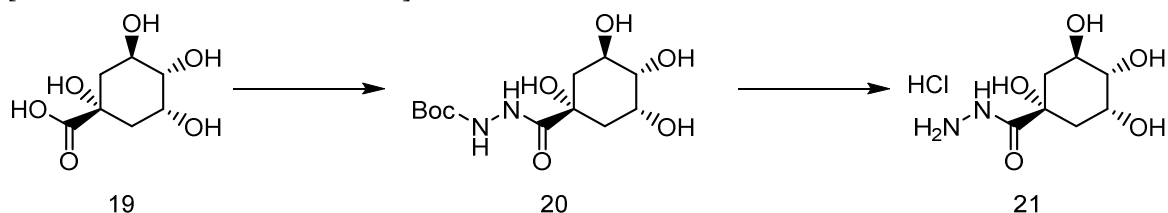
### Step 2 Synthesis of Compound 18

Compound 17 (2.9g, 11.6mmol) was dissolved into dichloromethane (30mL), and hydrochloric acid (4mol/L, dioxane solution, 6mL) was added. The mixture was stirred for an hour at room temperature. The reaction mixture was condensed to give Compound 18. Compound 18 was used to synthesis of Compound I-225 without purification.

$$\begin{bmatrix} 0 & 2 & 4 & 1 \end{bmatrix}$$

## Reference Example 9: Synthesis of Compound 21 (The side chain of Compound I-233)

[Chemical Formula 1 2 4]



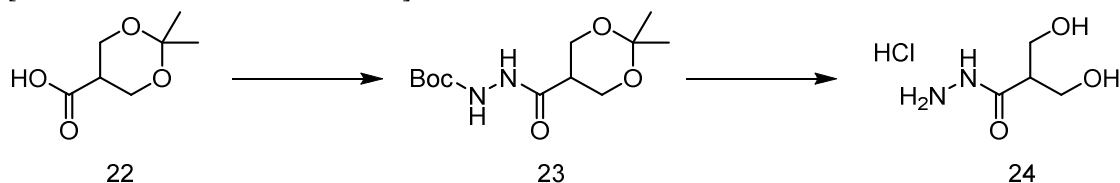
### Step 1 Synthesis of Compound 21

Compound 19 (1g, 5.2mmol) was dissolved into N,N-dimethylformamide (5mL), and Boc hydrazine (688mg, 5.2mmol), DIEA (1.8mL, 10.4mmol) and HATU (1.98g, 5.2mmol) were added. The mixture was stirred for 17 hours at room temperature. The mixture was oil-outed by adding diisopropyl ether (50mL), and the solvent was removed to give Compound 20. The obtained Compound 20 was suspended in dichloromethane (15mL), and hydrochloric acid (4mol/L, dioxane solution, 6mL) was added. The mixture was stirred for 2 hours at room temperature. The reaction mixture was filtrated and dried up to give Compound 21. Compound 21 was used to synthesis of Compound I-233 without purification.

$$\begin{bmatrix} 0 & 2 & 4 & 2 \end{bmatrix}$$

## Reference Example 10: Synthesis of Compound 24 (The side chain of Compound I-240)

[Chemical Formula 1 2 5]

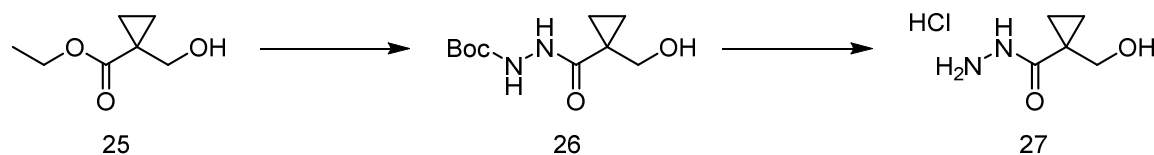


### Step 1 Synthesis of Compound 24

Compound 22 (2.75g, 17.2mmol) was dissolved into N,N-dimethylformamide (10mL), and Boc-hydrazine (2.27g, 17.2mmol), DIEA (6.0mL, 34.3mmol) and HATU (6.53g, 17.2mmol) were added. The mixture was stirred for 3 hours at room temperature. Saturated ammonium chloride aqueous solution was added, and the mixture was extracted with chloroform. After the organic phase was washed with brine, the organic phase was dried up with magnesium sulfate anhydrous. The solvent was removed in vacuo to give Compound 23. The obtained residue was suspended in dichloromethane (15mL), and hydrochloric acid (4mol/L, dioxane

solution, 14mL) was added. The mixture was stirred for 3.5 hours at room temperature. The reaction mixture was filtrated and dried up to give Compound 24. Compound 24 was used to systhesis of Compound I-240 without purification.  
[0 2 4 3]

Reference Example 11: Synthesis of Compound 27 (The side chain of Compound I-247)  
[Chemical Formula 1 2 6]



#### Step 1 Synthesis of Compound 26

Compound 25 (1g, 6.94mmol) was dissolved into ethanol (1mL), and hydrazine monohydrate (0.371mL, 7.63mmol) was added. The mixture was stirred for 6 days under heat reflux. After the mixture was cooled to room temperature, Boc<sub>2</sub>O (3.54mL, 15.3mmol) was added, and the mixture was stirred for 2 hours at room temperature. The obtained by evaporating solvent was purified by silica-gel column chromatography (hexane/ethyl acetate) to give Compound 26 (560mg, 35%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

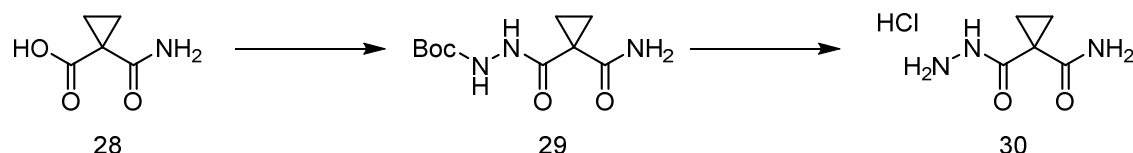
δ: 0.72-0.76 (m, 2H), 1.26-1.31 (m, 2H), 1.47 (s, 9H), 3.23 (s, 1H), 3.71 (s, 2H), 6.66 (s, 1H), 8.84 (s, 1H).

#### Step 2 Synthesis of Compound 27

Compound 26 (500mg, 2.17mmol) was suspended in dichloromethane (10mL), and hydrochloric acid (4mol/L, dioxane solution, 1mL) was added. The mixture was stirred for an hour at room temperature. The reaction mixtre was filtrated, and the obtained solids were dried up to give Compound 27. Compound 27 was used to systhesis of Compound I-247 without purification.

[0 2 4 4]

Reference Example 12: Synthesis of Compound 30 (The side chain of Compound I-256)  
[Chemical Formula 1 2 7]



#### Step 1 Synthesis of Compound 29

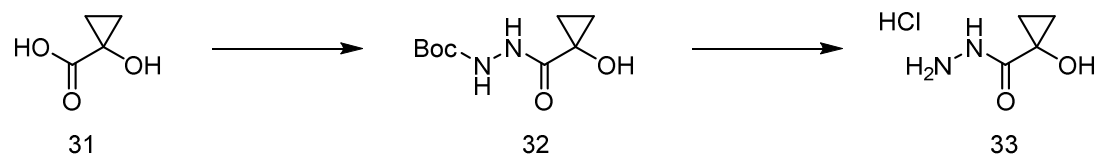
Compound 28 (2g, 15.5mmol) was dissolved into N,N-dimethylformamide (10mL), and Boc-hydrazine (2.05g, 15.5mmol), HATU (5.89g, 15.5mmol) and DIEA (5.41mL, 31mmol) were added. The mixture was stirred for 16 hours at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and dried up with magnesium sulfate anhydrous, and the solvent was removed in vacuo. The obtained residue was purified by silica-gel column chromatography (hexane/ethyl acetate) to give residue including Compound 29. Compound 29 was used to next reaction without purification. The obtained Compound 29 was dissolved into dichloromethane (10mL), and hydrochloric acid (4mol/L, dioxane solution, 15mL) was added. The mixture was stirred for 7 hours at room temperature. The reaction mixture was filtrated, and the obtained solids were dried up to give Compound 30.

Compound 30 was used to synthesis of Compound I-256 without purification.

[ 0 2 4 5 ]

Reference Example 13: Synthesis of Compound 33 (The side chain of Compound I-257)

[Chemical Formula 1 2 8]



#### Step 1 Synthesis of Compound 32

Compound 31 (1g, 9.8mmol) was dissolved into N,N-dimethylformamide (20mL), and Boc-hydrazine (1.3g, 9.8mmol), HATU (3.72g, 9.8mmol) and DIEA (3.42mL, 20mmol) were added. The mixture was stirred for 16 hours at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and dried up with magnesium sulfate anhydrous, and the solvent was removed in vacuo. The obtained residue was purified by silica-gel column chromatography (hexane/ethyl acetate) to give Compound 32 (1.38g, 65%).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ: 0.86 (q, J = 3.8 Hz, 2H), 1.01 (q, J = 3.8 Hz, 2H), 1.40 (s, 9H), 6.24 (s, 1H), 8.62 (s, 1H), 9.51 (s, 1H).

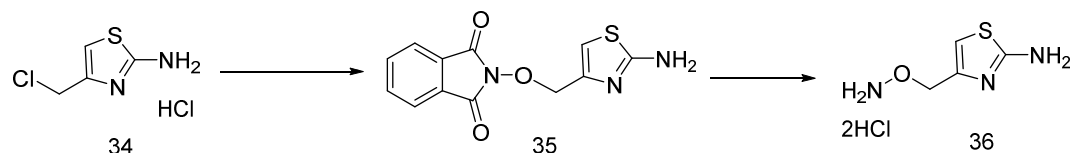
#### Step 2 Synthesis of Compound 33

Compound 32 (1.3g, 6.0mmol) was dissolved into dichloromethane (10mL), and hydrochloric acid (4mol/L, dioxane solution, 9mL) was added. The mixture was stirred for 7 hours at room temperature. The reaction mixture was filtrated, and the obtained solids were dried up to give Compound 33. Compound 33 was used to synthesis of Compound I-257 without purification.

[ 0 2 4 6 ]

Reference Example 14: Synthesis of Compound 36 (The side chain of Compound I-80)

[Chemical Formula 1 2 9]



#### Step 1 Synthesis of Compound 35

2-Hydroxyisoindoline-1,3-dione was dissolved into N,N-dimethylformamide (60mL), and Compound 34 (5.86g, 36mmol), potassium carbonate (9.12g, 66.0mmol) and potassium bromide (1.78g, 15mmol) were added. The mixture was stirred for 5 hours at room temperature. Ice was added to the reaction mixture, the resulted residue was filtrated and washed with water to give Compound 35 (5.16g, 63%).

Mass (M+1): 276

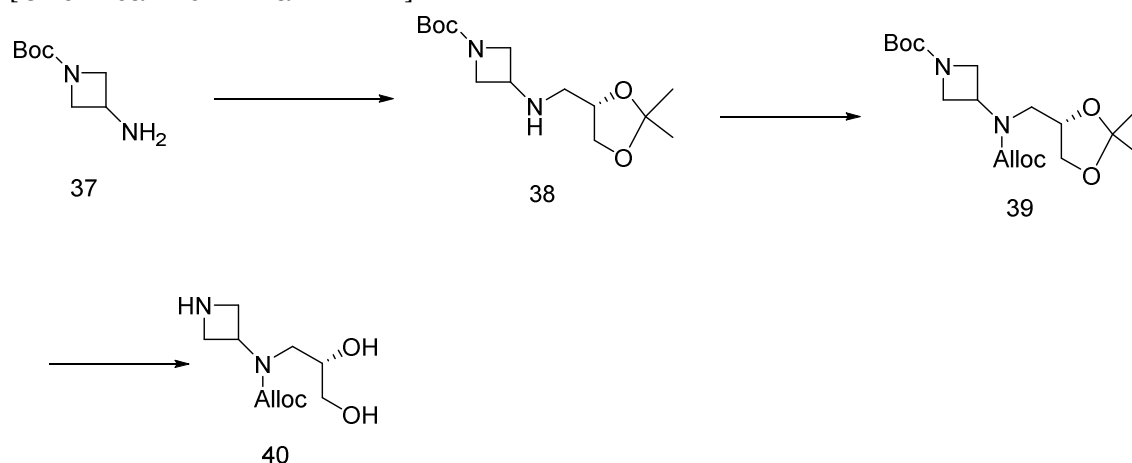
#### Step 2 Synthesis of Compound 36

Compound 35 (2.202g, 8mmol) was dissolved into dichloromethane (40mL), and methylhydrazine was added. The mixture was stirred for 2 hours. After concentration, the mixture was purified by silica-gel column chromatography. 4mmol/L HCl/AcOEt (5mL) was added to the condensed solution to give Compound 36 (1.08g, 62%). Compound 36 was used to synthesis of Compound I-80 without

purification.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 4.56 (s, 2H), 5.00-5.20 (br, 2H), 5.40-5.80 (br, 2H), 6.47 (s, 1H)  
[0 2 4 7]

Reference Example 15: Synthesis of Compound 40 (The side chain of Compound I-226)  
[Chemical Formula 1 3 0]



### Step 1 Synthesis of Compound 38

Dichloromethane solution (6mL) of tert-butyl 3-aminoazetidine-1-carboxylate (Compound 37: 1.26g, 7mmol) was added to dichloromethane solution (6mL) of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (1.00g, 7.70mmol). After the reaction mixture was cooled to 0°C, Sodium Triacetoxyborohydride (2.23g, 10.5mmol) was added. After the mixture was stirred for 4 hours at room temperature, the mixture was incubated for 12 hours. Saturated sodium hydrogen carbonate aqueous solution was added, and the mixture was extracted with ethyl acetate and washed with brine. The organic phase was dried up with magnesium sulfate, filtrated and condensed to give Compound 38 (2g, 99%).

### Step 2 Synthesis of Compound 39

After dichloromethane solution (20mL) of Compound 38 (2g, 6.98mmol) was cooled to 0°C, triethylamine (1.45mL, 10.5mmol) and allyl chloroformate (0.97mL, 9.08mmol) were added. The mixture was stirred for an hour at room temperature. After concentration, water was added. The mixture was extracted with ethyl acetate and washed with brine. The organic phase was dried up with magnesium sulfate, filtrated and condensed. The obtained residue was purified by silica-gel column chromatography to give Compound 39 (1.34g, 52%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.33 (s, 3H), 1.42 (s, 3H), 1.61 (s, 9H), 3.25-3.30 (m, 1H), 3.53-3.70 (m, 1H), 4.00-4.20 (m, 7H), 4.50-4.62 (m, 3H), 5.26 (dd,  $J=12\text{Hz}, 24\text{Hz}$ , 2H), 5.87-5.96 (m, 1H)

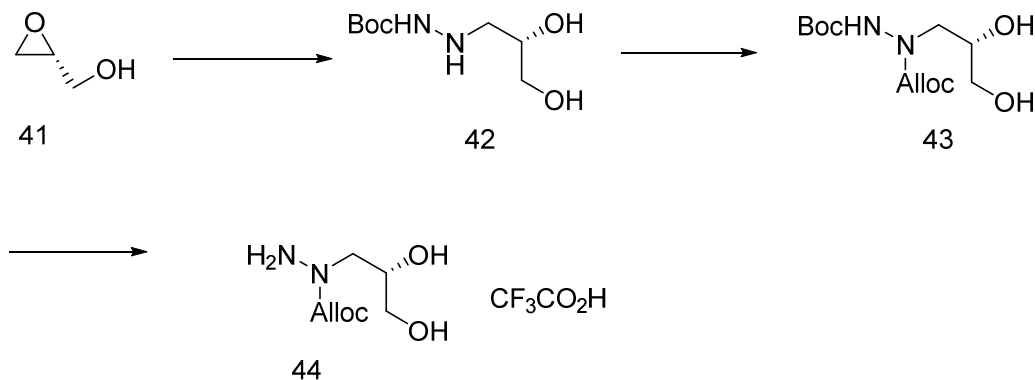
### Step 3 Synthesis of Compound 40

Concentrated hydrochloric acid (3mL) was added to toluene (3mL) and tetrahydrofuran (2mL) solution of Compound 5 (1.34g, 3.62mmol), and the mixture was stirred for 3 hours at 65°C. After that, concentrated hydrochloric acid (3mL) was added, and the mixture was stirred for 1.5 hours at 70°C. Compound 40 was obtained by azeotroping with toluene. Compound 40 was used to synthesis of Compound I-226 without purification.

[0 2 4 8]

Reference Example 16: Synthesis of Compound 44 (The side chain of Compound I-227)

[Chemical Formula 1 3 1]



### Step 1 Synthesis of Compound 42

Tert-buthyl hydrazine carboxylate (37.5g, 283mmol) was added to ethanol solution (67mL) of Compound 41 (7g, 94mmol), and the mixture was stirred for 3 days at room temperature. After concentration, the mixture was purified by silica-gel column chromatography to give Compound 42 (13.6g, 70%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ :1.51 (s,9H), 2.50-3.00 (m,2H), 3.50-3.60 (m,3H), 3.65-3.70 (m,1H), 3.71-3.90 (m,1H),4.00-4.50 (br,1H), 6.30-6.40 (br,1H)

### Step 2 Synthesis of Compound 43

Allyl 2,5-dioxopyrrolidine-1-yl carbonate (219mg, 1.1mmol) was added to tetrahydrofuran solution (2mL) of Compound 42 (206mg, 1mmol), and the mixture was stirred for 12 hours at room temperature. Allyl 2,5-dioxopyrrolidine-1-yl carbonate (299mg, 1.5mmol) was added, and the mixture was stirred for 8 hours. After concentration, the mixture was purified by silica-gel column chromatography to give Compound 43 (142mg, 49%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ :1.54 (s,9H), 1.70-1.75 (br,1H), 3.80-3.98 (m,4H), 3.99-4.02 (m,1H), 4.86-4.74 (br,2H), 4.82-4.90 (m,2H), 5.27-5.42 (m,2H), 5.88-5.90 (m,1H)

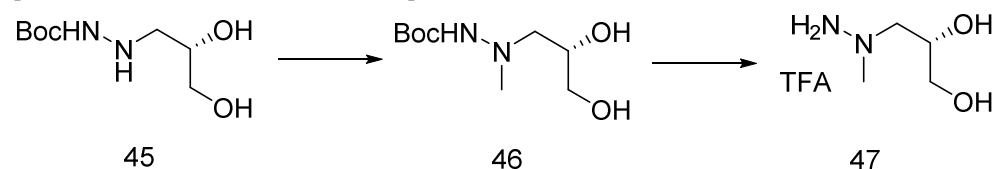
### Step 3 Synthesis of Compound 44

Dichloromethane solution (0.5mL) of Compound 43 (58.1mg, 0.2mmol) was cooled to  $0^\circ\text{C}$ . Trifluoroacetic acid (0.3mL) was added, and the mixture was stirred for an hour at room temperature. After concentration, Compound 44 was used for synthesis of Compound I-227

[0 2 4 9]

### Reference Example 17: Synthesis of Compound 47 (The side chain of Compound I-244)

[Chemical Formula 1 3 2]



### Step 1 Synthesis of Compound 46

After tetrahydrofuran:dichloromethane=1:1 (24mL) suspension solution of Compound 45 (1.24g, 6mmol) was cooled to  $0^\circ\text{C}$ , N,N-diisopropylethylamine (5.24mL, 30mmol) and iodomethane (3.75mL, 60mmol) were added. The mixture was stirred for 4 hours at room temperature. After concentration, the mixture was extracted by adding water. After the organic phase was washed with brine, the organic phase was dried up with magnesium sulfate, filtrated and condensed to give Compound 46 (1.02g, 77%).

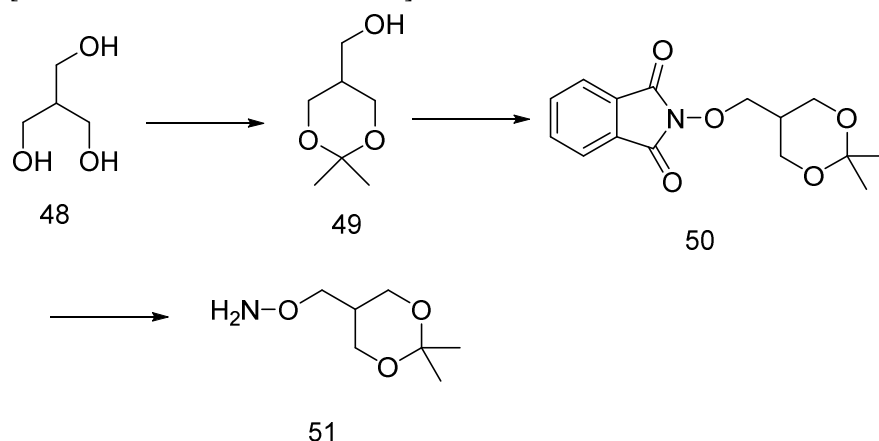
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ :1.46 (s,9H),1.62-1.73 (br,1H), 2.55 (d,  $J$ =12Hz, 2H), 2.67 (s,3H), 2.80 (t, $J$ =12Hz, 1H), 3.48-3.60 (br, 1H), 3.50-3.80 (m, 2H), 5.58-5.60 (br,1H)

#### Step 2 Synthesis of Compound 47

After dichloromethane solution (5mL) of Compound 11 (551mg, 2.5mmol) was cooled to  $0^\circ\text{C}$ , trifluoroacetic acid (3.8mL) was added. The mixture was stirred for 40 minutes at  $10^\circ\text{C}$ . After that, the mixture was heated to room temperature and stirred for 40 minutes. Trifluoroacetic acid (1.9mL) was added, and the mixture was stirred for 40 minutes at room temperature. Compound 47 was obtained by azeotroping with toluene. Compound 47 was used to synthesis of Compound I-244 without purification.

[0 2 5 0]

#### Reference Example 18: Synthesis of Compound 51 (The side chain of Compound I-255) [Chemical Formula 1 3 3]



#### Step 1 Synthesis of Compound 49

Compound 48 (5.93g, 55.9mmol) was dissolved into tetrahydrofuran (25mL), and 2,2-dimethoxypropane (10.27mL, 84mmol) and p-toluenesulfonic acid (1.063g, 5.59mmol) were added. The mixture was stirred for an hour at  $50^\circ\text{C}$ . After that, the mixture was incubated for 12 hours. Potassium carbonate (1.54g, 11.2mmol) was added, and the mixture was stirred for 30 minutes. The mixture was filtrated and condensed. Brine was added, and the mixture was extraceted with chloroform. The organic phase was washed with brine and dried up with magnesium sulfate, and filtrated and condensed to give Compound 40.

#### Step 2 Synthesis of Compound 50

N-hydroxyphthalimide (6.36g, 39.0mmol), triphenylphosphine (11.8g, 45.0mmol) were added to tetrahydrofuran solution (80mL) of Compound 49 (4.39g, 30mmol), and the mixture was cooled to  $0^\circ\text{C}$ . Diisopropyl Azodicarboxylate (8.75mL, 45.0mmol) was added, and the mixture was stirred for 2 hours. After concentration, the crude Compound 50 obtained by silica-gel column chromatography was used to next reaction.

#### Step 3 Synthesis of Compound 51

After dichloromethane:methanol=2:1 solution (15mL) of Compound 15 (628mg, 2.5mmol) was cooled, methylhydrazine (0.146mL, 2.75mmol) was added. After the mixture was stirred for an hour, the mixture was condensed to give Compound 51. Compound 51 was used to systhesis of Compound I-255 without purification.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ :1.80-2.00 (m,1H), 3.40 (d,  $J$ =8Hz,4H), 3.52 (d,  $J$ =8Hz, 2H)

[0 2 5 1]

The following compounds were synthesized by above examples. "No." in tables

means compound No.; “LC-MS” in tables means molecular weight of each compounds measured by liquid column chromatography/mass analysis; “Method” means method of liquid column chromatography/mass analysis.

[0 2 5 2]

(Method A)

Column: ACQUITY UPLC BEH C18 (1.7 $\mu$ m, 2.1x50mm) (Waters)

Column temperature: room temperature

Flow speed: 0.4 mL/minutes

UV wavelength of detection: 200 to 400 nm

Mobile phase: [A] aqueous solution with 0.1% formic acid, [B] acetonitrile solution with 0.1% formic acid

Gradient: linear gradient of 10%-95% of [B] for 8 minutes

Ionization: ESI Positive/Negative

[0 2 5 3]

(Method B)

Column: ACQUITY UPLC BEH C18 (1.7 $\mu$ m, 2.1x50mm) (Waters)

Column temperature: room temperature

Flow speed: 0.8 mL/minutes

UV wavelength of detection: 200 to 400 nm

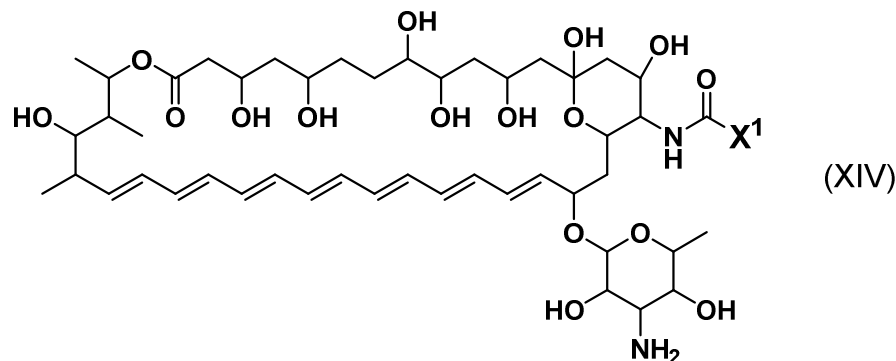
Mobile phase: [A] aqueous solution with 0.1% formic acid, [B] acetonitrile solution with 0.1% formic acid

Gradient: linear gradient of 5%-100% of [B] for 3.5 minutes, and hold 100% of [B] for 0.5 minutes

Ionization: ESI Positive/Negative

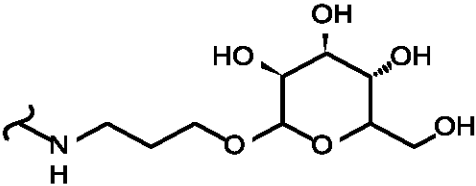
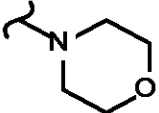
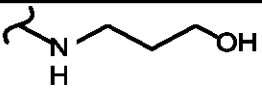
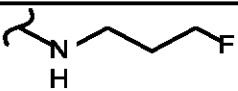
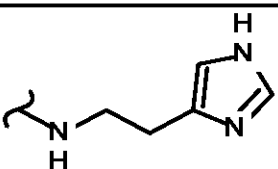
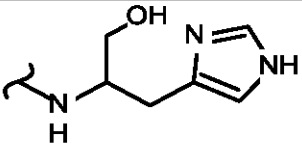
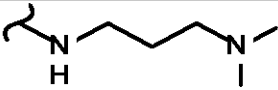
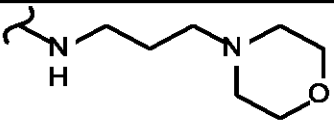
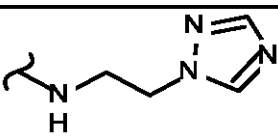
[0 2 5 4]

[Chemical Formula 1 3 4]

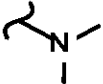
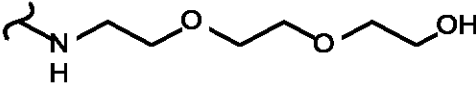
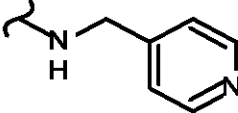
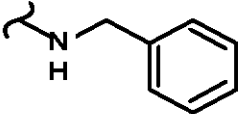
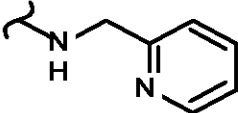
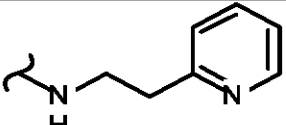
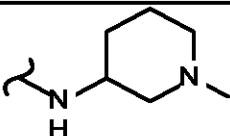
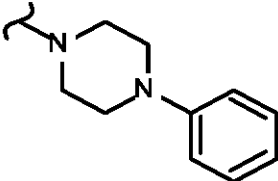


The structure and physical property of compound (XIV) are shown below.

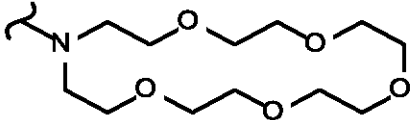
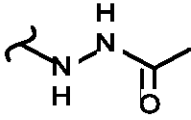
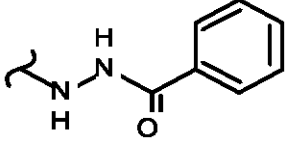
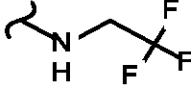
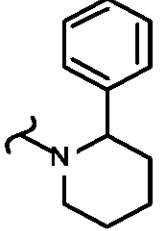
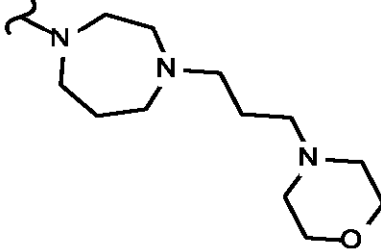
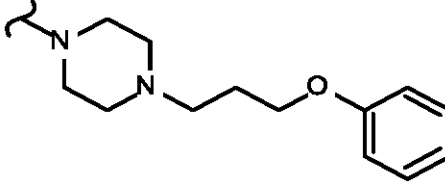
[Table 1]

| No. | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-1 |    | 1158.6 [M+H] <sup>+</sup>                                 | B      |
| I-2 |    | 1008.4 [M+H] <sup>+</sup> ,<br>1030.5 [M+Na] <sup>+</sup> | A      |
| I-3 |    | 996.9 [M+H] <sup>+</sup>                                  | B      |
| I-4 |    | 998.5 [M+H] <sup>+</sup>                                  | B      |
| I-5 |   | 1032.5 [M+H] <sup>+</sup>                                 | A      |
| I-6 |  | 1062.5 [M+H] <sup>+</sup>                                 | B      |
| I-7 |  | 1023.6 [M+H] <sup>+</sup>                                 | A      |
| I-8 |  | 1065.6 [M+H] <sup>+</sup>                                 | B      |
| I-9 |  | 1033.4 [M+H] <sup>+</sup>                                 | B      |

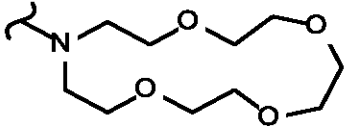
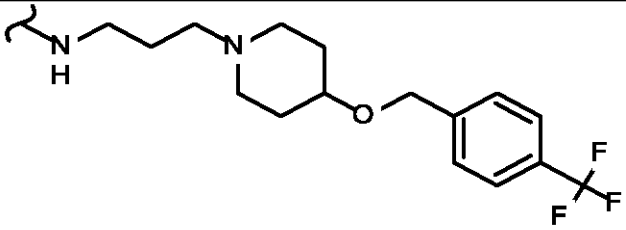
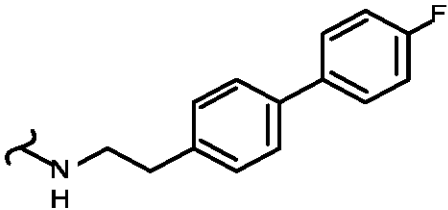
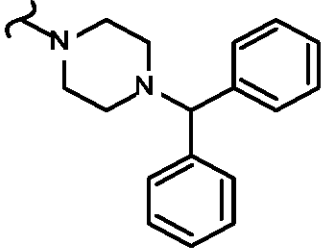
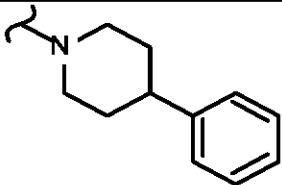
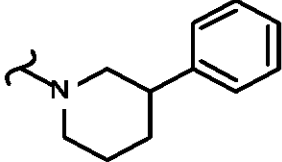
[Table 2]

| No.  | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-10 |    | 966.5 [M+H] <sup>+</sup>                                  | B      |
| I-11 |    | 1070.5 [M+H] <sup>+</sup> ,<br>1092.5 [M+Na] <sup>+</sup> | A      |
| I-12 |    | 1029.6 [M+H] <sup>+</sup> ,<br>1051.6 [M+Na] <sup>+</sup> | A      |
| I-13 |    | 1028.6 [M+H] <sup>+</sup> ,<br>1050.6 [M+Na] <sup>+</sup> | A      |
| I-14 |    | 1029.6 [M+H] <sup>+</sup>                                 | B      |
| I-15 |  | 1043.5 [M+H] <sup>+</sup>                                 | A      |
| I-16 |  | 1035.6 [M+H] <sup>+</sup>                                 | A      |
| I-17 |  | 1083.9 [M+H] <sup>+</sup>                                 | B      |

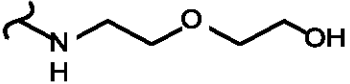
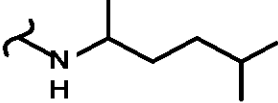
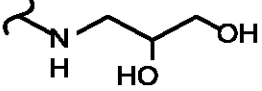
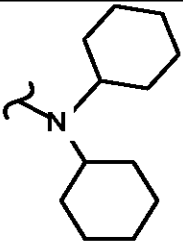
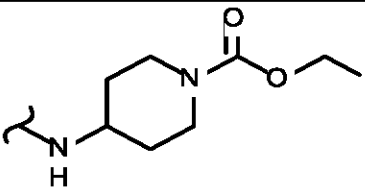
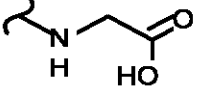
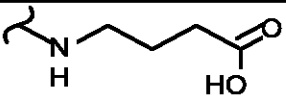
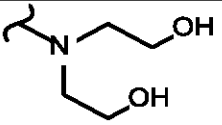
[Table 3]

| No.  | $X^1$                                                                               | LC-MS                     | Method |
|------|-------------------------------------------------------------------------------------|---------------------------|--------|
| I-18 |    | 1184.9 [M+H] <sup>+</sup> | B      |
| I-19 |    | 995.5 [M+H] <sup>+</sup>  | A      |
| I-20 |    | 1057.7 [M+H] <sup>+</sup> | B      |
| I-21 |    | 1020.5 [M+H] <sup>+</sup> | B      |
| I-22 |   | 1082.6 [M+H] <sup>+</sup> | B      |
| I-23 |  | 1148.8 [M+H] <sup>+</sup> | B      |
| I-24 |  | 1141.6 [M+H] <sup>+</sup> | B      |

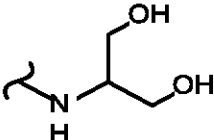
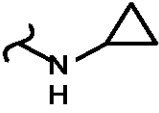
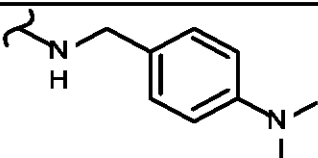
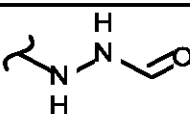
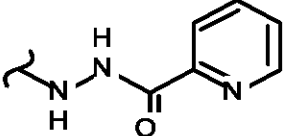
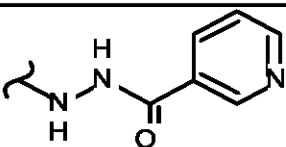
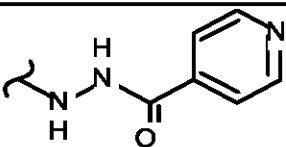
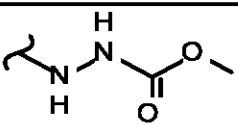
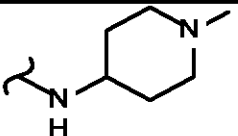
[Table 4]

| No.  | $X^1$                                                                               | LC-MS                     | Method |
|------|-------------------------------------------------------------------------------------|---------------------------|--------|
| I-25 |    | 1140.7 [M+H] <sup>+</sup> | B      |
| I-26 |    | 1237.9 [M+H] <sup>+</sup> | B      |
| I-27 |    | 1136.7 [M+H] <sup>+</sup> | B      |
| I-28 |   | 1173.9 [M+H] <sup>+</sup> | B      |
| I-29 |  | 1082.7 [M+H] <sup>+</sup> | B      |
| I-30 |  | 1082.7 [M+H] <sup>+</sup> | B      |

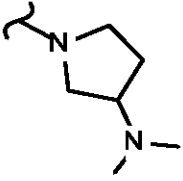
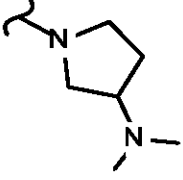
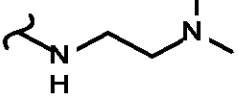
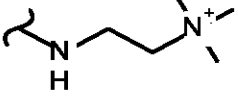
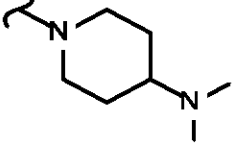
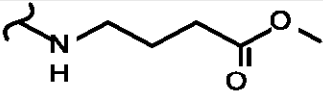
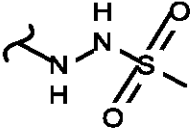
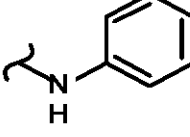
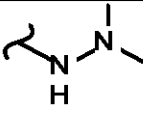
[Table 5]

| No.  | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-31 |    | 1026.4 [M+H] <sup>+</sup>                                 | A      |
| I-32 |    | 1036.9 [M+H] <sup>+</sup>                                 | B      |
| I-33 |    | 1012.8 [M+H] <sup>+</sup>                                 | B      |
| I-34 |    | 1102.8 [M+H] <sup>+</sup>                                 | B      |
| I-35 |   | 1094 [M+H] <sup>+</sup>                                   | B      |
| I-36 |  | 938.5 [M+H] <sup>+</sup>                                  | A      |
| I-37 |  | 996.2 [M+H] <sup>+</sup> ,<br>1018.3 [M+Na] <sup>+</sup>  | A      |
| I-38 |  | 1024.6 [M+H] <sup>+</sup>                                 | A      |
| I-39 |  | 1026.6 [M+H] <sup>+</sup> ,<br>1048.6 [M+Na] <sup>+</sup> | A      |

[Table 6]

| No.  | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-40 |    | 1012.4 [M+H] <sup>+</sup> ,<br>1034.5 [M+Na] <sup>+</sup> | B      |
| I-41 |    | 978.3 [M+H] <sup>+</sup> ,<br>1000.4 [M+Na] <sup>+</sup>  | A      |
| I-42 |    | 1071.6 [M+H] <sup>+</sup>                                 | B      |
| I-43 |    | 981.4 [M+H] <sup>+</sup>                                  | A      |
| I-44 |   | 1058.7 [M+H] <sup>+</sup>                                 | B      |
| I-45 |  | 1058.7 [M+H] <sup>+</sup>                                 | B      |
| I-46 |  | 1058.7 [M+H] <sup>+</sup>                                 | B      |
| I-47 |  | 1011.4 [M+H] <sup>+</sup> ,<br>1033.4 [M+Na] <sup>+</sup> | A      |
| I-48 |  | 1035.6 [M+H] <sup>+</sup>                                 | A      |

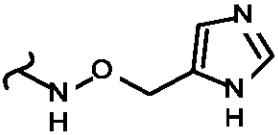
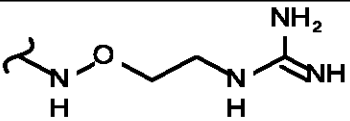
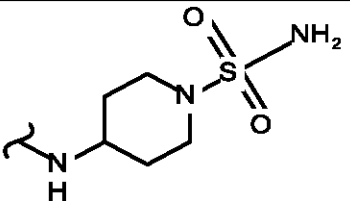
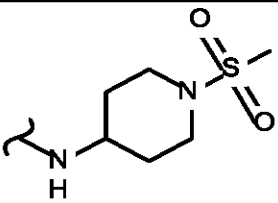
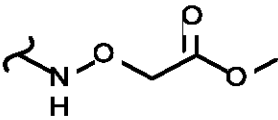
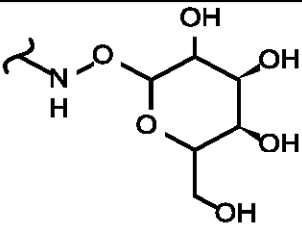
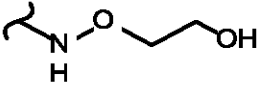
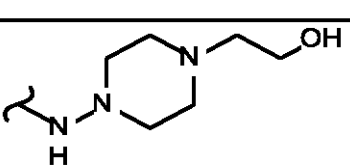
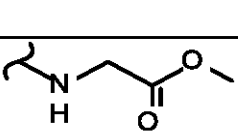
[Table 7]

| No.  | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-49 |    | 1035.7 [M+H] <sup>+</sup>                                 | B      |
| I-50 |    | 1035.7 [M+H] <sup>+</sup>                                 | B      |
| I-51 |    | 1009.5 [M+H] <sup>+</sup> ,<br>1031.5 [M+Na] <sup>+</sup> | A      |
| I-53 |    | 1023.7 [M+H] <sup>+</sup>                                 | A      |
| I-54 |   | 1049.7 [M+H] <sup>+</sup>                                 | B      |
| I-55 |  | 1038.6 [M+H] <sup>+</sup> ,<br>1060.6 [M+Na] <sup>+</sup> | A      |
| I-56 |  | 1031.5 [M+H] <sup>+</sup>                                 | A      |
| I-57 |  | 1014.5 [M+H] <sup>+</sup>                                 | A      |
| I-58 |  | 981.4 [M+H] <sup>+</sup>                                  | A      |

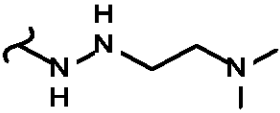
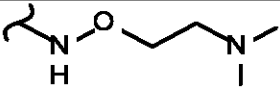
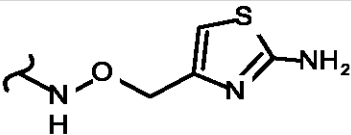
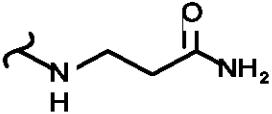
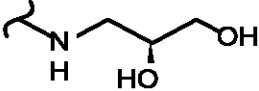
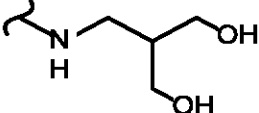
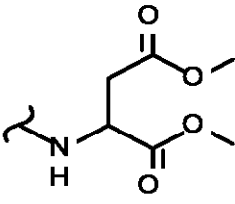
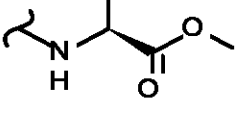
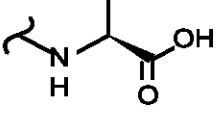
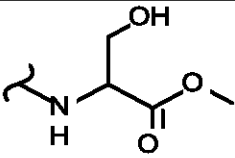
[Table 8]

| No.  | X <sup>1</sup> | LC-MS                                                     | Method |
|------|----------------|-----------------------------------------------------------|--------|
| I-59 |                | 968.5 [M+H] <sup>+</sup>                                  | A      |
| I-60 |                | 996.5 [M+H] <sup>+</sup>                                  | A      |
| I-61 |                | 994.5 [M+H] <sup>+</sup> ,<br>1016.5 [M+Na] <sup>+</sup>  | A      |
| I-62 |                | 1007.5 [M+H] <sup>+</sup> ,<br>1029.5 [M+Na] <sup>+</sup> | A      |
| I-63 |                | 1012.5 [M+H] <sup>+</sup>                                 | A      |
| I-64 |                | 1059.5 [M+H] <sup>+</sup> ,<br>1081.5 [M+Na] <sup>+</sup> | A      |
| I-65 |                | 1060.5 [M+H] <sup>+</sup> ,<br>1082.5 [M+Na] <sup>+</sup> | A      |
| I-66 |                | 1036.5 [M+H] <sup>+</sup> ,<br>1058.5 [M+Na] <sup>+</sup> | A      |
| I-67 |                | 1023.5 [M+H] <sup>+</sup>                                 | A      |
| I-68 |                | 1067.5 [M+H] <sup>+</sup>                                 | A      |

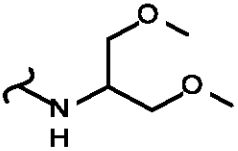
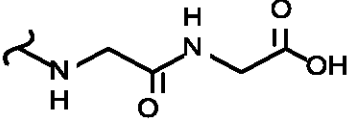
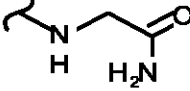
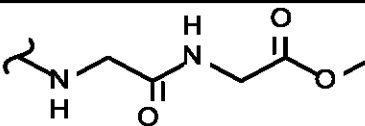
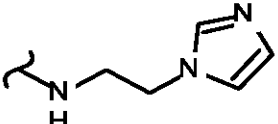
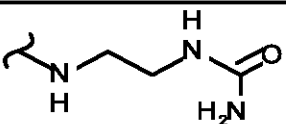
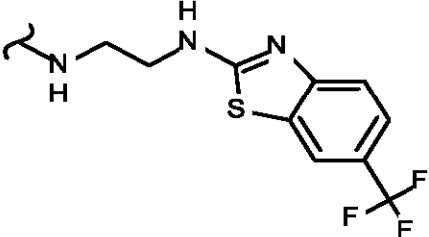
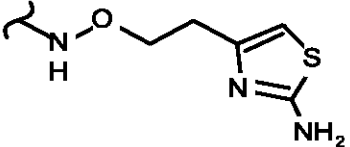
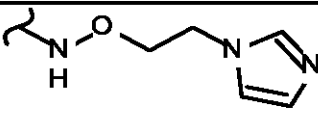
[Table 9]

| No.  | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-69 |    | 1034.5 [M+H] <sup>+</sup>                                 | A      |
| I-70 |    | 1039.5 [M+H] <sup>+</sup>                                 | A      |
| I-71 |    | 1100.4 [M+H] <sup>+</sup> ,<br>1122.5 [M+Na] <sup>+</sup> | A      |
| I-72 |    | 1099.4 [M+H] <sup>+</sup> ,<br>1121.5 [M+Na] <sup>+</sup> | A      |
| I-73 |   | 1026.5 [M+H] <sup>+</sup>                                 | A      |
| I-74 |  | 1116.5 [M+H] <sup>+</sup>                                 | A      |
| I-75 |  | 998.4 [M+H] <sup>+</sup>                                  | A      |
| I-76 |  | 1066.6 [M+H] <sup>+</sup>                                 | A      |
| I-77 |  | 1010.5 [M+H] <sup>+</sup>                                 | A      |

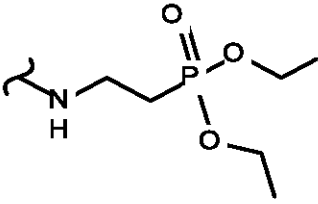
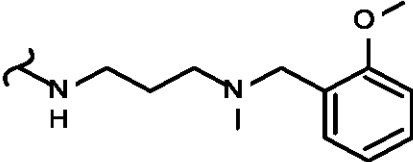
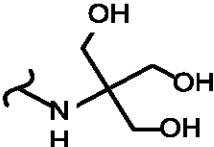
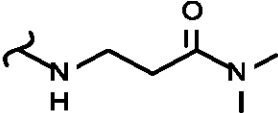
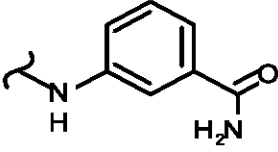
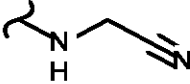
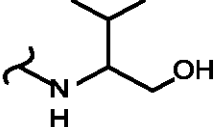
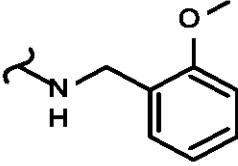
[Table 10]

| No.  | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-78 |    | 1024.5 [M+H] <sup>+</sup>                                 | A      |
| I-79 |    | 1025.7 [M+H] <sup>+</sup>                                 | A      |
| I-80 |    | 1066.5 [M+H] <sup>+</sup>                                 | A      |
| I-81 |    | 1009.6 [M+H] <sup>+</sup> ,<br>1031.6 [M+Na] <sup>+</sup> | A      |
| I-82 |    | 1012.4 [M+H] <sup>+</sup> ,<br>1034.4 [M+Na] <sup>+</sup> | B      |
| I-83 |   | 1026.5 [M+H] <sup>+</sup>                                 | A      |
| I-84 |  | 1082.5 [M+H] <sup>+</sup> ,<br>1104.5 [M+Na] <sup>+</sup> | A      |
| I-85 |  | 1024.5 [M+H] <sup>+</sup> ,<br>1046.5 [M+Na] <sup>+</sup> | A      |
| I-86 |  | 1010.5 [M+H] <sup>+</sup>                                 | A      |
| I-87 |  | 1040.4 [M+H] <sup>+</sup> ,<br>1062.5 [M+Na] <sup>+</sup> | A      |

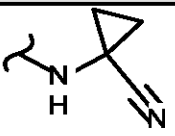
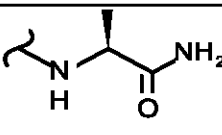
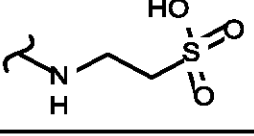
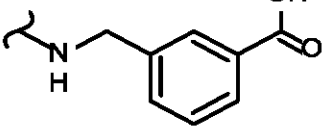
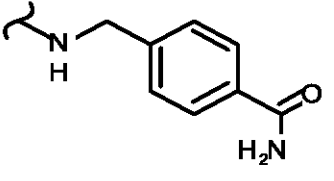
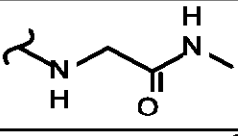
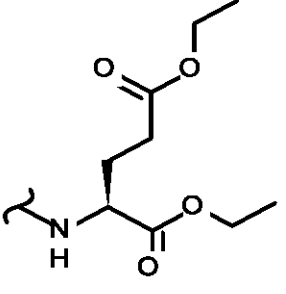
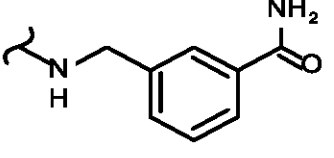
[Table 1 1]

| No.  | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-88 |    | 1040.6 [M+H] <sup>+</sup> ,<br>1062.6 [M+Na] <sup>+</sup> | A      |
| I-89 |    | 1053.5 [M+H] <sup>+</sup> ,<br>1075.5 [M+Na] <sup>+</sup> | A      |
| I-90 |    | 995.5 [M+H] <sup>+</sup>                                  | A      |
| I-91 |    | 1067.5 [M+H] <sup>+</sup> ,<br>1089.5 [M+Na] <sup>+</sup> | A      |
| I-92 |    | 1032.4 [M+H] <sup>+</sup> ,<br>1054.4 [M+Na] <sup>+</sup> | A      |
| I-93 |   | 1024.4 [M+H] <sup>+</sup> ,<br>1046.4 [M+Na] <sup>+</sup> | A      |
| I-94 |  | 1182.5 [M+H] <sup>+</sup> ,<br>1204.5 [M+Na] <sup>+</sup> | A      |
| I-95 |  | 1080.4 [M+H] <sup>+</sup> ,<br>1102.4 [M+Na] <sup>+</sup> | A      |
| I-96 |  | 1048.5 [M+H] <sup>+</sup> ,<br>1070.5 [M+Na] <sup>+</sup> | A      |

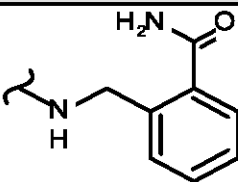
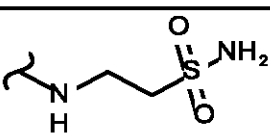
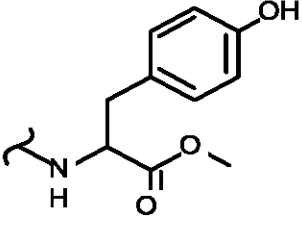
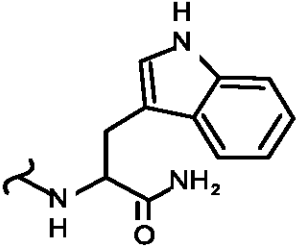
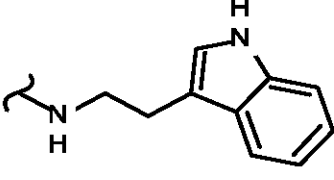
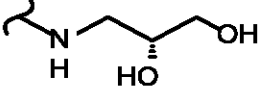
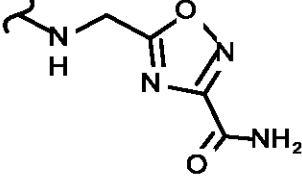
[Table 1 2]

| No.   | $X^1$                                                                               | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-97  |    | 1102.4 [M+H] <sup>+</sup> ,<br>1124.4 [M+Na] <sup>+</sup> | A      |
| I-98  |    | 1129.6 [M+H] <sup>+</sup>                                 | A      |
| I-99  |    | 1042.5 [M+H] <sup>+</sup>                                 | A      |
| I-100 |    | 1037.5 [M+H] <sup>+</sup>                                 | A      |
| I-101 |  | 1057.6 [M+H] <sup>+</sup>                                 | A      |
| I-102 |  | 977.4 [M+H] <sup>+</sup>                                  | A      |
| I-103 |  | 1024.6 [M+H] <sup>+</sup>                                 | A      |
| I-104 |  | 1058.6 [M+H] <sup>+</sup>                                 | A      |

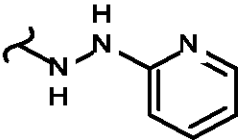
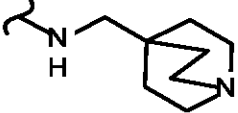
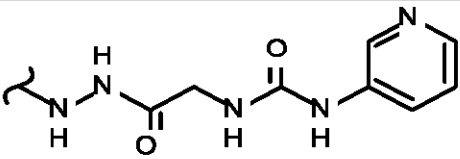
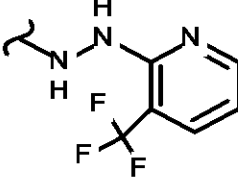
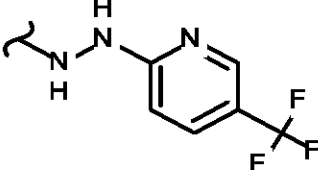
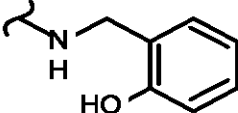
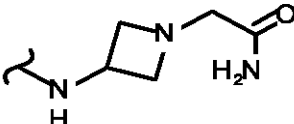
[Table 1 3]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-105 |    | 1003.5 [M+H] <sup>+</sup>                                 | A      |
| I-106 |    | 1009.6 [M+H] <sup>+</sup>                                 | A      |
| I-107 |    | 1046.5 [M+H] <sup>+</sup> ,<br>1068.4 [M+Na] <sup>+</sup> | A      |
| I-109 |    | 1072.5 [M+H] <sup>+</sup>                                 | A      |
| I-110 |   | 1071.6 [M+H] <sup>+</sup>                                 | A      |
| I-111 |  | 1009.6 [M+H] <sup>+</sup>                                 | A      |
| I-112 |  | 1124.6 [M+H] <sup>+</sup>                                 | A      |
| I-113 |  | 1071.6 [M+H] <sup>+</sup>                                 | A      |

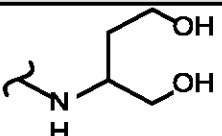
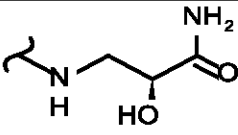
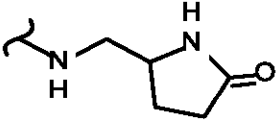
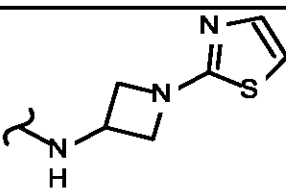
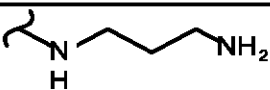
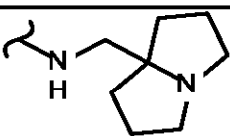
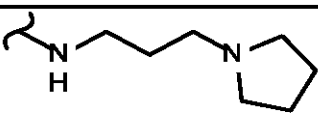
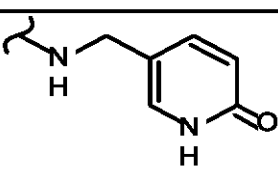
[Table 1 4]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-114 |    | 1071.6 [M+H] <sup>+</sup> ,<br>1093.6 [M+Na] <sup>+</sup> | A      |
| I-115 |    | 1045.5 [M+H] <sup>+</sup>                                 | A      |
| I-116 |    | 1116.6 [M+H] <sup>+</sup>                                 | A      |
| I-117 |   | 1124.6 [M+H] <sup>+</sup>                                 | A      |
| I-118 |  | 1081.6 [M+H] <sup>+</sup>                                 | A      |
| I-119 |  | 1012.5 [M+H] <sup>+</sup>                                 | A      |
| I-120 |  | 1063.6 [M+H] <sup>+</sup>                                 | A      |

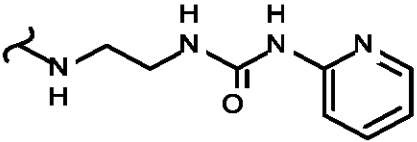
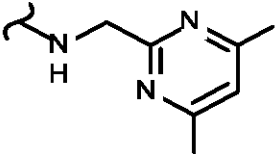
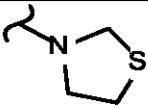
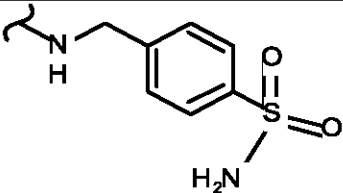
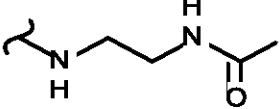
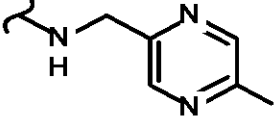
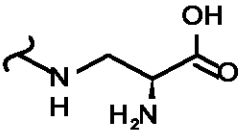
[Table 1 5]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-121 |    | 1030.6 [M+H] <sup>+</sup> ,<br>1052.6 [M+Na] <sup>+</sup> | A      |
| I-122 |    | 1061.6 [M+H] <sup>+</sup>                                 | A      |
| I-123 |    | 1130.7 [M+H] <sup>+</sup>                                 | A      |
| I-124 |    | 1098.6 [M+H] <sup>+</sup>                                 | A      |
| I-125 |   | 1098.6 [M+H] <sup>+</sup>                                 | A      |
| I-126 |  | 1044.6 [M+H] <sup>+</sup>                                 | A      |
| I-127 |  | 1050.6 [M+H] <sup>+</sup> ,<br>1072.6 [M+Na] <sup>+</sup> | A      |
| I-128 |  | 1051.7 [M+H] <sup>+</sup>                                 | A      |

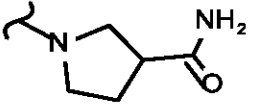
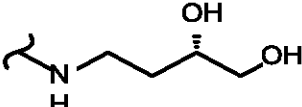
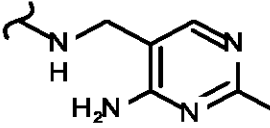
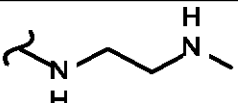
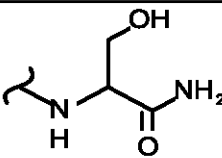
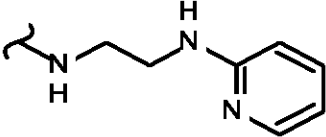
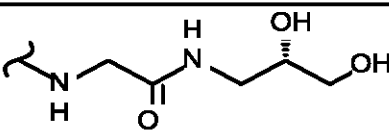
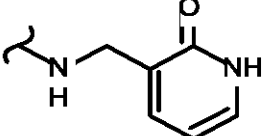
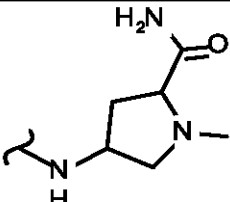
[Table 1 6]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-129 |    | 1026.6 [M+H] <sup>+</sup>                                 | A      |
| I-130 |    | 1025.6 [M+H] <sup>+</sup> ,<br>1047.6 [M+Na] <sup>+</sup> | A      |
| I-131 |    | 1035.6 [M+H] <sup>+</sup> ,<br>1057.6 [M+Na] <sup>+</sup> | A      |
| I-132 |    | 1076.5 [M+H] <sup>+</sup>                                 | A      |
| I-133 |   | 995.6 [M+H] <sup>+</sup> ,<br>1017.6 [M+Na] <sup>+</sup>  | A      |
| I-134 |  | 1061.7 [M+H] <sup>+</sup>                                 | A      |
| I-135 |  | 1049.6 [M+H] <sup>+</sup>                                 | A      |
| I-136 |  | 1045.5 [M+H] <sup>+</sup> ,<br>1067.5 [M+Na] <sup>+</sup> | A      |

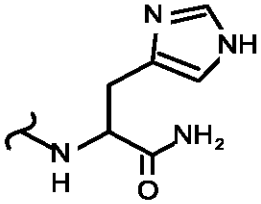
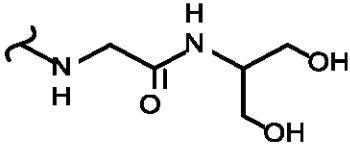
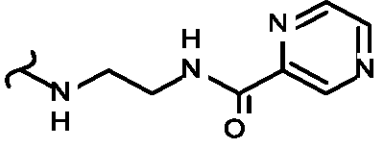
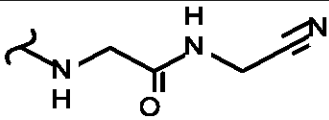
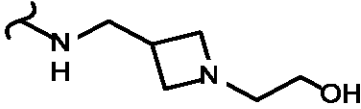
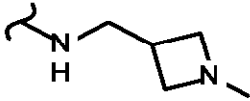
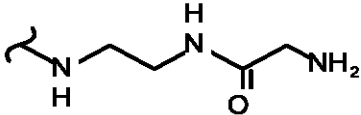
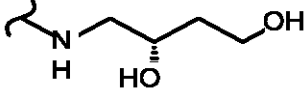
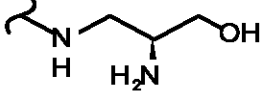
[Table 1 7]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-137 |    | 1101.6 [M+H] <sup>+</sup> ,<br>1123.6 [M+Na] <sup>+</sup> | A      |
| I-138 |    | 1058.6 [M+H] <sup>+</sup> ,<br>1080.6 [M+Na] <sup>+</sup> | A      |
| I-139 |    | 1010.5 [M+H] <sup>+</sup>                                 | A      |
| I-140 |    | 1072.6 [M+H] <sup>+</sup>                                 | A      |
| I-141 |   | 1107.6 [M+H] <sup>+</sup>                                 | A      |
| I-142 |  | 1023.6 [M+H] <sup>+</sup>                                 | A      |
| I-143 |  | 1044.5 [M+H] <sup>+</sup>                                 | A      |
| I-144 |  | 1025.5 [M+H] <sup>+</sup>                                 | B      |

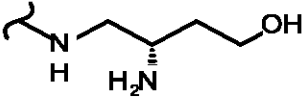
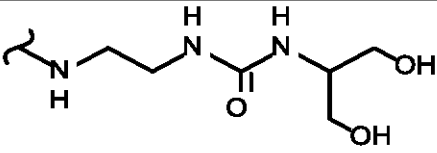
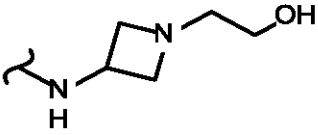
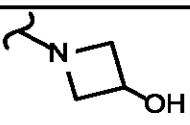
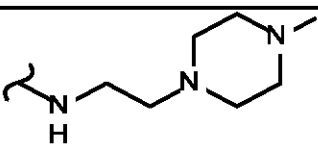
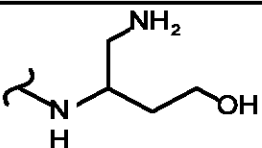
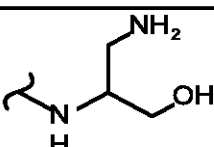
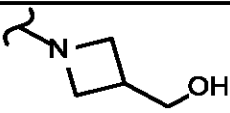
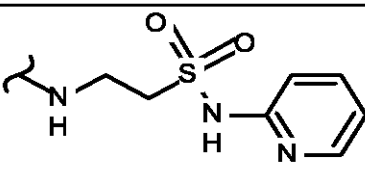
[Table 1 8]

| No.   | X <sup>1</sup>                                                                      | LC-MS                     | Method |
|-------|-------------------------------------------------------------------------------------|---------------------------|--------|
| I-145 |    | 1035.6 [M+H] <sup>+</sup> | B      |
| I-146 |    | 1026.6 [M+H] <sup>+</sup> | A      |
| I-147 |    | 1059.6 [M+H] <sup>+</sup> | A      |
| I-148 |    | 995.5 [M+H] <sup>+</sup>  | A      |
| I-149 |    | 1025.6 [M+H] <sup>+</sup> | A      |
| I-150 |   | 1059.6 [M+H] <sup>+</sup> | A      |
| I-151 |  | 1069.6 [M+H] <sup>+</sup> | A      |
| I-152 |  | 1045.6 [M+H] <sup>+</sup> | A      |
| I-153 |  | 1064.5 [M+H] <sup>+</sup> | A      |

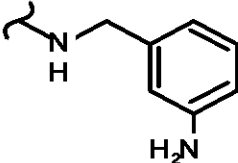
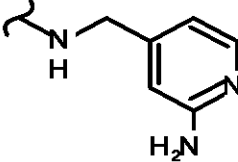
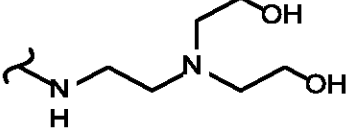
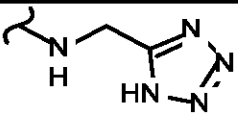
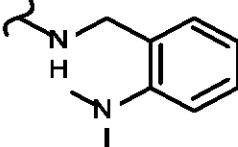
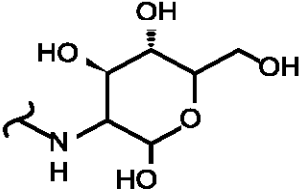
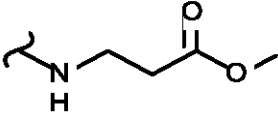
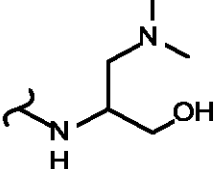
[Table 1 9]

| No.   | $X^1$                                                                               | LC-MS                     | Method |
|-------|-------------------------------------------------------------------------------------|---------------------------|--------|
| I-154 |    | 1075.5 [M+H] <sup>+</sup> | A      |
| I-155 |    | 1069.6 [M+H] <sup>+</sup> | A      |
| I-156 |    | 1087.6 [M+H] <sup>+</sup> | A      |
| I-157 |    | 1034.5 [M+H] <sup>+</sup> | A      |
| I-158 |   | 1051.6 [M+H] <sup>+</sup> | A      |
| I-159 |  | 1021.6 [M+H] <sup>+</sup> | A      |
| I-160 |  | 1038.6 [M+H] <sup>+</sup> | A      |
| I-161 |  | 1026.5 [M+H] <sup>+</sup> | A      |
| I-162 |  | 1011.5 [M+H] <sup>+</sup> | A      |

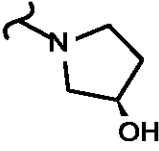
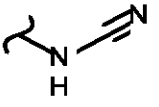
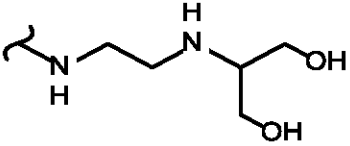
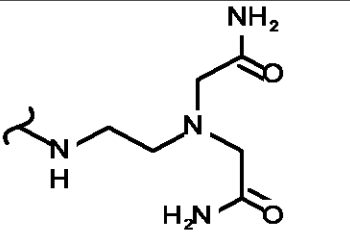
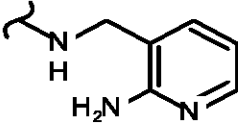
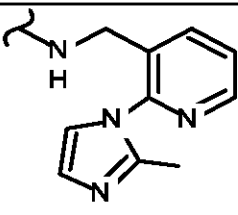
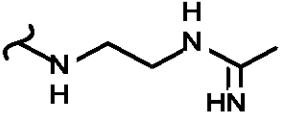
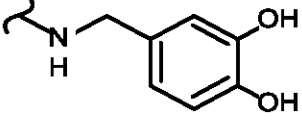
[Table 20]

| No.   | X <sup>1</sup>                                                                      | LC-MS                     | Method |
|-------|-------------------------------------------------------------------------------------|---------------------------|--------|
| I-163 |    | 1025.6 [M+H] <sup>+</sup> | A      |
| I-164 |    | 1098.6 [M+H] <sup>+</sup> | A      |
| I-165 |    | 1037.5 [M+H] <sup>+</sup> | A      |
| I-166 |    | 994.5 [M+H] <sup>+</sup>  | A      |
| I-167 |    | 1064.6 [M+H] <sup>+</sup> | A      |
| I-168 |  | 1025.5 [M+H] <sup>+</sup> | A      |
| I-169 |  | 1011.5 [M+H] <sup>+</sup> | A      |
| I-170 |  | 1008.4 [M+H] <sup>+</sup> | A      |
| I-171 |  | 1022.5 [M+H] <sup>+</sup> | A      |

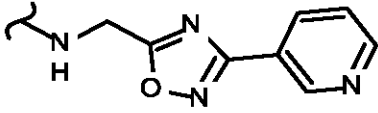
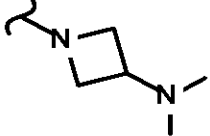
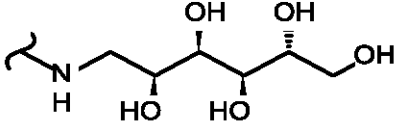
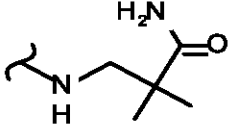
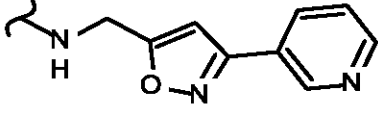
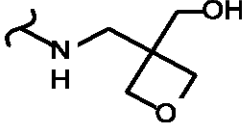
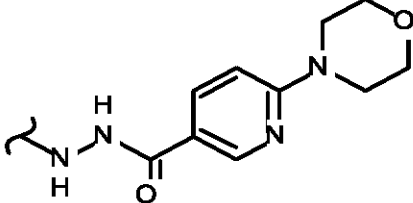
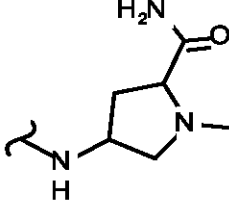
[Table 2 1]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-172 |    | 1043.5 [M+H] <sup>+</sup>                                 | A      |
| I-173 |    | 1044.5 [M+H] <sup>+</sup>                                 | A      |
| I-174 |    | 1069.5 [M+H] <sup>+</sup> ,<br>1091.5 [M+Na] <sup>+</sup> | A      |
| I-175 |    | 1020.5 [M+H] <sup>+</sup>                                 | A      |
| I-176 |   | 1071.5 [M+H] <sup>+</sup>                                 | A      |
| I-177 |  | 1100.5 [M+H] <sup>+</sup>                                 | A      |
| I-178 |  | 1024.5 [M+H] <sup>+</sup> ,<br>1046.6 [M+Na] <sup>+</sup> | A      |
| I-179 |  | 1039.5 [M+H] <sup>+</sup> ,<br>1061.6 [M+Na] <sup>+</sup> | A      |

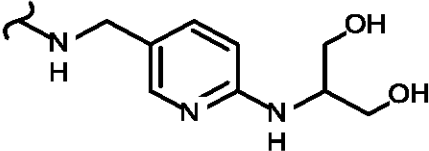
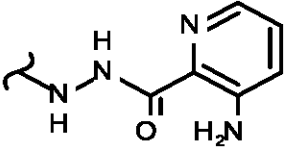
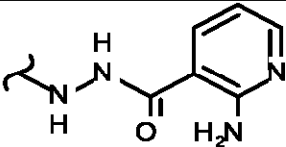
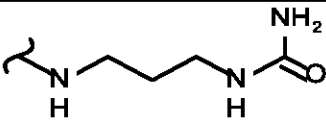
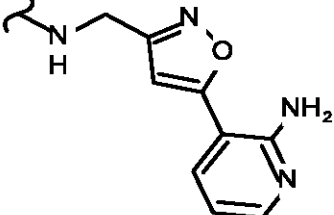
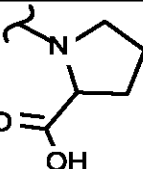
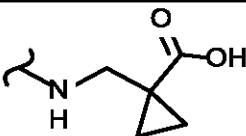
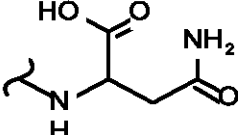
[Table 2 2]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-180 |    | 1030.5 [M+Na] <sup>+</sup>                                | A      |
| I-181 |    | 963 [M+H] <sup>+</sup>                                    | A      |
| I-182 |    | 1055.6 [M+H] <sup>+</sup> ,<br>1077.6 [M+Na] <sup>+</sup> | A      |
| I-183 |    | 1095.5 [M+H] <sup>+</sup>                                 | A      |
| I-184 |   | 1044.4 [M+H] <sup>+</sup>                                 | A      |
| I-185 |  | 1109.5 [M+H] <sup>+</sup> ,<br>1131.5 [M+Na] <sup>+</sup> | A      |
| I-186 |  | 1022.5 [M+H] <sup>+</sup>                                 | A      |
| I-187 |  | 1060.4 [M+H] <sup>+</sup>                                 | A      |

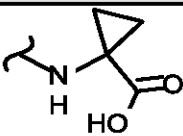
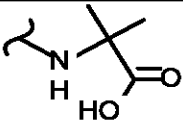
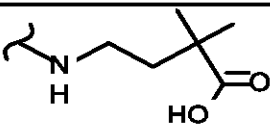
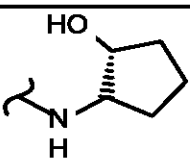
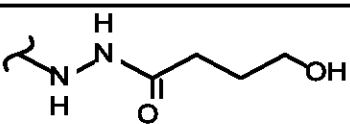
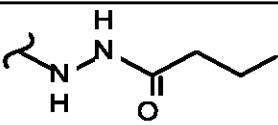
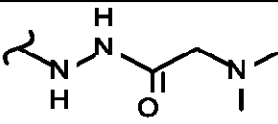
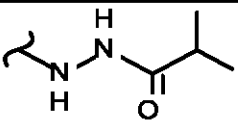
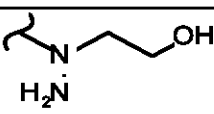
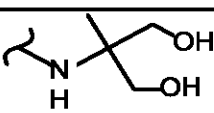
[Table 2 3]

| No.   | $X^1$                                                                               | LC-MS                     | Method |
|-------|-------------------------------------------------------------------------------------|---------------------------|--------|
| I-188 |    | 1097.5 [M+H] <sup>+</sup> | A      |
| I-189 |    | 1021.5 [M+H] <sup>+</sup> | A      |
| I-190 |    | 1102.4 [M+H] <sup>+</sup> | A      |
| I-191 |    | 1037.4 [M+H] <sup>+</sup> | A      |
| I-192 |    | 1096.4 [M+H] <sup>+</sup> | A      |
| I-193 |  | 1038.5 [M+H] <sup>+</sup> | A      |
| I-194 |  | 1143.4 [M+H] <sup>+</sup> | A      |
| I-195 |  | 1064.5 [M+H] <sup>+</sup> | A      |

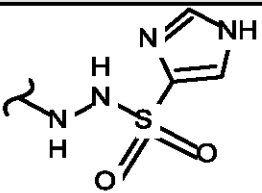
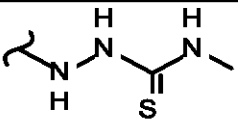
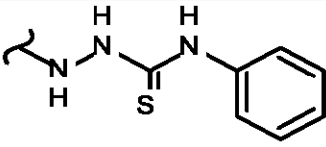
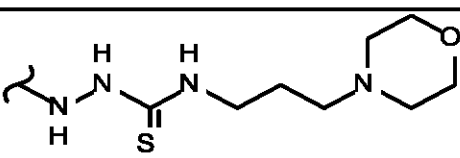
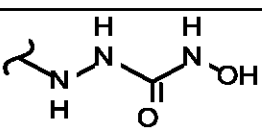
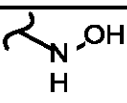
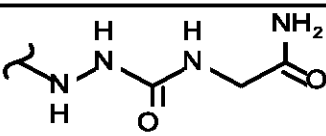
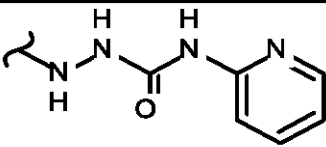
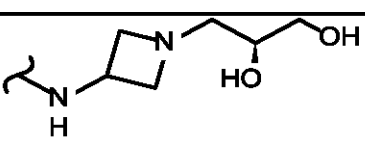
[Table 2 4]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-196 |    | 1118.5 [M+H] <sup>+</sup>                                 | A      |
| I-197 |    | 1073.4 [M+H] <sup>+</sup>                                 | A      |
| I-198 |    | 1073.6 [M+H] <sup>+</sup>                                 | A      |
| I-199 |    | 1038.6 [M+H] <sup>+</sup>                                 | A      |
| I-200 |   | 1111.6 [M+H] <sup>+</sup> ,<br>1133.6 [M+Na] <sup>+</sup> | A      |
| I-201 |  | 1036.5 [M+H] <sup>+</sup>                                 | A      |
| I-202 |  | 1036.5 [M+H] <sup>+</sup>                                 | A      |
| I-203 |  | 1053.3 [M+H] <sup>+</sup> ,<br>1075.4 [M+Na] <sup>+</sup> | A      |

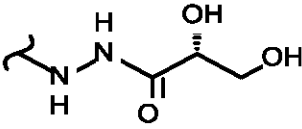
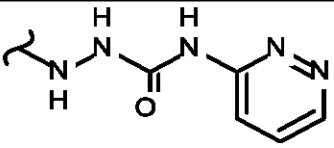
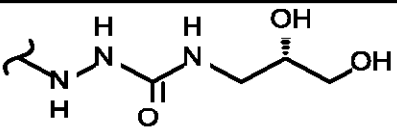
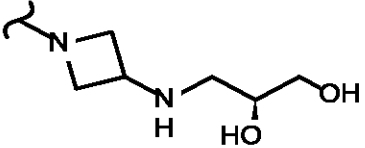
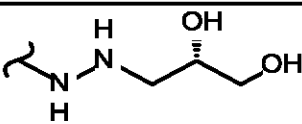
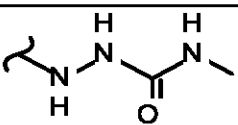
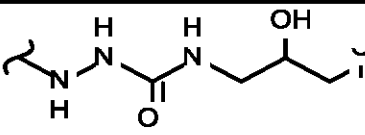
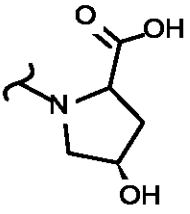
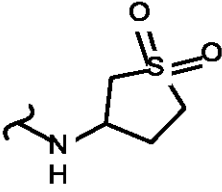
[Table 2 5]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-204 |    | 1022.4 [M+H] <sup>+</sup>                                 | A      |
| I-205 |    | 1024.4 [M+H] <sup>+</sup> ,<br>1046.4 [M+Na] <sup>+</sup> | A      |
| I-206 |    | 1052.6 [M+H] <sup>+</sup>                                 | A      |
| I-207 |    | 1022.6 [M+H] <sup>+</sup>                                 | A      |
| I-208 |    | 1039.5 [M+H] <sup>+</sup> ,<br>1061.6 [M+Na] <sup>+</sup> | A      |
| I-209 |  | 1023.5 [M+H] <sup>+</sup>                                 | A      |
| I-210 |  | 1038.6 [M+H] <sup>+</sup>                                 | A      |
| I-211 |  | 1023.5 [M+H] <sup>+</sup> ,<br>1045.6 [M+Na] <sup>+</sup> | A      |
| I-212 |  | 997.8 [M+H] <sup>+</sup>                                  | B      |
| I-213 |  | 1026.9 [M+H] <sup>+</sup>                                 | B      |

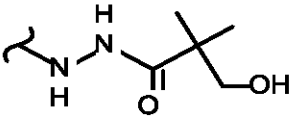
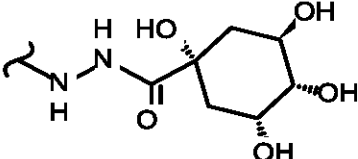
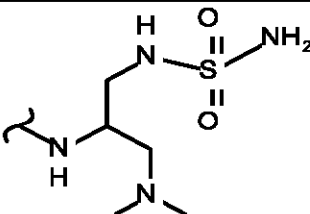
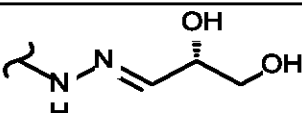
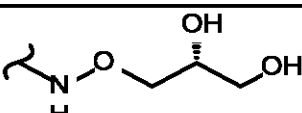
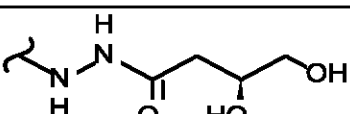
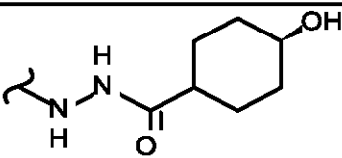
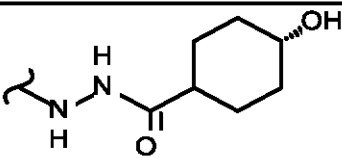
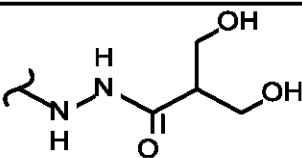
[Table 2 6]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-214 |    | 1083.4 [M+H] <sup>+</sup> ,<br>1105.4 [M+Na] <sup>+</sup> | A      |
| I-215 |    | 1026.3 [M+H] <sup>+</sup> ,<br>1048.4 [M+Na] <sup>+</sup> | A      |
| I-216 |    | 1088.4 [M+H] <sup>+</sup> ,<br>1110.4 [M+Na] <sup>+</sup> | A      |
| I-217 |    | 1139.5 [M+H] <sup>+</sup> ,<br>1161.5 [M+Na] <sup>+</sup> | A      |
| I-218 |   | 1012.4 [M+H] <sup>+</sup>                                 | A      |
| I-219 |  | 954.4 [M+H] <sup>+</sup> ,<br>976.5 [M+Na] <sup>+</sup>   | A      |
| I-220 |  | 1053.5 [M+H] <sup>+</sup>                                 | A      |
| I-221 |  | 1073.5 [M+H] <sup>+</sup>                                 | A      |
| I-222 |  | 1067.5 [M+H] <sup>+</sup> ,<br>1089.5 [M+Na] <sup>+</sup> | A      |

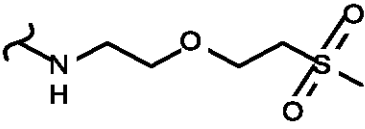
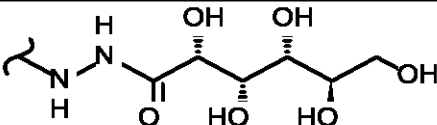
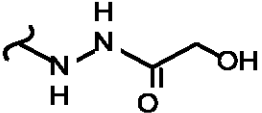
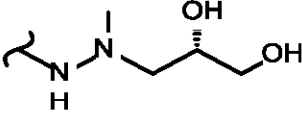
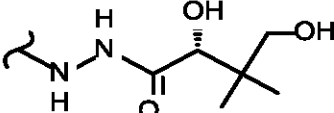
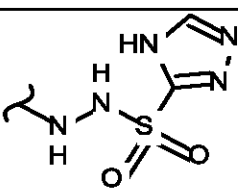
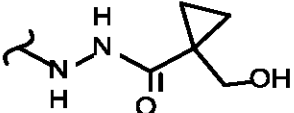
[Table 2 7]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-223 |    | 1041.4 [M+H] <sup>+</sup> ,<br>1063.5 [M+Na] <sup>+</sup> | A      |
| I-224 |    | 1074.4 [M+H] <sup>+</sup>                                 | A      |
| I-225 |    | 1070.4 [M+H] <sup>+</sup> ,<br>1192.4 [M+Na] <sup>+</sup> | A      |
| I-226 |    | 1067.5 [M+H] <sup>+</sup> ,<br>1089.5 [M+Na] <sup>+</sup> | A      |
| I-227 |    | 1027.4 [M+H] <sup>+</sup>                                 | A      |
| I-228 |   | 1010.4 [M+H] <sup>+</sup>                                 | A      |
| I-229 |  | 1088.4 [M+H] <sup>+</sup> ,<br>1110.4 [M+Na] <sup>+</sup> | A      |
| I-230 |  | 1052.4 [M+H] <sup>+</sup>                                 | A      |
| I-231 |  | 1056.4 [M+H] <sup>+</sup> ,<br>1078.5 [M+Na] <sup>+</sup> | A      |

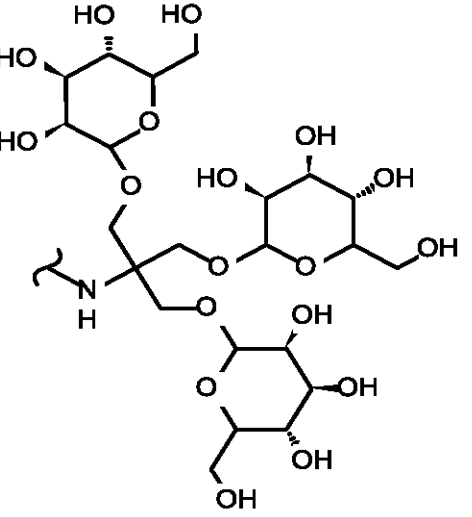
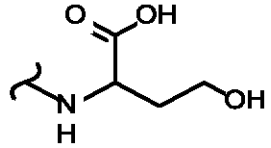
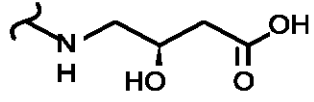
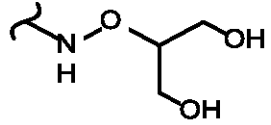
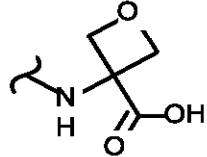
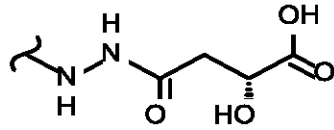
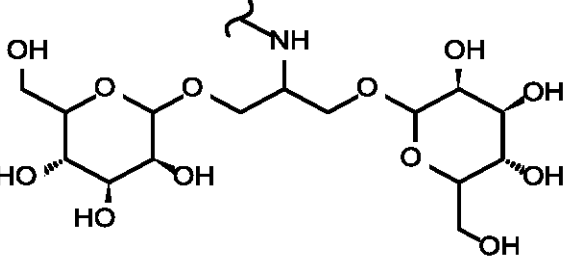
[Table 2 8]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-232 |    | 1053.6 [M+H] <sup>+</sup> ,<br>1075.6 [M+Na] <sup>+</sup> | A      |
| I-233 |    | 1027.6 [M+H] <sup>+</sup> ,<br>1049.7 [M+Na] <sup>+</sup> | A      |
| I-234 |    | 1117.5 [M+H] <sup>+</sup>                                 | B      |
| I-235 |    | 1025.5 [M+H] <sup>+</sup> ,<br>1047 [M+Na] <sup>+</sup>   | A      |
| I-236 |   | 1028.6 [M+H] <sup>+</sup>                                 | A      |
| I-237 |  | 1055.5 [M+H] <sup>+</sup> ,<br>1077.6 [M+Na] <sup>+</sup> | A      |
| I-238 |  | 1027.6 [M+H] <sup>+</sup> ,<br>1049.7 [M+Na] <sup>+</sup> | A      |
| I-239 |  | 1079.6 [M+H] <sup>+</sup>                                 | A      |
| I-240 |  | 1055.6 [M+H] <sup>+</sup>                                 | A      |

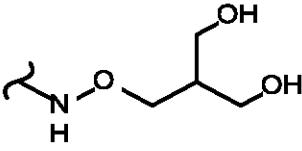
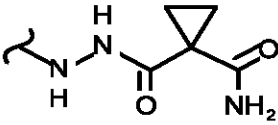
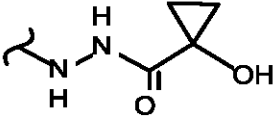
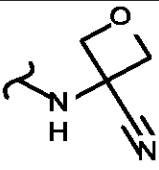
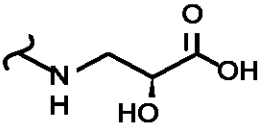
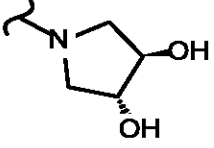
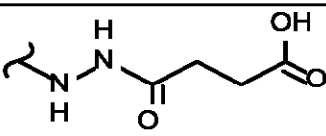
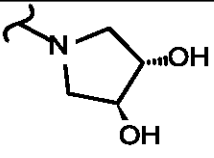
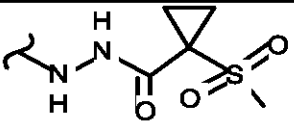
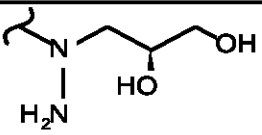
[Table 2 9]

| No.   | X <sup>1</sup>                                                                      | LC-MS                     | Method |
|-------|-------------------------------------------------------------------------------------|---------------------------|--------|
| I-241 |    | 1088.5 [M+H] <sup>+</sup> | A      |
| I-242 |    | 1131.4 [M+H] <sup>+</sup> | A      |
| I-243 |    | 1011.3 [M+H] <sup>+</sup> | A      |
| I-244 |    | 1041.4 [M+H] <sup>+</sup> | A      |
| I-245 |    | 1083.4 [M+H] <sup>+</sup> | A      |
| I-246 |   | 1084.4 [M+H] <sup>+</sup> | A      |
| I-247 |  | 1051.4 [M+H] <sup>+</sup> | A      |

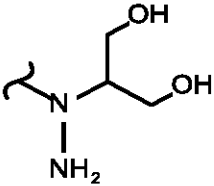
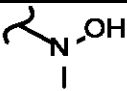
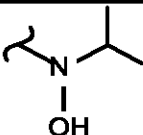
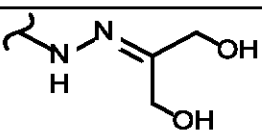
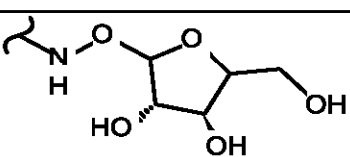
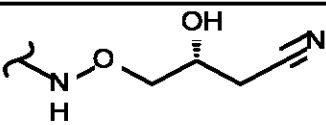
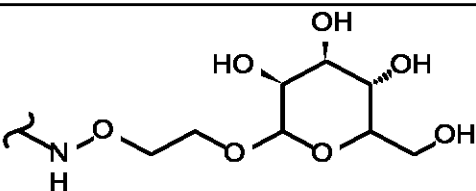
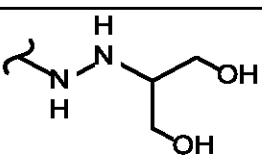
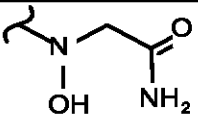
[Table 3 0]

| No.   | $X^1$                                                                               | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-248 |    | 1529.3 [M+H] <sup>+</sup>                                 | A      |
| I-249 |    | 1040.4 [M+H] <sup>+</sup> ,<br>1062.5 [M+Na] <sup>+</sup> | A      |
| I-250 |   | 1040.4 [M+H] <sup>+</sup> ,<br>1062.5 [M+Na] <sup>+</sup> | A      |
| I-251 |  | 1028.4 [M+H] <sup>+</sup> ,<br>1050.4 [M+Na] <sup>+</sup> | A      |
| I-252 |  | 1038.4 [M+H] <sup>+</sup>                                 | A      |
| I-253 |  | 1069.4 [M+H] <sup>+</sup>                                 | A      |
| I-254 |  | 1336.6 [M+H] <sup>+</sup>                                 | A      |

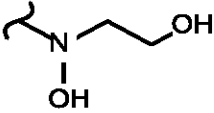
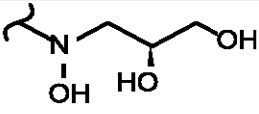
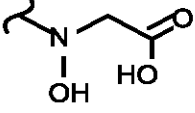
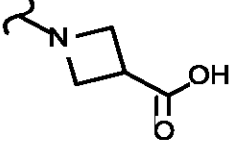
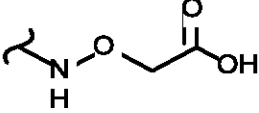
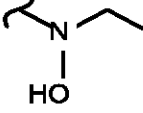
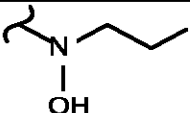
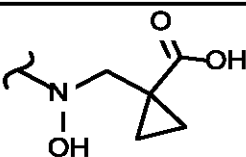
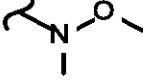
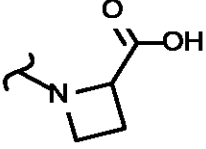
[Table 3 1]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-255 |    | 1042.4 [M+H] <sup>+</sup> ,<br>1064.5 [M+Na] <sup>+</sup> | A      |
| I-256 |    | 1064.5 [M+H] <sup>+</sup> ,<br>1086.5 [M+Na] <sup>+</sup> | A      |
| I-257 |    | 1037.4 [M+H] <sup>+</sup> ,<br>1059.5 [M+Na] <sup>+</sup> | A      |
| I-258 |    | 1019.6 [M+H] <sup>+</sup>                                 | A      |
| I-259 |    | 1026.5 [M+H] <sup>+</sup>                                 | A      |
| I-260 |   | 1024.5 [M+H] <sup>+</sup> ,<br>1046.6 [M+Na] <sup>+</sup> | A      |
| I-261 |  | 1053.5 [M+H] <sup>+</sup> ,<br>1075.6 [M+Na] <sup>+</sup> | A      |
| I-262 |  | 1024.3 [M+H] <sup>+</sup>                                 | A      |
| I-263 |  | 1099.4 [M+H] <sup>+</sup> ,<br>1121.5 [M+Na] <sup>+</sup> | A      |
| I-264 |  | 1027.5 [M+H] <sup>+</sup> ,<br>1049.6 [M+Na] <sup>+</sup> | A      |

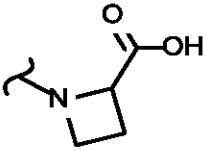
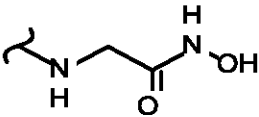
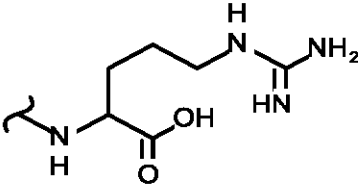
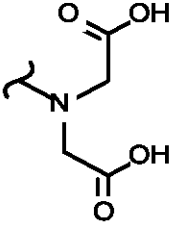
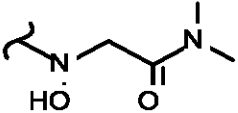
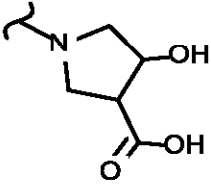
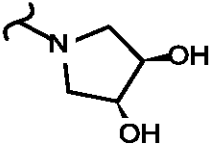
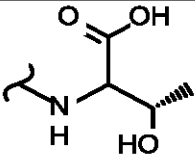
[Table 3 2]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-265 |    | 1027.4 [M+H] <sup>+</sup>                                 | B      |
| I-266 |    | 968.4 [M+H] <sup>+</sup> ,<br>990.4 [M+Na] <sup>+</sup>   | B      |
| I-267 |    | 996.5 [M+H] <sup>+</sup>                                  | B      |
| I-268 |    | 1025.4 [M+H] <sup>+</sup>                                 | B      |
| I-269 |    | 1086.4 [M+H] <sup>+</sup> ,<br>1108.5 [M+Na] <sup>+</sup> | A      |
| I-270 |  | 1037.4 [M+H] <sup>+</sup> ,<br>1059.5 [M+Na] <sup>+</sup> | A      |
| I-271 |  | 1160.5 [M+H] <sup>+</sup> ,<br>1182.6 [M+Na] <sup>+</sup> | A      |
| I-272 |  | 1027.4 [M+H] <sup>+</sup>                                 | A      |
| I-273 |  | 1011.4 [M+H] <sup>+</sup>                                 | A      |

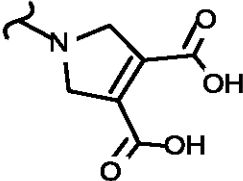
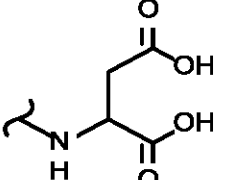
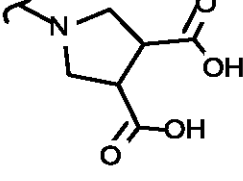
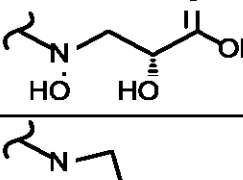
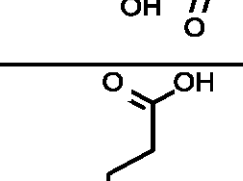
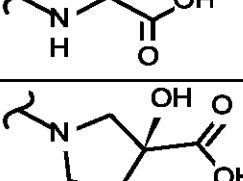
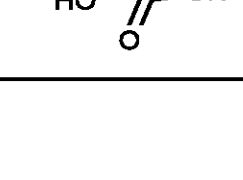
[Table 3 3]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-274 |    | 998.4 [M+H] <sup>+</sup> ,<br>1020.4 [M+Na] <sup>+</sup>  | A      |
| I-275 |    | 1028.4 [M+H] <sup>+</sup>                                 | B      |
| I-276 |    | 1012.5 [M+H] <sup>+</sup>                                 | B      |
| I-277 |    | 1095.5 [M+H] <sup>+</sup>                                 | A      |
| I-278 |    | 1012.3 [M+H] <sup>+</sup>                                 | A      |
| I-279 |   | 982.4 [M+H] <sup>+</sup>                                  | B      |
| I-280 |  | 996.4 [M+H] <sup>+</sup>                                  | B      |
| I-281 |  | 1052.4 [M+H] <sup>+</sup>                                 | B      |
| I-282 |  | 982.5 [M+H] <sup>+</sup>                                  | B      |
| I-283 |  | 1022.4 [M+H] <sup>+</sup> ,<br>1044.5 [M+Na] <sup>+</sup> | A      |

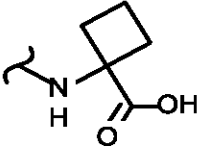
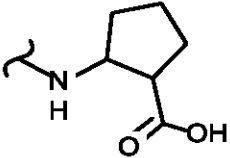
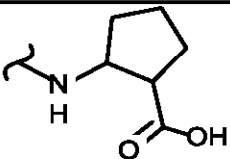
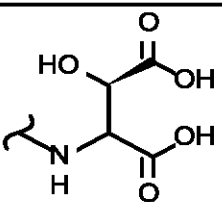
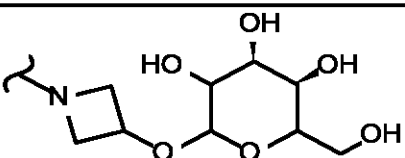
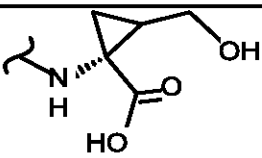
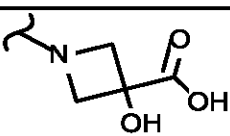
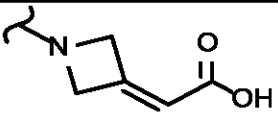
[Table 3 4]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-284 |    | 1022.4 [M+H] <sup>+</sup> ,<br>1044.5 [M+Na] <sup>+</sup> | A      |
| I-285 |    | 1011.4 [M+H] <sup>+</sup>                                 | A      |
| I-286 |    | 1095.5 [M+H] <sup>+</sup>                                 | A      |
| I-287 |    | 1054.4 [M+H] <sup>+</sup>                                 | B      |
| I-288 |   | 1039.5 [M+H] <sup>+</sup>                                 | B      |
| I-289 |  | 1052.4 [M+H] <sup>+</sup>                                 | B      |
| I-290 |  | 1024.4 [M+H] <sup>+</sup>                                 | B      |
| I-291 |  | 1040.4 [M+H] <sup>+</sup>                                 | A      |

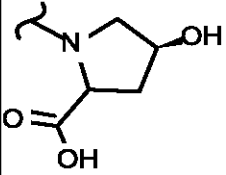
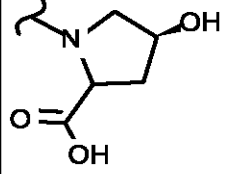
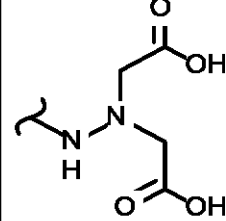
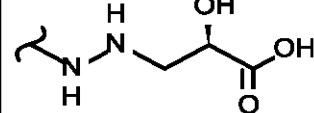
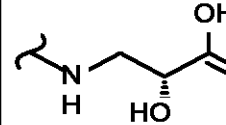
[Table 3 5]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-292 |    | 1078.5 [M+H] <sup>+</sup>                                 | B      |
| I-293 |    | 1054.4 [M+H] <sup>+</sup>                                 | B      |
| I-294 |    | 1080.4 [M+H] <sup>+</sup>                                 | B      |
| I-295 |   | 1042.4 [M+H] <sup>+</sup> ,<br>1064.5 [M+Na] <sup>+</sup> | A      |
| I-296 |  | 1052.5 [M+H] <sup>+</sup> ,<br>1074.5 [M+Na] <sup>+</sup> | A      |
| I-297 |  | 1068.4 [M+H] <sup>+</sup> ,<br>1090.5 [M+Na] <sup>+</sup> | A      |
| I-298 |  | 1112.4 [M+H] <sup>+</sup>                                 | B      |

[Table 3 6]

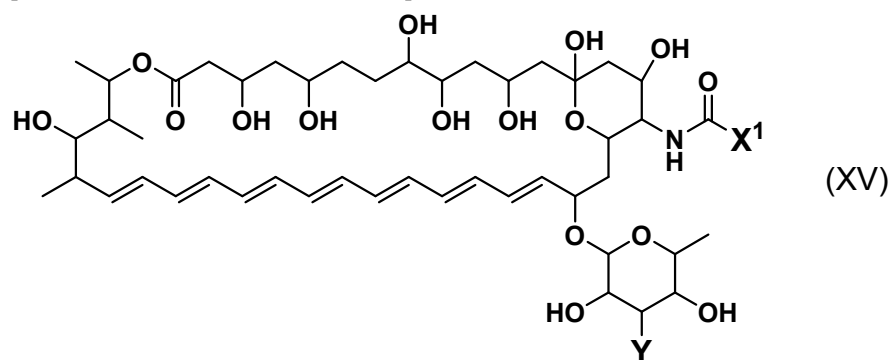
| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-299 |    | 1036.4 [M+H] <sup>+</sup>                                 | B      |
| I-300 |    | 1050.4 [M+H] <sup>+</sup>                                 | B      |
| I-301 |    | 1050.4 [M+H] <sup>+</sup>                                 | B      |
| I-302 |   | 1070.4 [M+H] <sup>+</sup>                                 | B      |
| I-303 |  | 1156.5 [M+H] <sup>+</sup> ,<br>1178.5 [M+Na] <sup>+</sup> | A      |
| I-304 |  | 1052.5 [M+H] <sup>+</sup> ,<br>1074.5 [M+Na] <sup>+</sup> | A      |
| I-305 |  | 1038.5 [M+H] <sup>+</sup>                                 | A      |
| I-306 |  | 1034.4 [M+H] <sup>+</sup>                                 | A      |

[Table 3 7]

| No.   | X <sup>1</sup>                                                                      | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-307 |    | 1052.5 [M+H] <sup>+</sup> ,<br>1074.5 [M+Na] <sup>+</sup> | A      |
| I-308 |    | 1052.5 [M+H] <sup>+</sup> ,<br>1074.6 [M+Na] <sup>+</sup> | A      |
| I-309 |    | 1069.4 [M+H] <sup>+</sup>                                 | A      |
| I-310 |   | 1041.6 [M+H] <sup>+</sup>                                 | A      |
| I-311 |  | 1026.6 [M+H] <sup>+</sup>                                 | A      |

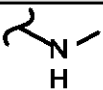
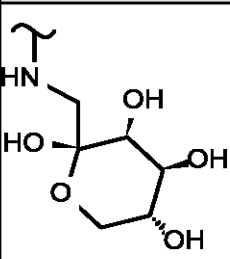
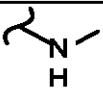
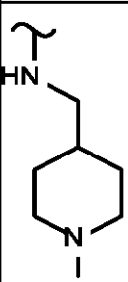
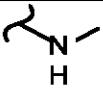
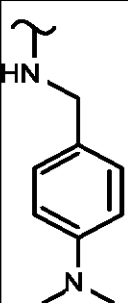
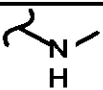
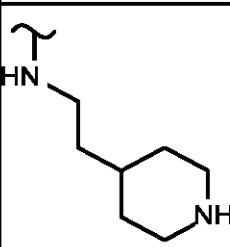
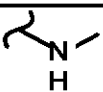
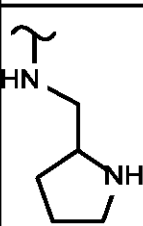
[0 2 5 5]

[Chemical Formula 1 3 5]



The structure and physical property of compound (XV) are shown below.

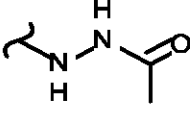
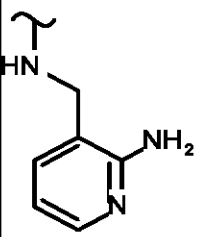
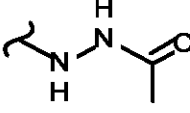
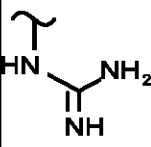
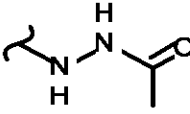
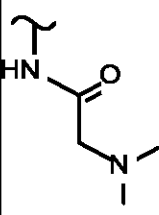
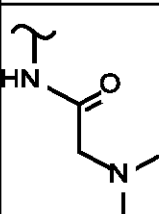
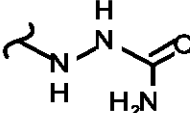
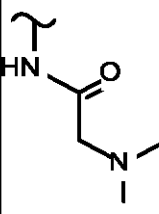
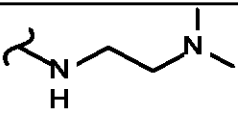
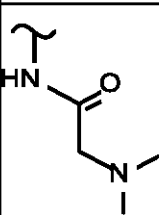
[Table 3 8]

| No.   | X <sup>1</sup>                                                                      | Y                                                                                   | LC-MS                      | Method |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------|--------|
| I-312 |    |    | 1114.5 [M+H] <sup>+</sup>  | B      |
| I-313 |    |    | 1064.2 [M+H] <sup>+</sup>  | B      |
| I-314 |    |   | 1085.91 [M+H] <sup>+</sup> | B      |
| I-315 |  |  | 1063.3 [M+H] <sup>+</sup>  | B      |
| I-316 |  |  | 1035.3 [M+H] <sup>+</sup>  | B      |

[Table 3 9]

| No.   | X <sup>1</sup> | Y | LC-MS                     | Method |
|-------|----------------|---|---------------------------|--------|
| I-317 |                |   | 1046.2 [M+H] <sup>+</sup> | B      |
| I-318 |                |   | 1049.3 [M+H] <sup>+</sup> | B      |
| I-319 |                |   | 1049.6 [M+H] <sup>+</sup> | B      |
| I-320 |                |   | 1049.5 [M+H] <sup>+</sup> | B      |
| I-321 |                |   | 1159.5 [M+H] <sup>+</sup> | B      |

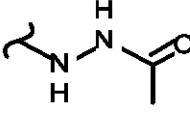
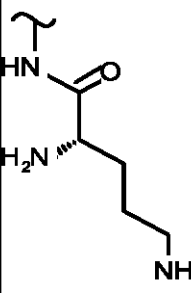
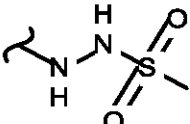
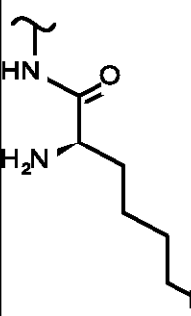
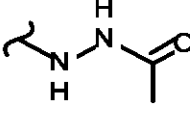
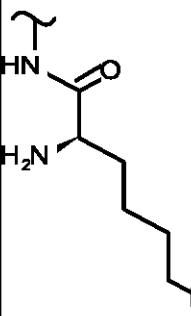
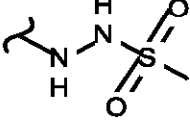
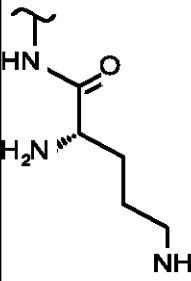
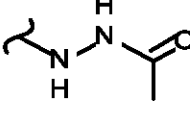
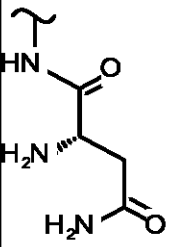
[Table 4 0]

| No.   | X <sup>1</sup>                                                                      | Y                                                                                   | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-322 |    |    | 1101.5 [M+H] <sup>+</sup>                                 | B      |
| I-323 |    |    | 1037.5 [M+H] <sup>+</sup>                                 | B      |
| I-324 |    |    | 1080.5 [M+H] <sup>+</sup>                                 | B      |
| I-325 |    |   | 1023.5 [M+H] <sup>+</sup>                                 | B      |
| I-326 |  |  | 1081.5 [M+H] <sup>+</sup>                                 | B      |
| I-327 |  |  | 1094.5 [M+H] <sup>+</sup> ,<br>1116.5 [M+Na] <sup>+</sup> | A      |

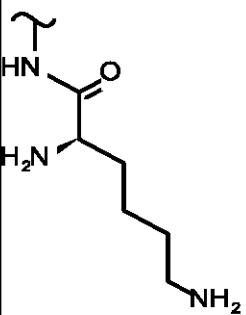
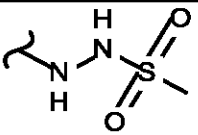
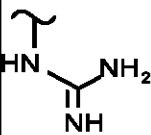
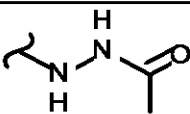
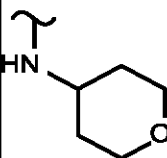
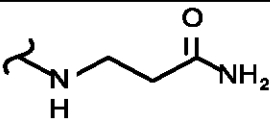
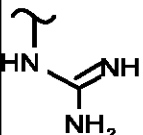
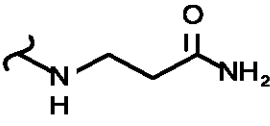
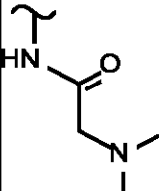
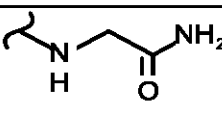
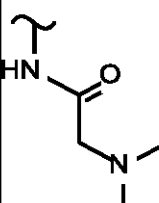
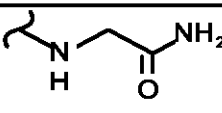
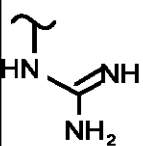
[Table 4 1]

| No.   | X <sup>1</sup> | Y | LC-MS                     | Method |
|-------|----------------|---|---------------------------|--------|
| I-328 |                |   | 1115.7 [M+H] <sup>+</sup> | B      |
| I-329 |                |   | 980.5 [M+H] <sup>+</sup>  | A      |
| I-330 |                |   | 1038.5 [M+H] <sup>+</sup> | A      |
| I-331 |                |   | 1010.6 [M+H] <sup>+</sup> | A      |
| I-332 |                |   | 1051.5 [M+H] <sup>+</sup> | A      |
| I-333 |                |   | 1054.5 [M+H] <sup>+</sup> | A      |
| I-334 |                |   | 1036.5 [M+H] <sup>+</sup> | A      |

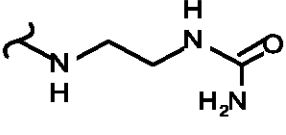
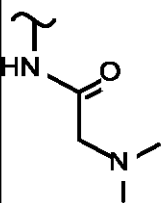
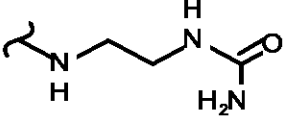
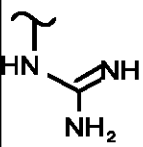
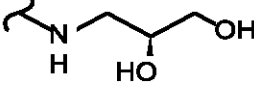
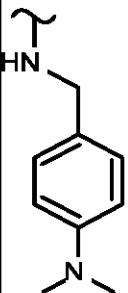
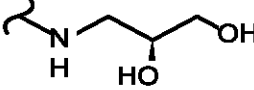
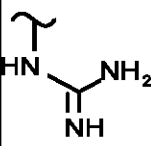
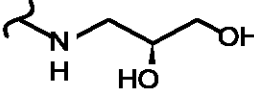
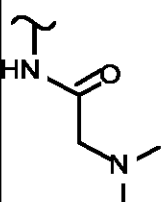
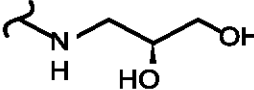
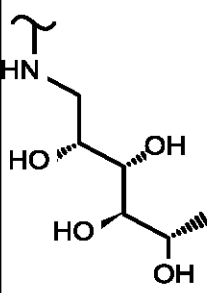
[Table 4 2]

| No.   | X <sup>1</sup>                                                                      | Y                                                                                   | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-335 |    |    | 1109.6 [M+H] <sup>+</sup> ,<br>1131.6 [M+Na] <sup>+</sup> | A      |
| I-336 |    |    | 1159.5 [M+H] <sup>+</sup>                                 | B      |
| I-337 |    |   | 1123.6 [M+H] <sup>+</sup> ,<br>1145.6 [M+Na] <sup>+</sup> | A      |
| I-338 |  |  | 1145.5 [M+H] <sup>+</sup>                                 | A      |
| I-339 |  |  | 1109.5 [M+H] <sup>+</sup>                                 | A      |

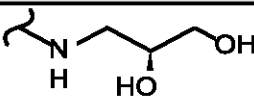
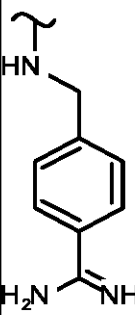
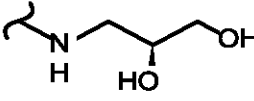
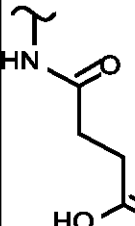
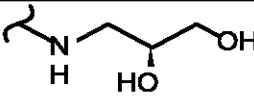
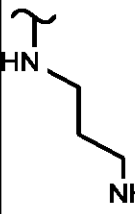
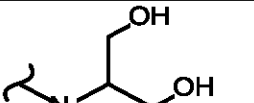
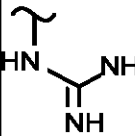
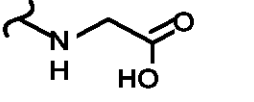
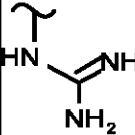
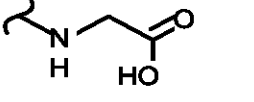
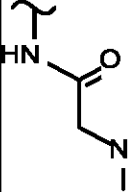
[Table 4 3]

| No.   | X <sup>1</sup>                                                                      | Y                                                                                   | LC-MS                     | Method |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------|--------|
| I-340 |    |    | 1066.5 [M+H] <sup>+</sup> | A      |
| I-341 |    |    | 1073.4 [M+H] <sup>+</sup> | B      |
| I-342 |    |    | 1079.5 [M+H] <sup>+</sup> | A      |
| I-343 |   |   | 1051.6 [M+H] <sup>+</sup> | A      |
| I-344 |  |  | 1094.6 [M+H] <sup>+</sup> | A      |
| I-345 |  |  | 1080.6 [M+H] <sup>+</sup> | A      |
| I-346 |  |  | 1037.5 [M+H] <sup>+</sup> | A      |

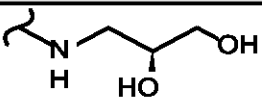
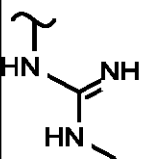
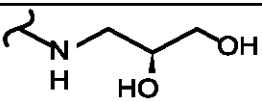
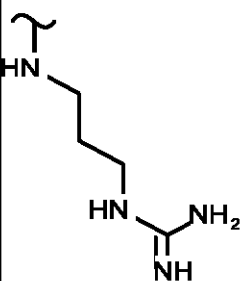
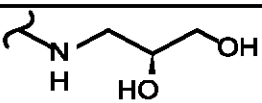
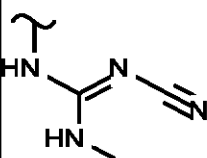
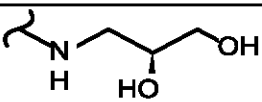
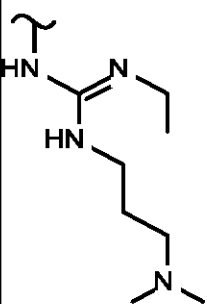
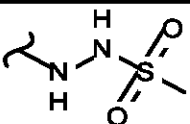
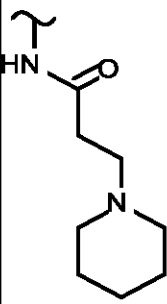
[Table 4 4]

| No.   | X <sup>1</sup>                                                                      | Y                                                                                   | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-347 |    |    | 1109.6 [M+H] <sup>+</sup> ,<br>1131.6 [M+Na] <sup>+</sup> | A      |
| I-348 |    |    | 1066.7 [M+H] <sup>+</sup>                                 | A      |
| I-349 |    |    | 1145.5 [M+H] <sup>+</sup>                                 | A      |
| I-350 |   |   | 1054.5 [M+H] <sup>+</sup>                                 | A      |
| I-351 |  |  | 1097.5 [M+H] <sup>+</sup>                                 | A      |
| I-352 |  |  | 1160.5 [M+H] <sup>+</sup>                                 | A      |

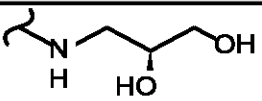
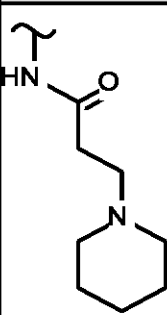
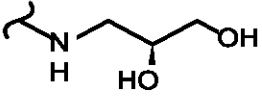
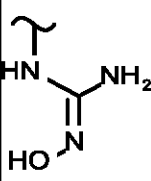
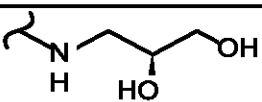
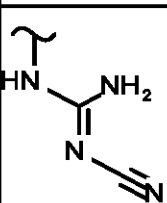
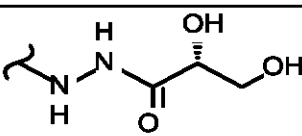
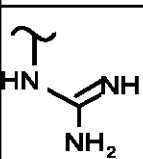
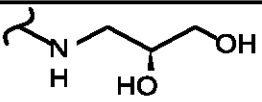
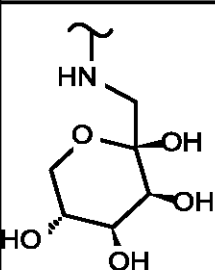
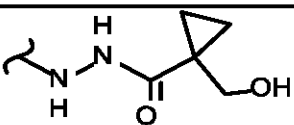
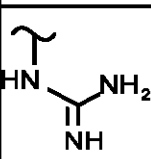
[Table 4 5]

| No.   | X <sup>1</sup>                                                                      | Y                                                                                   | LC-MS                     | Method |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------|--------|
| I-353 |    |    | 1145.5 [M+H] <sup>+</sup> | A      |
| I-354 |    |    | 1112.5 [M+H] <sup>+</sup> | A      |
| I-355 |    |   | 1069.5 [M+H] <sup>+</sup> | B      |
| I-356 |  |  | 1054.5 [M+H] <sup>+</sup> | A      |
| I-357 |  |  | 1038.6 [M+H] <sup>+</sup> | B      |
| I-358 |  |  | 1081.7 [M+H] <sup>+</sup> | B      |

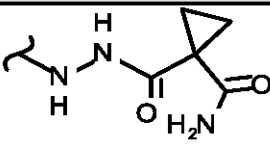
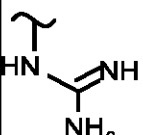
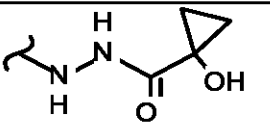
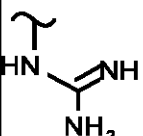
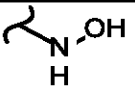
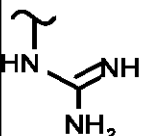
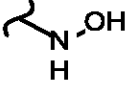
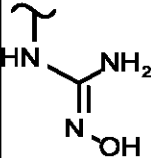
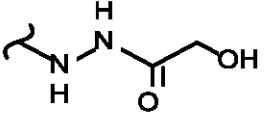
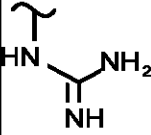
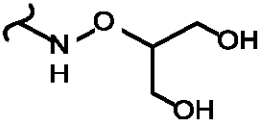
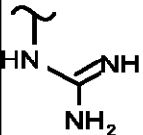
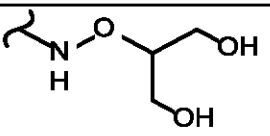
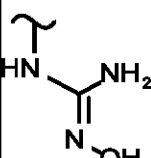
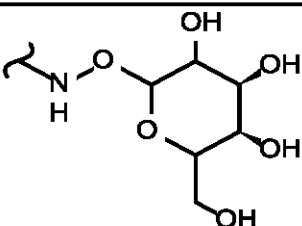
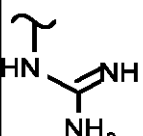
[Table 4 6]

| No.   | X <sup>1</sup>                                                                      | Y                                                                                   | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-359 |    |    | 1068.7 [M+H] <sup>+</sup>                                 | B      |
| I-360 |    |    | 1111.8 [M+H] <sup>+</sup>                                 | B      |
| I-361 |    |    | 1093.5 [M+H] <sup>+</sup> ,<br>1115.5 [M+Na] <sup>+</sup> | A      |
| I-362 |   |   | 1167.6 [M+H] <sup>+</sup>                                 | A      |
| I-363 |  |  | 1170.6 [M+H] <sup>+</sup>                                 | A      |

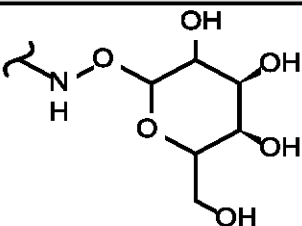
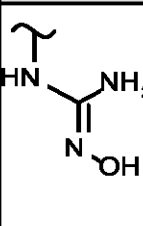
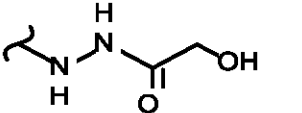
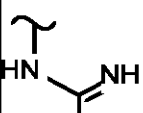
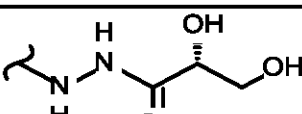
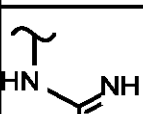
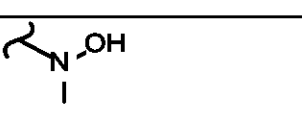
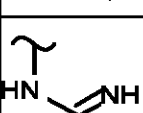
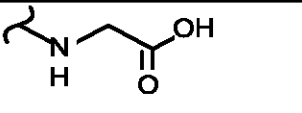
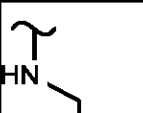
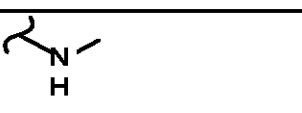
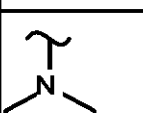
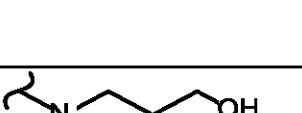
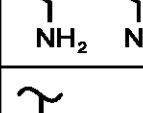
[Table 4 7]

| No.   | X <sup>1</sup>                                                                      | Y                                                                                   | LC-MS                                      | Method |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------|--------|
| I-364 |    |    | 1151.6 [M+H] <sup>+</sup>                  | A      |
| I-365 |    |    | 1071 [M+H] <sup>+</sup>                    | B      |
| I-366 |    |    | 1061.8 [M-H <sub>2</sub> O+H] <sup>+</sup> | B      |
| I-367 |   |   | 1083.3 [M+H] <sup>+</sup>                  | A      |
| I-368 |  |  | 1174 [M+H] <sup>+</sup>                    | B      |
| I-369 |  |  | 1093.4 [M+H] <sup>+</sup>                  | A      |

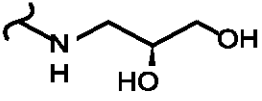
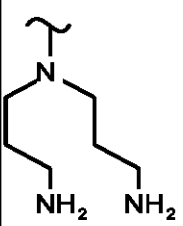
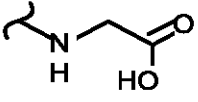
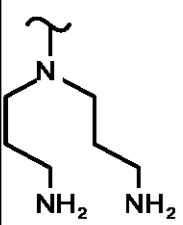
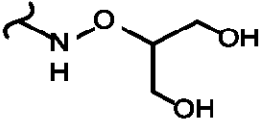
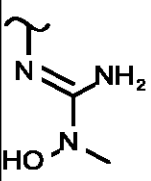
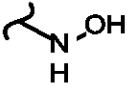
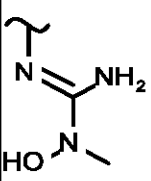
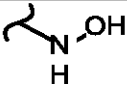
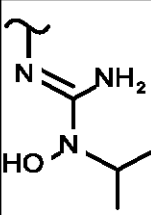
[Table 4 8]

| No.   | X <sup>1</sup>                                                                      | Y                                                                                   | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-370 |    |    | 1106.4 [M+H] <sup>+</sup> ,<br>1128.6 [M+Na] <sup>+</sup> | A      |
| I-371 |    |    | 1079.5 [M+H] <sup>+</sup>                                 | A      |
| I-372 |    |    | 996.4 [M+H] <sup>+</sup> ,<br>1018.5 [M+Na] <sup>+</sup>  | A      |
| I-373 |    |    | 1012.4 [M+H] <sup>+</sup>                                 | A      |
| I-374 |   |   | 1053.5 [M+H] <sup>+</sup> ,<br>1075.6 [M+Na] <sup>+</sup> | A      |
| I-375 |  |  | 1070.5 [M+H] <sup>+</sup> ,<br>1092.5 [M+Na] <sup>+</sup> | A      |
| I-376 |  |  | 1086.5 [M+H] <sup>+</sup> ,<br>1108.6 [M+Na] <sup>+</sup> | A      |
| I-377 |  |  | 1158.5 [M+H] <sup>+</sup> ,<br>1180.6 [M+Na] <sup>+</sup> | A      |

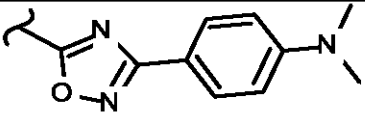
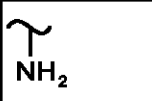
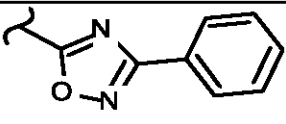
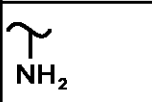
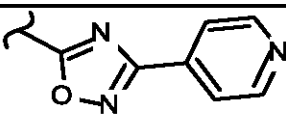
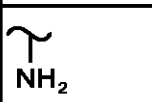
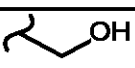
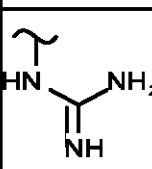
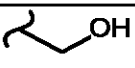
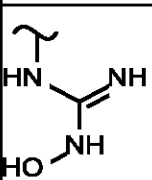
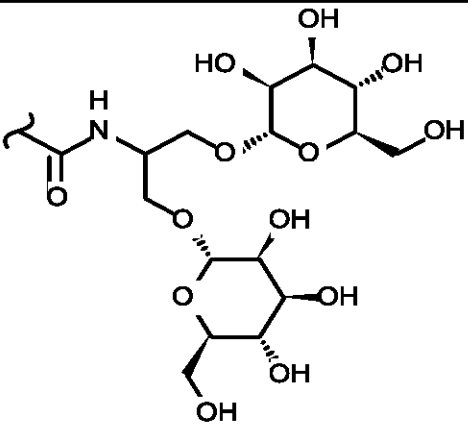
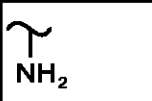
[Table 4 9]

| No.   | X <sup>1</sup>                                                                      | Y                                                                                   | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-378 |    |    | 1174.5 [M+H] <sup>+</sup>                                 | A      |
| I-379 |    |    | 1069.4 [M+H] <sup>+</sup>                                 | A      |
| I-380 |    |    | 1099.5 [M+H] <sup>+</sup> ,<br>1121.6 [M+Na] <sup>+</sup> | A      |
| I-381 |    |    | 1010.4 [M+H] <sup>+</sup> ,<br>1032.5 [M+Na] <sup>+</sup> | A      |
| I-382 |  |  | 1054.4 [M+H] <sup>+</sup>                                 | A      |
| I-383 |  |  | 1066.8 [M+H] <sup>+</sup>                                 | B      |
| I-384 |  |  | 1040.5 [M+H] <sup>+</sup>                                 | A      |

[Table 50]

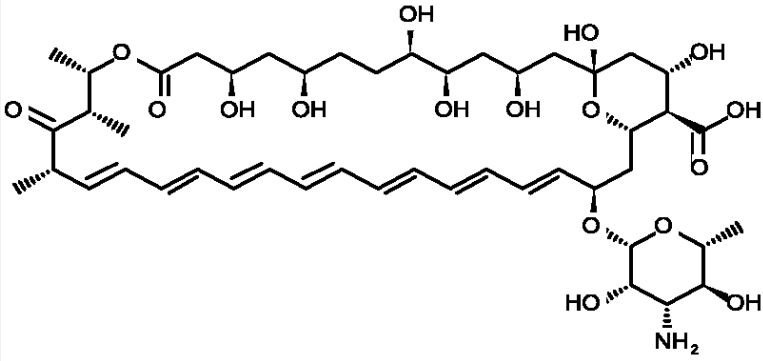
| No.   | X <sup>1</sup>                                                                      | Y                                                                                   | LC-MS                                                     | Method |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|
| I-385 |    |    | 1126.6 [M+H] <sup>+</sup>                                 | A      |
| I-386 |    |    | 1110.6 [M+H] <sup>+</sup>                                 | B      |
| I-387 |    |    | 1100.5 [M+H] <sup>+</sup> ,<br>1122.5 [M+Na] <sup>+</sup> | A      |
| I-388 |    |   | 1026.5 [M+H] <sup>+</sup> ,<br>1048.5 [M+Na] <sup>+</sup> | A      |
| I-389 |  |  | 1054.5 [M+H] <sup>+</sup>                                 | A      |

[Table 5 1]

| No.   | X                                                                                   | Y                                                                                    | LC-MS                     | Method |
|-------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------|--------|
| I-390 |    |    | 1067.5 [M+H] <sup>+</sup> | B      |
| I-391 |    |    | 1024.5 [M+H] <sup>+</sup> | B      |
| I-392 |    |    | 1025.5 [M+H] <sup>+</sup> | B      |
| I-394 |    |    | 952.8 [M+H] <sup>+</sup>  | A      |
| I-395 |    |   | 968.5 [M+H] <sup>+</sup>  | A      |
| I-396 |  |  | 1321.7 [M+H] <sup>+</sup> | A      |

In addition, the following compounds were prepared.

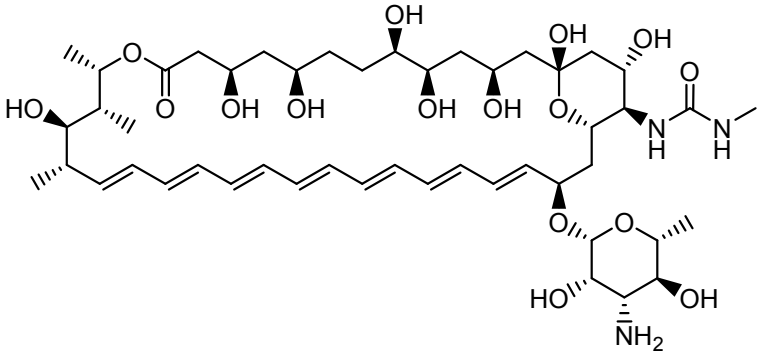
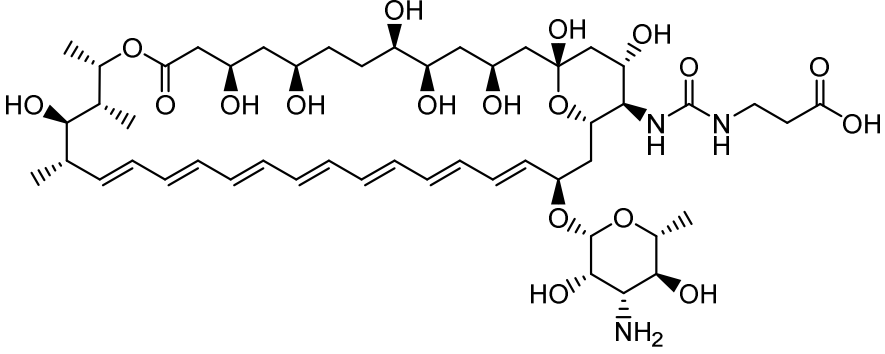
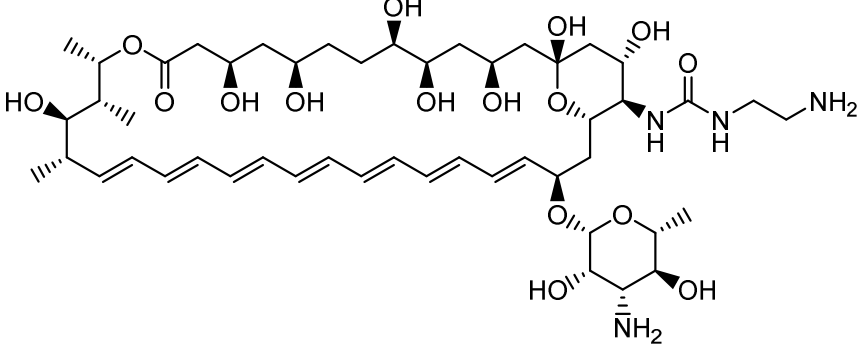
[Table 5 2]

| No.   | Structure                                                                          | LC-MS                    | Method |
|-------|------------------------------------------------------------------------------------|--------------------------|--------|
| I-393 |  | 922.9 [M+H] <sup>+</sup> | B      |

[0 2 5 6]

The structures of AmBMU, AmBCU and AmBAU described in non-patent documents 4, 5 and patent document 11 are shown below.

[Table 5 3]

|       |                                                                                      |
|-------|--------------------------------------------------------------------------------------|
| AmBMU |   |
| AmBCU |  |
| AmBAU |  |

[ 0 2 5 7 ]

Biological test examples for compounds of the present invention were described below.

[ 0 2 5 8 ]

(Test example 1: Antifungal activity test)

The Minimum Inhibitory Concentration (MIC) values of the present compound against yeast and filamentous fungi were determined by broth microdilution assay according to the Clinical Laboratory Standards Institute (CLSI) guidelines outlined in documents M27-A3 and M38-A2. The medium used in the assay consisted of RPMI1640 (with glutamine, without bicarbonate) with 2% glucose and 0.165 mol/L morpholinepropanesulfonic acid (MOPS) with pH adjusted to 7.0 using 1 mol/L sodium hydroxide. The present compound was dissolved in dimethyl sulfoxide (DMSO). A series of two-fold dilutions were prepared in DMSO, and then 2  $\mu$ L of the diluted compound was added to each well in 96-well sterile plates. Each inoculum was prepared by diluting a suspension of *Candida* spp. or a conidia suspension of *Aspergillus* spp. suspended in sterile saline solution, and then 200  $\mu$ L was added to each well to a predetermined concentration using RPMI/MOPS (final concentration for each solution: approximately  $1 \times 10^3$  cells/mL and approximately  $1 \times 10^4$  CFU/mL). Plates of *Candida* spp. and *Aspergillus* spp. were incubated at 35°C for 24-48 hours. The MIC was defined as the lowest concentration giving 100% inhibition compared to the growth control.

The results are shown below.

[Table 5 4]

| No.   | <i>C. albicans</i><br>ATCC90028<br>MIC (μg/mL) | <i>A. flavus</i><br>ATCC204304<br>MIC (μg/mL) | <i>A. fumigatus</i><br>ATCC204305<br>MIC (μg/mL) |
|-------|------------------------------------------------|-----------------------------------------------|--------------------------------------------------|
| I-19  | 0.25                                           | 1                                             | 1                                                |
| I-36  | 0.25                                           | 1                                             | 1                                                |
| I-40  | 0.125                                          | 0.5                                           | 0.25                                             |
| I-43  | 0.25                                           | 1                                             | 1                                                |
| I-45  | 0.25                                           | 0.5                                           | 1                                                |
| I-59  | 0.25                                           | 1                                             | 1                                                |
| I-60  | 0.125                                          | 0.5                                           | 0.5                                              |
| I-67  | 0.25                                           | 1                                             | 1                                                |
| I-90  | 0.25                                           | 0.5                                           | 0.5                                              |
| I-119 | 0.25                                           | 0.5                                           | 1                                                |
| I-155 | 0.5                                            | 0.5                                           | 1                                                |
| I-157 | 0.5                                            | 0.5                                           | 1                                                |
| I-158 | 0.25                                           | 1                                             | 1                                                |
| I-159 | 0.25                                           | 0.5                                           | 1                                                |
| I-162 | 0.25                                           | 1                                             | 1                                                |
| I-163 | 0.25                                           | 1                                             | 1                                                |
| I-165 | 0.25                                           | 1                                             | 1                                                |
| I-166 | 0.25                                           | 0.5                                           | 1                                                |
| I-169 | 0.25                                           | 1                                             | 1                                                |
| I-189 | 0.25                                           | 0.5                                           | 0.5                                              |
| I-190 | 0.25                                           | 1                                             | 0.5                                              |
| I-193 | 0.25                                           | 0.5                                           | 1                                                |

[Table 5 5]

| No.   | <i>C. albicans</i><br>ATCC90028<br>MIC (µg/mL) | <i>A. flavus</i><br>ATCC204304<br>MIC (µg/mL) | <i>A. fumigatus</i><br>ATCC204305<br>MIC (µg/mL) |
|-------|------------------------------------------------|-----------------------------------------------|--------------------------------------------------|
| I-202 | 0.5                                            | 0.5                                           | 1                                                |
| I-218 | 0.25                                           | 0.5                                           | 1                                                |
| I-227 | 0.5                                            | 0.5                                           | 1                                                |
| I-230 | 0.5                                            | 0.5                                           | 1                                                |
| I-237 | 0.5                                            | 0.5                                           | 1                                                |
| I-240 | 0.5                                            | 0.5                                           | 1                                                |
| I-250 | 0.5                                            | 0.5                                           | 1                                                |
| I-259 | 0.5                                            | 0.5                                           | 1                                                |
| I-260 | 0.5                                            | 0.5                                           | 1                                                |
| I-261 | 0.5                                            | 0.5                                           | 1                                                |
| I-266 | 0.25                                           | 0.5                                           | 0.5                                              |
| I-272 | 0.25                                           | 0.5                                           | 0.5                                              |
| I-273 | 0.25                                           | 0.5                                           | 0.5                                              |
| I-274 | 0.5                                            | 0.5                                           | 0.5                                              |
| I-275 | 0.5                                            | 1                                             | 0.5                                              |
| I-276 | 0.5                                            | 0.5                                           | 0.5                                              |
| I-278 | 0.5                                            | 0.5                                           | 0.5                                              |
| I-284 | 0.5                                            | 0.5                                           | 1                                                |
| I-298 | 0.5                                            | 1                                             | 0.5                                              |
| I-310 | 0.5                                            | 0.5                                           | 1                                                |
| I-311 | 0.5                                            | 0.5                                           | 0.5                                              |

[Table 5 6]

| No.   | <i>C. albicans</i><br>ATCC90028<br>MIC (μg/mL) | <i>A. flavus</i><br>ATCC204304<br>MIC (μg/mL) | <i>A. fumigatus</i><br>ATCC204305<br>MIC (μg/mL) |
|-------|------------------------------------------------|-----------------------------------------------|--------------------------------------------------|
| I-325 | 0.25                                           | 0.5                                           | 1                                                |
| I-326 | 0.25                                           | 1                                             | 1                                                |
| I-330 | 0.25                                           | 1                                             | 1                                                |
| I-331 | 0.25                                           | 1                                             | 1                                                |
| I-343 | 0.25                                           | 0.5                                           | 1                                                |
| I-344 | 0.5                                            | 0.5                                           | 1                                                |
| I-346 | 0.5                                            | 0.5                                           | 1                                                |
| I-350 | 0.25                                           | 0.5                                           | 0.5                                              |
| I-367 | 0.25                                           | 0.5                                           | 1                                                |
| I-380 | 0.5                                            | 0.5                                           | 1                                                |
| I-383 | 0.25                                           | 1                                             | 1                                                |

The results of the compounds as comparative example are shown below.

[Table 5 7]

| No.   | <i>C. albicans</i><br>ATCC90028<br>MIC (μg/mL) | <i>A. flavus</i><br>ATCC204304<br>MIC (μg/mL) | <i>A. fumigatus</i><br>ATCC204305<br>MIC (μg/mL) |
|-------|------------------------------------------------|-----------------------------------------------|--------------------------------------------------|
| AmBMU | 0.5                                            | 1                                             | 1                                                |
| AmBCU | 0.5                                            | 1                                             | 1                                                |
| AmBAU | 0.5                                            | 1                                             | 1                                                |

[0 2 5 9]

(Test example 2-1: Hemolytic activity test)

Nephrotoxic potentials of the compounds of the present invention except the compounds whose X is  $-N(R^F)-CO-X^1$  and  $X^1$  is the group represented by formula (III) and T is  $-N(R^{a5})-$  were investigated by *in vitro* hemolytic activity test under the condition, in that, the upper limit was 50 μmol/L, 80 μmol/L, 100 μmol/L, or 200 μmol/L as the required concentration to 50% of hemolysis (IC<sub>50</sub>).

Defibrinated sterile blood was centrifuged at 700 x g for 3 minutes and, and the supernatant was removed for 100% of red blood cells. After the cleaning with physiological saline, the washed blood cells was suspended in the medium (Earle's balanced salt sodium, bicarbonate, 0.1 g/L L-glutamine without phenol red), and was

diluted by 5% (5%RBC suspension).

The washed blood was diluted by 5% in water for injection (solution of complete hemolysis), and was used as the indication of optical density for complete hemolysis.

The compounds of the present invention solution in DMSO (several and doubling dilutions starting from 2.5 mmol/L, 4 mmol/L, 5 mmol/L, or 10 mmol/L), DMSO as the negative control, and Amphotericin B as the positive control were used, and each 5 µL of these was added in to a well of V-form 96 well type microplate.

Finally, the maximum concentration of the compounds of the present invention solution in DMSO was 50 µmol/L, 80 µmol/L, 100 µmol/L, or 200 µmol/L by adding 245 µL of the medium or 5%RBC suspension into the well.

Two hundred fifty µL of the solution of complete hemolysis was added into another well and the microplate was incubated at 37°C in 5% of CO<sub>2</sub> concentration for an hour.

After the incubation, each 100 µL of supernatants in wells was collected by centrifugation of the microplate at 300 x g for 5 minutes and was located on a well of flat-form 96 well type microplate. An absorbance of each supernatant was measured at wavelength of 540 nm.

Percent hemolysis was calculated by using the followed equation. The required concentration to 50% of hemolysis (IC<sub>50</sub>) was calculated based on the percent hemolysis. Smallness of IC<sub>50</sub> shows that the compound has potential of kidney toxicity.

$$\text{Hemolysis (\%)} = \frac{(\text{CR} - \text{VM}) \times 100}{(\text{VL} - \text{VR})}$$

Where:

CR: Absorbance of 5%RBC suspension incubated with the compounds of the present invention solution in DMSO

VM: Absorbance of medium incubated with the compounds of the present invention solution in DMSO

VL: Absorbance of solution of complete hemolysis

VR: Absorbance of 5%RBC suspension incubated with DMSO

The results are shown below. The “hemolysis method” in the table means any tests the upper concentration of above IC<sub>50</sub> are 50 µmol/L, 80 µmol/L, 100 µmol/L or 200 µmol/L. The “>50”, “>80”, “>100” or “>200” in the table means above IC<sub>50</sub> value exceeded the each upper concentration.

[Table 5 8]

| No.   | hemolysis<br>IC50 (μmol/L) | hemolysis<br>method | No.   | hemolysis<br>IC50 (μmol/L) | hemolysis<br>method |
|-------|----------------------------|---------------------|-------|----------------------------|---------------------|
| I-5   | 94                         | 100                 | I-54  | >80                        | 80                  |
| I-6   | 75                         | 100                 | I-55  | >50                        | 50                  |
| I-7   | 81                         | 100                 | I-62  | 50                         | 100                 |
| I-8   | 96                         | 100                 | I-81  | >50                        | 50                  |
| I-9   | >100                       | 100                 | I-93  | >50                        | 50                  |
| I-10  | >100                       | 100                 | I-105 | >200                       | 200                 |
| I-11  | >50                        | 50                  | I-146 | >50                        | 50                  |
| I-15  | >80                        | 80                  | I-207 | >100                       | 100                 |
| I-17  | >80                        | 80                  | I-212 | >100                       | 100                 |
| I-18  | >80                        | 80                  | I-213 | >100                       | 100                 |
| I-21  | >80                        | 80                  | I-226 | >50                        | 50                  |
| I-22  | >80                        | 80                  | I-231 | >50                        | 50                  |
| I-23  | 79                         | 80                  | I-234 | >50                        | 50                  |
| I-24  | >80                        | 80                  | I-241 | >50                        | 50                  |
| I-38  | >50                        | 50                  | I-249 | >50                        | 50                  |
| I-39  | >80                        | 80                  | I-250 | >50                        | 50                  |
| I-40  | >80                        | 80                  | I-252 | >50                        | 50                  |
| I-41  | >50                        | 50                  | I-254 | >50                        | 50                  |
| I-48  | >80                        | 80                  | I-255 | >50                        | 50                  |
| I-49  | >80                        | 80                  | I-258 | >50                        | 50                  |
| I-50  | >80                        | 80                  | I-259 | >50                        | 50                  |
| I-51  | >80                        | 80                  | I-279 | >50                        | 50                  |
| I-53  | >80                        | 80                  | I-280 | >50                        | 50                  |
| I-282 | >50                        | 50                  | I-328 | >50                        | 100                 |

[Table 5 9]

| No.   | hemolysis<br>IC <sub>50</sub> (μmol/L) | hemolysis<br>method | No.   | hemolysis<br>IC <sub>50</sub> (μmol/L) | hemolysis<br>method |
|-------|----------------------------------------|---------------------|-------|----------------------------------------|---------------------|
| I-283 | >50                                    | 50                  | I-365 | >50                                    | 50                  |
| I-284 | >50                                    | 50                  | I-366 | >50                                    | 50                  |
| I-291 | >50                                    | 50                  | I-368 | >50                                    | 50                  |
| I-295 | >50                                    | 50                  | I-390 | >50                                    | 50                  |
| I-303 | >50                                    | 50                  | I-391 | >50                                    | 50                  |
| I-311 | >50                                    | 50                  | I-392 | >50                                    | 50                  |
| I-314 | >80                                    | 100                 | I-396 | >100                                   | 100                 |
| I-327 | >50                                    | 100                 |       |                                        |                     |

(Test example 2-2: Hemolytic activity test)

Nephrotoxic potentials of the compounds of the present invention whose X is -N(R<sup>F</sup>)-CO-X<sup>1</sup> and X<sup>1</sup> is the group represented by formula (III) and T is -N(R<sup>a 5</sup>)- were investigated by *in vitro* hemolytic activity test under the condition that the upper limit was 200 μmol/L as the required concentration to 50% of hemolysis (IC<sub>50</sub>).

Defibrinated sterile blood was centrifuged at 700 x g for 3 minutes and, and the supernatant was removed for 100% of red blood cells. After the cleaning with physiological saline, the washed blood cells was suspended in the medium (Earle's balanced salt sodium, bicarbonate, 0.1 g/L L-glutamine without phenol red), and was diluted by 5% (5%RBC suspension).

The washed blood was diluted by 5% in water for injection (solution of complete hemolysis), and was used as the indication of optical density for complete hemolysis.

The compounds of the present invention solution in DMSO (several and doubling dilutions starting from 10 mmol/L), DMSO as the negative control, and Amphotericin B as the positive control were used, and each 5 μL of these was added in to a well of V-form 96 well type microplate. Finally, the maximum concentration of the compounds of the present invention solution in DMSO was 200 μmol/L by adding 245 μL of the medium or 5%RBC suspension into the well.

Two hundred fifty μL of the solution of complete hemolysis was added into another well and the microplate was incubated at 37°C in 5% of CO<sub>2</sub> concentration for an hour.

After the incubation, each 100 μL of supernatants in wells was collected by centrifugation of the microplate at 300 x g for 5 minutes and was located on a well of flat-form 96 well type microplate. An absorbance of each supernatant was measured at wavelength of 540 nm.

Percent hemolysis was calculated by using the followed equation. The required concentration to 50% of hemolysis (IC<sub>50</sub>) was calculated based on the percent hemolysis. Smallness of IC<sub>50</sub> shows that the compound has potential of kidney toxicity.

Hemolysis (%) =

$$(CR - VM) \times 100 \div (VL - VR)$$

Where:

CR: Absorbance of 5%RBC suspension incubated with the compounds of the present invention solution in DMSO

VM: Absorbance of medium incubated with the compounds of the present invention solution in DMSO

VL: Absorbance of solution of complete hemolysis

VR: Absorbance of 5%RBC suspension incubated with DMSO

The results are shown below. The “>200” in the table means above IC<sub>50</sub> value exceeded the upper concentration 200 µmol/L.

[Table 6 0]

| No.   | hemolysis<br>IC50 (μmol/L) | hemolysis<br>method | No.   | hemolysis<br>IC50 (μmol/L) | hemolysis<br>method |
|-------|----------------------------|---------------------|-------|----------------------------|---------------------|
| I-19  | > 200                      | 200                 | I-224 | > 200                      | 200                 |
| I-43  | > 200                      | 200                 | I-225 | > 200                      | 200                 |
| I-44  | > 200                      | 200                 | I-228 | > 200                      | 200                 |
| I-45  | > 200                      | 200                 | I-229 | > 200                      | 200                 |
| I-47  | > 200                      | 200                 | I-232 | > 200                      | 200                 |
| I-60  | > 200                      | 200                 | I-233 | > 200                      | 200                 |
| I-78  | > 200                      | 200                 | I-237 | > 200                      | 200                 |
| I-123 | > 200                      | 200                 | I-238 | > 200                      | 200                 |
| I-124 | > 200                      | 200                 | I-239 | > 200                      | 200                 |
| I-125 | > 200                      | 200                 | I-240 | > 200                      | 200                 |
| I-194 | > 200                      | 200                 | I-242 | > 200                      | 200                 |
| I-197 | > 200                      | 200                 | I-243 | > 200                      | 200                 |
| I-198 | > 200                      | 200                 | I-245 | > 200                      | 200                 |
| I-209 | > 200                      | 200                 | I-246 | > 200                      | 200                 |
| I-214 | > 200                      | 200                 | I-247 | > 200                      | 200                 |
| I-215 | > 200                      | 200                 | I-253 | > 200                      | 200                 |
| I-216 | > 200                      | 200                 | I-256 | > 200                      | 200                 |
| I-217 | > 200                      | 200                 | I-257 | > 200                      | 200                 |
| I-218 | > 200                      | 200                 | I-261 | > 200                      | 200                 |
| I-220 | > 200                      | 200                 | I-263 | > 200                      | 200                 |
| I-221 | > 200                      | 200                 | I-272 | > 200                      | 200                 |
| I-223 | > 200                      | 200                 | I-310 | > 200                      | 200                 |

The results of the comparative example are shown below.

[Table 6 1]

|       | hemolysis<br>IC50 (μmol/L) | hemolysis<br>method |
|-------|----------------------------|---------------------|
| AmB   | 1.6                        | 200                 |
| AmBMU | 129.8                      | 200                 |
| AmBAU | 58                         | 200                 |

[0 2 6 0]

(Test example 3: Cytotoxicity assay)

The Cytotoxicity of the compounds of the present invention was evaluated by measuring cell numbers automatically using the cell image analyzer, Toxinsight® (Thermofisher Scientific).

HepG2 cells were seeded in 384-well black plates (100000 cells/mL) and allowed to attach for approximately 24 hours at 37°C in humidified CO<sub>2</sub> incubator. Test compounds and positive control (fungizone®) were initially dissolved as concentrated 20mmol/L stock solutions in DMSO and added to culture medium, to the final concentration; 1.6, 3.1, 6.3, 12.5, 25, 50, 100 μmol/L. The negative control well was treated with DMSO alone. After exposure of each test compound for approximately 71 hours, each well were added with Hoechst 33342, for staining of nuclei, diluted in D-PBS to the final concentration; 1μg/mL, and after that, fixed with 4% paraformaldehyde. The cell number, stained with Hoechst 33342, was counted by Toxinsight® (Thermofisher Scientific) in each well. The mean value of cell number and the standard deviation (SD) was calculated (N=4). The lowest cytotoxicity concentration was evaluated as the concentration showed the cell numbers decreased more than 2SD from vehicle control values. The lower the cell numbers is indicated that the risk of cytotoxicity is higher.

The results are shown below.

[Table 6 2]

| No.   | cytotoxicity<br>(μmol/L) |
|-------|--------------------------|
| I-214 | >100                     |
| I-215 | >100                     |
| I-216 | >100                     |
| I-253 | >100                     |
| I-310 | >100                     |

The results of the comparative example are shown below.

[Table 6 3]

|       | cytotoxicity<br>( $\mu\text{mol/L}$ ) |
|-------|---------------------------------------|
| AmB   | <1.6                                  |
| AmBMU | 12.5                                  |
| AmBCU | 25.2                                  |
| AmBAU | 51.0                                  |

[0 2 6 1]

(Test example 4: Hemolytic activity test)

The expression level of marker genes for nephrotoxicity was determined by quantitative RT-PCR to evaluate nephrotoxicity of the compound of the present invention. The compound of the present invention or vehicle was intravenously administered to mice and their kidneys were isolated. After removal of the kidney capsule, all of the kidneys were sliced into two equal halves, and stored at  $-80^{\circ}\text{C}$  in RNeasy Lysis Reagent (Qiagen) until use. Samples were disrupted and homogenized in QIAzol Lysis Reagent with TissueLyser (Qiagen), and total RNA was extracted using an RNeasy® Mini kit (Qiagen). Total RNA concentrations were determined to read OD260 by absorptiometer.

The level of expression of the following target genes was determined using one-step quantitative real-time PCR: *Kim1*, *Timp1*, and *Lcn2*. Total RNA (80 ng/2  $\mu\text{L}$ ) was used as the template, and TaqMan Gene Expression Assays (Applied Biosystems, for *Havcr1* (*Kim1*), assay ID: Mm00506686\_m1; *Timp1*, Mm01341361\_m1; *Lcn2*, Mm01324470\_m1) or TaqMan Endogenous Controls (*Gapdh*, predesigned assay reagent supplied by ABI, Applied Biosystems) were employed as gene-specific probe and primer sets. Quantitative RT-PCR was performed using a QuantiTect™ Probe RT-PCR kit (Qiagen), and transcript levels were quantitated with an Applied Biosystems 7900HT Fast Real Time PCR System (Applied Biosystems). Reverse transcription and amplification conditions were set as follows:  $50^{\circ}\text{C}$  for 30 min,  $95^{\circ}\text{C}$  for 15 min, followed by 40 cycles at  $95^{\circ}\text{C}$  for 15 s and  $60^{\circ}\text{C}$  for 1 min. The resulting cycle threshold (Ct) value was processed based on the comparative Ct method ( $\Delta\Delta\text{Ct}$  Method), where *Gapdh* was used as an endogenous reference gene to normalize the expression level of target genes.

The  $\Delta\text{Ct}$  was calculated as follows:  $\text{Ct}_{\text{Gapdh}} - \text{Ct}_{\text{target gene}}$ .

The  $\Delta\Delta\text{Ct}$  was calculated as follows:  $\Delta\text{Ct}_{\text{treated sample}} - \Delta\text{Ct}_{\text{average of vehicle control sample}}$ .

Higher  $\Delta\Delta\text{Ct}$  values indicate higher expression rates of the target gene and therefore high risk for nephrotoxicity. When  $\Delta\Delta\text{Ct}$  values of two-third of target genes showed  $>3$ , it was considered to be nephrotoxicity positive.

The results are shown below.

[Table 6 4]

| No.   | nephrotoxicity<br>MTD (mg/kg) |
|-------|-------------------------------|
| I-105 | >24                           |
| I-219 | 16                            |
| I-235 | >24                           |
| I-394 | >24                           |
| I-396 | 16                            |

The results of the comparative example are shown below.

[Table 6 5]

|       | nephrotoxicity<br>MTD (mg/kg) |
|-------|-------------------------------|
| AmB   | 1                             |
| AmBMU | 12                            |
| AmBCU | 3                             |
| AmBAU | 12*                           |

The mark \* in above table is indicated that all mouses of 3 cases at 16 mg/kg dosing was died. It is showed that AmBAU has possibilities of acute toxicity.

#### INDUSTRIAL APPLICABILITY

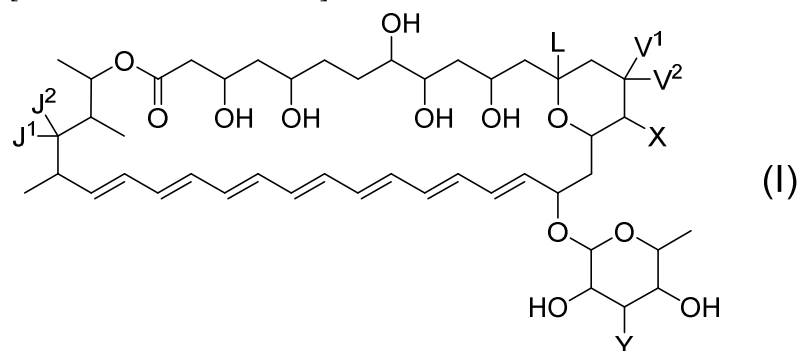
[0 2 6 2]

The compound of the present invention has antifungal activity against fungi. Therefore, the compound of the present invention is useful for prevention or treatment against various infections associated with fungi (examples: deep mycosis, fungemia, respiratory mycosis, fungal meningitis, disseminated mycosis and the like).

## CLAIMS

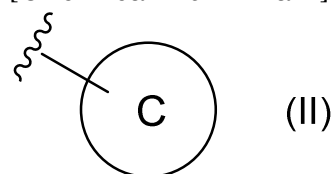
1. A compound represented by formula (I):

[Chemical Formula 1]



wherein X is a group of formula:

[Chemical Formula 2]



, -N(R<sup>F</sup>)-CO-X<sup>1</sup>, hydroxyalkyl or a group of formula: -CO-NH(R<sup>X</sup>)

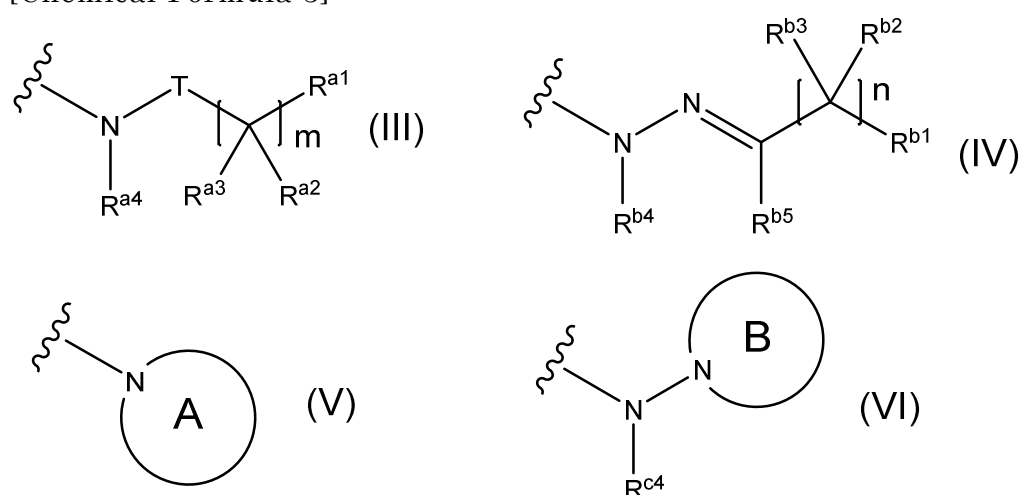
wherein R<sup>X</sup> is substituted or unsubstituted non-aromatic heterocycloxyalkyl;

Ring C is substituted or unsubstituted aromatic carbocycle, substituted or unsubstituted non-aromatic carbocycle, substituted or unsubstituted aromatic heterocycle or substituted or unsubstituted non-aromatic heterocycle;

R<sup>F</sup> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl; and

X<sup>1</sup> is any one of following groups:

[Chemical Formula 3]



L, J<sup>1</sup> and V<sup>1</sup> are each independently hydrogen, halogen, hydroxy, substituted or unsubstituted amino or substituted or unsubstituted alkyloxy;

J<sup>2</sup> and V<sup>2</sup> are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl; or J<sup>1</sup> and J<sup>2</sup> and/or V<sup>1</sup> and V<sup>2</sup> may be taken together to form oxo;

$R^{a\ 1}$  and  $R^{b\ 1}$  are each independently, hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, formyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, sulfo, cyano, substituted or unsubstituted ureido, guanidino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkyl ammonium, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkenylsulfonyl, substituted or unsubstituted alkynylsulfonyl, substituted or unsubstituted alkylphosphonyl, substituted or unsubstituted dialkynylphosphonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkenylcarbonyloxy, substituted or unsubstituted alkynylcarbonyloxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocycloxy, substituted or unsubstituted non-aromatic carbocycloxy, substituted or unsubstituted aromatic heterocycloxy, substituted or unsubstituted non-aromatic heterocycloxy, substituted or unsubstituted aromatic carbocyclylcarbonyl, substituted or unsubstituted non-aromatic carbocyclylcarbonyl, substituted or unsubstituted aromatic heterocyclylcarbonyl, substituted or unsubstituted non-aromatic heterocyclylcarbonyl, substituted or unsubstituted aromatic carbocyclylamino, substituted or unsubstituted non-aromatic carbocyclylamino, substituted or unsubstituted aromatic heterocyclylamino, substituted or unsubstituted non-aromatic heterocyclylamino, substituted or unsubstituted aromatic carbocyclylsulfonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted aromatic heterocyclylsulfonyl or substituted or unsubstituted non-aromatic heterocyclylsulfonyl;

$R^{a\ 2}$  and  $R^{b\ 2}$  are each independently hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted alkenylcarbonyloxy, substituted or unsubstituted alkynylcarbonyloxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted non-aromatic heterocycloxyalkyl, substituted or unsubstituted non-aromatic heterocycloxyalkenyl or substituted or unsubstituted non-aromatic heterocycloxyalkynyl;

$R^{a\ 3}$  and  $R^{b\ 3}$  are each independently, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted non-aromatic heterocycloxyalkyl, substituted or unsubstituted non-aromatic heterocycloxyalkenyl or substituted or unsubstituted non-aromatic heterocycloxyalkynyl;

or  $R^{a2}$  and  $R^{a3}$  and/or  $R^{b2}$  and  $R^{b3}$  are each independently may be taken together to form oxo, substituted or unsubstituted imino or thioxo, or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle or substituted or unsubstituted non-aromatic heterocycle;

$R^{a4}$ ,  $R^{b4}$  and  $R^{c4}$  are each independently, hydrogen, hydroxy, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl or substituted or unsubstituted non-aromatic carbocyclyl;

$R^{b5}$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;

Ring A and Ring B are each independently, substituted or unsubstituted nitrogen-containing aromatic heterocycle or substituted or unsubstituted nitrogen-containing non-aromatic heterocycle;

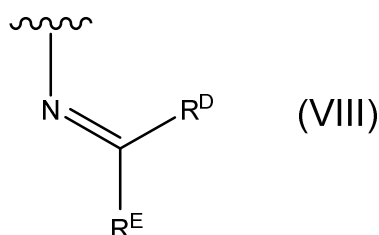
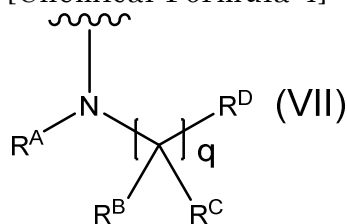
T is a bond,  $-N(R^{a5})-$  or  $-O-$ ;

$R^{a5}$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl or substituted or unsubstituted alkynylcarbonyl;

m and n are each independently an integer of 0 to 10;

Y is any one of following groups

[Chemical Formula 4]



$R^A$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;

$R^B$  and  $R^C$  are each independently hydrogen, hydroxy, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;

or  $R^B$  and  $R^C$  may be taken together to form oxo, substituted or unsubstituted imino or thioxo, or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle or substituted or unsubstituted non-aromatic heterocycle;

$R^D$  is hydrogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, substituted or unsubstituted amidino, substituted or unsubstituted guanidino, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl or substituted or unsubstituted non-aromatic heterocyclyl;

$R^E$  is hydrogen, hydroxy or substituted or unsubstituted amino;

q is an integer of 0 to 10;

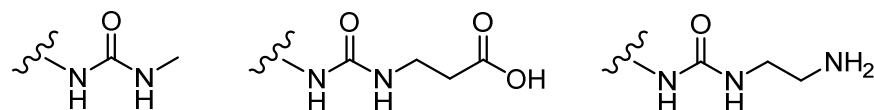
provided that the following compounds are excluded:

(i) The compounds which X is  $-CH_2-OH$ ; and Y is  $-NH_2$ ;

(ii) The compounds which X is either of following groups; and Y is any one of  $-NH_2$ ; a

group of formula:

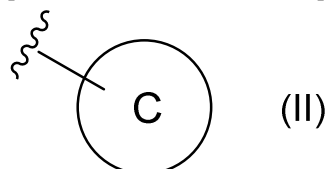
[Chemical Formula 5]



or a pharmaceutically acceptable salt thereof.

2. The compound or its pharmaceutically acceptable salt according to claim 1, wherein X is

[Chemical Formula 6]



or  $-N(R^F)-CO-X^1$ .

3. The compound or its pharmaceutically acceptable salt according to claim 1 or 2, wherein  $J^1$ , L and  $V^1$  are hydroxy; and  $J^2$  and  $V^2$  are hydrogen.

4. The compound or its pharmaceutically acceptable salt according to any one of claims 1 to 3, wherein X is a group of formula:  $-N(R^F)-CO-X^1$ ;  $X^1$  is a group represented by formula (III); and T is a bond.

5. The compound or its pharmaceutically acceptable salt according to claim 4, wherein  $R^{a1}$  is halogen, hydroxy, carboxy, substituted or unsubstituted amino, substituted or unsubstituted aromatic heterocyclamino, substituted or unsubstituted non-aromatic heterocyclamino, substituted or unsubstituted alkylammonium, carbamoyl, sulfamoyl, sulfo, cyano, substituted or unsubstituted ureido, guanidino, substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocycloxy, substituted or unsubstituted alkylphosphonyl, substituted sulfamoyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl or substituted or unsubstituted non-aromatic heterocyclyl;

wherein said substituted or unsubstituted amino is selected from unsubstituted amino, hydroxyamino, sulfamoylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkylsulfonamino, substituted or unsubstituted non-aromatic carbocyclylcarbonylamino, substituted or unsubstituted aromatic carbocyclylcarbonylamino, substituted or unsubstituted aromatic heterocyclylcarbonylamino and substituted or unsubstituted non-aromatic heterocyclylcarbonylamino;

wherein said substituted or unsubstituted ureido is selected from ureido, substituted or unsubstituted alkylureido, substituted or unsubstituted aromatic heterocyclylureido and substituted or unsubstituted aromatic heterocyclylureido;

wherein said substituted sulfamoyl is substituted or unsubstituted aromatic heterocyclylsulfamoyl.

6. The compound or its pharmaceutically acceptable salt according to claim 4 or 5, wherein  $R^{a2}$  are each independently hydrogen, halogen, hydroxy, carboxy, amino, carbamoyl, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic heterocycloxyalkyl or substituted or unsubstituted alkylcarbonyl;

$R^{a3}$  are each independently, hydrogen, halogen, substituted or unsubstituted alkyl or substituted or unsubstituted non-aromatic heterocycloxyalkyl; or  $R^{a2}$  and  $R^{a3}$  may be taken together to form oxo, or may be taken together with neighboring atoms to form non-aromatic carbocycle or non-aromatic heterocycle.

7. The compound or its pharmaceutically acceptable salt according to any one of claims 4 to 6, wherein  $R^{a4}$  is hydrogen, hydroxy, amino, substituted or unsubstituted alkyl or substituted or unsubstituted non-aromatic carbocyclyl.

8. The compound or its pharmaceutically acceptable salt according to any one of claims 1 to 3, wherein X is a group of formula:  $-N(R^F)-CO-X^1$ ;  $X^1$  is a group represented by formula (III); and T is  $-N(R^{a5})-$  or  $-O-$ .

9. The compound or its pharmaceutically acceptable salt according to claim 8, wherein  $R^{a1}$  is hydroxy, carboxy, substituted amino, substituted or unsubstituted aromatic heterocyclylamino, formyl, carbamoyl, cyano, guanidino, substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocycloxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted aromatic heterocyclylsulfonyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, or substituted ureido;

wherein said substituted amino is hydroxyamino or substituted or unsubstituted alkylamino;

wherein said substituted ureido is substituted or unsubstituted aromatic heterocyclylureido.

10. The compound or its pharmaceutically acceptable salt according to claim 8 or 9, wherein  $R^{a2}$  are each independently hydrogen, hydroxy or substituted or unsubstituted alkyl;

$R^{a3}$  are each independently hydrogen or substituted or unsubstituted alkyl; or  $R^{a2}$  and  $R^{a3}$  may be taken together to form oxo or thioxo, or may be taken together with neighboring atoms to form substituted or unsubstituted non-aromatic carbocycle.

11. The compound or its pharmaceutically acceptable salt according to any one of claims 8 to 10, wherein  $R^{a2}$  is hydrogen.

12. The compound or its pharmaceutically acceptable salt according to any one of claims 1 to 3, wherein X is a group of formula:  $-N(R^F)-CO-X^1$ ; and  $X^1$  is a group represented by formula (IV).

13. The compound or its pharmaceutically acceptable salt according to claim 12, wherein  $R^{b1}$  is hydroxy.

14. The compound or its pharmaceutically acceptable salt according to claim 12 or 13, wherein  $n$  is 1 or 2;  $R^{b\ 2}$  are each independently hydrogen or hydroxy; and  $R^{b\ 3}$  is hydrogen.

15. The compound or its pharmaceutically acceptable salt according to any one of claims 12 to 14, wherein  $R^{b\ 4}$  is hydrogen; and  $R^{b\ 3}$  is hydrogen or substituted or unsubstituted alkyl.

16. The compound or its pharmaceutically acceptable salt according to any one of claims 1 to 3, wherein  $X$  is  $-N(R^F)-CO-X^1$ ; and  $X^1$  is a group represented by formula (V).

17. The compound or its pharmaceutically acceptable salt according to claim 16, wherein ring A is substituted or unsubstituted nitrogen-containing non-aromatic heterocycle.

18. The compound or its pharmaceutically acceptable salt according to any one of claims 1 to 3, wherein  $X$  is a group of formula:  $-N(R^F)-CO-X^1$ ;  $X^1$  is a group represented by formula (VI).

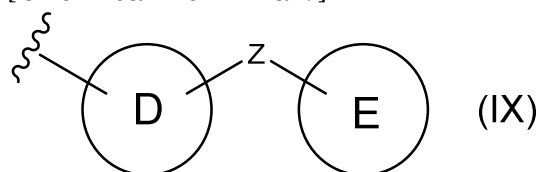
19. The compound or its pharmaceutically acceptable salt according to claim 18, wherein ring B is substituted or unsubstituted nitrogen-containing non-aromatic heterocycle.

20. The compound or its pharmaceutically acceptable salt according to claim 18 or 19, wherein  $R^{c\ 4}$  is hydrogen.

21. The compound or its pharmaceutically acceptable salt according to any one of claims 1 to 20, wherein  $R^F$  is hydrogen.

22. The compound or its pharmaceutically acceptable salt according to any one of claims 1 to 3, wherein  $X$  is a group represented by formula (II); and said group is represented by formula:

[Chemical Formula 7]



ring D and ring E are each independently substituted or unsubstituted aromatic carbocycle, substituted or unsubstituted non-aromatic carbocycle, substituted or unsubstituted aromatic heterocycle or substituted or unsubstituted non-aromatic heterocycle; and

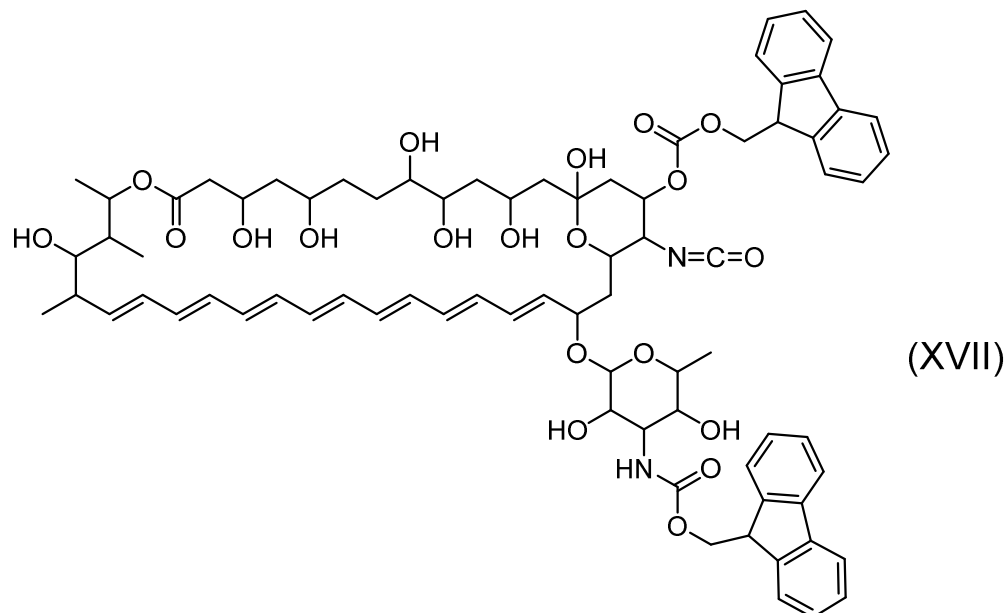
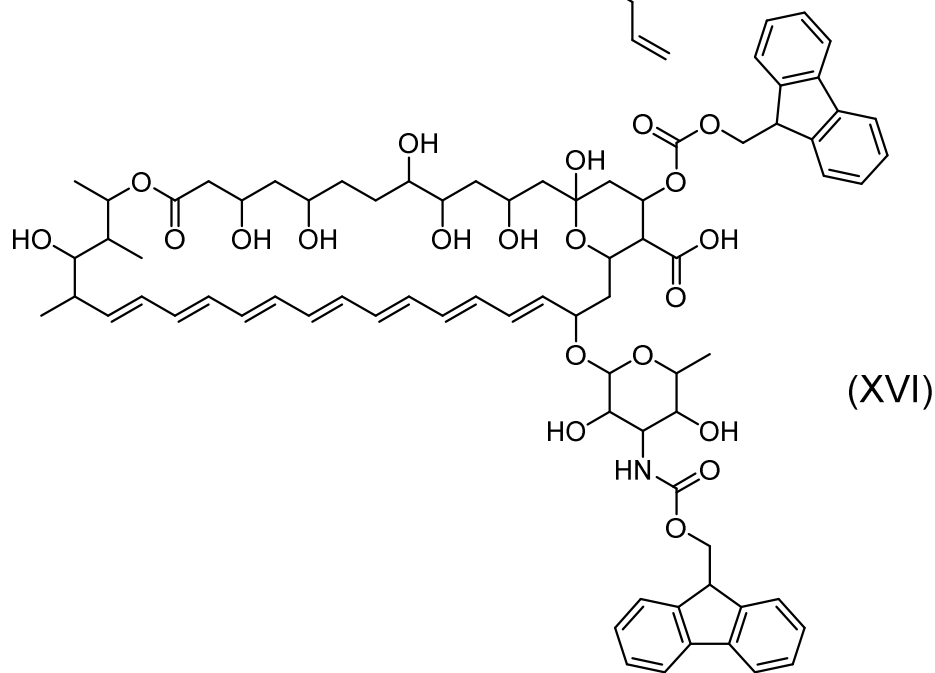
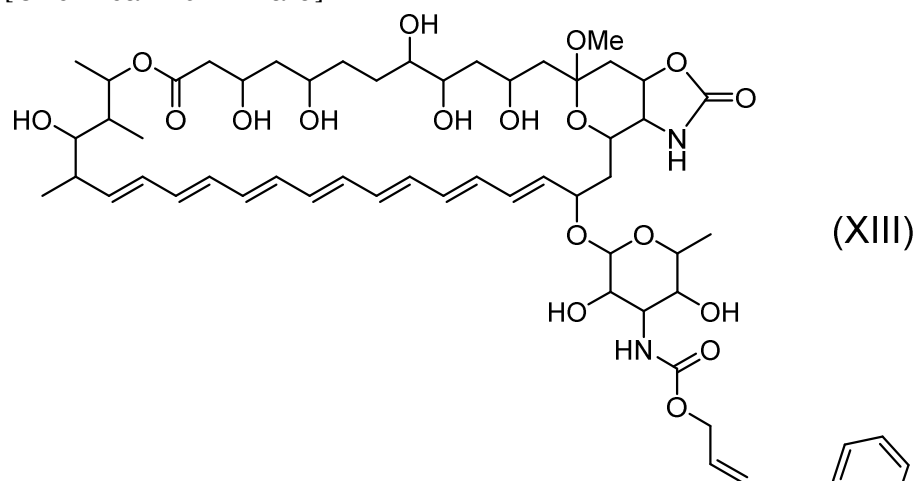
$Z$  is a bond, alkylene,  $-O-$ ,  $-S-$  or  $-N(H)-$ .

23. The compound or its pharmaceutically acceptable salt according to claim 22, wherein ring D is substituted or unsubstituted aromatic heterocycle; and ring E is substituted or unsubstituted aromatic carbocycle or substituted or unsubstituted aromatic heterocycle.

24. The compound or its pharmaceutically acceptable salt according to claim 22 or 23, wherein Z is a bond.
25. The compound or its pharmaceutically acceptable salt according to any one of claims 22 to 24, wherein the substituent(s) on ring E is/are alkylamino.
26. The compound or its pharmaceutically acceptable salt according to any one of claims 1 to 25, wherein R<sup>A</sup> are each independently hydrogen or substituted or unsubstituted alkyl; R<sup>B</sup> are each independently hydrogen or hydroxy or substituted or unsubstituted amino; R<sup>C</sup> are each independently hydrogen or hydroxy or substituted or unsubstituted amino; or R<sup>B</sup> and R<sup>C</sup> may be taken together to form oxo, substituted or unsubstituted imino, hydroxyimino or cyanoimino;  
R<sup>D</sup> is hydrogen, hydroxy, carboxy, substituted or unsubstituted amino, carbamoyl, guanidine, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl or substituted or unsubstituted non-aromatic heterocyclyl;  
R<sup>E</sup> is amino;  
wherein said substituted or unsubstituted amino is unsubstituted amino or substituted or unsubstituted alkylamino;  
wherein said substituted or unsubstituted imino is unsubstituted imino, hydroxyimino or cyanoimino.
27. The compound or its pharmaceutically acceptable salt according to any one of claims 1 to 25, wherein Y is NH<sub>2</sub>.
28. The compound or its pharmaceutically acceptable salt according to claim 1, wherein X is hydroxyalkyl; q is an integer of 0 to 10.
29. The compound or its pharmaceutically acceptable salt according to claim 1, wherein X is a group of formula: -CO-NH(R<sup>X</sup>), wherein R<sup>X</sup> is substituted or unsubstituted non-aromatic heterocycloxyalkyl.
30. The compound or its pharmaceutically acceptable salt according to claim 3, wherein X is a group of formula: -N(R<sup>F</sup>)-CO-X<sup>1</sup>, wherein X<sup>1</sup> is a group represented by formula (II);  
T is -N(H)-; R<sup>a 1</sup> is carboxy, carbamoyl or substituted amino; R<sup>a 2</sup> is each independently hydrogen or hydroxy; and R<sup>a 3</sup> and R<sup>a 4</sup> are hydrogen; m is 2; and Y is NH<sub>2</sub>.
31. A pharmaceutical composition containing the compound or its pharmaceutically acceptable salt according to any one of claims 1 to 30.
32. A pharmaceutical composition of claim 31 having antifungal activity.
33. A compound represented by any one of formula (X), (XI), (XII), (XIII), (XVI) or (XVII):



[Chemical Formula 9]



or its pharmaceutically acceptable salt.

34. A process for the preparation of the compound according to any one of claims 1 to 30, wherein X is a group of formula:  $-N(R^F)-CO-X^1$ , which is characterized in using

the compound or its pharmaceutically acceptable salt according to Claim 33.