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(54) **Titre : PROMEDICAMENT DERIVE DE CARBAMOYLPYRIDONE POLYCYCLIQUE SUBSTITUEE**  
(54) **Title: SUBSTITUTED POLYCYCLIC CARBAMOYL PYRIDONE DERIVATIVE PRODRUG**

(57) **Abrégé/Abstract:**

The present invention provides a compound having antiviral effects, particularly having growth inhibitory activity on influenza viruses, a preferred example of the compound being a substituted 3-hydroxy-4-pyridone derivative prodrug having cap-dependent endonuclease inhibitory activity.

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[Document Name] Abstract

The present invention provides a compound having antiviral effects, particularly having growth inhibitory activity on influenza viruses, a preferred example of the compound being a substituted 3-hydroxy-4-pyridone derivative prodrug having cap-dependent endonuclease inhibitory activity.

## **DEMANDES OU BREVETS VOLUMINEUX**

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS  
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**CECI EST LE TOME \_\_1\_\_ DE \_\_4\_\_**

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

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## **JUMBO APPLICATIONS / PATENTS**

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE  
THAN ONE VOLUME.**

**THIS IS VOLUME \_\_1\_\_ OF \_\_4\_\_**

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[Document Name] Description

[Title of Invention] SUBSTITUTED POLYCYCLIC CARBAMOYL PYRIDONE  
DERIVATIVE PRODRUG

[TECHNICAL FIELD]

[0001]

This invention relates to substituted polycyclic carbamoylpyridone derivatives having cap-dependent endonuclease inhibitory activity, prodrugs thereof, and pharmaceutical compositions including thereof.

[BACKGROUND ART]

[0002]

Influenza is an acute respiratory infectious disease caused by infection with an influenza virus. In Japan, there is a report of millions of influenza-like patients every winter, and influenza is accompanied with high morbidity and mortality. Influenza is a particularly important disease in a high risk population such as baby and elderly, a complication rate with pneumonia is high in elderly, and death with influenza is occupied with elderly in many cases.

[0003]

As anti-influenza drugs, Symmetrel (trade name: Amantadine) and Flumadine (trade name: Rimantadine) which inhibit the denuclease process of a virus, and Oseltamivir (trade name: Tamiflu) and Zanamivir (trade name: Relenza) which are neuraminidase inhibitors suppressing virus budding and release from a cell are known. However, since problems of appearances of resistant strains and side effects, and worldwide epidemic of a new-type influenza virus having high pathogenicity and mortality are feared, development of an anti-influenza drug having a novel mechanism has been desired.

[0004]

Since a cap-dependent endonuclease which is an influenza virus-derived enzyme is essential for virus proliferation, and has the virus-specific enzymatic activity which is not possessed by a host, it is believed that the endonuclease is suitable for a target of an anti-influenza drug. The cap-dependent endonuclease has a host mRNA precursor as a substrate, and has the endonuclease activity of producing a fragment of 9 to 13 bases including a cap structure (not including the number of bases of the cap structure). This fragment functions as a primer of a virus RNA polymerase, and is used in synthesizing mRNA encoding a virus protein. That is, it is believed that a substance which inhibits the cap-dependent endonuclease inhibits synthesis of a virus protein by inhibiting synthesis of virus mRNA and, as a result, inhibits virus proliferation.

[0005]

As the substance which inhibits the cap-dependent endonuclease, flutimide (Patent Document 1 and Non-Patent Documents 1 and 2) and 4-substituted 2,4-dioxobutanoic acid (Non-Patent Documents 3 to 5) and the like have been reported, but they have not yet led to clinical use as anti-influenza drugs. In addition, Patent Documents 2 to 16 and Non-Patent Document 6 describe compounds having a similar structure to that of this invention as a compound having integrase inhibitory activity, however, the documents do not describe cap-dependent endonuclease. In addition, Patent Document 17 describes an invention relating to "substituted polycyclic carbamoylpyridone derivative" having cap-dependent endonuclease inhibitory activity, that has been filed by the applicants, but does not describe the prodrug relating to the present invention.

[PRIOR ART DOCUMENTS]

[PATENT DOCUMENTS]

[0006]

[Patent Document 1] GB No. 2280435 specification

[Patent Document 2] International Publication No. 2007/049675 pamphlet

[Patent Document 3] International Publication No. 2006/088173 pamphlet

[Patent Document 4] International Publication No. 2006/066414 pamphlet

[Patent Document 5] International Publication No. 2005/092099 pamphlet

[Patent Document 6] International Publication No. 2005/087766 pamphlet

[Patent Document 7] International Publication No. 2005/016927 pamphlet

[Patent Document 8] International Publication No. 2004/024078 pamphlet

[Patent Document 9] International Publication No. 2006/116764 pamphlet

[Patent Document 10] International Publication No. 2010/011818 pamphlet

[Patent Document 11] International Publication No. 2010/011816 pamphlet

[Patent Document 12] International Publication No. 2010/011819 pamphlet

[Patent Document 13] International Publication No. 2010/011815 pamphlet

[Patent Document 14] International Publication No. 2010/011814 pamphlet

[Patent Document 15] International Publication No. 2010/011812 pamphlet

[Patent Document 16] International Publication No. 2011/011483 pamphlet

[Patent Document 17] International Publication No. 2010/147068 pamphlet

[NON-PATENT DOCUMENTS]

[0007]

[NON-PATENT DOCUMENT 1] Tetrahedron Lett 1995, 36 (12), 2005

[NON-PATENT DOCUMENT 2] Tetrahedron Lett 1995, 36 (12), 2009

[NON-PATENT DOCUMENT 3] Antimicrobial Agents And Chemotherapy,

Dec. 1994, p. 2827-2837

[NON-PATENT DOCUMENT 4] Antimicrobial Agents And Chemotherapy,  
May 1996, p. 1304-1307

[NON-PATENT DOCUMENT 5] J. Med. Chem. 2003, 46, 1153-1164

[NON-PATENT DOCUMENT 6] Bioorganic & Medicinal Chemistry Letters  
17 (2007) 5595-5599

[SUMMARY OF THE INVENTION]

[PROBLEMS TO BE SOLVED BY THE INVENTION]

[0008]

An object of the present invention is to provide compounds having antiviral activities, especially inhibiting growth activity of influenza virus. Another object of the present invention is to provide compounds being efficiently absorbed into the body after administration and showing high pharmacological effect by converting into a prodrug a compound used for in vivo administration (for example, oral administration). More preferably, this invention provides compounds and medicament containing the same which inhibit increase of influenza virus by exhibiting cap-dependent endonuclease inhibitory activity after in vivo administration.

[MEANS FOR SOLVING THE PROBLEMS]

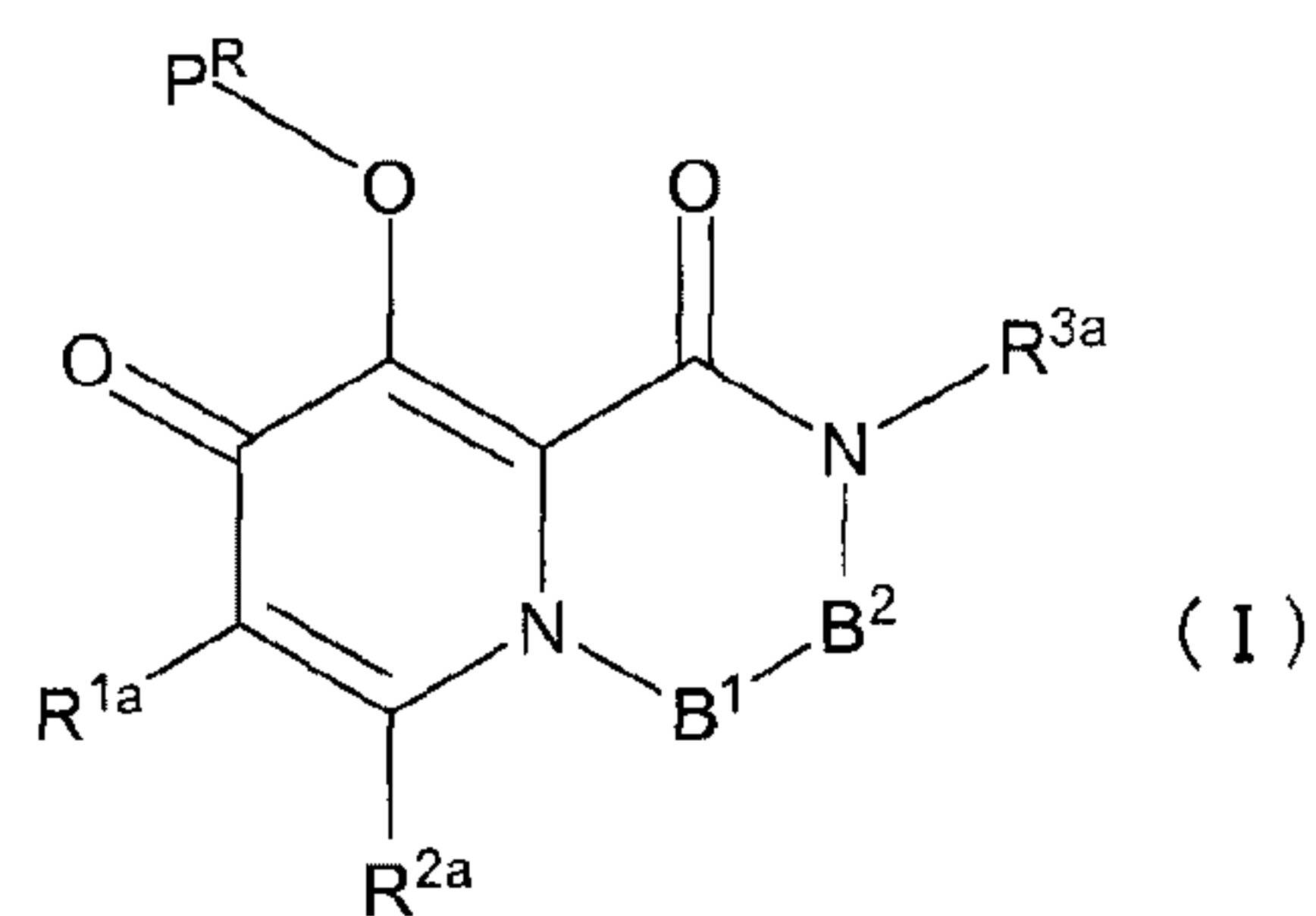
[0009]

The present invention provides inventions shown below.

(Item 1)

A compound represented by formula (I):

[Chemical formula 1]



, a pharmaceutically acceptable salt, or a solvate thereof:

(wherein

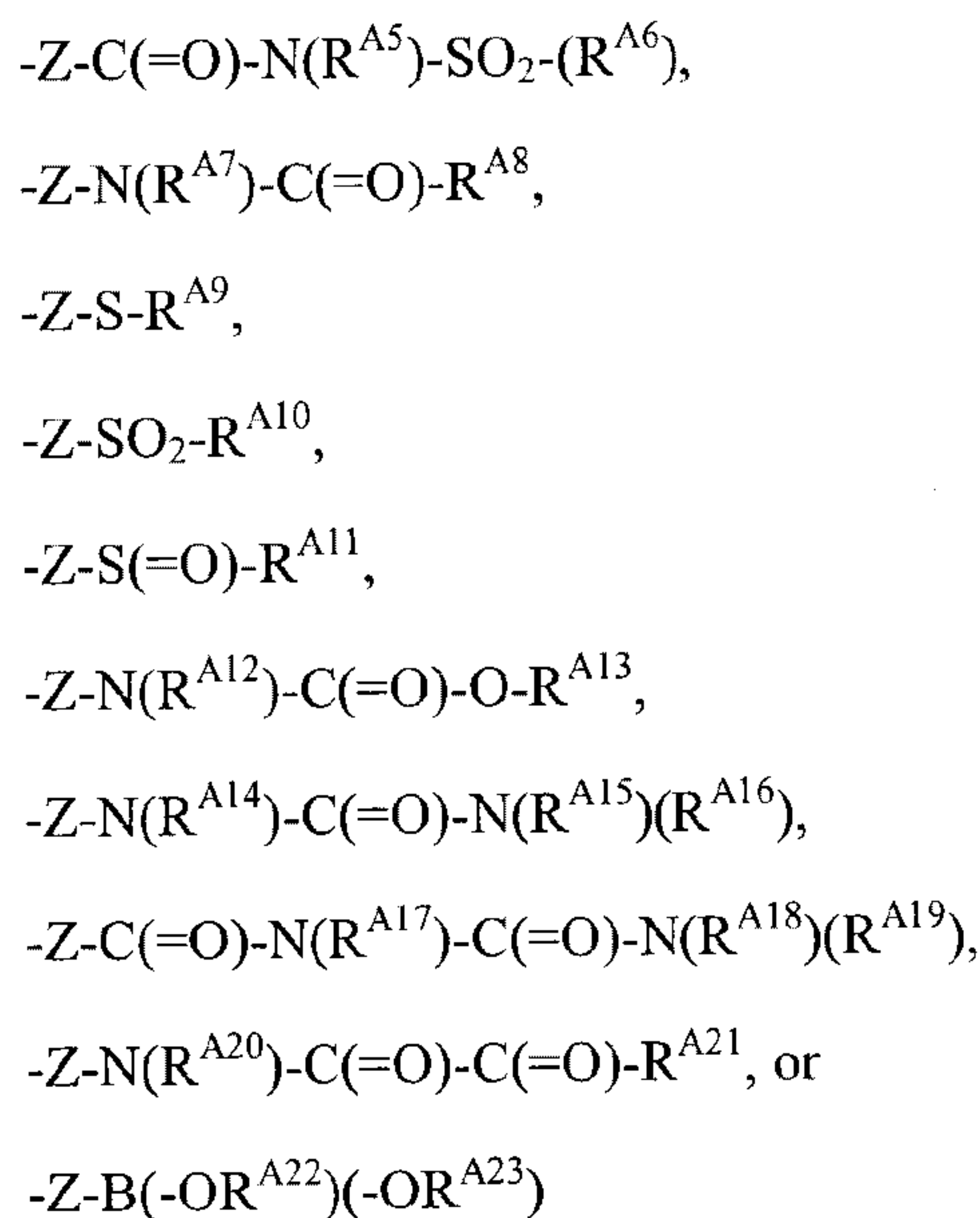
$P^R$  is a group to form a prodrug (preferably, except for a benzyl group and methoxy group);

[0010]

$R^{1a}$  is hydrogen, halogen, hydroxy, carboxy, cyano, formyl, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkenyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,

$-Z-N(R^{A1})(R^{A2})$ ,

$-Z-N(R^{A3})-SO_2-(R^{A4})$ ,



(wherein  $R^{A1}$ ,  $R^{A2}$ ,  $R^{A3}$ ,  $R^{A5}$ ,  $R^{A7}$ ,  $R^{A8}$ ,  $R^{A9}$ ,  $R^{A12}$ ,  $R^{A13}$ ,  $R^{A14}$ ,  $R^{A15}$ ,  $R^{A16}$ ,  $R^{A17}$ ,  $R^{A18}$ ,  $R^{A19}$ ,  $R^{A20}$ , and  $R^{A21}$  are each independently selected from a substituent group consisting of hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{A4}$ ,  $R^{A6}$ ,  $R^{A10}$ , and  $R^{A11}$  are each independently selected from a substituent group consisting of lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

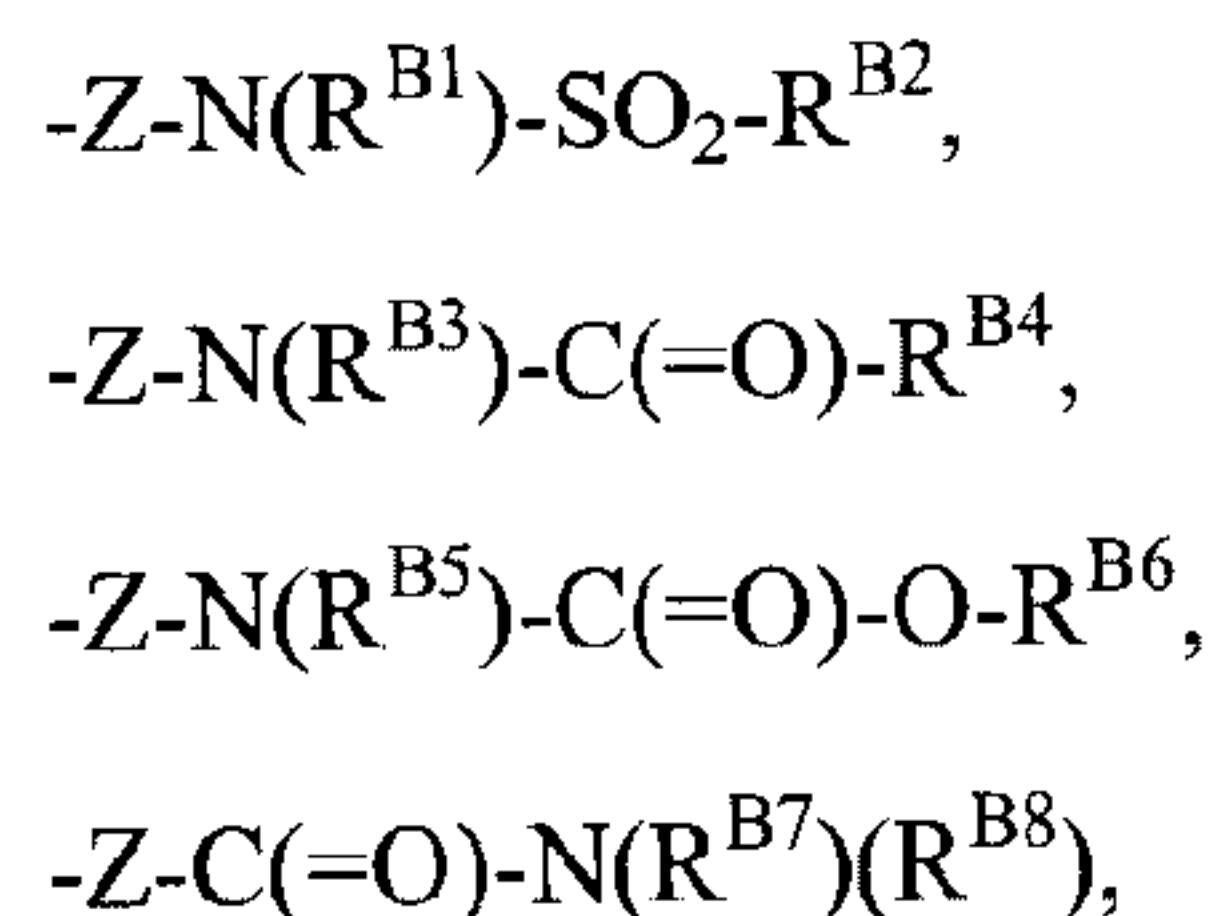
$R^{A1}$  and  $R^{A2}$ ,  $R^{A15}$  and  $R^{A16}$ , and  $R^{A18}$  and  $R^{A19}$ , each may be taken together with an adjacent atom to form heterocycle,

$R^{A22}$  and  $R^{A23}$  are each independently an hydrogen atom, lower alkyl optionally substituted by substituent group C, or  $R^{A22}$  and  $R^{A23}$  may be taken together with an adjacent atom to form heterocycle, and

Z is a single bond or straight or branched lower alkylene);

[0011]

$R^{2a}$  is hydrogen, halogen, carboxy, cyano, formyl, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkenyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C, carbocycleoxy optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxy optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,



$-Z-N(R^{B9})(R^{B10})$ , or

$-Z-SO_2-R^{B11}$

(wherein  $R^{B1}$ ,  $R^{B3}$ ,  $R^{B4}$ ,  $R^{B5}$ ,  $R^{B6}$ ,  $R^{B7}$ ,  $R^{B8}$ ,  $R^{B9}$ , and  $R^{B10}$  are each

independently selected from a substituent group consisting of hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{B2}$  and  $R^{B11}$  are each independently selected from a substituent group consisting of lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

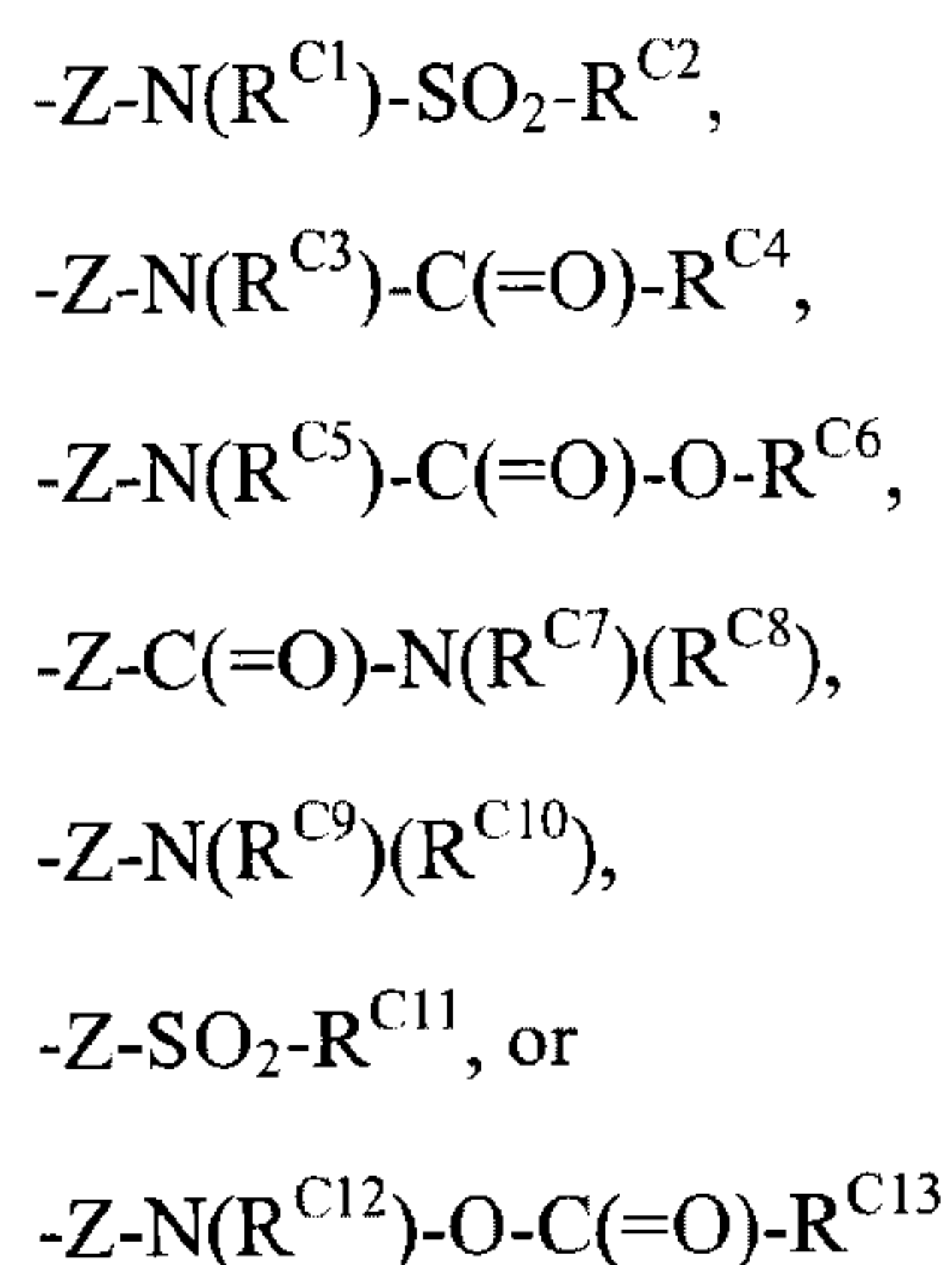
$R^{B7}$  and  $R^{B8}$ , and  $R^{B9}$  and  $R^{B10}$  may be taken together with an adjacent atom to form heterocycle and

Z is a single bond or straight or branched lower alkylene);

[0012]

$R^{3a}$  is hydrogen, halogen, hydroxy, carboxy, cyano, formyl, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkenyloxy optionally

substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C, carbocycleoxy optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxy optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,



(wherein  $R^{C1}$ ,  $R^{C3}$ ,  $R^{C4}$ ,  $R^{C5}$ ,  $R^{C6}$ ,  $R^{C7}$ ,  $R^{C8}$ ,  $R^{C9}$ ,  $R^{C10}$ ,  $R^{C12}$ , and  $R^{C13}$  are each independently selected from a substituent group consisting of hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally

substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{C2}$  and  $R^{C11}$  are each independently selected from a substituent group consisting of lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{C7}$  and  $R^{C8}$ , and  $R^{C9}$  and  $R^{C10}$  each may be taken together with an adjacent atom to form heterocycle, and

Z is a single bond or straight or branched lower alkylene) and;

[0013]

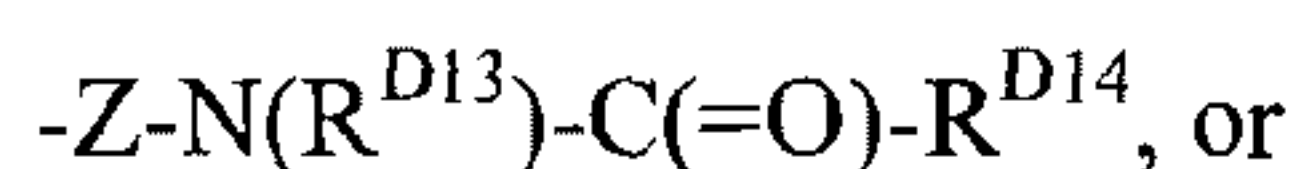
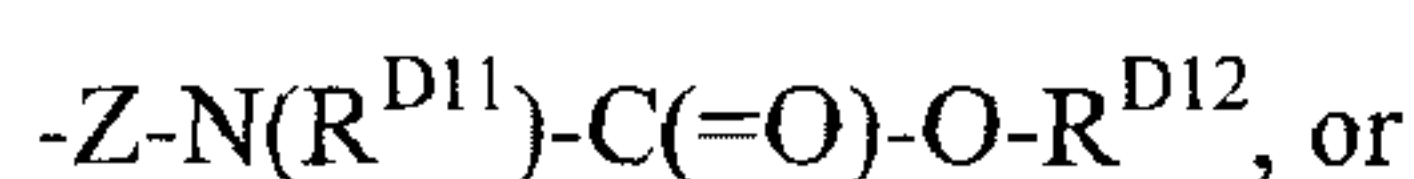
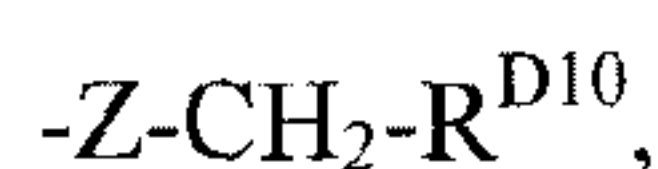
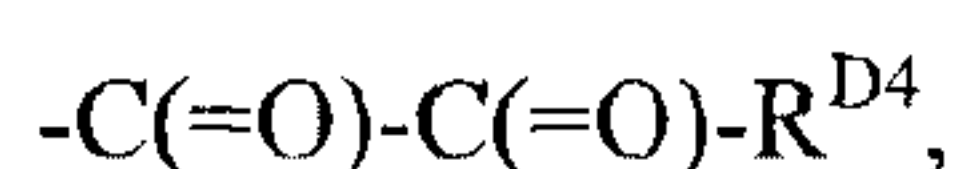
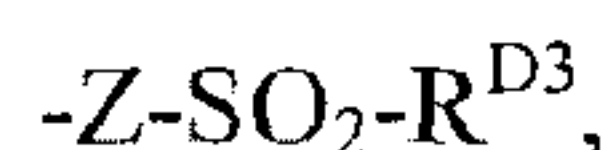
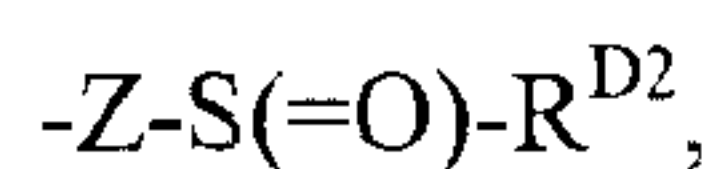
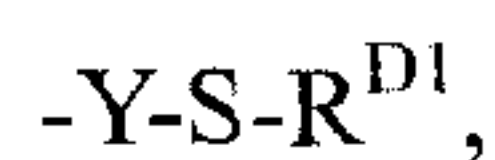
a) either  $B^1$  or  $B^2$  is  $CR^{5a}R^{6a}$ , and the other is  $NR^{7a}$ , or

b)  $B^1$  is  $CR^{8a}R^{9a}$ , and  $B^2$  is  $CR^{10a}R^{11a}$ ,

[0014]

$R^{5a}$ ,  $R^{6a}$ ,  $R^{7a}$ ,  $R^{8a}$ ,  $R^{9a}$ ,  $R^{10a}$ , and  $R^{11a}$  are each independently selected from a substituent group consisting of hydrogen, carboxy, cyano, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyl carbonyl optionally substituted by substituent group C, lower alkyl oxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C,

carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,



$R^{5a}$  and  $R^{6a}$  may be taken together to form heterocyclic group optionally substituted by substituent group C

(wherein  $R^{D1}$ ,  $R^{D4}$ ,  $R^{D5}$ ,  $R^{D6}$ ,  $R^{D9}$ ,  $R^{D11}$ ,  $R^{D12}$ ,  $R^{D13}$ , and  $R^{D14}$  are each independently selected from a substituent group consisting of hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{D2}$  and  $R^{D3}$  are each independently selected from a substituent group

consisting of lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{D7}$ ,  $R^{D8}$ , and  $R^{D10}$  are each independently carbocyclic group optionally substituted by substituent group C, or heterocyclic group optionally substituted by substituent group C,

$R^{D5}$  and  $R^{D6}$  may be taken together with an adjacent atom to form heterocycle,

Y is straight or branched lower alkylene, and

Z is a single bond or straight or branched lower alkylene), and

$R^{D5}$  and  $R^{D6}$  may be taken together with an adjacent atom to form carbocycle;

[0015]

1) when  $B^1$  is  $CR^{5a}R^{6a}$  and  $B^2$  is  $NR^{7a}$ ,

$R^{3a}$  and  $R^{7a}$  may be taken together with an adjacent atom to form heterocycle optionally substituted by substituent group D,

2) when  $B^1$  is  $NR^{7a}$  and  $B^2$  is  $CR^{5a}R^{6a}$ ,

$R^{3a}$  and  $R^{6a}$  may be taken together with an adjacent atom to form heterocycle optionally substituted by substituent group D, or

3) when  $B^1$  is  $CR^{8a}R^{9a}$ , and  $B^2$  is  $CR^{10a}R^{11a}$ ,

$R^{8a}$  and  $R^{10a}$  may be taken together with an adjacent atom to form carbocycle or heterocycle optionally substituted by substituent group D, or

$R^{3a}$  and  $R^{11a}$  may be taken together with an adjacent atom to form heterocycle optionally substituted by substituent group D;

[0016]

wherein

when  $B^1$  is  $CR^{8a}R^{9a}$ , and  $B^2$  is  $CR^{10a}R^{11a}$ , and  $R^{9a}$  is hydrogen, and  $R^{11a}$  is hydrogen,

i) either  $R^{8a}$  or  $R^{10a}$  is

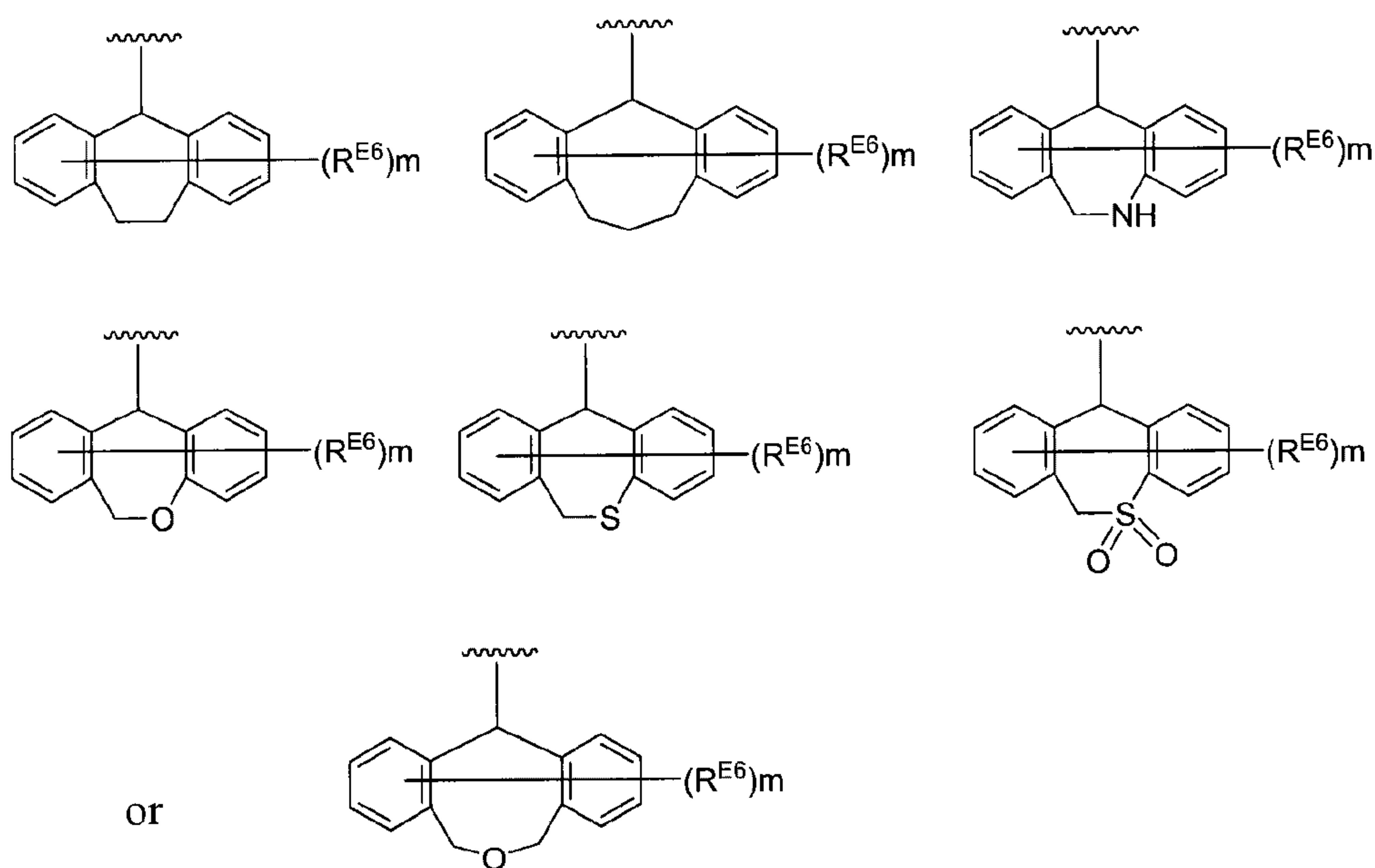
$-Z-C(R^{E1})(R^{E2})(R^{E3})$ ,

$-Y-S-R^{E4}$ ,

$-Z-CH_2-R^{E5}$ , or

a group shown below:

[Chemical formula 2]



(wherein  $R^{E1}$  and  $R^{E2}$  are each independently, selected from a substituent group consisting of carbocyclic group optionally substituted by substituent group C, and heterocyclic group optionally substituted by substituent group C,

$R^{E3}$  is selected from a substituent group consisting of hydrogen, lower alkyl

optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{E4}$  is selected from a substituent group consisting of carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{E5}$  is aromatic heterocyclic group optionally substituted by substituent group C,

$R^{E6}$  is selected from a substituent group C,

m is an integer of 0 or 1 or more, provided that

each  $R^{E6}$  is same or different groups selected from substituent group C,

Y is straight or branched lower alkylene, and

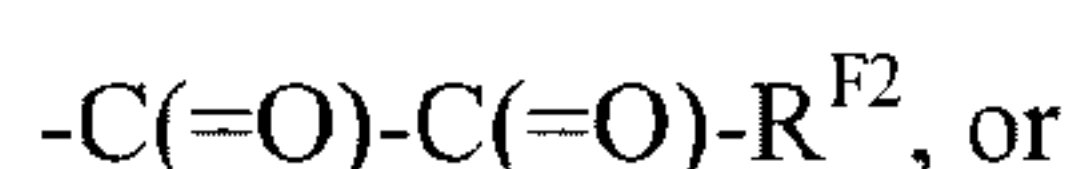
Z is a single bond or straight or branched lower alkylene); and

[0017]

ii) the other of  $R^{8a}$  or  $R^{10a}$  is

hydrogen, carboxy, cyano, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted

by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,



(wherein  $R^{F1}$ ,  $R^{F2}$ ,  $R^{F3}$ , and  $R^{F4}$  are each independently selected from a substituent group consisting of hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C, and

Y is straight or branched lower alkylene);

[0018]

with a proviso that the following c) and d) are excluded

c)  $R^{5a}$ ,  $R^{6a}$ , and  $R^{7a}$  are all hydrogens.

d)  $R^{8a}$ ,  $R^{9a}$ ,  $R^{10a}$ , and  $R^{11a}$  are all hydrogens.;

[0019]

Substituent group C: halogen, cyano, hydroxy, carboxy, formyl, amino, oxo, nitro, lower alkyl, lower alkenyl, lower alkynyl, halogeno lower alkyl, lower alkyloxy, lower alkynyloxy, lower alkylthio, hydroxy lower alkyl, carbocyclic group, heterocyclic

group, heterocyclic group substituted by oxo, carbocycle lower alkyloxy, carbocycleoxy lower alkyl, carbocycle lower alkyloxy lower alkyl, heterocycle lower alkyloxy, heterocycleoxy lower alkyl, heterocycle lower alkyloxy lower alkyl, halogeno lower alkyloxy, lower alkyloxy lower alkyl, lower alkyloxy lower alkyloxy, lower alkylcarbonyl, lower alkylcarbonyloxy, lower alkyloxycarbonyl, lower alkylamino, lower alkylcarbonylamino, halogeno lower alkyl carbonylamino, lower alkylaminocarbonyl, lower alkylsulfonyl, lower alkylsulfinyl, and lower alkylsulfonylamino;

[0020]

Substituent group D: halogen, cyano, hydroxy, carboxy, formyl, amino, oxo, nitro, lower alkyl, halogeno lower alkyl, lower alkyloxy, carbocycle lower alkyloxy, heterocycle lower alkyloxy, halogeno lower alkyloxy, lower alkyloxy lower alkyl, lower alkyloxy lower alkyloxy, lower alkylcarbonyl, lower alkyloxycarbonyl, lower alkylamino, lower alkylcarbonylamino, lower alkylaminocarbonyl, lower alkylsulfonyl, lower alkylsulfonylamino, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C).

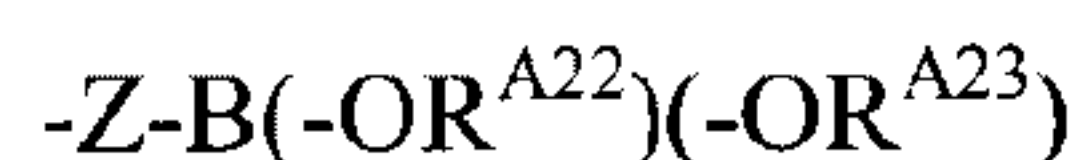
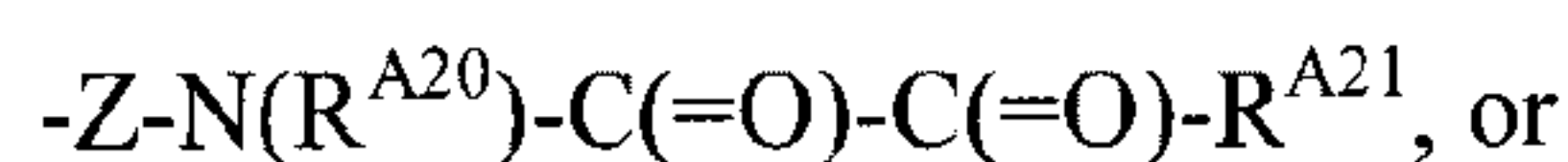
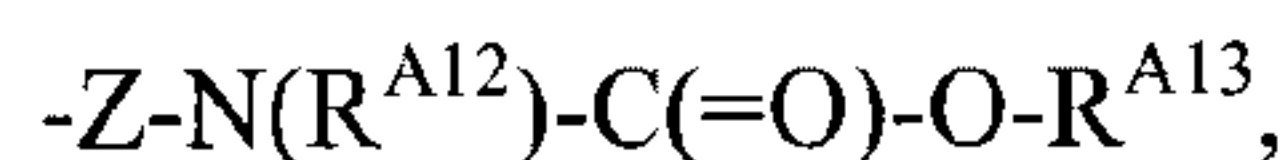
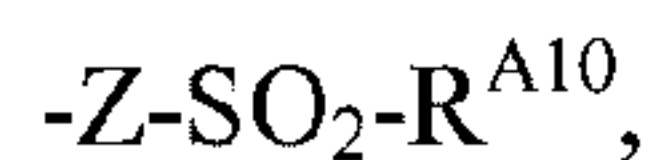
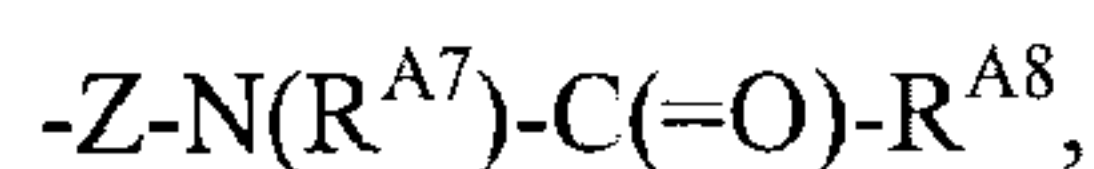
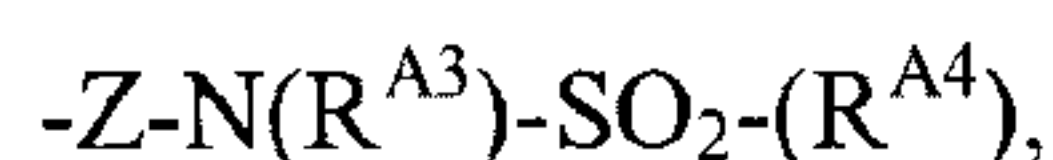
[0021]

(Item 2)

The compound according to item 1, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein R<sup>1a</sup> is hydrogen, halogen, hydroxy, carboxy, cyano, formyl, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C,

lower alkyloxy optionally substituted by substituent group C, lower alkenyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,



(substituent group C,  $R^{A1}$ ,  $R^{A2}$ ,  $R^{A3}$ ,  $R^{A4}$ ,  $R^{A7}$ ,  $R^{A8}$ ,  $R^{A9}$ ,  $R^{A10}$ ,  $R^{A12}$ ,  $R^{A13}$ ,  $R^{A20}$ ,  $R^{A21}$ ,  $R^{A22}$ ,  $R^{A23}$ , and Z are same as those of item 1).

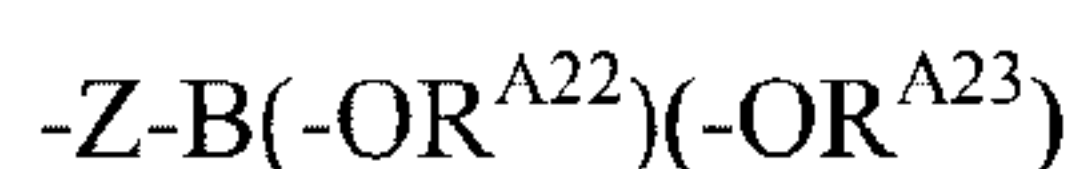
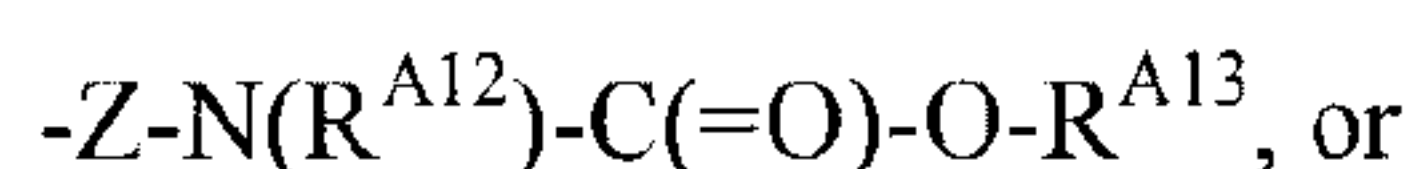
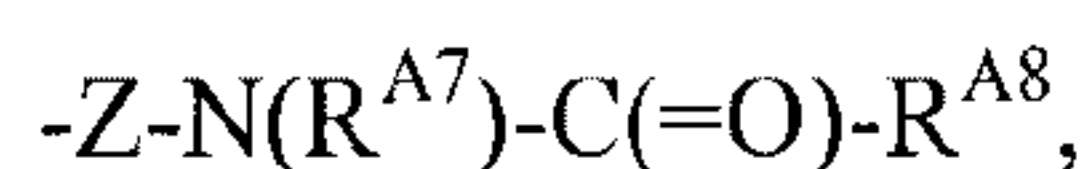
[0022]

(Item 3)

The compound according to item 1, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $R^{1a}$  is hydrogen, halogen, hydroxy, carboxy, lower alkyl optionally

substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C,



(substituent group C,  $R^{A1}$ ,  $R^{A2}$ ,  $R^{A7}$ ,  $R^{A8}$ ,  $R^{A12}$ ,  $R^{A13}$ ,  $R^{A22}$ ,  $R^{A23}$ , and Z are

same as those of item 1).

[0023]

(Item 4)

The compound according to item 1, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $R^{1a}$  is hydrogen, halogen, hydroxy, carboxy, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, or



(substituent group C,  $R^{A1}$ ,  $R^{A2}$ , and Z are same as those of item 1).

[0024]

(Item 5)

The compound according to item 1, or the pharmaceutically acceptable salt thereof or the solvate thereof, wherein  $R^{1a}$  is hydrogen, or carboxy.

[0025]

(Item 6)

The compound according to any one of items 1 to 5, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $R^{2a}$  is hydrogen, lower alkyl optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, or



(substituent group C,  $R^{B9}$ ,  $R^{B10}$ , and Z are same as those of item 1).

[0026]

(Item 7)

The compound according to any one of items 1 to 5, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $R^{2a}$  is hydrogen or lower alkyl optionally substituted by substituent group C

(substituent group C is same as that of item 1).

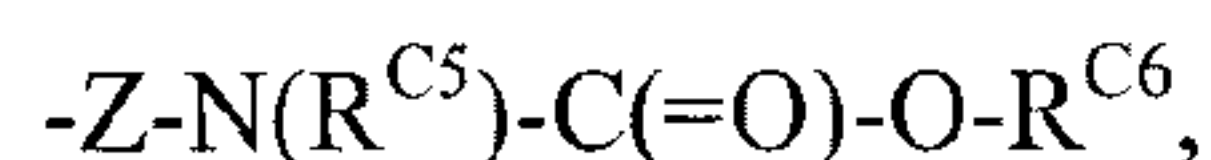
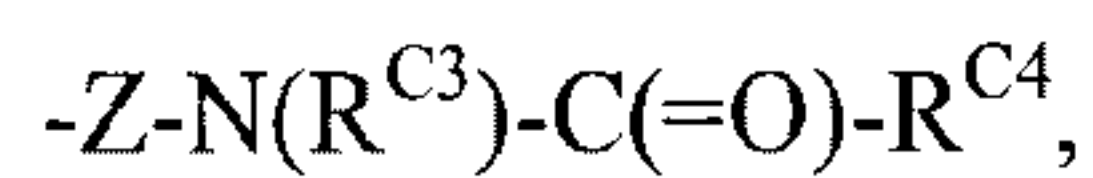
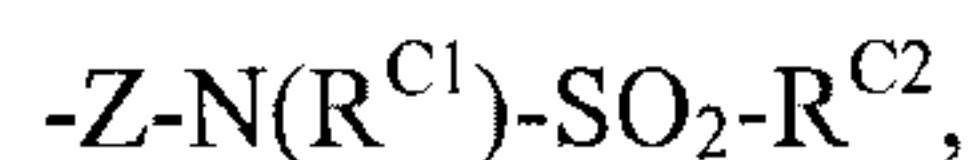
[0027]

(Item 8)

The compound according to any one of items 1 to 7, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $R^{3a}$  is hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted

by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C,



(substituent group C,  $R^{C1}$ ,  $R^{C2}$ ,  $R^{C3}$ ,  $R^{C4}$ ,  $R^{C5}$ ,  $R^{C6}$ ,  $R^{C7}$ ,  $R^{C8}$ ,  $R^{C9}$ ,  $R^{C10}$ , and Z

are same as those of item 1).

[0028]

(Item 9)

The compound according to any one of items 1 to 7, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $R^{3a}$  is hydrogen, lower alkyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C,

(substituent group C is same as that of item 1).

[0029]

(Item 10)

The compound according to any one of items 1 to 9, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $B^1$  is  $NR^{7a}$ , and  $B^2$  is  $CR^{5a}R^{6a}$ , and

$R^{5a}$ ,  $R^{6a}$  and  $R^{7a}$  are each independently hydrogen, carboxy, cyano, lower alkyl

optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyl carbonyl optionally substituted by substituent group C, lower alkyl oxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,

-Y-S-R<sup>D1</sup>,

-Z-S(=O)-R<sup>D2</sup>,

-Z-SO<sub>2</sub>-R<sup>D3</sup>,

-C(=O)-C(=O)-R<sup>D4</sup>,

-C(=O)-N(R<sup>D5</sup>)(R<sup>D6</sup>),

-Z-C(R<sup>D7</sup>)(R<sup>D8</sup>)(R<sup>D9</sup>),

-Z-N(R<sup>D11</sup>)-C(=O)-O-R<sup>D12</sup>, or

-Z-N(R<sup>D13</sup>)-C(=O)-R<sup>D14</sup>

(substituent group C, R<sup>D1</sup>, R<sup>D2</sup>, R<sup>D3</sup>, R<sup>D4</sup>, R<sup>D5</sup>, R<sup>D6</sup>, R<sup>D7</sup>, R<sup>D8</sup>, R<sup>D9</sup>, R<sup>D11</sup>, R<sup>D12</sup>,

R<sup>D13</sup>, R<sup>D14</sup>, Y, and Z are same as those of item 1).

[0030]

(Item 11)

The compound according to any one of items 1 to 9, or the pharmaceutically

acceptable salt thereof or the solvate thereof,

wherein  $B^1$  is  $NR^{7a}$ , and  $B^2$  is  $CR^{5a}R^{6a}$ ,

$R^{5a}$  is hydrogen,

$R^{6a}$  is hydrogen, or lower alkyl optionally substituted by substituent group C,

and

$R^{7a}$  is lower alkyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, or

$-Z-C(R^{D7})(R^{D8})(R^{D9})$

(substituent group C,  $R^{D7}$ ,  $R^{D8}$ ,  $R^{D9}$ , and Z are same as those of item 1).

[0031]

(Item 12)

The compound according to any one of items 1 to 9, or the pharmaceutically acceptable salt thereof or the solvate thereof,

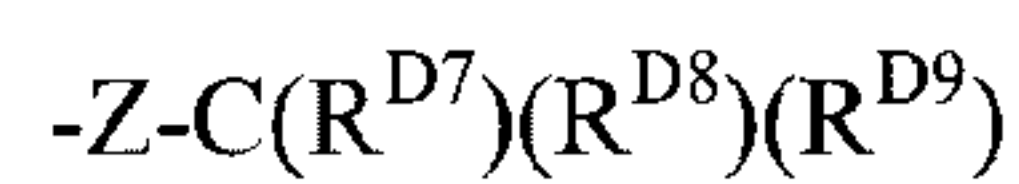
wherein  $B^1$  is  $CR^{5a}R^{6a}$ , and  $B^2$  is  $NR^{7a}$ ,

$R^{5a}$  is hydrogen,

$R^{6a}$  is hydrogen, or lower alkyl optionally substituted by substituent group C,

and

$R^{7a}$  is lower alkyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, or



(substituent group C,  $R^{D7}$ ,  $R^{D8}$ ,  $R^{D9}$ , and Z are same as those of item 1).

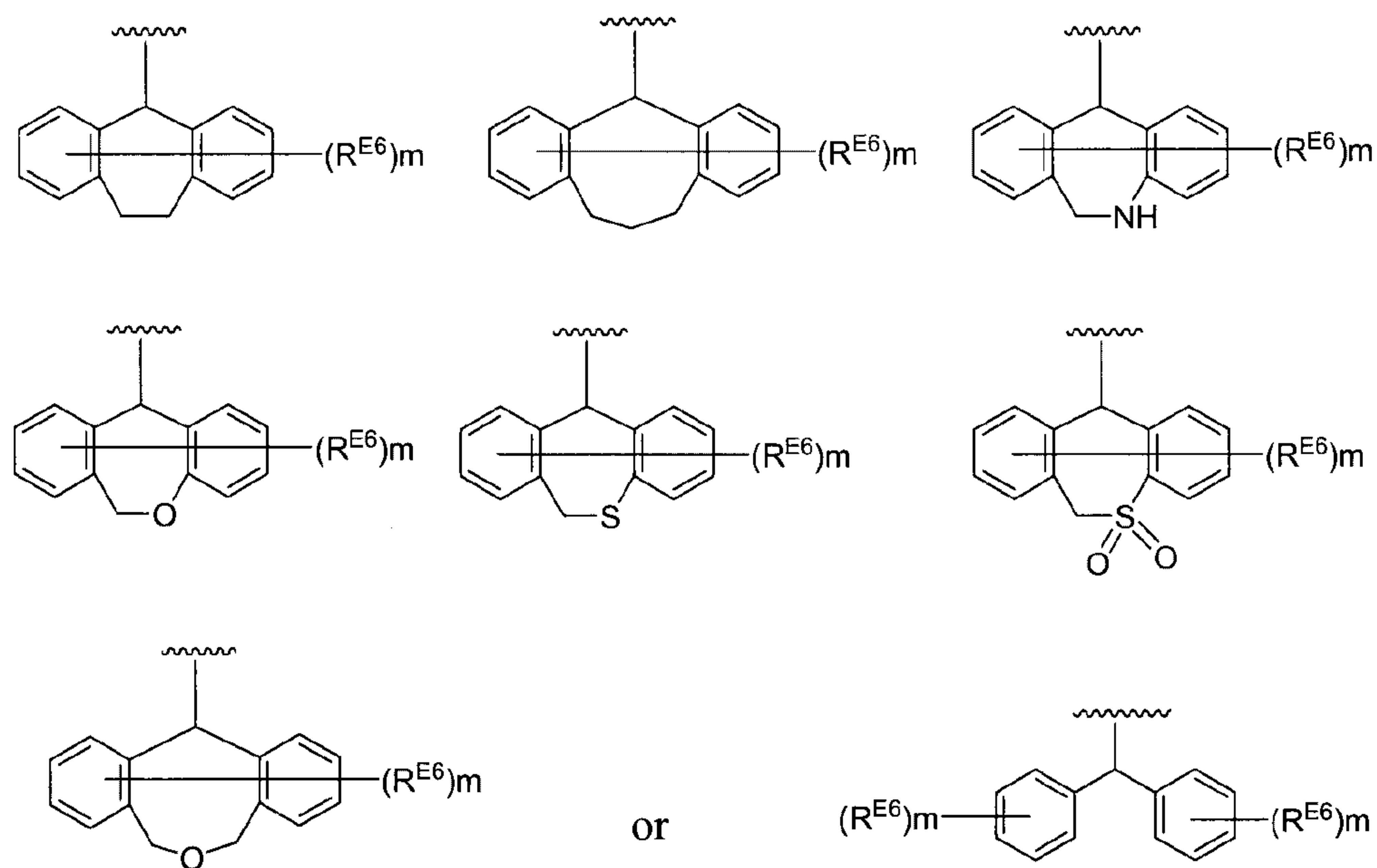
[0032]

(Item 13)

The compound according to items 11 or 12, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $R^{7a}$  is a group shown below:

[Chemical formula 3]



(wherein  $R^{E6}$  and m are same as those of item 1).

[0033]

(Item 14)

The compound according to item 1, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $R^{1a}$  is hydrogen, or carboxy,

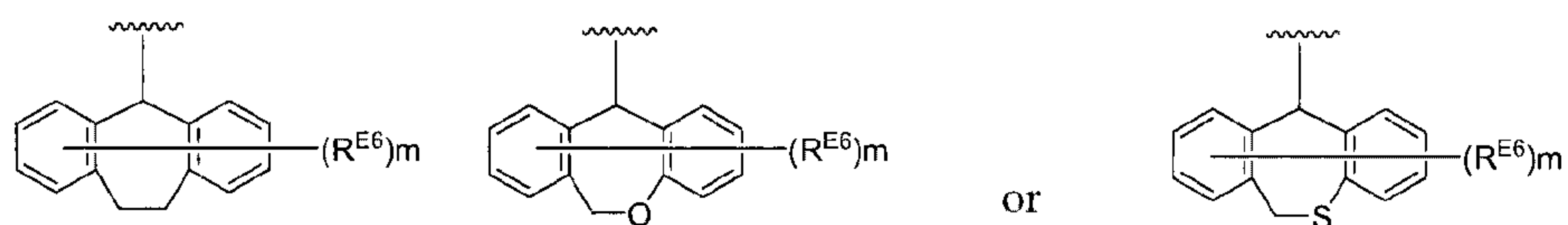
$R^{2a}$  is hydrogen,

$R^{3a}$  is lower alkyl optionally substituted by substituent group C,

$B^1$  is  $NR^{7a}$ , and  $B^2$  is  $CH_2$ , and

$R^{7a}$  is a group shown below:

[Chemical formula 4]



(wherein substituent group C,  $R^{E6}$ , and m are same as those of item 1).

[0034]

(Item 15)

The compound according to any one of items 1 to 9, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $B^1$  is  $CR^{8a}R^{9a}$ , and  $B^2$  is  $CR^{10a}R^{11a}$ ,

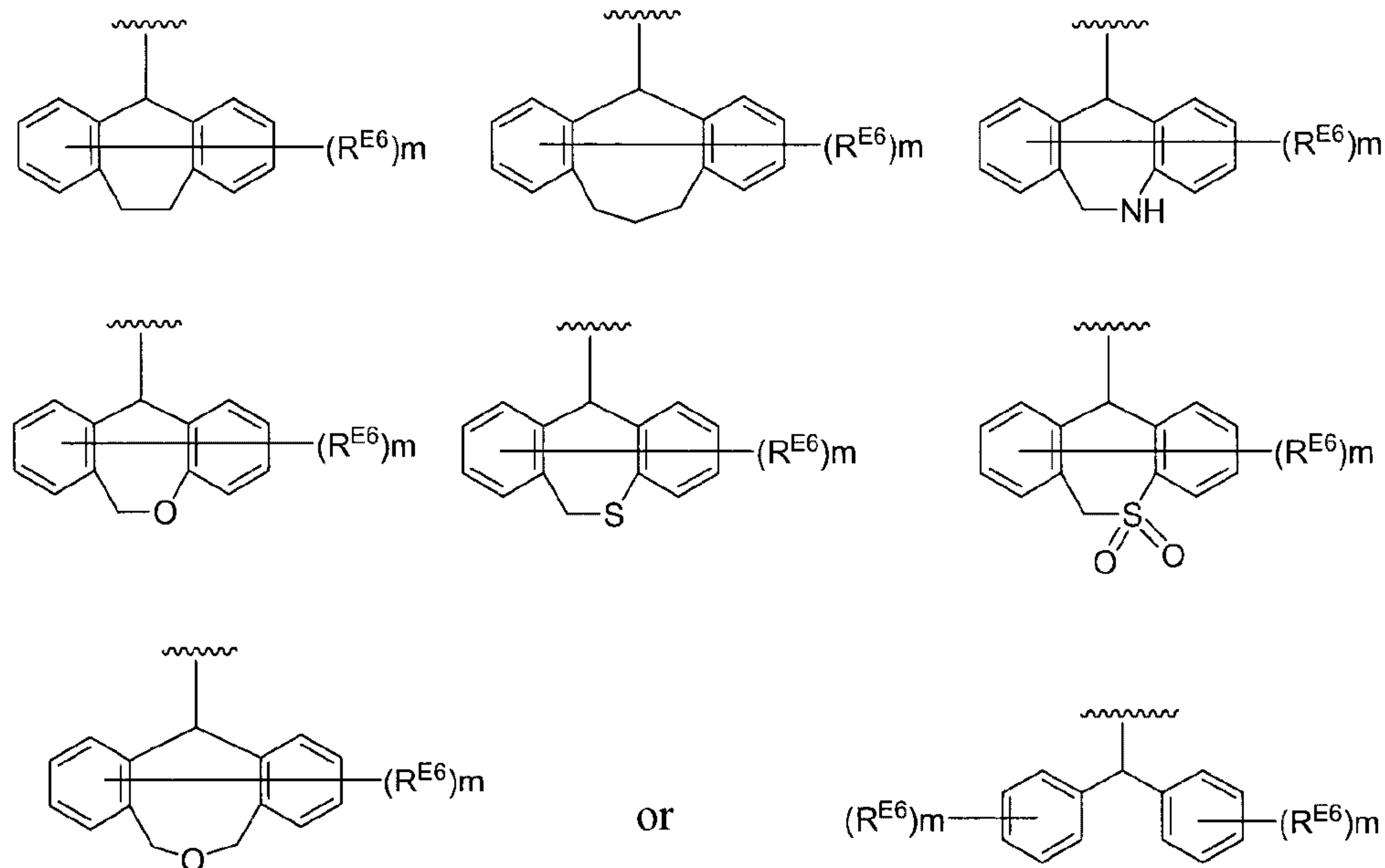
$R^{9a}$  is hydrogen, and  $R^{11a}$  is hydrogen, and

[0035]

i) either  $R^{8a}$  or  $R^{10a}$  is

a group shown below:

[Chemical formula 5]



(wherein  $R^{E6}$  and  $m$  are same as those of item 1); and

[0036]

ii) the other of  $R^{8a}$  or  $R^{10a}$  is

hydrogen, or lower alkyl optionally substituted by substituent group C

(substituent group C is same as that of item 1).

[0037]

(Item 16)

The compound according to any one of items 1 to 7, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $B^1$  is  $CR^{5a}R^{6a}$ , and  $B^2$  is  $NR^{7a}$ ,

$R^{6a}$  is hydrogen,

$R^{3a}$  and  $R^{7a}$  are taken together with an adjacent atom to form heterocycle

optionally substituted by substituent group D, and

$R^{5a}$  is hydrogen, lower alkyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C,

$-Y-S-R^{D1}$ ,

$-C(=O)-C(=O)-R^{D2}$ , or

$-C(=O)-N(R^{D3})(R^{D4})$

(wherein  $R^{D1}$ ,  $R^{D2}$ ,  $R^{D3}$ ,  $R^{D4}$ , Y, substituent group C and substituent group D are same as those of item 1).

[0038]

(Item 17)

The compound according to item 16, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $R^{5a}$  is hydrogen, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, or heterocycle lower alkyl optionally substituted by substituent group C

(wherein substituent group C is same as that of item 1).

[0039]

(Item 18)

The compound according to any one of items 1 to 7, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $B^1$  is  $CR^{8a}R^{9a}$ , and  $B^2$  is  $CR^{10a}R^{11a}$ ,

$R^{9a}$  is hydrogen, and  $R^{10a}$  is hydrogen,

$R^{3a}$  and  $R^{11a}$  are taken together with an adjacent atom to form heterocycle optionally substituted by substituent group D, and

$R^{8a}$  is hydrogen, lower alkyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C,

$-Y-S-R^{D1}$ ,

$-C(=O)-C(=O)-R^{D2}$ , or

$-C(=O)-N(R^{D3})(R^{D4})$

(wherein  $R^{D1}$ ,  $R^{D2}$ ,  $R^{D3}$ ,  $R^{D4}$ , Y, substituent group C and substituent group D are same as those of item 1).

[0040]

(Item 19)

The compound according to item 18, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $R^{8a}$  is hydrogen, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, or heterocycle lower alkyl optionally substituted by substituent group C

(wherein substituent group C is same as that of item 1).

[0041]

(Item 20)

The compound according to any one of items 16 to 19, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein substituent group D is carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, or heterocycle lower alkyl optionally substituted by substituent group C

(wherein substituent group C is same as that of item 1).

[0042]

(Item 21)

The compound according to any one of items 1 to 20, or the pharmaceutically acceptable salt thereof or the solvate thereof,

wherein  $P^R$  is a group selected from the following formulae a) to y):

- a)  $-C(=O)-P^{R0}$ ,
- b)  $-C(=O)-P^{R1}$ ,
- c)  $-C(=O)-L-P^{R1}$ ,
- d)  $-C(=O)-L-O-P^{R1}$ ,
- e)  $-C(=O)-L-O-L-O-P^{R1}$ ,
- f)  $-C(=O)-L-O-C(=O)-P^{R1}$ ,
- g)  $-C(=O)-O-P^{R2}$ ,
- h)  $-C(=O)-N(P^{R2})_2$ ,
- i)  $-C(=O)-O-L-O-P^{R2}$ ,
- j)  $-CH_2-O-P^{R3}$ ,
- k)  $-CH_2-O-L-O-P^{R3}$ ,
- l)  $-CH_2-O-C(=O)-P^{R3}$ ,
- m)  $-CH_2-O-C(=O)-O-P^{R3}$ ,

- n)  $-\text{CH}(-\text{CH}_3)-\text{O}-\text{C}(=\text{O})-\text{O}-\text{P}^{\text{R}3}$ ,
- o)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{P}^{\text{R}3}$ ,
- p)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- q)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{N}(\text{P}^{\text{R}3})_2$ ,
- r)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- s)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{L}-\text{N}(\text{P}^{\text{R}3})_2$ ,
- t)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- u)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{N}(-\text{K})-\text{C}(=\text{O})-\text{P}^{\text{R}3}$ ,
- v)  $-\text{CH}_2-\text{O}-\text{P}(=\text{O})(-\text{OH})_2$ ,
- w)  $-\text{CH}_2-\text{O}-\text{P}(=\text{O})(-\text{OBn})_2$ ,
- x)  $-\text{CH}_2-\text{P}^{\text{R}4}$  (except for a benzyl group)
- y)  $-\text{C}(=\text{N}^+\text{P}^{\text{R}5}_2)(-\text{NP}^{\text{R}5}_2)$

(wherein L is straight or branched lower alkylene, or straight or branched lower alkenylene,

K is hydrogen, or straight or branched lower alkylene,

$\text{P}^{\text{R}0}$  is lower alkyl optionally substituted by substituent group F, or lower alkenyl optionally substituted by substituent group F,

$\text{P}^{\text{R}1}$  is carbocyclic group optionally substituted by substituent group F, heterocyclic group optionally substituted by substituent group F, lower alkyl amino optionally substituted by substituent group F, or lower alkylthio optionally substituted by substituent group F,

$\text{P}^{\text{R}2}$  is lower alkyl optionally substituted by substituent group F, carbocyclic group optionally substituted by substituent group F, or heterocyclic group optionally substituted by substituent group F,

$\text{P}^{\text{R}3}$  is lower alkyl optionally substituted by substituent group F, carbocyclic

group optionally substituted by substituent group F, heterocyclic group optionally substituted by substituent group F, lower alkyl amino optionally substituted by substituent group F, carbocycle lower alkyl optionally substituted by substituent group F, heterocycle lower alkyl optionally substituted by substituent group F, or lower alkylsilyl,

$P^{R4}$  is carbocyclic group optionally substituted by substituent group F, or heterocyclic group optionally substituted by substituent group F, and

$P^{R5}$  is lower alkyl optionally substituted by substituent group F.

Substituent group F; oxo, lower alkyl, hydroxy lower alkyl, amino, lower alkylamino, carbocycle lower alkyl, lower alkylcarbonyl, halogen, hydroxy, carboxy, lower alkylcarbonylamino, lower alkylcarbonyloxy, lower alkyloxycarbonyl, lower alkyloxy, cyano, and nitro).

[0043]

(Item 22)

A pharmaceutical composition containing a compound according to any one of items 1 to 21, or a pharmaceutically acceptable salt thereof or a solvate thereof.

[0044]

(Item 23)

The pharmaceutical composition according to item 22 which exhibits anti influenza activity.

[0045]

(Item 24)

The pharmaceutical composition according to item 22 which exhibits cap-dependent endonuclease inhibitory activity.

[0046]

(Item 25)

The pharmaceutical composition according to item 22 for treating and/or preventing influenza infectious disease.

[0047]

(Item 26)

A cap-dependent endonuclease inhibitor containing a compound according to any one of items 1 to 21, or a pharmaceutically acceptable salt thereof or a solvate thereof.

[0048]

The present invention further provides a method for treating or preventing influenza infectious disease using the prodrug compound and the compound which exhibits anti influenza activity. The present invention further provides a parent compound of the prodrug compound. The parent compound is effective as an anti-influenza agent or an intermediate of the prodrug compound.

[EFFECT OF THE INVENTION]

[0049]

The compound according to the present invention has an inhibitory activity on cap-dependent endonuclease. More preferred compound is a prodrug, and the prodrug becomes a parent compound having an inhibitory activity on cap-dependent endonuclease in vivo after administration, thus is effective as a therapeutic agent and/or preventive agent for influenza infectious disease.

[BRIEF DESCRIPTION OF DRAWINGS]

[0050]

[Figure 1] Figure 1 is a result of measuring changes in the plasma concentration of Reference example 301, for compound of Example 114 obtained by

converting into a prodrug compound of Reference example 301 that is a parent compound, after oral administration to rat under non-fasting conditions.

[0051]

[Figure 2] Figure 2 is a graph showing an average of the changes in the plasma concentration when the measurement shown in Figure 1 is performed three times.

[0052]

[Figure 3] Figure 3 is a result of measuring changes in the plasma concentration of Reference example 301, for compound of Example 204 obtained by converting into a prodrug compound of Reference example 301 that is a parent compound, after oral administration to rat under non-fasting conditions.

[0053]

[Figure 4] Figure 4 is a graph showing an average of the changes in the plasma concentration when the measurement shown in Figure 3 is performed three times.

[BEST MODE FOR CARRYING OUT THE INVENTION]

[0054]

The meaning of each term used in the present description is explained below. Each term is used in a unified sense, and is used in the same sense when used alone, or when used in combination of other term.

[0055]

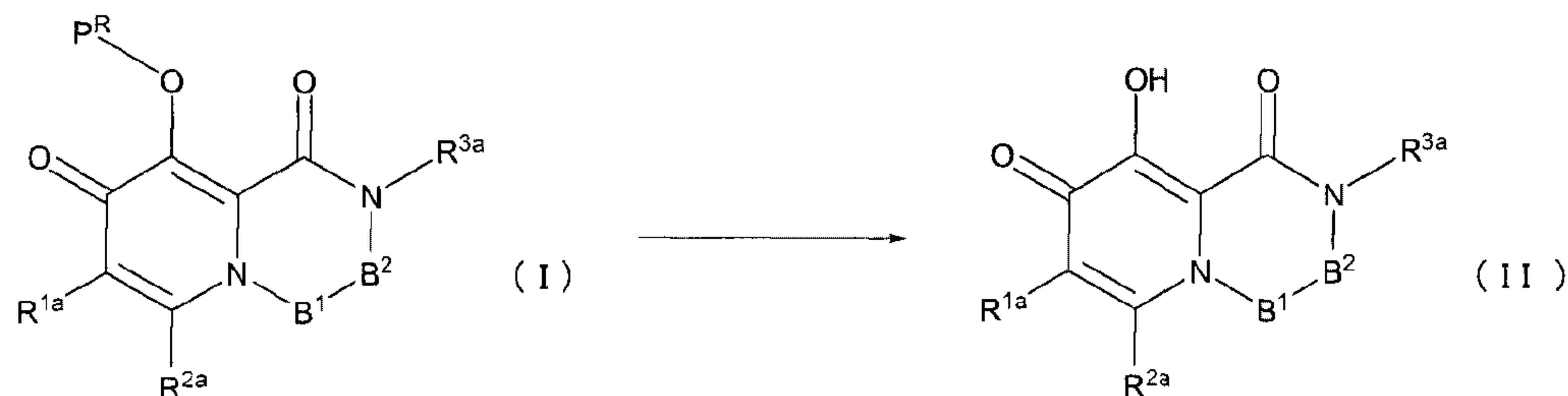
"Optionally substituted by substituent group C" means that an arbitrary position may be substituted by one, two or more same or different substituents selected from substituent group C.

"Optionally substituted by substituent group D", and "optionally substituted by substituent group F" are also as described above.

[0056]

"Prodrug" in the present description refers to a compound represented by formula (I) in the following reaction formula:

[Chemical formula 6]



[0057]

(wherein each symbol is same as that of item 1)

or a pharmaceutically acceptable salt thereof or a solvate thereof, and means a compound showing cap-dependant endonuclease (CEN) inhibitory activity and/or CPE inhibitory effect by being converted into a compound represented by formula (II) by a decomposition reaction caused by drug-metabolizing enzymes, hydrolases, gastric acids, enterobacteria, etc. under physiological conditions in vivo.

The prodrug more preferably means a compound in which bioavailability and/or AUC (area under the blood concentration curve) in in vivo administration is improved more than those of the compound represented by formula (II).

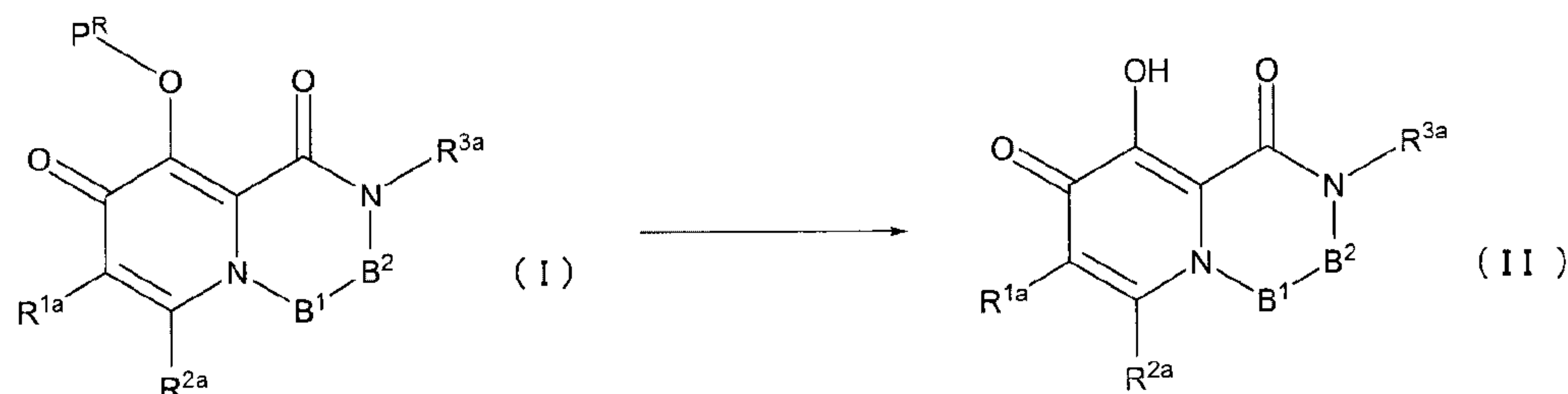
Therefore, the prodrug is efficiently absorbed into the body in the stomach and/or intestines after in vivo administration (for example, oral administration), then converted into the compound represented by formula (II). Thus, the prodrug preferably shows an effect of treating and/or preventing influenza higher than the compound represented by formula (II).

[0058]

"Group to form a prodrug" in the present description refers to a "P<sup>R</sup>" group in

the formula (I), in the following reaction formula:

[Chemical formula 7]



[0059]

(wherein each symbol is same as that of item 1)

and  $-\text{OP}^{\text{R}}$  group is converted into  $-\text{OH}$  group in the formula (II) by a decomposition reaction caused by drug-metabolizing enzymes, hydrolases, gastric acids, enterobacteria, etc. under physiological conditions in vivo. The "group to form a prodrug" more preferably means a group that improves bioavailability and/or AUC (area under the blood concentration curve) of the compound represented by formula (II) by being added to the compound represented by formula (II).

[0060]

Examples of the group to form a prodrug include the groups described in Prog. Med. 5: 2157-2161 (1985) and Supplied by The British Library - "The world's Knowledge".

The " $\text{P}^{\text{R}}$ " group in  $-\text{OP}^{\text{R}}$  group in the formula (I) may be a group converted into  $-\text{OH}$  group in vivo. Preferably the groups selected from various substituted carbonyl groups, substituted lower alkyl oxy groups (e.g., substituted oxymethyl), optionally substituted cyclic group lower alkyl (e.g., optionally substituted cyclic methyl group), and optionally substituted imino lower alkyl (e.g., optionally substituted imino methyl) are exemplified, and examples preferably include a group selected from the following formulae a) to y).

- a)  $-\text{C}(=\text{O})-\text{P}^{\text{R}0}$ ,
- b)  $-\text{C}(=\text{O})-\text{P}^{\text{R}1}$ ,
- c)  $-\text{C}(=\text{O})-\text{L}-\text{P}^{\text{R}1}$ ,
- d)  $-\text{C}(=\text{O})-\text{L}-\text{O}-\text{P}^{\text{R}1}$ ,
- e)  $-\text{C}(=\text{O})-\text{L}-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}1}$ ,
- f)  $-\text{C}(=\text{O})-\text{L}-\text{O}-\text{C}(=\text{O})-\text{P}^{\text{R}1}$ ,
- g)  $-\text{C}(=\text{O})-\text{O}-\text{P}^{\text{R}2}$ ,
- h)  $-\text{C}(=\text{O})-\text{N}(\text{P}^{\text{R}2})_2$ ,
- i)  $-\text{C}(=\text{O})-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}2}$ ,
- j)  $-\text{CH}_2-\text{O}-\text{P}^{\text{R}3}$ ,
- k)  $-\text{CH}_2-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- l)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{P}^{\text{R}3}$ ,
- m)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{P}^{\text{R}3}$ ,
- n)  $-\text{CH}(-\text{CH}_3)-\text{O}-\text{C}(=\text{O})-\text{O}-\text{P}^{\text{R}3}$ ,
- o)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{P}^{\text{R}3}$ ,
- p)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- q)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{N}(\text{P}^{\text{R}3})_2$ ,
- r)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- s)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{L}-\text{N}(\text{P}^{\text{R}3})_2$ ,
- t)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- u)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{N}(-\text{K})-\text{C}(=\text{O})-\text{P}^{\text{R}3}$ ,
- v)  $-\text{CH}_2-\text{O}-\text{P}(=\text{O})(-\text{OH})_2$ ,
- w)  $-\text{CH}_2-\text{O}-\text{P}(=\text{O})(-\text{OBn})_2$ ,
- x)  $-\text{CH}_2-\text{P}^{\text{R}4}$
- y)  $-\text{C}(=\text{N}^+\text{P}^{\text{R}5}_2)(-\text{NP}^{\text{R}5}_2)$

(wherein L is straight or branched lower alkylene,

K is hydrogen, or straight or branched lower alkylene, or straight or branched lower alkenylene,

$P^{R0}$  is lower alkyl optionally substituted by substituent group F, or lower alkenyl optionally substituted by substituent group F,

$P^{R1}$  is carbocyclic group optionally substituted by substituent group F, heterocyclic group optionally substituted by substituent group F, lower alkyl amino optionally substituted by substituent group F, or lower alkylthio optionally substituted by substituent group F,

$P^{R2}$  is lower alkyl optionally substituted by substituent group F, carbocyclic group optionally substituted by substituent group F, or heterocyclic group optionally substituted by substituent group F,

$P^{R3}$  is lower alkyl optionally substituted by substituent group F, carbocyclic group optionally substituted by substituent group F, heterocyclic group optionally substituted by substituent group F, lower alkyl amino optionally substituted by substituent group F, carbocycle lower alkyl optionally substituted by substituent group F, heterocycle lower alkyl optionally substituted by substituent group F, or lower alkylsilyl,

$P^{R4}$  is carbocyclic group optionally substituted by substituent group F, or heterocyclic group optionally substituted by substituent group F, and

$P^{R5}$  is lower alkyl optionally substituted by substituent group F.

Substituent group F; oxo, lower alkyl, hydroxy lower alkyl, amino, lower alkylamino, carbocycle lower alkyl, lower alkylcarbonyl, halogen, hydroxy, carboxy, lower alkylcarbonylamino, lower alkylcarbonyloxy, lower alkyloxycarbonyl, lower alkyloxy, cyano, and nitro)

[0061]

As the group to form a prodrug, the "P<sup>R</sup>" group in -OP<sup>R</sup> group in the formula (I) is preferably a group selected from the following b), k), l), and m).

b) -C(=O)-P<sup>R1</sup>,

l) -CH<sub>2</sub>-O-C(=O)-P<sup>R3</sup>,

m) -CH<sub>2</sub>-O-C(=O)-O-P<sup>R3</sup>,

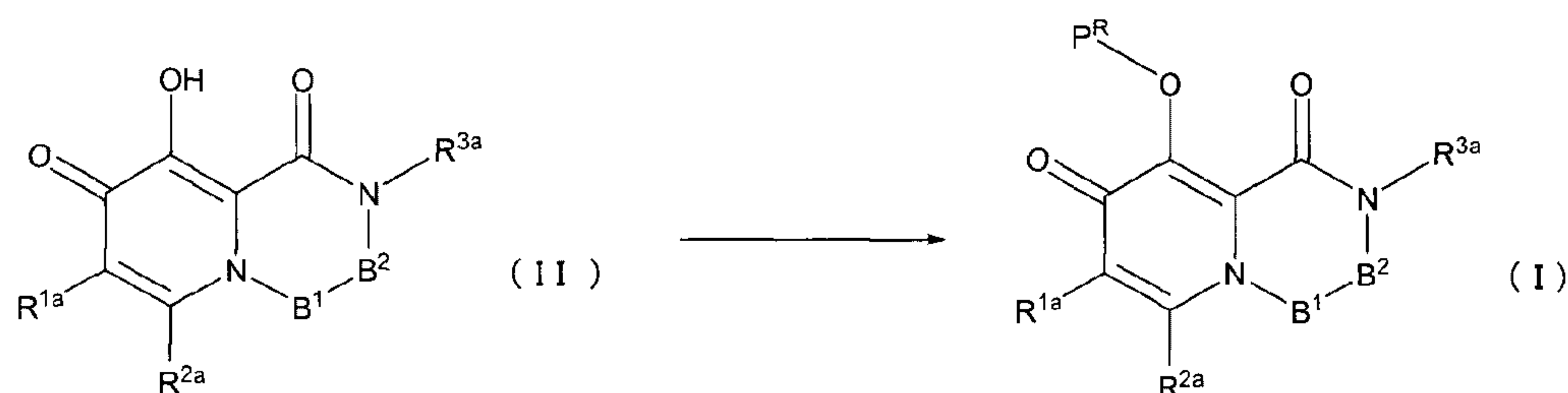
n) -CH(-CH<sub>3</sub>)-O-C(=O)-O-P<sup>R3</sup>,

(wherein each symbol is same as above)

[0062]

"Converted into a prodrug" in the present description means that, as shown in the following reaction formula:

[Chemical formula 8]



[0063]

(wherein each symbol is same as that of item 1)

a hydroxy group in the formula (II) or pharmaceutically acceptable salt thereof or a solvate thereof is converted into -OP<sup>R</sup> group.

[0064]

"Parent compound" in the present description means a compound to be a source before synthesizing the "prodrug" and/or a compound released from the "prodrug" by the reaction by enzymes, a gastric acid, and the like under physiological conditions in vivo, and specifically means a compound shown by the formula (II), or

pharmaceutically acceptable salt thereof or a solvate thereof.

[0065]

"Halogen" includes fluorine, chlorine, bromine and iodine. Preferable is fluorine, chlorine and bromine.

"Lower alkyl" includes straight or branched alkyl of a carbon number of 1 to 15, preferably a carbon number of 1 to 10, more preferably a carbon number of 1 to 6, further preferably a carbon number of 1 to 4, and examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, isohexyl, n-heptyl, isoheptyl, n-octyl, isooctyl, n-nonyl and n-decyl etc. Examples of a preferable embodiment of "lower alkyl" include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and n-pentyl. Examples of a further preferable embodiment include methyl, ethyl, n-propyl, isopropyl, and tert-butyl.

"Lower alkenyl" includes straight or branched alkenyl of a carbon number of 2 to 15, preferably a carbon number of 2 to 10, more preferably a carbon number of 2 to 6, further preferably a carbon number of 2 to 4, having one or more double bonds at an arbitrary position. Specifically, lower alkenyl includes vinyl, allyl, propenyl, isopropenyl, butenyl, isobutenyl, prenyl, butadienyl, pentenyl, isopentenyl, pentadienyl, hexenyl, isohexenyl, hexadienyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, pentadecenyl etc. Examples of a preferable embodiment of "lower alkenyl" include vinyl, allyl, propenyl, isopropenyl, and butenyl.

"Lower alkynyl" includes straight or branched alkynyl of a carbon number of 2 to 10, preferably a carbon number of 2 to 8, further preferably a carbon number of 3 to 6, having one or more triple bonds at an arbitrary position. Specifically, lower alkynyl includes ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl,

decynyl etc. These may further have a double bond at an arbitrary position.

Examples of a preferable embodiment of "lower alkynyl" include ethynyl, propynyl, butynyl, and pentynyl.

[0066]

A lower alkyl part of "lower alkyloxy", "lower alkylcarbonyl", "lower alkyloxycarbonyl", "carbocycle lower alkyl", "heterocycle lower alkyl", "carbocycleoxy lower alkyl", "heterocycleoxy lower alkyl", "halogeno lower alkyl", "carbocycle lower alkyloxy", "heterocycle lower alkyloxy", "halogeno lower alkyloxy", "lower alkyloxy lower alkyl", "lower alkyloxy lower alkyloxy", "lower alkylcarbonyl", "lower alkyloxycarbonyl", "lower alkylamino", "lower alkylcarbonylamino", "lower alkylaminocarbonyl", "lower alkylsulfonyl", "lower alkylsulfonylamino", "lower alkylthio", "hydroxy lower alkyl", "carbocycle lower alkyloxy lower alkyl", "heterocycle lower alkyloxy lower alkyl", "lower alkylcarbonyloxy", "halogeno lower alkylcarbonylamino", and "lower alkylsulfinyl" is the same as the "lower alkyl" as described above.

A lower alkenyl part of "lower alkenyloxy" is the same as the "lower alkenyl" as described above.

A halogen part of "halogeno lower alkyl", "halogeno lower alkyloxy", and "halogeno lower alkylcarbonylamino" is the same as the "halogen". Herein, an arbitrary position on an alkyl group of "lower alkyl", "lower alkyloxy", and "lower alkylcarbonylamino" may be substituted by same or different one or plural halogen atoms, respectively.

[0067]

"Carbocyclic group" or "carbocycle" means carbocyclic group of a carbon number of 3 to 20, preferably a carbon number of 3 to 16, more preferably a carbon

number of 4 to 12, and includes cycloalkyl, cycloalkenyl, aryl and a non-aromatic condensed carbocyclic group, etc.

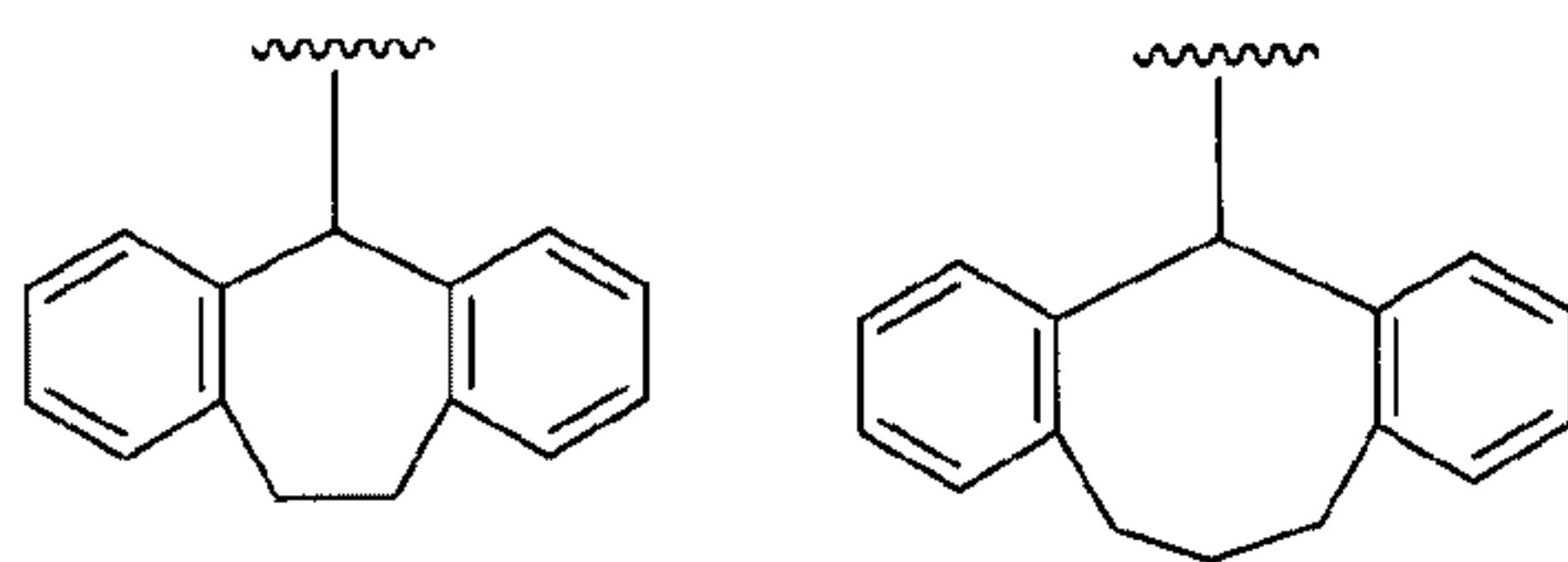
Specifically, "cycloalkyl" is carbocyclic group of a carbon number of 3 to 16, preferably a carbon number of 3 to 12, more preferably a carbon number of 4 to 8, and examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl, etc.

Specifically, "cycloalkenyl" includes cycloalkenyl having one or more double bonds at an arbitrary position in the cycloalkyl ring, and examples include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptynyl, cyclooctynyl and cyclohexadienyl, etc.

Specifically, "aryl" means an aromatic carbocyclic group, and includes phenyl, naphthyl, anthryl and phenanthryl, etc. and, particularly, phenyl is preferable.

Specifically, "non-aromatic condensed carbocyclic group" includes a group in which two or more cyclic groups selected from the "cycloalkyl", the "cycloalkenyl" and the "aryl" are condensed, and examples include indanyl, indenyl, tetrahydronaphthyl, fluorenyl, adamantyl, and groups shown below

[Chemical formula 9]



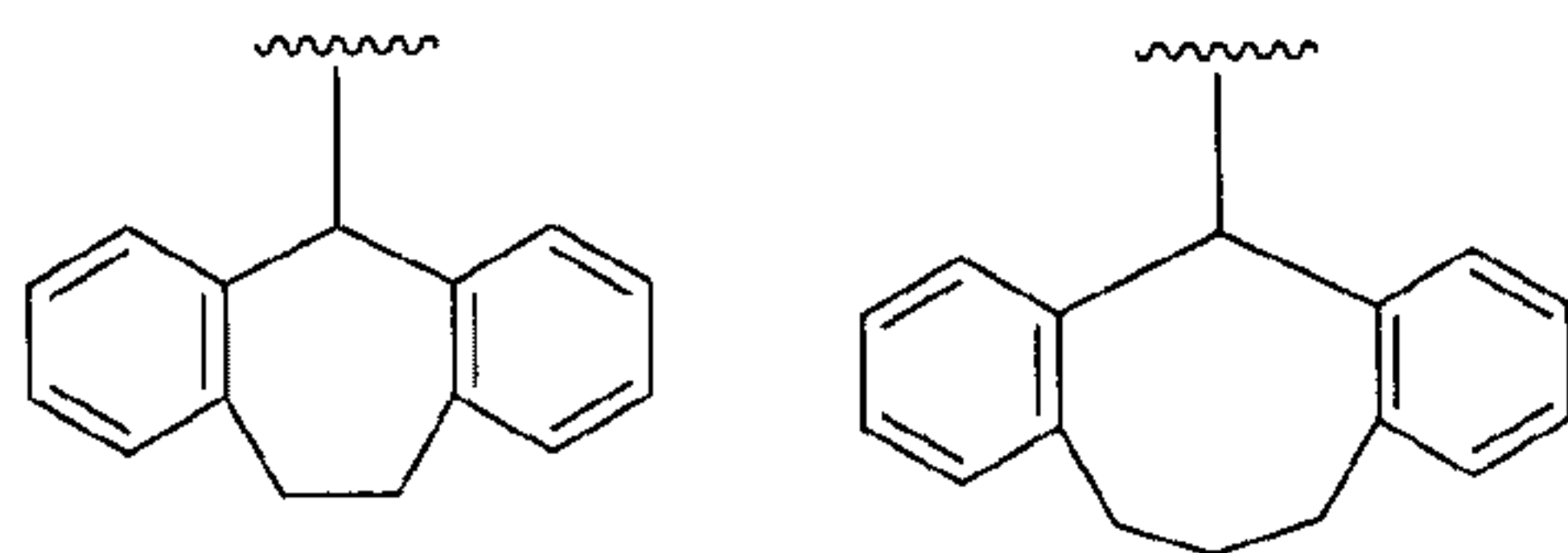
[0068]

etc.

Examples of a preferable embodiment of "carbocyclic group" or "carbocycle" include cycloalkyl, aryl and a non-aromatic condensed carbocyclic group, specifically

examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, naphthyl, and groups shown below

[Chemical formula 10]



[0069]

etc.

A carbocyclic part of "carbocycle lower alkyl", "carbocycle lower alkyloxy", "carbocycleoxy lower alkyl", "carbocyclecarbonyl", "carbocycleoxy", "carbocycleoxycarbonyl" and "carbocycle lower alkyloxy lower alkyl" is the same as the "carbocyclic group" or the "carbocycle" as described above.

[0070]

"Heterocyclic group" or "heterocycle" includes heterocyclic group such as heteroaryl, a non-aromatic heterocyclic group, a bicyclic condensed heterocyclic group, a tricyclic condensed heterocyclic group, a tetracyclic condensed heterocyclic group, etc., having one or more same or different hetero atoms arbitrarily selected from O, S and N in a ring.

Specifically, "heteroaryl" includes a 5- to 6-membered aromatic cyclic group such as pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazolyl, triazinyl, tetrazolyl, furyl, thienyl, isooxazolyl, oxazolyl, oxadiazolyl, isothiazolyl, thiazolyl, thiadiazolyl, etc.

Specifically, "non-aromatic heterocyclic group" includes a 4-to 8-membered non-aromatic heterocyclic group such as dioxanyl, thiiranyl, oxiranyl, oxetanyl,

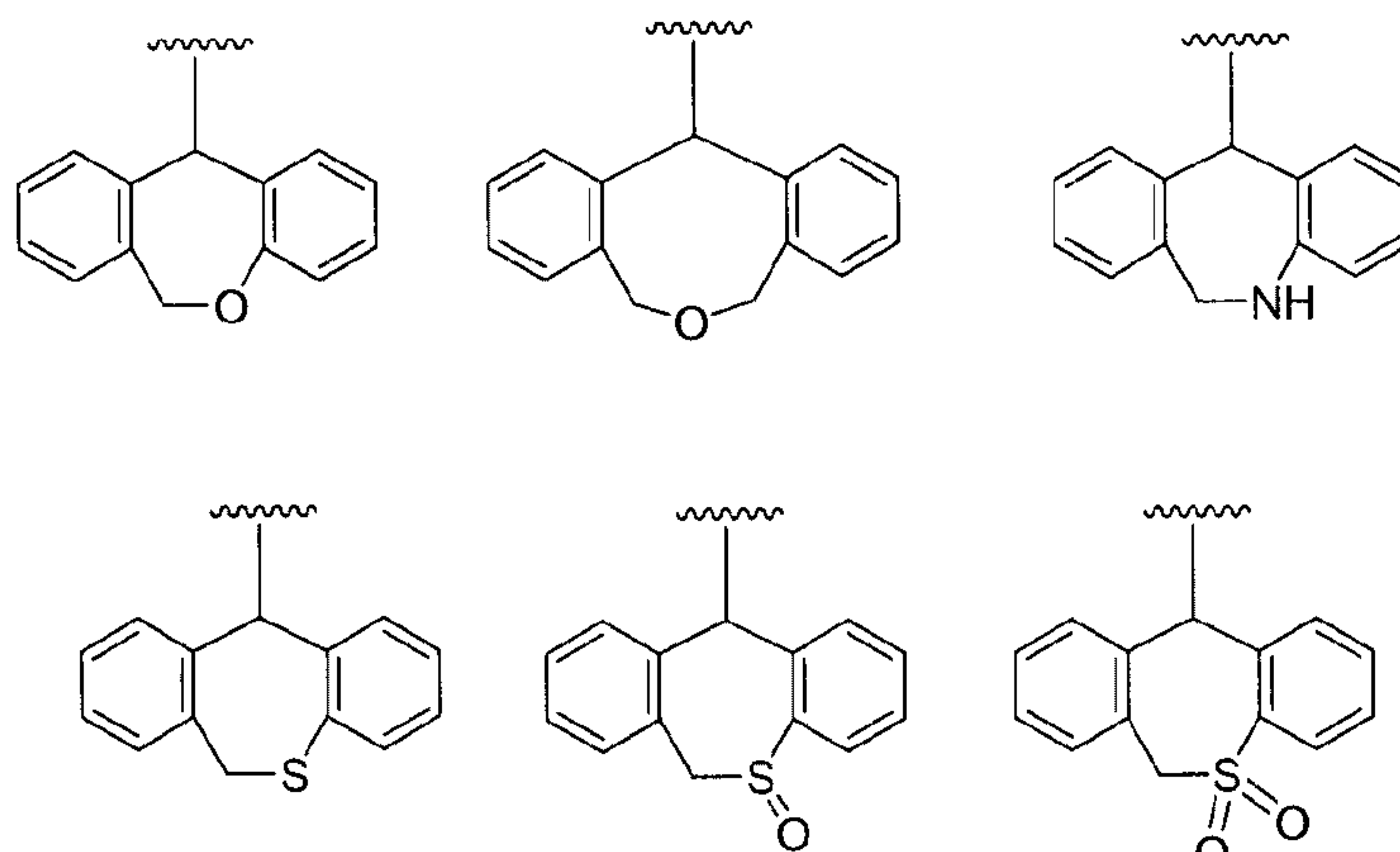
oxathiolanyl, azetidiny, thianyl, thiazolidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, dihydropyridyl, tetrahydropyridyl, tetrahydrofuryl, tetrahydropyranyl, dihydrothiazolyl, tetrahydrothiazolyl, tetrahydroisothiazolyl, dihydrooxazinyl, hexahydroazepinyl, tetrahydrodiazepinyl, tetrahydropyridazinyl, hexahydropyrimidinyl, dioxolanyl, dioxolyl, oxabicycloheptanyl, etc.

Specifically, "bicyclic condensed heterocyclic group" includes a cyclic group including at least one 4- to 8-membered aromatic or non-aromatic heterocyclic group such as indolyl, isoindolyl, indazolyl, indoliziny, indolinyl, isoindolinyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, naphthyridinyl, quinoxalinyl, purinyl, pteridinyl, benzopyranyl, benzimidazolyl, benzotriazolyl, benzisooxazolyl, benzoxazolyl, benzoxadiazolyl, benzisothiazolyl, benzothiazolyl, benzothiadiaazolyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, thienopyridyl, thienopyrrolyl, thienopyrazolyl, thienopyrazinyl, furopyrryl, thienothienyl, imidazopyridyl, pyrazolopyridyl, thiazolopyridyl, pyrazolopyrimidinyl, pyrazolotrianizyl, pyridazolopyridyl, triazolopyridyl, imidazothiazolyl, pyrazinopyridazinyl, quinazolinyl, quinolyl, isoquinolyl, naphthyridinyl, dihydrothiazolopyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, dihydrobenzofuryl, dihydrobenzoxazinyl, dihydrobenzimidazolyl, tetrahydrobenzothienyl, tetrahydrobenzofuryl, benzodioxolyl, benzodioxonyl, chromanyl, chromenyl, octahydrochromenyl, dihydrobenzodioxynyl, dihydrobenzooxeziny, dihydrobenzodioxepiny, dihydrothienodioxynyl, etc.

Specifically, "tricyclic condensed heterocyclic group" includes a cyclic group including at least one 4- to 8-membered aromatic or non-aromatic heterocyclic group such as carbazolyl, acridinyl, xanthenyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl,

dibenzofuryl, imidazoquinolyl, tetrahydrocarbazolyl, and groups shown below

[Chemical formula 11]



[0071]

etc.

Examples of a preferable embodiment of "heterocyclic group" include 5- to 6-membered heteroaryl, a non-aromatic heterocyclic group and a tricyclic condensed heterocyclic group.

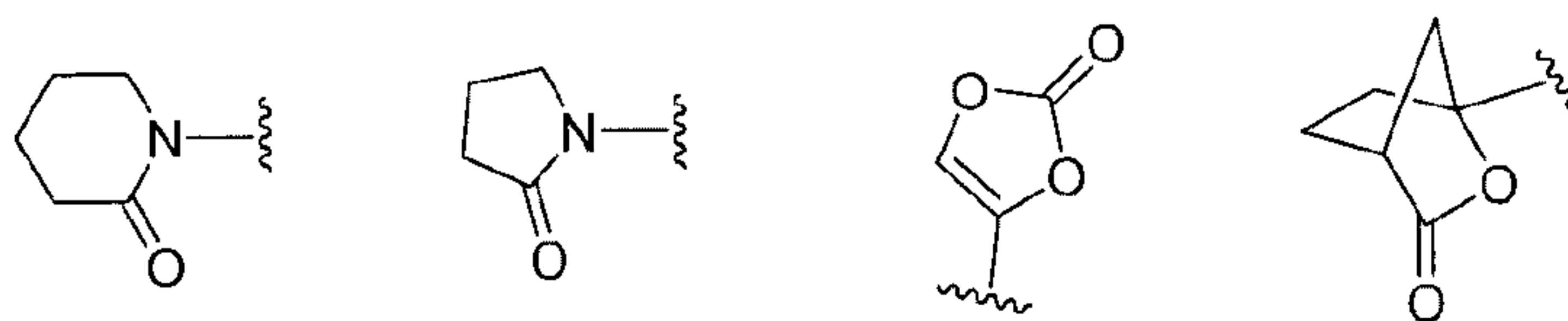
[0072]

A heterocyclic part of "heterocycle lower alkyl", "heterocycle lower alkyloxy", "carbocycleoxy lower alkyl", "heterocyclecarbonyl", "heterocycleoxy", "heterocycleoxycarbonyl", and "heterocycle lower alkyloxy lower alkyl" is the same as the "heterocyclic group" or the "heterocycle" as described above.

[0073]

"Heterocyclic group substituted by oxo" means the "heterocyclic group" as described above, substituted by oxo as shown below. Groups shown below

[Chemical formula 12]



[0074]

are exemplified.

[0075]

"Straight or branched lower alkylene" is divalent "lower alkyl" as described above, and includes, for example, methylene, ethylene, propylene, butylene, isobutylene, pentylene, heptylene, dimethylmethylene, ethylmethylmethylene, 1,2-dimethylethylene, etc.

[0076]

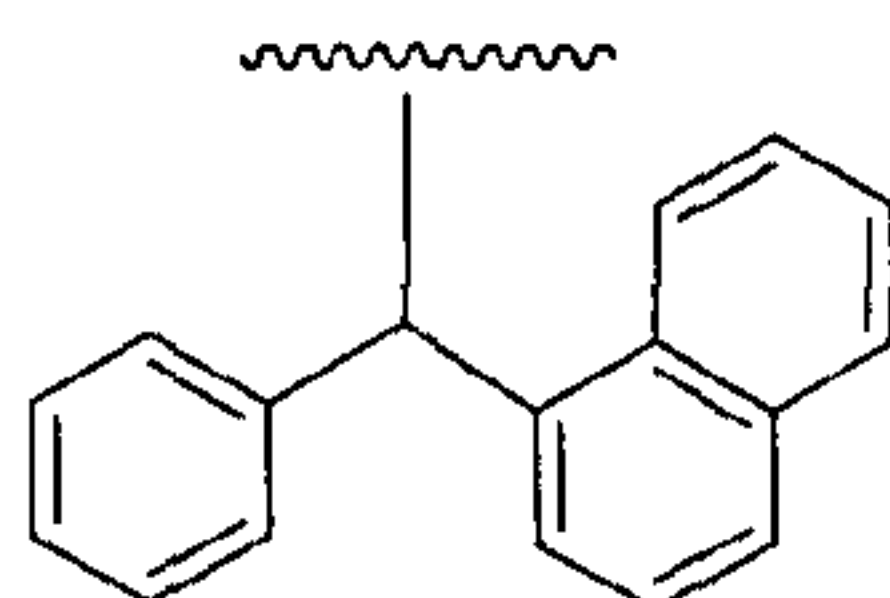
Examples of "lower alkyloxy" include methoxy, ethoxy, propyloxy, isopropyloxy, tert-butyloxy, isobutyloxy, sec-butyloxy, pentyloxy, isopentyloxy, hexyloxy, etc. Examples of a preferable embodiment include methoxy, ethoxy, propyloxy, isopropyloxy, and tert-butyloxy.

Examples of "lower alkylcarbonyl" include methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, tert-butylcarbonyl, isobutylcarbonyl, sec-butylcarbonyl, pentylcarbonyl, isopentylcarbonyl, hexylcarbonyl, etc. Examples of a preferable embodiment include methylcarbonyl, ethylcarbonyl, and propylcarbonyl.

Examples of "lower alkyloxycarbonyl" include methyloxycarbonyl, ethyloxycarbonyl, propyloxycarbonyl, isopropyloxycarbonyl, tert-butyloxycarbonyl, isobutyloxycarbonyl, sec-butyloxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, hexyloxycarbonyl, etc. Examples of a preferable embodiment include methyloxycarbonyl, ethyloxycarbonyl, and propyloxycarbonyl.

"Carbocycle lower alkyl" represents lower alkyl substituted by one, two or more carbocyclic groups, and examples of "carbocycle lower alkyl" include benzyl, phenethyl, phenylpropynyl, benzhydryl, trityl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, a group shown below

[Chemical formula 13]



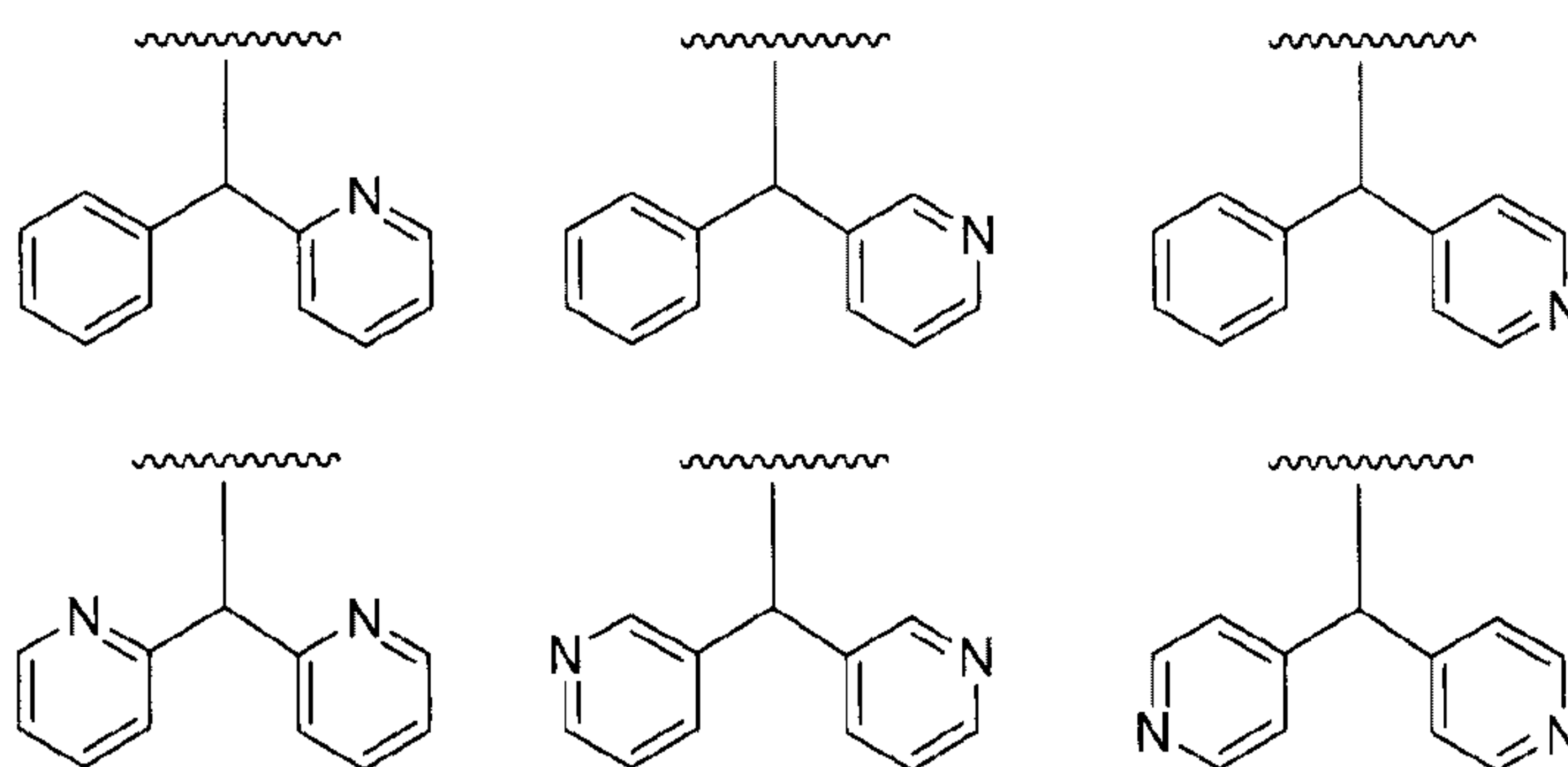
[0077]

etc.

Examples of a preferable embodiment include benzyl, phenethyl, and benzhydryl.

"Heterocycle lower alkyl" represents lower alkyl substituted by one, two or more heterocyclic groups, and also includes heterocycle lower alkyl in which an alkyl part is substituted by carbocyclic group. Examples of "heterocycle lower alkyl" include pyridylmethyl, tetrahydropyranylmethyl, furanylmethyl, morpholinylethyl, imidazolylmethyl, indolylmethyl, benzothiophenylmethyl, oxazolylmethyl, isooxazolylmethyl, thiazolylmethyl, isothiazolylmethyl, pyrazolylmethyl, isopyrazolylmethyl, pyrrolidinylmethyl, benzoxazolylmethyl, piperidinylmethyl, piperazinylmethyl, groups shown below

[Chemical formula 14]



[0078]

etc.

Examples of a preferable embodiment include pyridylmethyl, tetrahydropyranylmethyl, furanylmethyl, and morpholinylethyl.

Examples of "carbocycleoxy lower alkyl" include phenyloxymethyl, phenyloxyethyl, cyclopropyloxymethyl, cyclopropyloxyethyl, cyclobutyloxymethyl, cyclobutyloxyethyl, cyclohexyloxymethyl, cyclohexyloxyethyl, etc. Examples of a preferable embodiment include phenyloxymethyl, and phenyloxyethyl.

Examples of "heterocycleoxy lower alkyl" include pyridyloxymethyl, pyridyloxyethyl, morpholinylloxymethyl, morpholinylloxyethyl, benzoxazolylloxymethyl, etc. Examples of a preferable embodiment include pyridyloxymethyl, morpholinylloxymethyl, etc.

"Carbocycle lower alkyloxy" represents lower alkyloxy in which an alkyl part is substituted by one, two or more carbocyclic groups, and examples of "carbocycle lower alkyloxy" include phenylmethyloxy, phenylethyloxy, cyclopropylmethyloxy, cyclobutylmethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, etc. Examples of a preferable embodiment include phenylmethyloxy, cyclopropylmethyloxy, etc.

"Heterocycle lower alkyloxy" represents lower alkyloxy in which an alkyl part

is substituted by one, two or more heterocyclic groups, and also includes heterocycle lower alkyloxy in which an alkyl part is substituted by carbocyclic group. Examples of "heterocycle lower alkyloxy" include pyridylmethyloxy, pyridylethyloxy, imidazolylmethyloxy, imidazolylethyloxy, benzoxazolylmethyloxy, benzoxazolylethyloxy, etc.

Examples of "lower alkyloxy lower alkyl" include methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl, methoxypropyl, methoxybutyl, ethoxypropyl, ethoxybutyl, isopropylloxymethyl, tert-butyloxymethyl, etc. Examples of a preferable embodiment include methoxymethyl, methoxyethyl, ethoxymethyl, and ethoxyethyl.

Examples of "lower alkyloxy lower alkyloxy" include methoxymethoxy, methoxyethoxy, ethoxymethoxy, ethoxyethoxy, methoxypropyloxy, methoxybutyloxy, ethoxypropyloxy, ethoxybutyloxy, isopropylloxymethyloxy, tert-butyloxymethyloxy, etc. Examples of a preferable embodiment include methoxymethoxy, methoxyethoxy, ethoxymethoxy, and ethoxyethoxy.

Examples of "lower alkylamino" include methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, N,N-diisopropylamino, N-methyl-N-ethylamino, N-isopropyl-N-ethylamino, etc. Examples of a preferable embodiment include methylamino, dimethylamino, ethylamino, and diethylamino.

Examples of "lower alkylcarbonylamino" include methylcarbonylamino, ethylcarbonylamino, propylcarbonylamino, isopropylcarbonylamino, tert-butylcarbonylamino, isobutylcarbonylamino, sec-butylcarbonylamino, etc. Examples of a preferable embodiment include methylcarbonylamino, and ethylcarbonylamino.

Examples of "lower alkylaminocarbonyl" include methylaminocarbonyl, dimethylaminocarbonyl, ethylaminocarbonyl, diethylaminocarbonyl,

isopropylaminocarbonyl, N,N-diisopropylaminocarbonyl, N-methyl-N-ethylaminocarbonyl, N-isopropyl-N-ethylaminocarbonyl, etc. Examples of a preferable embodiment include methylaminocarbonyl, dimethylaminocarbonyl, ethylaminocarbonyl, and diethylaminocarbonyl.

Examples of "lower alkylsulfonyl" include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, tert-butylsulfonyl, isobutylsulfonyl, sec-butylsulfonyl, etc. Examples of a preferable embodiment include methylsulfonyl, and ethylsulfonyl.

Examples of "lower alkylsulfonylamino" include methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, isopropylsulfonylamino, tert-butylsulfonylamino, isobutylsulfonylamino, sec-butylsulfonylamino, etc. Examples of a preferable embodiment include methylsulfonylamino, and ethylsulfonylamino.

Examples of "lower alkenyloxy" include ethylenyloxy, 1-propylenyloxy, 2-propylenyloxy, 1-butylenyloxy, 2-butylenyloxy, 3-butylenyloxy, etc.

Examples of "halogeno lower alkyl" 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, etc. Examples of a preferable embodiment include trifluoromethyl, trichloromethyl, 1,1,1-trifluoropropan-2-yl.

Examples of "halogeno lower alkyloxy" include monofluoromethoxy, monofluoroethoxy, trifluoromethoxy, trichloromethoxy, trifluoroethoxy, trichloroethoxy, etc. Examples of a preferable embodiment include trifluoromethoxy, and trichloromethoxy.

Examples of "lower alkylthio" include methylthio, ethylthio, propylthio, etc.

Examples of "hydroxy lower alkyl" include hydroxymethyl, hydroxyethyl,

hydroxypropyl, etc.

Examples of "carbocycle lower alkyloxy lower alkyl" include benzyloxymethyl, benzyloxyethyl, benzhydryloxymethyl, etc.

Examples of "heterocycle lower alkyloxy lower alkyl" include pyridylmethyloxymethyl, pyridylmethyloxyethyl, etc.

Examples of "lower alkylcarbonyloxy" include methylcarbonyloxy, ethylcarbonyloxy, etc.

Examples of "halogeno lower alkylcarbonylamino" include trifluoromethylcarbonylamino, 2,2,3,3,3-pentafluoropropylcarbonylamino, etc.

Examples of "lower alkylsulfinyl" include methylsulfinyl, ethylsulfinyl, etc.

[0079]

Examples of "carbocyclecarbonyl" include phenylcarbonyl, naphthylcarbonyl, cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.

Examples of "carbocycleoxy" include phenyloxy, naphthyloxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, etc.

Examples of "carbocycleoxycarbonyl" include phenyloxycarbonyl, naphthyloxycarbonyl, cyclopropyloxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl, etc.

Examples of "heterocyclecarbonyl" include pyridylcarbonyl, benzoxazolylcarbonyl, morpholinylcarbonyl, tetrahydropyranylcabonyl, etc.

Examples of "heterocycleoxy" include pyridyloxy, benzoxazolyloxy, morpholinylloxy, tetrahydropyranyloxy, etc.

Examples of "heterocycleoxycarbonyl" include pyridyloxycarbonyl, benzoxazolyloxycarbonyl, morpholinylloxycarbonyl, tetrahydropyranyloxycarbonyl, etc.

[0080]

The terms:

"R<sup>A1</sup> and R<sup>A2</sup>, R<sup>A15</sup> and R<sup>A16</sup>, as well as R<sup>A19</sup> and R<sup>A20</sup>, each may be taken together with an adjacent atom to form a heterocycle",

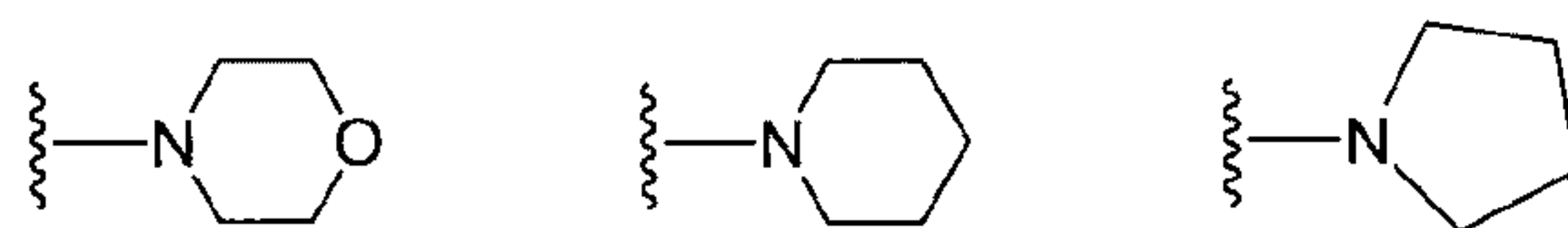
"R<sup>B7</sup> and R<sup>B8</sup>, as well as R<sup>B9</sup> and R<sup>B10</sup>, each may be taken together with an adjacent atom to form a heterocycle",

"R<sup>C7</sup> and R<sup>C8</sup>, as well as R<sup>C9</sup> and R<sup>C10</sup>, each may be taken together with an adjacent atom to form a heterocycle", and

"R<sup>D5</sup> and R<sup>D6</sup> may be taken together with an adjacent atom to form a heterocycle" in item 1

mean a heterocycle having N atom, and include, for example, groups shown below

[Chemical formula 15]



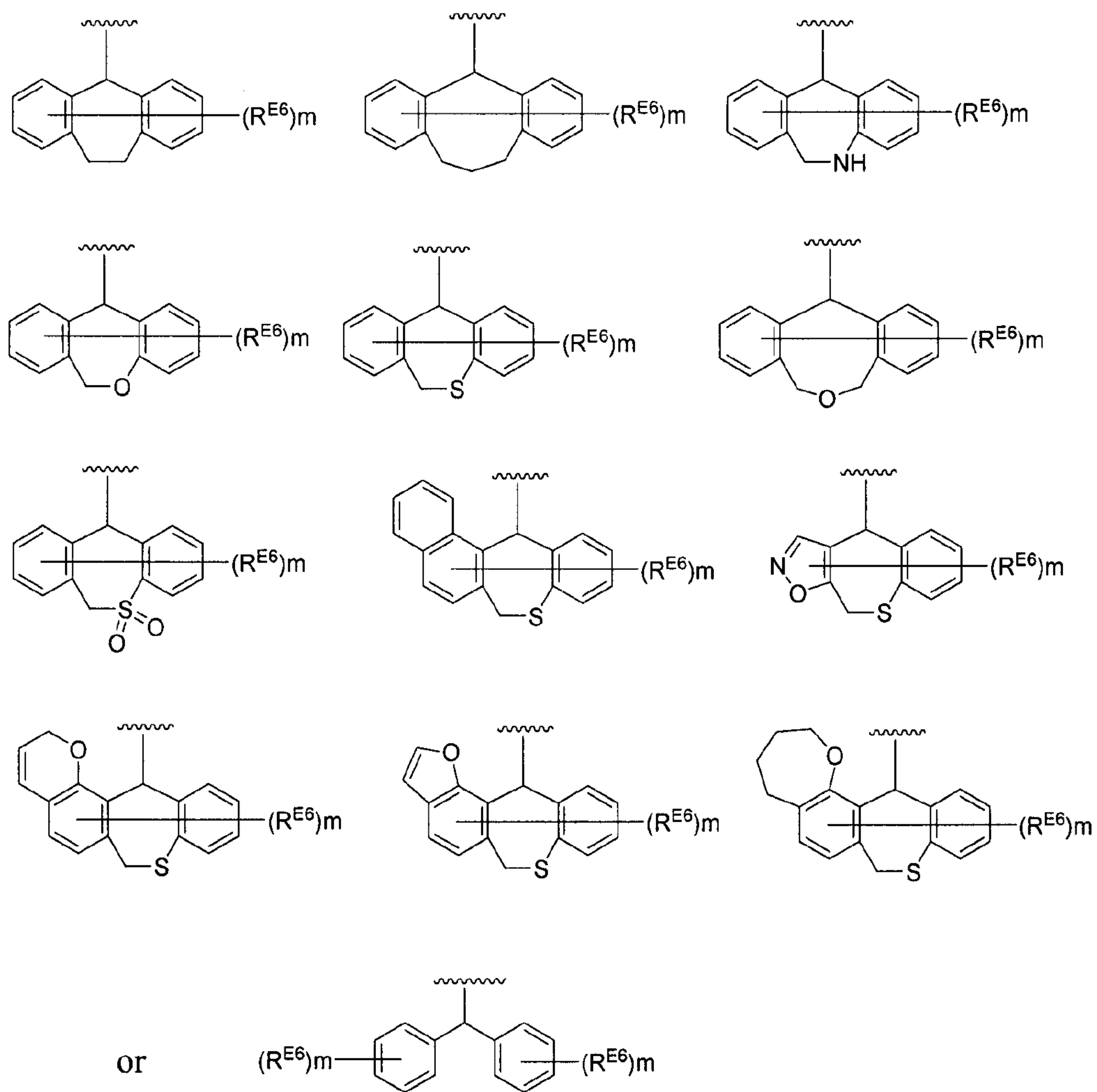
[0081]

etc.

[0082]

In the present description, (R<sup>E6</sup>)<sub>m</sub> in the formulae shown below

[Chemical formula 16]

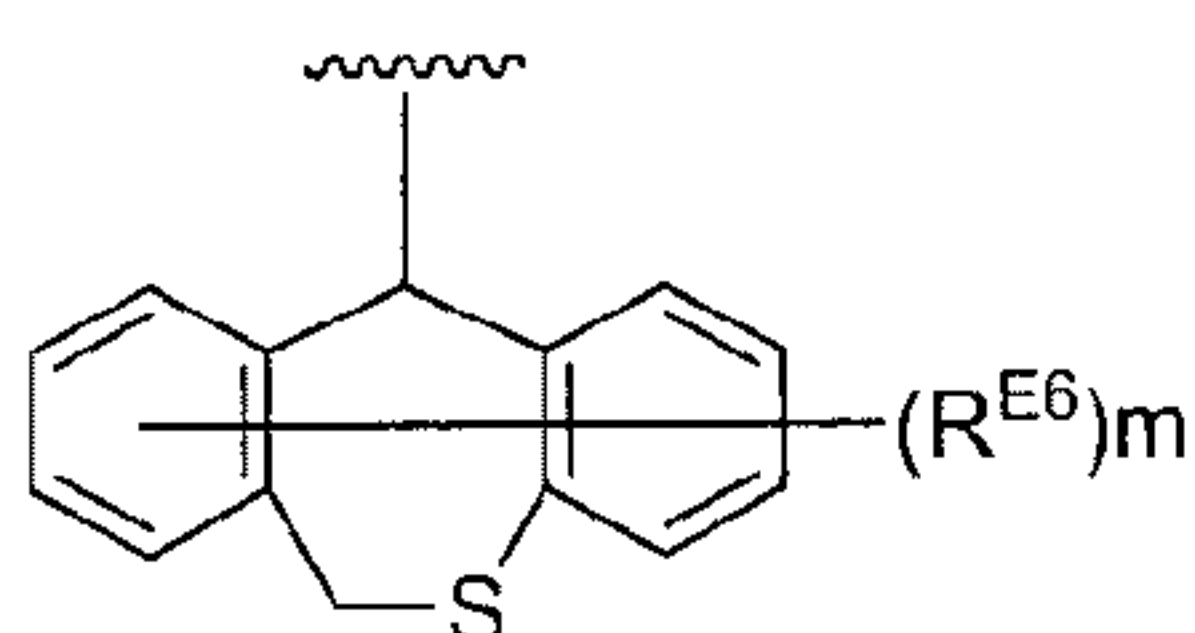


[0083]

means that an arbitrary carbon atom or nitrogen atom which can chemically have a substituent on a ring is substituted by each  $R^{E6}$  which are same or different.

For example, in the formula below

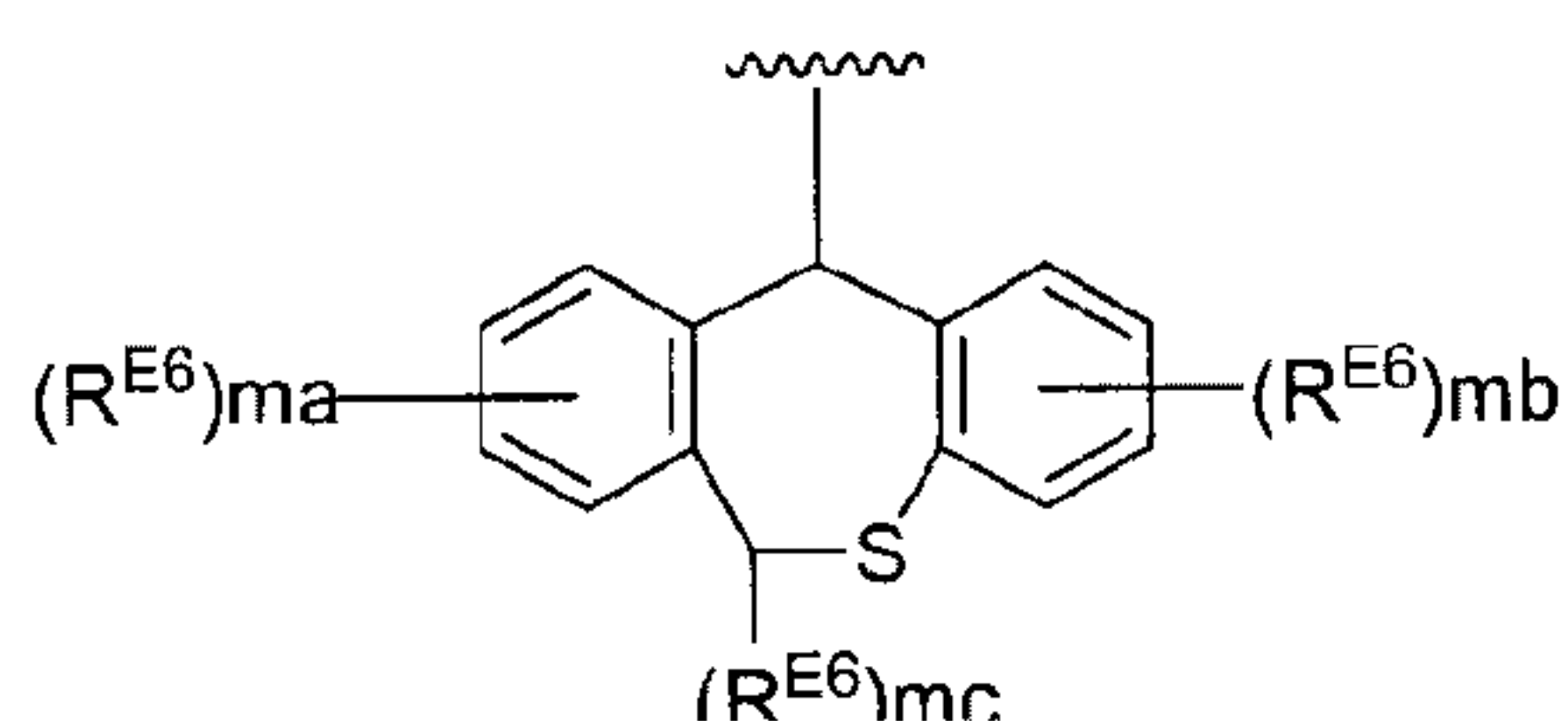
[Chemical formula 17]



[0084]

, as shown by a substituent below

[Chemical formula 18]



[0085]

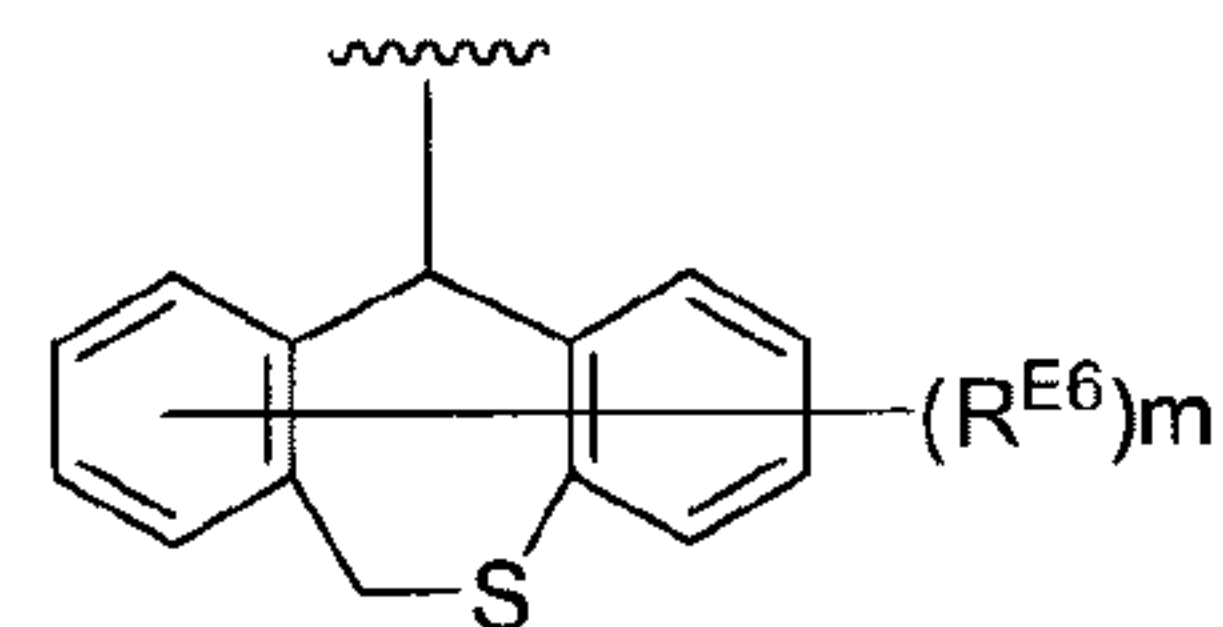
(wherein  $ma + mb + mc = m$ , and  $R^{E6}$  is same as above),

it is meant that any hydrogen atom on two benzene rings and a 7-membered ring containing a sulfur atom may be substituted by  $R^{E6}$ , and respective  $R^{E6}$ s may be the same or different.

And,  $ma$  is preferably an integer of 0 to 3,  $mb$  is preferably an integer of 0 to 3, and  $mc$  is preferably an integer of 0 or 1. And,  $ma$  is more preferably an integer of 0 or 1,  $mb$  is more preferably an integer of 0 or 1, and  $mc$  is more preferably 0.

For example, in the formula below

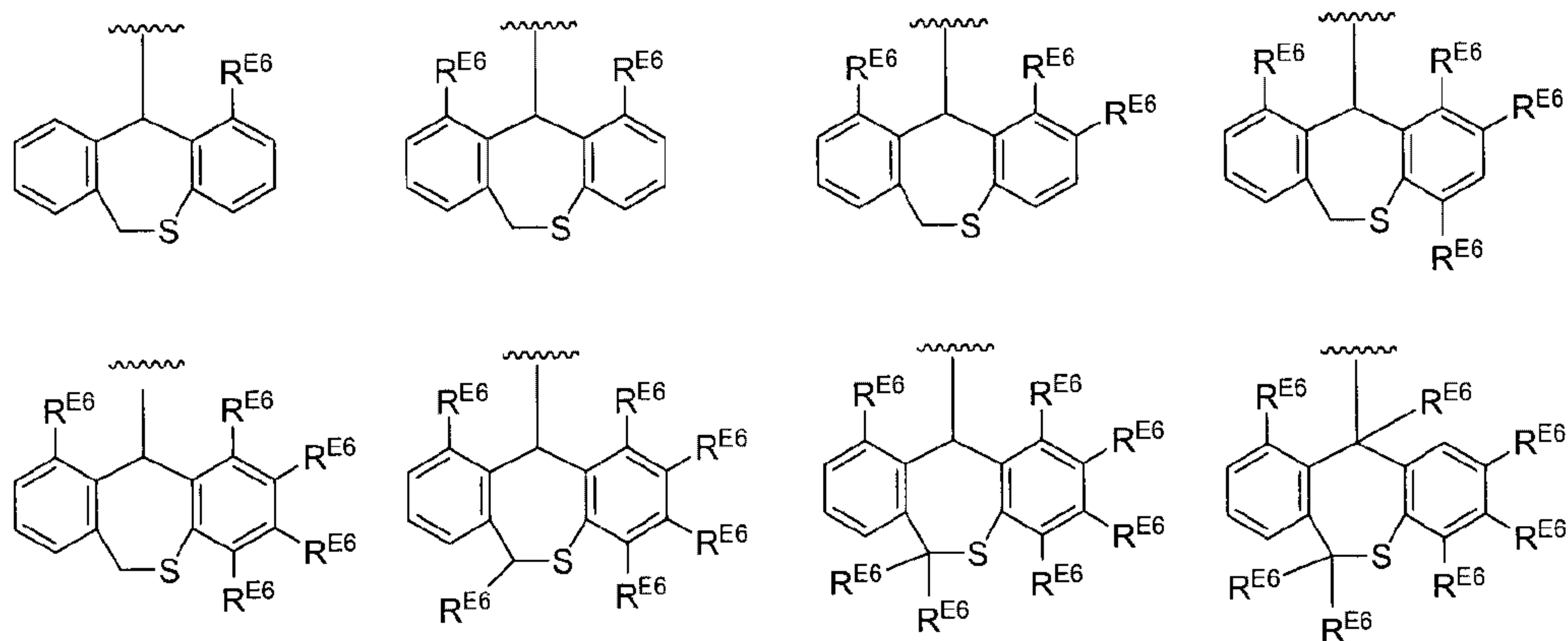
[Chemical formula 19]



[0086]

substituents shown below

[Chemical formula 20]



[0087]

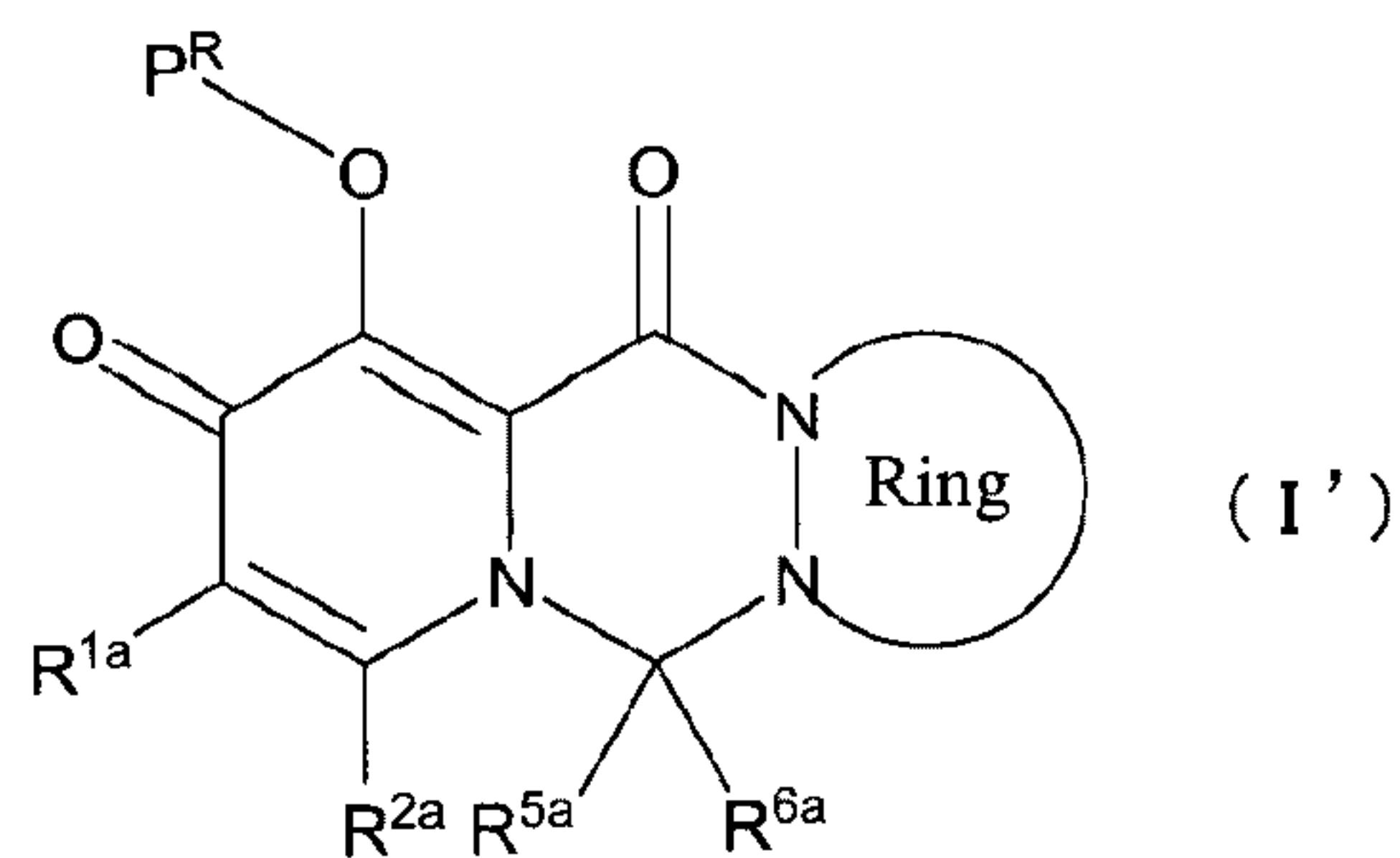
(wherein  $R^{E6}$ , and m are same as those of item 1)

etc. are included.

[0088]

"B<sup>1</sup> is CR<sup>5a</sup>R<sup>6a</sup>, and B<sup>2</sup> is NR<sup>7a</sup>, R<sup>3a</sup> and R<sup>7a</sup> may be taken together with an adjacent atom to form a heterocycle optionally substituted by substituent group D" in the formula (I) in item 1 represents the formula (I') shown below:

[Chemical formula 21]

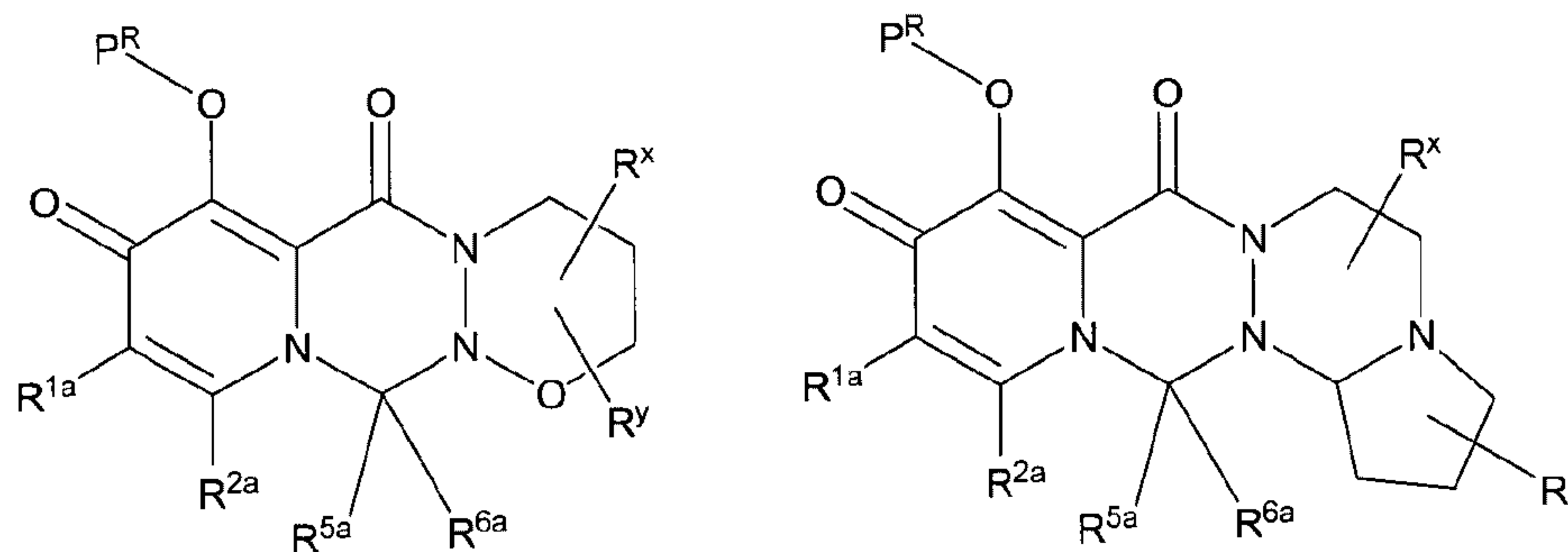


[0089]

(wherein  $P^R$ ,  $R^{1a}$ ,  $R^{2a}$ ,  $R^{5a}$  and  $R^{6a}$  are same as those of item 1), and indicates that a part of a ring may be substituted by one, two or more same or different substituents selected from substituent group D at an arbitrary position. The heterocycle is preferably a 5- to 7-membered ring. In addition, "the heterocycle may form a condensed ring" indicates that the ring in the formula (I') may be further condensed with a ring, and indicates that substituent group D may be bound to any of the ring in the formula (I') or the ring which is condensed with a ring.

Examples of the formula (I') include compounds shown by the following formulae

[Chemical formula 22]



[0090]

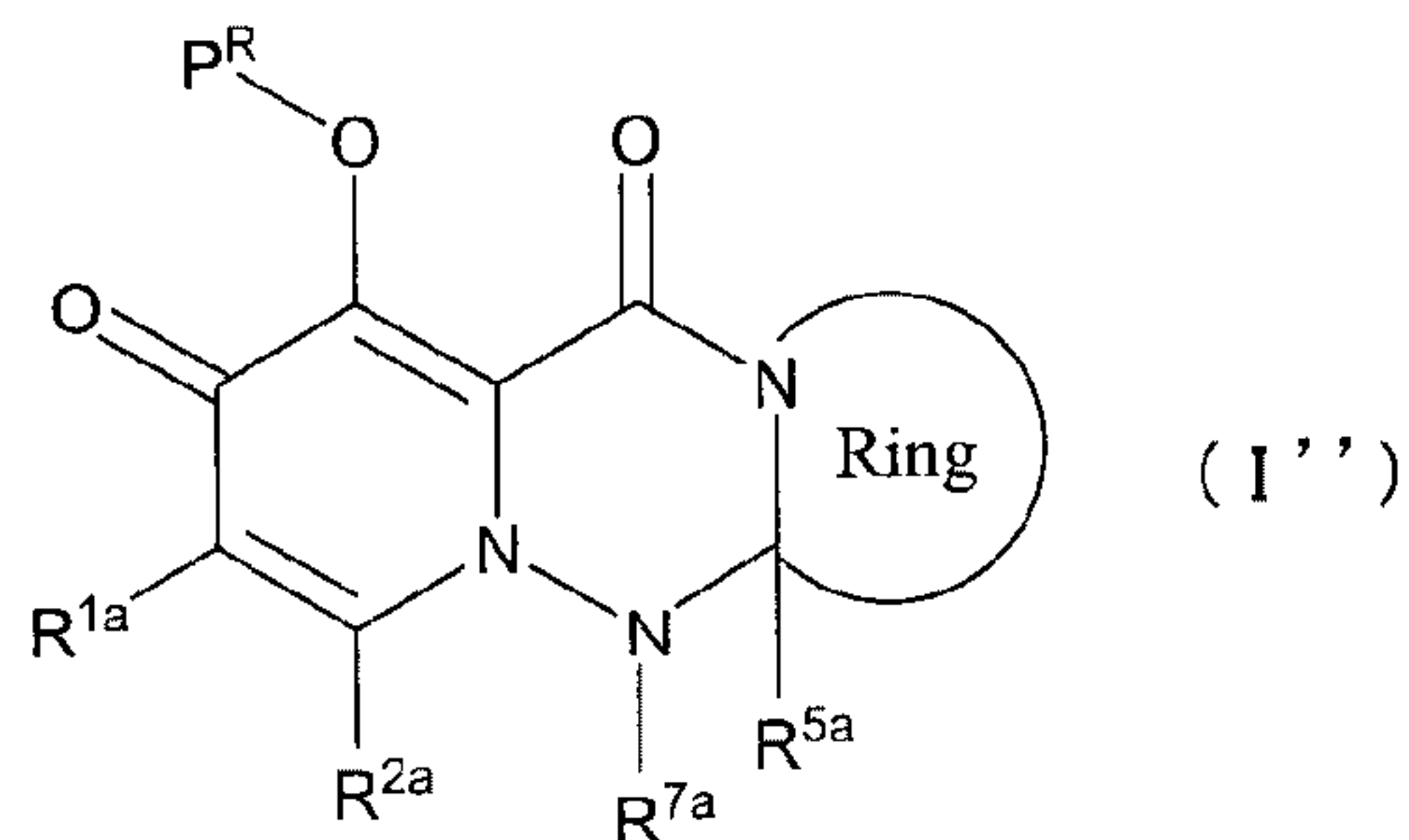
(wherein  $R^x$ , and  $R^y$  are a substituent selected from substituent group D, and  $P^R$ ,  $R^{1a}$ ,  $R^{2a}$ ,  $R^{5a}$ , and  $R^{6a}$  are same as those of item 1) etc.

[0091]

"When form a heterocycle" in " $B^1$  is  $NR^{7a}$ , and  $B^2$  is  $CR^{5a}R^{6a}$ ,  $R^{3a}$  and  $R^{6a}$  may be taken together with an adjacent atom to form a heterocycle optionally substituted by substituent group D" in the formula (I) in item 1 represents the formula (I'') shown

below:

[Chemical formula 23]

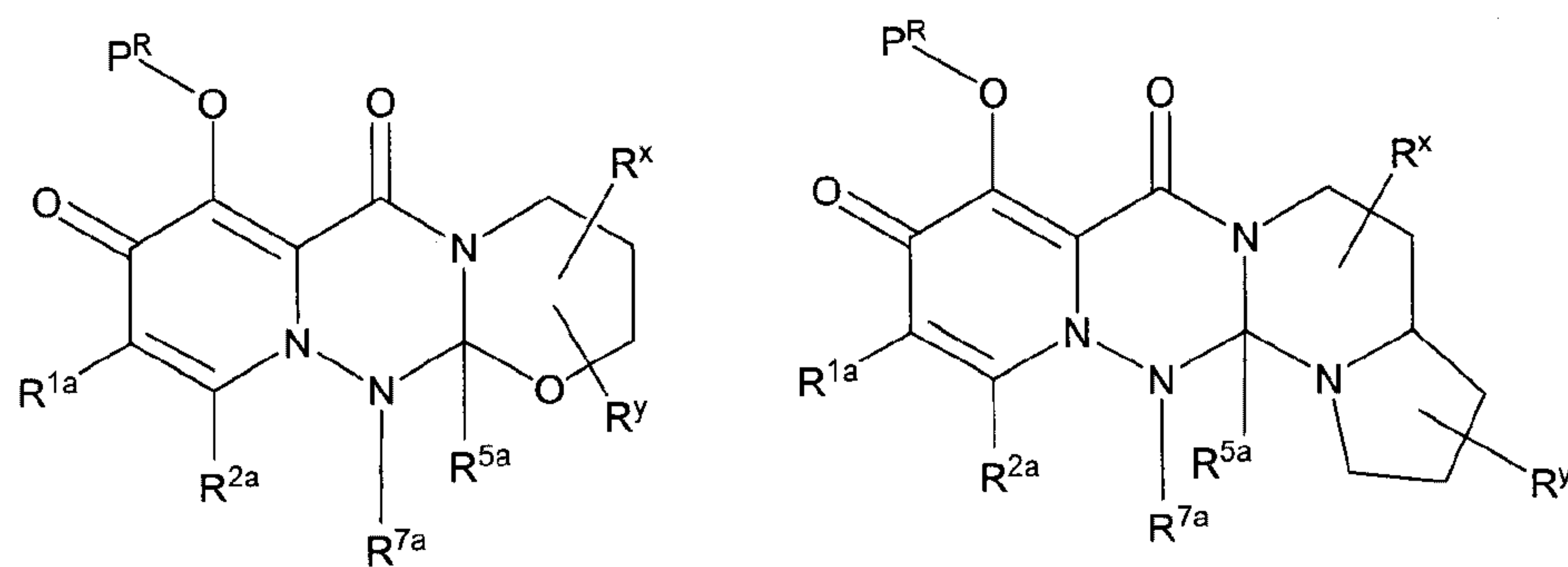


[0092]

(wherein  $P^R$ ,  $R^{1a}$ ,  $R^{2a}$ ,  $R^{5a}$  and  $R^{7a}$  are same as those of item 1), and indicates that "Ring" may be substituted by one, two or more same or different substituents selected from substituent group D at an arbitrary position. The heterocycle is preferably a 5- to 7-membered ring. In addition, "the heterocycle may form a condensed ring" indicates that the ring in the formula (I'') may be further condensed with a ring, and indicates that one, two or more of substituent group D may be bound to any of the ring in the formula (I'') or the ring which is condensed with a ring.

Examples of the formula (I'') include compounds shown by the following formulae

[Chemical formula 24]



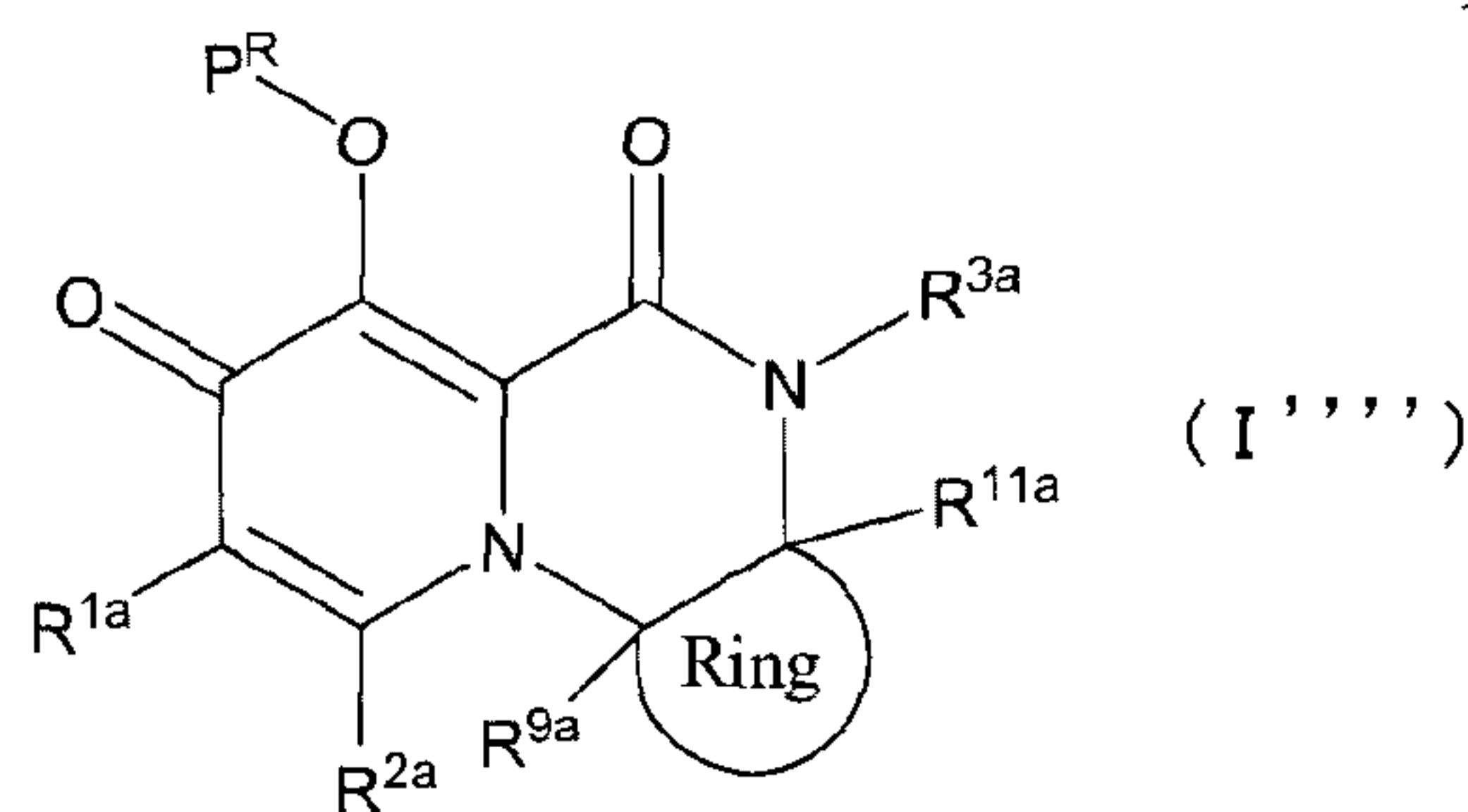
[0093]

(wherein  $R^x$ , and  $R^y$  are a substituent selected from substituent group D, and  $P^R$ ,  $R^{1a}$ ,  $R^{2a}$ ,  $R^{5a}$ , and  $R^{7a}$  are same as those of item 1) etc.

[0094]

"When form a carbocycle or heterocycle" in " $R^{8a}$  and  $R^{10a}$  may be taken together with an adjacent atom to form a carbocycle or heterocycle optionally substituted by substituent group D" in the formula (I) in item 1 represents the formula (I''') shown below:

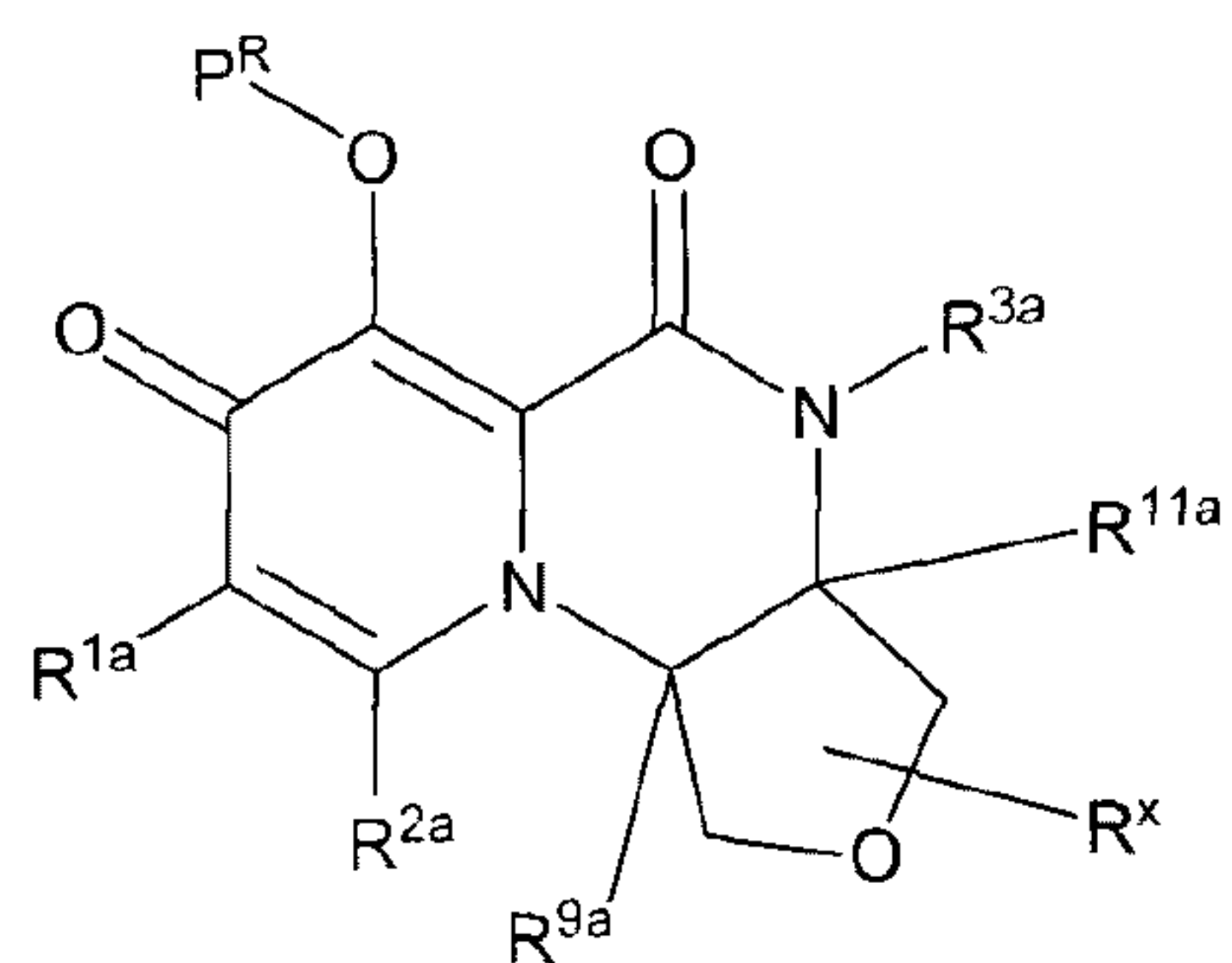
[Chemical formula 25]



[0095]

(wherein  $P^R$ ,  $R^{1a}$ ,  $R^{2a}$ ,  $R^{3a}$ ,  $R^{9a}$ , and  $R^{11a}$  are same as those of item 1), and indicates that "Ring" may be substituted by one, two or more same or different substituents selected from substituent group D at an arbitrary position. The carbocycle or the heterocycle is preferably a 5- to 7-membered ring. Examples of the formula (I''') include compounds shown by the following formula

[Chemical formula 26]



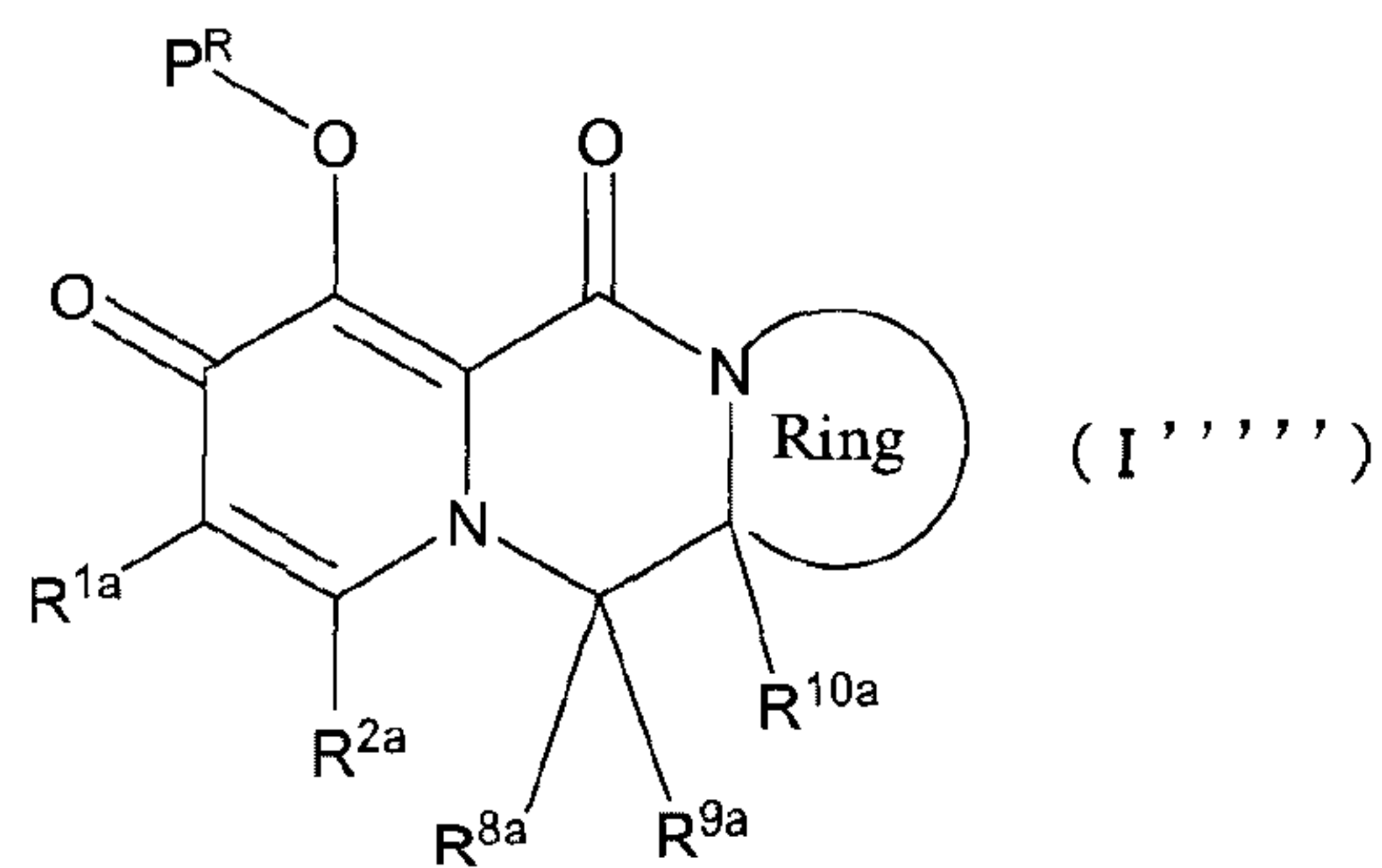
[0096]

(wherein  $R^x$  is a substituent selected from substituent group D, and  $P^R$ ,  $R^{1a}$ ,  $R^{2a}$ ,  $R^{3a}$ ,  $R^{9a}$ , and  $R^{11a}$  are same as those of item 1) etc.

[0097]

Further, " $R^{3a}$  and  $R^{11a}$  may be taken together with an adjacent atom to form a heterocycle optionally substituted by substituent group D, and the heterocycle may form a condensed ring" represents the formula (I''''') shown below:

[Chemical formula 27]

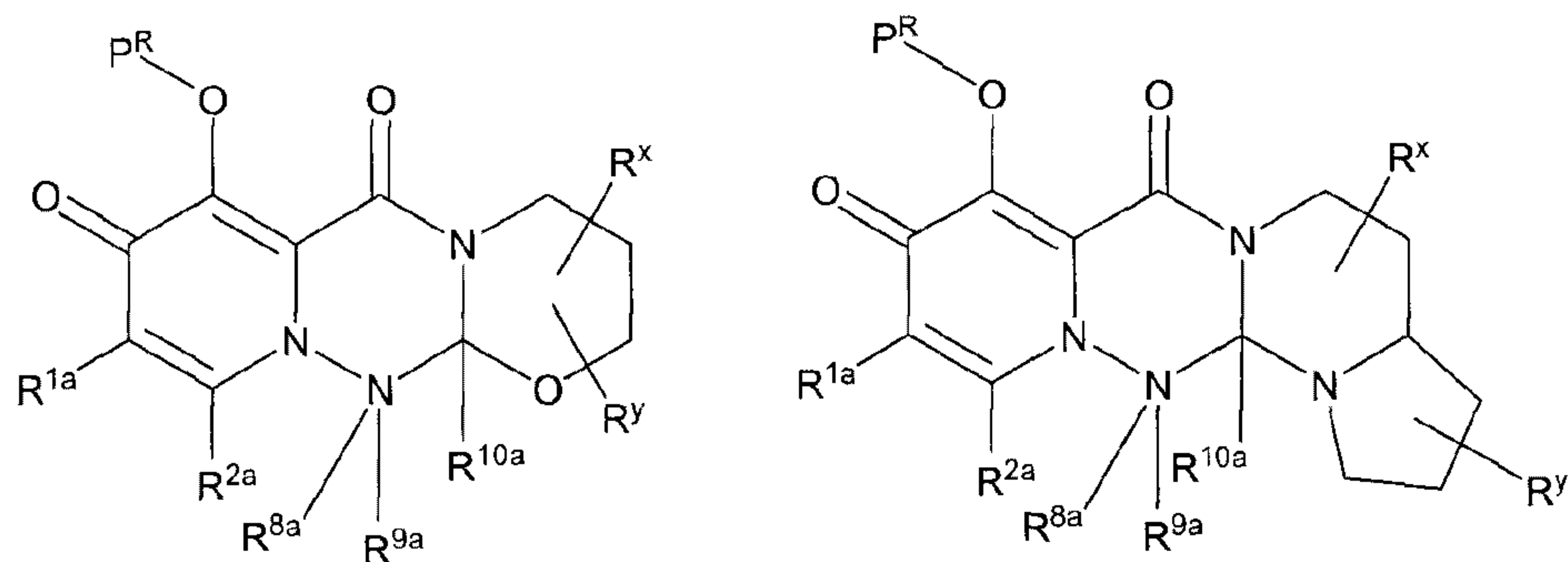


[0098]

(wherein  $P^R$ ,  $R^{1a}$ ,  $R^{2a}$ ,  $R^{8a}$ ,  $R^{9a}$ , and  $R^{10a}$  are same as those of item 1), and indicates that "Ring" may further form a condensed ring, and the same or different

substituents selected from substituent group D may be bound to any of the ring in the formula (I''') or the ring which is condensed with a ring at an arbitrary position. The heterocycle is preferably a 5- to 7-membered ring. Examples of the formula (I''') include compounds shown by the following formulae

[Chemical formula 28]



[0099]

(wherein R<sup>x</sup>, and R<sup>y</sup> are a substituent selected from substituent group D, and P<sup>R</sup>, R<sup>1a</sup>, R<sup>2a</sup>, R<sup>8a</sup>, R<sup>9a</sup>, and R<sup>10a</sup> are same as those of item 1) etc.

[0100]

"Solvate" includes, for example, a solvate with an organic solvent, a hydrate, etc. Preferred embodiment is a hydrate or alcoholate, and more preferred embodiment is a hydrate. When a hydrate is formed, the compound may be coordinated with an arbitrary number of water molecules. Examples include hemihydrate (1 water molecule is coordinated to 2 molecules of the present compound), monohydrate (1 water molecule is coordinated to 1 molecule of the present compound), dihydrate (2 water molecules are coordinated to 1 molecule of the present compound), trihydrate (3 water molecules are coordinated to 1 molecule of the present compound), etc. The same shall apply when an alcoholate is formed. Examples of alcohol when an

alcoholate is formed include methanol, ethanol, isopropanol, etc.

The compound of the present invention includes a pharmaceutically acceptable salt. Examples include salts with an alkali metal (lithium, sodium or potassium, etc.), an alkaline earth metal (magnesium or calcium, etc.), ammonium, an organic base and an amino acid, or salts with an inorganic acid (hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid or hydroiodic acid, etc.), and an organic acid (acetic 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, benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid or ethanesulfonic acid, etc.). These salts can be formed by the method which is usually performed.

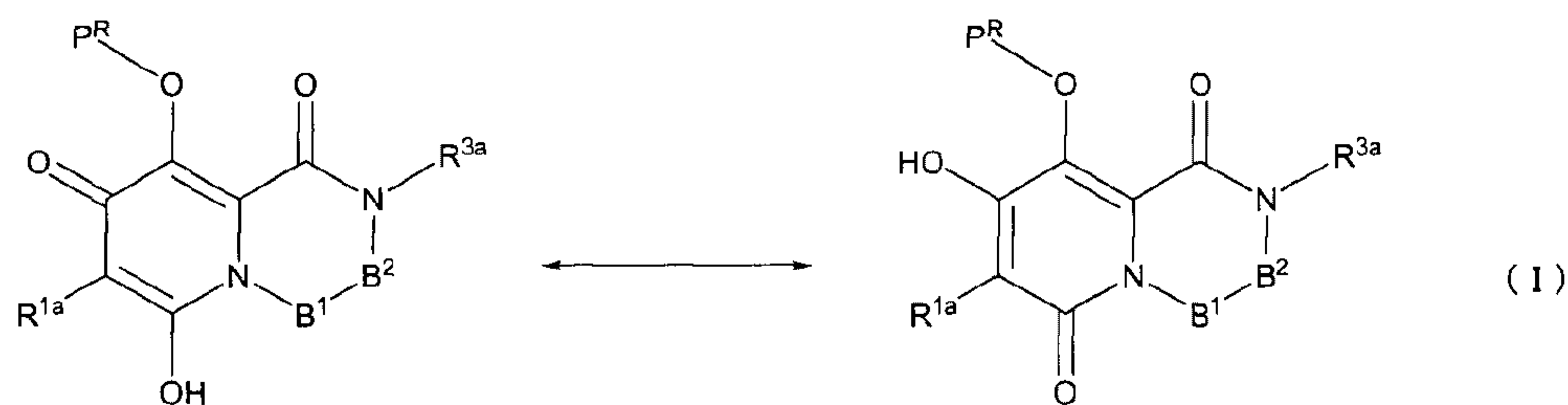
Examples of preferred salt of the formula (I) in the present invention include hydrochloride, hydrobromate, acetate, sulfate, etc.

In addition, the compound of the present invention is not limited to a particular isomer, but includes all possible isomers (keto-enol isomer, imine-enamine isomer, diastereoisomer, optical isomer and rotation isomer, etc.) and racemic bodies.

[0101]

The formula (I) in the present invention is not limited to a particular isomer, but includes all possible isomers and racemic bodies. For example, they also contain a tautomer and a steric isomer as shown below.

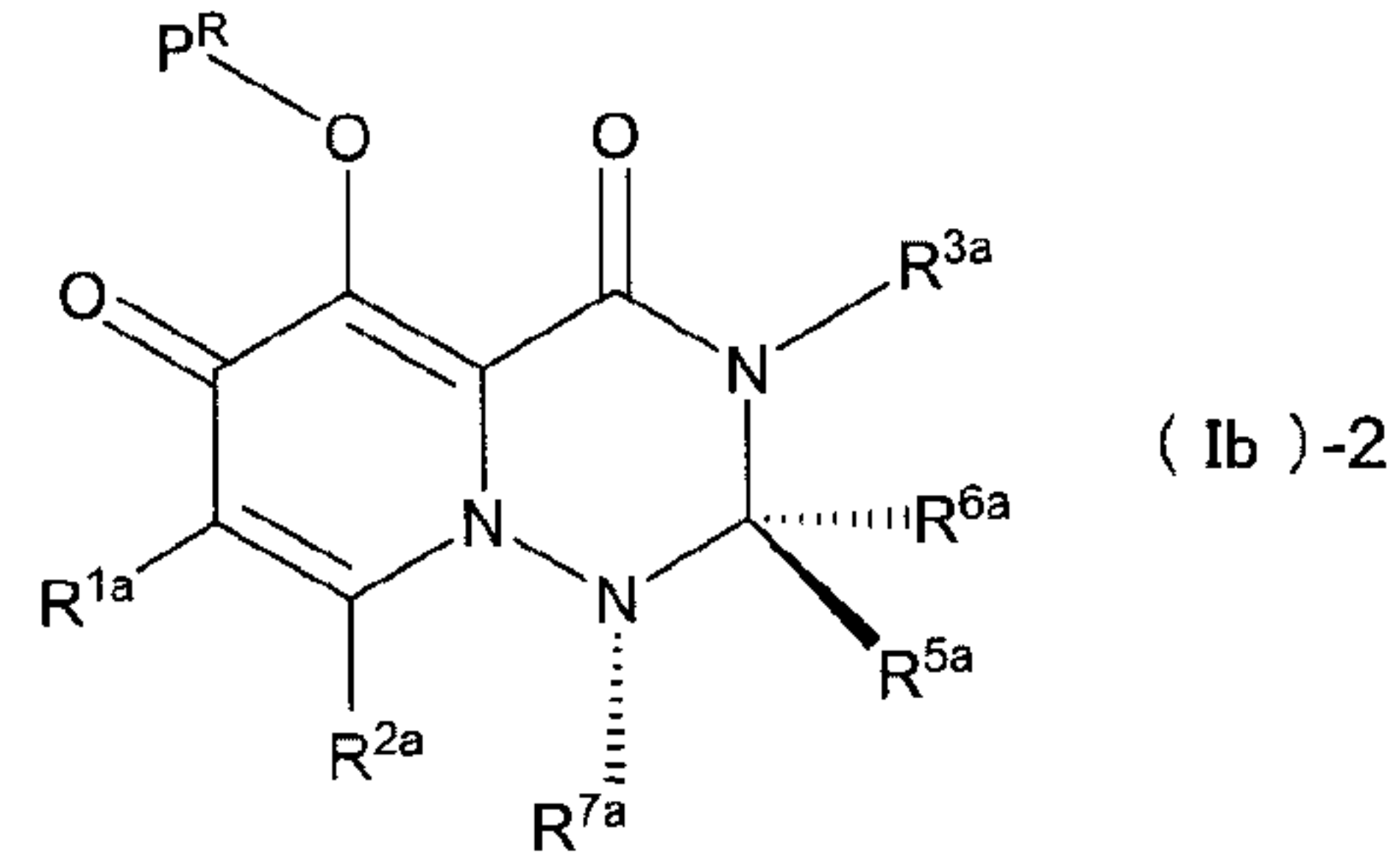
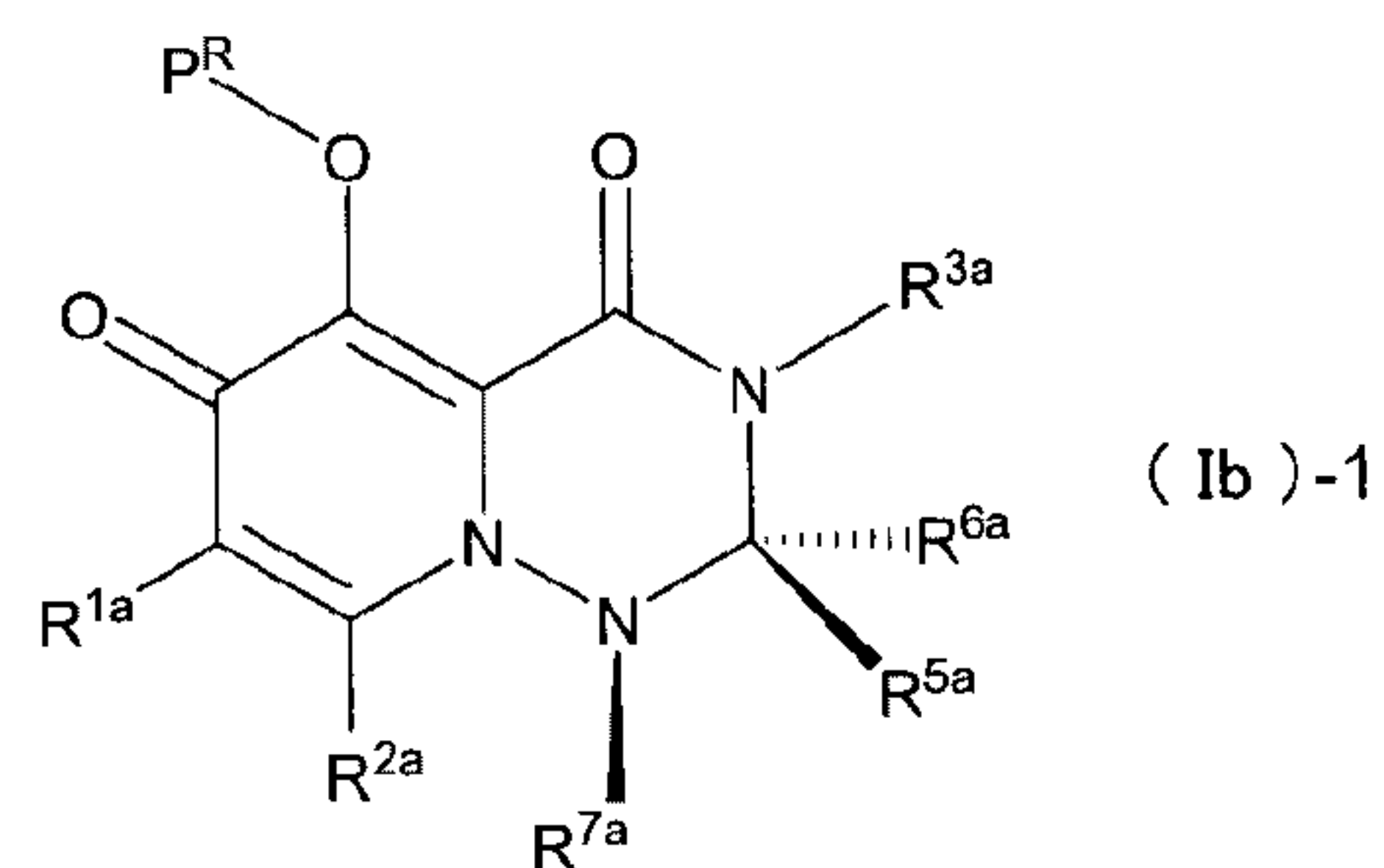
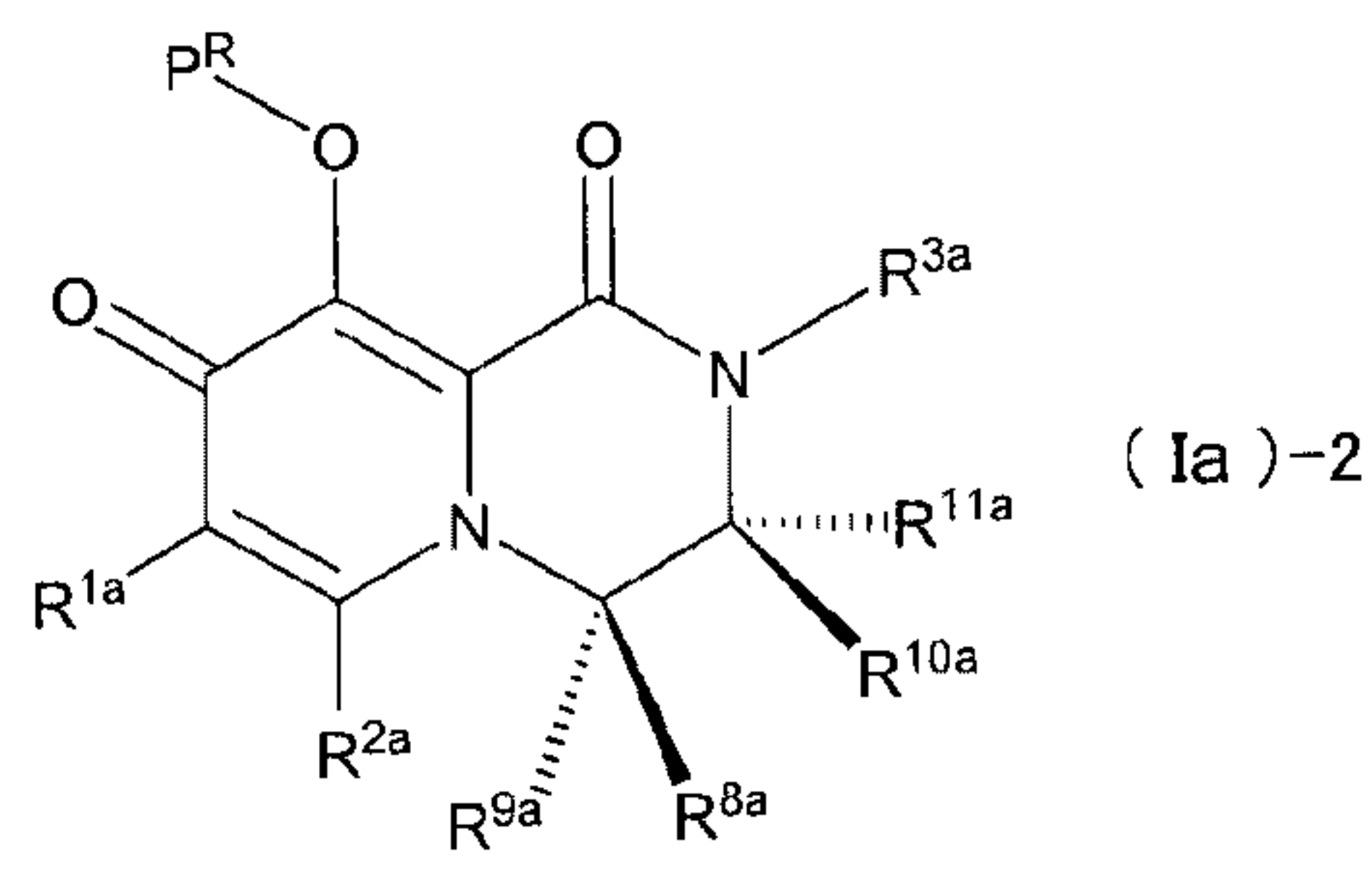
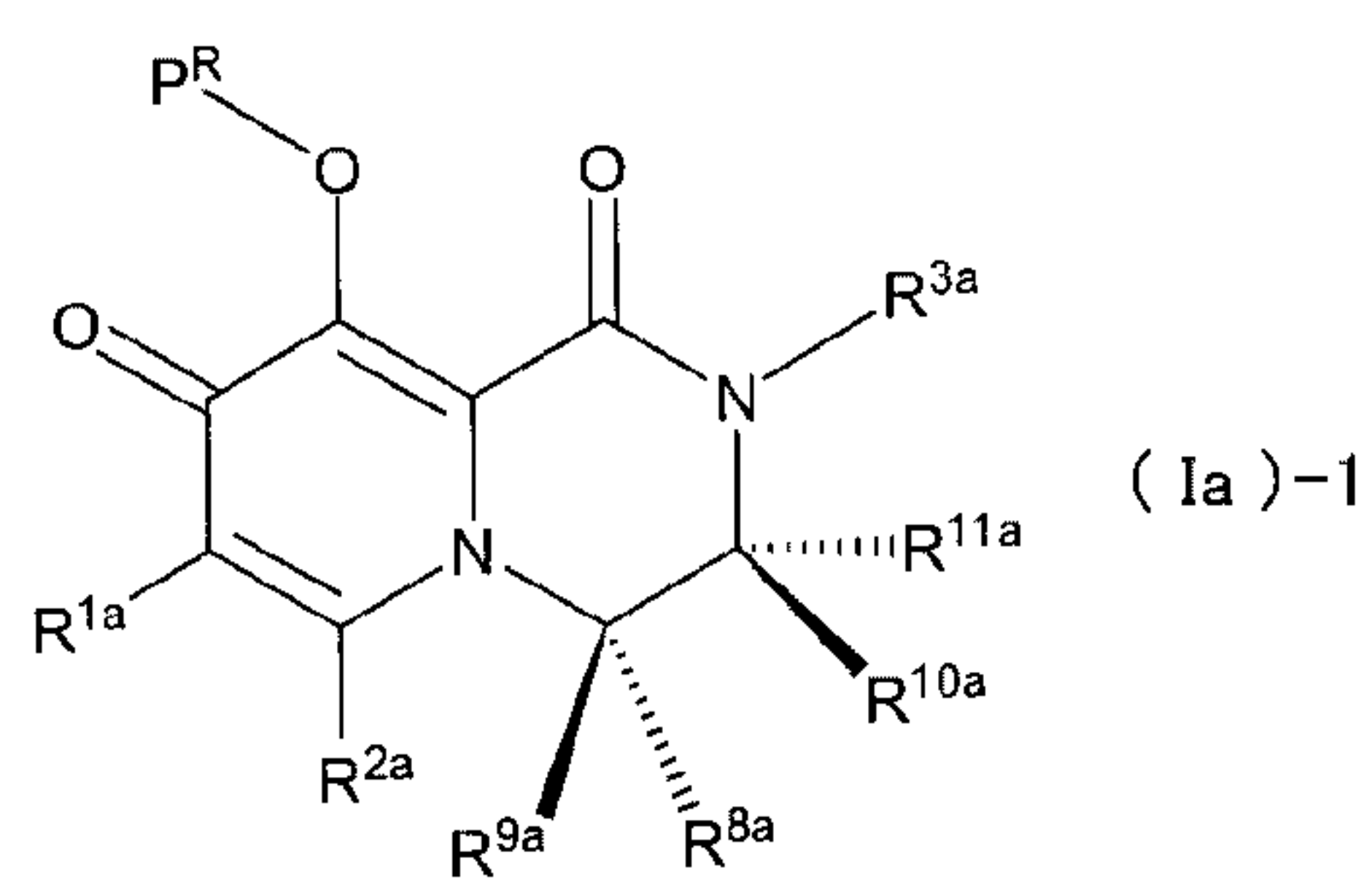
[Chemical formula 29]



(wherein each symbol is same as above)

[0102]

[Chemical formula 30]



(wherein each symbol is same as above)

[0103]

Further, one or more hydrogen atoms, carbon atoms or other atoms of the compound of the formula (I) can be substituted by an isotope of a hydrogen atom, a carbon atom or other atoms, respectively.

In addition, the compound of the formula (I) includes all radioactive labeled bodies thereof. Such the "radioactive labeling" and "radioactive labeled form" of the compound of the formula (I) are included in the present invention, respectively, and are useful as a study and/or diagnostic tool in metabolized drug dynamic state study and

binding assay.

Examples of an isotope which can be incorporated into the compound of the formula (I) of the present invention include a hydrogen atom, a carbon atom, a nitrogen atom, an oxygen atom, a phosphorus atom, a sulfur atom, a fluorine atom and a chlorine atom, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ , and  $^{36}\text{Cl}$ .

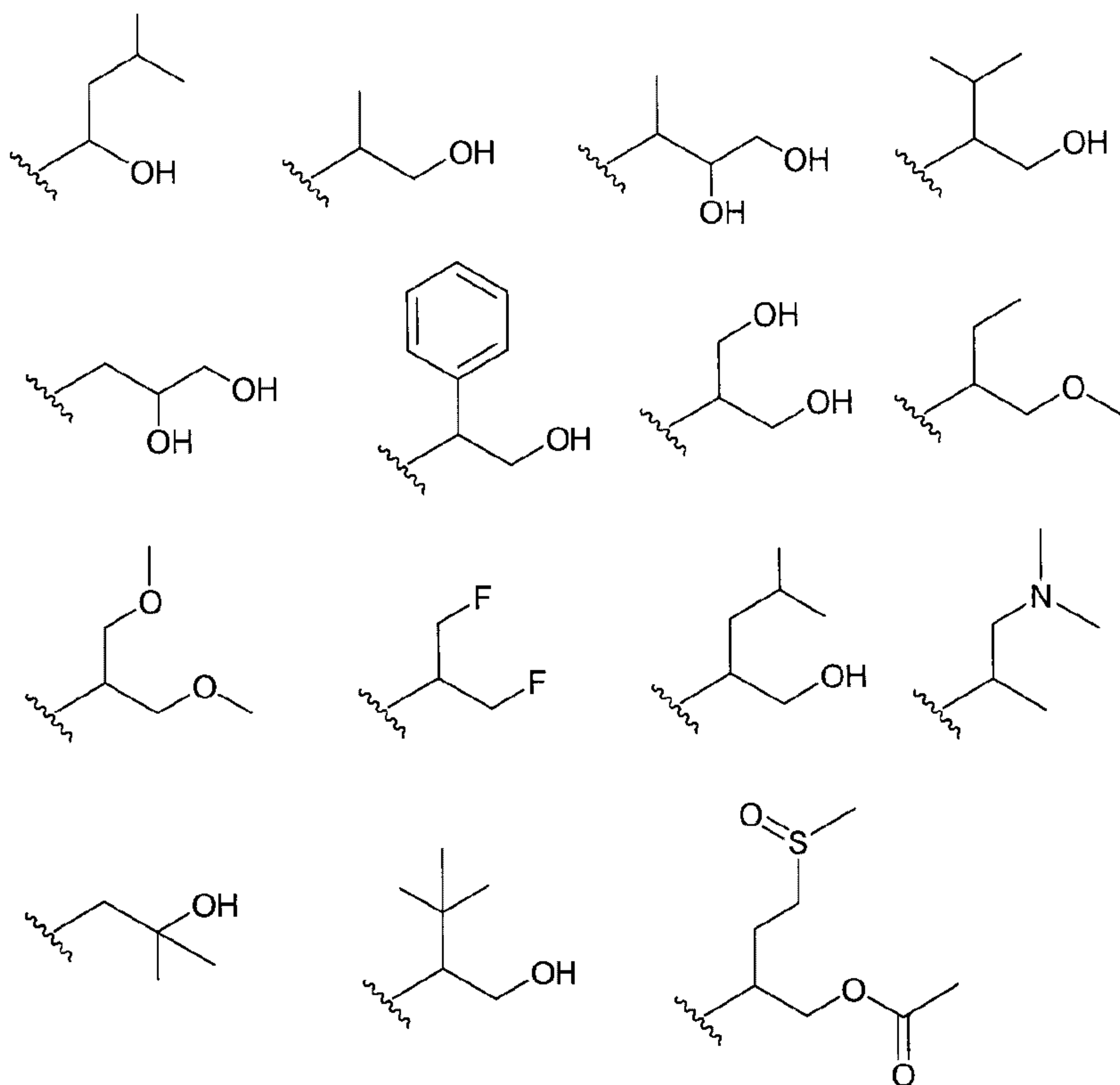
A particularly preferable example of an isotope which can be incorporated into the compound of the formula (I) of the present invention is  $^2\text{H}$  (i.e. heavy hydrogen atom), and can be prepared by the method shown in Reference examples of the present description, or the method well-known in the art. In addition, a heavy hydrogen atom is expressed as "D" in Reference examples of the present description. Compound of the formula (I) of the present invention in which a hydrogen atom has been converted into a heavy hydrogen atom are excellent in respect of bioavailability, metabolism safety, drug efficacy, and toxicity as compared with unconverted forms, in some cases, and can be useful as medicaments.

[0104]

Examples of "lower alkyl optionally substituted by substituent group C" include methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, sec-butyl, pentan-2-yl, hydroxymethyl, hydroxyethyl, carboxymethyl, carboxyethyl, carboxypropyl, ethoxycarbonylpropyl, cyanomethyl, cyanoethyl, fluoromethyl, fluoroethyl, fluoropropyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, ethyloxycarbonyl, methoxymethyl, dimethoxymethyl, methoxyethyl, methoxypropyl, ethoxyethyl, 1-methyl-1-methoxymethyl, propyloxymethyl, aminopropyl, dimethylaminomethyl, aminomethyl, aminoethyl, dimethylaminoethyl, diethylaminomethyl, diethylaminoethyl, dimethylaminopropyl, cyclopropylmethyloxymethyl, methylsulfonylaminomethyl, methylaminocarbonyl, ethyl,

1,1,1-trifluoropropan-2-yl, 1,1-difluoroethyl, 1,1,1-trifluoroethyl, 1,1,1-trifluoropropyl,  
trifluoromethoxyethyl, trifluoromethylcarbonylaminomethyl, methylsulfonylethyl,  
methylcarbonyloxyethyl, and groups shown below

[Chemical formula 31]



[0105]

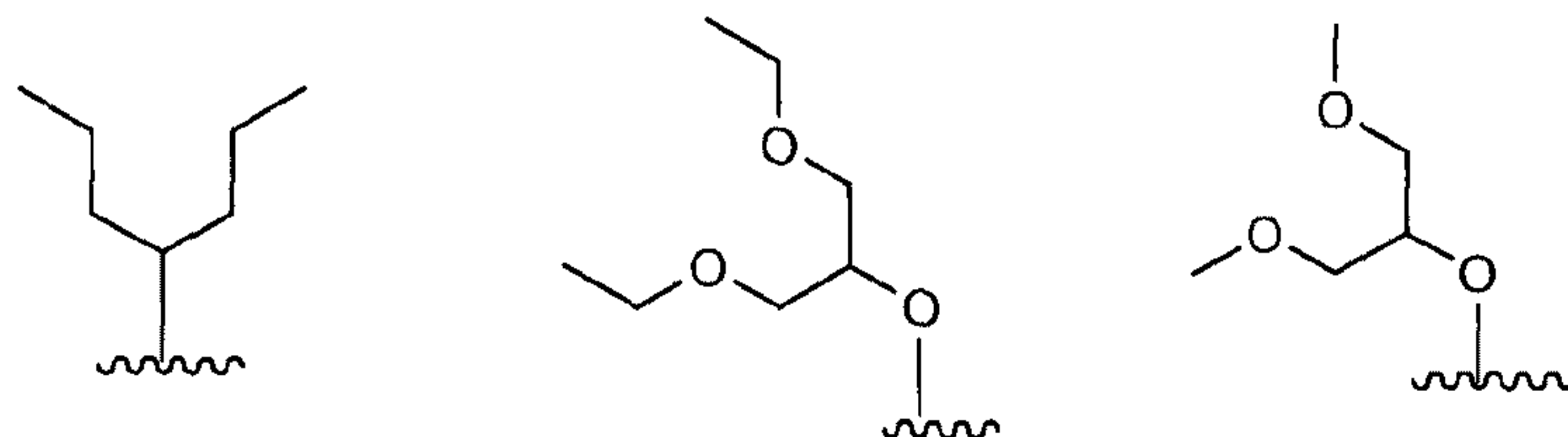
etc.

[0106]

Examples of "lower alkyl optionally substituted by substituent group F" include hydroxyethyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, iso-butyl, sec-butyl, pentan-2-yl, hydroxymethyl, hydroxyethyl, carboxymethyl, carboxyethyl,

carboxypropyl, ethoxycarbonylpropyl, and groups shown below

[Chemical formula 32]



[0107]

etc.

Examples of "lower alkenyl optionally substituted by substituent group C" include ethylenyl, 3-methylbuten-2-yl, carboxyethylenyl, hydroxyethylenyl, difluoroethylenyl, 1-propen-2-yl, etc.

Examples of "lower alkynyl optionally substituted by substituent group C" include 1-propynyl, 1-butylnyl, 3,3,3-trifluoromethylpropynyl, 3-hydroxy-propynyl, etc.

Examples of "lower alkyloxy optionally substituted by substituent group C" include methyloxy, ethyloxy, trifluoromethyloxy, trichloromethyloxy, hydroxymethyloxy, hydroxyethyloxy, carboxymethyloxy, carboxyethyloxy, etc.

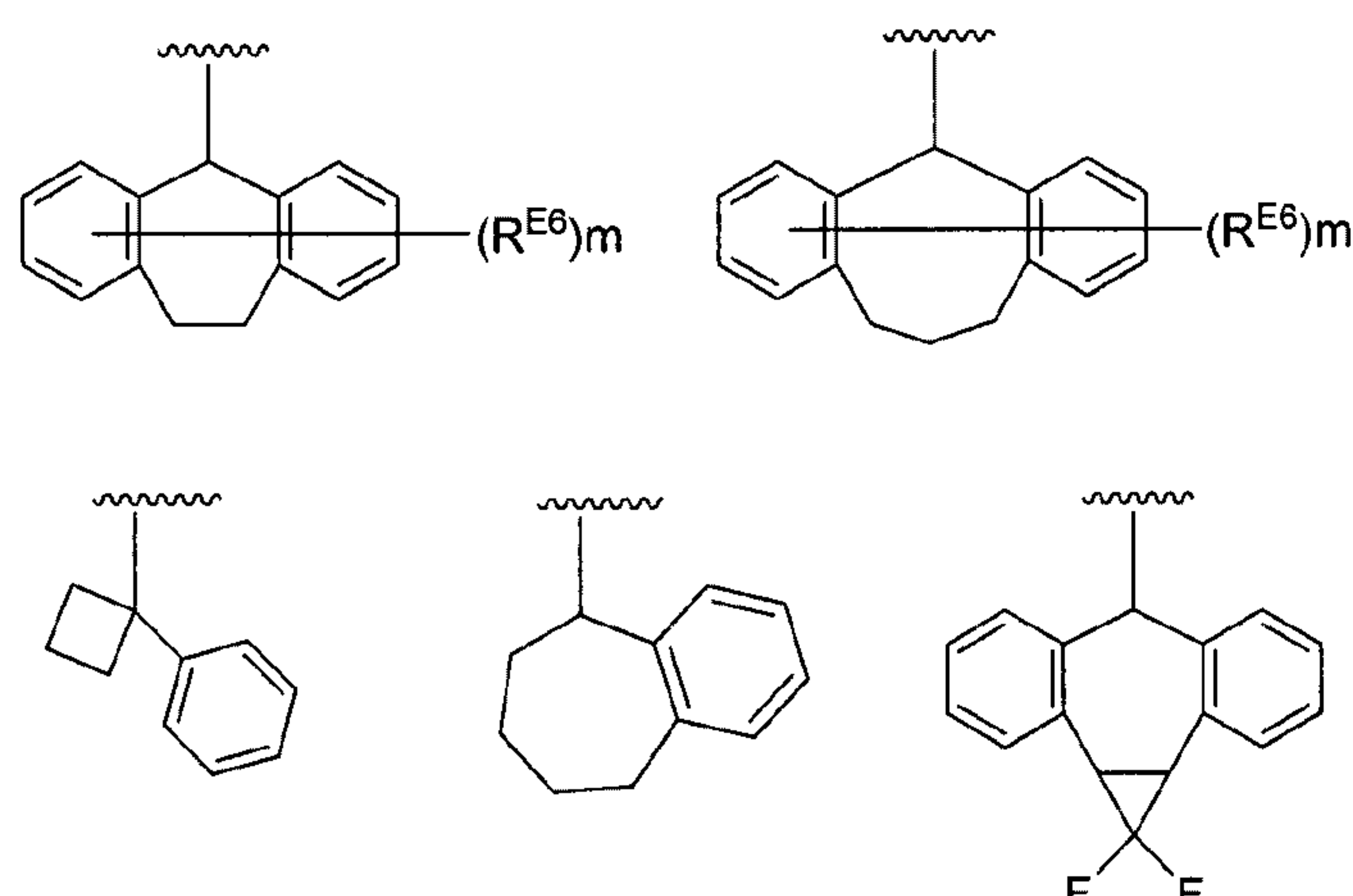
Examples of "lower alkenyloxy optionally substituted by substituent group C" include 3-fluoro-1-propenyloxy, ethylenyl, carboxyethylenyl, hydroxyethylenyloxy, difluoroethylenyloxy, etc.

Examples of "lower alkylcarbonyl optionally substituted by substituent group C" include methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, hydroxymethylcarbonyl, hydroxyethylcarbonyl, trifluoromethylcarbonyl, 2,2,2-trifluoromethylcarbonyl, carboxymethylcarbonyl, etc.

Examples of "lower alkyloxycarbonyl optionally substituted by substituent

group C" include methyloxycarbonyl, ethyloxycarbonyl, trifluoromethyl oxycarbonyl, trichloromethyloxycarbonyl, hydroxymethyloxycarbonyl, hydroxyethyloxycarbonyl, carboxymethyloxycarbonyl, etc.

Examples of "carbocyclic group optionally substituted by substituent group C" include phenyl, naphthyl, anthracenyl, phenanthracenyl, adamantyl, 1-hydroxyadamantyl, 2-hydroxyadamantyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, fluorocyclopropyl, difluorocyclobutanyl, difluorocyclohexyl, and groups shown below [Chemical formula 33]



[0108]

(wherein  $R^{E6}$  represents a group selected from substituent group C, and each  $R^{E6}$  may be the same or different) etc.

[0109]

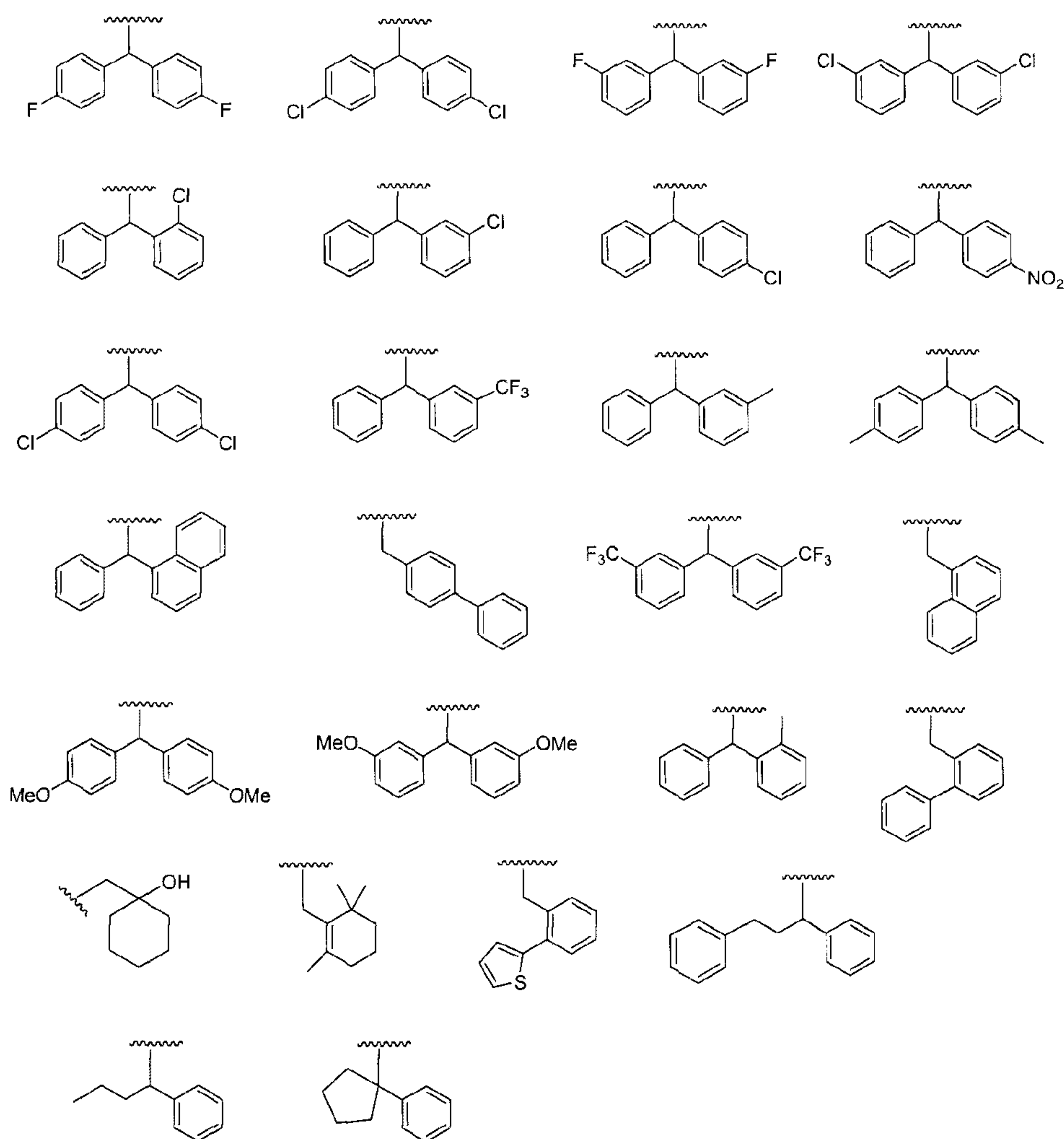
Examples of "carbocyclic group optionally substituted by substituent group F" include phenyl, naphthyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl,

4-methoxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 1,5-difluorophenyl, etc.

[0110]

Examples of "carbocycle lower alkyl optionally substituted by substituent group C" include cyclopropylmethyl, 4-hydroxybenzyl, cyclopentylmethyl, benzyl, 2-aminobenzyl, 2-cyanobenzyl, 2-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 1,3,5-trifluorobenzyl, 3,4,5-trifluorobenzyl, 4-methoxybenzyl, 2,4-difluorobenzyl, 2-fluoro-3-chlorobenzyl, benzhydryl, 4-phenylbenzyl, phenethyl, phenylpropyl, 4-methylcarbonylaminobenzyl, 3,4-dichlorobenzyl, 4-chloro-2-fluorobenzyl, 3,5-dihydroxybenzyl, and groups shown below

[Chemical formula 34]



[0111]

,etc.

Examples of "carbocycle lower alkyl optionally substituted by substituent group F" include cyclopropylmethyl, 4-hydroxybenzyl, cyclopentylmethyl, benzyl, 2-aminobenzyl, 2-cyanobenzyl, 2-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 1,3,5-trifluorobenzyl, 3,4,5-trifluorobenzyl, 4-methoxybenzyl, 2,4-difluorobenzyl, 2-fluoro-3-chlorobenzyl, benzhydryl, 4-phenylbenzyl, phenethyl, phenylpropyl,

4-methylcarbonylaminobenzyl, 3,4-dichlorobenzyl, 4-chloro-2-fluorobenzyl, 3,5-dihydroxybenzyl, etc.

[0112]

Examples of "carbocycleoxy lower alkyl optionally substituted by substituent group C" include 4-hydroxyphenyloxymethyl, 4-hydroxyphenyloxyethyl, cyclopropyloxymethyl, cyclopentyloxymethyl, 4-fluorophenyloxymethyl, 4-fluorophenyloxyethyl, 4-trifluoromethylphenyloxymethyl, 4-trifluoromethylphenyloxyethyl, 4-methoxyphenyloxymethyl, 4-methoxyphenyloxyethyl, etc.

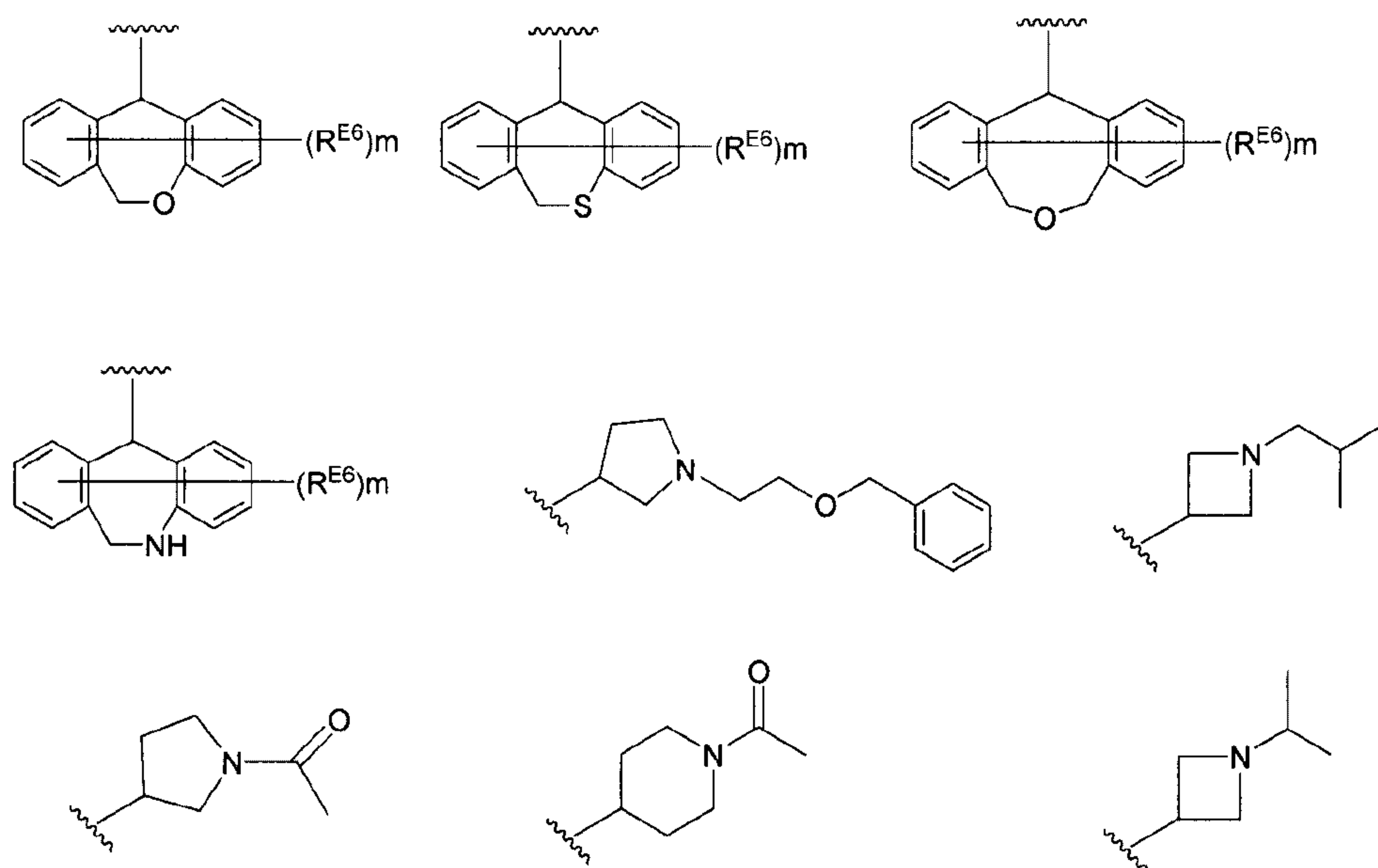
Examples of "carbocyclecarbonyl optionally substituted by substituent group C" include phenylcarbonyl, 4-fluorophenylcarbonyl, 4-trifluoromethylphenylcarbonyl, 4-methoxyphenylcarbonyl, cyclopropylcarbonyl, etc.

Examples of "carbocycleoxy optionally substituted by substituent group C" include phenyloxy, cyclopropyloxy, cyclopentyloxy, 4-fluorophenyloxy, 4-trifluoromethylphenyloxy, 4-methoxyphenyloxy, etc.

Examples of "carbocycleoxycarbonyl optionally substituted by substituent group C" include phenyloxycarbonyl, cyclopropyloxycarbonyl, cyclopentyloxycarbonyl, 4-fluorophenyloxycarbonyl, 4-trifluoromethylphenyloxycarbonyl, 4-methoxyphenyloxycarbonyl, etc.

Examples of "heterocyclic group optionally substituted by substituent group C" include pyrimidinyl, pyridyl, benzoxazolyl, morpholinyl, tetrahydropyranyl, furyl, thiophenyl, oxazolyl, thiazolyl, pyrazolyl, methylpyrrolidinyl, isopropylpyrrolidinyl, methylsulfonylpyrrolidinyl, hydroxyethylpyrrolidinyl, methylpiperidinyl, methylpiperazinyl, tetrahydrofuryl, and groups shown below

[Chemical formula 35]



[0113]

(wherein  $R^{E6}$  represents a group selected from substituent group C, and each  $R^{E6}$  may be the same or different) etc.

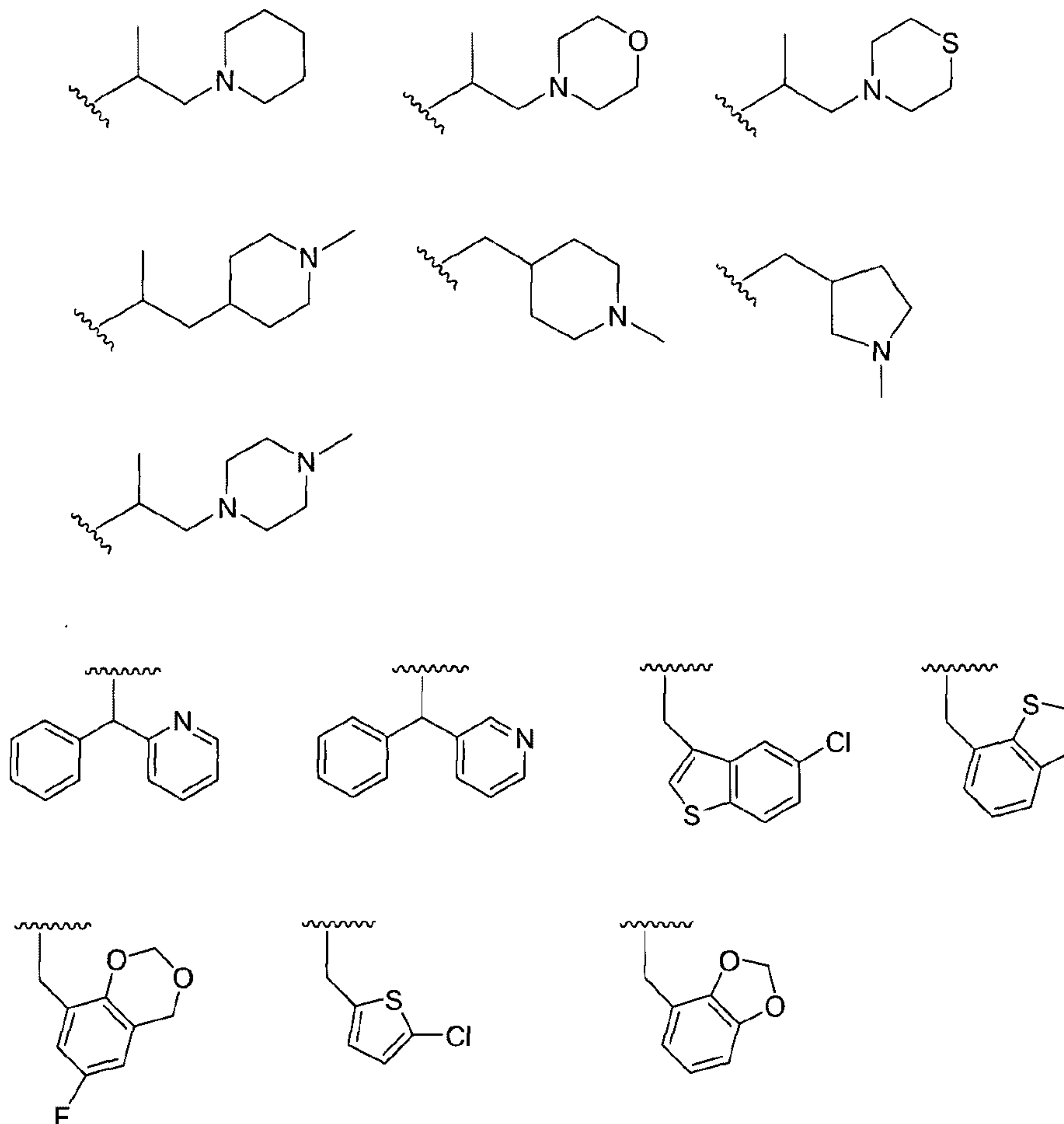
Examples of "heterocyclic group optionally substituted by substituent group F" include morpholinyl, pyridyl, methyl-1,3-dioxol-2-one, trimethyl-2-oxabicyclo[2.2.1]heptan-3-one, pyrrolidinyl, methyl-pyrrolidine-2-carboxylate, tetrahydropyranyl, hydroxymethylpyrrolidinyl, etc.

[0114]

Examples of "heterocycle lower alkyl optionally substituted by substituent group C" include tetrahydropyranylmethyl, pyridylmethyl, isoxazolylmethyl, 5-methyl-isoxazolylmethyl, 3-methyl-oxadiazolylmethyl, indolylmethyl, benzothiophenylmethyl, 5-chlorobenzothiophenylmethyl, thiazolylmethyl, 2-methylthiazolylmethyl, pyrazolylmethyl, 2-methylpyrazolylmethyl, dithiophenylmethyl, tetrazolylmethyl, quinazolylmethyl, morpholinylmethyl, and

groups shown below

[Chemical formula 36]



[0115]

etc.

Examples of "heterocycle lower alkyl optionally substituted by substituent group F" include tetrahydropyranylmethyl, pyridylmethyl, isoxazolylmethyl, 5-methyl-isoxazolylmethyl, 3-methyl-oxadiazolylmethyl, indolylmethyl, benzothiophenylmethyl, 5-chlorobenzothiophenylmethyl, thiazolylmethyl,

2-methylthiazolylmethyl, pyrazolylmethyl, 2-methylpyrazolylmethyl, dithiophenylmethyl, tetrazolylmethyl, quinazolylmethyl, morpholinylmethyl, etc.

[0116]

Examples of "heterocycleoxy lower alkyl optionally substituted by a substituent group C" include tetrahydropyranyloxymethyl, pyridyloxymethyl, isoxazolyloxymethyl, 5-methyl-isoxazolyloxymethyl, indolyloxymethyl, benzothiophenyloxymethyl, 5-chlorobenzothiophenyloxymethyl, thiazolyloxymethyl, 2-methylthiazolyloxymethyl, pyrazolyloxymethyl, 2-methylpyrazolyloxymethyl, etc.

Examples of "heterocyclecarbonyl optionally substituted by substituent group C" include tetrahydropyranylcarbonyl, pyridylcarbonyl, isoxazolylcarbonyl, 5-methyl-isoxazolylcarbonyl, indolylcarbonyl, benzothiophenylcarbonyl, 5-chlorobenzothiophenylcarbonyl, thiazolylcarbonyl, 2-methylthiazolylcarbonyl, pyrazolylcarbonyl, 2-methylpyrazolylcarbonyl, etc.

Examples of "heterocycleoxy optionally substituted by substituent C" include tetrahydropyranyloxy, pyridyloxy, isoxazolyloxy, 5-methyl-isoxazolyloxy, indolyloxy, benzothiophenyloxy, 5-chlorobenzothiophenyloxy, thiazolyloxy, 2-methylthiazolyloxy, pyrazolyloxy, 2-methylpyrazolyloxy, etc.

Examples of "heterocycleoxycarbonyl optionally substituted by substituent group C" include tetrahydropyranyloxycarbonyl, pyridyloxycarbonyl, isoxazolyloxycarbonyl, 5-methyl-isoxazolyloxycarbonyl, indolyloxycarbonyl, benzothiophenyloxycarbonyl, 5-chlorobenzothiophenyloxycarbonyl, thiazolyloxycarbonyl, 2-methylthiazolyloxycarbonyl, pyrazolyloxycarbonyl, 2-methylpyrazolyloxycarbonyl, etc.

[0117]

Examples of "lower alkylamino optionally substituted by substituent group F"

include methylamino, dimethylamino, ethylamino, diethylamino, etc.

Examples of "lower alkylthio optionally substituted by substituent group F" include methylthio, ethylthio, etc.

Examples of "lower alkylsilyl optionally substituted by substituent group F" include trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, etc.

[0118]

$P^R$  in  $-OP^R$  group is preferably a group converted into  $-OH$  group by action of drug-metabolizing enzymes, hydrolases, gastric acids, and/or enterobacteria, after in vivo administration (for example, oral administration).

[0119]

Examples of more preferred embodiment of  $P^R$  include a group selected from the following formulae b) to x).

- b)  $-C(=O)-P^{R1}$ ,
- c)  $-C(=O)-L-P^{R1}$ ,
- d)  $-C(=O)-L-O-P^{R1}$ ,
- e)  $-C(=O)-L-O-L-O-P^{R1}$ ,
- f)  $-C(=O)-L-O-C(=O)-P^{R1}$ ,
- g)  $-C(=O)-O-P^{R2}$ ,
- h)  $-C(=O)-N(P^{R2})_2$ ,
- i)  $-C(=O)-O-L-O-P^{R2}$ ,
- j)  $-CH_2-O-P^{R3}$ ,
- k)  $-CH_2-O-L-O-P^{R3}$ ,
- l)  $-CH_2-O-C(=O)-P^{R3}$ ,
- m)  $-CH_2-O-C(=O)-O-P^{R3}$ ,
- n)  $-CH(-CH_3)-O-C(=O)-O-P^{R3}$ ,

- o)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{P}^{\text{R}3}$ ,
- p)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- q)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{N}(\text{P}^{\text{R}3})_2$ ,
- r)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- s)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{L}-\text{N}(\text{P}^{\text{R}3})_2$ ,
- t)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- u)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{N}(-\text{K})-\text{C}(=\text{O})-\text{P}^{\text{R}3}$ ,
- v)  $-\text{CH}_2-\text{O}-\text{P}(=\text{O})(-\text{OH})_2$ ,
- w)  $-\text{CH}_2-\text{O}-\text{P}(=\text{O})(-\text{OBn})_2$ ,
- x)  $-\text{CH}_2-\text{P}^{\text{R}4}$

(wherein L is straight or branched lower alkylene,

K is hydrogen, or straight or branched lower alkylene, or straight or branched lower alkenylene,

$\text{P}^{\text{R}1}$  is carbocyclic group optionally substituted by substituent group F, heterocyclic group optionally substituted by substituent group F, lower alkyl amino optionally substituted by substituent group F, or lower alkylthio optionally substituted by substituent group F,

$\text{P}^{\text{R}2}$  is lower alkyl optionally substituted by substituent group F, carbocyclic group optionally substituted by substituent group F, or heterocyclic group optionally substituted by substituent group F,

$\text{P}^{\text{R}3}$  is lower alkyl optionally substituted by substituent group F, carbocyclic group optionally substituted by substituent group F, heterocyclic group optionally substituted by substituent group F, lower alkyl amino optionally substituted by substituent group F, carbocycle lower alkyl optionally substituted by substituent group F, heterocycle lower alkyl optionally substituted by substituent group F, or lower

alkylsilyl,

$P^{R4}$  is carbocyclic group optionally substituted by substituent group F, or heterocyclic group optionally substituted by substituent group F, and

substituent group F; oxo, lower alkyl, hydroxy lower alkyl, amino, lower alkylamino, carbocycle lower alkyl, lower alkylcarbonyl, halogen, hydroxy, carboxy, lower alkylcarbonylamino, lower alkylcarbonyloxy, lower alkyloxycarbonyl, lower alkyloxy, cyano, and nitro)

[0120]

Examples of further preferred embodiment of  $P^R$  include following b), k), l), and m).

b)  $-C(=O)-P^{R1}$ ,

l)  $-CH_2-O-C(=O)-P^{R3}$ ,

n)  $-CH_2-O-C(=O)-O-P^{R3}$ ,

n)  $-CH(-CH_3)-O-C(=O)-O-P^{R3}$ ,

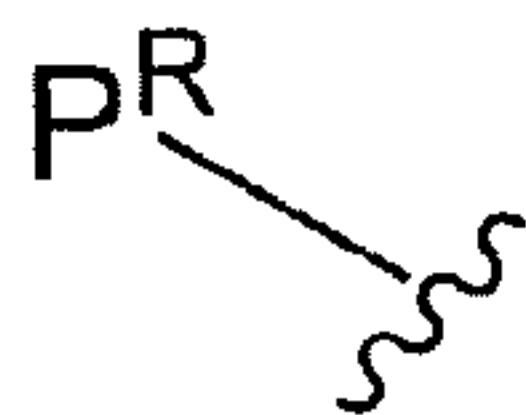
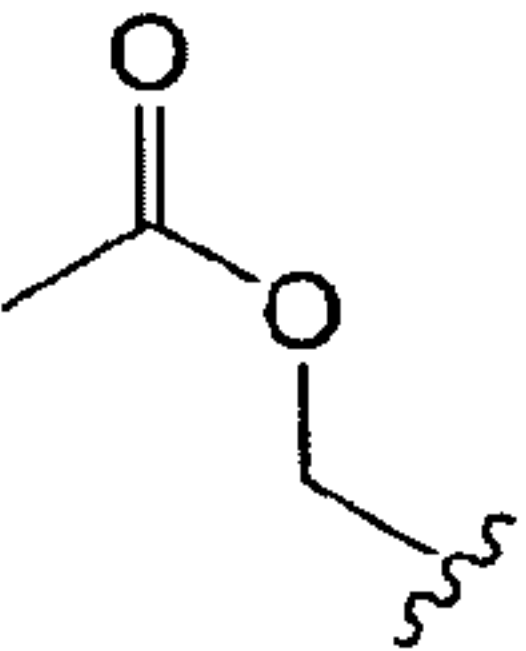
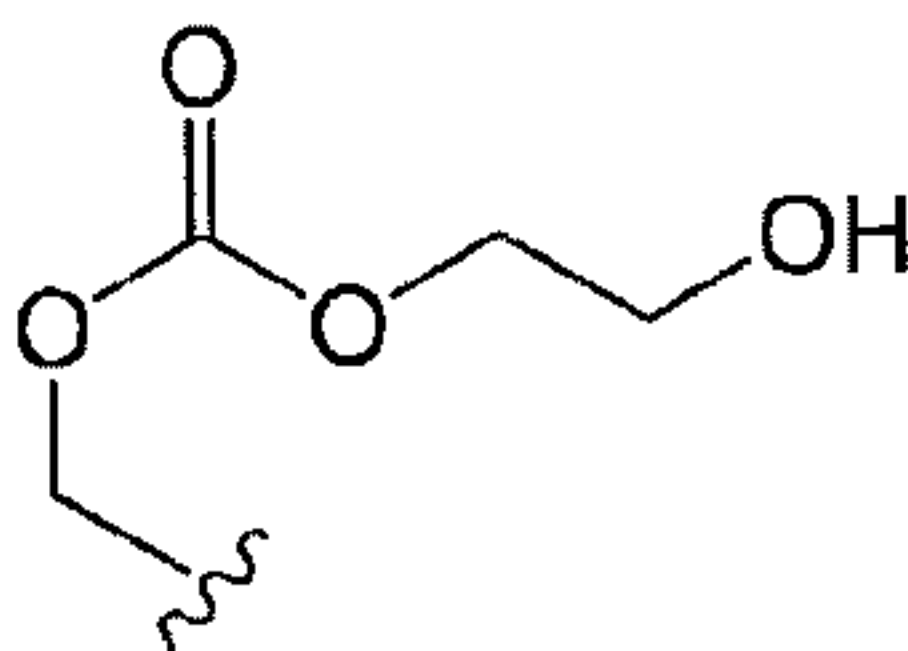
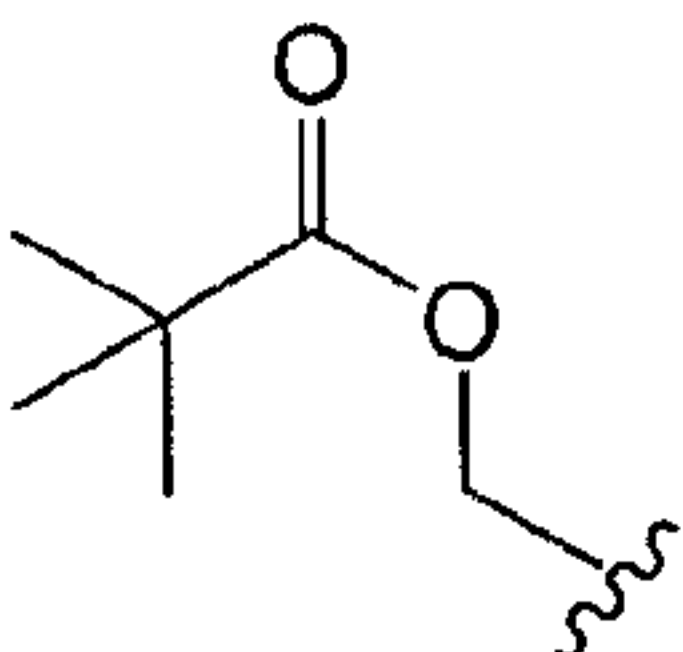
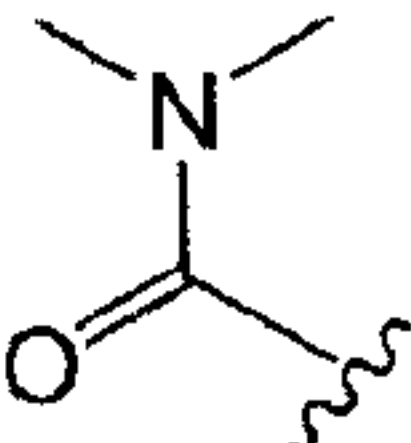
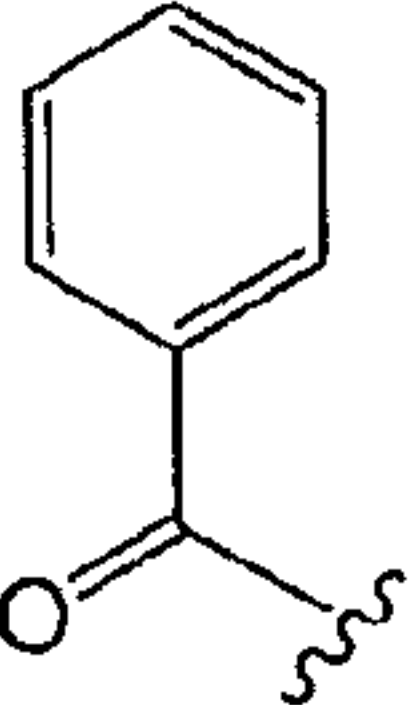
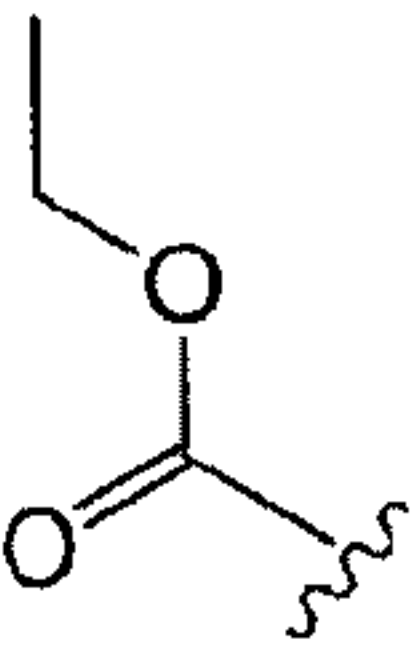
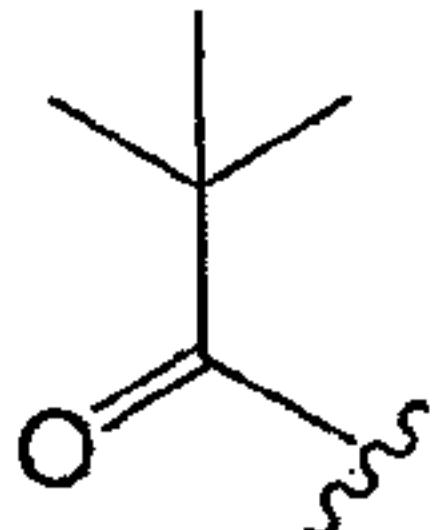
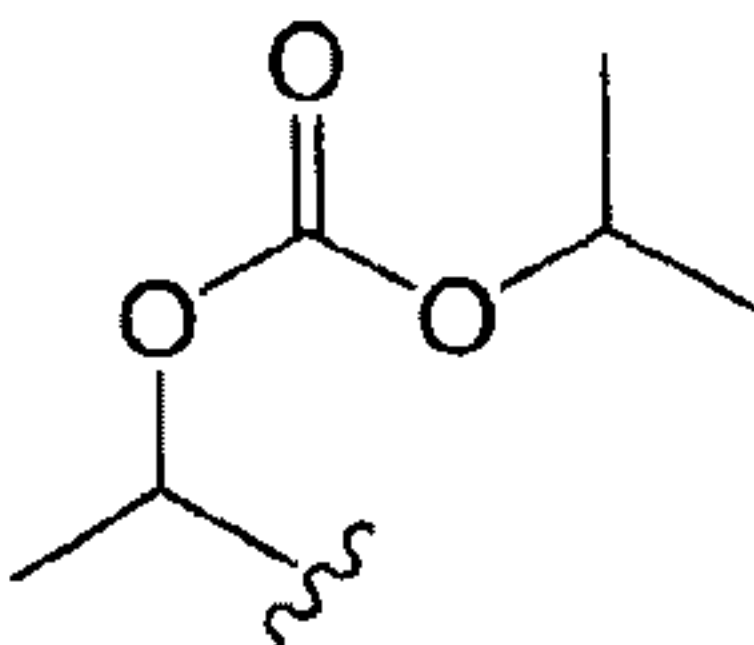
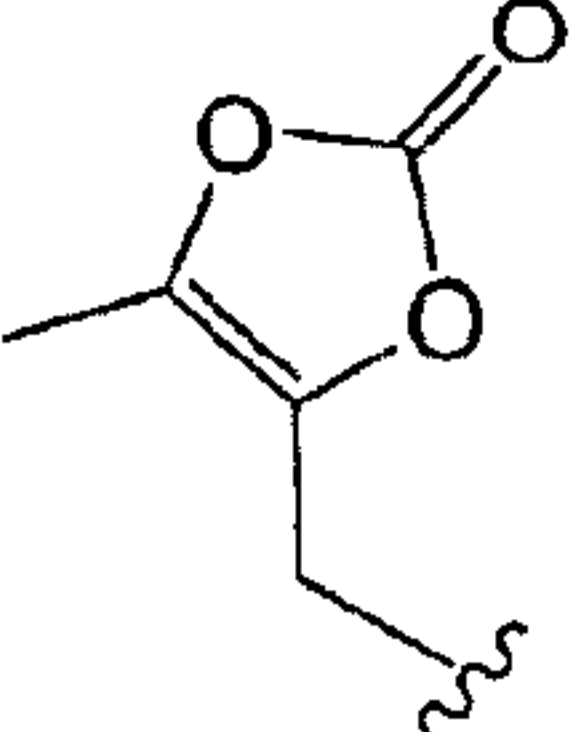
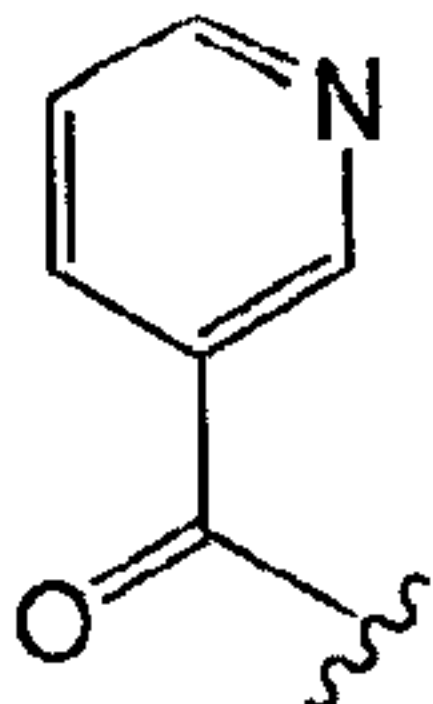
(wherein each symbol is same as above)

[0121]

Examples of another embodiment of a preferable substituent of  $P^R$  include groups of P-1 to P-83 in the following Tables 1 to 9.

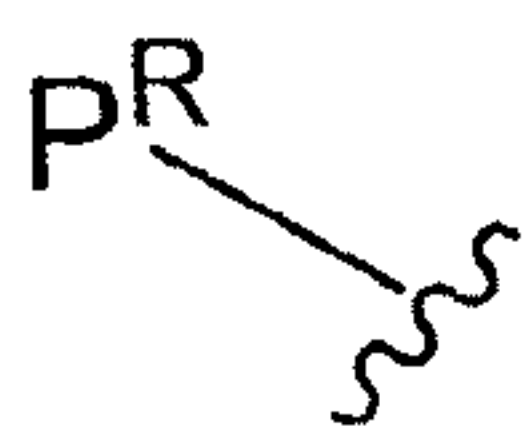
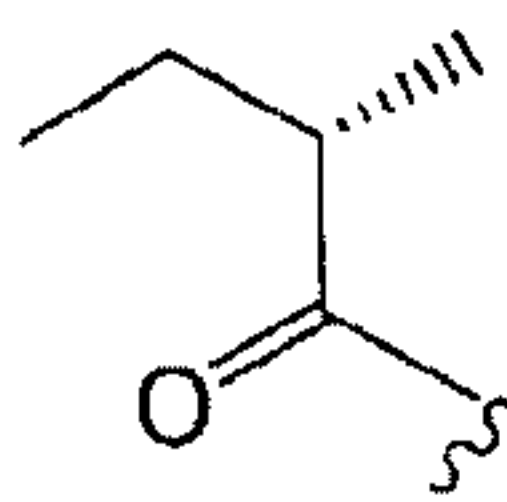
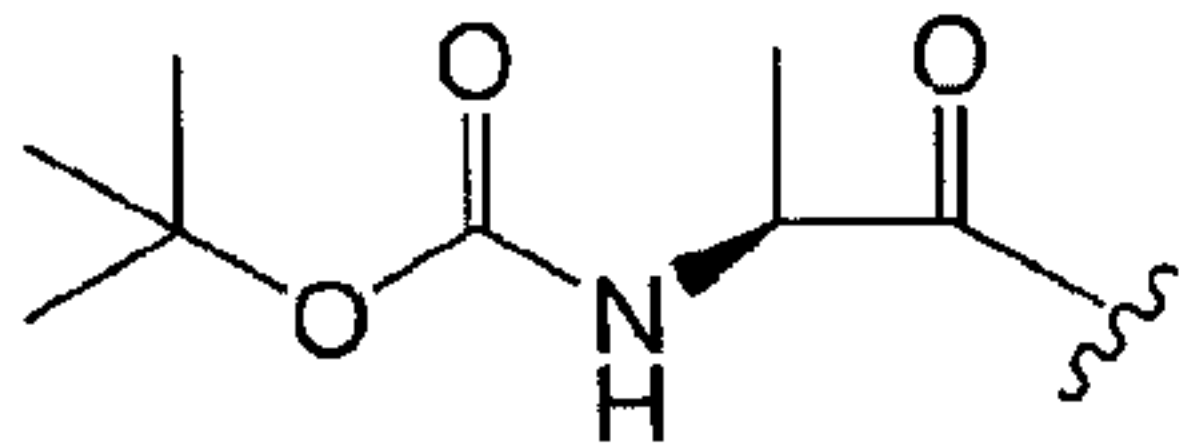
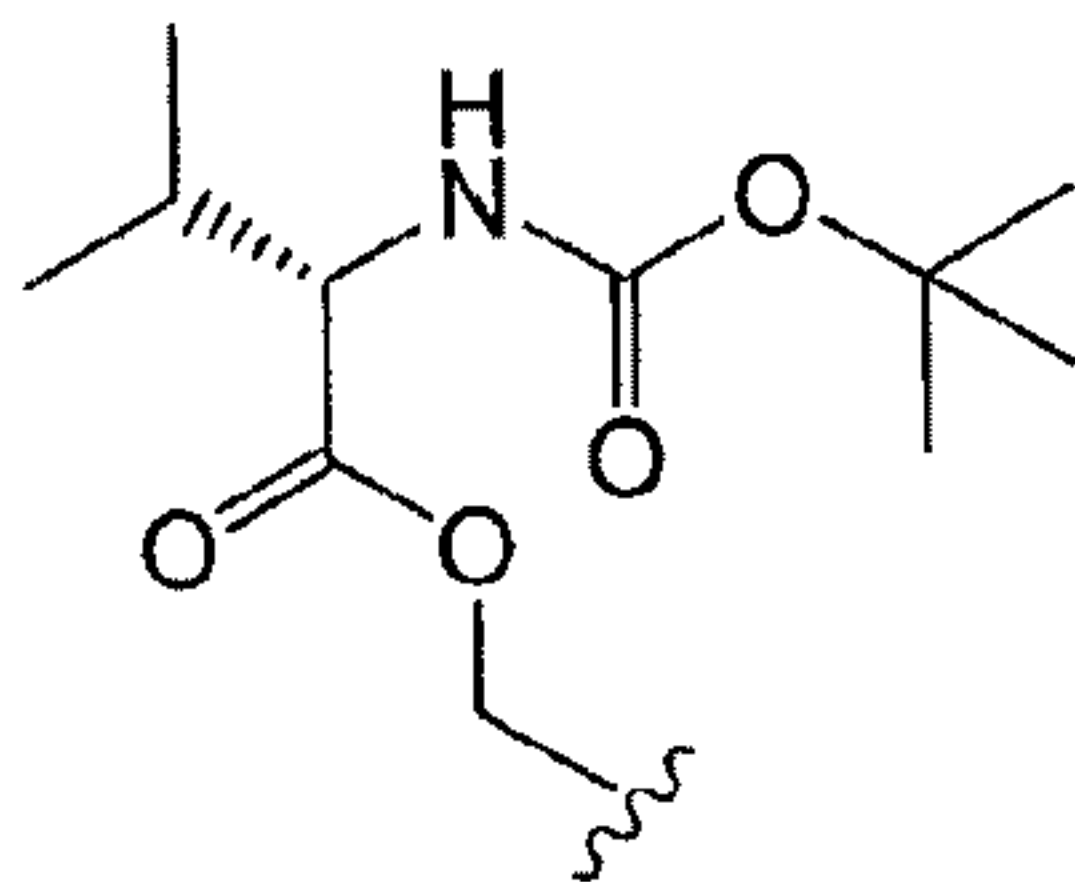
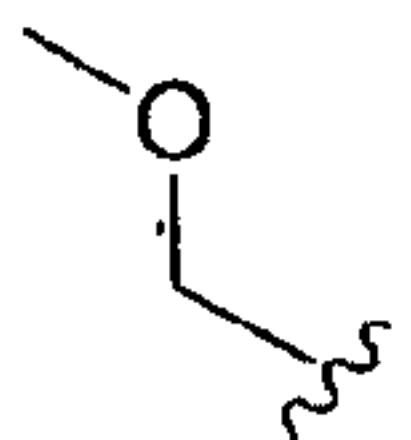
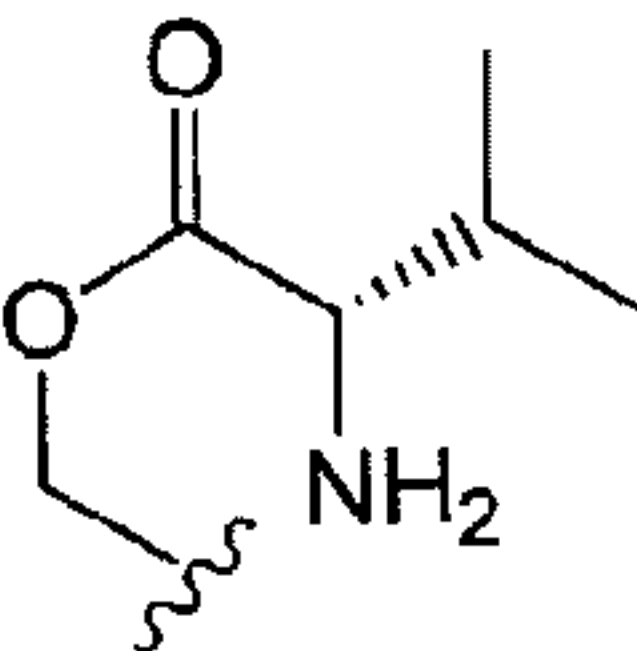
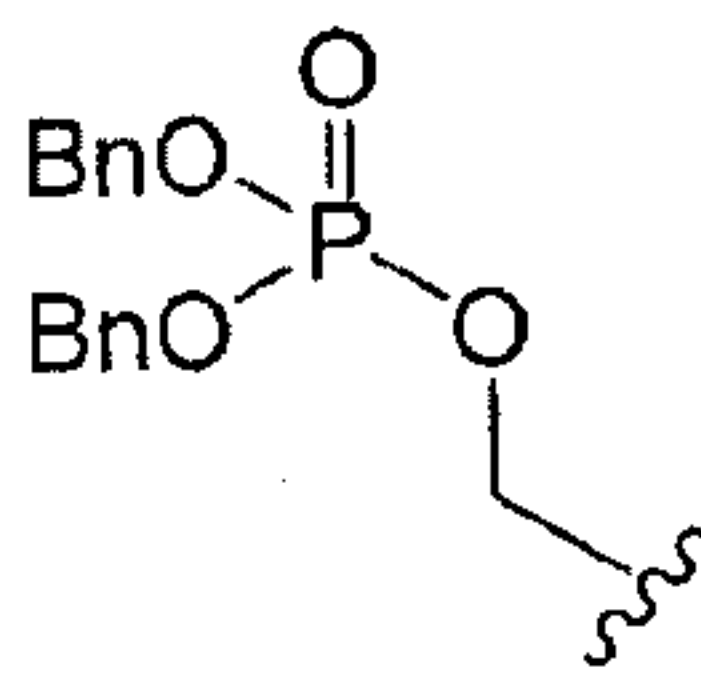
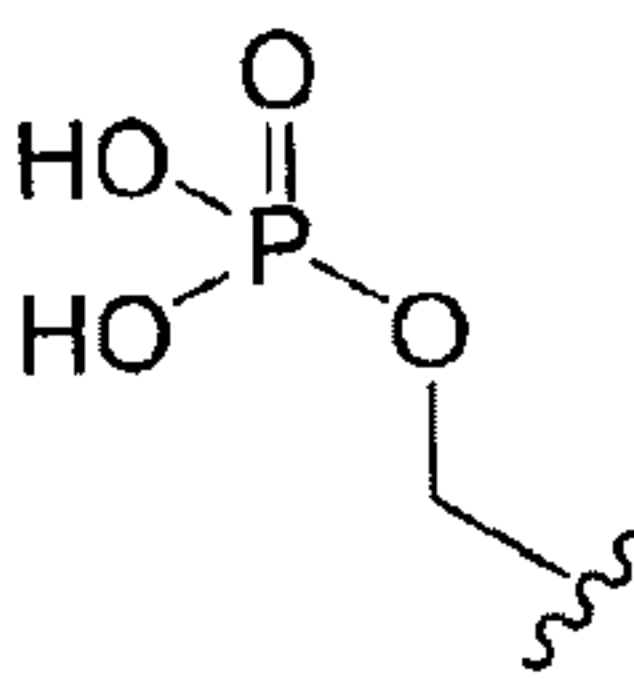
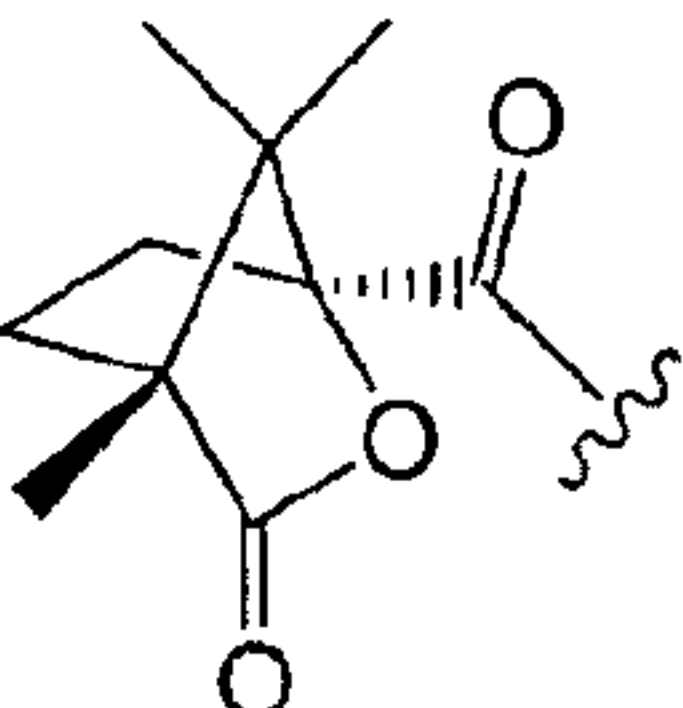
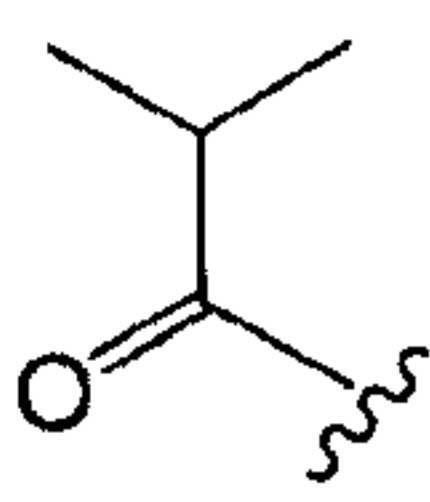
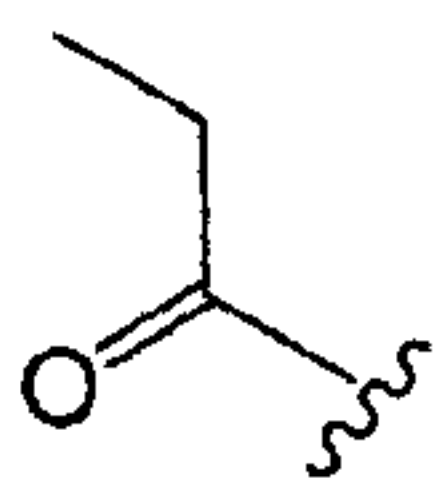
[0122]

[Table 1]

|     |                                                                                     |      |                                                                                       |
|-----|-------------------------------------------------------------------------------------|------|---------------------------------------------------------------------------------------|
|     |    |      |                                                                                       |
| P-1 |    | P-6  |    |
| P-2 |  | P-7  |  |
| P-3 |  | P-8  |  |
| P-4 |  | P-9  |  |
| P-5 |  | P-10 |  |

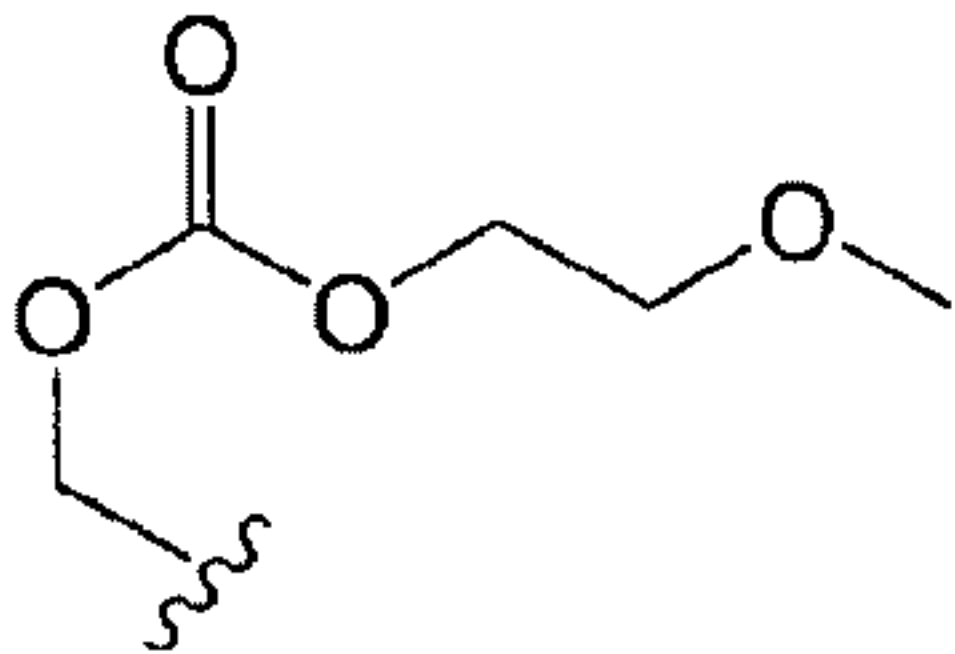
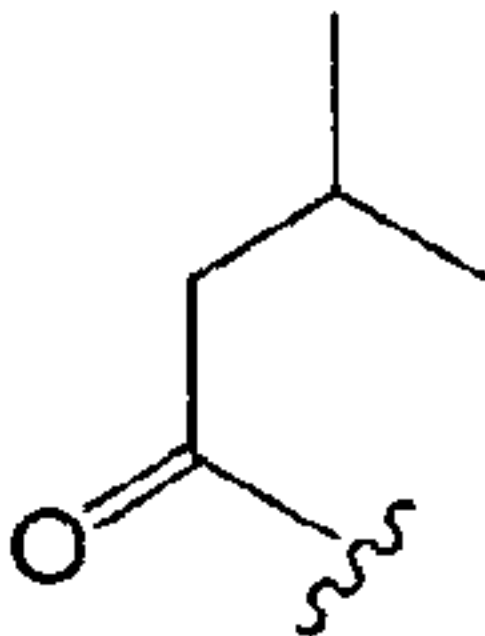
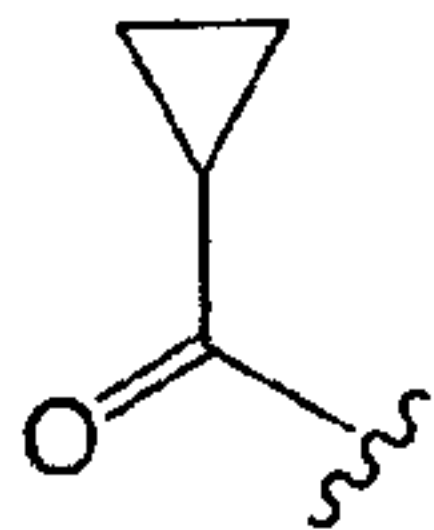
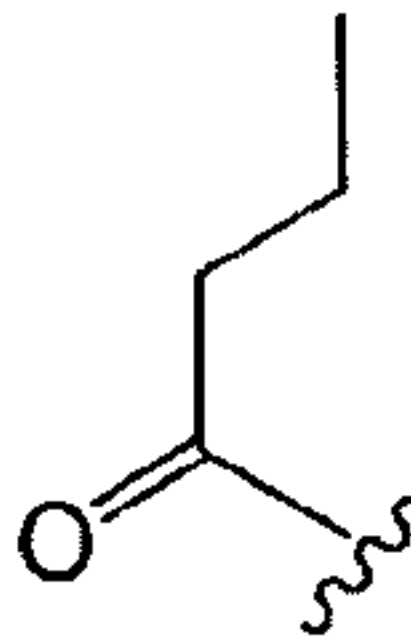
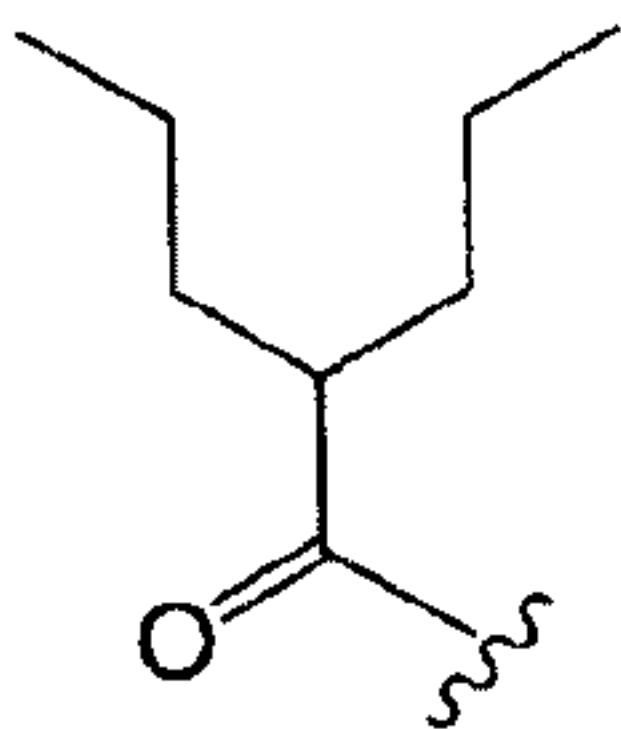
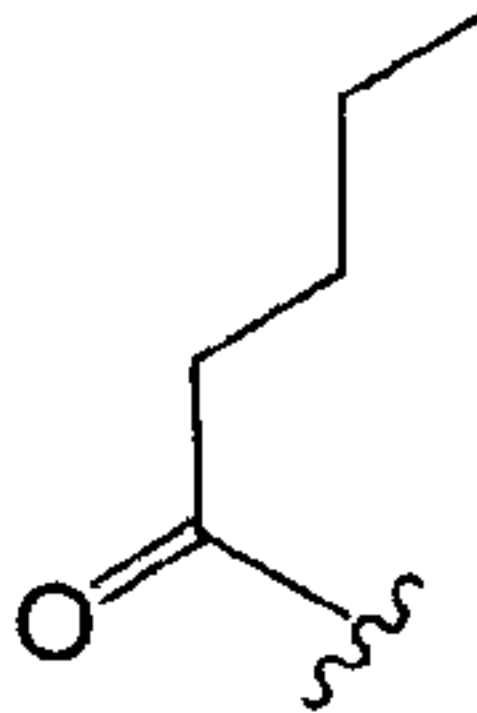
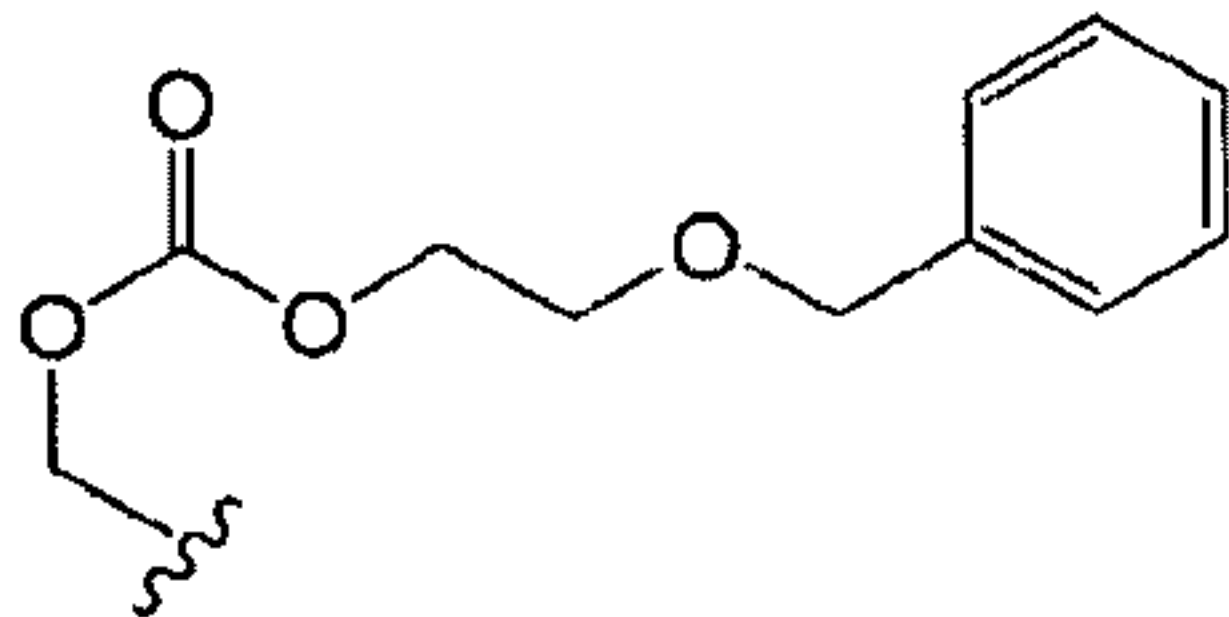
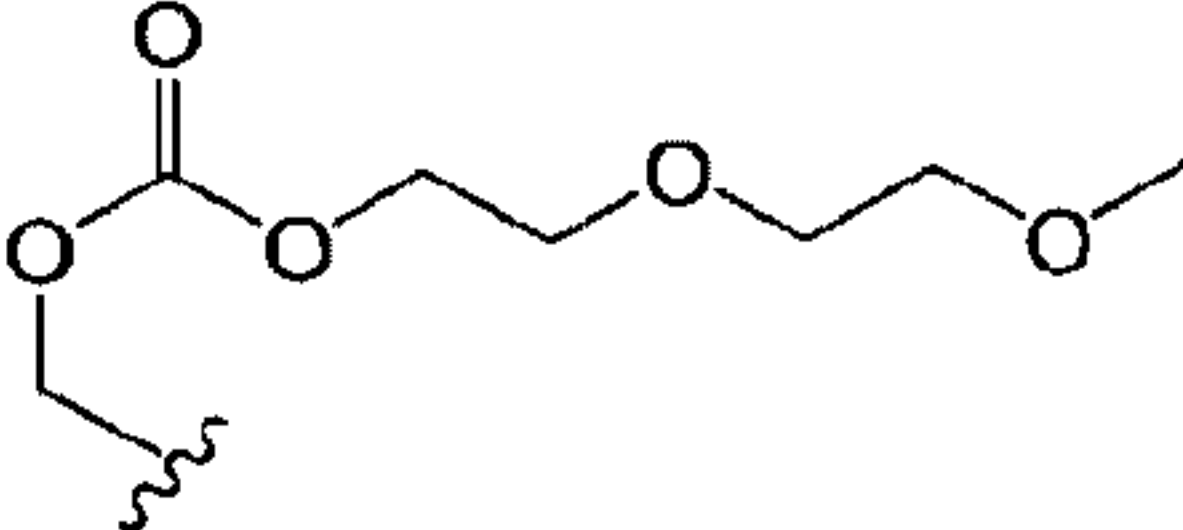
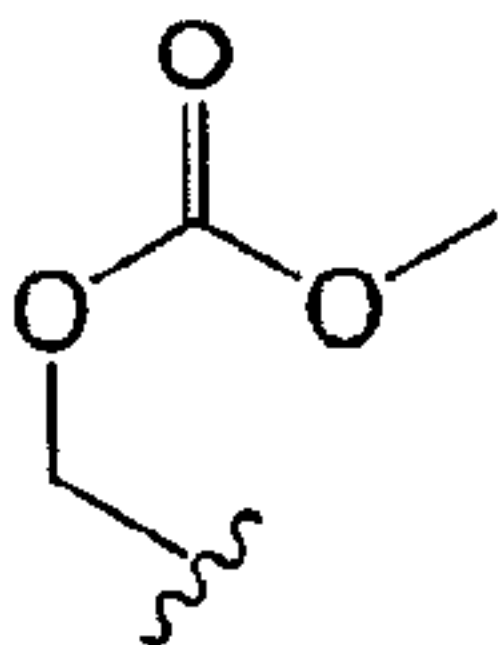
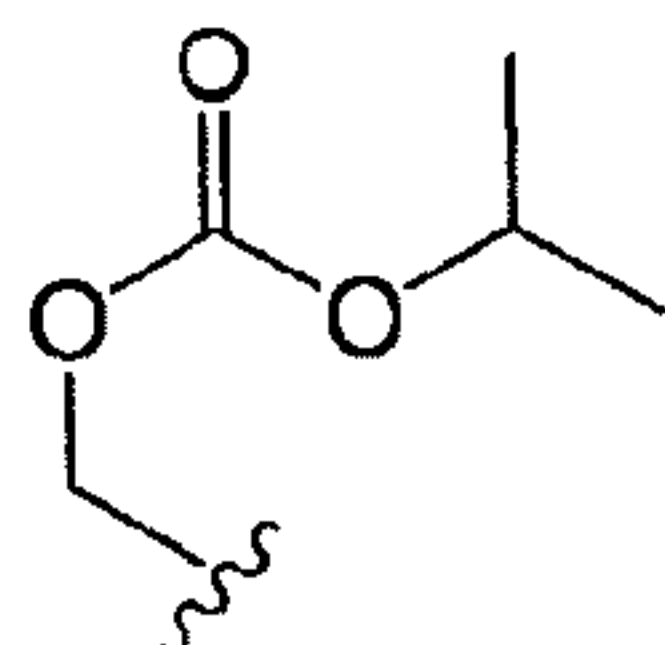
[0123]

[Table 2]

|      |                                                                                       |
|------|---------------------------------------------------------------------------------------|
|      |      |
| P-11 |      |
| P-12 |   |
| P-13 |   |
| P-14 |    |
| P-15 |    |
| P-16 |    |
| P-17 |   |
| P-18 |  |
| P-19 |  |
| P-20 |  |

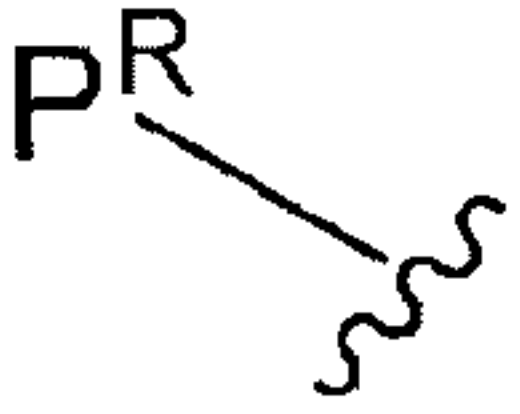
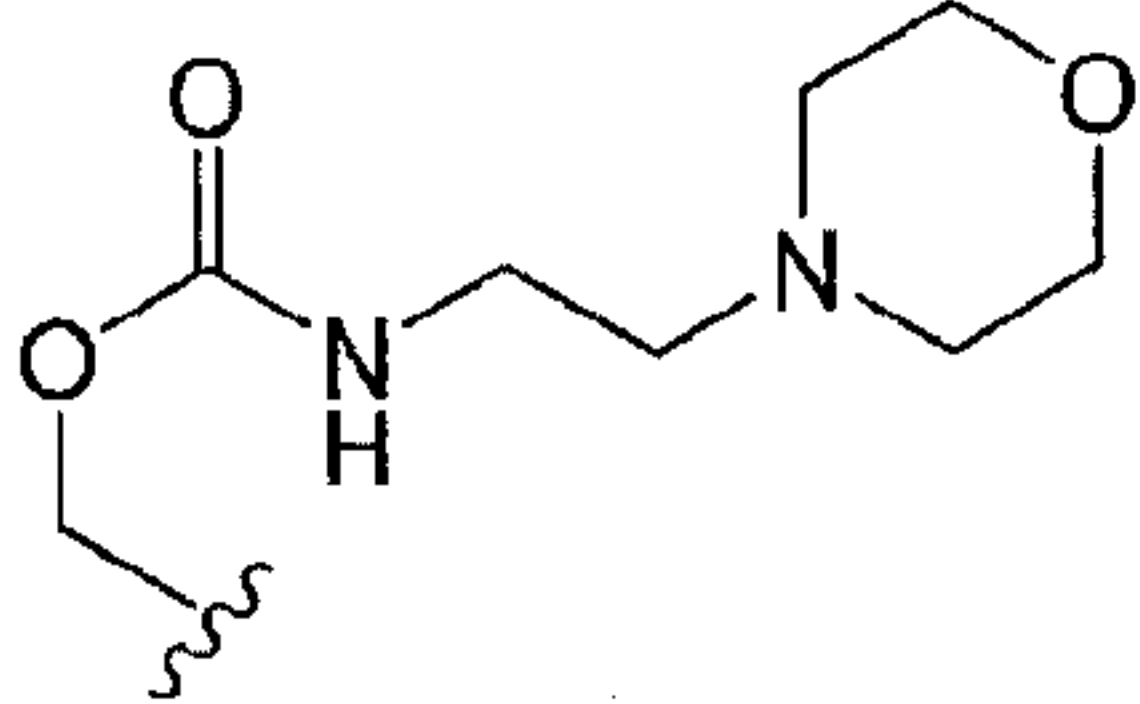
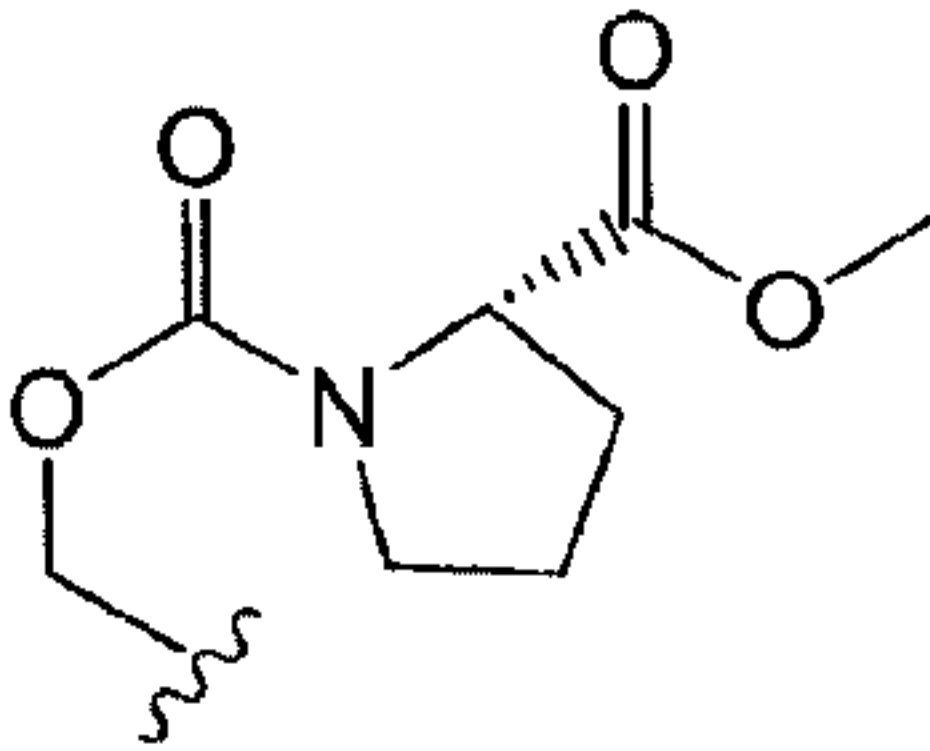
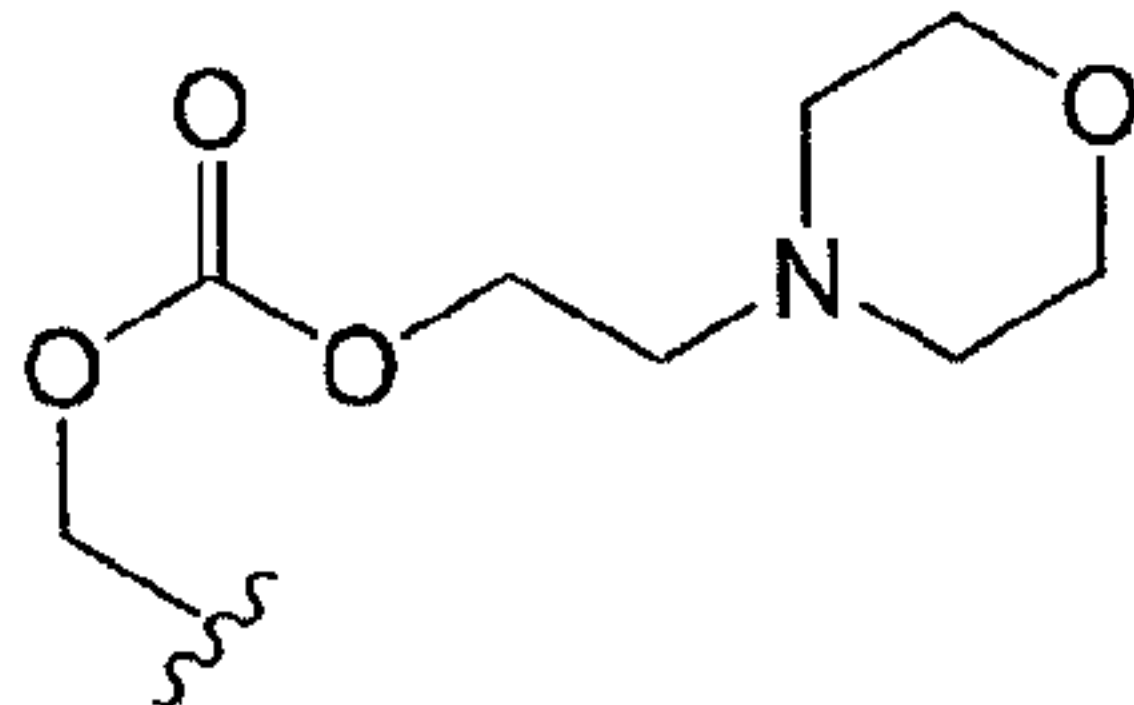
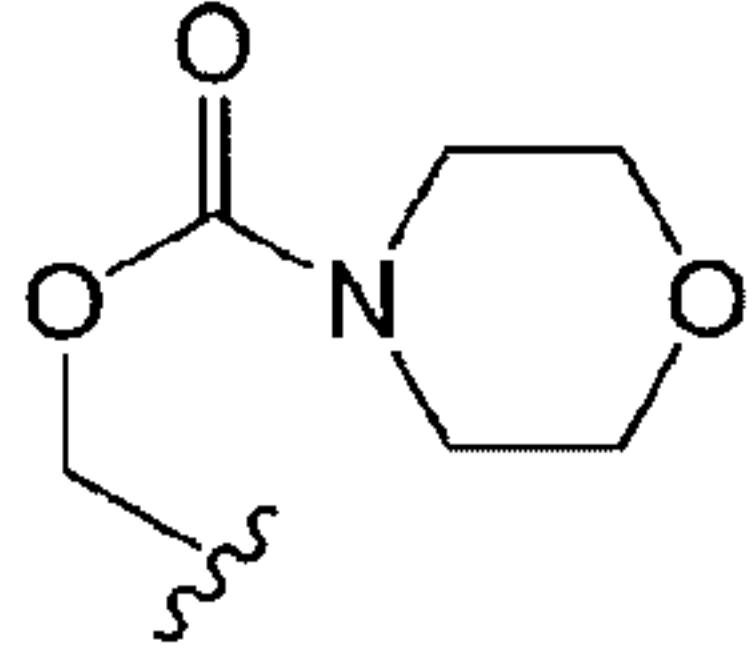
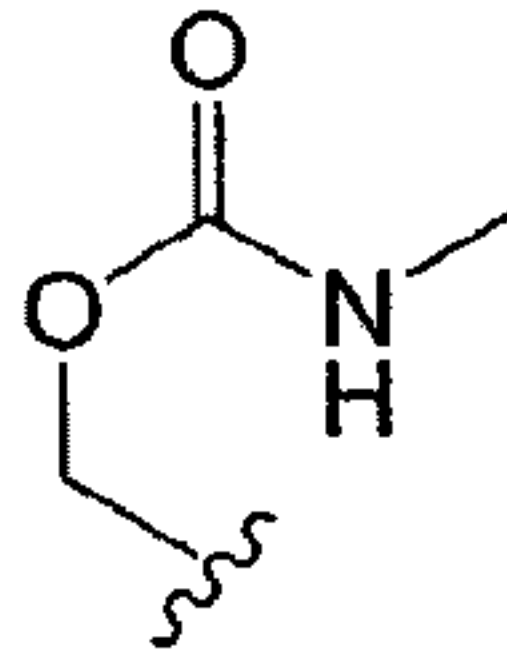
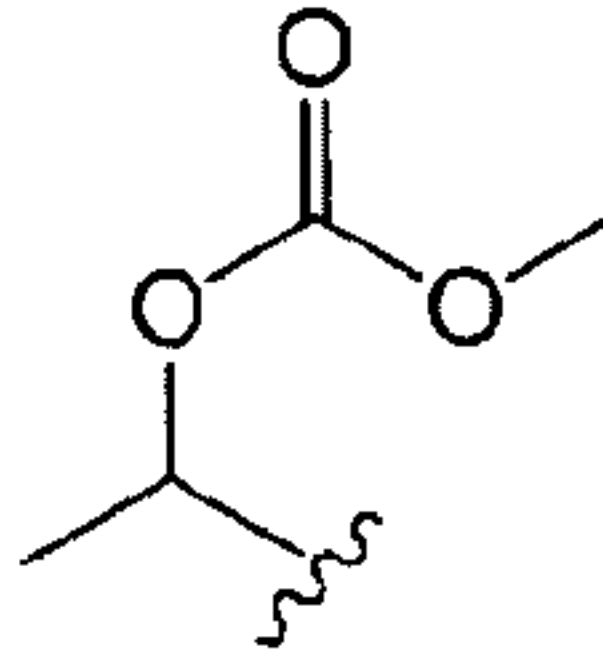
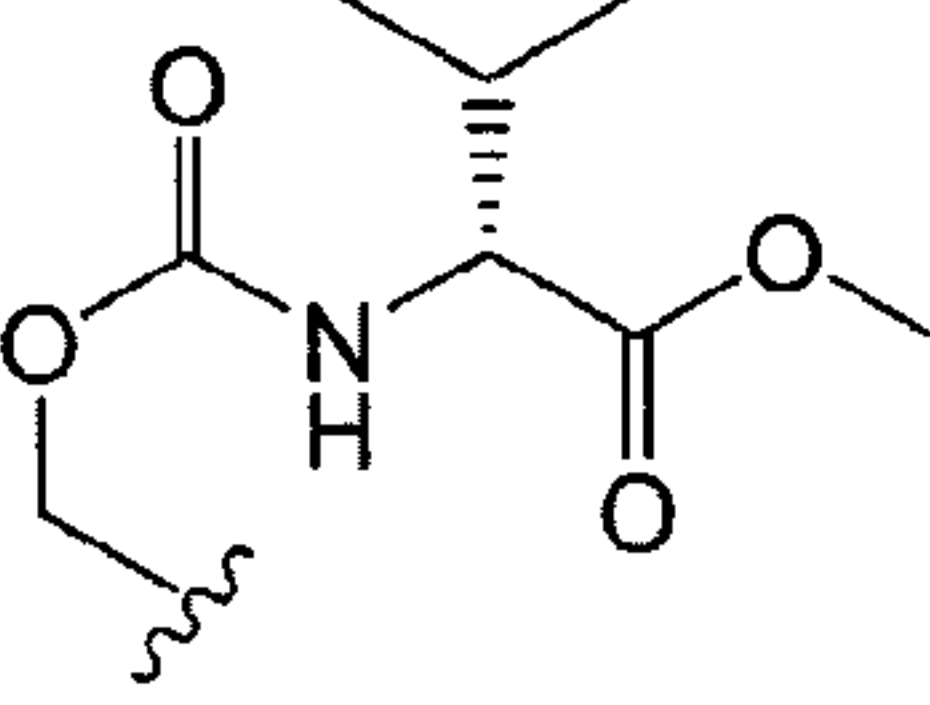
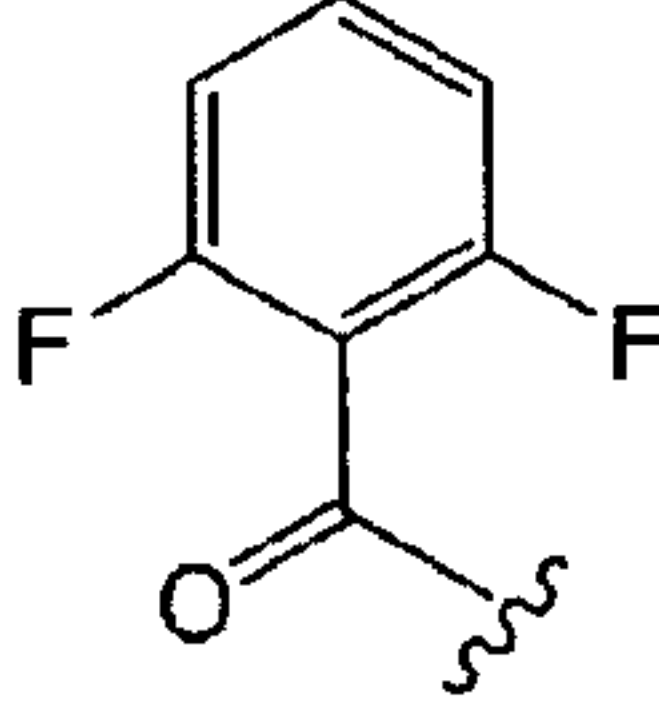
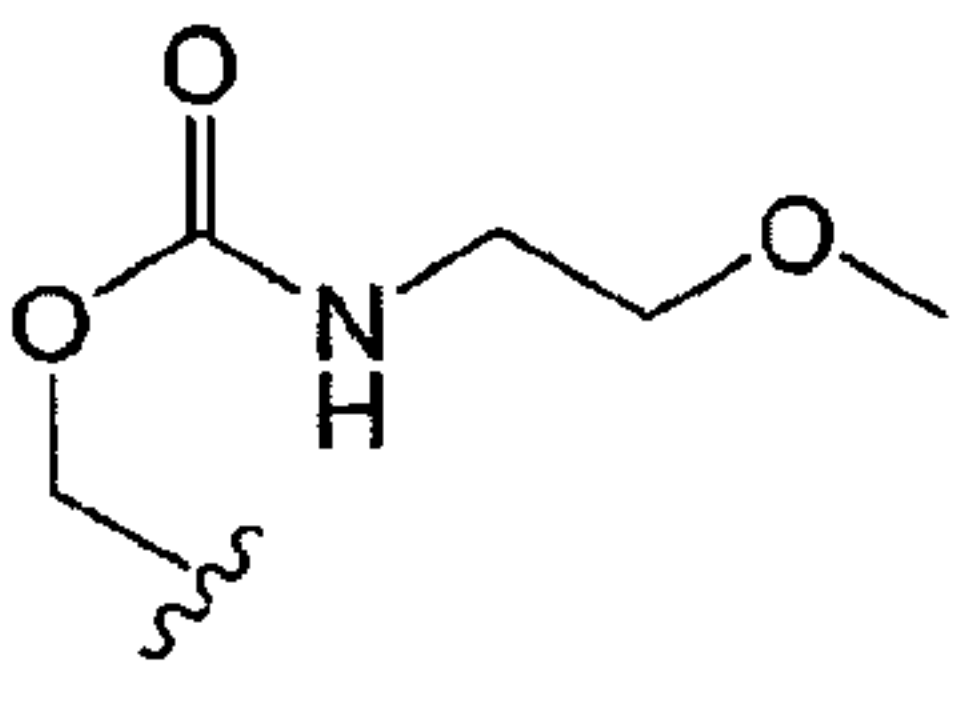
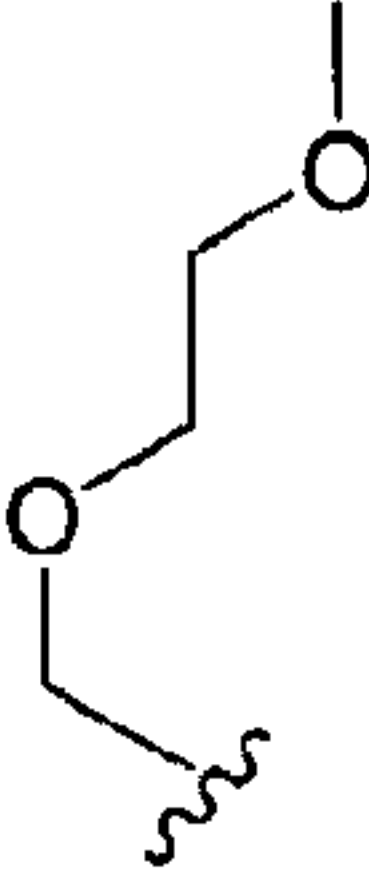
[0124]

[Table 3]

|      |                                                                                      |      |                                                                                       |
|------|--------------------------------------------------------------------------------------|------|---------------------------------------------------------------------------------------|
|      |     |      |                                                                                       |
| P-21 |     | P-26 |    |
| P-22 |   | P-27 |  |
| P-23 |   | P-28 |  |
| P-24 |  | P-29 |  |
| P-25 |   | P-30 |  |

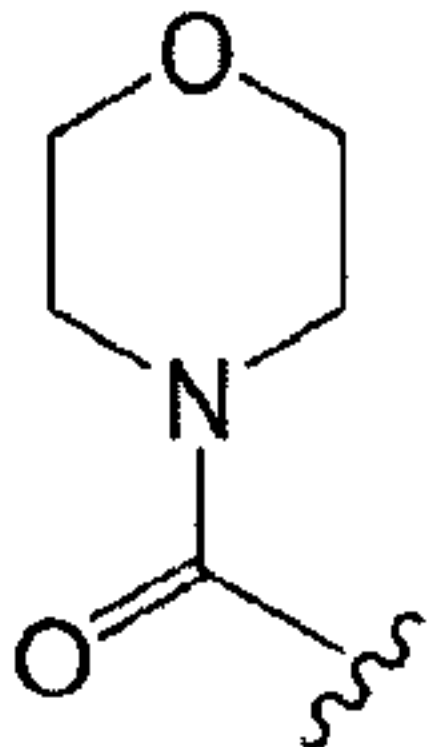
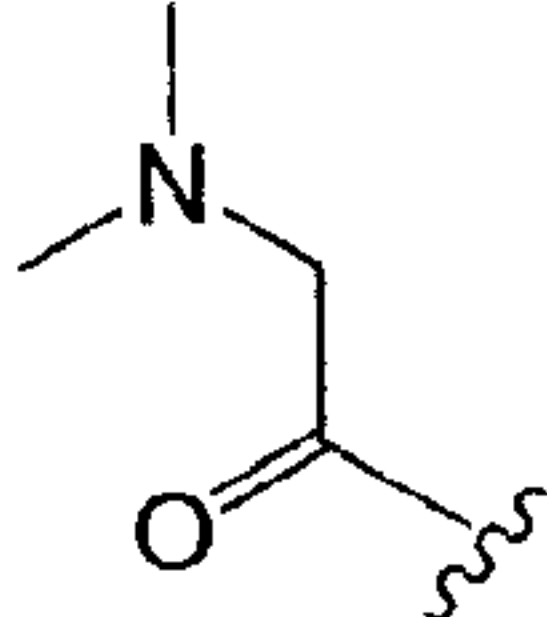
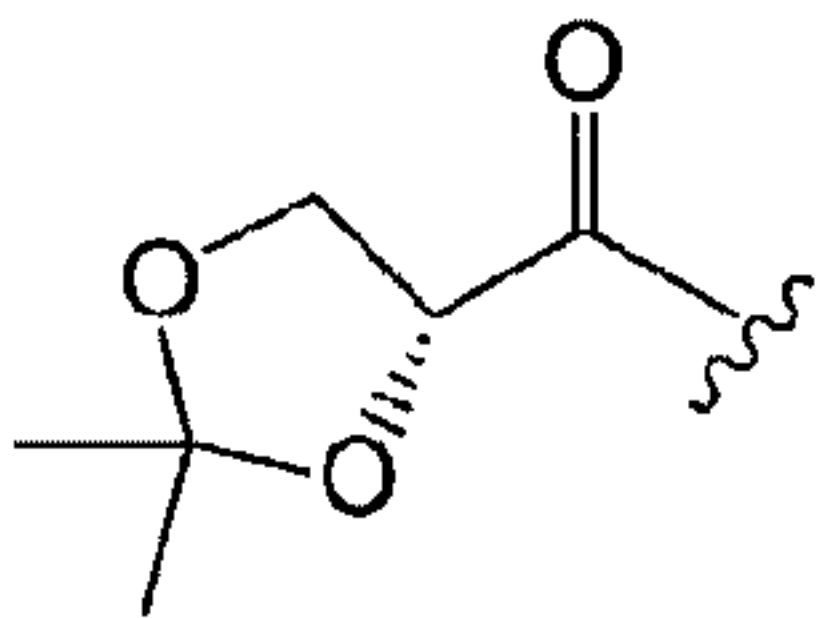
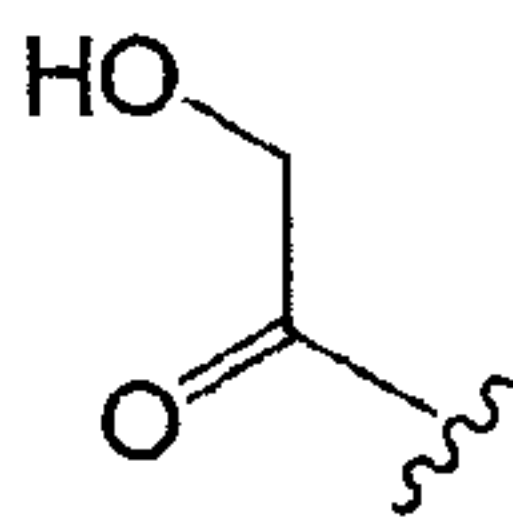
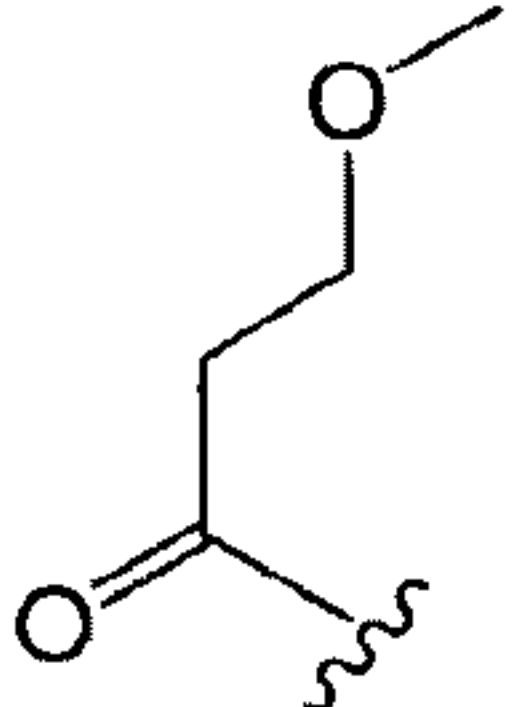
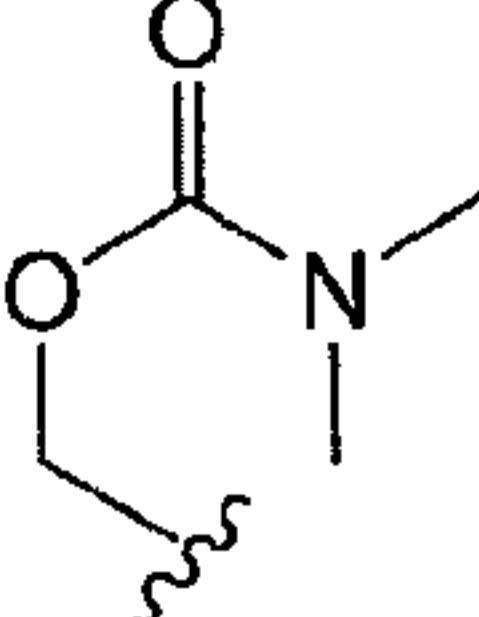
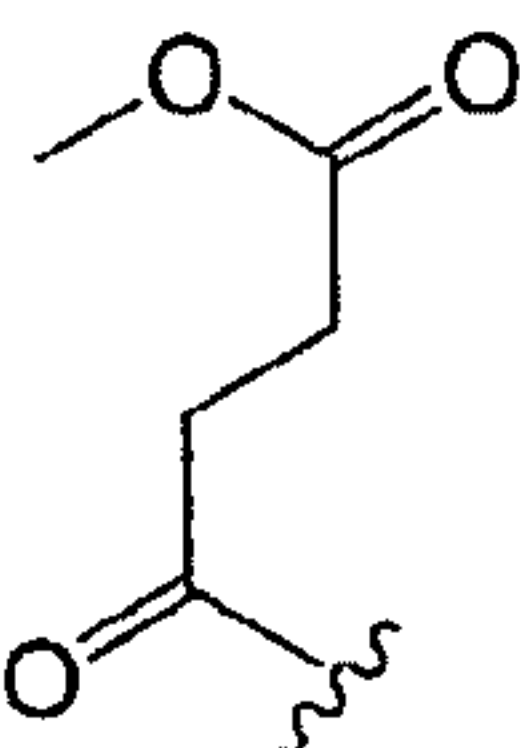
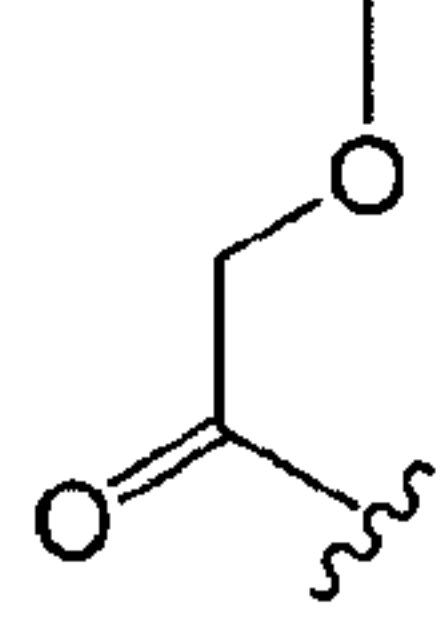
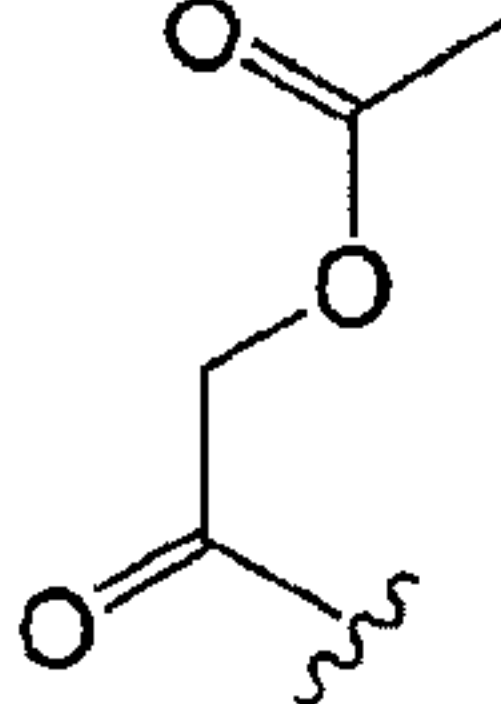
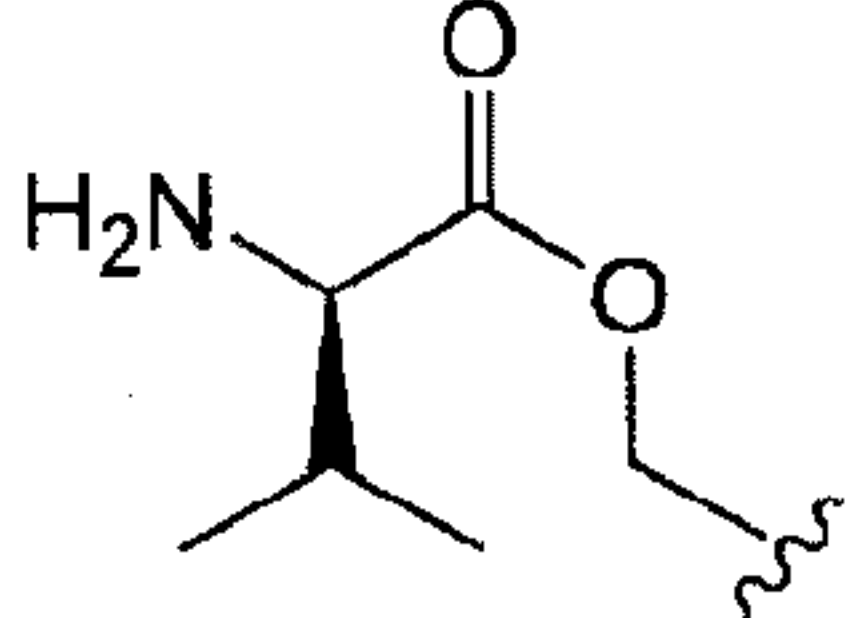
[0125]

[Table 4]

|      |                                                                                      |      |                                                                                       |
|------|--------------------------------------------------------------------------------------|------|---------------------------------------------------------------------------------------|
|      |     |      |                                                                                       |
| P-31 |    | P-36 |    |
| P-32 |  | P-37 |  |
| P-33 |   | P-38 |  |
| P-34 |  | P-39 |  |
| P-35 |  | P-40 |  |

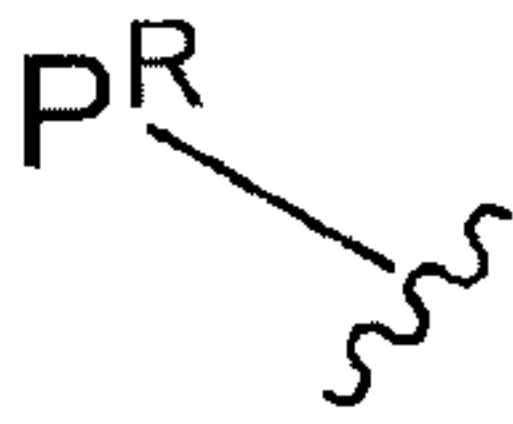
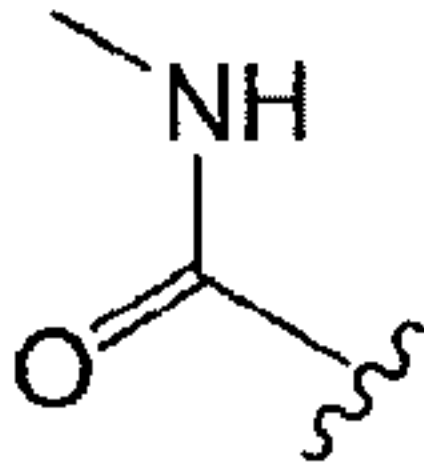
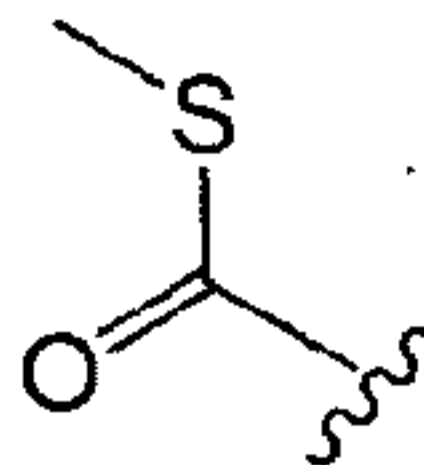
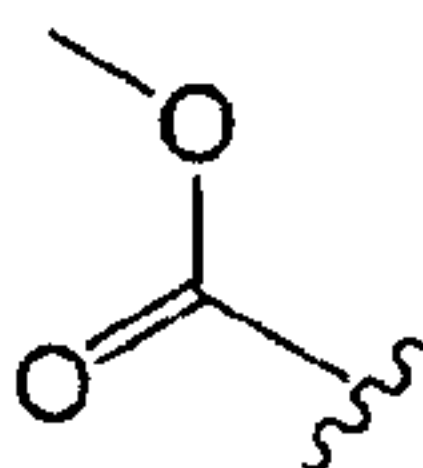
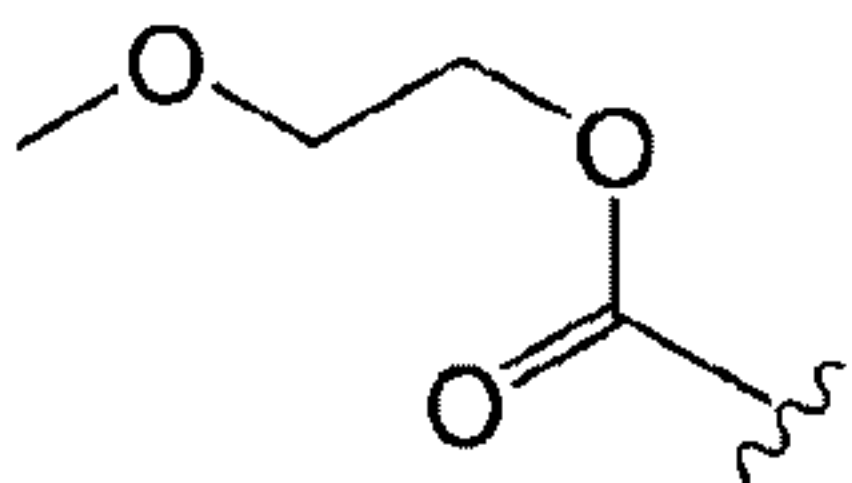
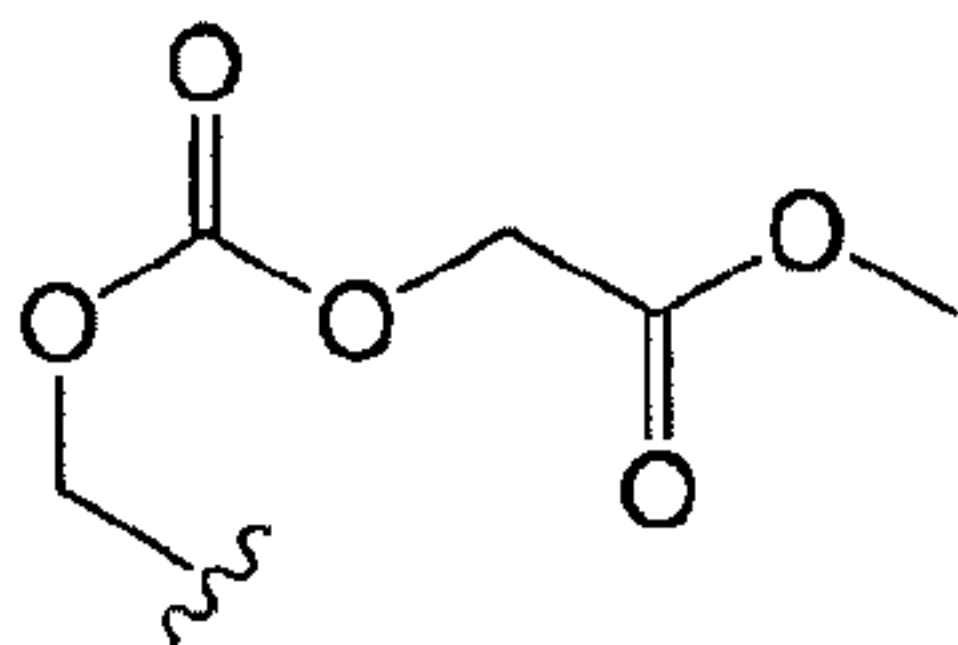
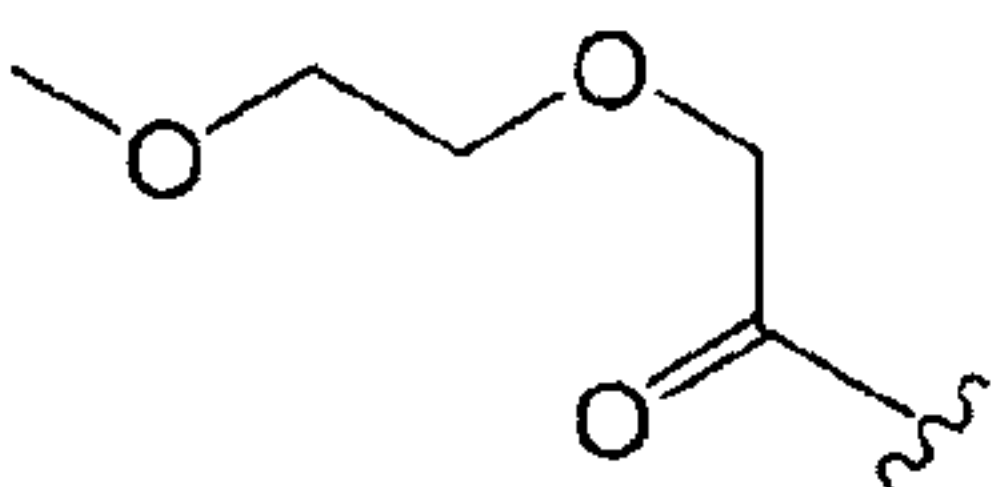
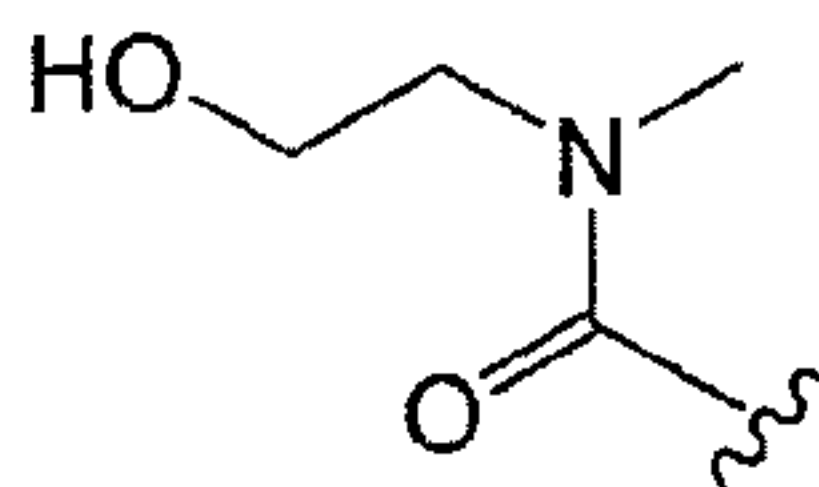
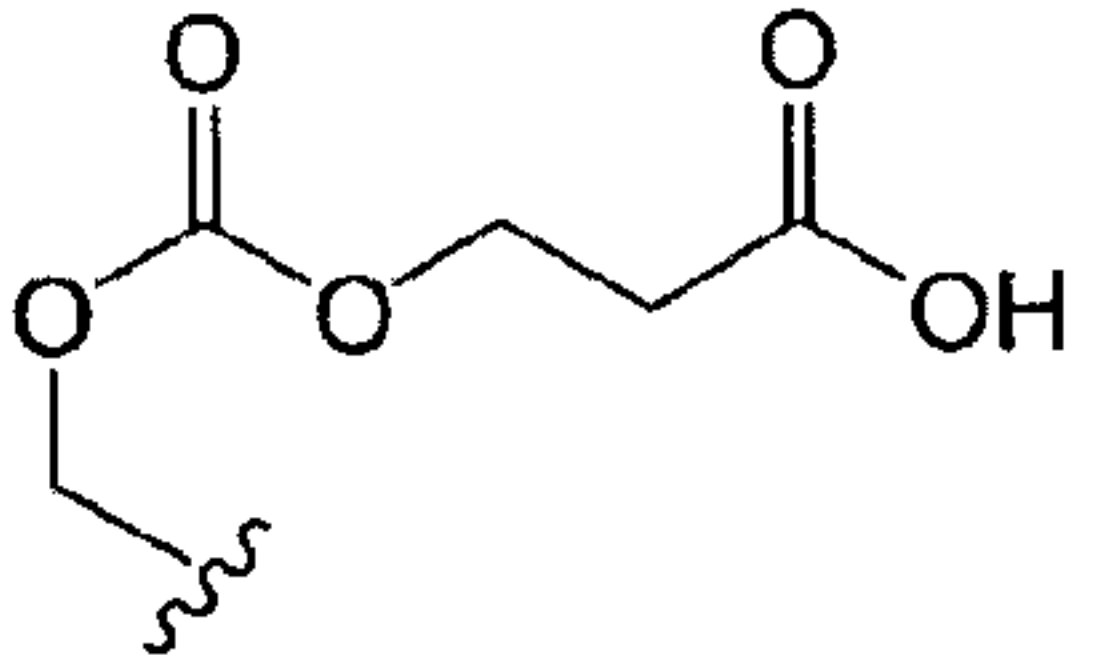
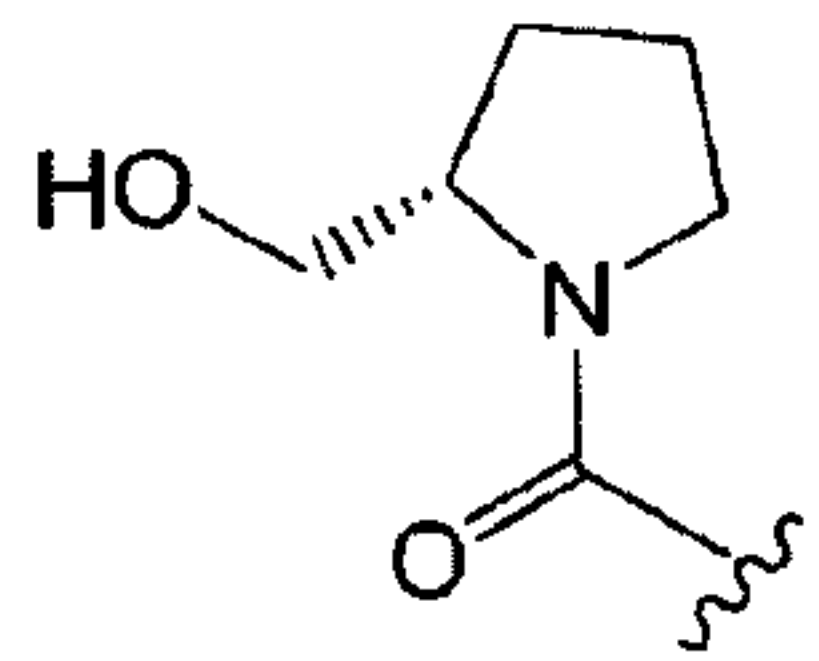
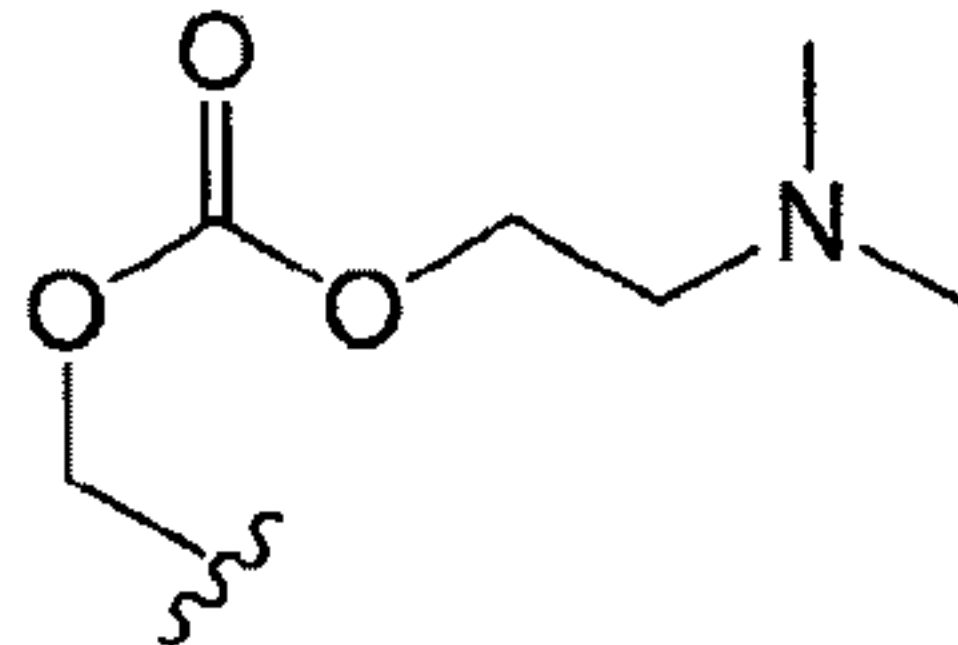
[0126]

[Table 5]

|      |                                                                                     |      |                                                                                       |
|------|-------------------------------------------------------------------------------------|------|---------------------------------------------------------------------------------------|
|      |    |      |                                                                                       |
| P-41 |    | P-46 |    |
| P-42 |  | P-47 |  |
| P-43 |  | P-48 |  |
| P-44 |  | P-49 |  |
| P-45 |  | P-50 |  |

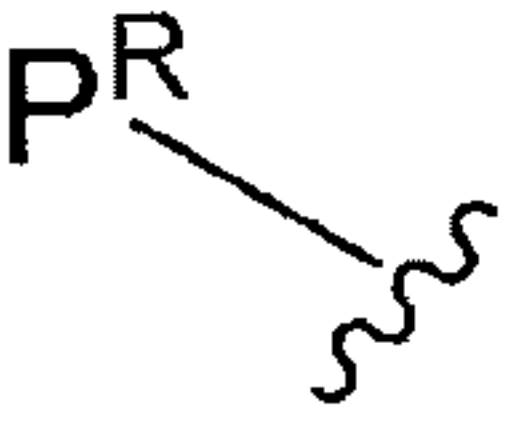
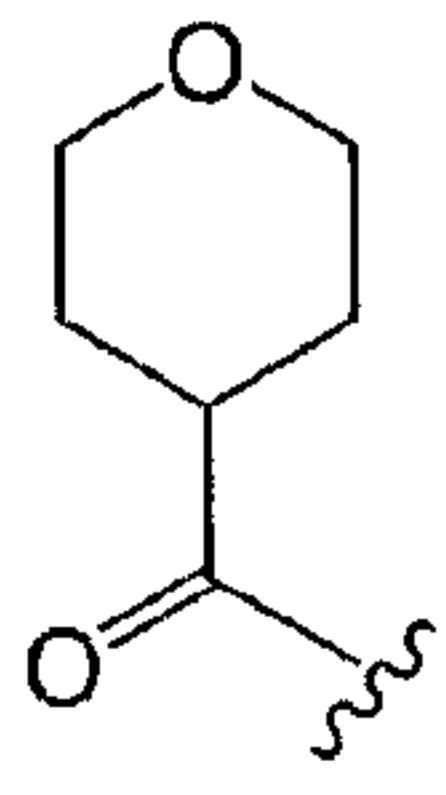
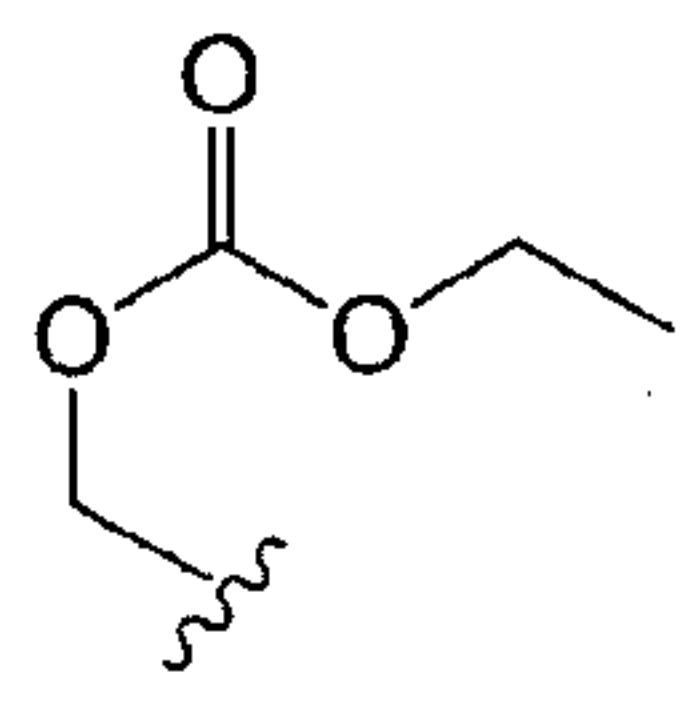
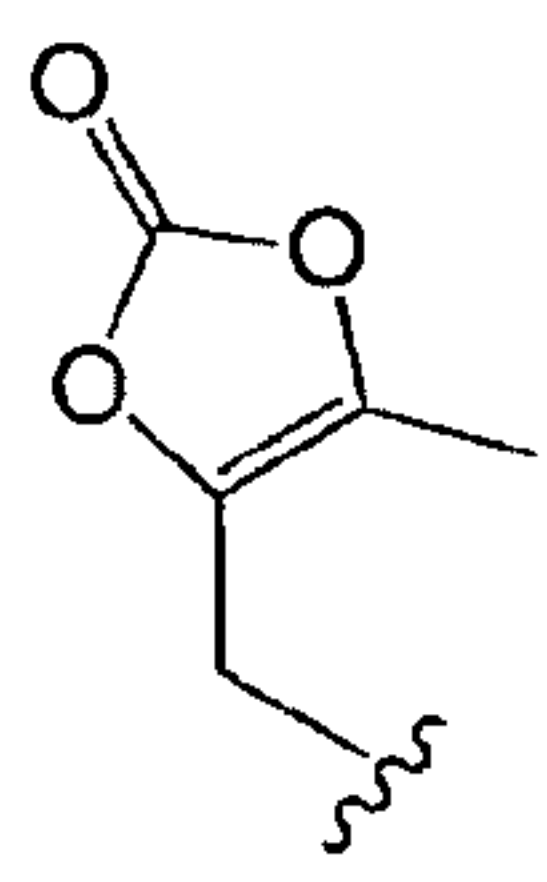
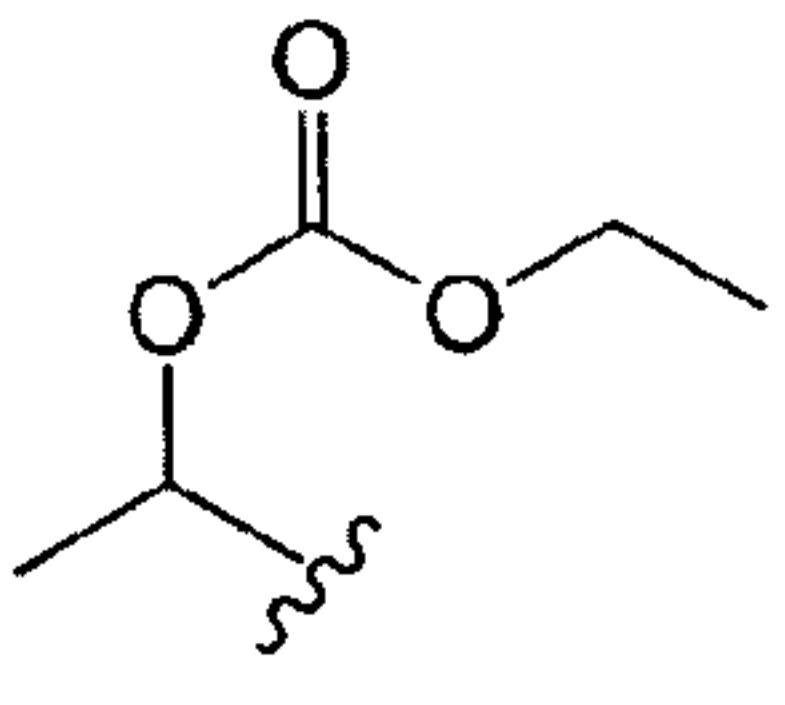
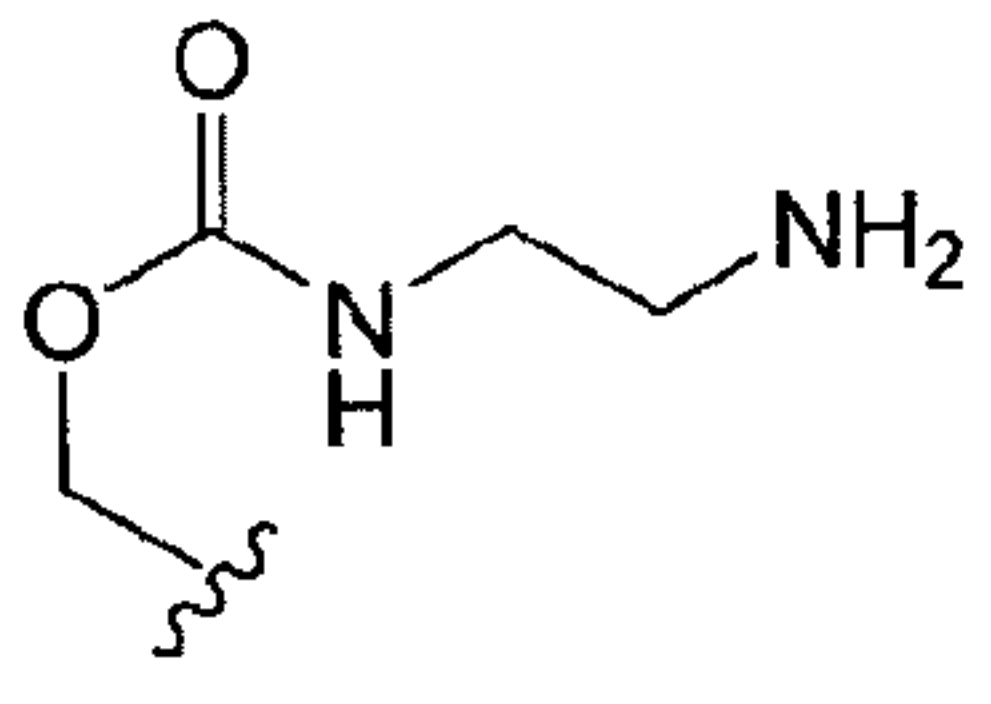
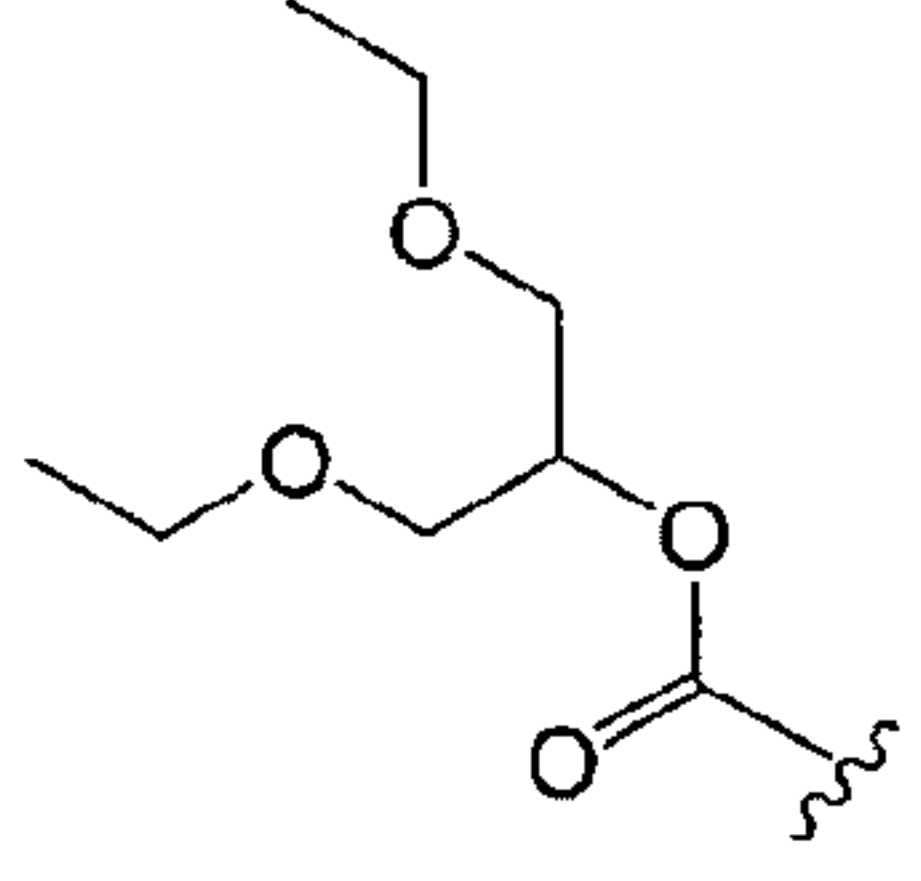
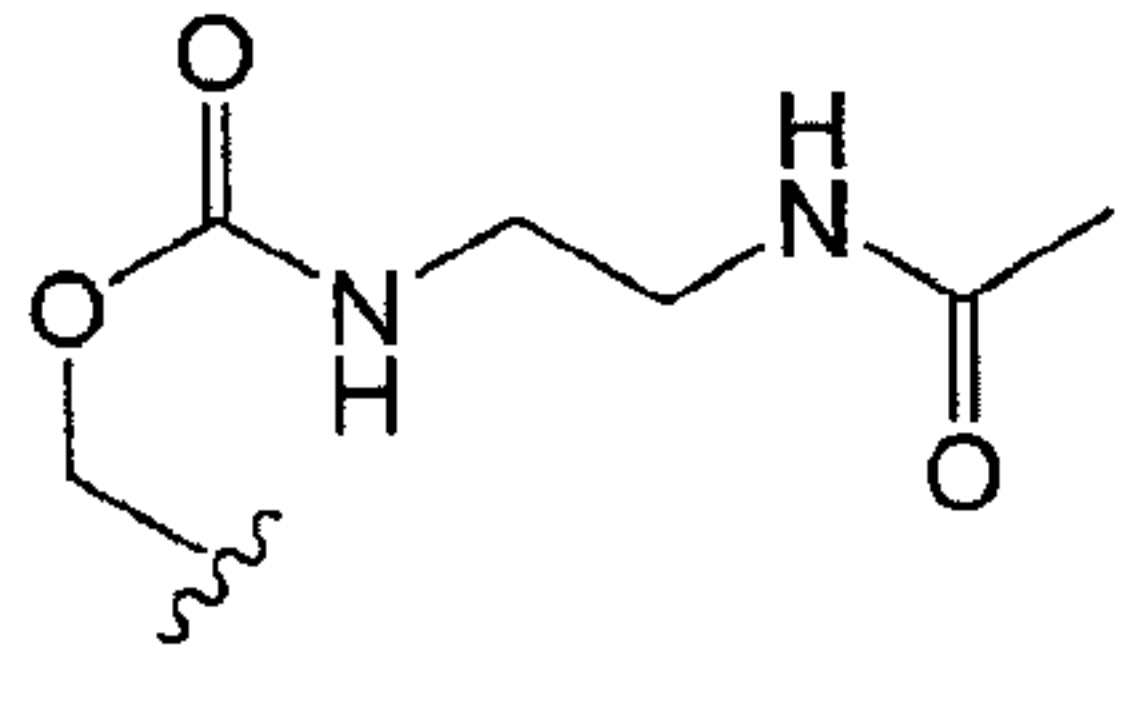
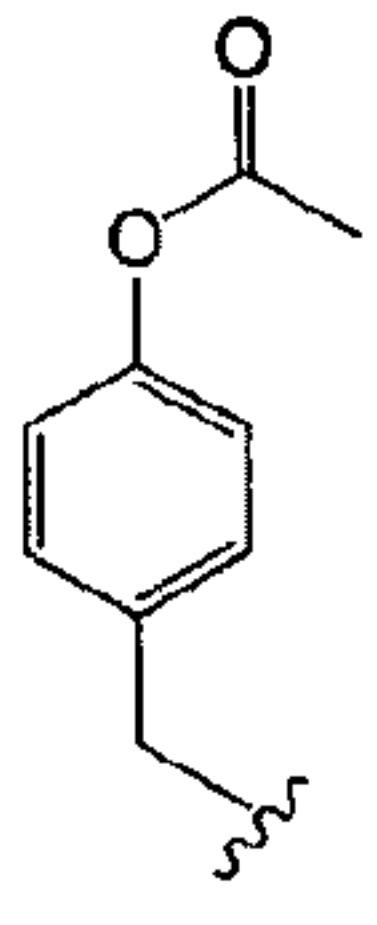
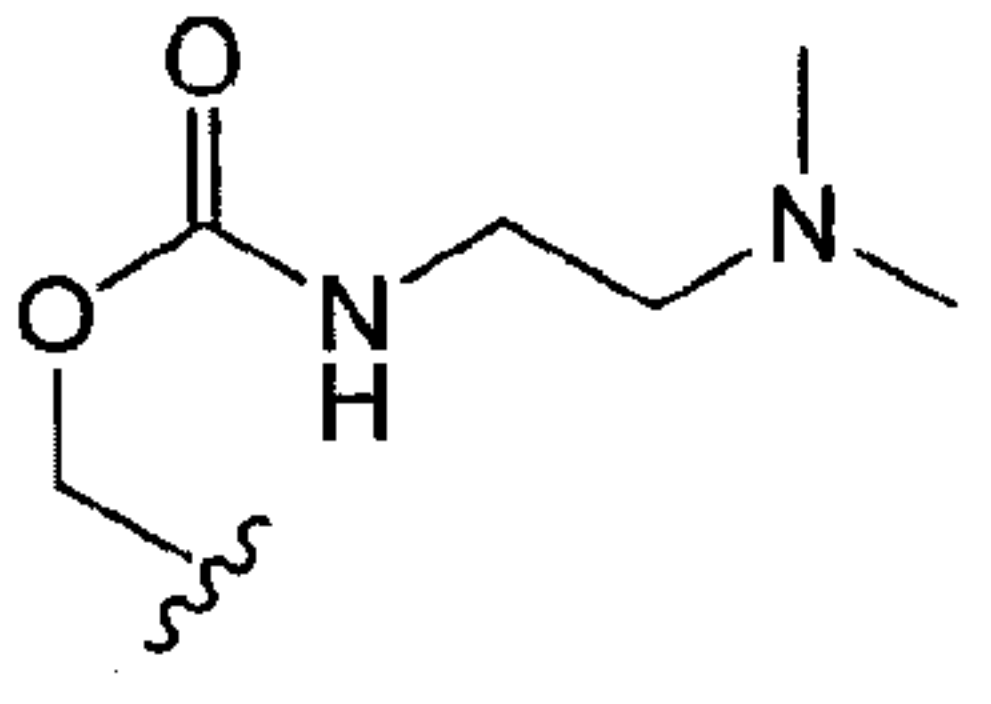
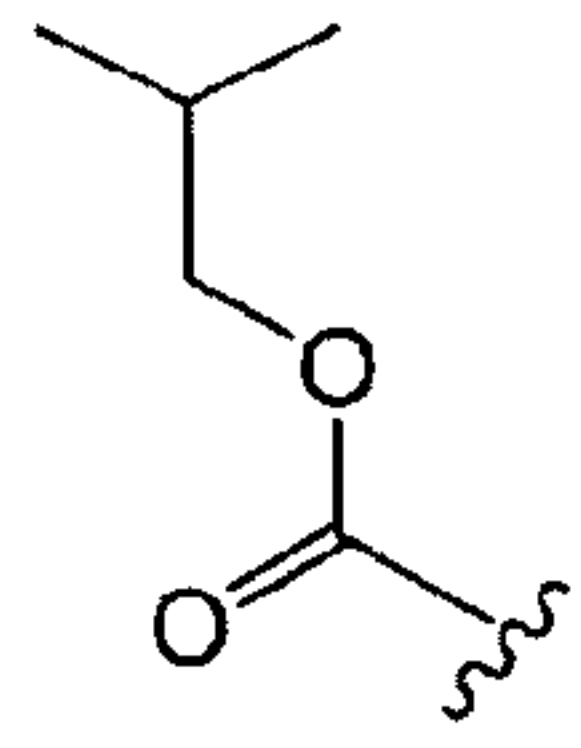
[0127]

[Table 6]

|      |                                                                                       |
|------|---------------------------------------------------------------------------------------|
|      |      |
| P-51 |      |
| P-52 |    |
| P-53 |    |
| P-54 |    |
| P-55 |   |
| P-56 |    |
| P-57 |  |
| P-58 |  |
| P-59 |  |
| P-60 |  |

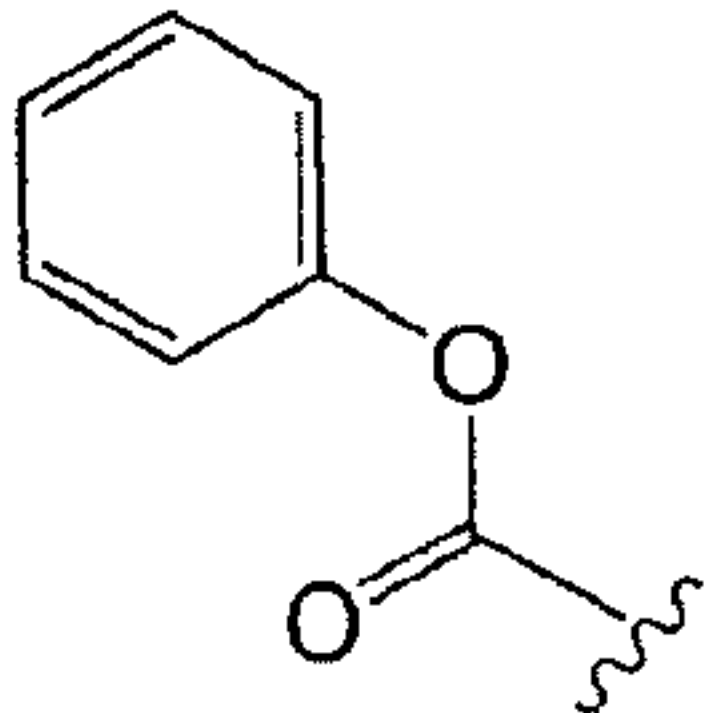
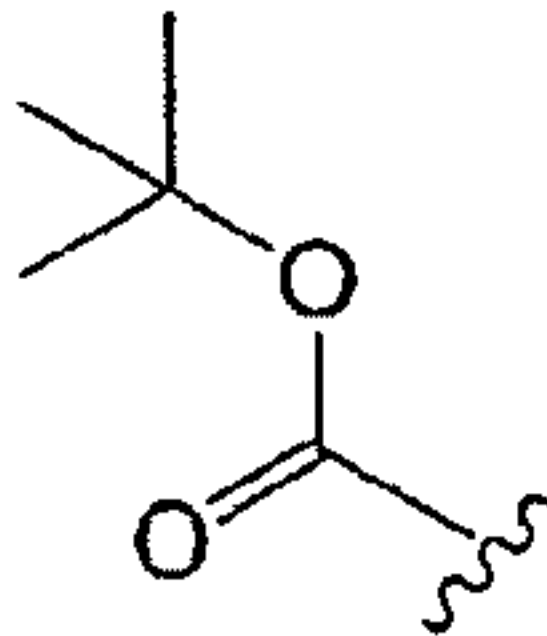
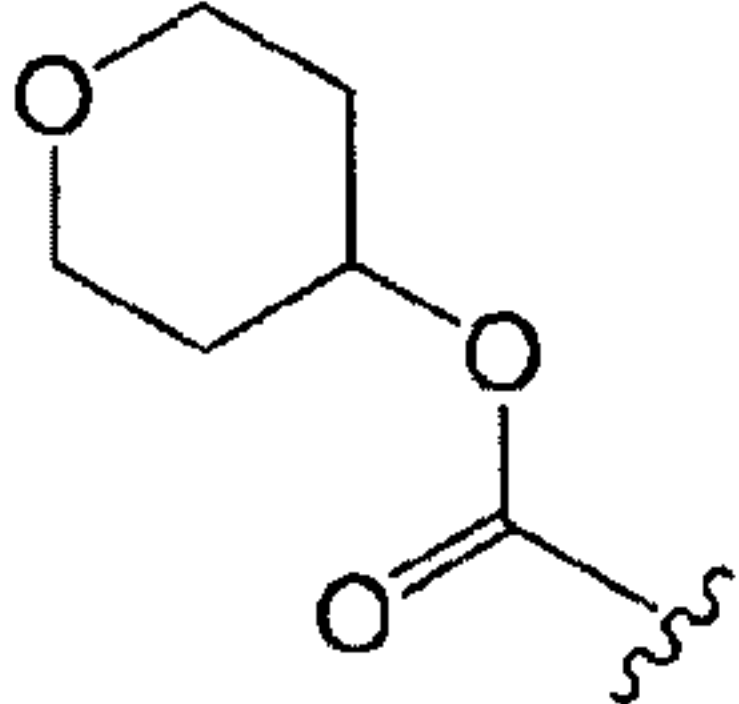
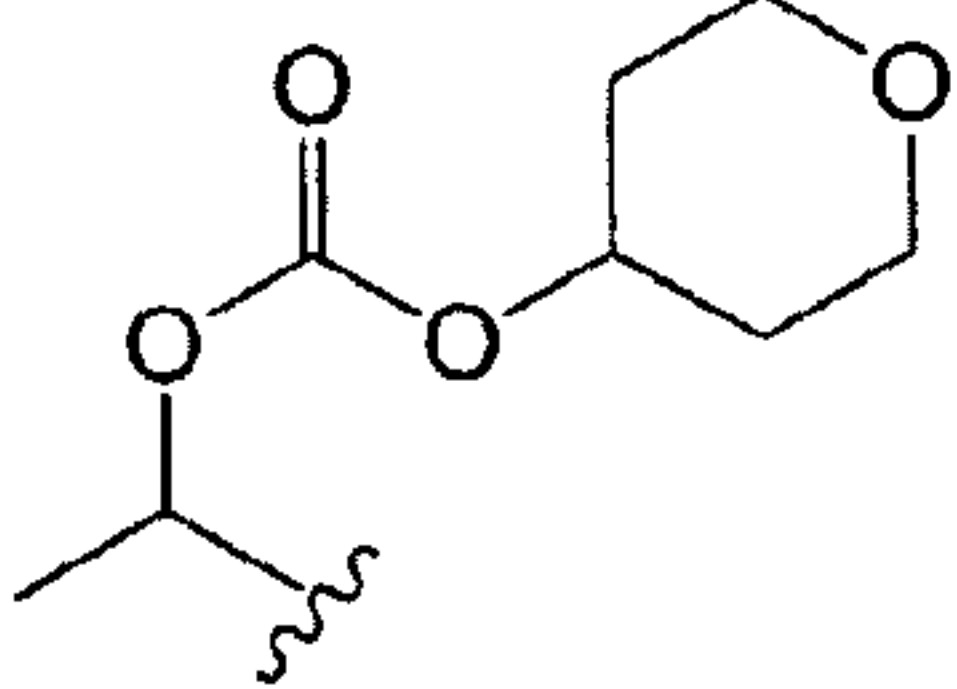
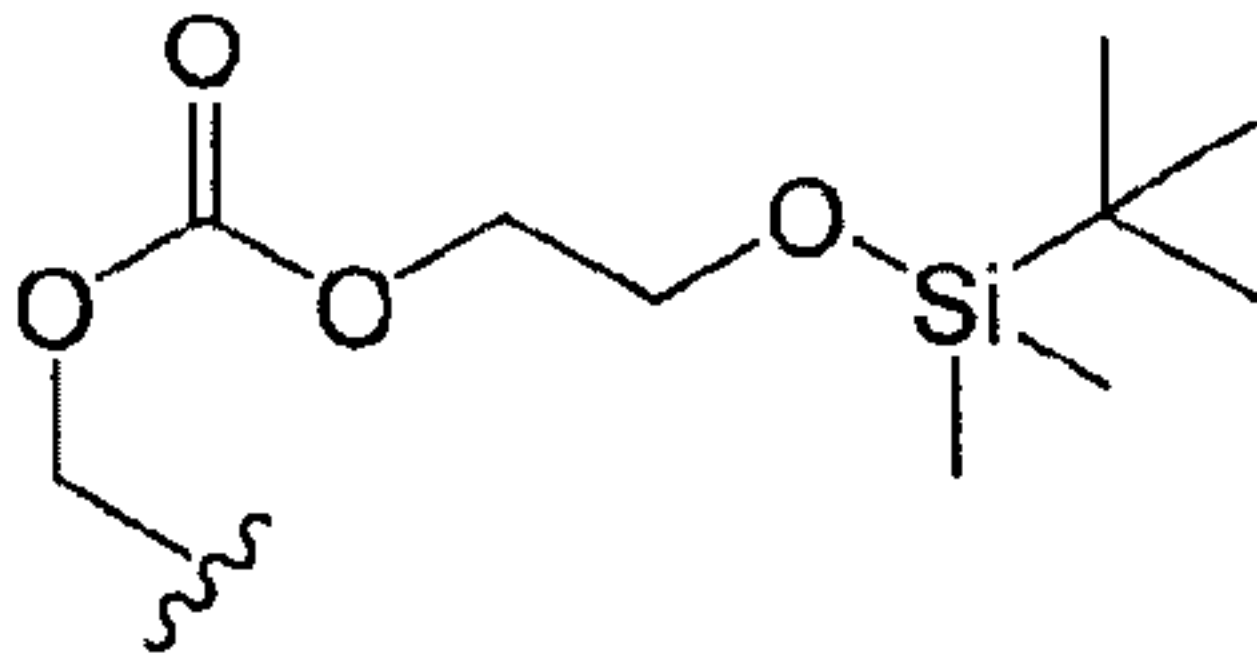
[0128]

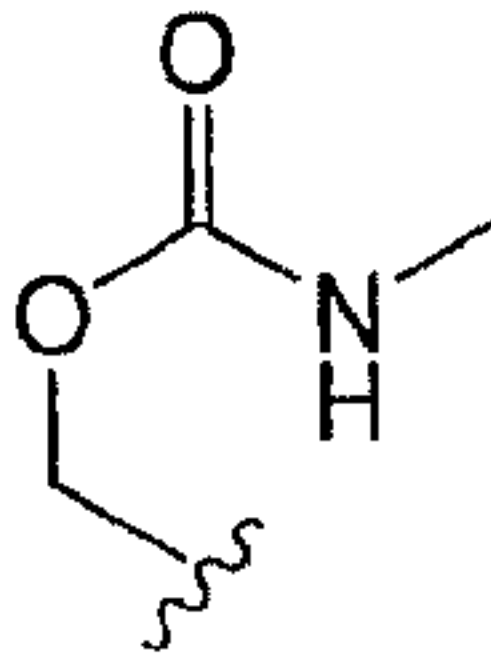
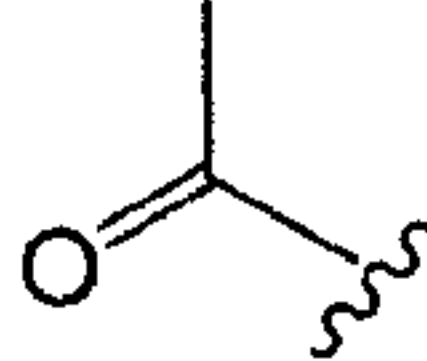
[Table 7]

|      |                                                                                      |      |                                                                                       |
|------|--------------------------------------------------------------------------------------|------|---------------------------------------------------------------------------------------|
|      |     |      |                                                                                       |
| P-61 |     | P-66 |    |
| P-62 |    | P-67 |  |
| P-63 |   | P-68 |  |
| P-64 |  | P-69 |  |
| P-65 |   | P-70 |  |

[0129]

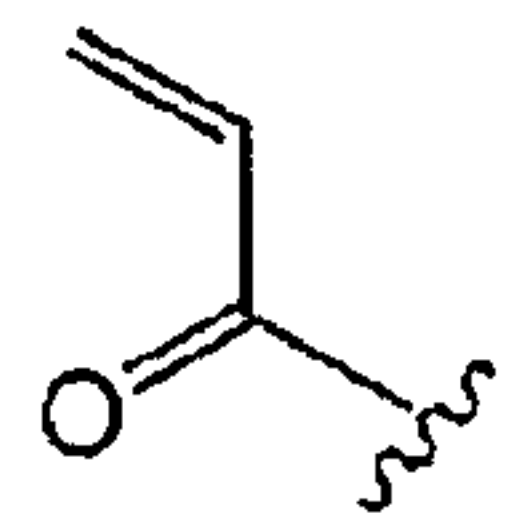
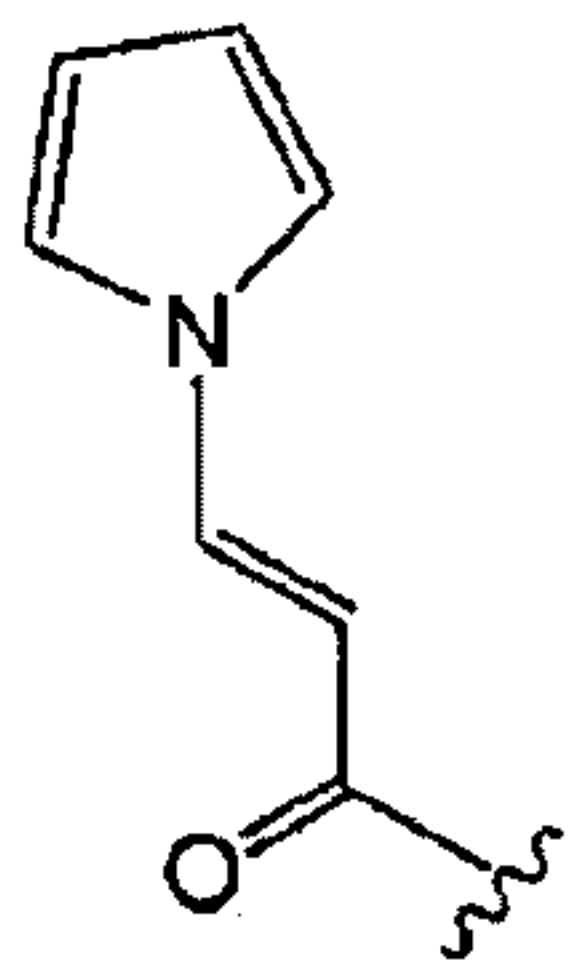
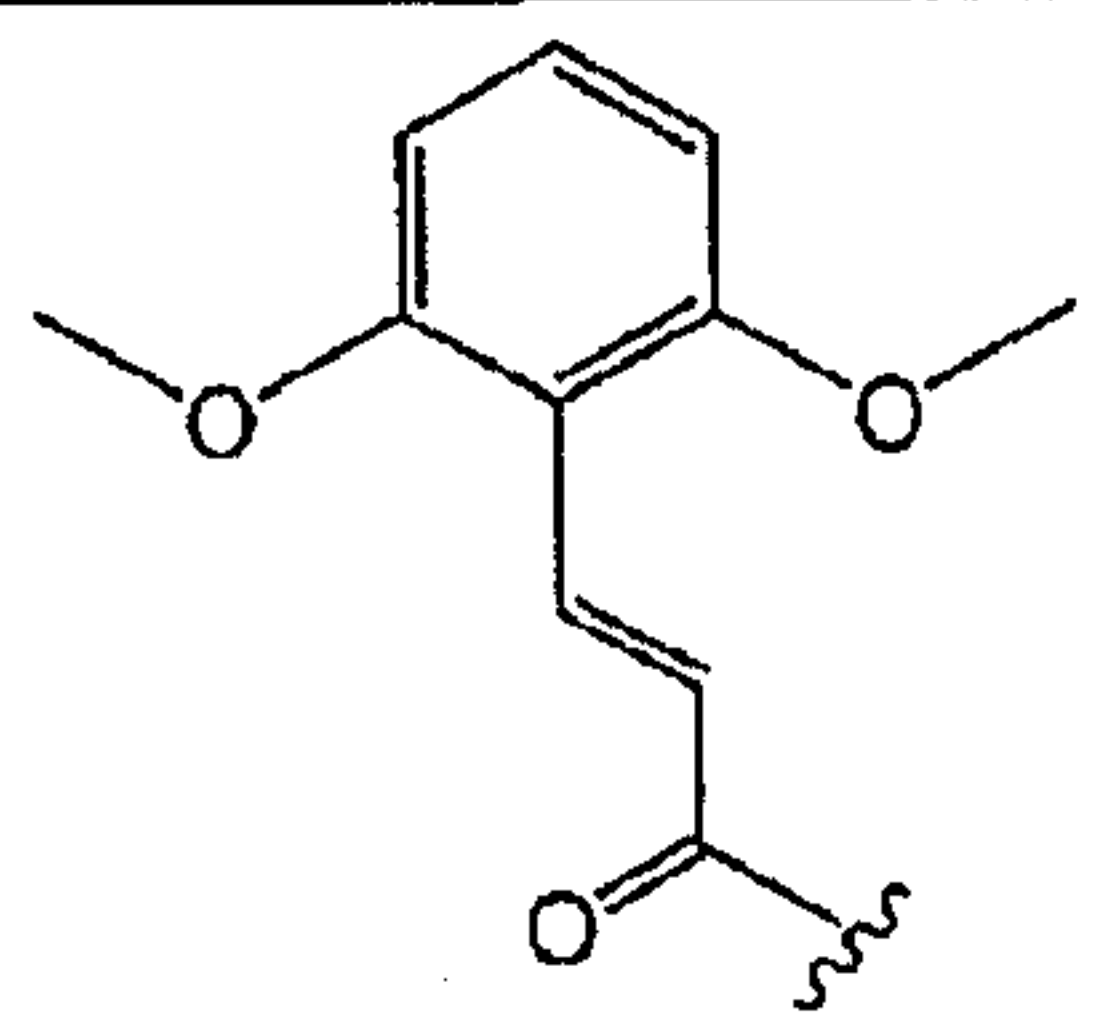
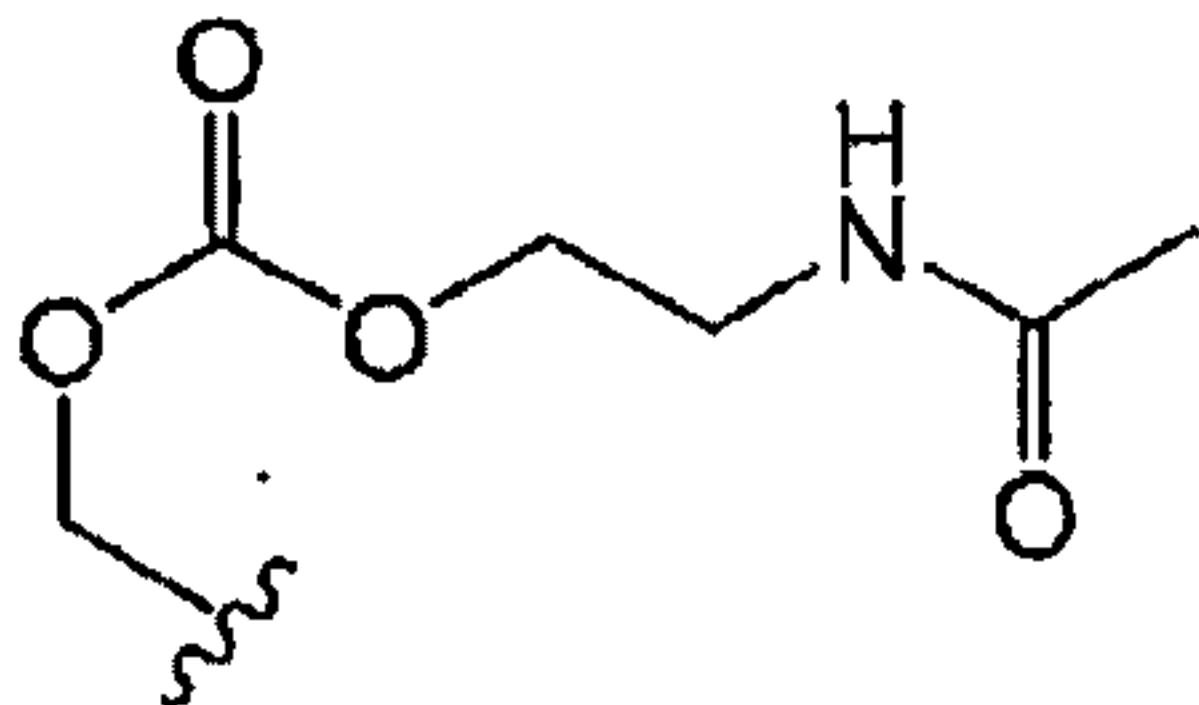
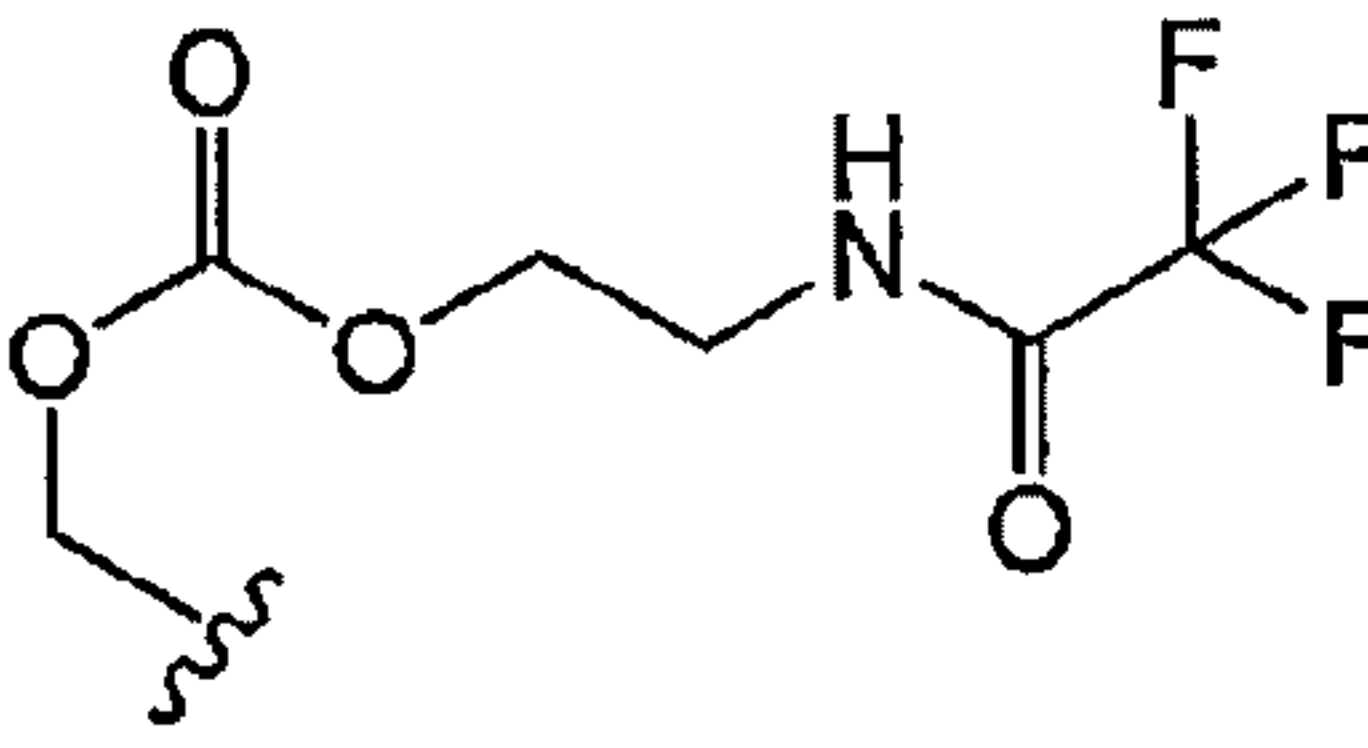
[Table 8]

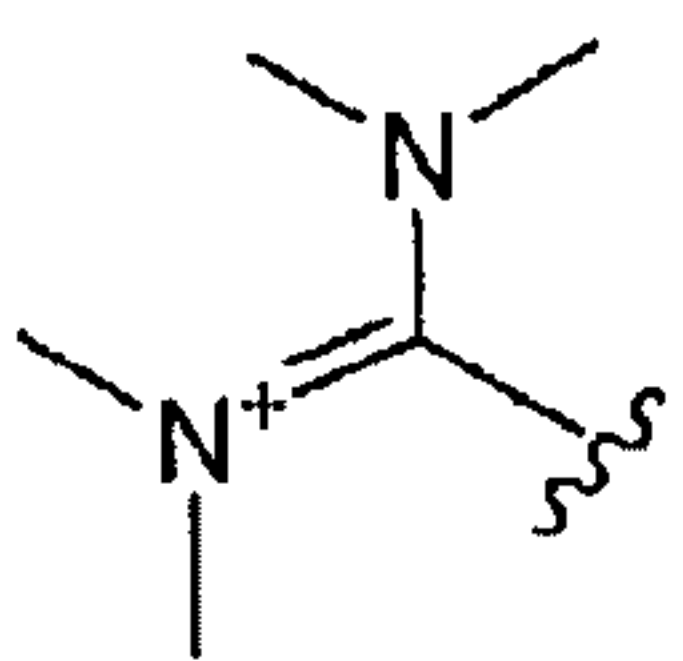
|      |                                                                                      |
|------|--------------------------------------------------------------------------------------|
|      |     |
| P-71 |     |
| P-72 |   |
| P-73 |   |
| P-74 |   |
| P-75 |  |

|      |                                                                                       |
|------|---------------------------------------------------------------------------------------|
| P-76 |    |
| P-77 |  |

[0130]

[Table 9]

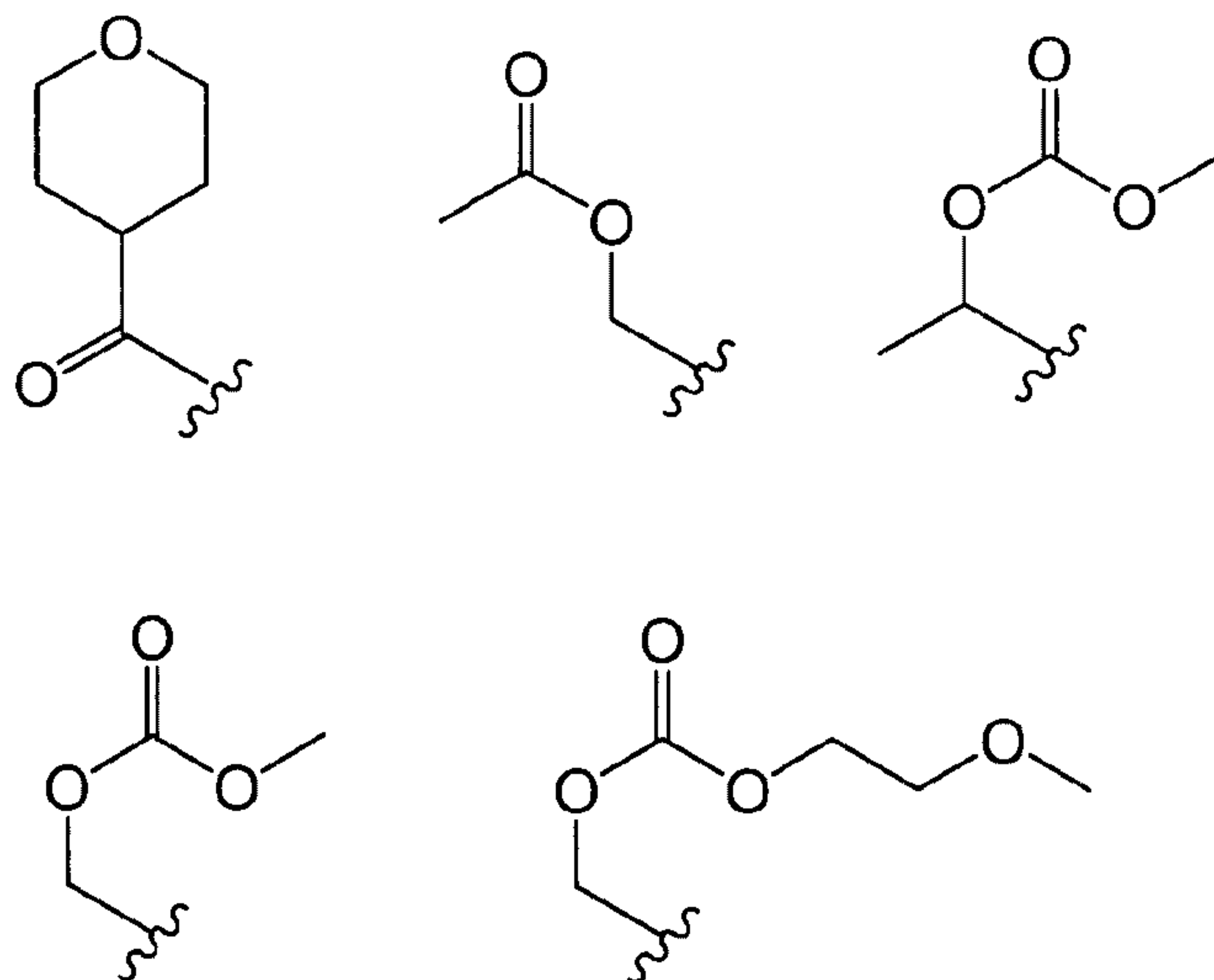
|      |                                                                                      |
|------|--------------------------------------------------------------------------------------|
|      |     |
| P-78 |     |
| P-79 |    |
| P-80 |  |
| P-81 |  |
| P-82 |  |

|      |                                                                                     |
|------|-------------------------------------------------------------------------------------|
| P-83 |  |
|------|-------------------------------------------------------------------------------------|

[0131]

Examples of another embodiment of a particularly preferable substituent of  $P^R$  include following groups.

[Chemical formula 37]



[0132]

Examples of a preferable substituent in  $R^{1a}$  include hydrogen, halogen, hydroxy, carboxy, cyano, formyl, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkenyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C,

carbocycleoxy optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxy optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,

$-Z-N(R^{A1})(R^{A2})$ ,

$-Z-N(R^{A3})-SO_2-(R^{A4})$ ,

$-Z-C(=O)-N(R^{A5})-SO_2-(R^{A6})$ ,

$-Z-N(R^{A7})-C(=O)-R^{A8}$ ,

$-Z-S-R^{A9}$ ,

$-Z-SO_2-R^{A10}$ ,

$-Z-S(=O)-R^{A11}$ ,

$-Z-N(R^{A12})-C(=O)-O-R^{A13}$ ,

$-Z-N(R^{A14})-C(=O)-N(R^{A15})(R^{A16})$ ,

$-Z-C(=O)-N(R^{A17})-C(=O)-N(R^{A18})(R^{A19})$ ,

$-Z-N(R^{A20})-C(=O)-C(=O)-R^{A21}$ , or

$-Z-B(-OR^{A22})(-OR^{A23})$

(substituent group C,  $R^{A1}$ ,  $R^{A2}$ ,  $R^{A3}$ ,  $R^{A5}$ ,  $R^{A7}$ ,  $R^{A8}$ ,  $R^{A9}$ ,  $R^{A10}$ ,  $R^{A11}$ ,  $R^{A12}$ ,  $R^{A13}$ ,  $R^{A14}$ ,  $R^{A15}$ ,  $R^{A16}$ ,  $R^{A17}$ ,  $R^{A18}$ ,  $R^{A19}$ ,  $R^{A20}$ ,  $R^{A21}$ ,  $R^{A22}$ ,  $R^{A23}$ , and Z are same as those of item 1).

[0133]

Examples of a more preferable substituent in  $R^{1a}$  include hydrogen, halogen, hydroxy, carboxy, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by

substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C,

$-Z-N(R^{A1})(R^{A2})$ ,

$-Z-N(R^{A7})-C(=O)-R^{A8}$ ,

$-Z-N(R^{A12})-C(=O)-O-R^{A13}$ , or

$-Z-B(-OR^{A22})(-OR^{A23})$

(substituent group C,  $R^{A1}$ ,  $R^{A2}$ ,  $R^{A7}$ ,  $R^{A8}$ ,  $R^{A12}$ ,  $R^{A13}$ ,  $R^{A22}$ ,  $R^{A23}$ , and Z are same as those of item 1).

[0134]

Examples of a preferable substituent in  $R^{1a}$  include hydrogen, halogen, hydroxy, carboxy, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, or

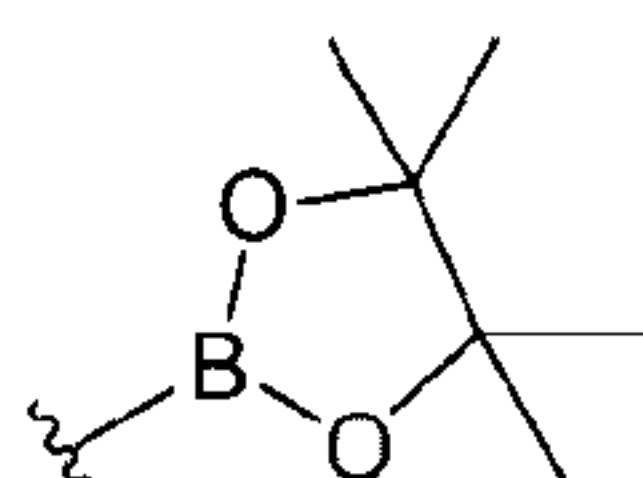
$-Z-N(R^{A1})(R^{A2})$

(substituent group C,  $R^{A1}$ ,  $R^{A2}$ , and Z are same as those of item 1).

[0135]

Examples of another embodiment of a preferable substituent in  $R^{1a}$  include hydrogen, carboxy, hydroxymethyl, methoxy, chlorine atom, bromine atom, ethoxymethyl, dimethylamino, hydroxy,  $-C(=O)-NH-S(=O)_2-Me$ , amino, methylamino, methylaminomethyl,  $-NH-C(=O)-CF_3$ , pyrazolyl,  $-NH-C(=O)-Me$ ,  $-C(=O)N-Me_2$ , tetrazolyl,  $-NH-C(=O)-Ph$ ,  $-C(=O)NH-Me$ ,  $-C(=O)NH-Et$ ,  $-C(=O)NH-cyclopropyl$ , methoxycarbonyl, methyl, propenyl, propyl, isopropyl, fluoromethyl, difluoromethyl, cyano,  $-C(=O)-Me$ ,  $-CH(-OH)-Me$ ,  $-B(-OH)_2$ ,

[Chemical formula 38]



(Me represents a methyl group, Ph represents a phenyl group, and Et represents an ethyl group) etc.

[0136]

Examples of another embodiment of a more preferable substituent in  $R^{1a}$  include hydrogen, carboxy, hydroxymethyl, methoxy, bromine atom, ethoxymethyl, dimethylamino, hydroxy,  $-C(=O)-NH-S(=O)_2-Me$ , amino, methylamino, methyl, propenyl,  $-C(=O)-Me$ ,  $-B(-OH)_2$  (Me represents a methyl group) etc.

[0137]

Examples of another embodiment of a further preferable substituent in  $R^{1a}$  include hydrogen, carboxy, and  $-C(=O)-Me$ .

[0138]

Examples of a most preferable substituent in  $R^{1a}$  include hydrogen.

[0139]

Examples of a preferable substituent in  $R^{2a}$  is hydrogen, halogen, carboxy, cyano, formyl, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkenyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally

substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C, carbocycleoxy optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxy optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,

$-Z-N(R^{B1})-SO_2-R^{B2}$ ,

$-Z-N(R^{B3})-C(=O)-R^{B4}$ ,

$-Z-N(R^{B5})-C(=O)-O-R^{B6}$ ,

$-Z-C(=O)-N(R^{B7})(R^{B8})$ ,

$-Z-N(R^{B9})(R^{B10})$ , or

$-Z-SO_2-R^{B11}$

(substituent group C,  $R^{B1}$ ,  $R^{B2}$ ,  $R^{B3}$ ,  $R^{B4}$ ,  $R^{B5}$ ,  $R^{B6}$ ,  $R^{B7}$ ,  $R^{B8}$ ,  $R^{B9}$ ,  $R^{B10}$ ,  $R^{B11}$ , and Z are same as those of item 1).

[0140]

Examples of a more preferable substituent in  $R^{2a}$  is hydrogen, lower alkyl optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, or

$-Z-N(R^{B9})(R^{B10})$

(substituent group C,  $R^{B9}$ ,  $R^{B10}$ , and Z are same as those of item 1).

[0141]

Examples of a further preferable substituent in  $R^{2a}$  include hydrogen, or lower alkyl optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C  
(substituent group C is same as that of item 1).

[0142]

Examples of another embodiment of a preferable substituent in  $R^{2a}$  include hydrogen, hydroxymethyl, amino, methoxymethyl, methoxymethylcyclopropylmethyloxymethyl, cyanomethyl, aminomethyl, propyloxymethyl,  $-\text{CH}_2\text{-NH-C(=O)-Me}$ , methylaminomethyl, imidazolyl, dimethylaminomethyl, pyrrolidinyl, fluoromethyl,  $-\text{CH}_2\text{-NH-C(=O)H}$  (Me represents a methyl group) etc.

[0143]

Examples of another embodiment of a more preferable substituent in  $R^{2a}$  include hydrogen, hydroxymethyl, methoxymethylcyclopropylmethyloxymethyl, aminomethyl, propyloxymethyl, etc.

[0144]

Examples of another embodiment of a further preferable substituent in  $R^{2a}$  include hydrogen.

[0145]

Examples of a preferable substituent in  $R^{3a}$  include hydrogen, halogen, hydroxy, carboxy, cyano, formyl, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkenyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group

C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C, carbocycleoxy optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxy optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,

$-Z-N(R^{C1})-SO_2-R^{C2}$ ,

$-Z-N(R^{C3})-C(=O)-R^{C4}$ ,

$-Z-N(R^{C5})-C(=O)-O-R^{C6}$ ,

$-Z-C(=O)-N(R^{C7})(R^{C8})$ ,

$-Z-N(R^{C9})(R^{C10})$ , or

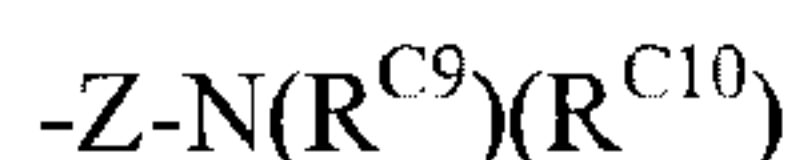
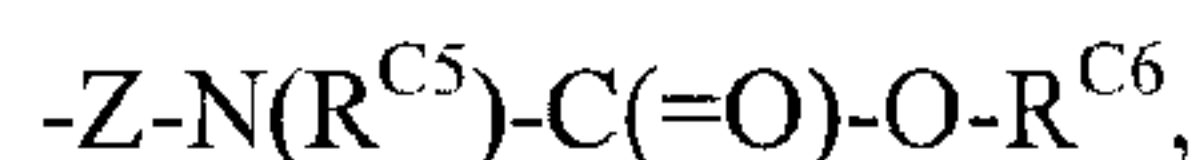
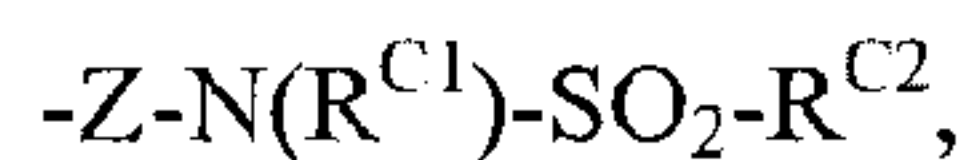
$-Z-SO_2-R^{C11}$

(substituent group C,  $R^{C1}$ ,  $R^{C2}$ ,  $R^{C3}$ ,  $R^{C4}$ ,  $R^{C5}$ ,  $R^{C6}$ ,  $R^{C7}$ ,  $R^{C8}$ ,  $R^{C9}$ ,  $R^{C10}$ ,  $R^{C11}$ , and Z are same as those of item 1).

[0146]

Examples of a more preferable substituent in  $R^{3a}$  is hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally

substituted by substituent group C,



(substituent group C,  $R^{C1}$ ,  $R^{C2}$ ,  $R^{C3}$ ,  $R^{C4}$ ,  $R^{C5}$ ,  $R^{C6}$ ,  $R^{C7}$ ,  $R^{C8}$ ,  $R^{C9}$ ,  $R^{C10}$ , and Z are same as those of item 1).

[0147]

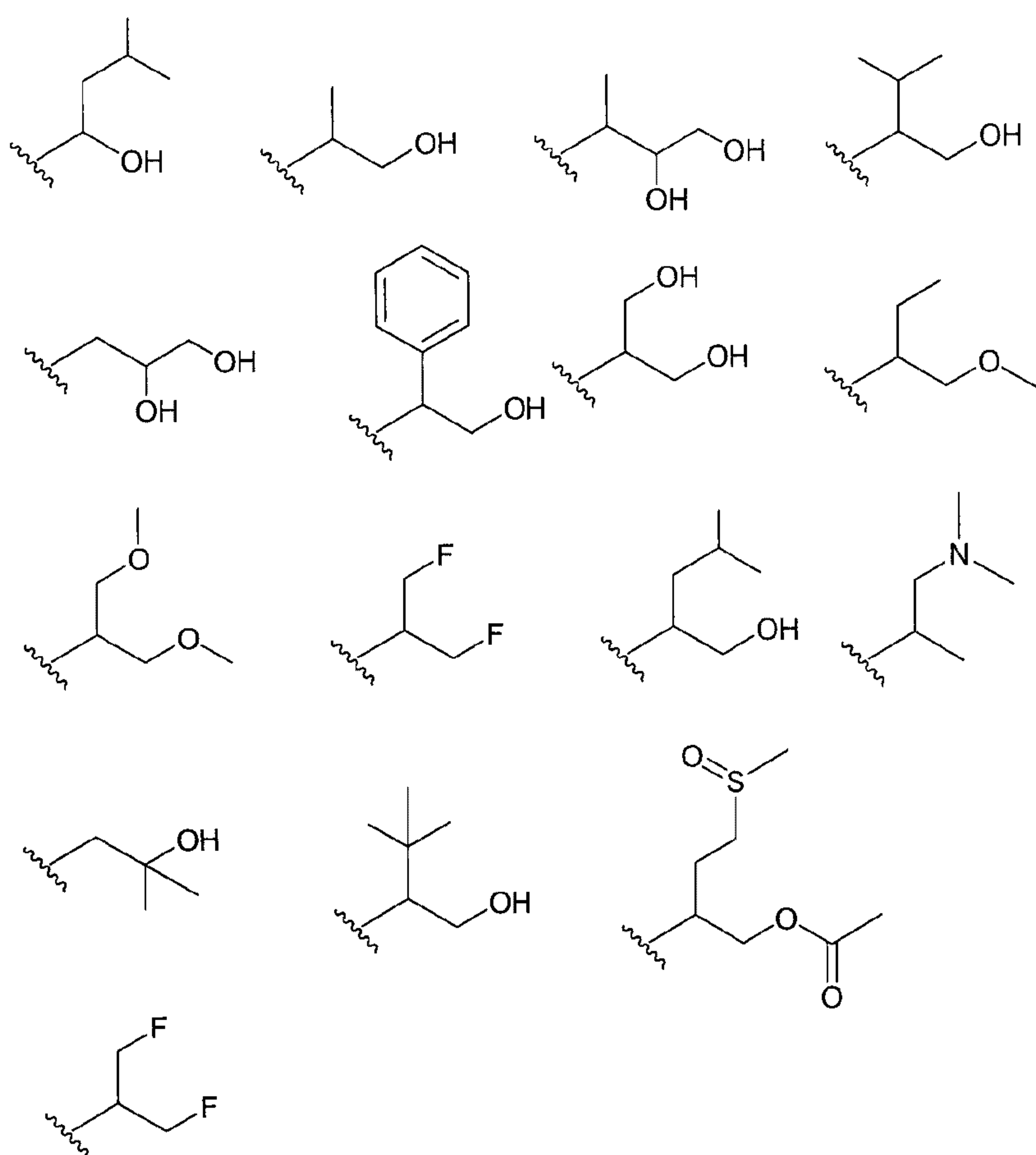
Examples of a further preferable substituent in  $R^{3a}$  include hydrogen, lower alkyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, or carbocycle lower alkyl optionally substituted by substituent group C (substituent group C is same as that of item 1).

[0148]

Examples of another embodiment of a preferable substituent in  $R^{3a}$  include hydrogen, ethoxyethyl, methyl, ethyl, propyl, 2,4-difluorobenzyl, methoxyethyl, cyanomethyl, cyanoethyl, 3-chloro-2-fluorobenzyl, 1-methoxypropyl, pyridylmethyl, isopropyl, tetrahydropyranylmethyl, cyclopropylmethyl, benzyl, methylisoxazolylmethyl, methyloxadiazolyl, isopropoxyethyl, hydroxyethyl, 4-fluorobenzyl, cyclopropyl, ethoxycarbonyl, ethyl, -CH(Me)CH<sub>2</sub>OMe, carboxyethyl, -CH<sub>2</sub>CH<sub>2</sub>C(=O)-N(Me)<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>N(Me)-S(=O)<sub>2</sub>-Ph, -CH<sub>2</sub>CH<sub>2</sub>-N(Me)-S(=O)<sub>2</sub>-Me, -CH<sub>2</sub>CH<sub>2</sub>-NHC(=O)-Ph, -CH(Me)-CH<sub>2</sub>-OMe, -CH<sub>2</sub>CH<sub>2</sub>-NH-S(=O)<sub>2</sub>-Ph, -CH<sub>2</sub>CH<sub>2</sub>-NH-C(=O)-O-CH(Me)<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>-C(=O)-NH-Ph, -CH<sub>2</sub>CH<sub>2</sub>-N(Me)C(=O)-Ph, -CH<sub>2</sub>CH<sub>2</sub>-NH-C(=O)-Me, -CH<sub>2</sub>CH<sub>2</sub>-NH-S(=O)<sub>2</sub>-Me,

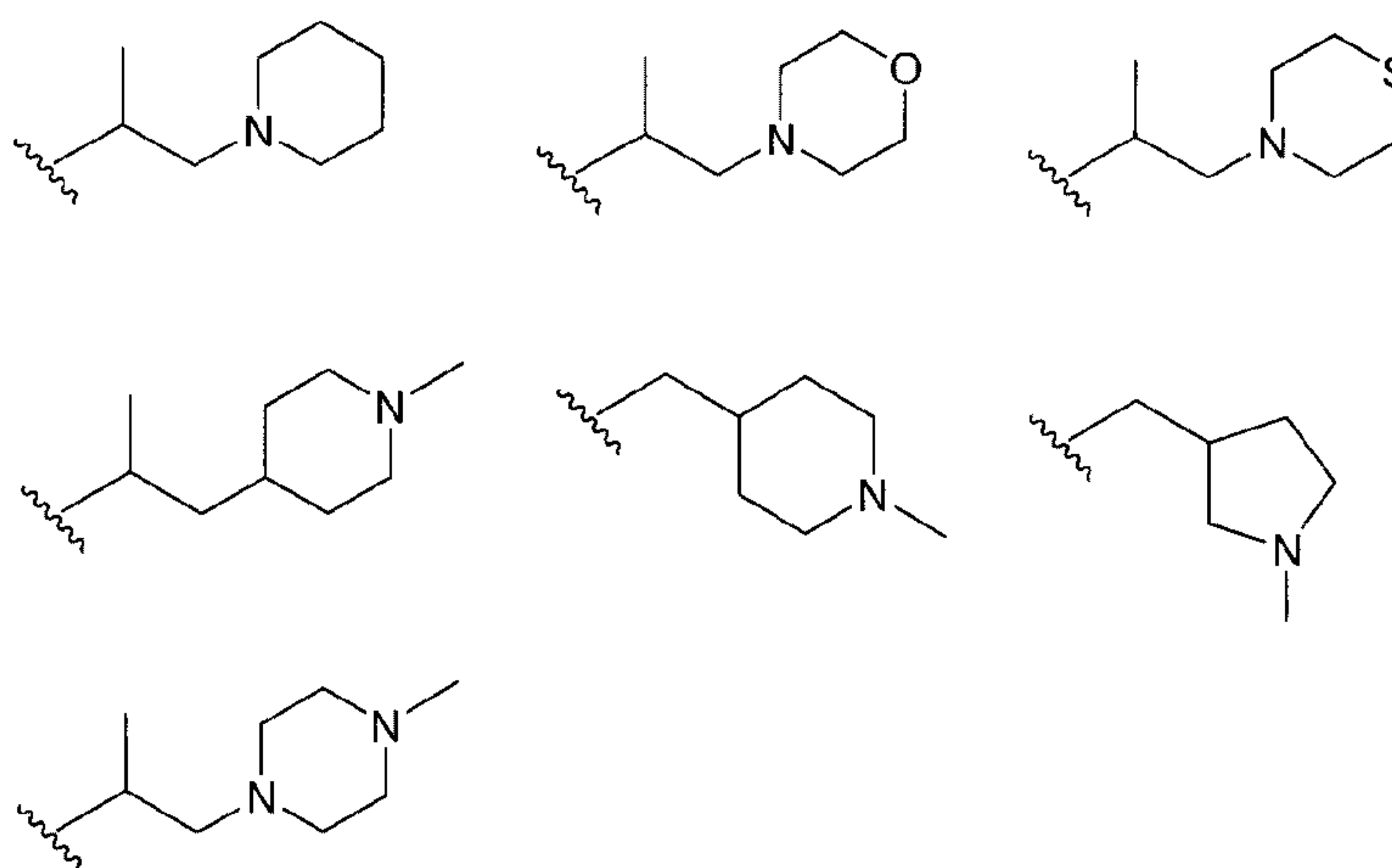
aminoethyl, -CH<sub>2</sub>CH<sub>2</sub>-N(Me)-C(=O)-Me, -CH<sub>2</sub>CH<sub>2</sub>-C(=O)-N(Me)-Ph,  
-CH<sub>2</sub>CH<sub>2</sub>-NH-C(=O)-O-tBu, piperidinylcarbonyl ethyl, dimethylaminoethyl,  
cyclopropylmethyl, methylaminoethyl, furanylmethyl, morpholinylcarbonyl ethyl,  
sec-butyl, pentan-2-yl, carboxypropyl, ethoxycarbonylpropyl, phenylpropyl,  
propyloxyethyl, aminopropyl, dimethylaminomethyl, dimethylaminoethyl,  
diethylaminomethyl, diethylaminoethyl, dimethylaminopropyl,  
methylaminocarbonyl ethyl, 1,1,1-trifluoropropan-2-yl, 1,1-difluoroethyl,  
1,1,1-trifluoroethyl, 1,1,1-trifluoropropyl, trifluoromethyloxyethyl,  
trifluoromethylcarbonylaminomethyl, methylsulfonyl ethyl, methylcarbonyloxyethyl,  
methylcarbonyloxypropyl, 1-fluoropropyl, fluorocyclopropyl, difluorocyclopropyl,  
3,3-dimethylbutan-2-yl, 1-fluoroethyl, 1-methoxypropan-2-yl, amino, thiazolylmethyl,  
methylsulfonyl ethyl, 4-fluorophenyloxyethyl, pyridyl, pentan-2-yl, butan-2-yl,  
3-methylbuten-2-yl, as well as groups shown below

[Chemical formula 39]



[0149]

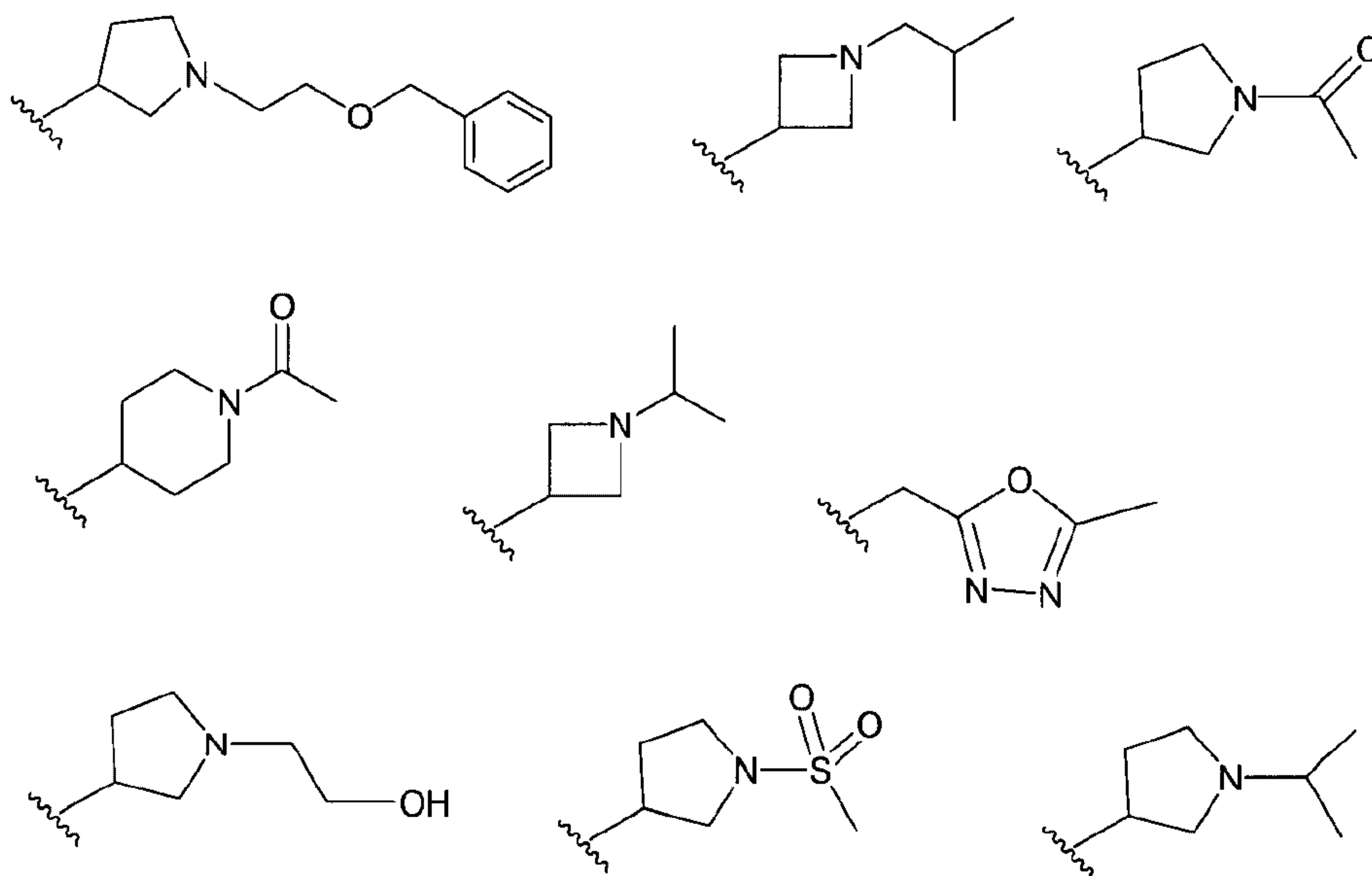
[Chemical formula 40]



[0150]

and

[Chemical formula 41]



[0151]

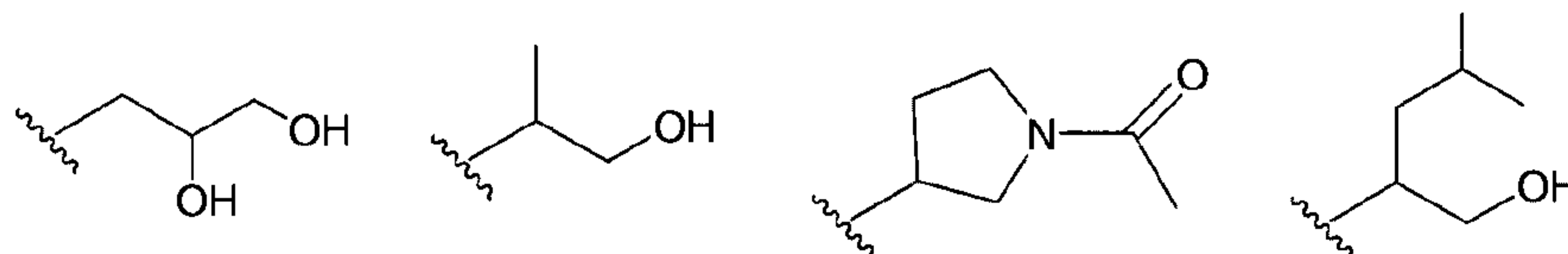
(Me represents a methyl group, Ph represents a phenyl group, and tBu represents a

tert-butyl group) etc.

[0152]

Examples of another embodiment of a more preferable substituent in  $R^{3a}$  include ethoxyethyl, methyl, ethyl, 2,4-difluorobenzyl, methoxyethyl, cyanomethyl, 3-chloro-2-fluorobenzyl, methoxypropyl, pyridylmethyl, isopropyl, tetrahydropyranylmethyl, cyclopropylmethyl, benzyl, methylisoxazolylmethyl, 4-fluorobenzyl, cyclopropyl, ethoxycarbonyl,  $-\text{CH}(\text{Me})\text{CH}_2\text{OMe}$ , carboxyethyl,  $-\text{CH}_2\text{CH}_2\text{C}(=\text{O})-\text{N}(\text{Me})_2$ ,  $-\text{CH}_2\text{CH}_2\text{N}(\text{Me})-\text{S}(=\text{O})_2-\text{Ph}$ ,  $-\text{CH}_2\text{CH}_2-\text{N}(\text{Me})-\text{S}(=\text{O})_2-\text{Me}$ ,  $-\text{CH}_2\text{CH}_2-\text{NHC}(=\text{O})-\text{Ph}$ ,  $-\text{CH}(\text{Me})-\text{CH}_2-\text{OMe}$ ,  $-\text{CH}_2\text{CH}_2-\text{NH}-\text{S}(=\text{O})_2-\text{Ph}$ ,  $-\text{CH}_2\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{CH}(\text{Me})_2$ ,  $-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{Ph}$ ,  $-\text{CH}_2\text{CH}_2-\text{N}(\text{Me})\text{C}(=\text{O})-\text{Ph}$ ,  $-\text{CH}_2\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{Me}$ ,  $-\text{CH}_2\text{CH}_2-\text{NH}-\text{S}(=\text{O})_2-\text{Me}$ , aminoethyl, 1,1,1-trifluoropropan-2-yl, propyl, methylthiomethyl, hydrogen, fluorocyclopropyl, trifluoromethoxyethyl, 1-fluoropropyl, 1-fluoroethyl, methylcarbonyloxymethyl, 1,1-difluoromethyl, and groups shown below

[Chemical formula 42]



[0153]

(Me represents methyl group, and Ph represents phenyl group) etc.

[0154]

Examples of another embodiment of a further preferable substituent in  $R^{3a}$  include ethoxyethyl, methyl, ethyl, 2,4-difluorobenzyl, methoxyethyl, cyanomethyl, 3-chloro-2-fluorobenzyl, methoxypropyl, pyridylmethyl, isopropyl,

tetrahydropyranylmethyl, cyclopropylmethyl, benzyl, 4-fluorobenzyl, cyclopropyl, ethoxycarbonylethyl, -CH(Me)CH<sub>2</sub>OMe, carboxyethyl, 1,1,1-trifluoropropan-2-yl, hydroxyethyl, 1-fluoroethyl  
(Me represents methyl group) etc.

[0155]

Examples of another embodiment of a most preferable substituent in R<sup>3a</sup> include 1,1,1-trifluoropropan-2-yl.

[0156]

Examples of a preferable substituent in R<sup>5a</sup>, R<sup>6a</sup>, R<sup>7a</sup>, R<sup>8a</sup>, R<sup>9a</sup>, R<sup>10a</sup>, and R<sup>11a</sup> include hydrogen, carboxy, cyano, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,  
-Y-S-R<sup>D1</sup>,  
-Z-S(=O)-R<sup>D2</sup>,  
-Z-SO<sub>2</sub>-R<sup>D3</sup>,

$-C(=O)-C(=O)-R^{D4}$ ,

$-C(=O)-N(R^{D5})(R^{D6})$ ,

$-Z-C(R^{D7})(R^{D8})(R^{D9})$ , or

$-Z-CH_2-R^{D10}$

(substituent group C,  $R^{D1}$ ,  $R^{D2}$ ,  $R^{D3}$ ,  $R^{D4}$ ,  $R^{D5}$ ,  $R^{D6}$ ,  $R^{D7}$ ,  $R^{D8}$ ,  $R^{D9}$ ,  $R^{D10}$ , and Z are same as those of item 1).

[0157]

Examples of a more preferable substituent in  $R^{5a}$ ,  $R^{6a}$ ,  $R^{7a}$ ,  $R^{8a}$ ,  $R^{9a}$ ,  $R^{10a}$ , and  $R^{11a}$  include hydrogen, lower alkyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, tricyclic condensed heterocyclic group optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C,

$-Y-S-R^{D1}$ , or

$-Z-C(R^{D7})(R^{D8})(R^{D9})$

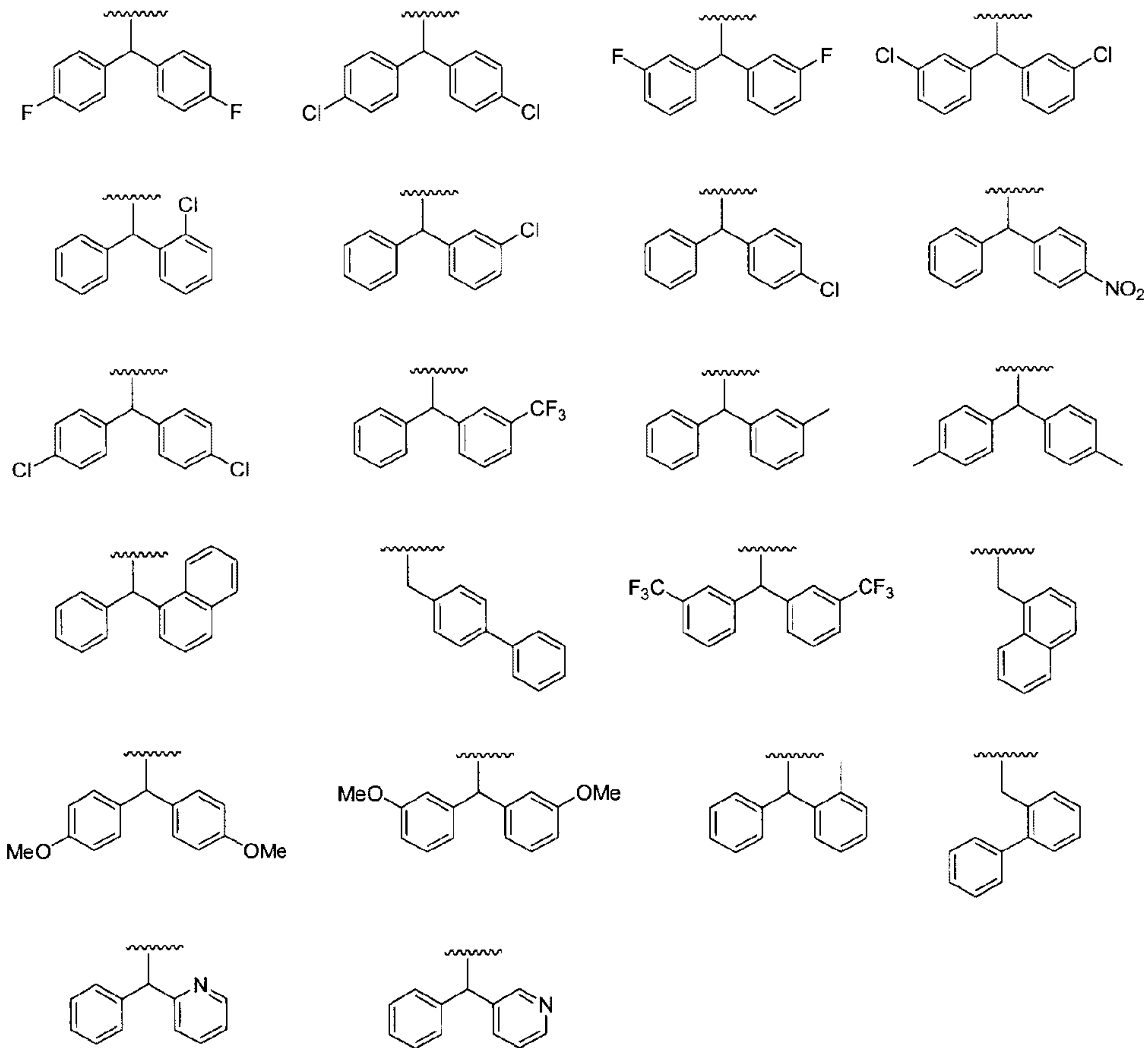
(substituent group C,  $R^{D1}$ ,  $R^{D7}$ ,  $R^{D8}$ ,  $R^{D9}$ , Y, and Z are same as those of item 1).

[0158]

Examples of another embodiment of a preferable substituent in  $R^{5a}$ ,  $R^{6a}$ ,  $R^{7a}$ ,  $R^{8a}$ ,  $R^{9a}$ ,  $R^{10a}$ , and  $R^{11a}$  include hydrogen, benzhydryl, benzyl, indolylmethyl, cyclohexylmethyl, phenethyl, benzylthiomethyl, 3,5-dimethylisoxazolyl, 5-chloro-3-ethylbenzothiophenyl, 4-fluorobenzyl, methylthiazolylmethyl, cyclopentylmethyl, 4-methoxybenzyl, 3-fluorobenzyl, naphthylmethyl, methyl, 3-trifluoromethylbenzyl, pyridylmethyl, 4-methylcarbonylaminobenzyl, pyrimidinyl, isobutyl, phenoxyethyl, methoxypropyl, phenylpropyl, as well as tricyclic or tetracyclic

condensed heterocyclic group optionally substituted by substituent group C such as the following groups

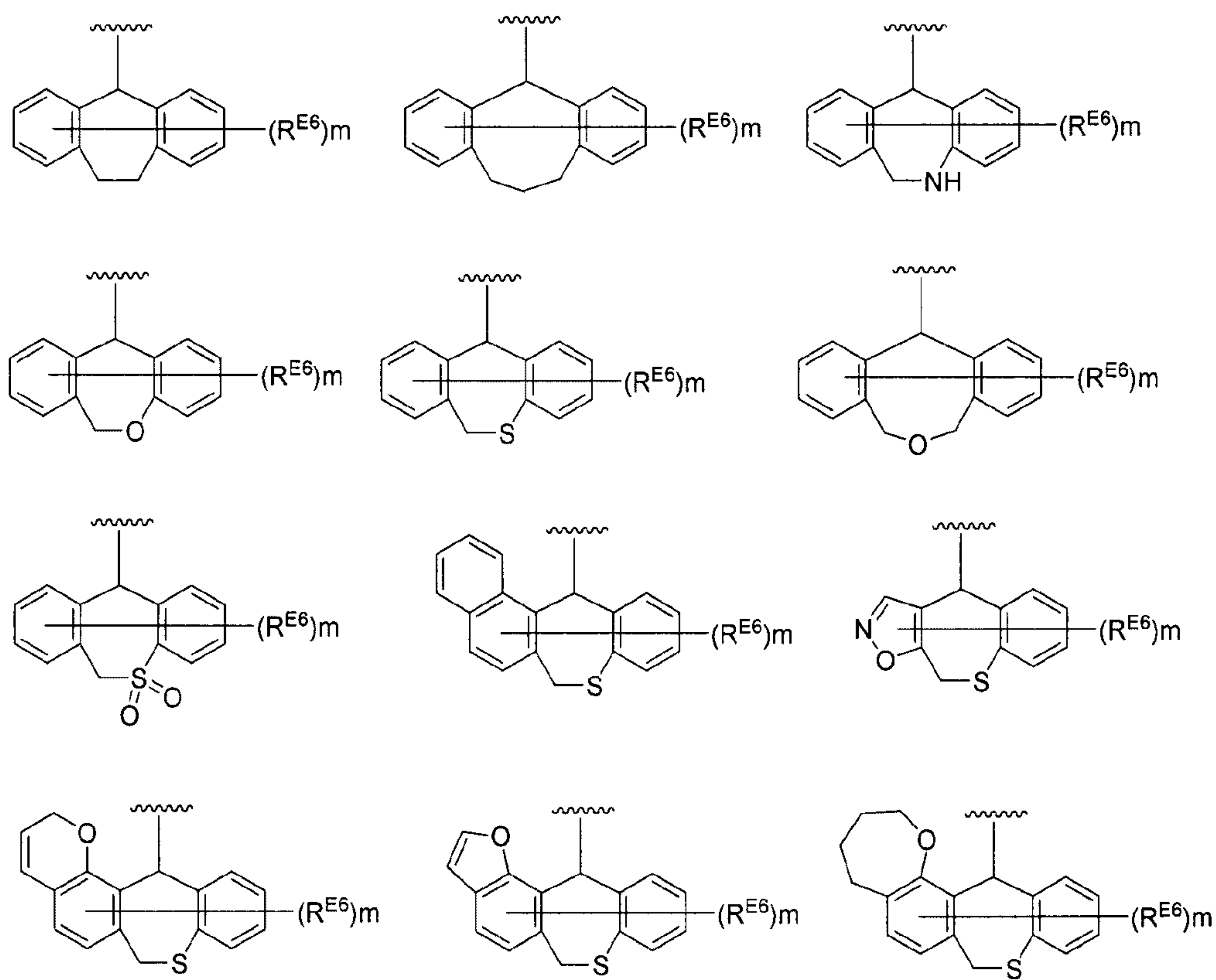
[Chemical formula 43]



[0159]

and

[Chemical formula 44]



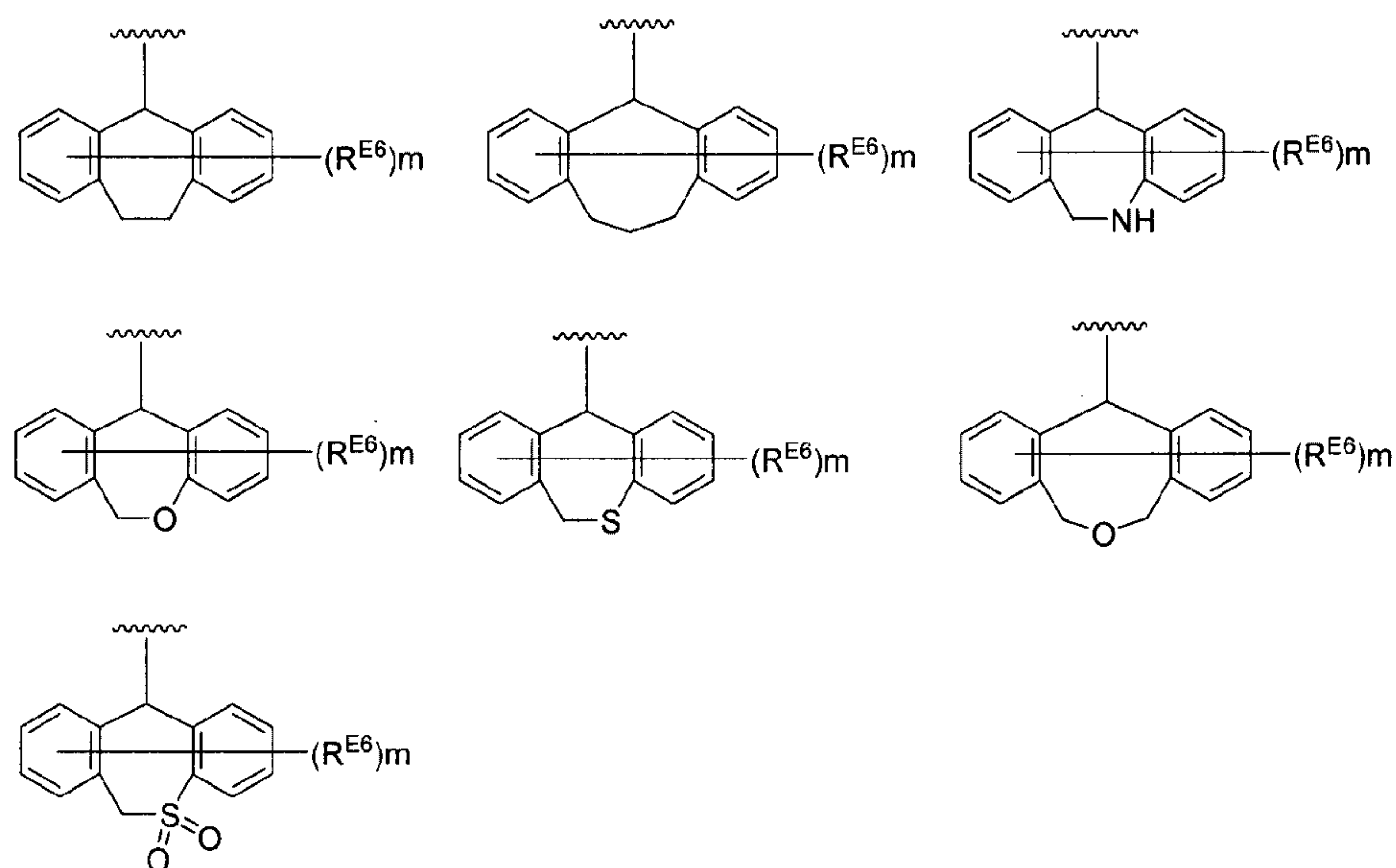
[0160]

(wherein  $R^{E6}$  represents a group selected from substituent group C, and each  $R^{E6}$  may be the same or different) etc.

[0161]

Examples of another embodiment of a more preferable substituent in  $R^{5a}$ ,  $R^{6a}$ ,  $R^{7a}$ ,  $R^{8a}$ ,  $R^{9a}$ ,  $R^{10a}$ , and  $R^{11a}$  include hydrogen, benzhydryl, benzyl, indolylmethyl, cyclohexylmethyl, phenethyl, 3,5-dimethylisoxazolyl, 5-chloro-3-ethylbenzothiophenyl, biphenylmethyl, 4-fluorobenzyl, methylthiazolylmethyl, cyclopentylmethyl, 4-methoxybenzyl, 3-fluorobenzyl, naphthylmethyl, methyl, 3-trifluoromethylbenzyl, pyridylmethyl, 4-methylcarbonylaminobenzyl, pyrimidinyl, and the following groups

[Chemical formula 45]



[0162]

(wherein  $R^{E6}$  represents a group selected from substituent group C, and each  $R^{E6}$  may be the same or different), etc.

[0163]

, etc.

[0164]

1) Examples of a preferable embodiment when  $B^1$  is  $CR^{5a}R^{6a}$ , and  $B^2$  is  $NR^{7a}$  include

the case where  $R^{3a}$  and  $R^{7a}$  are taken together with an adjacent atom to form a heterocycle optionally substituted by substituent group D.

2) Examples of a preferable embodiment when  $B^1$  is  $NR^{7a}$ , and  $B^2$  is  $CR^{5a}R^{6a}$  include

the case where  $R^{3a}$  and  $R^{6a}$  are taken together with an adjacent atom to form a

heterocycle optionally substituted by substituent group D.

3) Examples of a preferable embodiment when  $B^1$  is  $CR^{8a}R^{9a}$ , and  $B^2$  is  $CR^{10a}R^{11a}$  include

the case where  $R^{8a}$  and  $R^{10a}$  are taken together with an adjacent atom to form a carbocycle or a heterocycle optionally substituted by substituent group D.

4) Examples of another preferable embodiment when  $B^1$  is  $CR^{8a}R^{9a}$ , and  $B^2$  is  $CR^{10a}R^{11a}$  include

the case where  $R^{3a}$  and  $R^{11a}$  are taken together with an adjacent atom to form a heterocycle optionally substituted by substituent group D.

[0165]

When one of  $B^1$  and  $B^2$  is  $CR^{5a}R^{6a}$  and the other is  $NR^{7a}$ ,

the case where  $B^1$  is  $NR^{7a}$  and  $B^2$  is  $CR^{5a}R^{6a}$  is more preferable.

[0166]

When one of  $B^1$  and  $B^2$  is  $CR^{5a}R^{6a}$  and the other is  $NR^{7a}$ ,

it is preferable that at least one of  $R^{5a}$  or  $R^{6a}$  is hydrogen. A more preferable embodiment is such that  $R^{5a}$  is hydrogen and  $R^{6a}$  is hydrogen. In this case,  $R^{7a}$  is not a hydrogen atom.

[0167]

A particularly preferable embodiment of  $B^1$  and  $B^2$  is such that  $B^1$  is  $NR^{7a}$  and  $B^2$  is  $CR^{5a}R^{6a}$ .

[0168]

A most preferable embodiment of  $B^1$  and  $B^2$  is such that  $B^1$  is  $NR^{7a}$  and  $B^2$  is  $CH_2$ .

[0169]

A preferable embodiment of  $R^{7a}$  is carbocyclic group optionally substituted by

substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C.

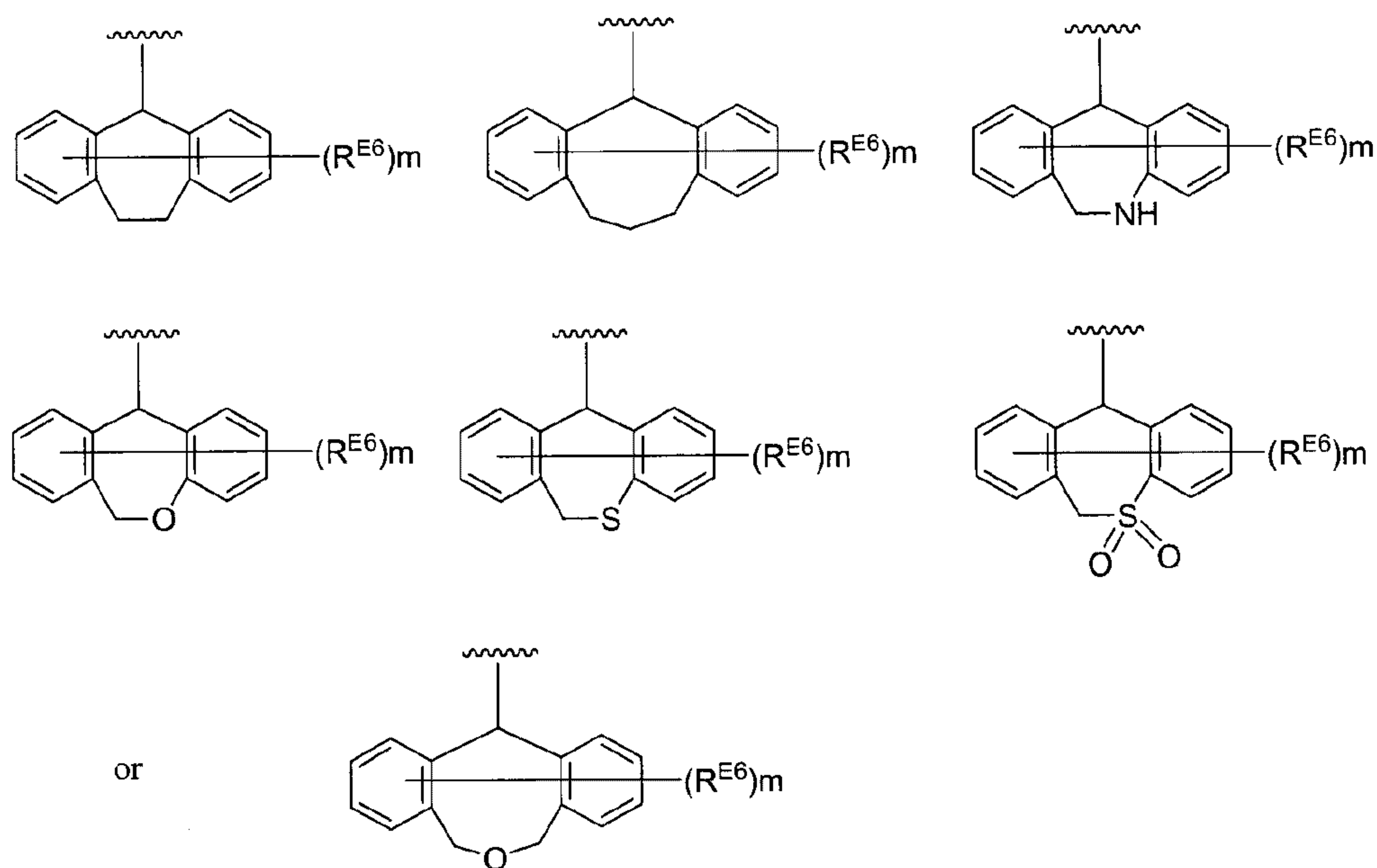
[0170]

A more preferable embodiment of  $R^{7a}$  is cycloalkyl, cycloalkenyl, aryl, non-aromatic condensed carbocyclic group, heteroaryl, non-aromatic heterocyclic group, bicyclic condensed heterocyclic group, tricyclic condensed heterocyclic group, lower alkyl substituted by one or two carbocyclic groups, and lower alkyl substituted by one or two heterocyclic groups.

[0171]

A further preferable embodiment of  $R^{7a}$  is benzyl, benzhydryl, 4-fluorobenzyl, p-methoxybenzyl, and the following groups

[Chemical formula 46]



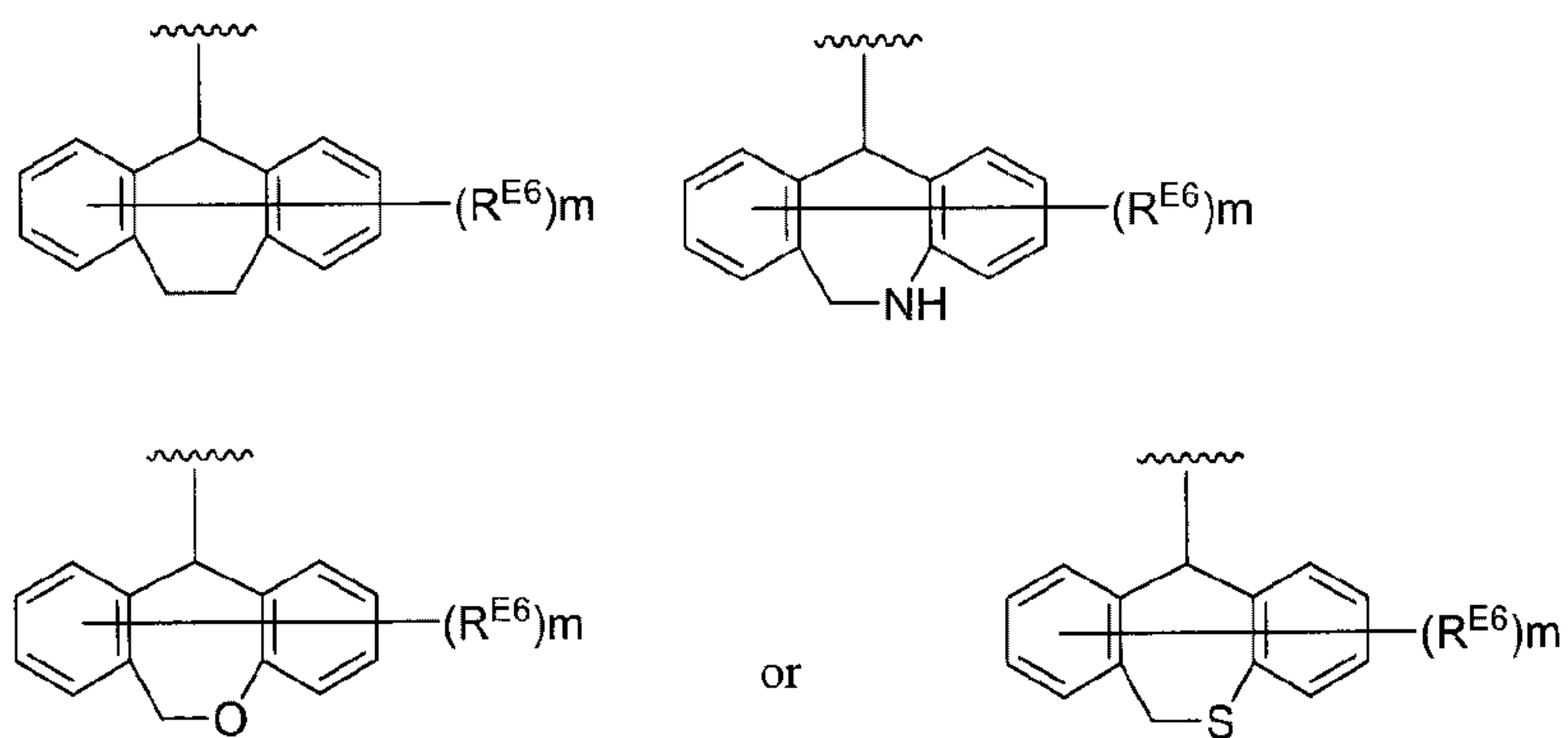
[0172]

(wherein  $R^{E6}$ , and m are same as those of item 1).

[0173]

A particularly preferable embodiment of  $R^{7a}$  is the following groups

[Chemical formula 47]



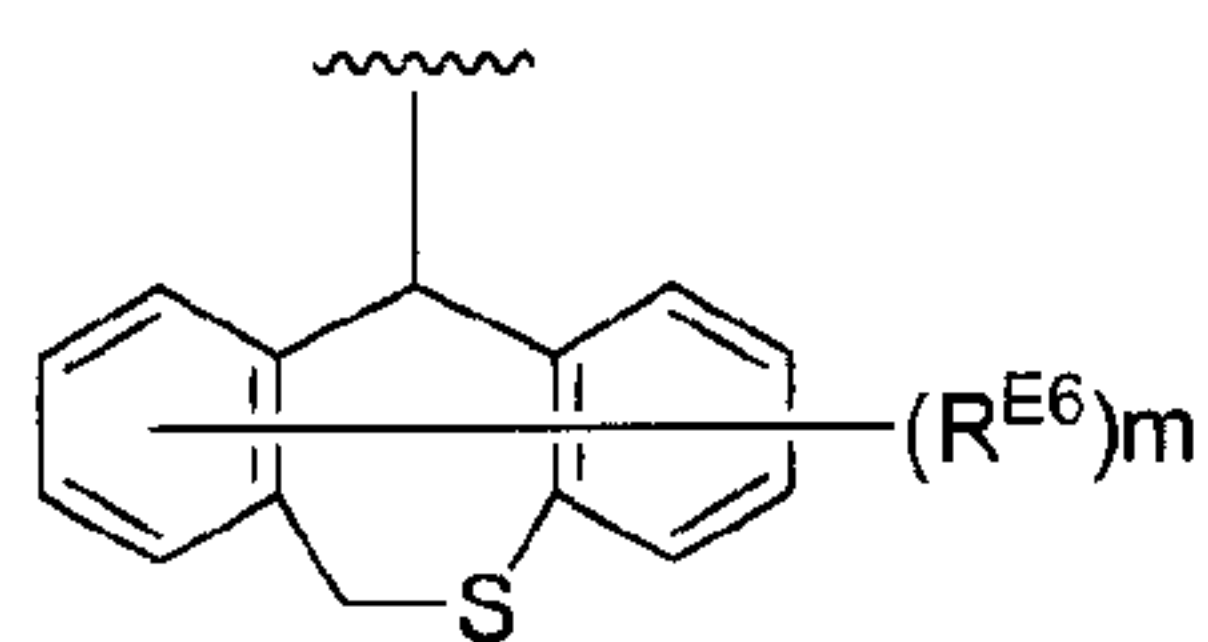
[0174]

(wherein  $R^{E6}$ , and m are same as those of item 1).

[0175]

A most preferable embodiment of  $R^{7a}$  is the following groups

[Chemical formula 48]



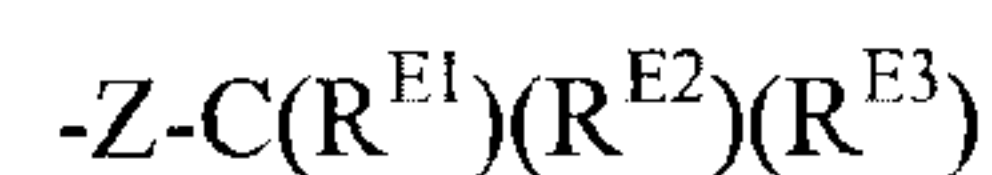
[0176]

(wherein  $R^{E6}$ , and m are same as those of item 1).

[0177]

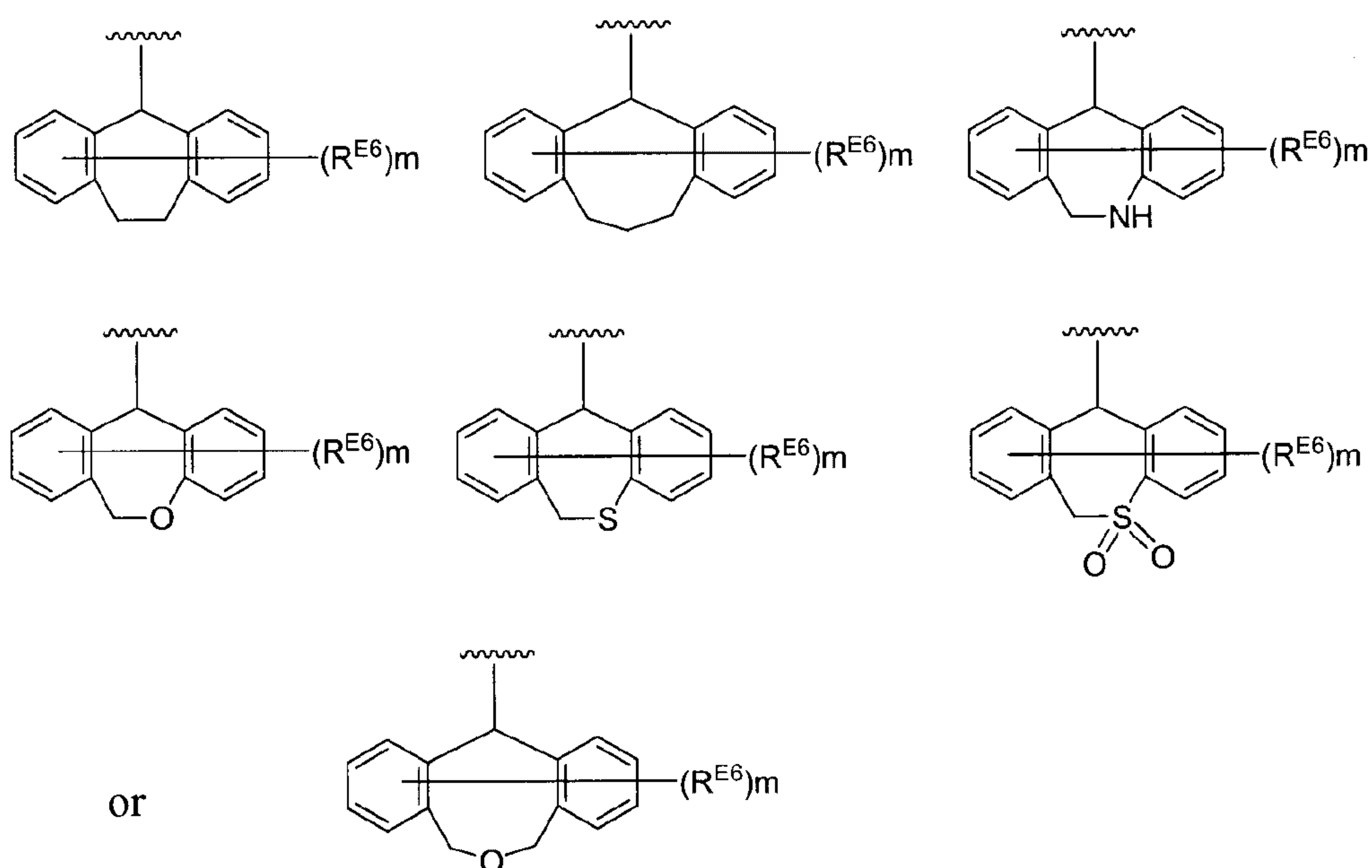
When  $B^1$  is  $CR^{8a}R^{9a}$ , and  $B^2$  is  $CR^{10a}R^{11a}$ , it is preferable that  $R^{9a}$  and  $R^{11a}$  are hydrogen. A preferable embodiment of  $R^{8a}$  and  $R^{10a}$  is such that any one of them is hydrogen.

When  $R^{9a}$  and  $R^{11a}$  are hydrogen, and any one of  $R^{8a}$  and  $R^{10a}$  is hydrogen, a preferable embodiment of the other of  $R^{8a}$  and  $R^{10a}$  is the following groups



or

[Chemical formula 49]



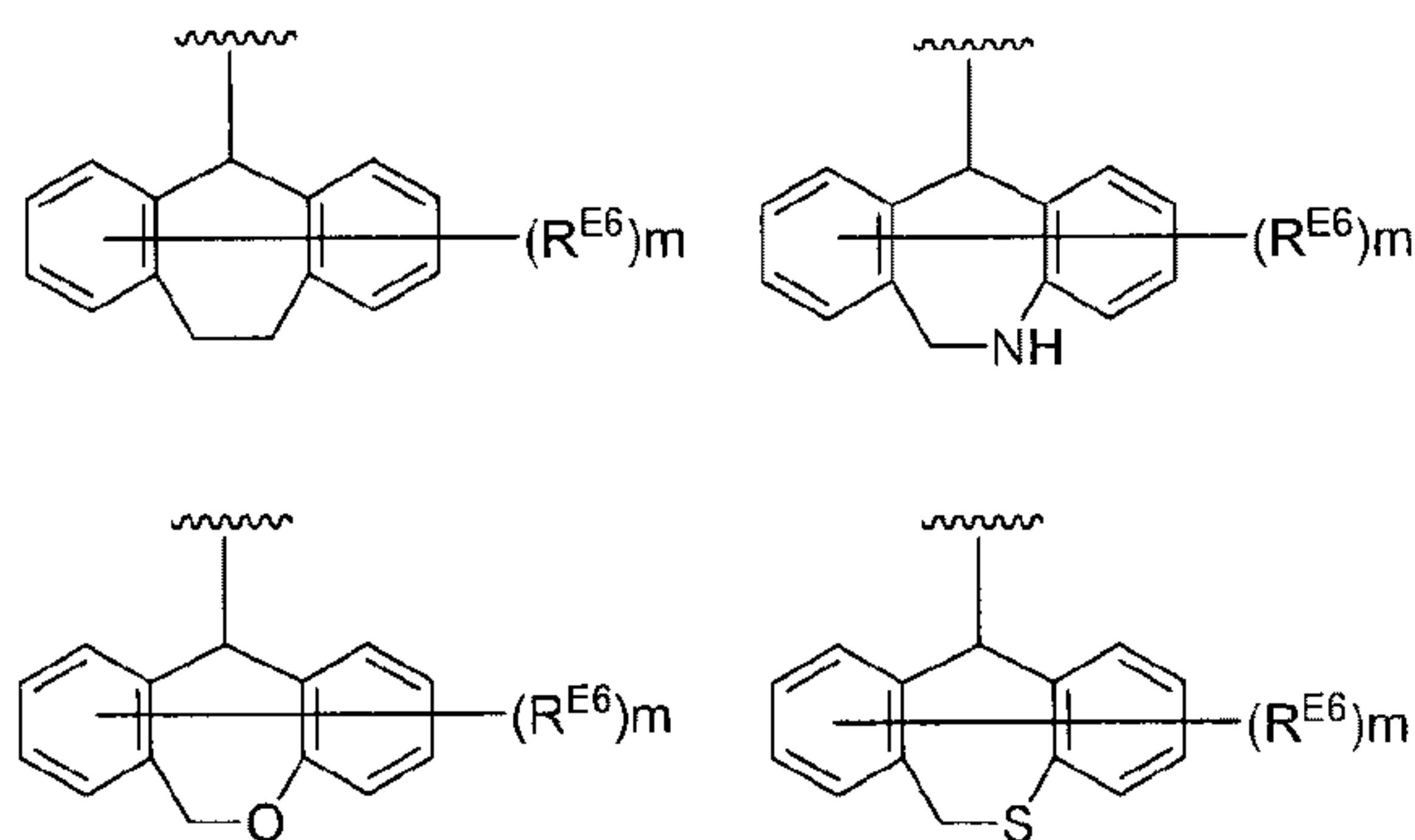
[0178]

(wherein  $Z$ ,  $R^{E1}$ ,  $R^{E2}$ ,  $R^{E3}$ ,  $R^{E6}$ , and  $m$  are same as those of item 1).

[0179]

When  $R^{9a}$  and  $R^{11a}$  are hydrogen, and any one of  $R^{8a}$  and  $R^{10a}$  is hydrogen, a further preferable embodiment of the other of  $R^{8a}$  and  $R^{10a}$  is the following groups

[Chemical formula 50]



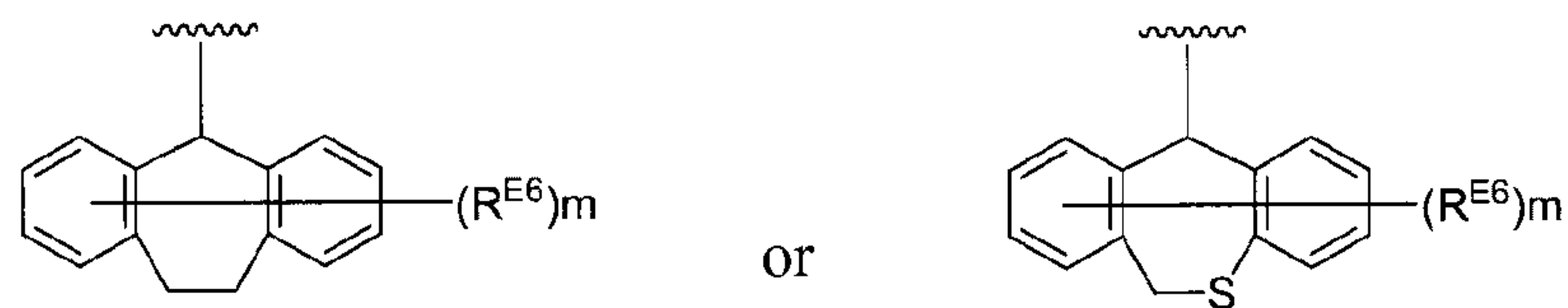
[0180]

(wherein  $R^{E6}$ , and  $m$  are same as those of item 1).

[0181]

When  $R^{9a}$  and  $R^{11a}$  are hydrogen, and any one of  $R^{8a}$  and  $R^{10a}$  is hydrogen, a most preferable embodiment of the other of  $R^{8a}$  and  $R^{10a}$  is the following groups

[Chemical formula 51]



[0182]

(wherein  $R^{E6}$ , and  $m$  are same as those of item 1).

[0183]

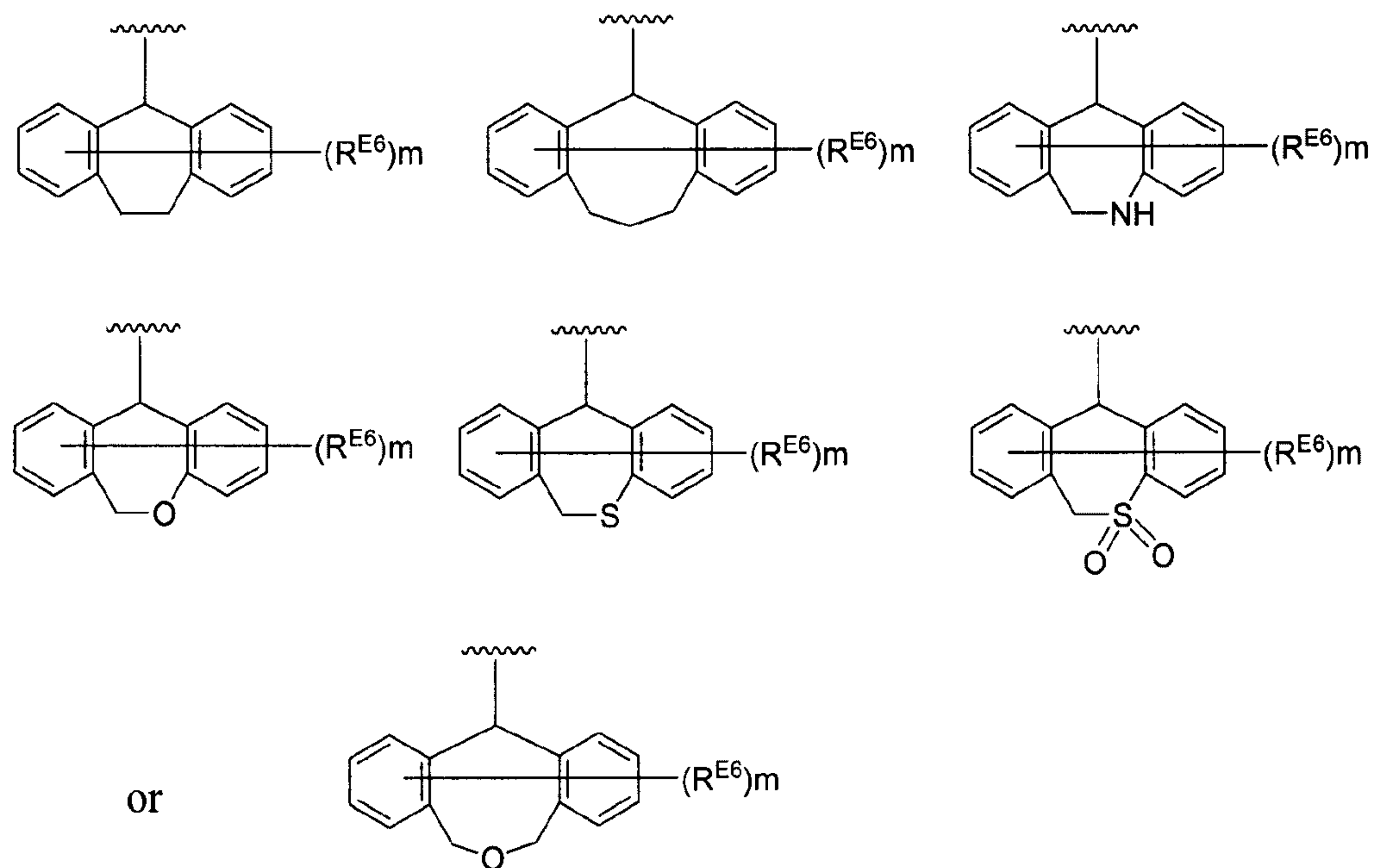
Examples of a preferable substituent in substituent group D include carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent

group C.

[0184]

Examples of another embodiment of a preferable substituent in substituent group D include benzyl, benzhydryl, 4-fluorobenzyl, p-methoxybenzyl,

[Chemical formula 52]



[0185]

(wherein  $R^{E6}$  represents a group selected from substituent group C, and each  $R^{E6}$  may be the same or different) etc.

[0186]

Examples of a preferable substituent of  $R^{E6}$  include halogen, cyano, hydroxy, carboxy, formyl, amino, oxo, nitro, lower alkyl, lower alkynyl, halogeno lower alkyl, lower alkyloxy, lower alkyl amino, halogeno lower alkyloxy, carbocyclic group, etc.

Examples of a more preferable substituent of  $R^{E6}$  include fluorine atom,

chlorine atom, bromine atom, cyano, hydroxy, methyl, ethyl, ethynyl, hydroxymethyl, isopropyl, methoxy, ethoxy, methoxymethyl, cyclopropyl, dimethylamino, trifluoromethyl, oxo, carboxy, etc.

Examples of a particularly preferable substituent of  $R^{E6}$  include fluorine atom, chlorine atom, bromine atom, methyl, methoxy, and trifluoromethyl.

A preferable embodiment of m is an integer of 0 to 6, further preferably an integer of 0 to 3, and most preferably an integer of 0 to 2.

[0187]

One of characteristics of the compound in the present invention is in that a prodrug of a polycyclic carbamoylpyridone derivative, in which two or more rings are condensed, such as shown in the formula (I) in item 1 and/or a composition including them, has high inhibitory activity on cap-dependent endonuclease, and has an effect of treating and/or preventing influenza infectious disease.

[0188]

The characteristic of the compound in the present invention is that cap-dependent endonuclease inhibitory activity was improved, by applying a functional group as shown below to  $R^{1a}$  in the formula (I).

Functional group: hydrogen, halogen, hydroxy, carboxy, cyano, formyl, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkenyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally

substituted by substituent group C, carbocycleoxy optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxy optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,

$-Z-N(R^{A1})(R^{A2})$ ,

$-Z-N(R^{A3})-SO_2-(R^{A4})$ ,

$-Z-C(=O)-N(R^{A5})-SO_2-(R^{A6})$ ,

$-Z-N(R^{A7})-C(=O)-R^{A8}$ ,

$-Z-S-R^{A9}$ ,

$-Z-SO_2-R^{A10}$ ,

$-Z-S(=O)-R^{A11}$ ,

$-Z-N(R^{A12})-C(=O)-O-R^{A13}$ ,

$-Z-N(R^{A14})-C(=O)-N(R^{A15})(R^{A16})$ ,

$-Z-C(=O)-N(R^{A17})-C(=O)-N(R^{A18})(R^{A19})$ , or

$-Z-N(R^{A20})-C(=O)-C(=O)-R^{A21}$

(substituent group C,  $R^{A1}$ ,  $R^{A2}$ ,  $R^{A3}$ ,  $R^{A5}$ ,  $R^{A7}$ ,  $R^{A8}$ ,  $R^{A9}$ ,  $R^{A12}$ ,  $R^{A13}$ ,  $R^{A14}$ ,  $R^{A15}$ ,  $R^{A16}$ ,  $R^{A17}$ ,  $R^{A18}$ ,  $R^{A19}$ ,  $R^{A20}$ , and  $R^{A21}$  are same as those of item 1)

[0189]

The characteristic of a more preferable compound in the present invention is that cap-dependent endonuclease inhibitory activity was improved, by applying a functional group as shown below to  $R^{1a}$  in the formula (I).

Functional group: hydrogen, halogen, hydroxy, carboxy, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent

group C, lower alkyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C,

$-Z-N(R^{A1})(R^{A2})$ ,

$-Z-N(R^{A7})-C(=O)-R^{A8}$ , or

$-Z-N(R^{A12})-C(=O)-O-R^{A13}$

(substituent group C,  $R^{A1}$ ,  $R^{A2}$ ,  $R^{A7}$ ,  $R^{A8}$ ,  $R^{A12}$ ,  $R^{A13}$ , and Z are same as those of item 1).

[0190]

The characteristic of a further preferable compound in the present invention is that cap-dependent endonuclease inhibitory activity was improved, by applying a functional group as shown below to  $R^{1a}$  in the formula (I).

Functional group: hydrogen, halogen, hydroxy, carboxy, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, or

$-Z-N(R^{A1})(R^{A2})$

(substituent group C,  $R^{A1}$ ,  $R^{A2}$ , and Z are same as those of item 1).

[0191]

The characteristic of a particularly preferable compound in the present invention is that cap-dependent endonuclease inhibitory activity was improved, by applying a functional group as shown below to  $R^{1a}$  in the formula (I).

Functional group: hydrogen, acetyl, or carboxy

[0192]

Another characteristic of the compound in the present invention is that cap-dependent endonuclease inhibitory activity was improved, by introducing one, two or more of lipid-soluble functional groups shown below on carbon atom or on nitrogen atom of B<sup>1</sup> and/or B<sup>2</sup> in the formula (I).

Lipid-soluble functional group: carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C

(substituent group C is same as that of item 1).

[0193]

Another characteristic of a more preferable compound in the present invention is that cap-dependent endonuclease inhibitory activity is improved, by introducing one lipid-soluble functional group shown below on carbon atom or on nitrogen atom of B<sup>1</sup> or B<sup>2</sup> in the formula (I).

Lipid-soluble functional group: carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C

(substituent group C is same as that of item 1).

[0194]

Another characteristic of a particularly preferable compound in the present invention is that cap-dependent endonuclease inhibitory activity is improved, by introducing one lipid-soluble functional group shown below on carbon atom or on nitrogen atom of B<sup>1</sup> or B<sup>2</sup> in the formula (I).

Lipid-soluble functional group: carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C (substituent group C is same as that of item 1).

[0195]

Other characteristic of a preferable compound in the present invention is that the compound is efficiently absorbed into the body after in vivo administration (for example, oral administration) and shows high drug efficacy by introducing a group to form a prodrug into a P<sup>R</sup> part in the formula (I).

[0196]

Other characteristic of a more preferable compound in the present invention is that the compound is efficiently absorbed into the body after administration and shows high drug efficacy by introducing a group selected from the following formulae a) to v) into a P<sup>R</sup> part in the formula (I).

- a) -C(=O)-P<sup>R0</sup>,
- b) -C(=O)-P<sup>R1</sup>,
- c) -C(=O)-L-O-P<sup>R1</sup>,
- d) -C(=O)-L-O-L-O-P<sup>R1</sup>,
- e) -C(=O)-L-O-C(=O)-P<sup>R1</sup>,
- f) -C(=O)-O-P<sup>R2</sup>,
- g) -C(=O)-N(P<sup>R2</sup>)<sub>2</sub>,

- h)  $-\text{C}(=\text{O})-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}2}$ ,
- i)  $-\text{CH}_2-\text{O}-\text{P}^{\text{R}3}$ ,
- j)  $-\text{CH}_2-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- k)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{P}^{\text{R}3}$ ,
- l)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{P}^{\text{R}3}$ ,
- m)  $-\text{CH}(-\text{CH}_3)-\text{O}-\text{C}(=\text{O})-\text{O}-\text{P}^{\text{R}3}$ ,
- n)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{P}^{\text{R}3}$ ,
- o)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- p)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{N}(\text{P}^{\text{R}3})_2$ ,
- q)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- r)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{L}-\text{N}(\text{P}^{\text{R}3})_2$ ,
- s)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- t)  $-\text{CH}_2-\text{O}-\text{P}(=\text{O})(-\text{OH})_2$ ,
- u)  $-\text{CH}_2-\text{O}-\text{P}(=\text{O})(-\text{OBn})_2$ ,
- v)  $-\text{CH}_2-\text{P}^{\text{R}4}$

(wherein L is straight or branched lower alkylene,

K is hydrogen, or straight or branched lower alkylene,

$\text{P}^{\text{R}0}$  is lower alkyl optionally substituted by substituent group F,

$\text{P}^{\text{R}1}$  is carbocyclic group optionally substituted by substituent group F,

heterocyclic group optionally substituted by substituent group F, lower alkyl amino optionally substituted by substituent group F, or lower alkylthio optionally substituted by substituent group F,

$\text{P}^{\text{R}2}$  is lower alkyl optionally substituted by substituent group F, carbocyclic group optionally substituted by substituent group F, or heterocyclic group optionally substituted by substituent group F,

$P^{R3}$  is lower alkyl optionally substituted by substituent group F, carbocyclic group optionally substituted by substituent group F, heterocyclic group optionally substituted by substituent group F, lower alkyl amino optionally substituted by substituent group F, carbocycle lower alkyl optionally substituted by substituent group F, heterocycle lower alkyl optionally substituted by substituent group F, or lower alkylsilyl,

$P^{R4}$  is carbocyclic group optionally substituted by substituent group F, or heterocyclic group optionally substituted by substituent group F.

Substituent group F; oxo, lower alkyl, hydroxyl lower alkyl, amino, lower alkylamino, carbocycle lower alkyl, lower alkylcarbonyl, halogen, hydroxy, carboxy, lower alkylcarbonylamino, lower alkylcarbonyloxy, lower alkyloxycarbonyl, lower alkyloxy, cyano, and nitro)

[0197]

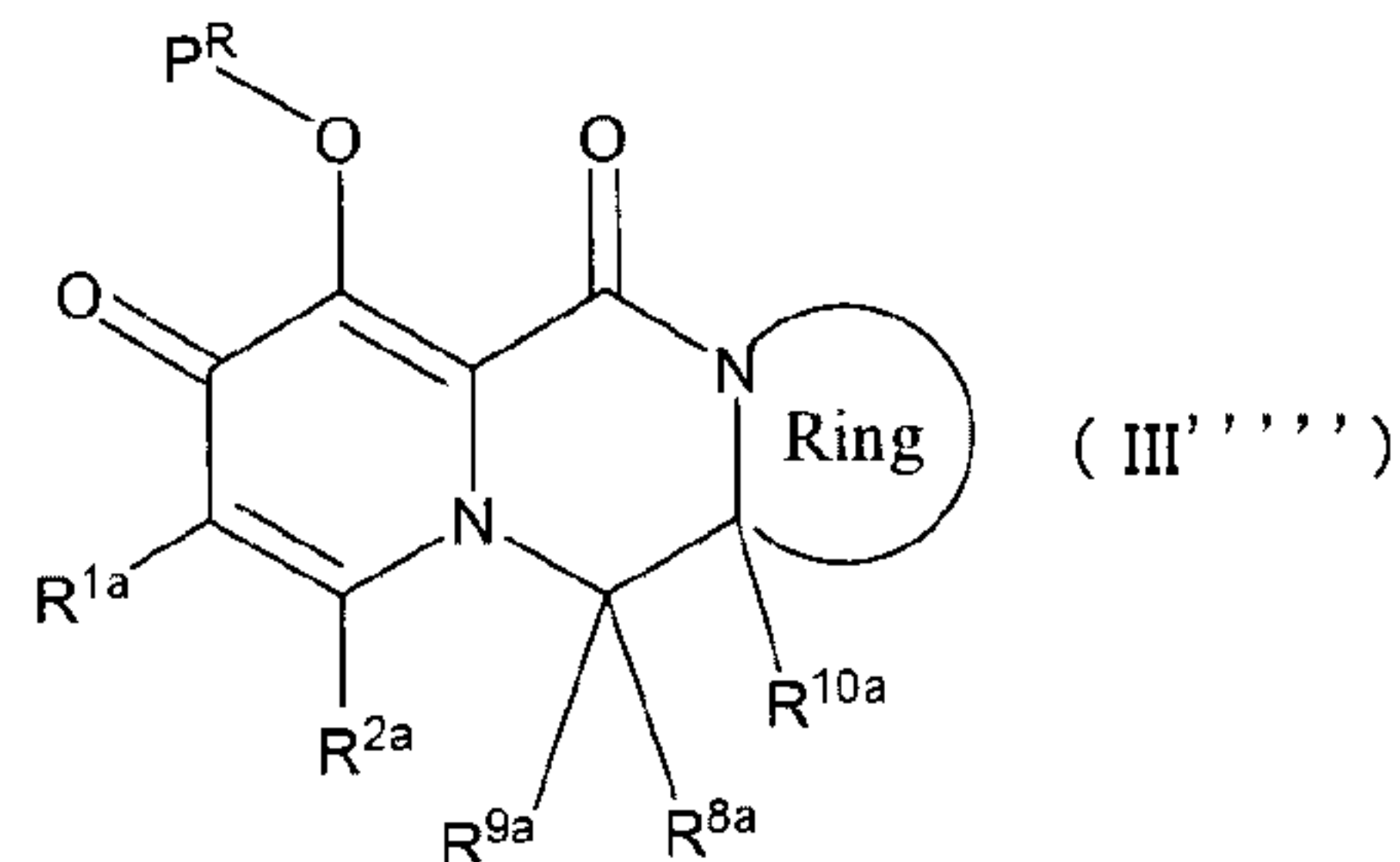
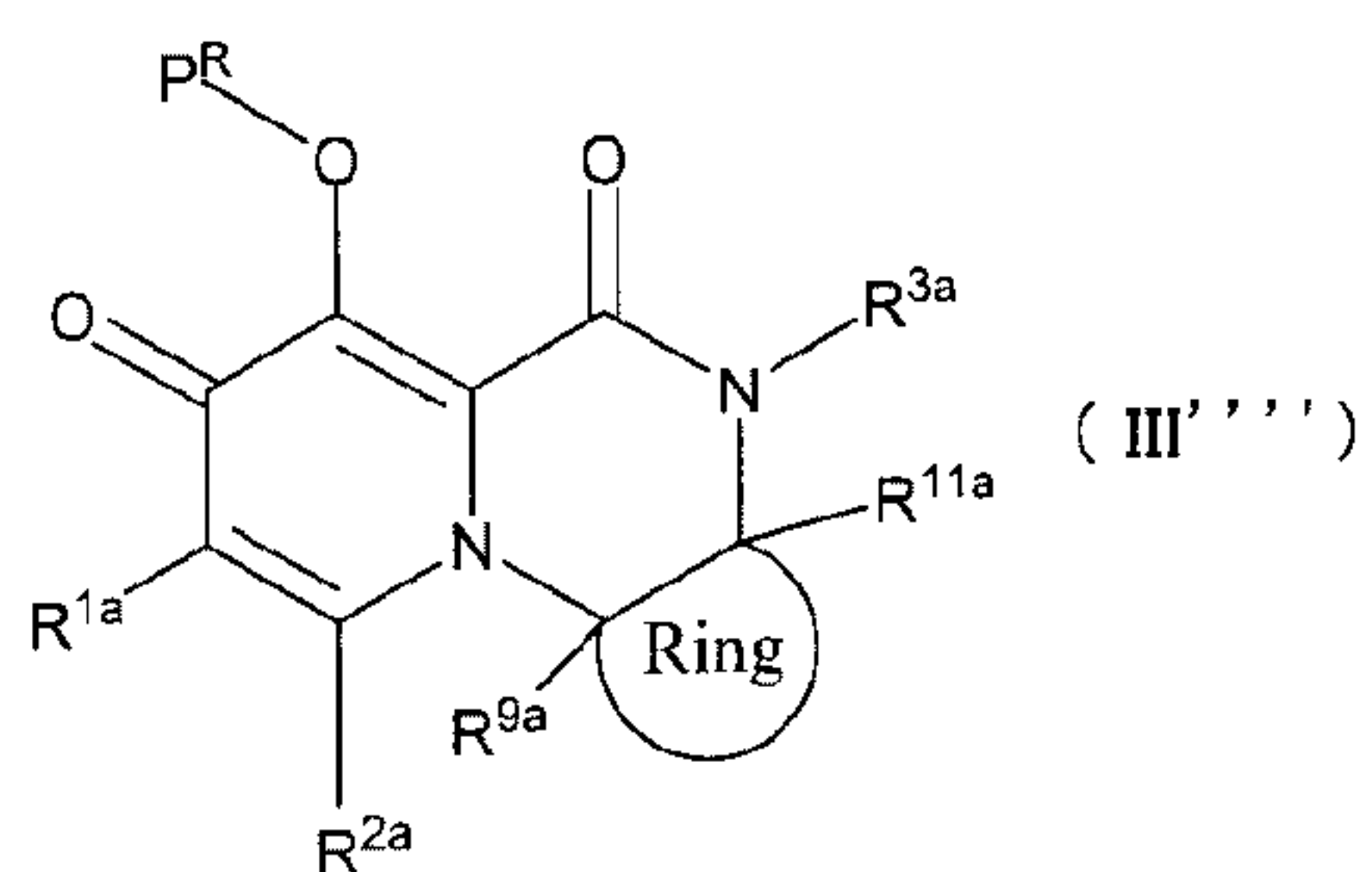
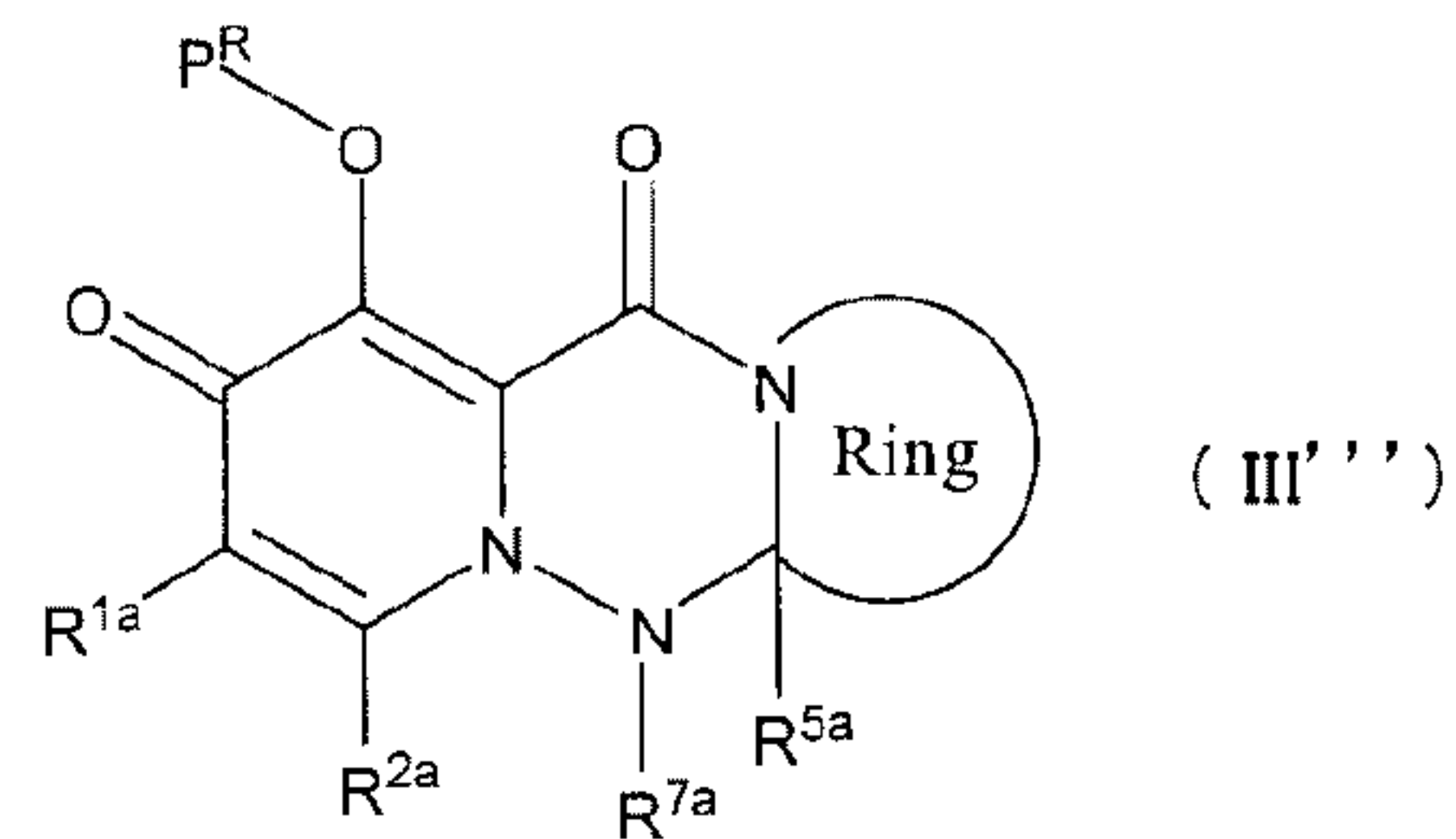
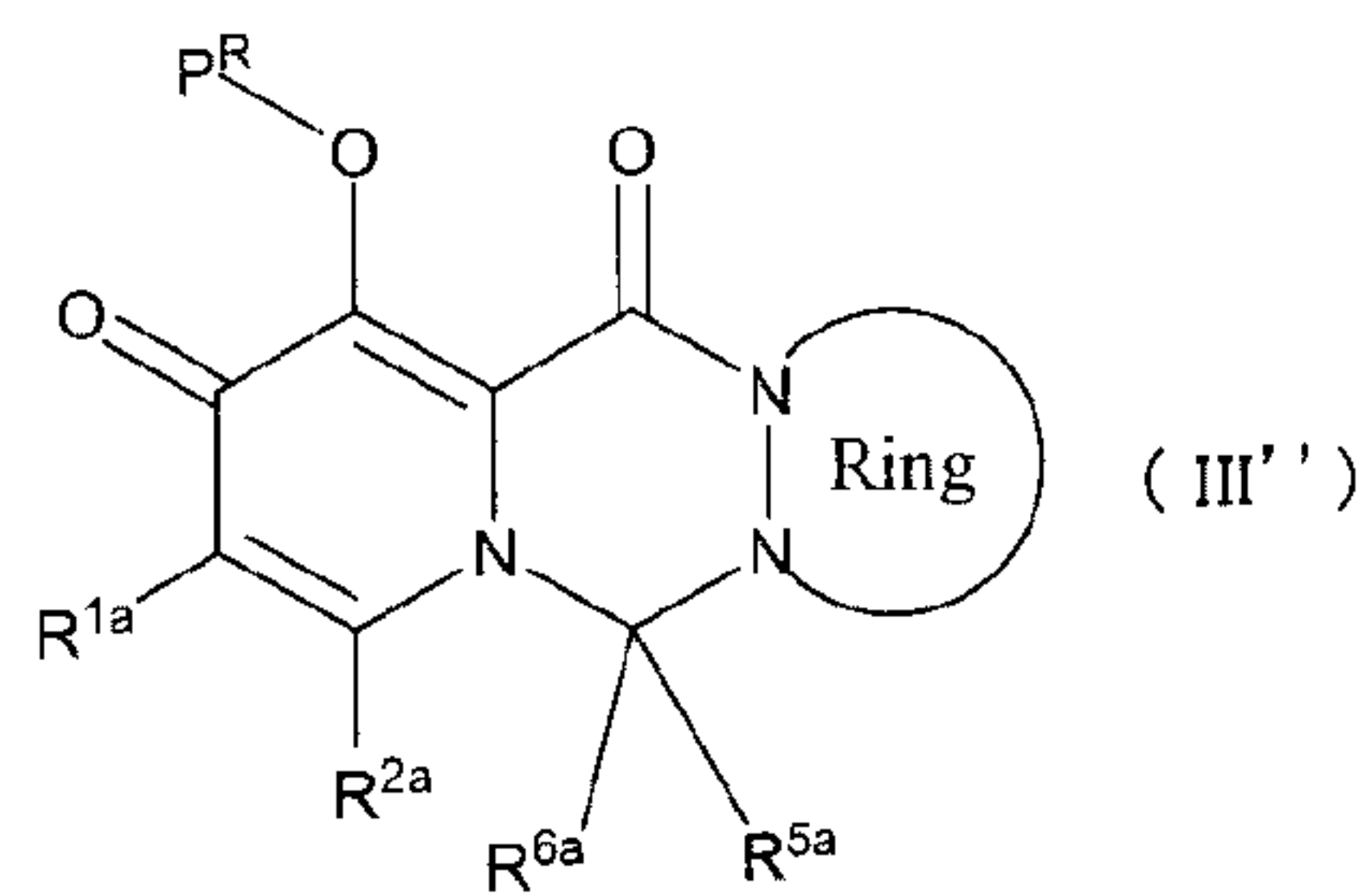
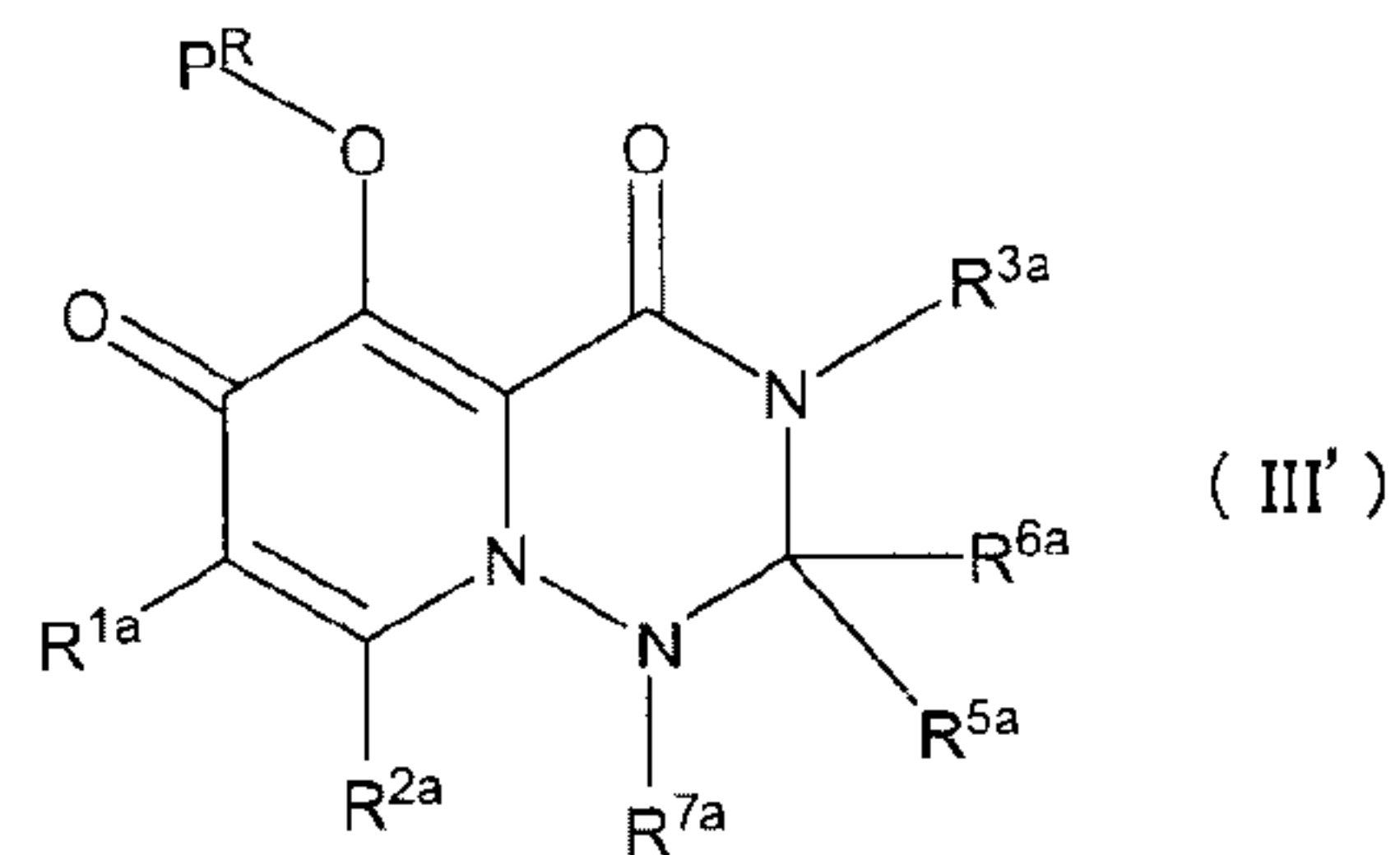
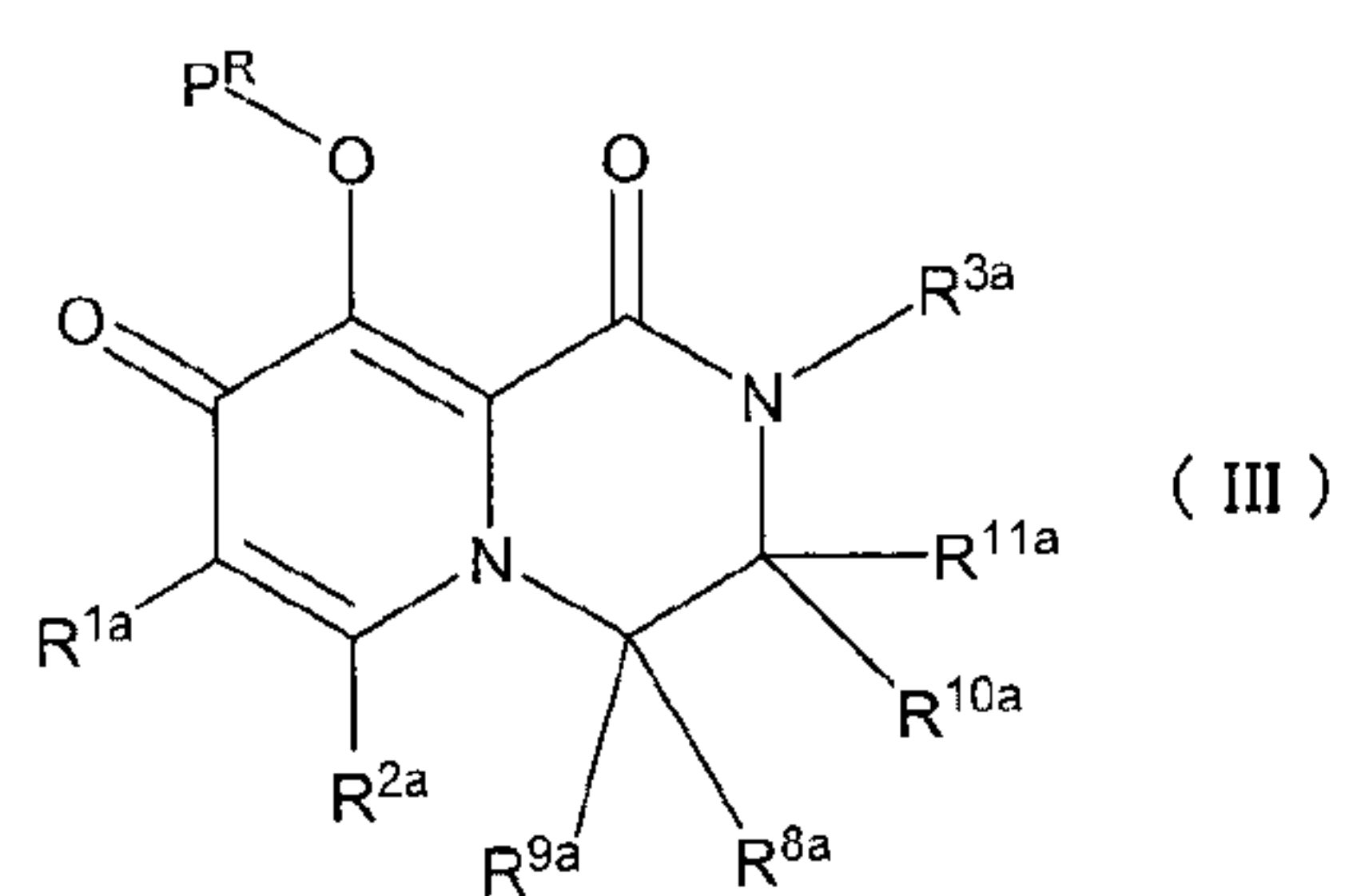
Other characteristic of a more preferable compound in the present invention is that the compound is efficiently absorbed into the body after administration and shows high drug efficacy by introducing groups of P-1 to P-77 in Tables 1 to 8 into a  $P^R$  part in the formula (I).

[0198]

A preferable embodiment of the present invention will be exemplified below.

In the formula (III), the formula (III'), the formula (III''), the formula (III'''), the formula (III''), the formula (III'''):

[Chemical formula 53]



[0199]

,

[0200]

1)

a compound in which R<sup>1a</sup> is hydrogen (hereinafter, R<sup>1a</sup> is R1-1),

a compound in which R<sup>1a</sup> is carboxy (hereinafter, R<sup>1a</sup> is R1-2),

a compound in which R<sup>1a</sup> is halogen (hereinafter R<sup>1a</sup> is R1-3),

a compound in which R<sup>1a</sup> is hydroxy (hereinafter, R<sup>1a</sup> is R1-4),

a compound in which R<sup>1a</sup> is lower alkyl optionally substituted by substituent group C (hereinafter, R<sup>1a</sup> is R1-5),

a compound in which  $R^{1a}$  is lower alkylcarbonyl optionally substituted by substituent group C (hereinafter,  $R^{1a}$  is R1-6),

a compound in which  $R^{1a}$  is lower alkyloxycarbonyl optionally substituted by substituent group C (hereinafter,  $R^{1a}$  is R1-7),

a compound in which  $R^{1a}$  is amino (hereinafter,  $R^{1a}$  is R1-8),

[0201]

2)

a compound in which  $R^{2a}$  is hydrogen (hereinafter,  $R^{2a}$  is R2-1),

a compound in which  $R^{2a}$  is lower alkyl optionally substituted by substituent group C (hereinafter,  $R^{2a}$  is R2-2),

[0202]

3)

a compound in which  $R^{3a}$  is lower alkyl optionally substituted by substituent group C (hereinafter,  $R^{3a}$  is R3-1),

a compound in which  $R^{3a}$  is carbocycle lower alkyl optionally substituted by substituent group C (hereinafter,  $R^{3a}$  is R3-2),

a compound in which  $R^{3a}$  is heterocycle lower alkyl optionally substituted by substituent group C (hereinafter,  $R^{3a}$  is R3-3),

a compound in which  $R^{3a}$  is carbocyclic group optionally substituted by substituent group C (hereinafter,  $R^{3a}$  is R3-4),

a compound in which  $R^{3a}$  is heterocyclic group optionally substituted by substituent group C (hereinafter,  $R^{3a}$  is R3-5),

[0203]

4)

a compound in which  $P^R$  is  $-C(=O)-P^{R1}$  (hereinafter,  $P^R$  is Pr-1),

a compound in which  $P^R$  is  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{P}^{\text{R}3}$  (hereinafter,  $P^R$  is Pr-2),

a compound in which  $P^R$  is  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{P}^{\text{R}3}$  (hereinafter,  $P^R$  is Pr-3),

a compound in which  $P^R$  is  $-\text{CH}(-\text{CH}_3)-\text{O}-\text{C}(=\text{O})-\text{O}-\text{P}^{\text{R}3}$  (hereinafter,  $P^R$  is Pr-4),

(wherein each symbol is same as above)

[0204]

in the formula (III'),

[0205]

a compound in which  $R^{7a}$  is carbocyclic group optionally substituted by substituent group C, and  $R^{5a}$  and  $R^{6a}$  are hydrogen (hereinafter, R7-1),

a compound in which  $R^{7a}$  is heterocyclic group optionally substituted by substituent group C, and  $R^{5a}$  and  $R^{6a}$  are hydrogen (hereinafter, R7-2),

a compound in which  $R^{7a}$  is carbocycle lower alkyl optionally substituted by substituent group C, and  $R^{5a}$  and  $R^{6a}$  are hydrogen (hereinafter, R7-3),

[0206]

in the formula (III),

[0207]

a compound in which  $R^{9a}$  is carbocyclic group optionally substituted by substituent group C, and  $R^{8a}$ ,  $R^{10a}$  and  $R^{11a}$  are hydrogen (hereinafter, R9-1),

a compound in which  $R^{9a}$  is heterocyclic group optionally substituted by substituent group C, and  $R^{8a}$ ,  $R^{10a}$  and  $R^{11a}$  are hydrogen (hereinafter, R9-2),

a compound in which  $R^{9a}$  is carbocycle lower alkyl optionally substituted by substituent group C, and  $R^{8a}$ ,  $R^{10a}$ , and  $R^{11a}$  are hydrogen (hereinafter, R9-3)

[0208]

Herein, the substituent group C is at least one selected from a substituent group

consisting of halogen, cyano, hydroxy, carboxy, formyl, amino, oxo, nitro, lower alkyl, halogeno lower alkyl, lower alkyloxy, carbocyclic group, heterocyclic group, carbocycle lower alkyloxy, heterocycle lower alkyloxy, halogeno lower alkyloxy, lower alkyloxy lower alkyl, lower alkyloxy lower alkyloxy, lower alkylcarbonyl, lower alkyloxycarbonyl, lower alkylamino, lower alkylcarbonylamino, lower alkylaminocarbonyl, lower alkylsulfonyl, and lower alkylsulfonylamino.

[0209]

Compounds in which, in the formula (III'), a combination of  $R^{1a}$ ,  $R^{2a}$ ,  $R^{3a}$ ,  $P^R$ , as well as ( $R^{5a}$ ,  $R^{6a}$ , and  $R^{7a}$ ) is as follows.

(R1-1, R2-1, R3-1, Pr-1, R7-1), (R1-1, R2-1, R3-1, Pr-1, R7-2), (R1-1, R2-1, R3-1, Pr-1, R7-3), (R1-1, R2-1, R3-1, Pr-2, R7-1), (R1-1, R2-1, R3-1, Pr-2, R7-2), (R1-1, R2-1, R3-1, Pr-2, R7-3), (R1-1, R2-1, R3-1, Pr-3, R7-1), (R1-1, R2-1, R3-1, Pr-3, R7-2), (R1-1, R2-1, R3-1, Pr-3, R7-3), (R1-1, R2-1, R3-1, Pr-4, R7-1), (R1-1, R2-1, R3-1, Pr-4, R7-2), (R1-1, R2-1, R3-1, Pr-4, R7-3), (R1-1, R2-1, R3-2, Pr-1, R7-1), (R1-1, R2-1, R3-2, Pr-1, R7-2), (R1-1, R2-1, R3-2, Pr-1, R7-3), (R1-1, R2-1, R3-2, Pr-2, R7-1), (R1-1, R2-1, R3-2, Pr-2, R7-2), (R1-1, R2-1, R3-2, Pr-2, R7-3), (R1-1, R2-1, R3-2, Pr-3, R7-1), (R1-1, R2-1, R3-2, Pr-3, R7-2), (R1-1, R2-1, R3-2, Pr-3, R7-3), (R1-1, R2-1, R3-2, Pr-4, R7-1), (R1-1, R2-1, R3-2, Pr-4, R7-2), (R1-1, R2-1, R3-2, Pr-4, R7-3), (R1-1, R2-1, R3-3, Pr-1, R7-1), (R1-1, R2-1, R3-3, Pr-1, R7-2), (R1-1, R2-1, R3-3, Pr-1, R7-3), (R1-1, R2-1, R3-3, Pr-2, R7-1), (R1-1, R2-1, R3-3, Pr-2, R7-2), (R1-1, R2-1, R3-3, Pr-2, R7-3), (R1-1, R2-1, R3-3, Pr-3, R7-1), (R1-1, R2-1, R3-3, Pr-3, R7-2), (R1-1, R2-1, R3-3, Pr-3, R7-3), (R1-1, R2-1, R3-3, Pr-4, R7-1), (R1-1, R2-1, R3-3, Pr-4, R7-2), (R1-1, R2-1, R3-3, Pr-4, R7-3), (R1-1, R2-1, R3-4, Pr-1, R7-1), (R1-1, R2-1, R3-4, Pr-1, R7-2), (R1-1, R2-1, R3-4, Pr-1, R7-3), (R1-1, R2-1, R3-4, Pr-2, R7-1), (R1-1, R2-1, R3-4, Pr-2, R7-2), (R1-1, R2-1, R3-4, Pr-2, R7-3), (R1-1, R2-1, R3-4, Pr-3,

R7-1)、(R1-1, R2-1, R3-4, Pr-3, R7-2)、(R1-1, R2-1, R3-4, Pr-3, R7-3)、(R1-1, R2-1,  
 R3-4, Pr-4, R7-1)、(R1-1, R2-1, R3-4, Pr-4, R7-2)、(R1-1, R2-1, R3-4, Pr-4, R7-3)、  
 (R1-1, R2-1, R3-5, Pr-1, R7-1)、(R1-1, R2-1, R3-5, Pr-1, R7-2)、(R1-1, R2-1, R3-5, Pr-1,  
 R7-3)、(R1-1, R2-1, R3-5, Pr-2, R7-1)、(R1-1, R2-1, R3-5, Pr-2, R7-2)、(R1-1, R2-1,  
 R3-5, Pr-2, R7-3)、(R1-1, R2-1, R3-5, Pr-3, R7-1)、(R1-1, R2-1, R3-5, Pr-3, R7-2)、  
 (R1-1, R2-1, R3-5, Pr-3, R7-3)、(R1-1, R2-1, R3-5, Pr-4, R7-1)、(R1-1, R2-1, R3-5, Pr-4,  
 R7-2)、(R1-1, R2-1, R3-5, Pr-4, R7-3)、(R1-1, R2-2, R3-1, Pr-1, R7-1)、(R1-1, R2-2,  
 R3-1, Pr-1, R7-2)、(R1-1, R2-2, R3-1, Pr-1, R7-3)、(R1-1, R2-2, R3-1, Pr-2, R7-1)、  
 (R1-1, R2-2, R3-1, Pr-2, R7-2)、(R1-1, R2-2, R3-1, Pr-2, R7-3)、(R1-1, R2-2, R3-1, Pr-3,  
 R7-1)、(R1-1, R2-2, R3-1, Pr-3, R7-2)、(R1-1, R2-2, R3-1, Pr-3, R7-3)、(R1-1, R2-2,  
 R3-1, Pr-4, R7-1)、(R1-1, R2-2, R3-1, Pr-4, R7-2)、(R1-1, R2-2, R3-1, Pr-4, R7-3)、  
 (R1-1, R2-2, R3-2, Pr-1, R7-1)、(R1-1, R2-2, R3-2, Pr-1, R7-2)、(R1-1, R2-2, R3-2, Pr-1,  
 R7-3)、(R1-1, R2-2, R3-2, Pr-2, R7-1)、(R1-1, R2-2, R3-2, Pr-2, R7-2)、(R1-1, R2-2,  
 R3-2, Pr-2, R7-3)、(R1-1, R2-2, R3-2, Pr-3, R7-1)、(R1-1, R2-2, R3-2, Pr-3, R7-2)、  
 (R1-1, R2-2, R3-2, Pr-3, R7-3)、(R1-1, R2-2, R3-2, Pr-4, R7-1)、(R1-1, R2-2, R3-2, Pr-4,  
 R7-2)、(R1-1, R2-2, R3-2, Pr-4, R7-3)、(R1-1, R2-2, R3-3, Pr-1, R7-1)、(R1-1, R2-2,  
 R3-3, Pr-1, R7-2)、(R1-1, R2-2, R3-3, Pr-1, R7-3)、(R1-1, R2-2, R3-3, Pr-2, R7-1)、  
 (R1-1, R2-2, R3-3, Pr-2, R7-2)、(R1-1, R2-2, R3-3, Pr-2, R7-3)、(R1-1, R2-2, R3-3, Pr-3,  
 R7-1)、(R1-1, R2-2, R3-3, Pr-3, R7-2)、(R1-1, R2-2, R3-3, Pr-3, R7-3)、(R1-1, R2-2,  
 R3-3, Pr-4, R7-1)、(R1-1, R2-2, R3-3, Pr-4, R7-2)、(R1-1, R2-2, R3-3, Pr-4, R7-3)、  
 (R1-1, R2-2, R3-4, Pr-1, R7-1)、(R1-1, R2-2, R3-4, Pr-1, R7-2)、(R1-1, R2-2, R3-4, Pr-1,  
 R7-3)、(R1-1, R2-2, R3-4, Pr-2, R7-1)、(R1-1, R2-2, R3-4, Pr-2, R7-2)、(R1-1, R2-2,  
 R3-4, Pr-2, R7-3)、(R1-1, R2-2, R3-4, Pr-3, R7-1)、(R1-1, R2-2, R3-4, Pr-3, R7-2)、  
 (R1-1, R2-2, R3-4, Pr-3, R7-3)、(R1-1, R2-2, R3-4, Pr-4, R7-1)、(R1-1, R2-2, R3-4, Pr-4,  
 R7-2)、(R1-1, R2-2, R3-4, Pr-4, R7-3)、(R1-1, R2-2, R3-5, Pr-1, R7-1)、(R1-1, R2-2,

R3-5, Pr-1, R7-2)、(R1-1, R2-2, R3-5, Pr-1, R7-3)、(R1-1, R2-2, R3-5, Pr-2, R7-1)、  
 (R1-1, R2-2, R3-5, Pr-2, R7-2)、(R1-1, R2-2, R3-5, Pr-2, R7-3)、(R1-1, R2-2, R3-5, Pr-3,  
 R7-1)、(R1-1, R2-2, R3-5, Pr-3, R7-2)、(R1-1, R2-2, R3-5, Pr-3, R7-3)、(R1-1, R2-2,  
 R3-5, Pr-4, R7-1)、(R1-1, R2-2, R3-5, Pr-4, R7-2)、(R1-1, R2-2, R3-5, Pr-4, R7-3)、  
 [0210]

(R1-2, R2-1, R3-1, Pr-1, R7-1)、(R1-2, R2-1, R3-1, Pr-1, R7-2)、(R1-2, R2-1, R3-1,  
 Pr-1, R7-3)、(R1-2, R2-1, R3-1, Pr-2, R7-1)、(R1-2, R2-1, R3-1, Pr-2, R7-2)、(R1-2,  
 R2-1, R3-1, Pr-2, R7-3)、(R1-2, R2-1, R3-1, Pr-3, R7-1)、(R1-2, R2-1, R3-1, Pr-3, R7-2)、  
 (R1-2, R2-1, R3-1, Pr-3, R7-3)、(R1-2, R2-1, R3-1, Pr-4, R7-1)、(R1-2, R2-1, R3-1, Pr-4,  
 R7-2)、(R1-2, R2-1, R3-1, Pr-4, R7-3)、(R1-2, R2-1, R3-2, Pr-1, R7-1)、(R1-2, R2-1,  
 R3-2, Pr-1, R7-2)、(R1-2, R2-1, R3-2, Pr-1, R7-3)、(R1-2, R2-1, R3-2, Pr-2, R7-1)、  
 (R1-2, R2-1, R3-2, Pr-2, R7-2)、(R1-2, R2-1, R3-2, Pr-2, R7-3)、(R1-2, R2-1, R3-2, Pr-3,  
 R7-1)、(R1-2, R2-1, R3-2, Pr-3, R7-2)、(R1-2, R2-1, R3-2, Pr-3, R7-3)、(R1-2, R2-1,  
 R3-2, Pr-4, R7-1)、(R1-2, R2-1, R3-2, Pr-4, R7-2)、(R1-2, R2-1, R3-2, Pr-4, R7-3)、  
 (R1-2, R2-1, R3-3, Pr-1, R7-1)、(R1-2, R2-1, R3-3, Pr-1, R7-2)、(R1-2, R2-1, R3-3, Pr-1,  
 R7-3)、(R1-2, R2-1, R3-3, Pr-2, R7-1)、(R1-2, R2-1, R3-3, Pr-2, R7-2)、(R1-2, R2-1,  
 R3-3, Pr-2, R7-3)、(R1-2, R2-1, R3-3, Pr-3, R7-1)、(R1-2, R2-1, R3-3, Pr-3, R7-2)、  
 (R1-2, R2-1, R3-3, Pr-3, R7-3)、(R1-2, R2-1, R3-3, Pr-4, R7-1)、(R1-2, R2-1, R3-3, Pr-4,  
 R7-2)、(R1-2, R2-1, R3-3, Pr-4, R7-3)、(R1-2, R2-1, R3-4, Pr-1, R7-1)、(R1-2, R2-1,  
 R3-4, Pr-1, R7-2)、(R1-2, R2-1, R3-4, Pr-1, R7-3)、(R1-2, R2-1, R3-4, Pr-2, R7-1)、  
 (R1-2, R2-1, R3-4, Pr-2, R7-2)、(R1-2, R2-1, R3-4, Pr-2, R7-3)、(R1-2, R2-1, R3-4, Pr-3,  
 R7-1)、(R1-2, R2-1, R3-4, Pr-3, R7-2)、(R1-2, R2-1, R3-4, Pr-3, R7-3)、(R1-2, R2-1,  
 R3-4, Pr-4, R7-1)、(R1-2, R2-1, R3-4, Pr-4, R7-2)、(R1-2, R2-1, R3-4, Pr-4, R7-3)、  
 (R1-2, R2-1, R3-5, Pr-1, R7-1)、(R1-2, R2-1, R3-5, Pr-1, R7-2)、(R1-2, R2-1, R3-5, Pr-1,  
 R7-3)、(R1-2, R2-1, R3-5, Pr-2, R7-1)、(R1-2, R2-1, R3-5, Pr-2, R7-2)、(R1-2, R2-1,

R3-5, Pr-2, R7-3)、(R1-2, R2-1, R3-5, Pr-3, R7-1)、(R1-2, R2-1, R3-5, Pr-3, R7-2)、  
 (R1-2, R2-1, R3-5, Pr-3, R7-3)、(R1-2, R2-1, R3-5, Pr-4, R7-1)、(R1-2, R2-1, R3-5, Pr-4,  
 R7-2)、(R1-2, R2-1, R3-5, Pr-4, R7-3)、(R1-2, R2-2, R3-1, Pr-1, R7-1)、(R1-2, R2-2,  
 R3-1, Pr-1, R7-2)、(R1-2, R2-2, R3-1, Pr-1, R7-3)、(R1-2, R2-2, R3-1, Pr-2, R7-1)、  
 (R1-2, R2-2, R3-1, Pr-2, R7-2)、(R1-2, R2-2, R3-1, Pr-2, R7-3)、(R1-2, R2-2, R3-1, Pr-3,  
 R7-1)、(R1-2, R2-2, R3-1, Pr-3, R7-2)、(R1-2, R2-2, R3-1, Pr-3, R7-3)、(R1-2, R2-2,  
 R3-1, Pr-4, R7-1)、(R1-2, R2-2, R3-1, Pr-4, R7-2)、(R1-2, R2-2, R3-1, Pr-4, R7-3)、  
 (R1-2, R2-2, R3-2, Pr-1, R7-1)、(R1-2, R2-2, R3-2, Pr-1, R7-2)、(R1-2, R2-2, R3-2, Pr-1,  
 R7-3)、(R1-2, R2-2, R3-2, Pr-2, R7-1)、(R1-2, R2-2, R3-2, Pr-2, R7-2)、(R1-2, R2-2,  
 R3-2, Pr-2, R7-3)、(R1-2, R2-2, R3-2, Pr-3, R7-1)、(R1-2, R2-2, R3-2, Pr-3, R7-2)、  
 (R1-2, R2-2, R3-2, Pr-3, R7-3)、(R1-2, R2-2, R3-2, Pr-4, R7-1)、(R1-2, R2-2, R3-2, Pr-4,  
 R7-2)、(R1-2, R2-2, R3-2, Pr-4, R7-3)、(R1-2, R2-2, R3-3, Pr-1, R7-1)、(R1-2, R2-2,  
 R3-3, Pr-1, R7-2)、(R1-2, R2-2, R3-3, Pr-1, R7-3)、(R1-2, R2-2, R3-3, Pr-2, R7-1)、  
 (R1-2, R2-2, R3-3, Pr-2, R7-2)、(R1-2, R2-2, R3-3, Pr-2, R7-3)、(R1-2, R2-2, R3-3, Pr-3,  
 R7-1)、(R1-2, R2-2, R3-3, Pr-3, R7-2)、(R1-2, R2-2, R3-3, Pr-3, R7-3)、(R1-2, R2-2,  
 R3-3, Pr-4, R7-1)、(R1-2, R2-2, R3-3, Pr-4, R7-2)、(R1-2, R2-2, R3-3, Pr-4, R7-3)、  
 (R1-2, R2-2, R3-4, Pr-1, R7-1)、(R1-2, R2-2, R3-4, Pr-1, R7-2)、(R1-2, R2-2, R3-4, Pr-1,  
 R7-3)、(R1-2, R2-2, R3-4, Pr-2, R7-1)、(R1-2, R2-2, R3-4, Pr-2, R7-2)、(R1-2, R2-2,  
 R3-4, Pr-2, R7-3)、(R1-2, R2-2, R3-4, Pr-3, R7-1)、(R1-2, R2-2, R3-4, Pr-3, R7-2)、  
 (R1-2, R2-2, R3-4, Pr-3, R7-3)、(R1-2, R2-2, R3-4, Pr-4, R7-1)、(R1-2, R2-2, R3-4, Pr-4,  
 R7-2)、(R1-2, R2-2, R3-4, Pr-4, R7-3)、(R1-2, R2-2, R3-5, Pr-1, R7-1)、(R1-2, R2-2,  
 R3-5, Pr-1, R7-2)、(R1-2, R2-2, R3-5, Pr-1, R7-3)、(R1-2, R2-2, R3-5, Pr-2, R7-1)、  
 (R1-2, R2-2, R3-5, Pr-2, R7-2)、(R1-2, R2-2, R3-5, Pr-2, R7-3)、(R1-2, R2-2, R3-5, Pr-3,  
 R7-1)、(R1-2, R2-2, R3-5, Pr-3, R7-2)、(R1-2, R2-2, R3-5, Pr-3, R7-3)、(R1-2, R2-2,  
 R3-5, Pr-4, R7-1)、(R1-2, R2-2, R3-5, Pr-4, R7-2)、(R1-2, R2-2, R3-5, Pr-4, R7-3)、

[0211]

(R1-3, R2-1, R3-1, Pr-1, R7-1)、(R1-3, R2-1, R3-1, Pr-1, R7-2)、(R1-3, R2-1, R3-1, Pr-1, R7-3)、(R1-3, R2-1, R3-1, Pr-2, R7-1)、(R1-3, R2-1, R3-1, Pr-2, R7-2)、(R1-3, R2-1, R3-1, Pr-2, R7-3)、(R1-3, R2-1, R3-1, Pr-3, R7-1)、(R1-3, R2-1, R3-1, Pr-3, R7-2)、(R1-3, R2-1, R3-1, Pr-3, R7-3)、(R1-3, R2-1, R3-1, Pr-4, R7-1)、(R1-3, R2-1, R3-1, Pr-4, R7-2)、(R1-3, R2-1, R3-1, Pr-4, R7-3)、(R1-3, R2-1, R3-2, Pr-1, R7-1)、(R1-3, R2-1, R3-2, Pr-1, R7-2)、(R1-3, R2-1, R3-2, Pr-1, R7-3)、(R1-3, R2-1, R3-2, Pr-2, R7-1)、(R1-3, R2-1, R3-2, Pr-2, R7-2)、(R1-3, R2-1, R3-2, Pr-2, R7-3)、(R1-3, R2-1, R3-2, Pr-3, R7-1)、(R1-3, R2-1, R3-2, Pr-3, R7-2)、(R1-3, R2-1, R3-2, Pr-3, R7-3)、(R1-3, R2-1, R3-2, Pr-4, R7-1)、(R1-3, R2-1, R3-2, Pr-4, R7-2)、(R1-3, R2-1, R3-2, Pr-4, R7-3)、(R1-3, R2-1, R3-3, Pr-1, R7-1)、(R1-3, R2-1, R3-3, Pr-1, R7-2)、(R1-3, R2-1, R3-3, Pr-1, R7-3)、(R1-3, R2-1, R3-3, Pr-2, R7-1)、(R1-3, R2-1, R3-3, Pr-2, R7-2)、(R1-3, R2-1, R3-3, Pr-2, R7-3)、(R1-3, R2-1, R3-3, Pr-3, R7-1)、(R1-3, R2-1, R3-3, Pr-3, R7-2)、(R1-3, R2-1, R3-3, Pr-3, R7-3)、(R1-3, R2-1, R3-3, Pr-4, R7-1)、(R1-3, R2-1, R3-3, Pr-4, R7-2)、(R1-3, R2-1, R3-3, Pr-4, R7-3)、(R1-3, R2-1, R3-4, Pr-1, R7-1)、(R1-3, R2-1, R3-4, Pr-1, R7-2)、(R1-3, R2-1, R3-4, Pr-1, R7-3)、(R1-3, R2-1, R3-4, Pr-2, R7-1)、(R1-3, R2-1, R3-4, Pr-2, R7-2)、(R1-3, R2-1, R3-4, Pr-2, R7-3)、(R1-3, R2-1, R3-4, Pr-3, R7-1)、(R1-3, R2-1, R3-4, Pr-3, R7-2)、(R1-3, R2-1, R3-4, Pr-3, R7-3)、(R1-3, R2-1, R3-4, Pr-4, R7-1)、(R1-3, R2-1, R3-4, Pr-4, R7-2)、(R1-3, R2-1, R3-4, Pr-4, R7-3)、(R1-3, R2-1, R3-5, Pr-1, R7-1)、(R1-3, R2-1, R3-5, Pr-1, R7-2)、(R1-3, R2-1, R3-5, Pr-1, R7-3)、(R1-3, R2-1, R3-5, Pr-2, R7-1)、(R1-3, R2-1, R3-5, Pr-2, R7-2)、(R1-3, R2-1, R3-5, Pr-2, R7-3)、(R1-3, R2-1, R3-5, Pr-3, R7-1)、(R1-3, R2-1, R3-5, Pr-3, R7-2)、(R1-3, R2-1, R3-5, Pr-3, R7-3)、(R1-3, R2-1, R3-5, Pr-4, R7-1)、(R1-3, R2-1, R3-5, Pr-4, R7-2)、(R1-3, R2-1, R3-5, Pr-4, R7-3)、(R1-3, R2-2, R3-1, Pr-1, R7-1)、(R1-3, R2-2, R3-1, Pr-1, R7-2)、(R1-3, R2-2, R3-1, Pr-1, R7-3)、(R1-3, R2-2, R3-1, Pr-2, R7-1)、

(R1-3, R2-2, R3-1, Pr-2, R7-2)、(R1-3, R2-2, R3-1, Pr-2, R7-3)、(R1-3, R2-2, R3-1, Pr-3, R7-1)、(R1-3, R2-2, R3-1, Pr-3, R7-2)、(R1-3, R2-2, R3-1, Pr-3, R7-3)、(R1-3, R2-2, R3-1, Pr-4, R7-1)、(R1-3, R2-2, R3-1, Pr-4, R7-2)、(R1-3, R2-2, R3-1, Pr-4, R7-3)、(R1-3, R2-2, R3-2, Pr-1, R7-1)、(R1-3, R2-2, R3-2, Pr-1, R7-2)、(R1-3, R2-2, R3-2, Pr-1, R7-3)、(R1-3, R2-2, R3-2, Pr-2, R7-1)、(R1-3, R2-2, R3-2, Pr-2, R7-2)、(R1-3, R2-2, R3-2, Pr-2, R7-3)、(R1-3, R2-2, R3-2, Pr-3, R7-1)、(R1-3, R2-2, R3-2, Pr-3, R7-2)、(R1-3, R2-2, R3-2, Pr-3, R7-3)、(R1-3, R2-2, R3-2, Pr-4, R7-1)、(R1-3, R2-2, R3-2, Pr-4, R7-2)、(R1-3, R2-2, R3-2, Pr-4, R7-3)、(R1-3, R2-2, R3-3, Pr-1, R7-1)、(R1-3, R2-2, R3-3, Pr-1, R7-2)、(R1-3, R2-2, R3-3, Pr-1, R7-3)、(R1-3, R2-2, R3-3, Pr-2, R7-1)、(R1-3, R2-2, R3-3, Pr-2, R7-2)、(R1-3, R2-2, R3-3, Pr-2, R7-3)、(R1-3, R2-2, R3-3, Pr-3, R7-1)、(R1-3, R2-2, R3-3, Pr-3, R7-2)、(R1-3, R2-2, R3-3, Pr-3, R7-3)、(R1-3, R2-2, R3-3, Pr-4, R7-1)、(R1-3, R2-2, R3-3, Pr-4, R7-2)、(R1-3, R2-2, R3-3, Pr-4, R7-3)、(R1-3, R2-2, R3-4, Pr-1, R7-1)、(R1-3, R2-2, R3-4, Pr-1, R7-2)、(R1-3, R2-2, R3-4, Pr-1, R7-3)、(R1-3, R2-2, R3-4, Pr-2, R7-1)、(R1-3, R2-2, R3-4, Pr-2, R7-2)、(R1-3, R2-2, R3-4, Pr-2, R7-3)、(R1-3, R2-2, R3-4, Pr-3, R7-1)、(R1-3, R2-2, R3-4, Pr-3, R7-2)、(R1-3, R2-2, R3-4, Pr-3, R7-3)、(R1-3, R2-2, R3-4, Pr-4, R7-1)、(R1-3, R2-2, R3-4, Pr-4, R7-2)、(R1-3, R2-2, R3-4, Pr-4, R7-3)、(R1-3, R2-2, R3-5, Pr-1, R7-1)、(R1-3, R2-2, R3-5, Pr-1, R7-2)、(R1-3, R2-2, R3-5, Pr-1, R7-3)、(R1-3, R2-2, R3-5, Pr-2, R7-1)、(R1-3, R2-2, R3-5, Pr-2, R7-2)、(R1-3, R2-2, R3-5, Pr-2, R7-3)、(R1-3, R2-2, R3-5, Pr-3, R7-1)、(R1-3, R2-2, R3-5, Pr-3, R7-2)、(R1-3, R2-2, R3-5, Pr-3, R7-3)、(R1-3, R2-2, R3-5, Pr-4, R7-1)、(R1-3, R2-2, R3-5, Pr-4, R7-2)、(R1-3, R2-2, R3-5, Pr-4, R7-3)、

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(R1-4, R2-1, R3-1, Pr-1, R7-1)、(R1-4, R2-1, R3-1, Pr-1, R7-2)、(R1-4, R2-1, R3-1, Pr-1, R7-3)、(R1-4, R2-1, R3-1, Pr-2, R7-1)、(R1-4, R2-1, R3-1, Pr-2, R7-2)、(R1-4, R2-1, R3-1, Pr-2, R7-3)、(R1-4, R2-1, R3-1, Pr-3, R7-1)、(R1-4, R2-1, R3-1, Pr-3, R7-2)、

(R1-4, R2-1, R3-1, Pr-3, R7-3)、(R1-4, R2-1, R3-1, Pr-4, R7-1)、(R1-4, R2-1, R3-1, Pr-4, R7-2)、(R1-4, R2-1, R3-1, Pr-4, R7-3)、(R1-4, R2-1, R3-2, Pr-1, R7-1)、(R1-4, R2-1, R3-2, Pr-1, R7-2)、(R1-4, R2-1, R3-2, Pr-1, R7-3)、(R1-4, R2-1, R3-2, Pr-2, R7-1)、(R1-4, R2-1, R3-2, Pr-2, R7-2)、(R1-4, R2-1, R3-2, Pr-2, R7-3)、(R1-4, R2-1, R3-2, Pr-3, R7-1)、(R1-4, R2-1, R3-2, Pr-3, R7-2)、(R1-4, R2-1, R3-2, Pr-3, R7-3)、(R1-4, R2-1, R3-2, Pr-4, R7-1)、(R1-4, R2-1, R3-2, Pr-4, R7-2)、(R1-4, R2-1, R3-2, Pr-4, R7-3)、(R1-4, R2-1, R3-3, Pr-1, R7-1)、(R1-4, R2-1, R3-3, Pr-1, R7-2)、(R1-4, R2-1, R3-3, Pr-1, R7-3)、(R1-4, R2-1, R3-3, Pr-2, R7-1)、(R1-4, R2-1, R3-3, Pr-2, R7-2)、(R1-4, R2-1, R3-3, Pr-2, R7-3)、(R1-4, R2-1, R3-3, Pr-3, R7-1)、(R1-4, R2-1, R3-3, Pr-3, R7-2)、(R1-4, R2-1, R3-3, Pr-3, R7-3)、(R1-4, R2-1, R3-3, Pr-4, R7-1)、(R1-4, R2-1, R3-3, Pr-4, R7-2)、(R1-4, R2-1, R3-3, Pr-4, R7-3)、(R1-4, R2-1, R3-4, Pr-1, R7-1)、(R1-4, R2-1, R3-4, Pr-1, R7-2)、(R1-4, R2-1, R3-4, Pr-1, R7-3)、(R1-4, R2-1, R3-4, Pr-2, R7-1)、(R1-4, R2-1, R3-4, Pr-2, R7-2)、(R1-4, R2-1, R3-4, Pr-2, R7-3)、(R1-4, R2-1, R3-4, Pr-3, R7-1)、(R1-4, R2-1, R3-4, Pr-3, R7-2)、(R1-4, R2-1, R3-4, Pr-3, R7-3)、(R1-4, R2-1, R3-4, Pr-4, R7-1)、(R1-4, R2-1, R3-4, Pr-4, R7-2)、(R1-4, R2-1, R3-4, Pr-4, R7-3)、(R1-4, R2-1, R3-5, Pr-1, R7-1)、(R1-4, R2-1, R3-5, Pr-1, R7-2)、(R1-4, R2-1, R3-5, Pr-1, R7-3)、(R1-4, R2-1, R3-5, Pr-2, R7-1)、(R1-4, R2-1, R3-5, Pr-2, R7-2)、(R1-4, R2-1, R3-5, Pr-2, R7-3)、(R1-4, R2-1, R3-5, Pr-3, R7-1)、(R1-4, R2-1, R3-5, Pr-3, R7-2)、(R1-4, R2-1, R3-5, Pr-3, R7-3)、(R1-4, R2-1, R3-5, Pr-4, R7-1)、(R1-4, R2-1, R3-5, Pr-4, R7-2)、(R1-4, R2-1, R3-5, Pr-4, R7-3)、(R1-4, R2-2, R3-1, Pr-1, R7-1)、(R1-4, R2-2, R3-1, Pr-1, R7-2)、(R1-4, R2-2, R3-1, Pr-1, R7-3)、(R1-4, R2-2, R3-1, Pr-2, R7-1)、(R1-4, R2-2, R3-1, Pr-2, R7-2)、(R1-4, R2-2, R3-1, Pr-2, R7-3)、(R1-4, R2-2, R3-1, Pr-3, R7-1)、(R1-4, R2-2, R3-1, Pr-3, R7-2)、(R1-4, R2-2, R3-1, Pr-3, R7-3)、(R1-4, R2-2, R3-1, Pr-4, R7-1)、(R1-4, R2-2, R3-1, Pr-4, R7-2)、(R1-4, R2-2, R3-1, Pr-4, R7-3)、(R1-4, R2-2, R3-2, Pr-1, R7-1)、(R1-4, R2-2, R3-2, Pr-1, R7-2)、(R1-4, R2-2, R3-2, Pr-1,

R7-3)、(R1-4, R2-2, R3-2, Pr-2, R7-1)、(R1-4, R2-2, R3-2, Pr-2, R7-2)、(R1-4, R2-2,  
 R3-2, Pr-2, R7-3)、(R1-4, R2-2, R3-2, Pr-3, R7-1)、(R1-4, R2-2, R3-2, Pr-3, R7-2)、  
 (R1-4, R2-2, R3-2, Pr-3, R7-3)、(R1-4, R2-2, R3-2, Pr-4, R7-1)、(R1-4, R2-2, R3-2, Pr-4,  
 R7-2)、(R1-4, R2-2, R3-2, Pr-4, R7-3)、(R1-4, R2-2, R3-3, Pr-1, R7-1)、(R1-4, R2-2,  
 R3-3, Pr-1, R7-2)、(R1-4, R2-2, R3-3, Pr-1, R7-3)、(R1-4, R2-2, R3-3, Pr-2, R7-1)、  
 (R1-4, R2-2, R3-3, Pr-2, R7-2)、(R1-4, R2-2, R3-3, Pr-2, R7-3)、(R1-4, R2-2, R3-3, Pr-3,  
 R7-1)、(R1-4, R2-2, R3-3, Pr-3, R7-2)、(R1-4, R2-2, R3-3, Pr-3, R7-3)、(R1-4, R2-2,  
 R3-3, Pr-4, R7-1)、(R1-4, R2-2, R3-3, Pr-4, R7-2)、(R1-4, R2-2, R3-3, Pr-4, R7-3)、  
 (R1-4, R2-2, R3-4, Pr-1, R7-1)、(R1-4, R2-2, R3-4, Pr-1, R7-2)、(R1-4, R2-2, R3-4, Pr-1,  
 R7-3)、(R1-4, R2-2, R3-4, Pr-2, R7-1)、(R1-4, R2-2, R3-4, Pr-2, R7-2)、(R1-4, R2-2,  
 R3-4, Pr-2, R7-3)、(R1-4, R2-2, R3-4, Pr-3, R7-1)、(R1-4, R2-2, R3-4, Pr-3, R7-2)、  
 (R1-4, R2-2, R3-4, Pr-3, R7-3)、(R1-4, R2-2, R3-4, Pr-4, R7-1)、(R1-4, R2-2, R3-4, Pr-4,  
 R7-2)、(R1-4, R2-2, R3-4, Pr-4, R7-3)、(R1-4, R2-2, R3-5, Pr-1, R7-1)、(R1-4, R2-2,  
 R3-5, Pr-1, R7-2)、(R1-4, R2-2, R3-5, Pr-1, R7-3)、(R1-4, R2-2, R3-5, Pr-2, R7-1)、  
 (R1-4, R2-2, R3-5, Pr-2, R7-2)、(R1-4, R2-2, R3-5, Pr-2, R7-3)、(R1-4, R2-2, R3-5, Pr-3,  
 R7-1)、(R1-4, R2-2, R3-5, Pr-3, R7-2)、(R1-4, R2-2, R3-5, Pr-3, R7-3)、(R1-4, R2-2,  
 R3-5, Pr-4, R7-1)、(R1-4, R2-2, R3-5, Pr-4, R7-2)、(R1-4, R2-2, R3-5, Pr-4, R7-3)、

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(R1-5, R2-1, R3-1, Pr-1, R7-1)、(R1-5, R2-1, R3-1, Pr-1, R7-2)、(R1-5, R2-1, R3-1,  
 Pr-1, R7-3)、(R1-5, R2-1, R3-1, Pr-2, R7-1)、(R1-5, R2-1, R3-1, Pr-2, R7-2)、(R1-5,  
 R2-1, R3-1, Pr-2, R7-3)、(R1-5, R2-1, R3-1, Pr-3, R7-1)、(R1-5, R2-1, R3-1, Pr-3, R7-2)、  
 (R1-5, R2-1, R3-1, Pr-3, R7-3)、(R1-5, R2-1, R3-1, Pr-4, R7-1)、(R1-5, R2-1, R3-1, Pr-4,  
 R7-2)、(R1-5, R2-1, R3-1, Pr-4, R7-3)、(R1-5, R2-1, R3-2, Pr-1, R7-1)、(R1-5, R2-1,  
 R3-2, Pr-1, R7-2)、(R1-5, R2-1, R3-2, Pr-1, R7-3)、(R1-5, R2-1, R3-2, Pr-2, R7-1)、  
 (R1-5, R2-1, R3-2, Pr-2, R7-2)、(R1-5, R2-1, R3-2, Pr-2, R7-3)、(R1-5, R2-1, R3-2, Pr-3,

R7-1)、(R1-5, R2-1, R3-2, Pr-3, R7-2)、(R1-5, R2-1, R3-2, Pr-3, R7-3)、(R1-5, R2-1,  
 R3-2, Pr-4, R7-1)、(R1-5, R2-1, R3-2, Pr-4, R7-2)、(R1-5, R2-1, R3-2, Pr-4, R7-3)、  
 (R1-5, R2-1, R3-3, Pr-1, R7-1)、(R1-5, R2-1, R3-3, Pr-1, R7-2)、(R1-5, R2-1, R3-3, Pr-1,  
 R7-3)、(R1-5, R2-1, R3-3, Pr-2, R7-1)、(R1-5, R2-1, R3-3, Pr-2, R7-2)、(R1-5, R2-1,  
 R3-3, Pr-2, R7-3)、(R1-5, R2-1, R3-3, Pr-3, R7-1)、(R1-5, R2-1, R3-3, Pr-3, R7-2)、  
 (R1-5, R2-1, R3-3, Pr-3, R7-3)、(R1-5, R2-1, R3-3, Pr-4, R7-1)、(R1-5, R2-1, R3-3, Pr-4,  
 R7-2)、(R1-5, R2-1, R3-3, Pr-4, R7-3)、(R1-5, R2-1, R3-4, Pr-1, R7-1)、(R1-5, R2-1,  
 R3-4, Pr-1, R7-2)、(R1-5, R2-1, R3-4, Pr-1, R7-3)、(R1-5, R2-1, R3-4, Pr-2, R7-1)、  
 (R1-5, R2-1, R3-4, Pr-2, R7-2)、(R1-5, R2-1, R3-4, Pr-2, R7-3)、(R1-5, R2-1, R3-4, Pr-3,  
 R7-1)、(R1-5, R2-1, R3-4, Pr-3, R7-2)、(R1-5, R2-1, R3-4, Pr-3, R7-3)、(R1-5, R2-1,  
 R3-4, Pr-4, R7-1)、(R1-5, R2-1, R3-4, Pr-4, R7-2)、(R1-5, R2-1, R3-4, Pr-4, R7-3)、  
 (R1-5, R2-1, R3-5, Pr-1, R7-1)、(R1-5, R2-1, R3-5, Pr-1, R7-2)、(R1-5, R2-1, R3-5, Pr-1,  
 R7-3)、(R1-5, R2-1, R3-5, Pr-2, R7-1)、(R1-5, R2-1, R3-5, Pr-2, R7-2)、(R1-5, R2-1,  
 R3-5, Pr-2, R7-3)、(R1-5, R2-1, R3-5, Pr-3, R7-1)、(R1-5, R2-1, R3-5, Pr-3, R7-2)、  
 (R1-5, R2-1, R3-5, Pr-3, R7-3)、(R1-5, R2-1, R3-5, Pr-4, R7-1)、(R1-5, R2-1, R3-5, Pr-4,  
 R7-2)、(R1-5, R2-1, R3-5, Pr-4, R7-3)、(R1-5, R2-2, R3-1, Pr-1, R7-1)、(R1-5, R2-2,  
 R3-1, Pr-1, R7-2)、(R1-5, R2-2, R3-1, Pr-1, R7-3)、(R1-5, R2-2, R3-1, Pr-2, R7-1)、  
 (R1-5, R2-2, R3-1, Pr-2, R7-2)、(R1-5, R2-2, R3-1, Pr-2, R7-3)、(R1-5, R2-2, R3-1, Pr-3,  
 R7-1)、(R1-5, R2-2, R3-1, Pr-3, R7-2)、(R1-5, R2-2, R3-1, Pr-3, R7-3)、(R1-5, R2-2,  
 R3-1, Pr-4, R7-1)、(R1-5, R2-2, R3-1, Pr-4, R7-2)、(R1-5, R2-2, R3-1, Pr-4, R7-3)、  
 (R1-5, R2-2, R3-2, Pr-1, R7-1)、(R1-5, R2-2, R3-2, Pr-1, R7-2)、(R1-5, R2-2, R3-2, Pr-1,  
 R7-3)、(R1-5, R2-2, R3-2, Pr-2, R7-1)、(R1-5, R2-2, R3-2, Pr-2, R7-2)、(R1-5, R2-2,  
 R3-2, Pr-2, R7-3)、(R1-5, R2-2, R3-2, Pr-3, R7-1)、(R1-5, R2-2, R3-2, Pr-3, R7-2)、  
 (R1-5, R2-2, R3-2, Pr-3, R7-3)、(R1-5, R2-2, R3-2, Pr-4, R7-1)、(R1-5, R2-2, R3-2, Pr-4,  
 R7-2)、(R1-5, R2-2, R3-2, Pr-4, R7-3)、(R1-5, R2-2, R3-3, Pr-1, R7-1)、(R1-5, R2-2,

R3-3, Pr-1, R7-2)、(R1-5, R2-2, R3-3, Pr-1, R7-3)、(R1-5, R2-2, R3-3, Pr-2, R7-1)、  
(R1-5, R2-2, R3-3, Pr-2, R7-2)、(R1-5, R2-2, R3-3, Pr-2, R7-3)、(R1-5, R2-2, R3-3, Pr-3,  
R7-1)、(R1-5, R2-2, R3-3, Pr-3, R7-2)、(R1-5, R2-2, R3-3, Pr-3, R7-3)、(R1-5, R2-2,  
R3-3, Pr-4, R7-1)、(R1-5, R2-2, R3-3, Pr-4, R7-2)、(R1-5, R2-2, R3-3, Pr-4, R7-3)、  
(R1-5, R2-2, R3-4, Pr-1, R7-1)、(R1-5, R2-2, R3-4, Pr-1, R7-2)、(R1-5, R2-2, R3-4, Pr-1,  
R7-3)、(R1-5, R2-2, R3-4, Pr-2, R7-1)、(R1-5, R2-2, R3-4, Pr-2, R7-2)、(R1-5, R2-2,  
R3-4, Pr-2, R7-3)、(R1-5, R2-2, R3-4, Pr-3, R7-1)、(R1-5, R2-2, R3-4, Pr-3, R7-2)、  
(R1-5, R2-2, R3-4, Pr-3, R7-3)、(R1-5, R2-2, R3-4, Pr-4, R7-1)、(R1-5, R2-2, R3-4, Pr-4,  
R7-2)、(R1-5, R2-2, R3-4, Pr-4, R7-3)、(R1-5, R2-2, R3-5, Pr-1, R7-1)、(R1-5, R2-2,  
R3-5, Pr-1, R7-2)、(R1-5, R2-2, R3-5, Pr-1, R7-3)、(R1-5, R2-2, R3-5, Pr-2, R7-1)、  
(R1-5, R2-2, R3-5, Pr-2, R7-2)、(R1-5, R2-2, R3-5, Pr-2, R7-3)、(R1-5, R2-2, R3-5, Pr-3,  
R7-1)、(R1-5, R2-2, R3-5, Pr-3, R7-2)、(R1-5, R2-2, R3-5, Pr-3, R7-3)、(R1-5, R2-2,  
R3-5, Pr-4, R7-1)、(R1-5, R2-2, R3-5, Pr-4, R7-2)、(R1-5, R2-2, R3-5, Pr-4, R7-3)、

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(R1-6, R2-1, R3-1, Pr-1, R7-1)、(R1-6, R2-1, R3-1, Pr-1, R7-2)、(R1-6, R2-1, R3-1, Pr-1, R7-3)、(R1-6, R2-1, R3-1, Pr-2, R7-1)、(R1-6, R2-1, R3-1, Pr-2, R7-2)、(R1-6, R2-1, R3-1, Pr-2, R7-3)、(R1-6, R2-1, R3-1, Pr-3, R7-1)、(R1-6, R2-1, R3-1, Pr-3, R7-2)、(R1-6, R2-1, R3-1, Pr-3, R7-3)、(R1-6, R2-1, R3-1, Pr-4, R7-1)、(R1-6, R2-1, R3-1, Pr-4, R7-2)、(R1-6, R2-1, R3-1, Pr-4, R7-3)、(R1-6, R2-1, R3-2, Pr-1, R7-1)、(R1-6, R2-1, R3-2, Pr-1, R7-2)、(R1-6, R2-1, R3-2, Pr-1, R7-3)、(R1-6, R2-1, R3-2, Pr-2, R7-1)、(R1-6, R2-1, R3-2, Pr-2, R7-2)、(R1-6, R2-1, R3-2, Pr-2, R7-3)、(R1-6, R2-1, R3-2, Pr-3, R7-1)、(R1-6, R2-1, R3-2, Pr-3, R7-2)、(R1-6, R2-1, R3-2, Pr-3, R7-3)、(R1-6, R2-1, R3-2, Pr-4, R7-1)、(R1-6, R2-1, R3-2, Pr-4, R7-2)、(R1-6, R2-1, R3-2, Pr-4, R7-3)、(R1-6, R2-1, R3-3, Pr-1, R7-1)、(R1-6, R2-1, R3-3, Pr-1, R7-2)、(R1-6, R2-1, R3-3, Pr-1, R7-3)、(R1-6, R2-1, R3-3, Pr-2, R7-1)、(R1-6, R2-1, R3-3, Pr-2, R7-2)、(R1-6, R2-1,

R3-3, Pr-2, R7-3)、(R1-6, R2-1, R3-3, Pr-3, R7-1)、(R1-6, R2-1, R3-3, Pr-3, R7-2)、  
 (R1-6, R2-1, R3-3, Pr-3, R7-3)、(R1-6, R2-1, R3-3, Pr-4, R7-1)、(R1-6, R2-1, R3-3, Pr-4,  
 R7-2)、(R1-6, R2-1, R3-3, Pr-4, R7-3)、(R1-6, R2-1, R3-4, Pr-1, R7-1)、(R1-6, R2-1,  
 R3-4, Pr-1, R7-2)、(R1-6, R2-1, R3-4, Pr-1, R7-3)、(R1-6, R2-1, R3-4, Pr-2, R7-1)、  
 (R1-6, R2-1, R3-4, Pr-2, R7-2)、(R1-6, R2-1, R3-4, Pr-2, R7-3)、(R1-6, R2-1, R3-4, Pr-3,  
 R7-1)、(R1-6, R2-1, R3-4, Pr-3, R7-2)、(R1-6, R2-1, R3-4, Pr-3, R7-3)、(R1-6, R2-1,  
 R3-4, Pr-4, R7-1)、(R1-6, R2-1, R3-4, Pr-4, R7-2)、(R1-6, R2-1, R3-4, Pr-4, R7-3)、  
 (R1-6, R2-1, R3-5, Pr-1, R7-1)、(R1-6, R2-1, R3-5, Pr-1, R7-2)、(R1-6, R2-1, R3-5, Pr-1,  
 R7-3)、(R1-6, R2-1, R3-5, Pr-2, R7-1)、(R1-6, R2-1, R3-5, Pr-2, R7-2)、(R1-6, R2-1,  
 R3-5, Pr-2, R7-3)、(R1-6, R2-1, R3-5, Pr-3, R7-1)、(R1-6, R2-1, R3-5, Pr-3, R7-2)、  
 (R1-6, R2-1, R3-5, Pr-3, R7-3)、(R1-6, R2-1, R3-5, Pr-4, R7-1)、(R1-6, R2-1, R3-5, Pr-4,  
 R7-2)、(R1-6, R2-1, R3-5, Pr-4, R7-3)、(R1-6, R2-2, R3-1, Pr-1, R7-1)、(R1-6, R2-2,  
 R3-1, Pr-1, R7-2)、(R1-6, R2-2, R3-1, Pr-1, R7-3)、(R1-6, R2-2, R3-1, Pr-2, R7-1)、  
 (R1-6, R2-2, R3-1, Pr-2, R7-2)、(R1-6, R2-2, R3-1, Pr-2, R7-3)、(R1-6, R2-2, R3-1, Pr-3,  
 R7-1)、(R1-6, R2-2, R3-1, Pr-3, R7-2)、(R1-6, R2-2, R3-1, Pr-3, R7-3)、(R1-6, R2-2,  
 R3-1, Pr-4, R7-1)、(R1-6, R2-2, R3-1, Pr-4, R7-2)、(R1-6, R2-2, R3-1, Pr-4, R7-3)、  
 (R1-6, R2-2, R3-2, Pr-1, R7-1)、(R1-6, R2-2, R3-2, Pr-1, R7-2)、(R1-6, R2-2, R3-2, Pr-1,  
 R7-3)、(R1-6, R2-2, R3-2, Pr-2, R7-1)、(R1-6, R2-2, R3-2, Pr-2, R7-2)、(R1-6, R2-2,  
 R3-2, Pr-2, R7-3)、(R1-6, R2-2, R3-2, Pr-3, R7-1)、(R1-6, R2-2, R3-2, Pr-3, R7-2)、  
 (R1-6, R2-2, R3-2, Pr-3, R7-3)、(R1-6, R2-2, R3-2, Pr-4, R7-1)、(R1-6, R2-2, R3-2, Pr-4,  
 R7-2)、(R1-6, R2-2, R3-2, Pr-4, R7-3)、(R1-6, R2-2, R3-3, Pr-1, R7-1)、(R1-6, R2-2,  
 R3-3, Pr-1, R7-2)、(R1-6, R2-2, R3-3, Pr-1, R7-3)、(R1-6, R2-2, R3-3, Pr-2, R7-1)、  
 (R1-6, R2-2, R3-3, Pr-2, R7-2)、(R1-6, R2-2, R3-3, Pr-2, R7-3)、(R1-6, R2-2, R3-3, Pr-3,  
 R7-1)、(R1-6, R2-2, R3-3, Pr-3, R7-2)、(R1-6, R2-2, R3-3, Pr-3, R7-3)、(R1-6, R2-2,  
 R3-3, Pr-4, R7-1)、(R1-6, R2-2, R3-3, Pr-4, R7-2)、(R1-6, R2-2, R3-3, Pr-4, R7-3)、

(R1-6, R2-2, R3-4, Pr-1, R7-1)、(R1-6, R2-2, R3-4, Pr-1, R7-2)、(R1-6, R2-2, R3-4, Pr-1, R7-3)、(R1-6, R2-2, R3-4, Pr-2, R7-1)、(R1-6, R2-2, R3-4, Pr-2, R7-2)、(R1-6, R2-2, R3-4, Pr-2, R7-3)、(R1-6, R2-2, R3-4, Pr-3, R7-1)、(R1-6, R2-2, R3-4, Pr-3, R7-2)、(R1-6, R2-2, R3-4, Pr-3, R7-3)、(R1-6, R2-2, R3-4, Pr-4, R7-1)、(R1-6, R2-2, R3-4, Pr-4, R7-2)、(R1-6, R2-2, R3-4, Pr-4, R7-3)、(R1-6, R2-2, R3-5, Pr-1, R7-1)、(R1-6, R2-2, R3-5, Pr-1, R7-2)、(R1-6, R2-2, R3-5, Pr-1, R7-3)、(R1-6, R2-2, R3-5, Pr-2, R7-1)、(R1-6, R2-2, R3-5, Pr-2, R7-2)、(R1-6, R2-2, R3-5, Pr-2, R7-3)、(R1-6, R2-2, R3-5, Pr-3, R7-1)、(R1-6, R2-2, R3-5, Pr-3, R7-2)、(R1-6, R2-2, R3-5, Pr-3, R7-3)、(R1-6, R2-2, R3-5, Pr-4, R7-1)、(R1-6, R2-2, R3-5, Pr-4, R7-2)、(R1-6, R2-2, R3-5, Pr-4, R7-3)、

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(R1-7, R2-1, R3-1, Pr-1, R7-1)、(R1-7, R2-1, R3-1, Pr-1, R7-2)、(R1-7, R2-1, R3-1, Pr-1, R7-3)、(R1-7, R2-1, R3-1, Pr-2, R7-1)、(R1-7, R2-1, R3-1, Pr-2, R7-2)、(R1-7, R2-1, R3-1, Pr-2, R7-3)、(R1-7, R2-1, R3-1, Pr-3, R7-1)、(R1-7, R2-1, R3-1, Pr-3, R7-2)、(R1-7, R2-1, R3-1, Pr-3, R7-3)、(R1-7, R2-1, R3-1, Pr-4, R7-1)、(R1-7, R2-1, R3-1, Pr-4, R7-2)、(R1-7, R2-1, R3-1, Pr-4, R7-3)、(R1-7, R2-1, R3-2, Pr-1, R7-1)、(R1-7, R2-1, R3-2, Pr-1, R7-2)、(R1-7, R2-1, R3-2, Pr-1, R7-3)、(R1-7, R2-1, R3-2, Pr-2, R7-1)、(R1-7, R2-1, R3-2, Pr-2, R7-2)、(R1-7, R2-1, R3-2, Pr-2, R7-3)、(R1-7, R2-1, R3-2, Pr-3, R7-1)、(R1-7, R2-1, R3-2, Pr-3, R7-2)、(R1-7, R2-1, R3-2, Pr-3, R7-3)、(R1-7, R2-1, R3-2, Pr-4, R7-1)、(R1-7, R2-1, R3-2, Pr-4, R7-2)、(R1-7, R2-1, R3-2, Pr-4, R7-3)、(R1-7, R2-1, R3-3, Pr-1, R7-1)、(R1-7, R2-1, R3-3, Pr-1, R7-2)、(R1-7, R2-1, R3-3, Pr-1, R7-3)、(R1-7, R2-1, R3-3, Pr-2, R7-1)、(R1-7, R2-1, R3-3, Pr-2, R7-2)、(R1-7, R2-1, R3-3, Pr-2, R7-3)、(R1-7, R2-1, R3-3, Pr-3, R7-1)、(R1-7, R2-1, R3-3, Pr-3, R7-2)、(R1-7, R2-1, R3-3, Pr-3, R7-3)、(R1-7, R2-1, R3-3, Pr-4, R7-1)、(R1-7, R2-1, R3-3, Pr-4, R7-2)、(R1-7, R2-1, R3-3, Pr-4, R7-3)、(R1-7, R2-1, R3-4, Pr-1, R7-1)、(R1-7, R2-1, R3-4, Pr-1, R7-2)、(R1-7, R2-1, R3-4, Pr-1, R7-3)、(R1-7, R2-1, R3-4, Pr-2, R7-1)、

(R1-7, R2-1, R3-4, Pr-2, R7-2)、(R1-7, R2-1, R3-4, Pr-2, R7-3)、(R1-7, R2-1, R3-4, Pr-3, R7-1)、(R1-7, R2-1, R3-4, Pr-3, R7-2)、(R1-7, R2-1, R3-4, Pr-3, R7-3)、(R1-7, R2-1, R3-4, Pr-4, R7-1)、(R1-7, R2-1, R3-4, Pr-4, R7-2)、(R1-7, R2-1, R3-4, Pr-4, R7-3)、(R1-7, R2-1, R3-5, Pr-1, R7-1)、(R1-7, R2-1, R3-5, Pr-1, R7-2)、(R1-7, R2-1, R3-5, Pr-1, R7-3)、(R1-7, R2-1, R3-5, Pr-2, R7-1)、(R1-7, R2-1, R3-5, Pr-2, R7-2)、(R1-7, R2-1, R3-5, Pr-2, R7-3)、(R1-7, R2-1, R3-5, Pr-3, R7-1)、(R1-7, R2-1, R3-5, Pr-3, R7-2)、(R1-7, R2-1, R3-5, Pr-3, R7-3)、(R1-7, R2-1, R3-5, Pr-4, R7-1)、(R1-7, R2-1, R3-5, Pr-4, R7-2)、(R1-7, R2-1, R3-5, Pr-4, R7-3)、(R1-7, R2-2, R3-1, Pr-1, R7-1)、(R1-7, R2-2, R3-1, Pr-1, R7-2)、(R1-7, R2-2, R3-1, Pr-1, R7-3)、(R1-7, R2-2, R3-1, Pr-2, R7-1)、(R1-7, R2-2, R3-1, Pr-2, R7-2)、(R1-7, R2-2, R3-1, Pr-2, R7-3)、(R1-7, R2-2, R3-1, Pr-3, R7-1)、(R1-7, R2-2, R3-1, Pr-3, R7-2)、(R1-7, R2-2, R3-1, Pr-3, R7-3)、(R1-7, R2-2, R3-1, Pr-4, R7-1)、(R1-7, R2-2, R3-1, Pr-4, R7-2)、(R1-7, R2-2, R3-1, Pr-4, R7-3)、(R1-7, R2-2, R3-2, Pr-1, R7-1)、(R1-7, R2-2, R3-2, Pr-1, R7-2)、(R1-7, R2-2, R3-2, Pr-1, R7-3)、(R1-7, R2-2, R3-2, Pr-2, R7-1)、(R1-7, R2-2, R3-2, Pr-2, R7-2)、(R1-7, R2-2, R3-2, Pr-2, R7-3)、(R1-7, R2-2, R3-2, Pr-3, R7-1)、(R1-7, R2-2, R3-2, Pr-3, R7-2)、(R1-7, R2-2, R3-2, Pr-3, R7-3)、(R1-7, R2-2, R3-2, Pr-4, R7-1)、(R1-7, R2-2, R3-2, Pr-4, R7-2)、(R1-7, R2-2, R3-2, Pr-4, R7-3)、(R1-7, R2-2, R3-3, Pr-1, R7-1)、(R1-7, R2-2, R3-3, Pr-1, R7-2)、(R1-7, R2-2, R3-3, Pr-1, R7-3)、(R1-7, R2-2, R3-3, Pr-2, R7-1)、(R1-7, R2-2, R3-3, Pr-2, R7-2)、(R1-7, R2-2, R3-3, Pr-2, R7-3)、(R1-7, R2-2, R3-3, Pr-3, R7-1)、(R1-7, R2-2, R3-3, Pr-3, R7-2)、(R1-7, R2-2, R3-3, Pr-3, R7-3)、(R1-7, R2-2, R3-3, Pr-4, R7-1)、(R1-7, R2-2, R3-3, Pr-4, R7-2)、(R1-7, R2-2, R3-3, Pr-4, R7-3)、(R1-7, R2-2, R3-4, Pr-1, R7-1)、(R1-7, R2-2, R3-4, Pr-1, R7-2)、(R1-7, R2-2, R3-4, Pr-1, R7-3)、(R1-7, R2-2, R3-4, Pr-2, R7-1)、(R1-7, R2-2, R3-4, Pr-2, R7-2)、(R1-7, R2-2, R3-4, Pr-2, R7-3)、(R1-7, R2-2, R3-4, Pr-3, R7-1)、(R1-7, R2-2, R3-4, Pr-3, R7-2)、(R1-7, R2-2, R3-4, Pr-3, R7-3)、(R1-7, R2-2, R3-4, Pr-4, R7-1)、(R1-7, R2-2, R3-4, Pr-4, R7-2)、(R1-7, R2-2, R3-4, Pr-4, R7-3)、

R7-2)、(R1-7, R2-2, R3-4, Pr-4, R7-3)、(R1-7, R2-2, R3-5, Pr-1, R7-1)、(R1-7, R2-2, R3-5, Pr-1, R7-2)、(R1-7, R2-2, R3-5, Pr-1, R7-3)、(R1-7, R2-2, R3-5, Pr-2, R7-1)、(R1-7, R2-2, R3-5, Pr-2, R7-2)、(R1-7, R2-2, R3-5, Pr-2, R7-3)、(R1-7, R2-2, R3-5, Pr-3, R7-1)、(R1-7, R2-2, R3-5, Pr-3, R7-2)、(R1-7, R2-2, R3-5, Pr-3, R7-3)、(R1-7, R2-2, R3-5, Pr-4, R7-1)、(R1-7, R2-2, R3-5, Pr-4, R7-2)、(R1-7, R2-2, R3-5, Pr-4, R7-3)、  
[0216]

(R1-8, R2-1, R3-1, Pr-1, R7-1)、(R1-8, R2-1, R3-1, Pr-1, R7-2)、(R1-8, R2-1, R3-1, Pr-1, R7-3)、(R1-8, R2-1, R3-1, Pr-2, R7-1)、(R1-8, R2-1, R3-1, Pr-2, R7-2)、(R1-8, R2-1, R3-1, Pr-2, R7-3)、(R1-8, R2-1, R3-1, Pr-3, R7-1)、(R1-8, R2-1, R3-1, Pr-3, R7-2)、(R1-8, R2-1, R3-1, Pr-3, R7-3)、(R1-8, R2-1, R3-1, Pr-4, R7-1)、(R1-8, R2-1, R3-1, Pr-4, R7-2)、(R1-8, R2-1, R3-1, Pr-4, R7-3)、(R1-8, R2-1, R3-2, Pr-1, R7-1)、(R1-8, R2-1, R3-2, Pr-1, R7-2)、(R1-8, R2-1, R3-2, Pr-1, R7-3)、(R1-8, R2-1, R3-2, Pr-2, R7-1)、(R1-8, R2-1, R3-2, Pr-2, R7-2)、(R1-8, R2-1, R3-2, Pr-2, R7-3)、(R1-8, R2-1, R3-2, Pr-3, R7-1)、(R1-8, R2-1, R3-2, Pr-3, R7-2)、(R1-8, R2-1, R3-2, Pr-3, R7-3)、(R1-8, R2-1, R3-2, Pr-4, R7-1)、(R1-8, R2-1, R3-2, Pr-4, R7-2)、(R1-8, R2-1, R3-2, Pr-4, R7-3)、(R1-8, R2-1, R3-3, Pr-1, R7-1)、(R1-8, R2-1, R3-3, Pr-1, R7-2)、(R1-8, R2-1, R3-3, Pr-1, R7-3)、(R1-8, R2-1, R3-3, Pr-2, R7-1)、(R1-8, R2-1, R3-3, Pr-2, R7-2)、(R1-8, R2-1, R3-3, Pr-2, R7-3)、(R1-8, R2-1, R3-3, Pr-3, R7-1)、(R1-8, R2-1, R3-3, Pr-3, R7-2)、(R1-8, R2-1, R3-3, Pr-3, R7-3)、(R1-8, R2-1, R3-3, Pr-4, R7-1)、(R1-8, R2-1, R3-3, Pr-4, R7-2)、(R1-8, R2-1, R3-3, Pr-4, R7-3)、(R1-8, R2-1, R3-4, Pr-1, R7-1)、(R1-8, R2-1, R3-4, Pr-1, R7-2)、(R1-8, R2-1, R3-4, Pr-1, R7-3)、(R1-8, R2-1, R3-4, Pr-2, R7-1)、(R1-8, R2-1, R3-4, Pr-2, R7-2)、(R1-8, R2-1, R3-4, Pr-2, R7-3)、(R1-8, R2-1, R3-4, Pr-3, R7-1)、(R1-8, R2-1, R3-4, Pr-3, R7-2)、(R1-8, R2-1, R3-4, Pr-3, R7-3)、(R1-8, R2-1, R3-4, Pr-4, R7-1)、(R1-8, R2-1, R3-4, Pr-4, R7-2)、(R1-8, R2-1, R3-4, Pr-4, R7-3)、(R1-8, R2-1, R3-5, Pr-1, R7-1)、(R1-8, R2-1, R3-5, Pr-1, R7-2)、(R1-8, R2-1, R3-5, Pr-1,

R7-3)、(R1-8, R2-1, R3-5, Pr-2, R7-1)、(R1-8, R2-1, R3-5, Pr-2, R7-2)、(R1-8, R2-1,  
 R3-5, Pr-2, R7-3)、(R1-8, R2-1, R3-5, Pr-3, R7-1)、(R1-8, R2-1, R3-5, Pr-3, R7-2)、  
 (R1-8, R2-1, R3-5, Pr-3, R7-3)、(R1-8, R2-1, R3-5, Pr-4, R7-1)、(R1-8, R2-1, R3-5, Pr-4,  
 R7-2)、(R1-8, R2-1, R3-5, Pr-4, R7-3)、(R1-8, R2-2, R3-1, Pr-1, R7-1)、(R1-8, R2-2,  
 R3-1, Pr-1, R7-2)、(R1-8, R2-2, R3-1, Pr-1, R7-3)、(R1-8, R2-2, R3-1, Pr-2, R7-1)、  
 (R1-8, R2-2, R3-1, Pr-2, R7-2)、(R1-8, R2-2, R3-1, Pr-2, R7-3)、(R1-8, R2-2, R3-1, Pr-3,  
 R7-1)、(R1-8, R2-2, R3-1, Pr-3, R7-2)、(R1-8, R2-2, R3-1, Pr-3, R7-3)、(R1-8, R2-2,  
 R3-1, Pr-4, R7-1)、(R1-8, R2-2, R3-1, Pr-4, R7-2)、(R1-8, R2-2, R3-1, Pr-4, R7-3)、  
 (R1-8, R2-2, R3-2, Pr-1, R7-1)、(R1-8, R2-2, R3-2, Pr-1, R7-2)、(R1-8, R2-2, R3-2, Pr-1,  
 R7-3)、(R1-8, R2-2, R3-2, Pr-2, R7-1)、(R1-8, R2-2, R3-2, Pr-2, R7-2)、(R1-8, R2-2,  
 R3-2, Pr-2, R7-3)、(R1-8, R2-2, R3-2, Pr-3, R7-1)、(R1-8, R2-2, R3-2, Pr-3, R7-2)、  
 (R1-8, R2-2, R3-2, Pr-3, R7-3)、(R1-8, R2-2, R3-2, Pr-4, R7-1)、(R1-8, R2-2, R3-2, Pr-4,  
 R7-2)、(R1-8, R2-2, R3-2, Pr-4, R7-3)、(R1-8, R2-2, R3-3, Pr-1, R7-1)、(R1-8, R2-2,  
 R3-3, Pr-1, R7-2)、(R1-8, R2-2, R3-3, Pr-1, R7-3)、(R1-8, R2-2, R3-3, Pr-2, R7-1)、  
 (R1-8, R2-2, R3-3, Pr-2, R7-2)、(R1-8, R2-2, R3-3, Pr-2, R7-3)、(R1-8, R2-2, R3-3, Pr-3,  
 R7-1)、(R1-8, R2-2, R3-3, Pr-3, R7-2)、(R1-8, R2-2, R3-3, Pr-3, R7-3)、(R1-8, R2-2,  
 R3-3, Pr-4, R7-1)、(R1-8, R2-2, R3-3, Pr-4, R7-2)、(R1-8, R2-2, R3-3, Pr-4, R7-3)、  
 (R1-8, R2-2, R3-4, Pr-1, R7-1)、(R1-8, R2-2, R3-4, Pr-1, R7-2)、(R1-8, R2-2, R3-4, Pr-1,  
 R7-3)、(R1-8, R2-2, R3-4, Pr-2, R7-1)、(R1-8, R2-2, R3-4, Pr-2, R7-2)、(R1-8, R2-2,  
 R3-4, Pr-2, R7-3)、(R1-8, R2-2, R3-4, Pr-3, R7-1)、(R1-8, R2-2, R3-4, Pr-3, R7-2)、  
 (R1-8, R2-2, R3-4, Pr-3, R7-3)、(R1-8, R2-2, R3-4, Pr-4, R7-1)、(R1-8, R2-2, R3-4, Pr-4,  
 R7-2)、(R1-8, R2-2, R3-4, Pr-4, R7-3)、(R1-8, R2-2, R3-5, Pr-1, R7-1)、(R1-8, R2-2,  
 R3-5, Pr-1, R7-2)、(R1-8, R2-2, R3-5, Pr-1, R7-3)、(R1-8, R2-2, R3-5, Pr-2, R7-1)、  
 (R1-8, R2-2, R3-5, Pr-2, R7-2)、(R1-8, R2-2, R3-5, Pr-2, R7-3)、(R1-8, R2-2, R3-5, Pr-3,  
 R7-1)、(R1-8, R2-2, R3-5, Pr-3, R7-2)、(R1-8, R2-2, R3-5, Pr-3, R7-3)、(R1-8, R2-2,

R3-5, Pr-4, R7-1)、(R1-8, R2-2, R3-5, Pr-4, R7-2)、(R1-8, R2-2, R3-5, Pr-4, R7-3)。

[0217]

Compounds in which, in the formula (III), a combination of  $R^{1a}$ ,  $R^{2a}$ ,  $R^{3a}$ ,  $P^R$ , as well as ( $R^{8a}$ ,  $R^{9a}$ ,  $R^{10a}$ , and  $R^{11a}$ ) is as follows.

(R1-1, R2-1, R3-1, Pr-1, R9-1)、(R1-1, R2-1, R3-1, Pr-1, R9-2)、(R1-1, R2-1, R3-1, Pr-1, R9-3)、(R1-1, R2-1, R3-1, Pr-2, R9-1)、(R1-1, R2-1, R3-1, Pr-2, R9-2)、(R1-1, R2-1, R3-1, Pr-2, R9-3)、(R1-1, R2-1, R3-1, Pr-3, R9-1)、(R1-1, R2-1, R3-1, Pr-3, R9-2)、(R1-1, R2-1, R3-1, Pr-3, R9-3)、(R1-1, R2-1, R3-1, Pr-4, R9-1)、(R1-1, R2-1, R3-1, Pr-4, R9-2)、(R1-1, R2-1, R3-1, Pr-4, R9-3)、(R1-1, R2-1, R3-2, Pr-1, R9-1)、(R1-1, R2-1, R3-2, Pr-1, R9-2)、(R1-1, R2-1, R3-2, Pr-1, R9-3)、(R1-1, R2-1, R3-2, Pr-2, R9-1)、(R1-1, R2-1, R3-2, Pr-2, R9-2)、(R1-1, R2-1, R3-2, Pr-2, R9-3)、(R1-1, R2-1, R3-2, Pr-3, R9-1)、(R1-1, R2-1, R3-2, Pr-3, R9-2)、(R1-1, R2-1, R3-2, Pr-3, R9-3)、(R1-1, R2-1, R3-2, Pr-4, R9-1)、(R1-1, R2-1, R3-2, Pr-4, R9-2)、(R1-1, R2-1, R3-2, Pr-4, R9-3)、(R1-1, R2-1, R3-3, Pr-1, R9-1)、(R1-1, R2-1, R3-3, Pr-1, R9-2)、(R1-1, R2-1, R3-3, Pr-1, R9-3)、(R1-1, R2-1, R3-3, Pr-2, R9-1)、(R1-1, R2-1, R3-3, Pr-2, R9-2)、(R1-1, R2-1, R3-3, Pr-2, R9-3)、(R1-1, R2-1, R3-3, Pr-3, R9-1)、(R1-1, R2-1, R3-3, Pr-3, R9-2)、(R1-1, R2-1, R3-3, Pr-3, R9-3)、(R1-1, R2-1, R3-3, Pr-4, R9-1)、(R1-1, R2-1, R3-3, Pr-4, R9-2)、(R1-1, R2-1, R3-3, Pr-4, R9-3)、(R1-1, R2-1, R3-4, Pr-1, R9-1)、(R1-1, R2-1, R3-4, Pr-1, R9-2)、(R1-1, R2-1, R3-4, Pr-1, R9-3)、(R1-1, R2-1, R3-4, Pr-2, R9-1)、(R1-1, R2-1, R3-4, Pr-2, R9-2)、(R1-1, R2-1, R3-4, Pr-2, R9-3)、(R1-1, R2-1, R3-4, Pr-3, R9-1)、(R1-1, R2-1, R3-4, Pr-3, R9-2)、(R1-1, R2-1, R3-4, Pr-3, R9-3)、(R1-1, R2-1, R3-4, Pr-4, R9-1)、(R1-1, R2-1, R3-4, Pr-4, R9-2)、(R1-1, R2-1, R3-4, Pr-4, R9-3)、(R1-1, R2-1, R3-5, Pr-1, R9-1)、(R1-1, R2-1, R3-5, Pr-1, R9-2)、(R1-1, R2-1, R3-5, Pr-1, R9-3)、(R1-1, R2-1, R3-5, Pr-2, R9-1)、(R1-1, R2-1, R3-5, Pr-2, R9-2)、(R1-1, R2-1, R3-5, Pr-2, R9-3)、(R1-1, R2-1, R3-5, Pr-3, R9-1)、(R1-1, R2-1, R3-5, Pr-3, R9-2)、

(R1-1, R2-1, R3-5, Pr-3, R9-3)、(R1-1, R2-1, R3-5, Pr-4, R9-1)、(R1-1, R2-1, R3-5, Pr-4, R9-2)、(R1-1, R2-1, R3-5, Pr-4, R9-3)、(R1-1, R2-2, R3-1, Pr-1, R9-1)、(R1-1, R2-2, R3-1, Pr-1, R9-2)、(R1-1, R2-2, R3-1, Pr-1, R9-3)、(R1-1, R2-2, R3-1, Pr-2, R9-1)、(R1-1, R2-2, R3-1, Pr-2, R9-2)、(R1-1, R2-2, R3-1, Pr-2, R9-3)、(R1-1, R2-2, R3-1, Pr-3, R9-1)、(R1-1, R2-2, R3-1, Pr-3, R9-2)、(R1-1, R2-2, R3-1, Pr-3, R9-3)、(R1-1, R2-2, R3-1, Pr-4, R9-1)、(R1-1, R2-2, R3-1, Pr-4, R9-2)、(R1-1, R2-2, R3-1, Pr-4, R9-3)、(R1-1, R2-2, R3-2, Pr-1, R9-1)、(R1-1, R2-2, R3-2, Pr-1, R9-2)、(R1-1, R2-2, R3-2, Pr-1, R9-3)、(R1-1, R2-2, R3-2, Pr-2, R9-1)、(R1-1, R2-2, R3-2, Pr-2, R9-2)、(R1-1, R2-2, R3-2, Pr-2, R9-3)、(R1-1, R2-2, R3-2, Pr-3, R9-1)、(R1-1, R2-2, R3-2, Pr-3, R9-2)、(R1-1, R2-2, R3-2, Pr-3, R9-3)、(R1-1, R2-2, R3-2, Pr-4, R9-1)、(R1-1, R2-2, R3-2, Pr-4, R9-2)、(R1-1, R2-2, R3-2, Pr-4, R9-3)、(R1-1, R2-2, R3-3, Pr-1, R9-1)、(R1-1, R2-2, R3-3, Pr-1, R9-2)、(R1-1, R2-2, R3-3, Pr-1, R9-3)、(R1-1, R2-2, R3-3, Pr-2, R9-1)、(R1-1, R2-2, R3-3, Pr-2, R9-2)、(R1-1, R2-2, R3-3, Pr-2, R9-3)、(R1-1, R2-2, R3-3, Pr-3, R9-1)、(R1-1, R2-2, R3-3, Pr-3, R9-2)、(R1-1, R2-2, R3-3, Pr-3, R9-3)、(R1-1, R2-2, R3-3, Pr-4, R9-1)、(R1-1, R2-2, R3-3, Pr-4, R9-2)、(R1-1, R2-2, R3-3, Pr-4, R9-3)、(R1-1, R2-2, R3-4, Pr-1, R9-1)、(R1-1, R2-2, R3-4, Pr-1, R9-2)、(R1-1, R2-2, R3-4, Pr-1, R9-3)、(R1-1, R2-2, R3-4, Pr-2, R9-1)、(R1-1, R2-2, R3-4, Pr-2, R9-2)、(R1-1, R2-2, R3-4, Pr-2, R9-3)、(R1-1, R2-2, R3-4, Pr-3, R9-1)、(R1-1, R2-2, R3-4, Pr-3, R9-2)、(R1-1, R2-2, R3-4, Pr-3, R9-3)、(R1-1, R2-2, R3-4, Pr-4, R9-1)、(R1-1, R2-2, R3-4, Pr-4, R9-2)、(R1-1, R2-2, R3-4, Pr-4, R9-3)、(R1-1, R2-2, R3-5, Pr-1, R9-1)、(R1-1, R2-2, R3-5, Pr-1, R9-2)、(R1-1, R2-2, R3-5, Pr-1, R9-3)、(R1-1, R2-2, R3-5, Pr-2, R9-1)、(R1-1, R2-2, R3-5, Pr-2, R9-2)、(R1-1, R2-2, R3-5, Pr-2, R9-3)、(R1-1, R2-2, R3-5, Pr-3, R9-1)、(R1-1, R2-2, R3-5, Pr-3, R9-2)、(R1-1, R2-2, R3-5, Pr-3, R9-3)、(R1-1, R2-2, R3-5, Pr-4, R9-1)、(R1-1, R2-2, R3-5, Pr-4, R9-2)、(R1-1, R2-2, R3-5, Pr-4, R9-3)、

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(R1-2, R2-1, R3-1, Pr-1, R9-1)、(R1-2, R2-1, R3-1, Pr-1, R9-2)、(R1-2, R2-1, R3-1, Pr-1, R9-3)、(R1-2, R2-1, R3-1, Pr-2, R9-1)、(R1-2, R2-1, R3-1, Pr-2, R9-2)、(R1-2, R2-1, R3-1, Pr-2, R9-3)、(R1-2, R2-1, R3-1, Pr-3, R9-1)、(R1-2, R2-1, R3-1, Pr-3, R9-2)、(R1-2, R2-1, R3-1, Pr-3, R9-3)、(R1-2, R2-1, R3-1, Pr-4, R9-1)、(R1-2, R2-1, R3-1, Pr-4, R9-2)、(R1-2, R2-1, R3-1, Pr-4, R9-3)、(R1-2, R2-1, R3-2, Pr-1, R9-1)、(R1-2, R2-1, R3-2, Pr-1, R9-2)、(R1-2, R2-1, R3-2, Pr-1, R9-3)、(R1-2, R2-1, R3-2, Pr-2, R9-1)、(R1-2, R2-1, R3-2, Pr-2, R9-2)、(R1-2, R2-1, R3-2, Pr-2, R9-3)、(R1-2, R2-1, R3-2, Pr-3, R9-1)、(R1-2, R2-1, R3-2, Pr-3, R9-2)、(R1-2, R2-1, R3-2, Pr-3, R9-3)、(R1-2, R2-1, R3-2, Pr-4, R9-1)、(R1-2, R2-1, R3-2, Pr-4, R9-2)、(R1-2, R2-1, R3-2, Pr-4, R9-3)、(R1-2, R2-1, R3-3, Pr-1, R9-1)、(R1-2, R2-1, R3-3, Pr-1, R9-2)、(R1-2, R2-1, R3-3, Pr-1, R9-3)、(R1-2, R2-1, R3-3, Pr-2, R9-1)、(R1-2, R2-1, R3-3, Pr-2, R9-2)、(R1-2, R2-1, R3-3, Pr-2, R9-3)、(R1-2, R2-1, R3-3, Pr-3, R9-1)、(R1-2, R2-1, R3-3, Pr-3, R9-2)、(R1-2, R2-1, R3-3, Pr-3, R9-3)、(R1-2, R2-1, R3-3, Pr-4, R9-1)、(R1-2, R2-1, R3-3, Pr-4, R9-2)、(R1-2, R2-1, R3-3, Pr-4, R9-3)、(R1-2, R2-1, R3-4, Pr-1, R9-1)、(R1-2, R2-1, R3-4, Pr-1, R9-2)、(R1-2, R2-1, R3-4, Pr-1, R9-3)、(R1-2, R2-1, R3-4, Pr-2, R9-1)、(R1-2, R2-1, R3-4, Pr-2, R9-2)、(R1-2, R2-1, R3-4, Pr-2, R9-3)、(R1-2, R2-1, R3-4, Pr-3, R9-1)、(R1-2, R2-1, R3-4, Pr-3, R9-2)、(R1-2, R2-1, R3-4, Pr-3, R9-3)、(R1-2, R2-1, R3-4, Pr-4, R9-1)、(R1-2, R2-1, R3-4, Pr-4, R9-2)、(R1-2, R2-1, R3-4, Pr-4, R9-3)、(R1-2, R2-1, R3-5, Pr-1, R9-1)、(R1-2, R2-1, R3-5, Pr-1, R9-2)、(R1-2, R2-1, R3-5, Pr-1, R9-3)、(R1-2, R2-1, R3-5, Pr-2, R9-1)、(R1-2, R2-1, R3-5, Pr-2, R9-2)、(R1-2, R2-1, R3-5, Pr-2, R9-3)、(R1-2, R2-1, R3-5, Pr-3, R9-1)、(R1-2, R2-1, R3-5, Pr-3, R9-2)、(R1-2, R2-1, R3-5, Pr-3, R9-3)、(R1-2, R2-1, R3-5, Pr-4, R9-1)、(R1-2, R2-1, R3-5, Pr-4, R9-2)、(R1-2, R2-1, R3-5, Pr-4, R9-3)、(R1-2, R2-2, R3-1, Pr-1, R9-1)、(R1-2, R2-2, R3-1, Pr-1, R9-2)、(R1-2, R2-2, R3-1, Pr-1, R9-3)、(R1-2, R2-2, R3-1, Pr-2, R9-1)、(R1-2, R2-2, R3-1, Pr-2, R9-2)、(R1-2, R2-2, R3-1, Pr-2,

R9-3)、(R1-2, R2-2, R3-1, Pr-3, R9-1)、(R1-2, R2-2, R3-1, Pr-3, R9-2)、(R1-2, R2-2, R3-1, Pr-3, R9-3)、(R1-2, R2-2, R3-1, Pr-4, R9-1)、(R1-2, R2-2, R3-1, Pr-4, R9-2)、(R1-2, R2-2, R3-1, Pr-4, R9-3)、(R1-2, R2-2, R3-2, Pr-1, R9-1)、(R1-2, R2-2, R3-2, Pr-1, R9-2)、(R1-2, R2-2, R3-2, Pr-1, R9-3)、(R1-2, R2-2, R3-2, Pr-2, R9-1)、(R1-2, R2-2, R3-2, Pr-2, R9-2)、(R1-2, R2-2, R3-2, Pr-2, R9-3)、(R1-2, R2-2, R3-2, Pr-3, R9-1)、(R1-2, R2-2, R3-2, Pr-3, R9-2)、(R1-2, R2-2, R3-2, Pr-3, R9-3)、(R1-2, R2-2, R3-2, Pr-4, R9-1)、(R1-2, R2-2, R3-2, Pr-4, R9-2)、(R1-2, R2-2, R3-2, Pr-4, R9-3)、(R1-2, R2-2, R3-3, Pr-1, R9-1)、(R1-2, R2-2, R3-3, Pr-1, R9-2)、(R1-2, R2-2, R3-3, Pr-1, R9-3)、(R1-2, R2-2, R3-3, Pr-2, R9-1)、(R1-2, R2-2, R3-3, Pr-2, R9-2)、(R1-2, R2-2, R3-3, Pr-2, R9-3)、(R1-2, R2-2, R3-3, Pr-3, R9-1)、(R1-2, R2-2, R3-3, Pr-3, R9-2)、(R1-2, R2-2, R3-3, Pr-3, R9-3)、(R1-2, R2-2, R3-3, Pr-4, R9-1)、(R1-2, R2-2, R3-3, Pr-4, R9-2)、(R1-2, R2-2, R3-3, Pr-4, R9-3)、(R1-2, R2-2, R3-4, Pr-1, R9-1)、(R1-2, R2-2, R3-4, Pr-1, R9-2)、(R1-2, R2-2, R3-4, Pr-1, R9-3)、(R1-2, R2-2, R3-4, Pr-2, R9-1)、(R1-2, R2-2, R3-4, Pr-2, R9-2)、(R1-2, R2-2, R3-4, Pr-2, R9-3)、(R1-2, R2-2, R3-4, Pr-3, R9-1)、(R1-2, R2-2, R3-4, Pr-3, R9-2)、(R1-2, R2-2, R3-4, Pr-3, R9-3)、(R1-2, R2-2, R3-4, Pr-4, R9-1)、(R1-2, R2-2, R3-4, Pr-4, R9-2)、(R1-2, R2-2, R3-4, Pr-4, R9-3)、(R1-2, R2-2, R3-5, Pr-1, R9-1)、(R1-2, R2-2, R3-5, Pr-1, R9-2)、(R1-2, R2-2, R3-5, Pr-1, R9-3)、(R1-2, R2-2, R3-5, Pr-2, R9-1)、(R1-2, R2-2, R3-5, Pr-2, R9-2)、(R1-2, R2-2, R3-5, Pr-2, R9-3)、(R1-2, R2-2, R3-5, Pr-3, R9-1)、(R1-2, R2-2, R3-5, Pr-3, R9-2)、(R1-2, R2-2, R3-5, Pr-3, R9-3)、(R1-2, R2-2, R3-5, Pr-4, R9-1)、(R1-2, R2-2, R3-5, Pr-4, R9-2)、(R1-2, R2-2, R3-5, Pr-4, R9-3)、

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(R1-3, R2-1, R3-1, Pr-1, R9-1)、(R1-3, R2-1, R3-1, Pr-1, R9-2)、(R1-3, R2-1, R3-1, Pr-1, R9-3)、(R1-3, R2-1, R3-1, Pr-2, R9-1)、(R1-3, R2-1, R3-1, Pr-2, R9-2)、(R1-3, R2-1, R3-1, Pr-2, R9-3)、(R1-3, R2-1, R3-1, Pr-3, R9-1)、(R1-3, R2-1, R3-1, Pr-3, R9-2)、

(R1-3, R2-1, R3-1, Pr-3, R9-3)、(R1-3, R2-1, R3-1, Pr-4, R9-1)、(R1-3, R2-1, R3-1, Pr-4, R9-2)、(R1-3, R2-1, R3-1, Pr-4, R9-3)、(R1-3, R2-1, R3-2, Pr-1, R9-1)、(R1-3, R2-1, R3-2, Pr-1, R9-2)、(R1-3, R2-1, R3-2, Pr-1, R9-3)、(R1-3, R2-1, R3-2, Pr-2, R9-1)、(R1-3, R2-1, R3-2, Pr-2, R9-2)、(R1-3, R2-1, R3-2, Pr-2, R9-3)、(R1-3, R2-1, R3-2, Pr-3, R9-1)、(R1-3, R2-1, R3-2, Pr-3, R9-2)、(R1-3, R2-1, R3-2, Pr-3, R9-3)、(R1-3, R2-1, R3-2, Pr-4, R9-1)、(R1-3, R2-1, R3-2, Pr-4, R9-2)、(R1-3, R2-1, R3-2, Pr-4, R9-3)、(R1-3, R2-1, R3-3, Pr-1, R9-1)、(R1-3, R2-1, R3-3, Pr-1, R9-2)、(R1-3, R2-1, R3-3, Pr-1, R9-3)、(R1-3, R2-1, R3-3, Pr-2, R9-1)、(R1-3, R2-1, R3-3, Pr-2, R9-2)、(R1-3, R2-1, R3-3, Pr-2, R9-3)、(R1-3, R2-1, R3-3, Pr-3, R9-1)、(R1-3, R2-1, R3-3, Pr-3, R9-2)、(R1-3, R2-1, R3-3, Pr-3, R9-3)、(R1-3, R2-1, R3-3, Pr-4, R9-1)、(R1-3, R2-1, R3-3, Pr-4, R9-2)、(R1-3, R2-1, R3-3, Pr-4, R9-3)、(R1-3, R2-1, R3-4, Pr-1, R9-1)、(R1-3, R2-1, R3-4, Pr-1, R9-2)、(R1-3, R2-1, R3-4, Pr-1, R9-3)、(R1-3, R2-1, R3-4, Pr-2, R9-1)、(R1-3, R2-1, R3-4, Pr-2, R9-2)、(R1-3, R2-1, R3-4, Pr-2, R9-3)、(R1-3, R2-1, R3-4, Pr-3, R9-1)、(R1-3, R2-1, R3-4, Pr-3, R9-2)、(R1-3, R2-1, R3-4, Pr-3, R9-3)、(R1-3, R2-1, R3-4, Pr-4, R9-1)、(R1-3, R2-1, R3-4, Pr-4, R9-2)、(R1-3, R2-1, R3-4, Pr-4, R9-3)、(R1-3, R2-1, R3-5, Pr-1, R9-1)、(R1-3, R2-1, R3-5, Pr-1, R9-2)、(R1-3, R2-1, R3-5, Pr-1, R9-3)、(R1-3, R2-1, R3-5, Pr-2, R9-1)、(R1-3, R2-1, R3-5, Pr-2, R9-2)、(R1-3, R2-1, R3-5, Pr-2, R9-3)、(R1-3, R2-1, R3-5, Pr-3, R9-1)、(R1-3, R2-1, R3-5, Pr-3, R9-2)、(R1-3, R2-1, R3-5, Pr-3, R9-3)、(R1-3, R2-1, R3-5, Pr-4, R9-1)、(R1-3, R2-1, R3-5, Pr-4, R9-2)、(R1-3, R2-1, R3-5, Pr-4, R9-3)、(R1-3, R2-2, R3-1, Pr-1, R9-1)、(R1-3, R2-2, R3-1, Pr-1, R9-2)、(R1-3, R2-2, R3-1, Pr-1, R9-3)、(R1-3, R2-2, R3-1, Pr-2, R9-1)、(R1-3, R2-2, R3-1, Pr-2, R9-2)、(R1-3, R2-2, R3-1, Pr-2, R9-3)、(R1-3, R2-2, R3-1, Pr-3, R9-1)、(R1-3, R2-2, R3-1, Pr-3, R9-2)、(R1-3, R2-2, R3-1, Pr-3, R9-3)、(R1-3, R2-2, R3-1, Pr-4, R9-1)、(R1-3, R2-2, R3-1, Pr-4, R9-2)、(R1-3, R2-2, R3-1, Pr-4, R9-3)、(R1-3, R2-2, R3-2, Pr-1, R9-1)、(R1-3, R2-2, R3-2, Pr-1, R9-2)、(R1-3, R2-2, R3-2, Pr-1,

R9-3)、(R1-3, R2-2, R3-2, Pr-2, R9-1)、(R1-3, R2-2, R3-2, Pr-2, R9-2)、(R1-3, R2-2,  
 R3-2, Pr-2, R9-3)、(R1-3, R2-2, R3-2, Pr-3, R9-1)、(R1-3, R2-2, R3-2, Pr-3, R9-2)、  
 (R1-3, R2-2, R3-2, Pr-3, R9-3)、(R1-3, R2-2, R3-2, Pr-4, R9-1)、(R1-3, R2-2, R3-2, Pr-4,  
 R9-2)、(R1-3, R2-2, R3-2, Pr-4, R9-3)、(R1-3, R2-2, R3-3, Pr-1, R9-1)、(R1-3, R2-2,  
 R3-3, Pr-1, R9-2)、(R1-3, R2-2, R3-3, Pr-1, R9-3)、(R1-3, R2-2, R3-3, Pr-2, R9-1)、  
 (R1-3, R2-2, R3-3, Pr-2, R9-2)、(R1-3, R2-2, R3-3, Pr-2, R9-3)、(R1-3, R2-2, R3-3, Pr-3,  
 R9-1)、(R1-3, R2-2, R3-3, Pr-3, R9-2)、(R1-3, R2-2, R3-3, Pr-3, R9-3)、(R1-3, R2-2,  
 R3-3, Pr-4, R9-1)、(R1-3, R2-2, R3-3, Pr-4, R9-2)、(R1-3, R2-2, R3-3, Pr-4, R9-3)、  
 (R1-3, R2-2, R3-4, Pr-1, R9-1)、(R1-3, R2-2, R3-4, Pr-1, R9-2)、(R1-3, R2-2, R3-4, Pr-1,  
 R9-3)、(R1-3, R2-2, R3-4, Pr-2, R9-1)、(R1-3, R2-2, R3-4, Pr-2, R9-2)、(R1-3, R2-2,  
 R3-4, Pr-2, R9-3)、(R1-3, R2-2, R3-4, Pr-3, R9-1)、(R1-3, R2-2, R3-4, Pr-3, R9-2)、  
 (R1-3, R2-2, R3-4, Pr-3, R9-3)、(R1-3, R2-2, R3-4, Pr-4, R9-1)、(R1-3, R2-2, R3-4, Pr-4,  
 R9-2)、(R1-3, R2-2, R3-4, Pr-4, R9-3)、(R1-3, R2-2, R3-5, Pr-1, R9-1)、(R1-3, R2-2,  
 R3-5, Pr-1, R9-2)、(R1-3, R2-2, R3-5, Pr-1, R9-3)、(R1-3, R2-2, R3-5, Pr-2, R9-1)、  
 (R1-3, R2-2, R3-5, Pr-2, R9-2)、(R1-3, R2-2, R3-5, Pr-2, R9-3)、(R1-3, R2-2, R3-5, Pr-3,  
 R9-1)、(R1-3, R2-2, R3-5, Pr-3, R9-2)、(R1-3, R2-2, R3-5, Pr-3, R9-3)、(R1-3, R2-2,  
 R3-5, Pr-4, R9-1)、(R1-3, R2-2, R3-5, Pr-4, R9-2)、(R1-3, R2-2, R3-5, Pr-4, R9-3)、

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(R1-4, R2-1, R3-1, Pr-1, R9-1)、(R1-4, R2-1, R3-1, Pr-1, R9-2)、(R1-4, R2-1, R3-1,  
 Pr-1, R9-3)、(R1-4, R2-1, R3-1, Pr-2, R9-1)、(R1-4, R2-1, R3-1, Pr-2, R9-2)、(R1-4,  
 R2-1, R3-1, Pr-2, R9-3)、(R1-4, R2-1, R3-1, Pr-3, R9-1)、(R1-4, R2-1, R3-1, Pr-3, R9-2)、  
 (R1-4, R2-1, R3-1, Pr-3, R9-3)、(R1-4, R2-1, R3-1, Pr-4, R9-1)、(R1-4, R2-1, R3-1, Pr-4,  
 R9-2)、(R1-4, R2-1, R3-1, Pr-4, R9-3)、(R1-4, R2-1, R3-2, Pr-1, R9-1)、(R1-4, R2-1,  
 R3-2, Pr-1, R9-2)、(R1-4, R2-1, R3-2, Pr-1, R9-3)、(R1-4, R2-1, R3-2, Pr-2, R9-1)、  
 (R1-4, R2-1, R3-2, Pr-2, R9-2)、(R1-4, R2-1, R3-2, Pr-2, R9-3)、(R1-4, R2-1, R3-2, Pr-3,

R9-1)、(R1-4, R2-1, R3-2, Pr-3, R9-2)、(R1-4, R2-1, R3-2, Pr-3, R9-3)、(R1-4, R2-1,  
 R3-2, Pr-4, R9-1)、(R1-4, R2-1, R3-2, Pr-4, R9-2)、(R1-4, R2-1, R3-2, Pr-4, R9-3)、  
 (R1-4, R2-1, R3-3, Pr-1, R9-1)、(R1-4, R2-1, R3-3, Pr-1, R9-2)、(R1-4, R2-1, R3-3, Pr-1,  
 R9-3)、(R1-4, R2-1, R3-3, Pr-2, R9-1)、(R1-4, R2-1, R3-3, Pr-2, R9-2)、(R1-4, R2-1,  
 R3-3, Pr-2, R9-3)、(R1-4, R2-1, R3-3, Pr-3, R9-1)、(R1-4, R2-1, R3-3, Pr-3, R9-2)、  
 (R1-4, R2-1, R3-3, Pr-3, R9-3)、(R1-4, R2-1, R3-3, Pr-4, R9-1)、(R1-4, R2-1, R3-3, Pr-4,  
 R9-2)、(R1-4, R2-1, R3-3, Pr-4, R9-3)、(R1-4, R2-1, R3-4, Pr-1, R9-1)、(R1-4, R2-1,  
 R3-4, Pr-1, R9-2)、(R1-4, R2-1, R3-4, Pr-1, R9-3)、(R1-4, R2-1, R3-4, Pr-2, R9-1)、  
 (R1-4, R2-1, R3-4, Pr-2, R9-2)、(R1-4, R2-1, R3-4, Pr-2, R9-3)、(R1-4, R2-1, R3-4, Pr-3,  
 R9-1)、(R1-4, R2-1, R3-4, Pr-3, R9-2)、(R1-4, R2-1, R3-4, Pr-3, R9-3)、(R1-4, R2-1,  
 R3-4, Pr-4, R9-1)、(R1-4, R2-1, R3-4, Pr-4, R9-2)、(R1-4, R2-1, R3-4, Pr-4, R9-3)、  
 (R1-4, R2-1, R3-5, Pr-1, R9-1)、(R1-4, R2-1, R3-5, Pr-1, R9-2)、(R1-4, R2-1, R3-5, Pr-1,  
 R9-3)、(R1-4, R2-1, R3-5, Pr-2, R9-1)、(R1-4, R2-1, R3-5, Pr-2, R9-2)、(R1-4, R2-1,  
 R3-5, Pr-2, R9-3)、(R1-4, R2-1, R3-5, Pr-3, R9-1)、(R1-4, R2-1, R3-5, Pr-3, R9-2)、  
 (R1-4, R2-1, R3-5, Pr-3, R9-3)、(R1-4, R2-1, R3-5, Pr-4, R9-1)、(R1-4, R2-1, R3-5, Pr-4,  
 R9-2)、(R1-4, R2-1, R3-5, Pr-4, R9-3)、(R1-4, R2-2, R3-1, Pr-1, R9-1)、(R1-4, R2-2,  
 R3-1, Pr-1, R9-2)、(R1-4, R2-2, R3-1, Pr-1, R9-3)、(R1-4, R2-2, R3-1, Pr-2, R9-1)、  
 (R1-4, R2-2, R3-1, Pr-2, R9-2)、(R1-4, R2-2, R3-1, Pr-2, R9-3)、(R1-4, R2-2, R3-1, Pr-3,  
 R9-1)、(R1-4, R2-2, R3-1, Pr-3, R9-2)、(R1-4, R2-2, R3-1, Pr-3, R9-3)、(R1-4, R2-2,  
 R3-1, Pr-4, R9-1)、(R1-4, R2-2, R3-1, Pr-4, R9-2)、(R1-4, R2-2, R3-1, Pr-4, R9-3)、  
 (R1-4, R2-2, R3-2, Pr-1, R9-1)、(R1-4, R2-2, R3-2, Pr-1, R9-2)、(R1-4, R2-2, R3-2, Pr-1,  
 R9-3)、(R1-4, R2-2, R3-2, Pr-2, R9-1)、(R1-4, R2-2, R3-2, Pr-2, R9-2)、(R1-4, R2-2,  
 R3-2, Pr-2, R9-3)、(R1-4, R2-2, R3-2, Pr-3, R9-1)、(R1-4, R2-2, R3-2, Pr-3, R9-2)、  
 (R1-4, R2-2, R3-2, Pr-3, R9-3)、(R1-4, R2-2, R3-2, Pr-4, R9-1)、(R1-4, R2-2, R3-2, Pr-4,  
 R9-2)、(R1-4, R2-2, R3-2, Pr-4, R9-3)、(R1-4, R2-2, R3-3, Pr-1, R9-1)、(R1-4, R2-2,

R3-3, Pr-1, R9-2)、(R1-4, R2-2, R3-3, Pr-1, R9-3)、(R1-4, R2-2, R3-3, Pr-2, R9-1)、  
 (R1-4, R2-2, R3-3, Pr-2, R9-2)、(R1-4, R2-2, R3-3, Pr-2, R9-3)、(R1-4, R2-2, R3-3, Pr-3,  
 R9-1)、(R1-4, R2-2, R3-3, Pr-3, R9-2)、(R1-4, R2-2, R3-3, Pr-3, R9-3)、(R1-4, R2-2,  
 R3-3, Pr-4, R9-1)、(R1-4, R2-2, R3-3, Pr-4, R9-2)、(R1-4, R2-2, R3-3, Pr-4, R9-3)、  
 (R1-4, R2-2, R3-4, Pr-1, R9-1)、(R1-4, R2-2, R3-4, Pr-1, R9-2)、(R1-4, R2-2, R3-4, Pr-1,  
 R9-3)、(R1-4, R2-2, R3-4, Pr-2, R9-1)、(R1-4, R2-2, R3-4, Pr-2, R9-2)、(R1-4, R2-2,  
 R3-4, Pr-2, R9-3)、(R1-4, R2-2, R3-4, Pr-3, R9-1)、(R1-4, R2-2, R3-4, Pr-3, R9-2)、  
 (R1-4, R2-2, R3-4, Pr-3, R9-3)、(R1-4, R2-2, R3-4, Pr-4, R9-1)、(R1-4, R2-2, R3-4, Pr-4,  
 R9-2)、(R1-4, R2-2, R3-4, Pr-4, R9-3)、(R1-4, R2-2, R3-5, Pr-1, R9-1)、(R1-4, R2-2,  
 R3-5, Pr-1, R9-2)、(R1-4, R2-2, R3-5, Pr-1, R9-3)、(R1-4, R2-2, R3-5, Pr-2, R9-1)、  
 (R1-4, R2-2, R3-5, Pr-2, R9-2)、(R1-4, R2-2, R3-5, Pr-2, R9-3)、(R1-4, R2-2, R3-5, Pr-3,  
 R9-1)、(R1-4, R2-2, R3-5, Pr-3, R9-2)、(R1-4, R2-2, R3-5, Pr-3, R9-3)、(R1-4, R2-2,  
 R3-5, Pr-4, R9-1)、(R1-4, R2-2, R3-5, Pr-4, R9-2)、(R1-4, R2-2, R3-5, Pr-4, R9-3)、

[0221]

(R1-5, R2-1, R3-1, Pr-1, R9-1)、(R1-5, R2-1, R3-1, Pr-1, R9-2)、(R1-5, R2-1, R3-1,  
 Pr-1, R9-3)、(R1-5, R2-1, R3-1, Pr-2, R9-1)、(R1-5, R2-1, R3-1, Pr-2, R9-2)、(R1-5,  
 R2-1, R3-1, Pr-2, R9-3)、(R1-5, R2-1, R3-1, Pr-3, R9-1)、(R1-5, R2-1, R3-1, Pr-3, R9-2)、  
 (R1-5, R2-1, R3-1, Pr-3, R9-3)、(R1-5, R2-1, R3-1, Pr-4, R9-1)、(R1-5, R2-1, R3-1, Pr-4,  
 R9-2)、(R1-5, R2-1, R3-1, Pr-4, R9-3)、(R1-5, R2-1, R3-2, Pr-1, R9-1)、(R1-5, R2-1,  
 R3-2, Pr-1, R9-2)、(R1-5, R2-1, R3-2, Pr-1, R9-3)、(R1-5, R2-1, R3-2, Pr-2, R9-1)、  
 (R1-5, R2-1, R3-2, Pr-2, R9-2)、(R1-5, R2-1, R3-2, Pr-2, R9-3)、(R1-5, R2-1, R3-2, Pr-3,  
 R9-1)、(R1-5, R2-1, R3-2, Pr-3, R9-2)、(R1-5, R2-1, R3-2, Pr-3, R9-3)、(R1-5, R2-1,  
 R3-2, Pr-4, R9-1)、(R1-5, R2-1, R3-2, Pr-4, R9-2)、(R1-5, R2-1, R3-2, Pr-4, R9-3)、  
 (R1-5, R2-1, R3-3, Pr-1, R9-1)、(R1-5, R2-1, R3-3, Pr-1, R9-2)、(R1-5, R2-1, R3-3, Pr-1,  
 R9-3)、(R1-5, R2-1, R3-3, Pr-2, R9-1)、(R1-5, R2-1, R3-3, Pr-2, R9-2)、(R1-5, R2-1,

R3-3, Pr-2, R9-3)、(R1-5, R2-1, R3-3, Pr-3, R9-1)、(R1-5, R2-1, R3-3, Pr-3, R9-2)、  
 (R1-5, R2-1, R3-3, Pr-3, R9-3)、(R1-5, R2-1, R3-3, Pr-4, R9-1)、(R1-5, R2-1, R3-3, Pr-4,  
 R9-2)、(R1-5, R2-1, R3-3, Pr-4, R9-3)、(R1-5, R2-1, R3-4, Pr-1, R9-1)、(R1-5, R2-1,  
 R3-4, Pr-1, R9-2)、(R1-5, R2-1, R3-4, Pr-1, R9-3)、(R1-5, R2-1, R3-4, Pr-2, R9-1)、  
 (R1-5, R2-1, R3-4, Pr-2, R9-2)、(R1-5, R2-1, R3-4, Pr-2, R9-3)、(R1-5, R2-1, R3-4, Pr-3,  
 R9-1)、(R1-5, R2-1, R3-4, Pr-3, R9-2)、(R1-5, R2-1, R3-4, Pr-3, R9-3)、(R1-5, R2-1,  
 R3-4, Pr-4, R9-1)、(R1-5, R2-1, R3-4, Pr-4, R9-2)、(R1-5, R2-1, R3-4, Pr-4, R9-3)、  
 (R1-5, R2-1, R3-5, Pr-1, R9-1)、(R1-5, R2-1, R3-5, Pr-1, R9-2)、(R1-5, R2-1, R3-5, Pr-1,  
 R9-3)、(R1-5, R2-1, R3-5, Pr-2, R9-1)、(R1-5, R2-1, R3-5, Pr-2, R9-2)、(R1-5, R2-1,  
 R3-5, Pr-2, R9-3)、(R1-5, R2-1, R3-5, Pr-3, R9-1)、(R1-5, R2-1, R3-5, Pr-3, R9-2)、  
 (R1-5, R2-1, R3-5, Pr-3, R9-3)、(R1-5, R2-1, R3-5, Pr-4, R9-1)、(R1-5, R2-1, R3-5, Pr-4,  
 R9-2)、(R1-5, R2-1, R3-5, Pr-4, R9-3)、(R1-5, R2-2, R3-1, Pr-1, R9-1)、(R1-5, R2-2,  
 R3-1, Pr-1, R9-2)、(R1-5, R2-2, R3-1, Pr-1, R9-3)、(R1-5, R2-2, R3-1, Pr-2, R9-1)、  
 (R1-5, R2-2, R3-1, Pr-2, R9-2)、(R1-5, R2-2, R3-1, Pr-2, R9-3)、(R1-5, R2-2, R3-1, Pr-3,  
 R9-1)、(R1-5, R2-2, R3-1, Pr-3, R9-2)、(R1-5, R2-2, R3-1, Pr-3, R9-3)、(R1-5, R2-2,  
 R3-1, Pr-4, R9-1)、(R1-5, R2-2, R3-1, Pr-4, R9-2)、(R1-5, R2-2, R3-1, Pr-4, R9-3)、  
 (R1-5, R2-2, R3-2, Pr-1, R9-1)、(R1-5, R2-2, R3-2, Pr-1, R9-2)、(R1-5, R2-2, R3-2, Pr-1,  
 R9-3)、(R1-5, R2-2, R3-2, Pr-2, R9-1)、(R1-5, R2-2, R3-2, Pr-2, R9-2)、(R1-5, R2-2,  
 R3-2, Pr-2, R9-3)、(R1-5, R2-2, R3-2, Pr-3, R9-1)、(R1-5, R2-2, R3-2, Pr-3, R9-2)、  
 (R1-5, R2-2, R3-2, Pr-3, R9-3)、(R1-5, R2-2, R3-2, Pr-4, R9-1)、(R1-5, R2-2, R3-2, Pr-4,  
 R9-2)、(R1-5, R2-2, R3-2, Pr-4, R9-3)、(R1-5, R2-2, R3-3, Pr-1, R9-1)、(R1-5, R2-2,  
 R3-3, Pr-1, R9-2)、(R1-5, R2-2, R3-3, Pr-1, R9-3)、(R1-5, R2-2, R3-3, Pr-2, R9-1)、  
 (R1-5, R2-2, R3-3, Pr-2, R9-2)、(R1-5, R2-2, R3-3, Pr-2, R9-3)、(R1-5, R2-2, R3-3, Pr-3,  
 R9-1)、(R1-5, R2-2, R3-3, Pr-3, R9-2)、(R1-5, R2-2, R3-3, Pr-3, R9-3)、(R1-5, R2-2,  
 R3-3, Pr-4, R9-1)、(R1-5, R2-2, R3-3, Pr-4, R9-2)、(R1-5, R2-2, R3-3, Pr-4, R9-3)、

(R1-5, R2-2, R3-4, Pr-1, R9-1)、(R1-5, R2-2, R3-4, Pr-1, R9-2)、(R1-5, R2-2, R3-4, Pr-1, R9-3)、(R1-5, R2-2, R3-4, Pr-2, R9-1)、(R1-5, R2-2, R3-4, Pr-2, R9-2)、(R1-5, R2-2, R3-4, Pr-2, R9-3)、(R1-5, R2-2, R3-4, Pr-3, R9-1)、(R1-5, R2-2, R3-4, Pr-3, R9-2)、(R1-5, R2-2, R3-4, Pr-3, R9-3)、(R1-5, R2-2, R3-4, Pr-4, R9-1)、(R1-5, R2-2, R3-4, Pr-4, R9-2)、(R1-5, R2-2, R3-4, Pr-4, R9-3)、(R1-5, R2-2, R3-5, Pr-1, R9-1)、(R1-5, R2-2, R3-5, Pr-1, R9-2)、(R1-5, R2-2, R3-5, Pr-1, R9-3)、(R1-5, R2-2, R3-5, Pr-2, R9-1)、(R1-5, R2-2, R3-5, Pr-2, R9-2)、(R1-5, R2-2, R3-5, Pr-2, R9-3)、(R1-5, R2-2, R3-5, Pr-3, R9-1)、(R1-5, R2-2, R3-5, Pr-3, R9-2)、(R1-5, R2-2, R3-5, Pr-3, R9-3)、(R1-5, R2-2, R3-5, Pr-4, R9-1)、(R1-5, R2-2, R3-5, Pr-4, R9-2)、(R1-5, R2-2, R3-5, Pr-4, R9-3)、

[0222]

(R1-6, R2-1, R3-1, Pr-1, R9-1)、(R1-6, R2-1, R3-1, Pr-1, R9-2)、(R1-6, R2-1, R3-1, Pr-1, R9-3)、(R1-6, R2-1, R3-1, Pr-2, R9-1)、(R1-6, R2-1, R3-1, Pr-2, R9-2)、(R1-6, R2-1, R3-1, Pr-2, R9-3)、(R1-6, R2-1, R3-1, Pr-3, R9-1)、(R1-6, R2-1, R3-1, Pr-3, R9-2)、(R1-6, R2-1, R3-1, Pr-3, R9-3)、(R1-6, R2-1, R3-1, Pr-4, R9-1)、(R1-6, R2-1, R3-1, Pr-4, R9-2)、(R1-6, R2-1, R3-1, Pr-4, R9-3)、(R1-6, R2-1, R3-2, Pr-1, R9-1)、(R1-6, R2-1, R3-2, Pr-1, R9-2)、(R1-6, R2-1, R3-2, Pr-1, R9-3)、(R1-6, R2-1, R3-2, Pr-2, R9-1)、(R1-6, R2-1, R3-2, Pr-2, R9-2)、(R1-6, R2-1, R3-2, Pr-2, R9-3)、(R1-6, R2-1, R3-2, Pr-3, R9-1)、(R1-6, R2-1, R3-2, Pr-3, R9-2)、(R1-6, R2-1, R3-2, Pr-3, R9-3)、(R1-6, R2-1, R3-2, Pr-4, R9-1)、(R1-6, R2-1, R3-2, Pr-4, R9-2)、(R1-6, R2-1, R3-2, Pr-4, R9-3)、(R1-6, R2-1, R3-3, Pr-1, R9-1)、(R1-6, R2-1, R3-3, Pr-1, R9-2)、(R1-6, R2-1, R3-3, Pr-1, R9-3)、(R1-6, R2-1, R3-3, Pr-2, R9-1)、(R1-6, R2-1, R3-3, Pr-2, R9-2)、(R1-6, R2-1, R3-3, Pr-2, R9-3)、(R1-6, R2-1, R3-3, Pr-3, R9-1)、(R1-6, R2-1, R3-3, Pr-3, R9-2)、(R1-6, R2-1, R3-3, Pr-3, R9-3)、(R1-6, R2-1, R3-3, Pr-4, R9-1)、(R1-6, R2-1, R3-3, Pr-4, R9-2)、(R1-6, R2-1, R3-3, Pr-4, R9-3)、(R1-6, R2-1, R3-4, Pr-1, R9-1)、(R1-6, R2-1, R3-4, Pr-1, R9-2)、(R1-6, R2-1, R3-4, Pr-1, R9-3)、(R1-6, R2-1, R3-4, Pr-2, R9-1)、

(R1-6, R2-1, R3-4, Pr-2, R9-2)、(R1-6, R2-1, R3-4, Pr-2, R9-3)、(R1-6, R2-1, R3-4, Pr-3, R9-1)、(R1-6, R2-1, R3-4, Pr-3, R9-2)、(R1-6, R2-1, R3-4, Pr-3, R9-3)、(R1-6, R2-1, R3-4, Pr-4, R9-1)、(R1-6, R2-1, R3-4, Pr-4, R9-2)、(R1-6, R2-1, R3-4, Pr-4, R9-3)、(R1-6, R2-1, R3-5, Pr-1, R9-1)、(R1-6, R2-1, R3-5, Pr-1, R9-2)、(R1-6, R2-1, R3-5, Pr-1, R9-3)、(R1-6, R2-1, R3-5, Pr-2, R9-1)、(R1-6, R2-1, R3-5, Pr-2, R9-2)、(R1-6, R2-1, R3-5, Pr-2, R9-3)、(R1-6, R2-1, R3-5, Pr-3, R9-1)、(R1-6, R2-1, R3-5, Pr-3, R9-2)、(R1-6, R2-1, R3-5, Pr-3, R9-3)、(R1-6, R2-1, R3-5, Pr-4, R9-1)、(R1-6, R2-1, R3-5, Pr-4, R9-2)、(R1-6, R2-1, R3-5, Pr-4, R9-3)、(R1-6, R2-2, R3-1, Pr-1, R9-1)、(R1-6, R2-2, R3-1, Pr-1, R9-2)、(R1-6, R2-2, R3-1, Pr-1, R9-3)、(R1-6, R2-2, R3-1, Pr-2, R9-1)、(R1-6, R2-2, R3-1, Pr-2, R9-2)、(R1-6, R2-2, R3-1, Pr-2, R9-3)、(R1-6, R2-2, R3-1, Pr-3, R9-1)、(R1-6, R2-2, R3-1, Pr-3, R9-2)、(R1-6, R2-2, R3-1, Pr-3, R9-3)、(R1-6, R2-2, R3-1, Pr-4, R9-1)、(R1-6, R2-2, R3-1, Pr-4, R9-2)、(R1-6, R2-2, R3-1, Pr-4, R9-3)、(R1-6, R2-2, R3-2, Pr-1, R9-1)、(R1-6, R2-2, R3-2, Pr-1, R9-2)、(R1-6, R2-2, R3-2, Pr-1, R9-3)、(R1-6, R2-2, R3-2, Pr-2, R9-1)、(R1-6, R2-2, R3-2, Pr-2, R9-2)、(R1-6, R2-2, R3-2, Pr-2, R9-3)、(R1-6, R2-2, R3-2, Pr-3, R9-1)、(R1-6, R2-2, R3-2, Pr-3, R9-2)、(R1-6, R2-2, R3-2, Pr-3, R9-3)、(R1-6, R2-2, R3-2, Pr-4, R9-1)、(R1-6, R2-2, R3-2, Pr-4, R9-2)、(R1-6, R2-2, R3-2, Pr-4, R9-3)、(R1-6, R2-2, R3-3, Pr-1, R9-1)、(R1-6, R2-2, R3-3, Pr-1, R9-2)、(R1-6, R2-2, R3-3, Pr-1, R9-3)、(R1-6, R2-2, R3-3, Pr-2, R9-1)、(R1-6, R2-2, R3-3, Pr-2, R9-2)、(R1-6, R2-2, R3-3, Pr-2, R9-3)、(R1-6, R2-2, R3-3, Pr-3, R9-1)、(R1-6, R2-2, R3-3, Pr-3, R9-2)、(R1-6, R2-2, R3-3, Pr-3, R9-3)、(R1-6, R2-2, R3-3, Pr-4, R9-1)、(R1-6, R2-2, R3-3, Pr-4, R9-2)、(R1-6, R2-2, R3-3, Pr-4, R9-3)、(R1-6, R2-2, R3-4, Pr-1, R9-1)、(R1-6, R2-2, R3-4, Pr-1, R9-2)、(R1-6, R2-2, R3-4, Pr-1, R9-3)、(R1-6, R2-2, R3-4, Pr-2, R9-1)、(R1-6, R2-2, R3-4, Pr-2, R9-2)、(R1-6, R2-2, R3-4, Pr-2, R9-3)、(R1-6, R2-2, R3-4, Pr-3, R9-1)、(R1-6, R2-2, R3-4, Pr-3, R9-2)、(R1-6, R2-2, R3-4, Pr-3, R9-3)、(R1-6, R2-2, R3-4, Pr-4, R9-1)、(R1-6, R2-2, R3-4, Pr-4, R9-2)、(R1-6, R2-2, R3-4, Pr-4, R9-3)、

R9-2)、(R1-6, R2-2, R3-4, Pr-4, R9-3)、(R1-6, R2-2, R3-5, Pr-1, R9-1)、(R1-6, R2-2, R3-5, Pr-1, R9-2)、(R1-6, R2-2, R3-5, Pr-1, R9-3)、(R1-6, R2-2, R3-5, Pr-2, R9-1)、(R1-6, R2-2, R3-5, Pr-2, R9-2)、(R1-6, R2-2, R3-5, Pr-2, R9-3)、(R1-6, R2-2, R3-5, Pr-3, R9-1)、(R1-6, R2-2, R3-5, Pr-3, R9-2)、(R1-6, R2-2, R3-5, Pr-3, R9-3)、(R1-6, R2-2, R3-5, Pr-4, R9-1)、(R1-6, R2-2, R3-5, Pr-4, R9-2)、(R1-6, R2-2, R3-5, Pr-4, R9-3)、

[0223]

(R1-7, R2-1, R3-1, Pr-1, R9-1)、(R1-7, R2-1, R3-1, Pr-1, R9-2)、(R1-7, R2-1, R3-1, Pr-1, R9-3)、(R1-7, R2-1, R3-1, Pr-2, R9-1)、(R1-7, R2-1, R3-1, Pr-2, R9-2)、(R1-7, R2-1, R3-1, Pr-2, R9-3)、(R1-7, R2-1, R3-1, Pr-3, R9-1)、(R1-7, R2-1, R3-1, Pr-3, R9-2)、(R1-7, R2-1, R3-1, Pr-3, R9-3)、(R1-7, R2-1, R3-1, Pr-4, R9-1)、(R1-7, R2-1, R3-1, Pr-4, R9-2)、(R1-7, R2-1, R3-1, Pr-4, R9-3)、(R1-7, R2-1, R3-2, Pr-1, R9-1)、(R1-7, R2-1, R3-2, Pr-1, R9-2)、(R1-7, R2-1, R3-2, Pr-1, R9-3)、(R1-7, R2-1, R3-2, Pr-2, R9-1)、(R1-7, R2-1, R3-2, Pr-2, R9-2)、(R1-7, R2-1, R3-2, Pr-2, R9-3)、(R1-7, R2-1, R3-2, Pr-3, R9-1)、(R1-7, R2-1, R3-2, Pr-3, R9-2)、(R1-7, R2-1, R3-2, Pr-3, R9-3)、(R1-7, R2-1, R3-2, Pr-4, R9-1)、(R1-7, R2-1, R3-2, Pr-4, R9-2)、(R1-7, R2-1, R3-2, Pr-4, R9-3)、(R1-7, R2-1, R3-3, Pr-1, R9-1)、(R1-7, R2-1, R3-3, Pr-1, R9-2)、(R1-7, R2-1, R3-3, Pr-1, R9-3)、(R1-7, R2-1, R3-3, Pr-2, R9-1)、(R1-7, R2-1, R3-3, Pr-2, R9-2)、(R1-7, R2-1, R3-3, Pr-2, R9-3)、(R1-7, R2-1, R3-3, Pr-3, R9-1)、(R1-7, R2-1, R3-3, Pr-3, R9-2)、(R1-7, R2-1, R3-3, Pr-3, R9-3)、(R1-7, R2-1, R3-3, Pr-4, R9-1)、(R1-7, R2-1, R3-3, Pr-4, R9-2)、(R1-7, R2-1, R3-3, Pr-4, R9-3)、(R1-7, R2-1, R3-4, Pr-1, R9-1)、(R1-7, R2-1, R3-4, Pr-1, R9-2)、(R1-7, R2-1, R3-4, Pr-1, R9-3)、(R1-7, R2-1, R3-4, Pr-2, R9-1)、(R1-7, R2-1, R3-4, Pr-2, R9-2)、(R1-7, R2-1, R3-4, Pr-2, R9-3)、(R1-7, R2-1, R3-4, Pr-3, R9-1)、(R1-7, R2-1, R3-4, Pr-3, R9-2)、(R1-7, R2-1, R3-4, Pr-3, R9-3)、(R1-7, R2-1, R3-4, Pr-4, R9-1)、(R1-7, R2-1, R3-4, Pr-4, R9-2)、(R1-7, R2-1, R3-4, Pr-4, R9-3)、(R1-7, R2-1, R3-5, Pr-1, R9-1)、(R1-7, R2-1, R3-5, Pr-1, R9-2)、(R1-7, R2-1, R3-5, Pr-1,

R9-3)、(R1-7, R2-1, R3-5, Pr-2, R9-1)、(R1-7, R2-1, R3-5, Pr-2, R9-2)、(R1-7, R2-1,  
 R3-5, Pr-2, R9-3)、(R1-7, R2-1, R3-5, Pr-3, R9-1)、(R1-7, R2-1, R3-5, Pr-3, R9-2)、  
 (R1-7, R2-1, R3-5, Pr-3, R9-3)、(R1-7, R2-1, R3-5, Pr-4, R9-1)、(R1-7, R2-1, R3-5, Pr-4,  
 R9-2)、(R1-7, R2-1, R3-5, Pr-4, R9-3)、(R1-7, R2-2, R3-1, Pr-1, R9-1)、(R1-7, R2-2,  
 R3-1, Pr-1, R9-2)、(R1-7, R2-2, R3-1, Pr-1, R9-3)、(R1-7, R2-2, R3-1, Pr-2, R9-1)、  
 (R1-7, R2-2, R3-1, Pr-2, R9-2)、(R1-7, R2-2, R3-1, Pr-2, R9-3)、(R1-7, R2-2, R3-1, Pr-3,  
 R9-1)、(R1-7, R2-2, R3-1, Pr-3, R9-2)、(R1-7, R2-2, R3-1, Pr-3, R9-3)、(R1-7, R2-2,  
 R3-1, Pr-4, R9-1)、(R1-7, R2-2, R3-1, Pr-4, R9-2)、(R1-7, R2-2, R3-1, Pr-4, R9-3)、  
 (R1-7, R2-2, R3-2, Pr-1, R9-1)、(R1-7, R2-2, R3-2, Pr-1, R9-2)、(R1-7, R2-2, R3-2, Pr-1,  
 R9-3)、(R1-7, R2-2, R3-2, Pr-2, R9-1)、(R1-7, R2-2, R3-2, Pr-2, R9-2)、(R1-7, R2-2,  
 R3-2, Pr-2, R9-3)、(R1-7, R2-2, R3-2, Pr-3, R9-1)、(R1-7, R2-2, R3-2, Pr-3, R9-2)、  
 (R1-7, R2-2, R3-2, Pr-3, R9-3)、(R1-7, R2-2, R3-2, Pr-4, R9-1)、(R1-7, R2-2, R3-2, Pr-4,  
 R9-2)、(R1-7, R2-2, R3-2, Pr-4, R9-3)、(R1-7, R2-2, R3-3, Pr-1, R9-1)、(R1-7, R2-2,  
 R3-3, Pr-1, R9-2)、(R1-7, R2-2, R3-3, Pr-1, R9-3)、(R1-7, R2-2, R3-3, Pr-2, R9-1)、  
 (R1-7, R2-2, R3-3, Pr-2, R9-2)、(R1-7, R2-2, R3-3, Pr-2, R9-3)、(R1-7, R2-2, R3-3, Pr-3,  
 R9-1)、(R1-7, R2-2, R3-3, Pr-3, R9-2)、(R1-7, R2-2, R3-3, Pr-3, R9-3)、(R1-7, R2-2,  
 R3-3, Pr-4, R9-1)、(R1-7, R2-2, R3-3, Pr-4, R9-2)、(R1-7, R2-2, R3-3, Pr-4, R9-3)、  
 (R1-7, R2-2, R3-4, Pr-1, R9-1)、(R1-7, R2-2, R3-4, Pr-1, R9-2)、(R1-7, R2-2, R3-4, Pr-1,  
 R9-3)、(R1-7, R2-2, R3-4, Pr-2, R9-1)、(R1-7, R2-2, R3-4, Pr-2, R9-2)、(R1-7, R2-2,  
 R3-4, Pr-2, R9-3)、(R1-7, R2-2, R3-4, Pr-3, R9-1)、(R1-7, R2-2, R3-4, Pr-3, R9-2)、  
 (R1-7, R2-2, R3-4, Pr-3, R9-3)、(R1-7, R2-2, R3-4, Pr-4, R9-1)、(R1-7, R2-2, R3-4, Pr-4,  
 R9-2)、(R1-7, R2-2, R3-4, Pr-4, R9-3)、(R1-7, R2-2, R3-5, Pr-1, R9-1)、(R1-7, R2-2,  
 R3-5, Pr-1, R9-2)、(R1-7, R2-2, R3-5, Pr-1, R9-3)、(R1-7, R2-2, R3-5, Pr-2, R9-1)、  
 (R1-7, R2-2, R3-5, Pr-2, R9-2)、(R1-7, R2-2, R3-5, Pr-2, R9-3)、(R1-7, R2-2, R3-5, Pr-3,  
 R9-1)、(R1-7, R2-2, R3-5, Pr-3, R9-2)、(R1-7, R2-2, R3-5, Pr-3, R9-3)、(R1-7, R2-2,

R3-5, Pr-4, R9-1)、(R1-7, R2-2, R3-5, Pr-4, R9-2)、(R1-7, R2-2, R3-5, Pr-4, R9-3)、

[0224]

(R1-8, R2-1, R3-1, Pr-1, R9-1)、(R1-8, R2-1, R3-1, Pr-1, R9-2)、(R1-8, R2-1, R3-1, Pr-1, R9-3)、(R1-8, R2-1, R3-1, Pr-2, R9-1)、(R1-8, R2-1, R3-1, Pr-2, R9-2)、(R1-8, R2-1, R3-1, Pr-2, R9-3)、(R1-8, R2-1, R3-1, Pr-3, R9-1)、(R1-8, R2-1, R3-1, Pr-3, R9-2)、(R1-8, R2-1, R3-1, Pr-3, R9-3)、(R1-8, R2-1, R3-1, Pr-4, R9-1)、(R1-8, R2-1, R3-1, Pr-4, R9-2)、(R1-8, R2-1, R3-1, Pr-4, R9-3)、(R1-8, R2-1, R3-2, Pr-1, R9-1)、(R1-8, R2-1, R3-2, Pr-1, R9-2)、(R1-8, R2-1, R3-2, Pr-1, R9-3)、(R1-8, R2-1, R3-2, Pr-2, R9-1)、(R1-8, R2-1, R3-2, Pr-2, R9-2)、(R1-8, R2-1, R3-2, Pr-2, R9-3)、(R1-8, R2-1, R3-2, Pr-3, R9-1)、(R1-8, R2-1, R3-2, Pr-3, R9-2)、(R1-8, R2-1, R3-2, Pr-3, R9-3)、(R1-8, R2-1, R3-2, Pr-4, R9-1)、(R1-8, R2-1, R3-2, Pr-4, R9-2)、(R1-8, R2-1, R3-2, Pr-4, R9-3)、(R1-8, R2-1, R3-3, Pr-1, R9-1)、(R1-8, R2-1, R3-3, Pr-1, R9-2)、(R1-8, R2-1, R3-3, Pr-1, R9-3)、(R1-8, R2-1, R3-3, Pr-2, R9-1)、(R1-8, R2-1, R3-3, Pr-2, R9-2)、(R1-8, R2-1, R3-3, Pr-2, R9-3)、(R1-8, R2-1, R3-3, Pr-3, R9-1)、(R1-8, R2-1, R3-3, Pr-3, R9-2)、(R1-8, R2-1, R3-3, Pr-3, R9-3)、(R1-8, R2-1, R3-3, Pr-4, R9-1)、(R1-8, R2-1, R3-3, Pr-4, R9-2)、(R1-8, R2-1, R3-3, Pr-4, R9-3)、(R1-8, R2-1, R3-4, Pr-1, R9-1)、(R1-8, R2-1, R3-4, Pr-1, R9-2)、(R1-8, R2-1, R3-4, Pr-1, R9-3)、(R1-8, R2-1, R3-4, Pr-2, R9-1)、(R1-8, R2-1, R3-4, Pr-2, R9-2)、(R1-8, R2-1, R3-4, Pr-2, R9-3)、(R1-8, R2-1, R3-4, Pr-3, R9-1)、(R1-8, R2-1, R3-4, Pr-3, R9-2)、(R1-8, R2-1, R3-4, Pr-3, R9-3)、(R1-8, R2-1, R3-4, Pr-4, R9-1)、(R1-8, R2-1, R3-4, Pr-4, R9-2)、(R1-8, R2-1, R3-4, Pr-4, R9-3)、(R1-8, R2-1, R3-5, Pr-1, R9-1)、(R1-8, R2-1, R3-5, Pr-1, R9-2)、(R1-8, R2-1, R3-5, Pr-1, R9-3)、(R1-8, R2-1, R3-5, Pr-2, R9-1)、(R1-8, R2-1, R3-5, Pr-2, R9-2)、(R1-8, R2-1, R3-5, Pr-2, R9-3)、(R1-8, R2-1, R3-5, Pr-3, R9-1)、(R1-8, R2-1, R3-5, Pr-3, R9-2)、(R1-8, R2-1, R3-5, Pr-3, R9-3)、(R1-8, R2-1, R3-5, Pr-4, R9-1)、(R1-8, R2-1, R3-5, Pr-4, R9-2)、(R1-8, R2-1, R3-5, Pr-4, R9-3)、(R1-8, R2-2, R3-1, Pr-1, R9-1)、(R1-8, R2-2,

R3-1, Pr-1, R9-2)、(R1-8, R2-2, R3-1, Pr-1, R9-3)、(R1-8, R2-2, R3-1, Pr-2, R9-1)、  
 (R1-8, R2-2, R3-1, Pr-2, R9-2)、(R1-8, R2-2, R3-1, Pr-2, R9-3)、(R1-8, R2-2, R3-1, Pr-3,  
 R9-1)、(R1-8, R2-2, R3-1, Pr-3, R9-2)、(R1-8, R2-2, R3-1, Pr-3, R9-3)、(R1-8, R2-2,  
 R3-1, Pr-4, R9-1)、(R1-8, R2-2, R3-1, Pr-4, R9-2)、(R1-8, R2-2, R3-1, Pr-4, R9-3)、  
 (R1-8, R2-2, R3-2, Pr-1, R9-1)、(R1-8, R2-2, R3-2, Pr-1, R9-2)、(R1-8, R2-2, R3-2, Pr-1,  
 R9-3)、(R1-8, R2-2, R3-2, Pr-2, R9-1)、(R1-8, R2-2, R3-2, Pr-2, R9-2)、(R1-8, R2-2,  
 R3-2, Pr-2, R9-3)、(R1-8, R2-2, R3-2, Pr-3, R9-1)、(R1-8, R2-2, R3-2, Pr-3, R9-2)、  
 (R1-8, R2-2, R3-2, Pr-3, R9-3)、(R1-8, R2-2, R3-2, Pr-4, R9-1)、(R1-8, R2-2, R3-2, Pr-4,  
 R9-2)、(R1-8, R2-2, R3-2, Pr-4, R9-3)、(R1-8, R2-2, R3-3, Pr-1, R9-1)、(R1-8, R2-2,  
 R3-3, Pr-1, R9-2)、(R1-8, R2-2, R3-3, Pr-1, R9-3)、(R1-8, R2-2, R3-3, Pr-2, R9-1)、  
 (R1-8, R2-2, R3-3, Pr-2, R9-2)、(R1-8, R2-2, R3-3, Pr-2, R9-3)、(R1-8, R2-2, R3-3, Pr-3,  
 R9-1)、(R1-8, R2-2, R3-3, Pr-3, R9-2)、(R1-8, R2-2, R3-3, Pr-3, R9-3)、(R1-8, R2-2,  
 R3-3, Pr-4, R9-1)、(R1-8, R2-2, R3-3, Pr-4, R9-2)、(R1-8, R2-2, R3-3, Pr-4, R9-3)、  
 (R1-8, R2-2, R3-4, Pr-1, R9-1)、(R1-8, R2-2, R3-4, Pr-1, R9-2)、(R1-8, R2-2, R3-4, Pr-1,  
 R9-3)、(R1-8, R2-2, R3-4, Pr-2, R9-1)、(R1-8, R2-2, R3-4, Pr-2, R9-2)、(R1-8, R2-2,  
 R3-4, Pr-2, R9-3)、(R1-8, R2-2, R3-4, Pr-3, R9-1)、(R1-8, R2-2, R3-4, Pr-3, R9-2)、  
 (R1-8, R2-2, R3-4, Pr-3, R9-3)、(R1-8, R2-2, R3-4, Pr-4, R9-1)、(R1-8, R2-2, R3-4, Pr-4,  
 R9-2)、(R1-8, R2-2, R3-4, Pr-4, R9-3)、(R1-8, R2-2, R3-5, Pr-1, R9-1)、(R1-8, R2-2,  
 R3-5, Pr-1, R9-2)、(R1-8, R2-2, R3-5, Pr-1, R9-3)、(R1-8, R2-2, R3-5, Pr-2, R9-1)、  
 (R1-8, R2-2, R3-5, Pr-2, R9-2)、(R1-8, R2-2, R3-5, Pr-2, R9-3)、(R1-8, R2-2, R3-5, Pr-3,  
 R9-1)、(R1-8, R2-2, R3-5, Pr-3, R9-2)、(R1-8, R2-2, R3-5, Pr-3, R9-3)、(R1-8, R2-2,  
 R3-5, Pr-4, R9-1)、(R1-8, R2-2, R3-5, Pr-4, R9-2)、(R1-8, R2-2, R3-5, Pr-4, R9-3)。

[0225]

(Method for producing compound of the present invention)

A general method for producing the compound of the present invention will be

exemplified below. And, as extraction and purification, treatment which is performed in a normal experiment of organic chemistry may be conducted.

Synthesis of the compound of the present invention can be carried out referring to the procedures known in the art.

[0226]

As a raw material compound, commercially available compounds, compounds described in the present description, compounds described in the references cited in the present description, and other known compounds can be utilized.

Among the compounds of the present invention, there are compounds in which a tautomer can be present, and the present invention includes all possible isomers and a mixture thereof, including them.

When one wants to obtain a salt of the compound of the present invention, in the case where the compound of the present invention is obtained in a form of a salt, it may be purified as it is and, in the case where the compound of the present invention is obtained in a free form, a salt may be formed by a normal method by dissolving or suspending the compound in a suitable organic solvent, and adding an acid or a base.

In addition, the compound of the present invention and a pharmaceutically acceptable salt thereof are present in a form of adducts with water or various solvents (hydrate or solvate) in some cases, and these adducts are included in the present invention.

[0227]

In a general synthesis method as well as Reference examples, Examples, and Intermediate Synthesis Examples, the meaning of each abbreviation is as follows.

DMF: N,N-dimethylformamide

DMA: N,N-dimethylacetamide,

NMP: N-methylpyrrolidone

DMI: dimethylimidazolidinone

THF: tetrahydrofuran

Ms: methanesulfonyl

Ts: paratoluenesulfonyl

Boc: tert-butoxycarbonyl

DIBALH: diisobutylaluminum hydride

WSC or EDCI: N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide

HOBt: 1-hydroxybenzotriazole

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

NBS: N-bromosuccinimide

NCS: N-chlorosuccinimide

TEMPO: 2,2,6,6-tetramethylpiperidine-1-oxyl radical

PDC: pyridinium dichloromate

DEAD: diethyl azodicarboxylate

DIAD: diisopropyl azodicarboxylate

DMAP: 4-dimethylaminopyridine

mCPBA: m-chloroperbenzoic acid

DBU: 1,8-diazabicyclo[5.4.0]-7-undecene

DIPEA: diisopropylethylamine

TBAF: tetrabutylammonium fluoride

IBX: 2-iodoxybenzoic acid

DMSO: dimethyl sulfoxide

NaHMDS: sodium hexamethyldisilazide

TFA: trifluoroacetic acid

Ac: acetyl

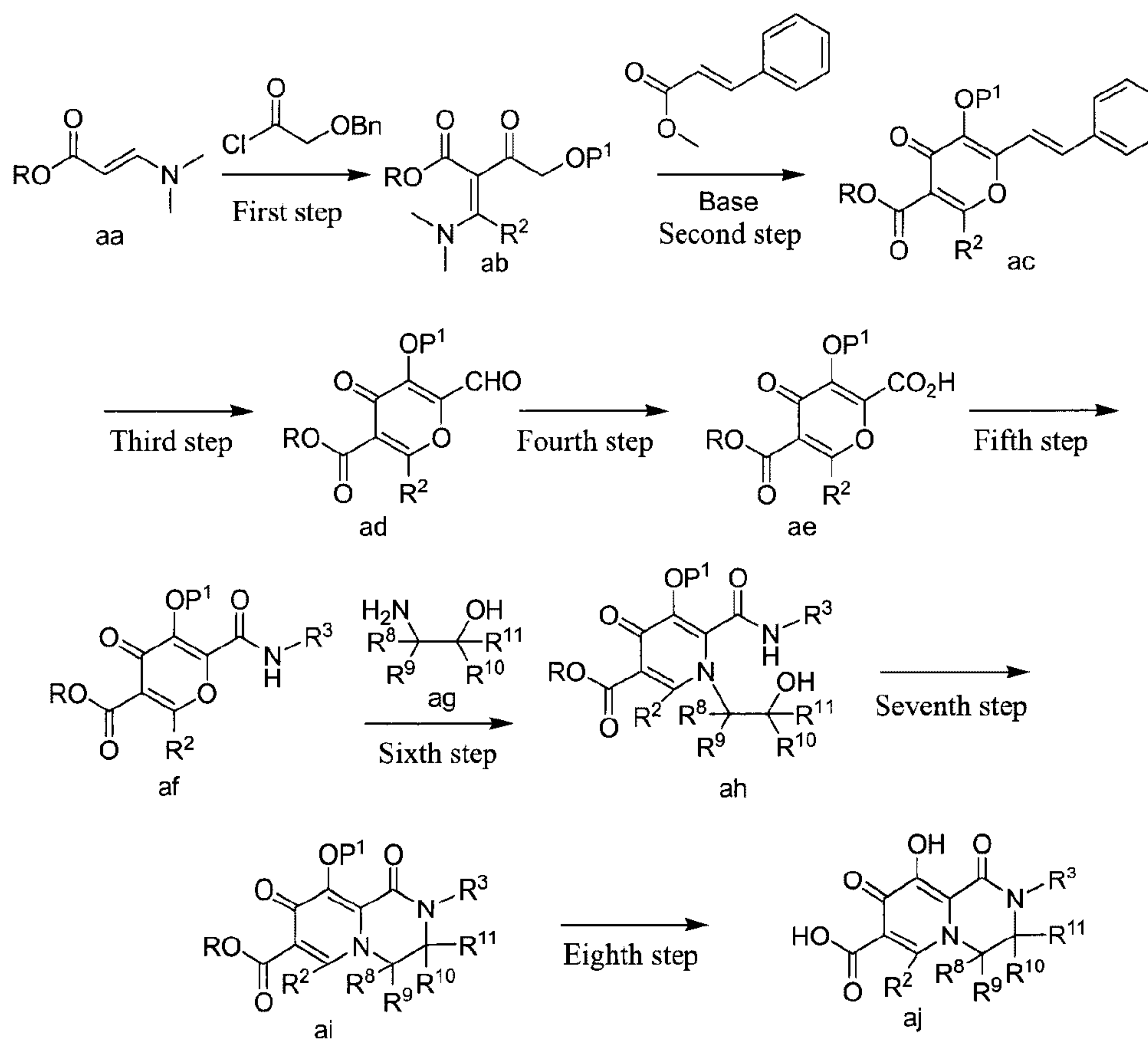
TBS: tert-butyldimethylsilyl

PEPPSI<sup>TM</sup>-IPr: (1,3-diisopropylimidazol-2-ylidene)(3-chloropyridyl)palladium(II)  
dichloride

BEMP: 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine  
[0228]

Synthesis of compound aj of Reference example (see: Reference example 1)

[Chemical formula 54]



[0229]

(wherein R is carboxy protective group, P<sup>1</sup> is hydroxyl protective group, R<sup>2</sup>, R<sup>3</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> and R<sup>11</sup> are same as R<sup>2a</sup>, R<sup>3a</sup>, R<sup>8a</sup>, R<sup>9a</sup>, R<sup>10a</sup> and R<sup>11a</sup> in item 1, respectively, R and P<sup>1</sup> may be a group which can be protected and/or deprotected by the method described in Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) etc. and, for example, R is lower alkyl etc., and P<sup>1</sup> is arylalkyl etc.)

First step

A compound ab can be obtained by reacting a compound aa which is commercially available or can be prepared by the known method at -20°C to 30°C, preferably 0°C to 20°C for 0.1 hours to 24 hours, preferably 0.5 hours to 12 hours in a solvent such as dichloromethane, toluene, THF etc. or a mixed solvent thereof, by adding dropwise tertiary amine such as pyridine, trimethylamine, N-methylmorpholine, 4-dimethylaminopyridine etc. and benzyloxyacetyl chloride.

Second step

A compound ac can be obtained by adding an organometallic base such as lithium hexamethyldisilazane, lithium diisopropylamide, butyllithium, tert-butyllithium etc. to the compound ab in a solvent such as ether, dichloromethane, THF etc. or a mixed solvent thereof, in the presence of cinnamoyl chloride, and performing a reaction at -80°C to 0°C, preferably -80°C to -40°C for 1 minute to 2 hours, preferably 10 minutes to 1 hour.

Third step

A compound ad can be obtained by adding a catalytic amount of an oxidizing agent such as ruthenium chloride and sodium periodate, TEMPO, manganese dioxide, as well as PDC etc. to the compound ac in a solvent such as ether, dichloromethane, THF, acetonitrile etc. or a mixed solvent thereof, and performing a reaction at -40°C to

80°C, preferably 0°C to 40°C for 0.1 hours to 24 hours, preferably 0.2 hours to 3 hours.

#### Fourth step

Concentrated sulfuric acid and an aqueous solution of amidosululic acid are added to the compound ad at 0°C to 60°C, preferably 10°C to 40°C in the presence of a solvent such as ether, dichloromethane, THF, acetonitrile, acetone, water etc. or in a mixed solvent thereof. An aqueous sodium chlorite solution is added dropwise thereto at the same temperature to perform a reaction for 1 minute to 3 hours, preferably 5 minutes to 1 hour, thereby, a compound ae can be obtained.

#### Fifth step

A compound af can be obtained by adding a compound R<sup>3</sup>-NH<sub>2</sub> having a substituent corresponding to an objective compound to the compound ae in a solvent such as DMF, THF, dichloromethane, acetonitrile etc. in the presence of a dehydration-condensation agent such as dicyclohexylcarbodiimide, carbonyldiimidazole, dicyclohexylcarbodiimido-N-hydroxybenzotriazole, 4-(4,6-dimethoxy-1,3,5,-triazin-2-yl)-4-methylmorpholinium chloride, hexafluorophosphoric acid 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium, WSC·HCl, HATU etc., and performing a reaction at -20°C to 60°C, preferably -10°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

#### Sixth step

A compound ah can be obtained by adding a compound ag to the compound af in the presence of a solvent such as toluene, xylene, THF, dioxane etc. or in a mixed solvent thereof, and performing a reaction for 0.1 hours to 12 hours, preferably 0.2 hours to 6 hours under the heat-refluxing condition.

#### Seventh step

A compound ai can be obtained by adding triphenylphosphine and a

condensation agent such as DEAD, DIAD etc. to the compound ah in the presence of a solvent such as THF, dioxane, ethyl acetate, acetonitrile etc. or in a mixed solvent thereof, and performing a reaction at 0°C to 60°C, preferably 10°C to 40°C for 0.1 hours to 12 hours, preferably 0.2 hours to 6 hours.

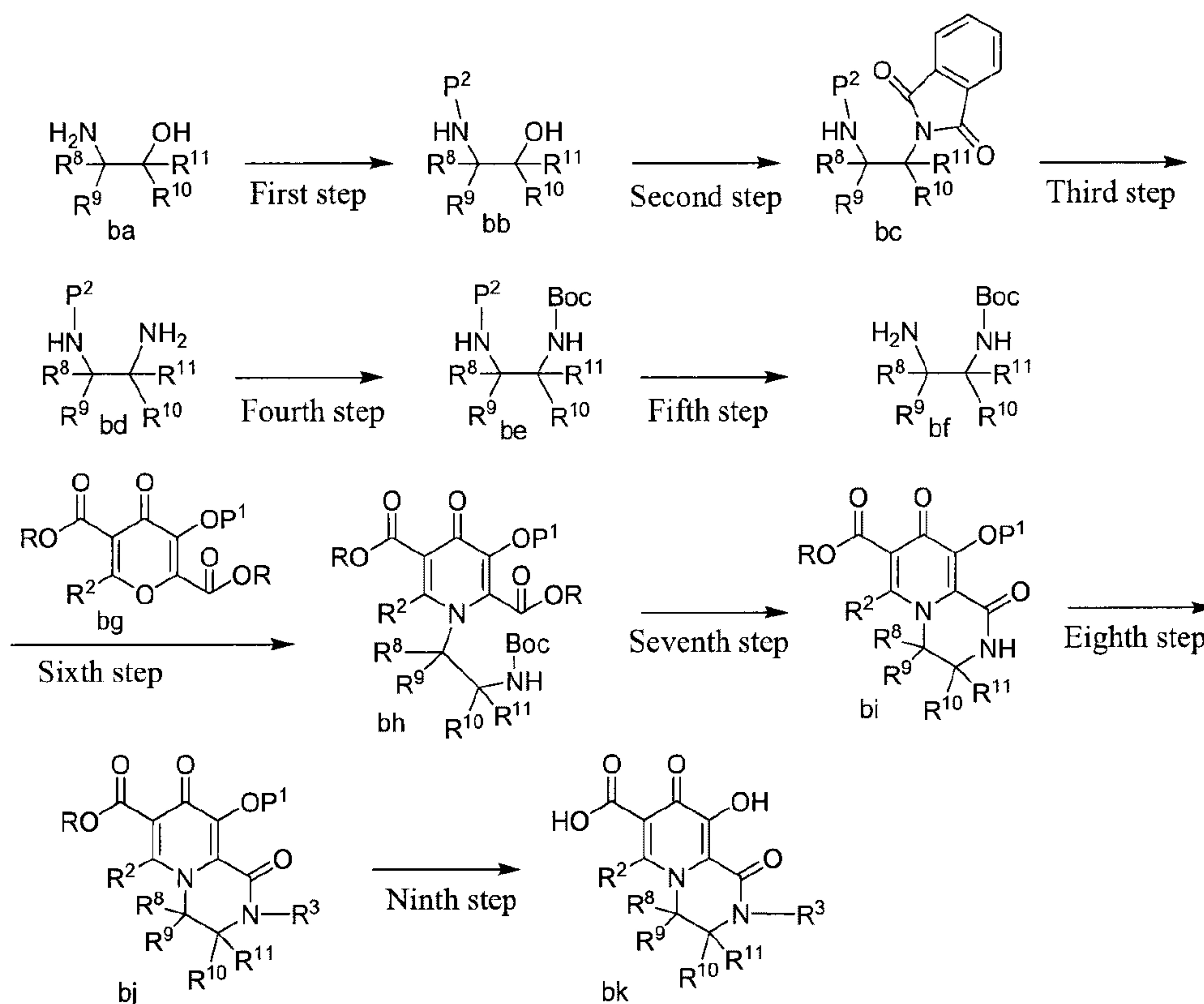
#### Eighth step

By subjecting the compound ai to the known general deprotecting reaction of a carboxyl protective group and a hydroxyl protective group, a compound aj can be obtained.

[0230]

Synthesis of compound bk of Reference example (see: Reference example 12)

[Chemical formula 55]



[0231]

(wherein  $P^2$  is amino protective group,  $P^2$  may be a group which can be protected and/or deprotected by the method described in Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) etc. and, for example,  $P^2$  is arylalkyloxycarbonyl, lower alkyloxycarbonyl, etc. Other each symbol is same as above. )

First step

A compound **bb** can be obtained by adding a base such as potassium carbonate, sodium carbonate, cesium carbonate etc. and a compound  $P^2$ -L (wherein L is a leaving

group such as halogen, OMs etc.) having a substituent corresponding to an objective compound to a compound ba in the presence of a solvent such as DMF, THF, dioxane, acetonitrile etc. or in a mixed solvent thereof, and performing a reaction at -20°C to 80°C, preferably 0°C to 50°C for 0.1 hours to 6 hours, preferably 0.2 hours to 6 hours.

#### Second step

A compound bc can be obtained by adding triphenylphosphine and phthalimide to the compound bb in the presence of a solvent such as DMF, THF, dioxane, acetonitrile etc. or in a mixed solvent thereof, adding a dehydration-condensation reagent such as DIAD, DEAD etc., and performing a reaction at -10°C to 60°C, preferably 0°C to 50°C for 0.1 hours to 24 hours, preferably 0.2 hours to 12 hours.

#### Third step

A compound bd can be obtained by adding hydrazine hydrate or methylhydrazine to the compound bc in the presence of a solvent such as methanol, THF, dioxane, acetonitrile, etc. or in a mixed solvent thereof, and performing a reaction at -10°C to 80°C, preferably 10°C to 60°C for 0.5 hours to 24 hours, preferably 1 to 12 hours.

#### Fourth step

A compound be can be obtained by adding Boc<sub>2</sub>O to the compound bd in the presence of a solvent such as THF, dioxane, acetonitrile etc. or in a mixed solvent thereof, and performing a reaction at -10°C to 80°C, preferably 10°C to 60°C for 0.5 hours to 24 hours, preferably 1 to 12 hours.

#### Fifth step

A compound bf can be obtained by subjecting the compound be to the known general deprotecting reaction of an amino protective group.

#### Sixth step

A compound bh can be obtained by adding a compound bg to the compound bf in the presence of a solvent such as toluene, THF, dioxane, acetonitrile etc. or in a mixed solvent thereof, and performing a reaction at 20°C to 110°C, preferably 40°C to under heat-refluxing for 0.5 hours to 24 hours, preferably 1 hour to 12 hours.

#### Seventh step

HCl-ethyl acetate, HCl-dioxane, formic acid etc. is added to the compound bh, and they are reacted at 0°C to 40°C, preferably 0°C to 20°C for 0.5 hours to 12 hours, preferably 1 hour to 6 hours. After the solvent is distilled off under reduced pressure, an aqueous saturated sodium bicarbonate solution is added, and the mixture is stirred, thereby, a compound bi can be obtained.

#### Eighth step

A compound bj can be obtained by adding a base such as potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate etc. and a compound R<sup>3</sup>-L (L is a leaving group such as halogen, OMs etc.) to the compound bi in the presence of a solvent such as DMF, THF, DMA, NMP etc. or in a mixed solvent thereof, and performing a reaction at 0°C to 60°C, preferably 10°C to 30°C for 0.5 hours to 12 hours, preferably 1 hour to 6 hours.

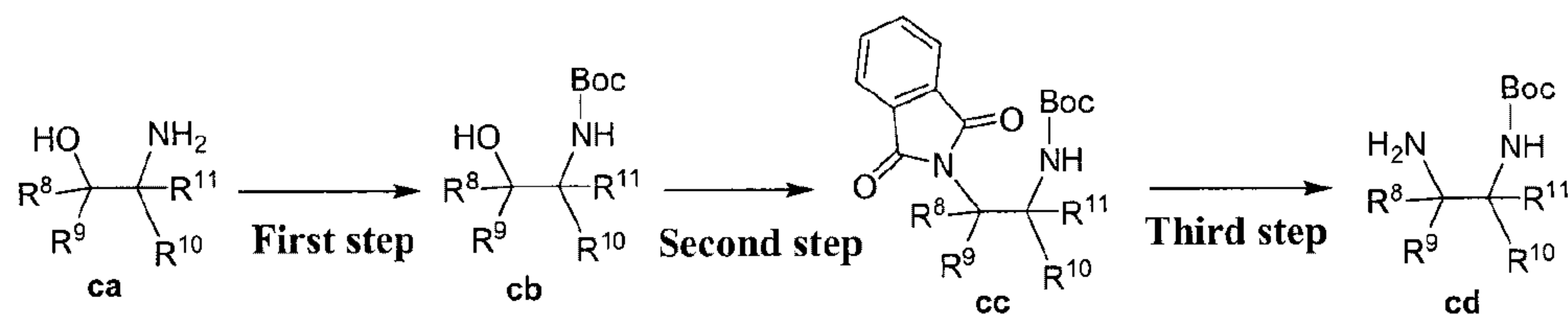
#### Ninth step

A compound bk can be obtained by subjecting the compound bj to the known general deprotecting reaction of a carboxyl protective group and a hydroxyl protective group.

[0232]

Synthesis of compound cd of Reference example (see: Reference examples 28 and 43)

[Chemical formula 56]



[0233]

(wherein each symbol is same as above)

**First step**

A compound **cb** can be obtained by adding tertiary amine such as triethylamine, DMAP, morpholine etc. or a base such as sodium carbonate, sodium bicarbonate etc. to a compound **ca** in the presence of a solvent such as THF, dioxane, acetonitrile, water etc. or in a mixed solvent thereof, adding  $\text{Boc}_2\text{O}$ , and performing a reaction at  $-10^\circ\text{C}$  to  $80^\circ\text{C}$ , preferably  $10^\circ\text{C}$  to  $60^\circ\text{C}$  for 0.5 hours to 24 hours, preferably 1 to 12 hours.

**Second step**

A compound **cc** can be obtained by adding triphenylphosphine and phthalimide to the compound **cb** in the presence of a solvent such as DMF, THF, dioxane, acetonitrile etc. or in a mixed solvent thereof, adding a dehydration-condensation reagent such as DIAD, DEAD etc., and performing a reaction at  $-10^\circ\text{C}$  to  $60^\circ\text{C}$ , preferably  $0^\circ\text{C}$  to  $50^\circ\text{C}$  for 0.1 hours to 24 hours, preferably 0.2 hours to 12 hours.

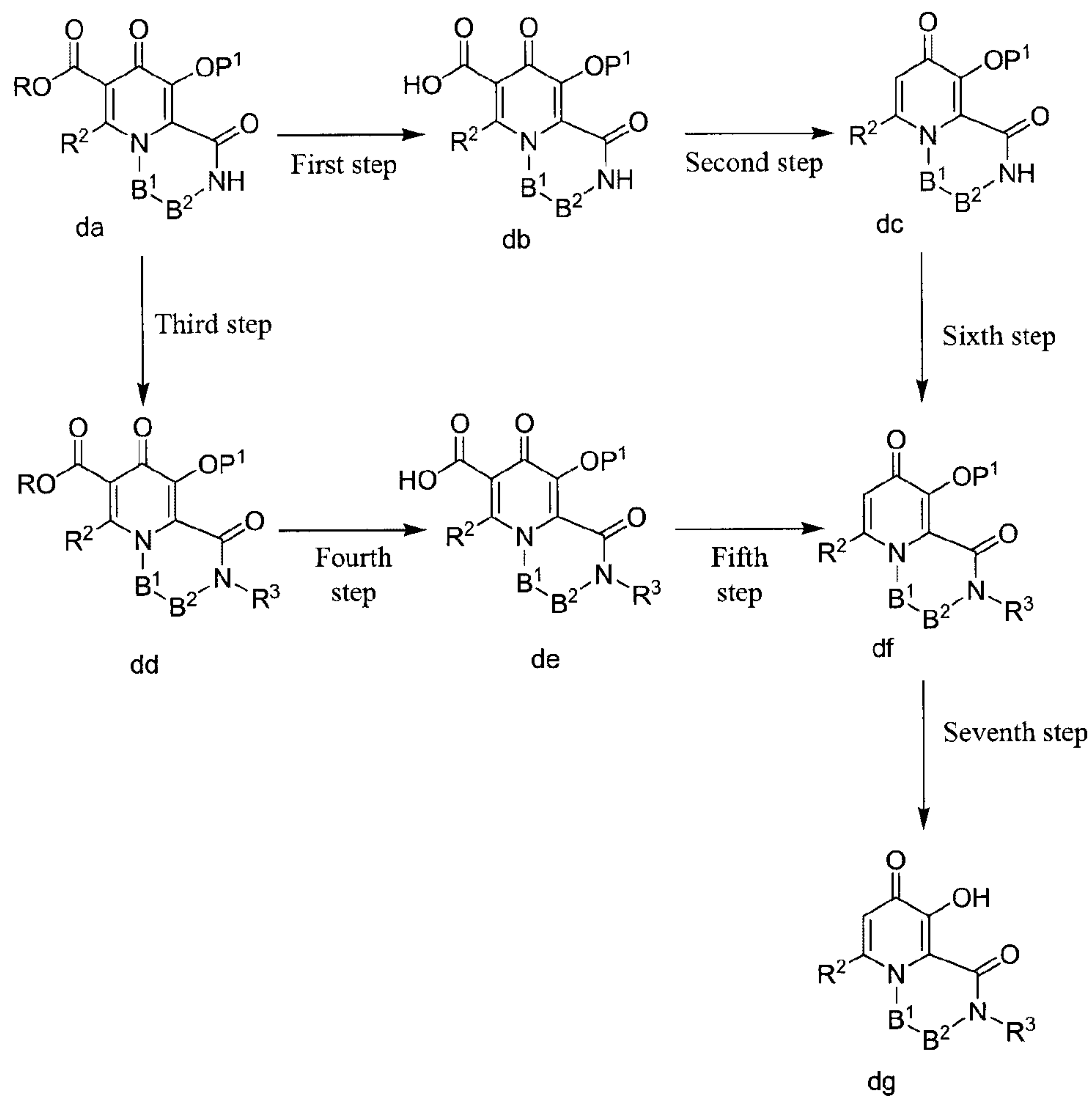
**Third step**

A compound **cd** can be obtained by adding hydrazine hydrate to the compound **cc** in the presence of a solvent such as methanol, THF, dioxane, acetonitrile etc. or in a mixed solvent thereof, and performing a reaction at  $-10^\circ\text{C}$  to  $80^\circ\text{C}$ , preferably  $10^\circ\text{C}$  to  $60^\circ\text{C}$  for 0.5 hours to 24 hours, preferably 1 to 12 hours.

[0234]

Synthesis of compound dg of Reference example (see: Reference examples 36, 41, and 46)

[Chemical formula 57]



[0235]

(wherein B<sup>1</sup> and B<sup>2</sup> are same as those of item 1, and other each symbol is same as above).

First step

A compound db can be obtained by subjecting the compound da obtained by

the same method as the synthesis method of bi to the known general carboxyl deprotecting reaction.

#### Second step

A decarbonized compound dc can be obtained by reacting the compound db for 1 minute to 2 hours under microwave irradiation in a solvent such as diphenyl ether etc. And, a decarbonized compound d can be obtained by adding copper in a quinoline solvent, and performing a reaction at 180°C for 2 to 48 hours.

#### Third step

A compound bd can be obtained by adding a base such as potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate etc. and a compound R<sup>3</sup>-L (L is a leaving group such as halogen, OMs etc.) to the compound da obtained by the method described in Reference example 12 in the presence of a solvent such as DMF, THF, DMA, NMP etc. or in a mixed solvent thereof, and performing a reaction at 0°C to 60°C, preferably 10°C to 30°C for 0.5 hours to 12 hours, preferably 1 hour to 6 hours.

#### Fourth step

A compound de can be obtained by the same method as that of the first step.

#### Fifth step

A compound df can be obtained by the same method as that of the second step.

#### Sixth step

A compound df can be obtained by the same method as that of the third step.

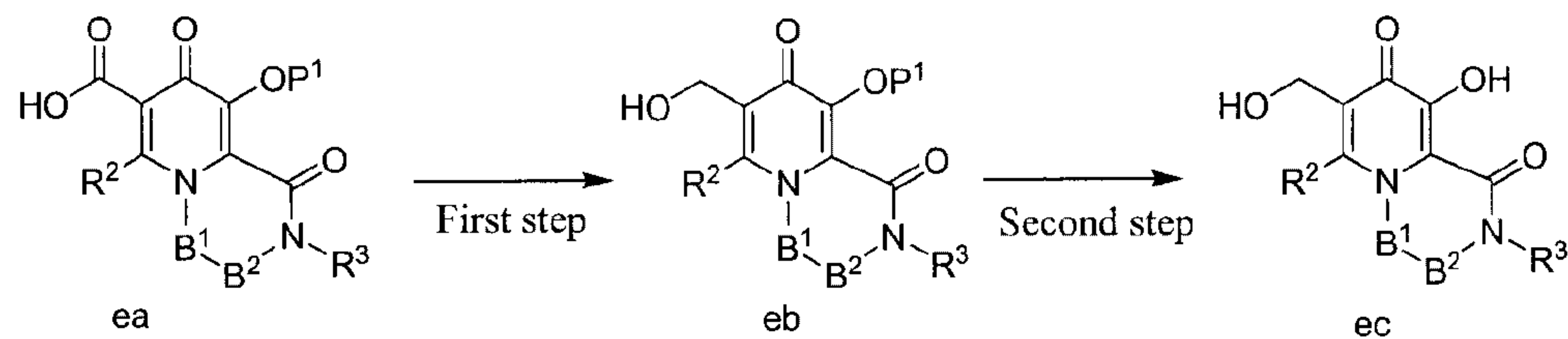
#### Seventh step

A compound dg can be obtained by subjecting the compound df to the known general hydroxyl group deprotecting reaction.

[0236]

Synthesis of compound ec of Reference example (see: Reference example 48)

[Chemical formula 58]



[0237]

(wherein each symbol is same as above)

First step

A base such as triethylamine, N-methylmorpholine, diisopropylethylamine etc. and ethyl chloroformate are added to a compound **ea** in the presence of a solvent such as THF, dioxane, dichloromethane, toluene etc. or in a mixed solvent thereof. A reducing agent having a low reducing power such as sodium borohydride etc. is added thereto, and a reaction is performed at  $-20^{\circ}\text{C}$  to  $60^{\circ}\text{C}$ , preferably  $-10^{\circ}\text{C}$  to  $20^{\circ}\text{C}$  for 0.2 hours to 12 hours, preferably 0.5 hours to 6 hours, thereby, a compound **eb** can be obtained.

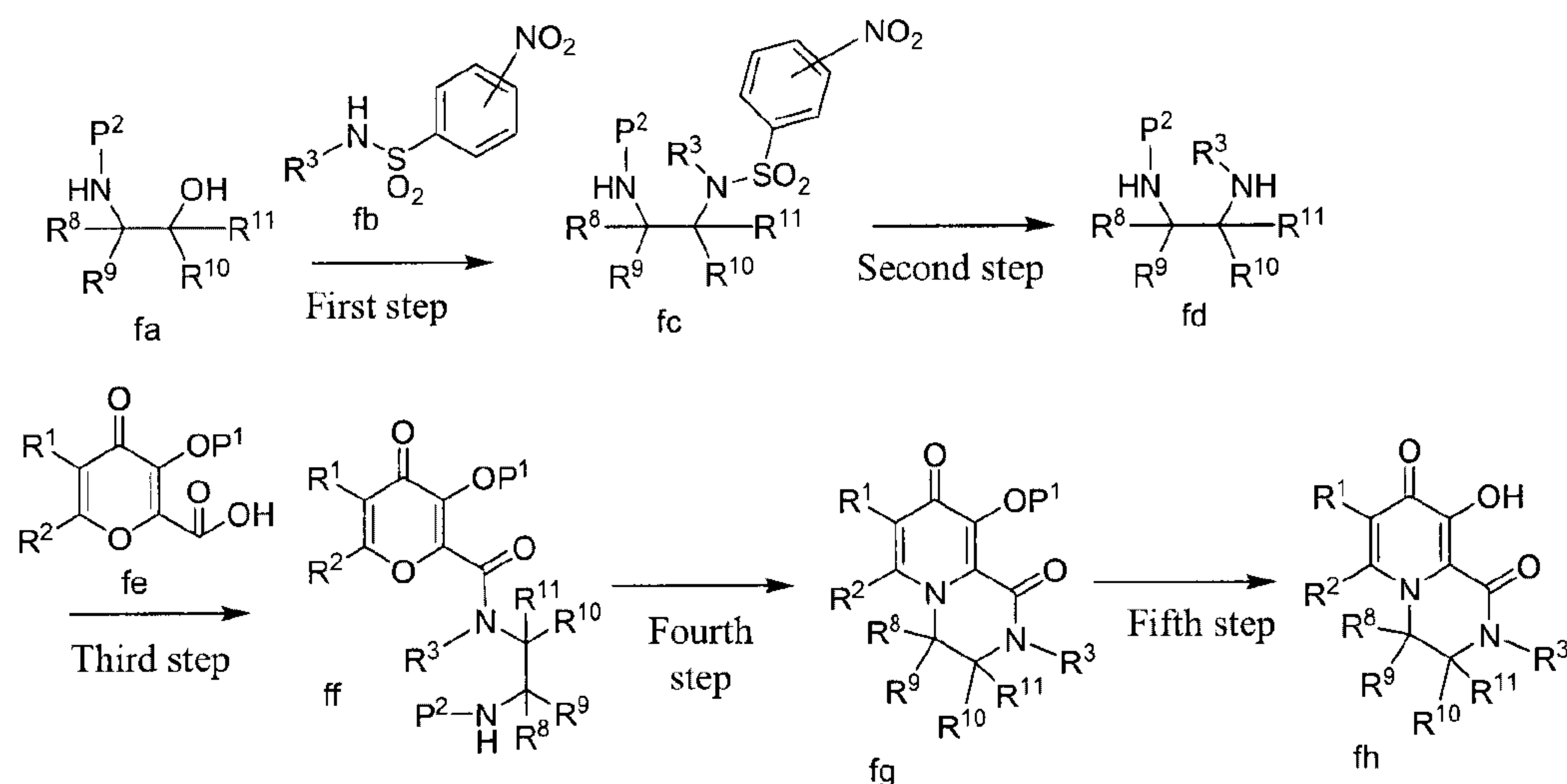
Second step

A compound **ec** can be obtained by subjecting the compound **eb** to the known general hydroxyl group deprotecting reaction.

[0238]

Synthesis of compound **fh** of Reference example (see: Reference example 50)

[Chemical formula 59]



[0239]

(wherein R<sup>1</sup> is a group corresponding to R<sup>1a</sup> in item 1, and other each symbol is same as above)

#### First step

A compound fb and triphenylphosphine are added to a compound fa in the presence of a solvent such as THF, dichloromethane, dioxane, acetonitrile etc. or in a mixed solvent thereof. DIAD is added thereto, and a reaction is performed at 0°C to 60°C, preferably 10°C to 30°C for 0.5 hours to 12 hours, preferably 1 hour to 12 hours, thereby, a compound fc can be obtained.

#### Second step

A compound fd can be obtained by adding a base such as potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate etc. and thiol such as benzenethiol etc. to the compound fc in the presence of a solvent such as THF, dioxane, acetonitrile etc. or in a mixed solvent thereof, and performing a reaction at 0°C to 60°C, preferably 10°C to 30°C for 0.5 hours to 12 hours, preferably 1 hour to 12 hours.

#### Third step

A compound ff can be obtained by adding a compound fe having a substituent corresponding to an objective compound to the compound fd in a solvent such as DMF, THF, dichloromethane, acetonitrile etc. in the presence of a dehydration-condensation agent such as dicyclohexylcarbodiimide, carbonyldiimidazole, dicyclohexylcarbodiimido-N-hydroxybenzotriazole, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, hexafluorophosphoric acid 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium, WSC·HCl etc., and performing a reaction at 0°C to 60°C, preferably 10°C to 40°C for 1 hour to 48 hours, preferably 2 hours to 24 hours.

#### Fourth step

A compound fd can be obtained by subjecting the compound ff to the known general deprotecting reaction concerning a P<sup>2</sup> group on an amino group, subsequently, adding a base such as an aqueous sodium carbonate solution, an aqueous potassium carbonate solution etc. in a solvent such as water, ethanol, methanol, acetonitrile etc. or in a mixed solvent thereof, and performing a reaction at 20°C to 80°C, preferably 20°C to 70°C for 0.5 hours to 24 hours, preferably 1 hour to 6 hours.

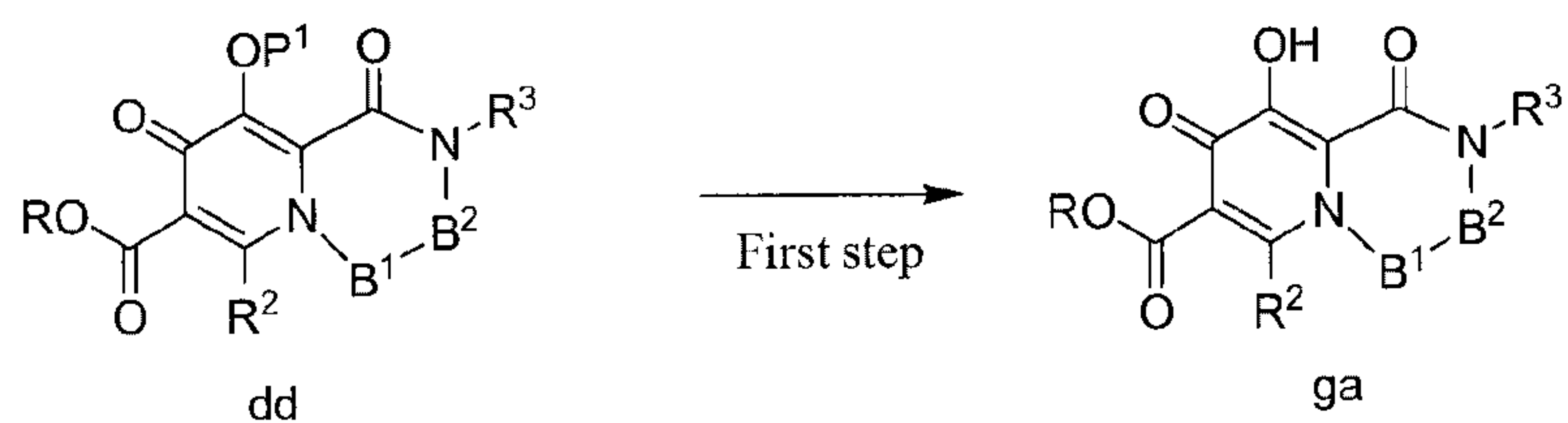
#### Fifth step

A compound fh can be obtained by subjecting the compound fg to the known general hydroxyl group deprotecting reaction.

[0240]

Synthesis of compound ga of Reference example (see: Reference example 51)

[Chemical formula 60]



[0241]

(wherein each symbol is same as above)

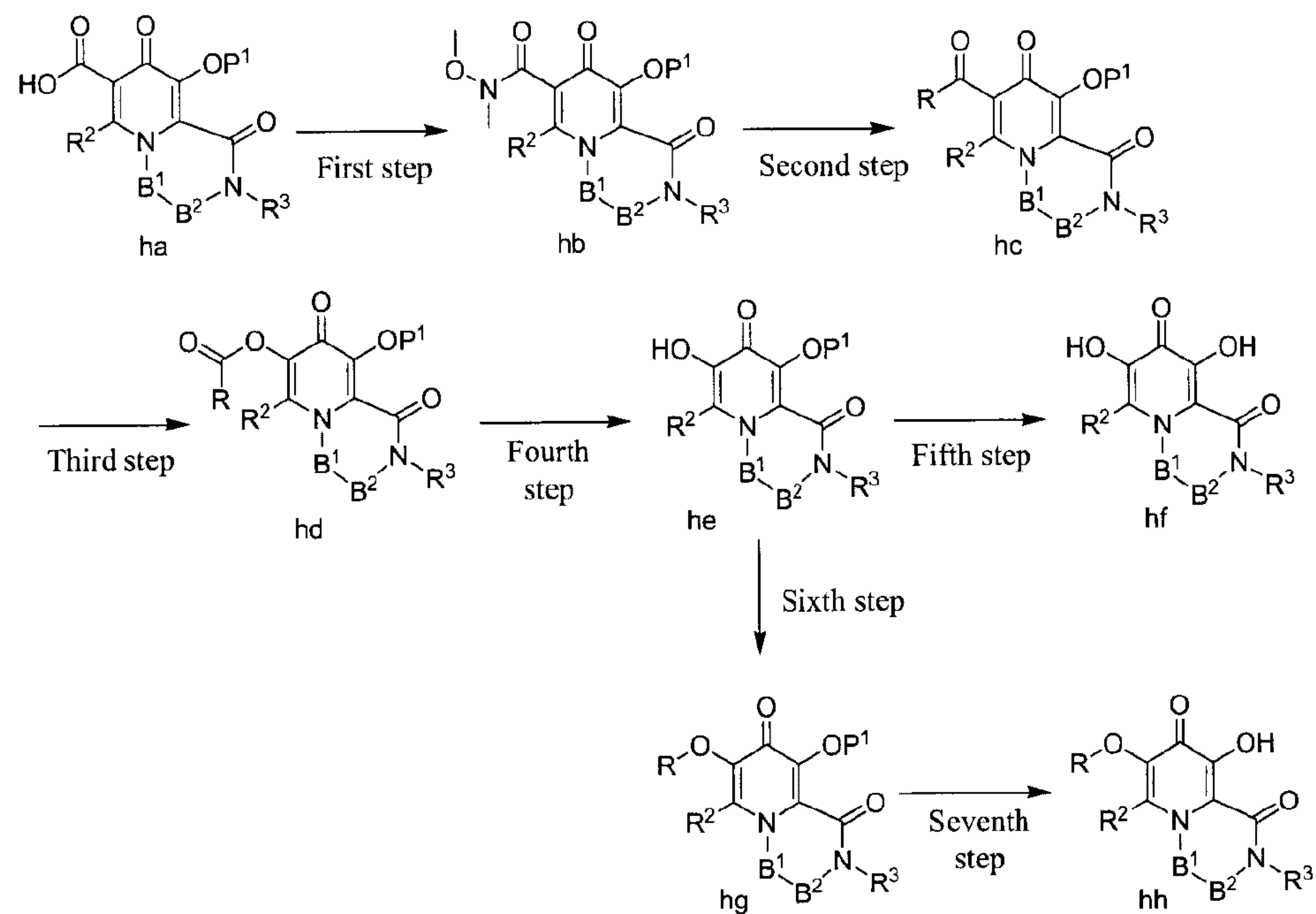
First step

A compound **ga** can be obtained by subjecting a compound **dd** to the known general hydroxyl group deprotecting reaction.

[0242]

Synthesis of compound **hh** of Reference example (see: Reference example 52)

[Chemical formula 61]



[0243]

(wherein each symbol is same as above)

#### First step

A compound hb can be obtained by adding O,N-dimethylhydroxylamine hydrochloride to a compound ha in a solvent such as DMF, THF, dichloromethane, acetonitrile etc. in the presence of a dehydration-condensation agent such as dicyclohexylcarbodiimide, carbonyldiimidazole, dicyclohexylcarbodiimido-N-hydroxybenzotriazole, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, hexafluorophosphoric acid 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium, WSC·HCl, HATU etc., adding a tertiary base such as triethylamine, diisopropylethylamine, N-methylmorpholine etc., and performing a reaction at 0°C to 60°C, preferably 10°C to 40°C for 1 hour to 24 hours, preferably 1 hour to 12 hours.

#### Second step

A compound hc can be obtained by adding a Grignard reagent (R-MgBr) to the compound hb at -80°C to -40°C in the presence of a solvent such as THF, ether, dichloromethane, dioxane etc. or in a mixed solvent thereof, and performing a reaction at -80°C to 0°C, preferably -60°C to -20°C for 0.5 hours to 24 hours, preferably 0.5 hours to 6 hours.

#### Third step

A compound hd can be obtained by adding mCPBA to the compound hc in the presence of a solvent such as chloroform and dichloromethane, and performing a reaction at -20°C to 30°C, preferably 10°C to 30°C for 0.1 hours to 12 hours, preferably 0.5 hours to 6 hours.

#### Fourth step

A compound he can be obtained by adding an aqueous sodium hydroxide solution to the compound hd in the presence of a solvent such as ethanol etc., and performing a reaction at 0°C to 120°C, preferably 30°C to 90°C for 1 minute to 10 hours, preferably 30 minutes to 120 minutes.

Fifth step

A compound hf can be obtained by subjecting the compound he to the known general hydroxyl group deprotecting reaction.

Sixth step

A compound hg can be obtained by adding a compound R-Br etc. corresponding to an objective compound to a compound he in the presence of a solvent such as chloroform, dichloromethane, THF, toluene etc. or in a mixed solvent thereof, adding a metal base such as sodium hydride, sodium methylate, n-butyllithium etc., and performing a reaction at -20°C to 120°C, preferably 0°C to 30°C for 0.5 hours to 12 hours, preferably 1 hour to 6 hours.

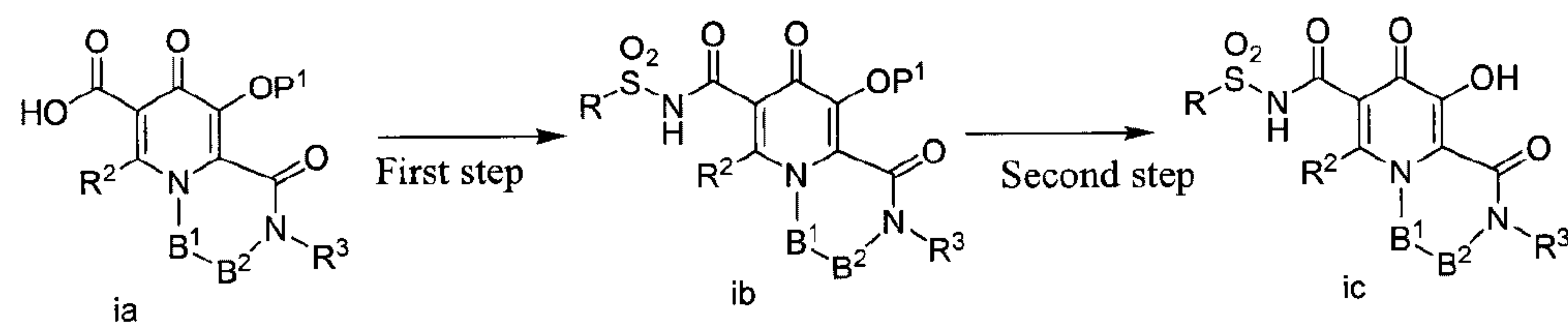
Seventh step

A compound hh can be obtained by subjecting the compound hg to the known general hydroxyl group deprotecting reaction.

[0244]

Synthesis of compound ic of Reference example (see: Reference example 53)

[Chemical formula 62]



[0245]

(wherein each symbol is same as above)

#### First step

Tertiary amine such as triethylamine, diisopropylethylamine, N-methylmorpholine etc., and a chlorinating reagent such as ethyl chlorocarbonate, and ethyl chloroformate are added to a compound ia in the presence of a solvent such as DMF, DMA, NMP, THF etc. or in a mixed solvent thereof, and the mixture is stirred at 0°C to 30°C for 0.1 hours to 1 hour. A compound R-SO<sub>2</sub>-NH<sub>2</sub> (e.g.: methanesulfonylamide) corresponding to an objective substance and DMAP are added thereto, and a reaction is performed at 40°C to 100°C, preferably 40°C to 80°C for 0.5 hours to 12 hours, preferably 1 hour to 6 hours, thereby, a compound ib can be obtained.

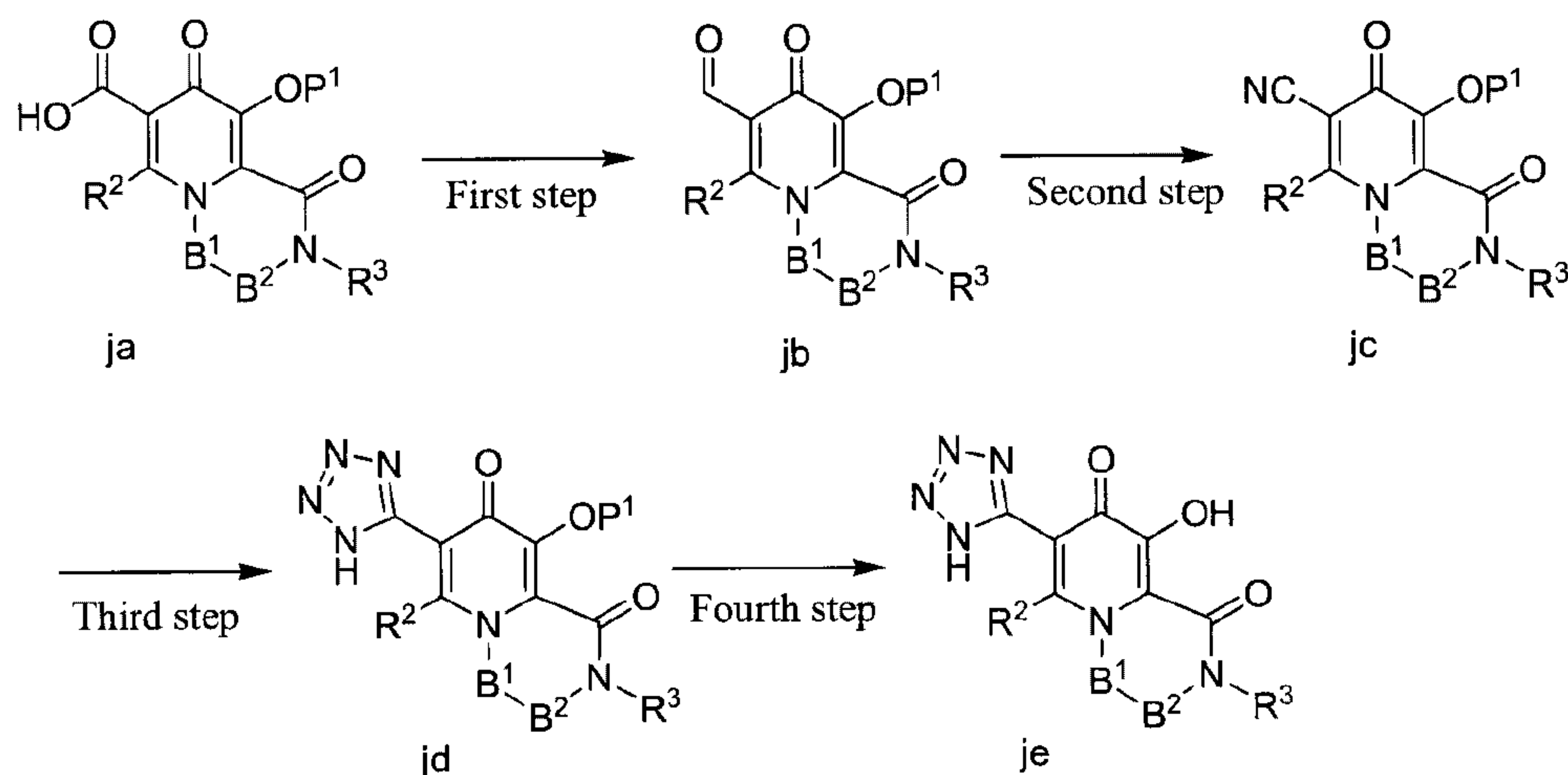
#### Second step

A compound ic can be obtained by subjecting the compound ib to the known general hydroxyl group deprotecting reaction.

[0246]

Synthesis of compound je of Reference example (see: Reference example 54)

[Chemical formula 63]



[0247]

(wherein each symbol is same as above)

#### First step

Tertiary amine such as triethylamine, N-methylmorpholine, diisopropylethylamine etc. and ethyl chloroformate or ethyl chlorocarbonate are added to a compound ja in the presence of a solvent such as THF, dioxane, dichloromethane, toluene, DMF etc. or in a mixed solvent thereof. A reducing agent having low reactivity such as sodium borohydride etc. is added thereto, and a reaction is performed at -20°C to 40°C, preferably -10°C to 20°C for 0.2 hours to 12 hours, preferably 0.5 hours to 6 hours to obtain an alcohol intermediate. This intermediate is dissolved in dichloromethane, chloroform, etc., an oxidizing agent such as TEMPO, manganese dioxide, PDC etc. is added, and a reaction is performed at -40°C to 30°C, preferably 0°C to 30°C for 0.1 hours to 24 hours, preferably 0.5 hours to 12 hours, thereby, a compound jb can be obtained.

#### Second step

A compound jc can be obtained by adding 28% aqueous ammonia and iodine to the compound jb in the presence of a solvent such as THF, dioxane, dichloromethane etc., and performing a reaction at 0°C to 40°C, preferably 10°C to 30°C for 0.5 hours to 24 hours, preferably 1 hour to 6 hours.

#### Third step

A compound jd can be obtained by adding sodium azide, and tertiary amine such as triethylamine, diisopropylethylamine, N-methylmorpholine etc. to the compound jc in the presence of a solvent such as toluene, xylene, THF, dioxane etc. or in a mixed solvent thereof, and performing a reaction at 0°C to 60°C, preferably 10°C to 40°C for 0.5 hours to 24 hours, preferably 1 hour to 12 hours.

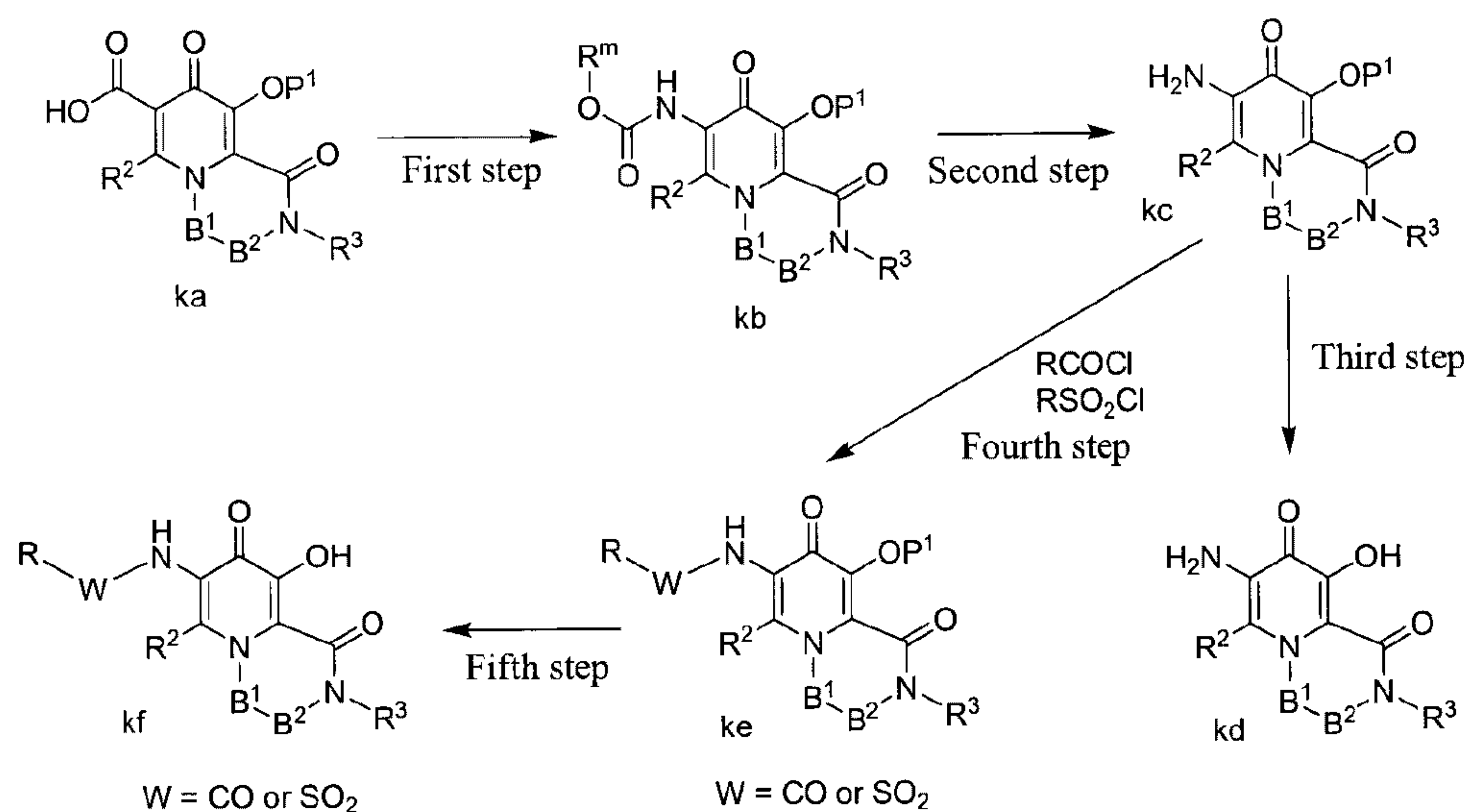
## Fourth step

A compound je can be obtained by subjecting the compound jd to the known general hydroxyl group deprotecting reaction.

[0248]

Synthesis of compounds kd and kf of Reference example (see: Reference example 56 and derivative thereof)

[Chemical formula 64]



[0249]

(wherein  $R^m$  is lower alkyl,  $R$  is a substituent corresponding to an objective compound,  $W$  is  $-C(=O)-$  or  $-SO_2-$ , and other each symbol is same as above)

## First step

Tertiary amine such as triethylamine, N-methylmorpholine, diisopropylethylamine etc. and ethyl chloroformate or ethyl chlorocarbonate are added to a compound **ka** in the presence of a solvent such as THF, dioxane, dichloromethane,

toluene, DMF etc. or in a mixed solvent thereof. Sodium azide is added thereto to perform a reaction at 0°C to 40°C, preferably 10°C to 30°C for 0.5 hours to 24 hours, preferably 1 hour to 12 hours. Thereafter, an alcohol ( $R^m$ -OH) is added, and a reaction is performed at 20°C to 60°C, preferably 20°C to 50°C for 0.5 hours to 24 hours, preferably 1 hour to 12 hours, thereby, a compound kb can be obtained.

#### Second step

A compound kc can be obtained by adding a base such as an aqueous sodium hydroxide solution, an aqueous potassium hydroxide solution etc. to the compound kb in a solvent such as ethanol, methanol, water etc. or in a mixed solvent thereof, and performing a reaction at 20°C to 80°C, preferably 40°C to 60°C for 0.5 hours to 24 hours, preferably 1 hour to 12 hours.

#### Third step

A compound kd can be obtained by subjecting the compound kc to the known general hydroxyl group deprotecting reaction.

#### Fourth step

A compound ke can be obtained by adding acid chloride ( $R$ -CO-Cl) or sulfonyl chloride ( $R$ -SO<sub>2</sub>-Cl) corresponding to an objective substance to a compound kc in a solvent such as THF, dioxane, toluene, dichloromethane etc., adding tertiary amine such as pyridine, triethylamine, N-methylmorpholine etc. as necessary, and performing a reaction at -20°C to 40°C, preferably 0°C to 30°C for 0.1 hours to 12 hours, preferably 0.2 hours to 6 hours.

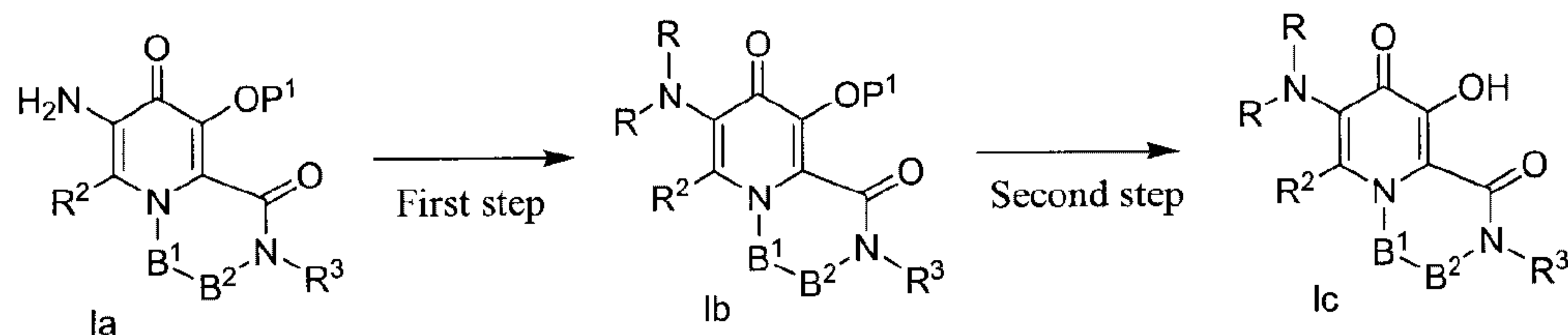
#### Fifth step

A compound kf can be obtained by subjecting the compound ke to the known general hydroxyl group deprotecting reaction.

[0250]

Synthesis of compound lc of Reference example (see: Reference example 60)

[Chemical formula 65]



[0251]

(wherein R is a substituent corresponding to an objective compound, and other each symbol is same as above)

First step

Sodium hydride is added to a compound la in a solvent such as THF, dichloromethane, DMF etc. R-L (L is a leaving group such as halogen, OMs etc.) corresponding to an objective substance is added thereto, and a reaction is performed at -20°C to 40°C, preferably 0°C to 30°C for 0.1 hours to 12 hours, preferably 0.2 hours to 6 hours, thereby, a compound lb can be obtained.

Alternatively, a compound lb can be obtained by adding formaldehyde to a compound la in a solvent of formic acid, and performing a reaction at 70°C to 110°C for 0.5 hours to 24 hours, preferably 1 hour to 12 hours.

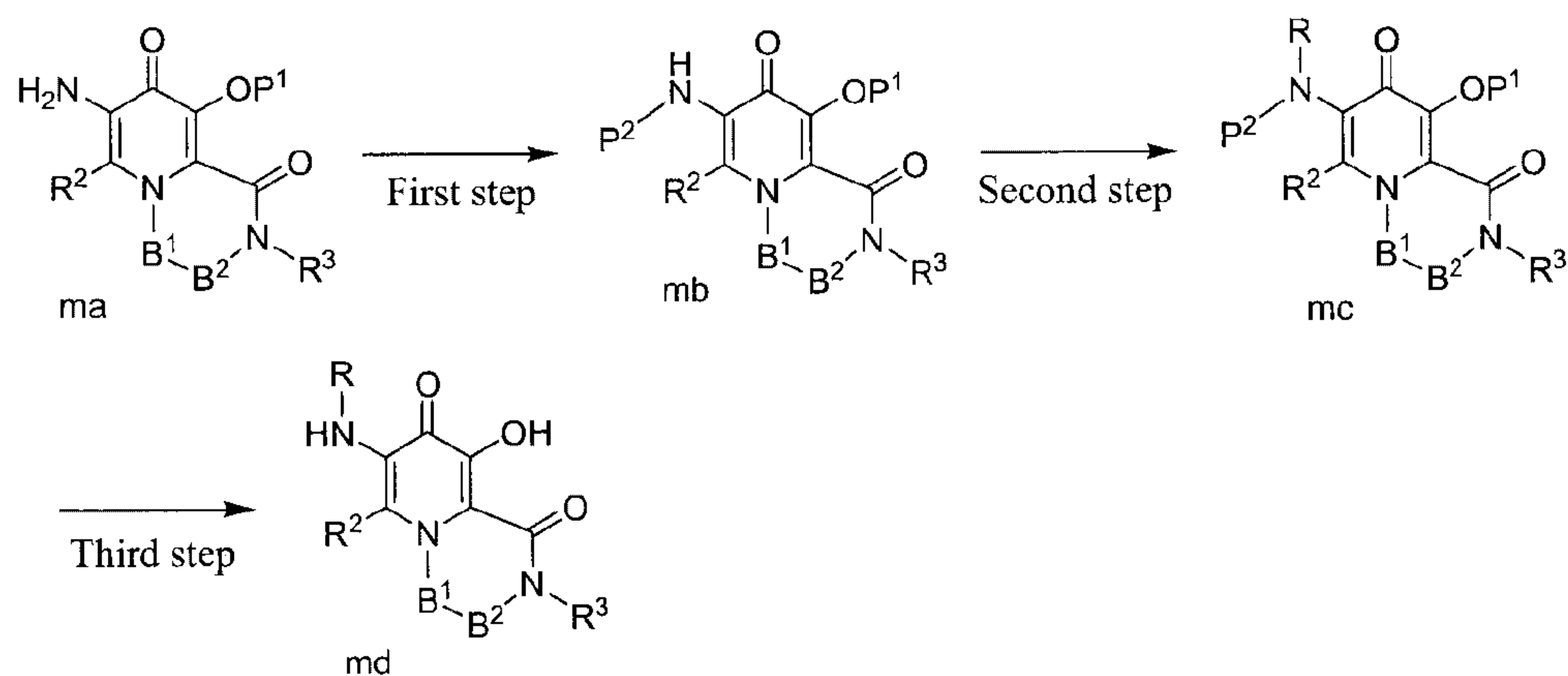
Second step

A compound lc can be obtained by subjecting the compound lb to the known general hydroxyl group deprotecting reaction.

[0252]

Synthesis of compound md of Reference example (see: Reference example 61)

[Chemical formula 66]



[0253]

(wherein R is a substituent corresponding to an objective compound, and other each symbol is same as above)

#### First step

An amino-protected body **mb** can be obtained by adding  $\text{Boc}_2\text{O}$  etc. to a compound **ma** in a solvent such as THF, dioxane, acetonitrile, water etc. or in a mixed solvent thereof, and subjecting this to an amine protecting reaction.

#### Second step

Sodium hydride is added to a compound **mb** in a solvent such as THF, dichloromethane, DMF etc.  $\text{R-L}$  (L is a leaving group such as halogen, OMs etc.) corresponding to an objective substance is added thereto, and a reaction is performed at  $-20^\circ\text{C}$  to  $40^\circ\text{C}$ , preferably  $0^\circ\text{C}$  to  $30^\circ\text{C}$  for 0.1 hours to 12 hours, preferably 0.2 hours to 6 hours, thereby, a compound **mc** can be obtained.

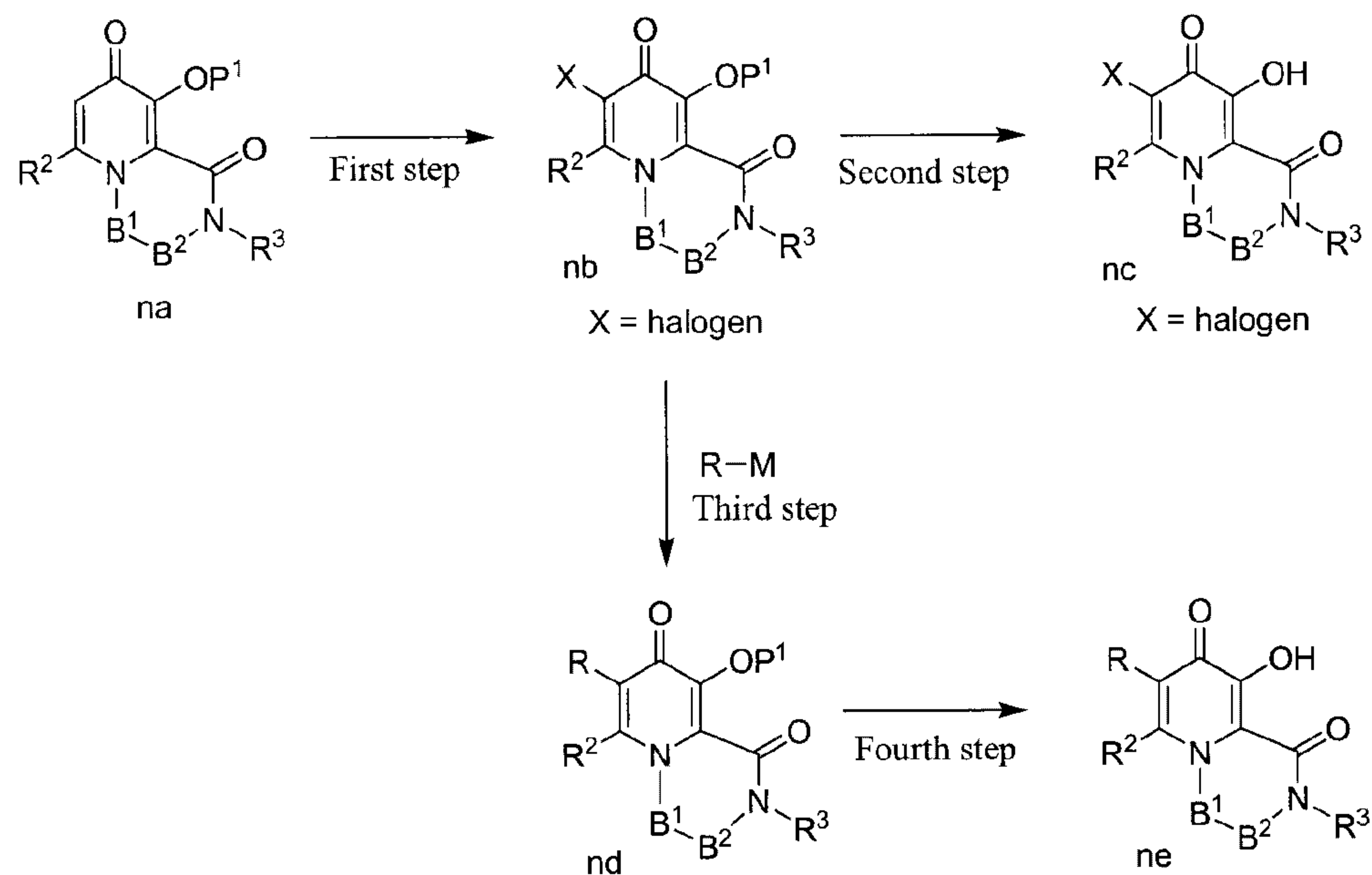
#### Third step

A compound **md** can be obtained by subjecting the compound **mc** to the known general amino group and hydroxyl group deprotecting reaction.

[0254]

Synthesis of compound nc and compound ne of Reference example (see: Reference examples 63 and 64)

[Chemical formula 67]



[0255]

(wherein  $X$  is halogen,  $M$  is boronic acid ester such as  $B(O\text{-phenyl})_3$  etc., and other each symbol is same as above)

First step

A compound nb can be obtained by adding a halogenating reagent (e.g. NBS, NCS, bromine etc.) to a compound na in a solvent such as dichloromethane, toluene, THF, dioxane etc., and performing a reaction for 0.1 hours to 12 hours, preferably 0.2 hours to 6 hours under the overheating refluxing condition.

Second step

A compound nc can be obtained by subjecting the compound nb to the known general hydroxyl group deprotecting reaction.

## Third step

Boronic acid ester (R-M) corresponding to an objective substance is added to a compound nb in a solvent such as toluene, THF, DMF etc. or in a mixed solvent thereof, and a base such as potassium carbonate, sodium carbonate, sodium hydroxide etc. is added. A 0-valent palladium catalyst (e.g.: Pd(PPh<sub>3</sub>)<sub>4</sub>) is added thereto under nitrogen stream, and a reaction is performed at 60°C to 120°C, preferably 80°C to 110°C for 1 hour to 48 hours, preferably 2 hours to 24 hours, thereby, a compound nd can be obtained.

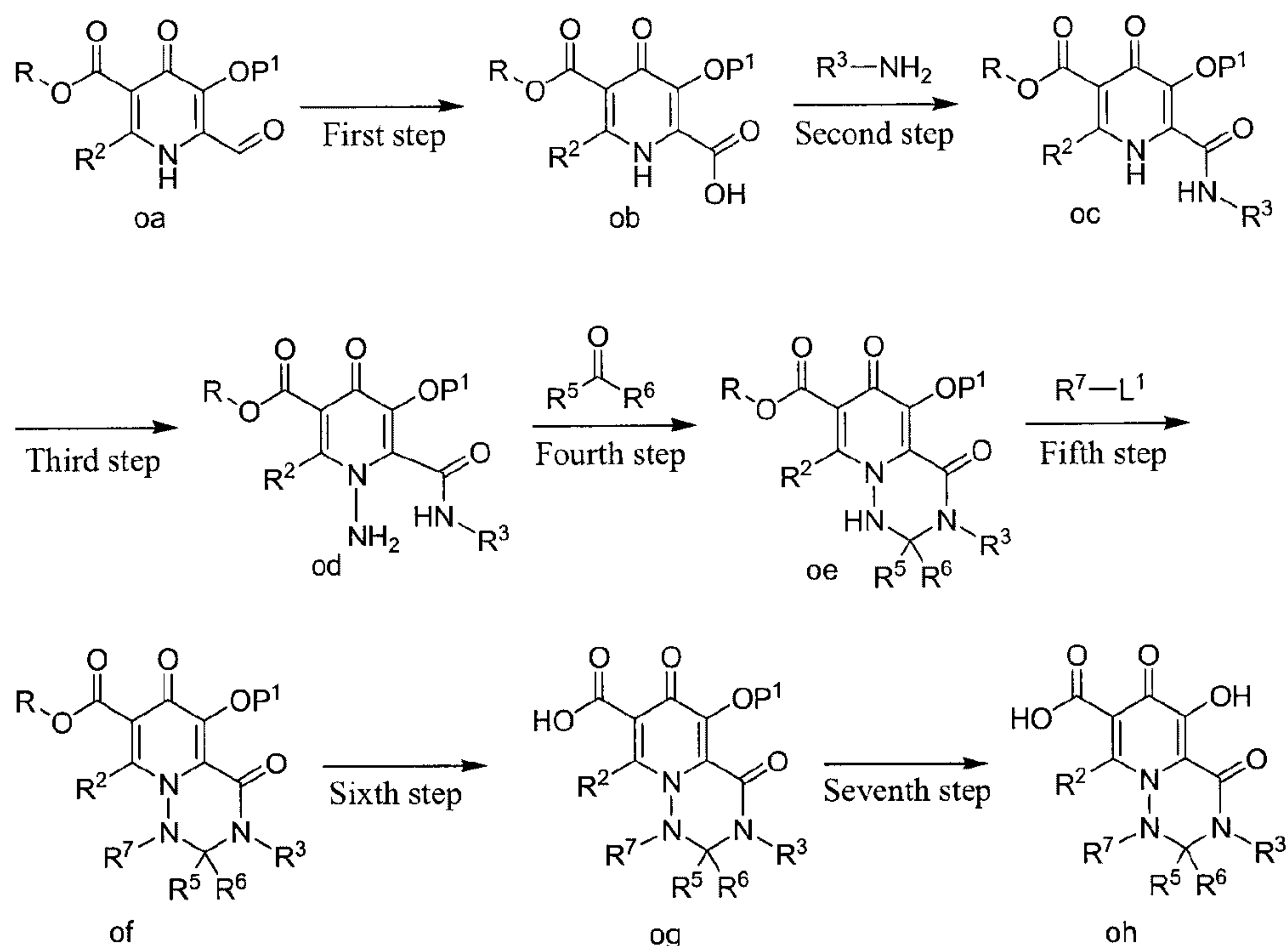
## Fourth step

A compound ne can be obtained by subjecting the compound nd to the known general hydroxyl group deprotecting reaction.

[0256]

Synthesis of compound oh of Reference example (see: Reference example 65)

[Chemical formula 68]



[0257]

(wherein  $R$  is a carboxyl protective group such as lower alkyl etc.,  $R^7$  is same as  $R^{7a}$  in item 1,  $L^1$  is a leaving group such as halogen, OM, OTs etc., and other symbol is same as above)

#### First step

A compound **ob** can be obtained by adding sodium chlorite and amidosulfuric acid to a compound **oa** in the presence of a solvent such as THF, dioxane, dichloromethane, acetonitrile etc., and performing a reaction at  $0^\circ\text{C}$  to  $40^\circ\text{C}$ , preferably  $0^\circ\text{C}$  to  $30^\circ\text{C}$  for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

#### Second step

A compound **oc** can be obtained by adding a condensation agent such as HATU, WSC $\cdot$ HCl etc. to the compound **ob** in the presence of a solvent such as DMF, DMA,

NMP, THF etc., adding amine ( $R^3-NH_2$ ) corresponding to an objective substance, and tertiary amine such as triethylamine, N-methylmorpholine, pyridine etc., and performing a reaction at 10°C to 60°C, preferably 20°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

#### Third step

A compound od can be obtained by adding potassium carbonate, sodium carbonate, and O-(2,4-dinitrophenyl)hydroxylamine to the compound oc in the presence of a solvent such as DMF, DMA, NMP, THF etc., and performing a reaction at 10°C to 60°C, preferably 20°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

#### Fourth step

A compound oe can be obtained by adding  $R^5-C(=O)-R^6$  and acetic acid to the compound od in the presence of a solvent such as toluene, DMF, DMA, NMP, THF etc., and performing a reaction at 60°C to 120°C, preferably 80°C to 110°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

#### Fifth step

A compound of can be obtained by adding a compound  $R^7-L^1$  corresponding to an objective substance, and a base such as sodium carbonate, potassium carbonate, cesium carbonate etc. to the compound oe in the presence of a solvent such as DMF, DMA, NMP, THF etc., and performing a reaction at 0°C to 60°C, preferably 10°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

#### Sixth step

A compound og can be obtained by subjecting the compound of to the known general carboxyl group deprotecting reaction.

#### Seventh step

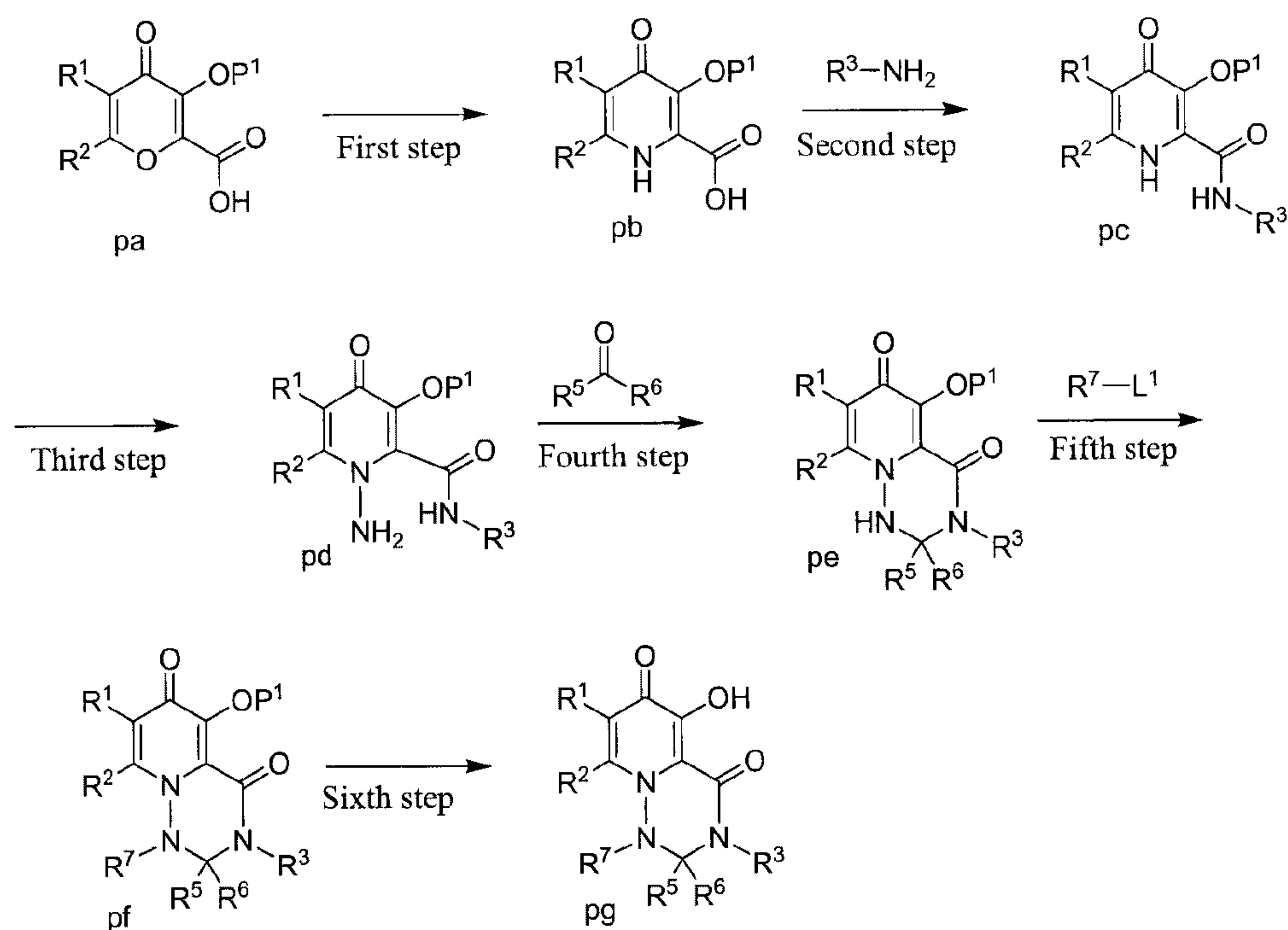
A compound oh can be obtained by subjecting the compound og to the known

general hydroxyl group deprotecting reaction.

[0258]

Synthesis of compound pg of Reference example (see: Reference example 95)

[Chemical formula 69]



[0259]

(wherein each symbol is same as above)

First step

A compound pb can be obtained by adding aqueous ammonia to a compound pa, and performing a reaction at 0°C to 30°C, preferably 10°C to 30°C for 0.5 hours to 48 hours, preferably 1 hour to 24 hours.

Second step

A compound pc can be obtained by adding a condensation agent such as HATU,

WSC·HCl etc. to the compound pb in the presence of a solvent such as DMF, DMA, NMP, THF etc. or in a mixed solvent thereof, adding amine ( $R^3$ -NH<sub>2</sub>) corresponding to an objective substance and, if necessary, tertiary amine such as triethylamine, N-methylmorpholine etc., and performing a reaction at 10°C to 60°C, preferably 20°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

#### Third step

A compound pd can be obtained by adding potassium carbonate, sodium carbonate, and O-(2,4-dinitrophenyl)hydroxylamine to the compound pc in the presence of a solvent such as DMF, DMA, NMP, THF etc., and performing a reaction at 10°C to 60°C, preferably 20°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

#### Fourth step

A compound pe can be obtained by adding  $R^5$ -C(=O)- $R^6$  and acetic acid to the compound pd in the presence of a solvent such as toluene, DMF, DMA, NMP, THF etc., and performing a reaction at 60°C to 120°C, preferably 80°C to 110°C for 0.1 hours to 12 hours, preferably 0.2 hours to 6 hours.

#### Fifth step

A compound pf can be obtained by adding a compound  $R^7$ -L<sup>1</sup> corresponding to an objective substance, and a base such as sodium carbonate, potassium carbonate, cesium carbonate etc. to the compound pe in the presence of a solvent such as DMF, DMA, NMP, THF etc., and performing a reaction at 0°C to 60°C, preferably 10°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

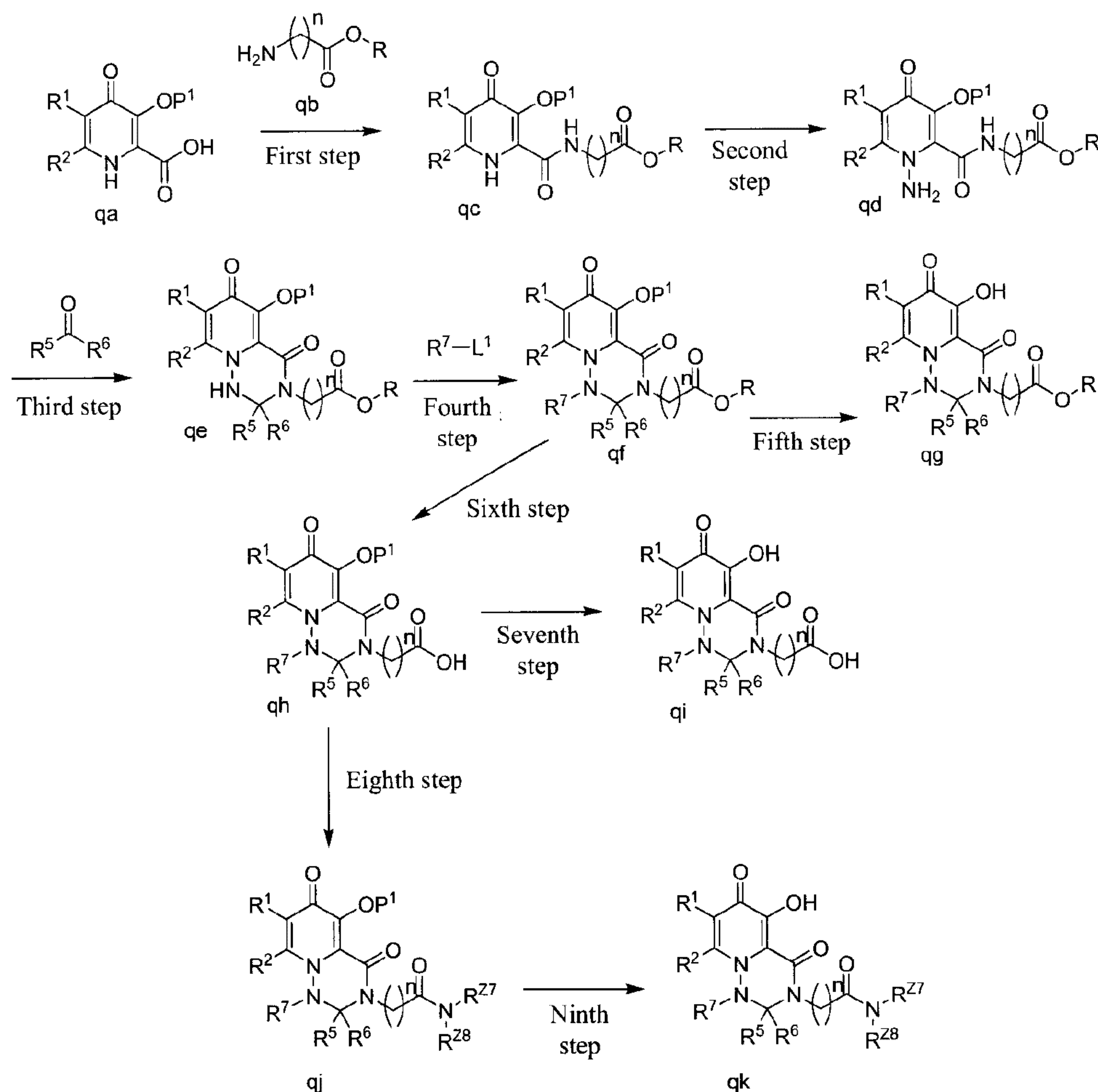
#### Sixth step

A compound pg can be obtained by subjecting the compound pf to the known general hydroxyl group deprotecting reaction.

[0260]

Synthesis of compound qg, compound qi, and compound qk of Reference example (see: Reference example 128)

[Chemical formula 70]



[0261]

(wherein R represents a carboxyl protective group, n represents an integer of 0 to 6, R<sup>Z7</sup> and R<sup>Z8</sup> are same as R<sup>C7</sup> and R<sup>C8</sup> in item 1, and other each symbol is same as above)

First step

A compound qc can be obtained by adding a condensation agent such as HATU,

WSC·HCl etc. to a compound qa in the presence of a solvent such as pyridine, DMF, DMA, NMP, THF etc. or in a mixed solvent thereof, adding a compound qb and, if necessary, tertiary amine such as triethylamine, N-methylmorpholine etc., and performing a reaction at 10°C to 60°C, preferably 20°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

#### Second step

A compound qd can be obtained by adding potassium carbonate, sodium carbonate, and O-(2,4-dinitrophenyl)hydroxylamine to the compound qc in the presence of a solvent such as DMF, DMA, NMP, THF etc. or in a mixed solvent thereof, and performing a reaction at 10°C to 60°C, preferably 20°C to 40°C for 0.1 hours to 48 hours, preferably 1 hour to 24 hours.

#### Third step

A compound pe can be obtained by adding  $R^5-C(=O)-R^6$  and acetic acid to the compound qd in the presence of a solvent such as toluene, DMF, DMA, NMP, THF etc. or in a mixed solvent thereof, and performing a reaction at 60°C to 120°C, preferably 80°C to 110°C for 0.1 hours to 12 hours, preferably 0.2 hours to 6 hours.

Alternatively, a compound qe can be obtained by performing a reaction at 100°C to 200°C for 5 minutes to 1 hour under microwave irradiation condition in a solvent such as ethanol, isopropyl alcohol etc.

#### Fourth step

A compound qf can be obtained by adding a compound  $R^7-L^1$  corresponding to an objective substance, and a base such as sodium carbonate, potassium carbonate, cesium carbonate etc. to the compound qe in the presence of a solvent such as DMF, DMA, NMP etc. or in a mixed solvent thereof, and performing a reaction at 0°C to 60°C, preferably 10°C to 40°C for 0.1 hours to 48 hours, preferably 1 hour to 24 hours.

## Fifth step

A compound qg can be obtained by subjecting the compound qf to the known general hydroxyl group deprotecting reaction.

## Sixth step

A compound qh can be obtained by subjecting the compound qf to the known general carboxyl group deprotecting reaction.

## Seventh step

A compound qi can be obtained by subjecting the compound qh to the known general hydroxyl group deprotecting reaction.

## Eighth step

A compound qj can be obtained by adding a condensation agent such as HATU, WSC•HCl etc. to a compound qh in the presence of a solvent such as pyridine, DMF, DMA, NMP, THF etc. or in a mixed solvent thereof, adding a compound  $\text{HNR}^{Z7}\text{R}^{Z8}$  and, if necessary, tertiary amine such as triethylamine, diisopropylethylamine, N-methylmorpholine etc., and performing a reaction at 10°C to 60°C, preferably 20°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

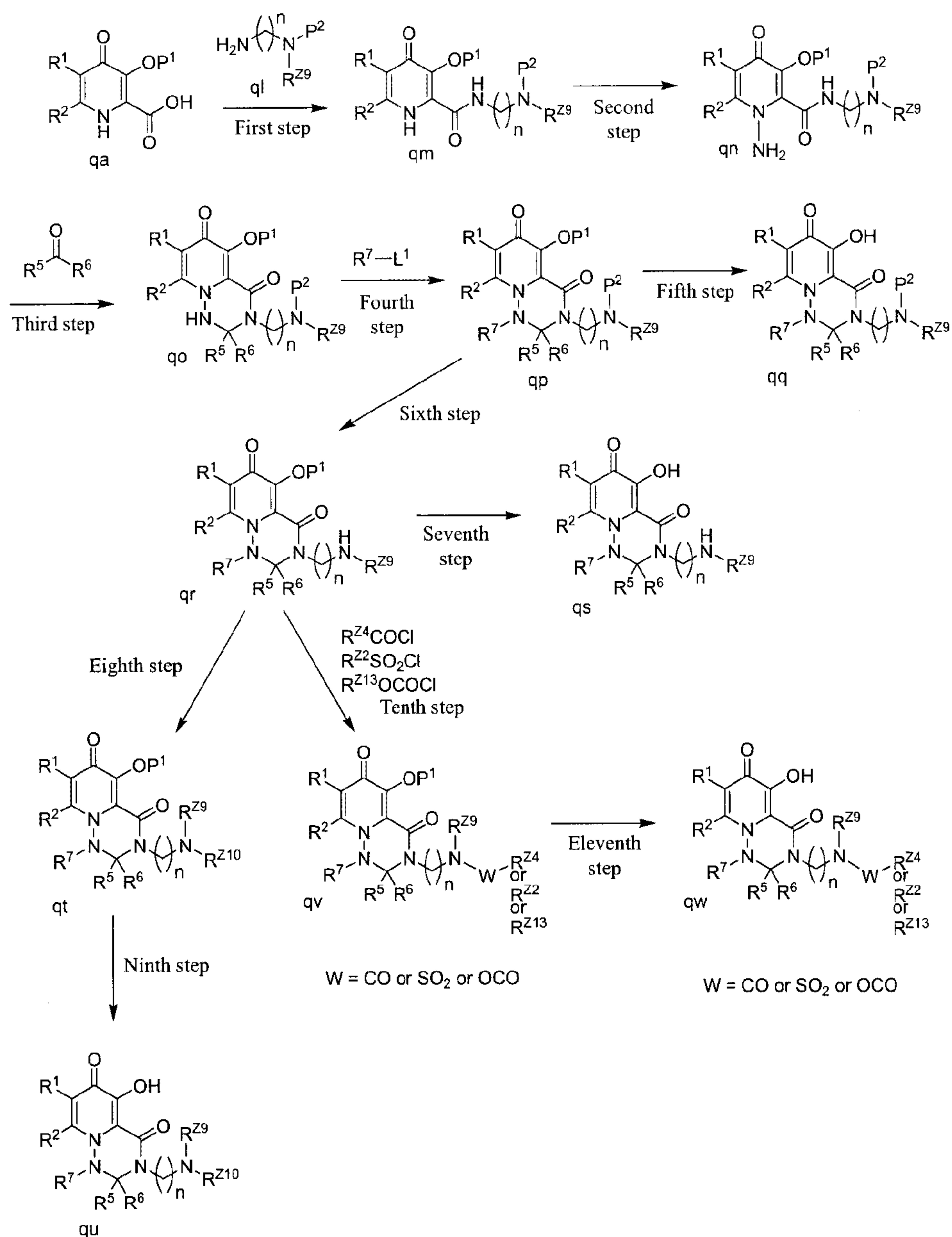
## Ninth step

A compound qk can be obtained by subjecting the compound qj to the known general hydroxyl group deprotecting reaction.

[0262]

Synthesis of compound qq of Reference example, compound qs of Reference example, compound qu of Reference example, and compound qw of Reference example (see: Reference example 128)

[Chemical formula 71]



[0263]

(wherein  $R^{Z2}$ ,  $R^{Z4}$ ,  $R^{Z9}$ ,  $R^{Z10}$ , and  $R^{Z13}$  are same as  $R^{C2}$ ,  $R^{C4}$ ,  $R^{C9}$ ,  $R^{C10}$ , and  $R^{C13}$

in item 1, and other each symbol is same as above)

First step

A compound qm can be obtained by adding a condensation agent such as HATU, WSC·HCl, etc. to a compound qa in the presence of a solvent such as pyridine, DMF, DMA, NMP etc. or in a mixed solvent thereof, adding a compound ql and, if necessary, tertiary amine such as triethylamine, diisopropylethylamine, N-methylmorpholine, etc., and performing a reaction at 10°C to 60°C, preferably 20°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

#### Second step

A compound qn can be obtained by adding potassium carbonate, sodium carbonate, and O-(2,4-dinitrophenyl)hydroxylamine to the compound qm in the presence of a solvent such as DMF, DMA, NMP, THF etc., and performing a reaction at 10°C to 60°C, preferably 20°C to 40°C for 0.1 hours to 48 hours, preferably 1 hour to 24 hours.

#### Third step

A compound pe can be obtained by adding  $R^5-C(=O)-R^6$  and acetic acid to the compound qn in the presence of a solvent such as toluene, DMF, DMA, NMP, THF etc. or in a mixed solvent thereof, and performing a reaction at 60°C to 120°C, preferably 80°C to 110°C for 0.1 hours to 12 hours, preferably 0.2 hours to 6 hours.

Alternatively, a compound qo can be obtained by performing a reaction at 100°C to 200°C for 5 minutes to 1 hour under microwave irradiation condition in a solvent such as ethanol etc.

#### Fourth step

A compound qp can be obtained by adding a compound  $R^7-L^1$  corresponding to an objective substance, and a base such as sodium carbonate, potassium carbonate, cesium carbonate, etc. to the compound qo in the presence of a solvent such as DMF, DMA, NMP, THF, etc. or in a mixed solvent thereof, and performing a reaction at 0°C

to 60°C, preferably 10°C to 40°C for 0.1 hours to 48 hours, preferably 1 hour to 24 hours.

#### Fifth step

A compound qq can be obtained by subjecting the compound qp to the known general hydroxyl group deprotecting reaction.

#### Sixth step

A compound qr can be obtained by subjecting the compound qp to the known general amino group deprotecting reaction.

#### Seventh step

A compound qs can be obtained by subjecting the compound qr to the known general hydroxyl group deprotecting reaction.

#### Eighth step

A compound qt can be obtained by adding a compound  $R^{Z10}-L^1$  corresponding to an objective substance, and a base such as sodium carbonate, potassium carbonate, cesium carbonate, etc. to the compound qr in the presence of a solvent such as DMF, DMA, NMP, THF, etc. or in a mixed solvent thereof, and performing a reaction at 0°C to 60°C, preferably 10°C to 40°C for 0.1 hours to 48 hours, preferably 1 hour to 24 hours.

#### Ninth step

A compound qu can be obtained by subjecting the compound qt to the known general hydroxyl group deprotecting reaction.

#### Tenth step

A base such as sodium carbonate, potassium carbonate, cesium carbonate etc. is added to the compound qr in the presence of a solvent such as THF, dioxane, dichloromethane, acetonitrile, etc. A compound ( $R^{Z4}COCl$ ,  $R^{Z2}SO_2Cl$ , or  $R^{Z13}OCOCl$ )

corresponding to an objective substance is slowly added thereto, and a reaction is performed at -20°C to 60°C, preferably 0°C to 30°C for 0.1 hours to 48 hours, preferably 1 hour to 24 hours, thereby, a compound qv can be obtained.

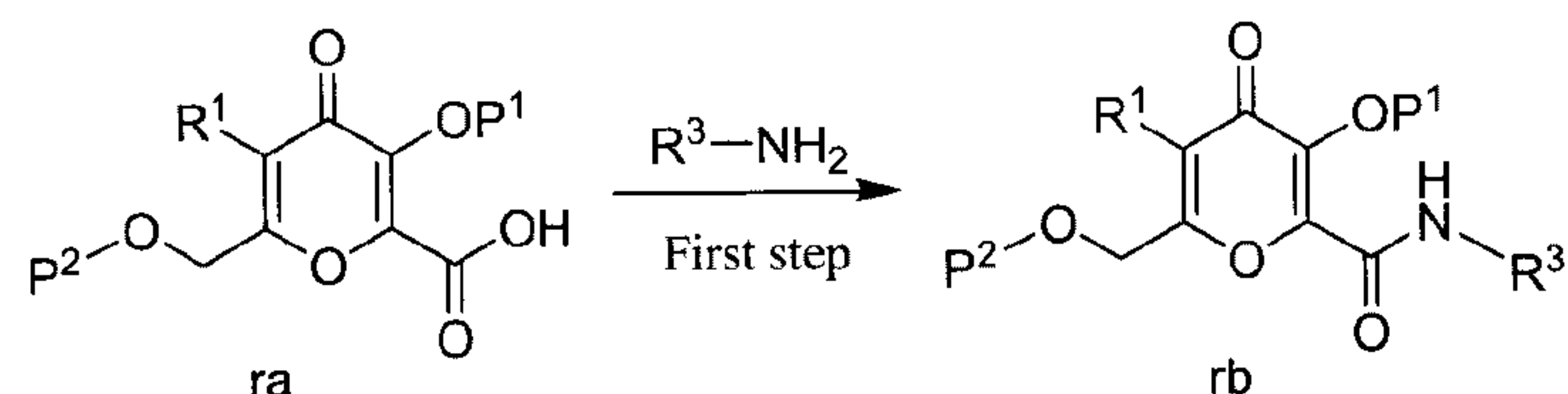
Eleventh step

A compound qw can be obtained by subjecting the compound qv to the known general hydroxyl group deprotecting reaction.

[0264]

Synthesis of compound rb of Reference example (see: Reference example 155)

[Chemical formula 72]



[0265]

(wherein each symbol is same as above)

A compound rb can be obtained by adding a compound  $R^3NH_2$  having a substituent corresponding to an objective compound to a compound ra in the presence of a dehydration-condensation agent such as dicyclohexylcarbodiimide, carbonyldiimidazole, dicyclohexylcarbodiimido-N-hydroxybenzotriazole, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, hexafluorophosphoric acid 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium, WSC·HCl, HATU, etc. in a solvent such as DMF, THF, dichloromethane, acetonitrile, etc. or in a mixed solvent thereof, and performing a reaction at -20°C to 60°C, preferably -10°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

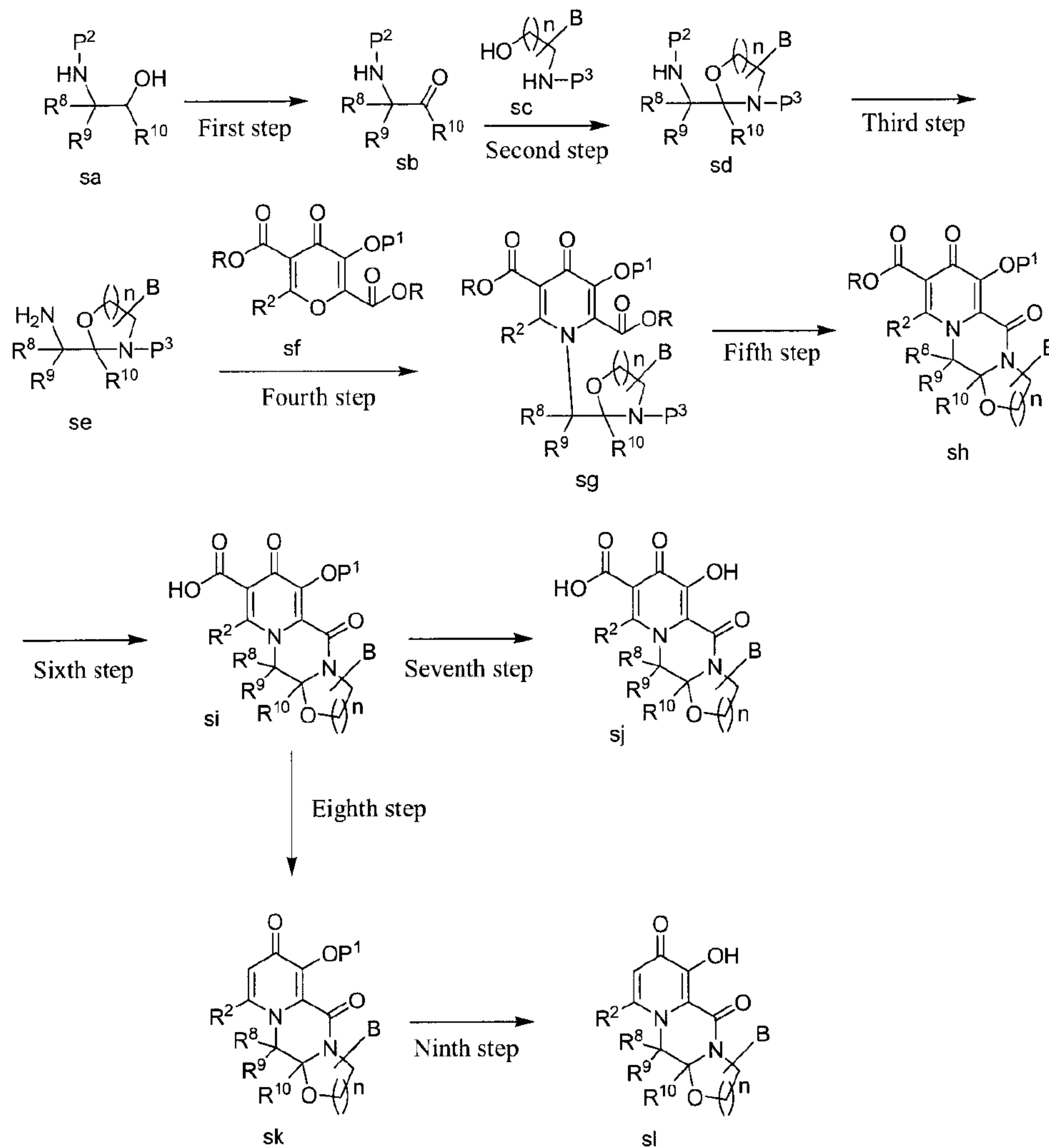
Alternatively, a compound rb can be obtained by adding an acylating reagent

such as diphenylchlorophosphate, thionyl chloride, oxalyl chloride, etc. to a compound  
ra in the presence or absence of a base such as pyridine, triethylamine,  
diisopropylethylamine, 1-methylimidazole, etc. in the presence of a solvent such as THF,  
dioxane, dichloromethane, DMF, etc. to generate acid chloride, adding a compound  
 $R^3-NH_2$  having a substituent corresponding to an objective compound, and performing a  
reaction at  $-20^{\circ}C$  to  $60^{\circ}C$ , preferably  $-10^{\circ}C$  to  $40^{\circ}C$  for 0.1 hours to 24 hours,  
preferably 0.5 hours to 12 hours.

[0266]

Synthesis of compound sl of Reference example (see: Reference example 49)

[Chemical formula 73]



[0267]

(wherein  $P^3$  is an amino protective group, and may be a group which can be protected and/or deprotected by the method described in Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) etc. and, for example,  $P^3$  is aryl lower alkylloxycarbonyl, lower alkylcarbonyl, etc. B is same as substituent group D in item 1, and other each symbol is same as above)

First step

A compound sb can be obtained by adding an oxidizing reagent such as Dess Martin Periodinane, manganese dioxide, PDC, etc, to a compound sa in the presence of a solvent such as dichloromethane, THF, dioxane, toluene etc., and performing a reaction at -20°C to 60°C, preferably 0°C to 40°C for 0.1 hours to 24 hours, preferably 0.5 hours to 12 hours.

#### Second step

A compound sd can be obtained by adding sodium sulfate and an aminoalcohol sc corresponding to an objective substance to the compound sb in the presence or absence of a solvent such as toluene, THF etc., and performing a reaction at 0°C to 80°C, preferably 20°C to 60°C for 0.1 hours to 24 hours, preferably 0.5 hours to 12 hours.

#### Third step

A compound se can be obtained by subjecting the compound sd to the known general amino group deprotecting reaction.

#### Fourth step

A compound sg can be obtained by adding a compound sf to the compound se in the presence of a solvent such as toluene, THF, dioxane etc., and performing a reaction at 40°C to 110°C, preferably 60°C to 100°C for 0.5 hours to 24 hours, preferably 1 hour to 12 hours.

#### Fifth step

A compound sh can be obtained by subjecting the compound sg to the known general amino group deprotecting reaction and, thereafter, performing a reaction at 40°C to 110°C, preferably 60°C to 100°C for 0.1 hours to 12 hours, preferably 0.2 hours to 6 hours in the presence of a solvent such as toluene, THF, dioxane, etc.

#### Sixth step

A compound si can be obtained by subjecting the compound sh to the known general carboxyl group deprotecting reaction.

Seventh step

A compound sj can be obtained by subjecting the compound si to the known general hydroxyl group deprotecting reaction.

Eighth step

A decarbonized compound sk can be obtained by reacting the compound si for 1 minute to 2 hours under microwave irradiation in a solvent such as diphenyl ether etc.

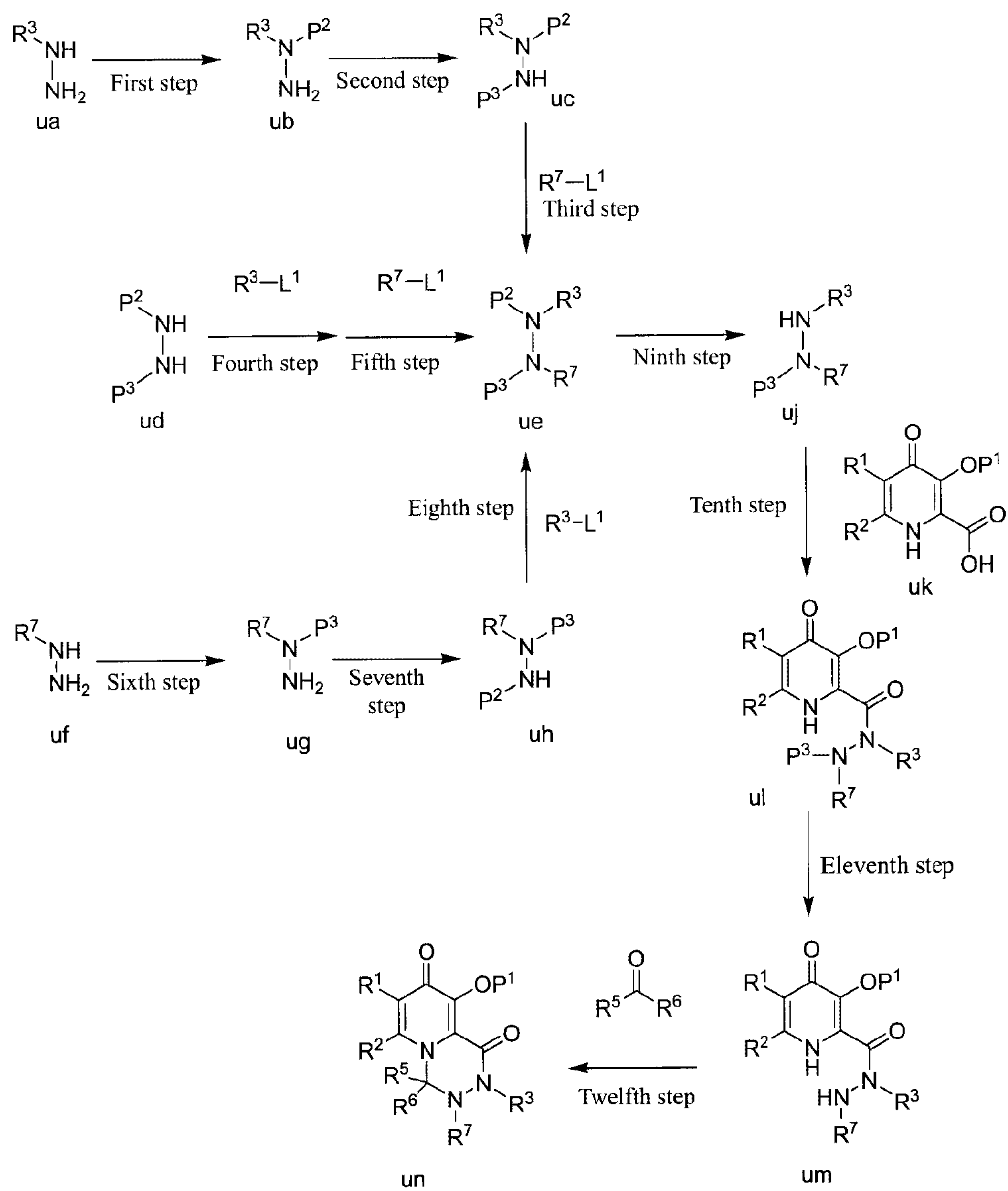
Ninth step

A compound sl can be obtained by subjecting the compound sk to the known general hydroxyl group deprotecting reaction.

[0268]

Synthesis of compound un of Reference example (see: Reference example 177)

[Chemical formula 74]



[0269]

(wherein  $\text{L}^1$  represents a leaving group such as halogen, OMs, OTs etc., and other each symbol is same as above)

First step

A compound ub can be obtained by subjecting a compound ua to a secondary amino group protecting reaction.

Second step

A compound uc can be obtained by subjecting the compound ub to a general amino group protecting reaction.

Third step

A compound ue can be obtained by adding a compound  $R^7-L^1$  corresponding to an objective compound to the compound uc in the presence of a solvent such as DMF, DMA, NMP, etc. and a base such as NaH etc., and performing a reaction at 0°C to 80°C, preferably 20°C to 60°C for 0.5 hours to 12 hours, preferably 1 hour to 6 hours.

Fourth step, Fifth step

(wherein  $R^3$  and  $R^7$  may be bound adjacently and, in this case, a fourth step and a fifth step are performed simultaneously)

A compound ue can be obtained by reacting a compound ud sequentially with compounds corresponding to an objective compound,  $R^3-L^1$  and  $R^7-L^1$  in the presence of a solvent such as DMF, DMA, NMP etc. and a base such as NaH etc.

Sixth step

A compound ug can be obtained by subjecting a compound uf to a secondary amino group protecting reaction.

Seventh step

A compound uh can be obtained by subjecting the compound ug to a secondary amino group protecting reaction.

Eighth step

A compound ue can be obtained by adding a base such as NaH etc. to the compound uh in the presence of a solvent such as DMF, DMA, NMP, acetonitrile etc. or

in a mixed solvent thereof, and performing a reaction with a compound  $R^3-L^1$  corresponding to an objective compound.

#### Ninth step

A compound uj can be obtained by subjecting the compound ue to a general secondary amine deprotecting reaction.

#### Tenth step

A compound ul can be obtained by adding a condensation agent such as HATU, WSC·HCl etc. to a compound uk in the presence of a solvent such as DMF, DMA, THF, etc., adding amine uj corresponding to an objective substance, and tertiary amine such as pyridine, triethylamine, N-methylmorpholine etc., and performing a reaction at 10°C to 60°C, preferably 20°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

#### Eleventh step

A compound um can be obtained by subjecting the compound ul to a general amino group protecting reaction.

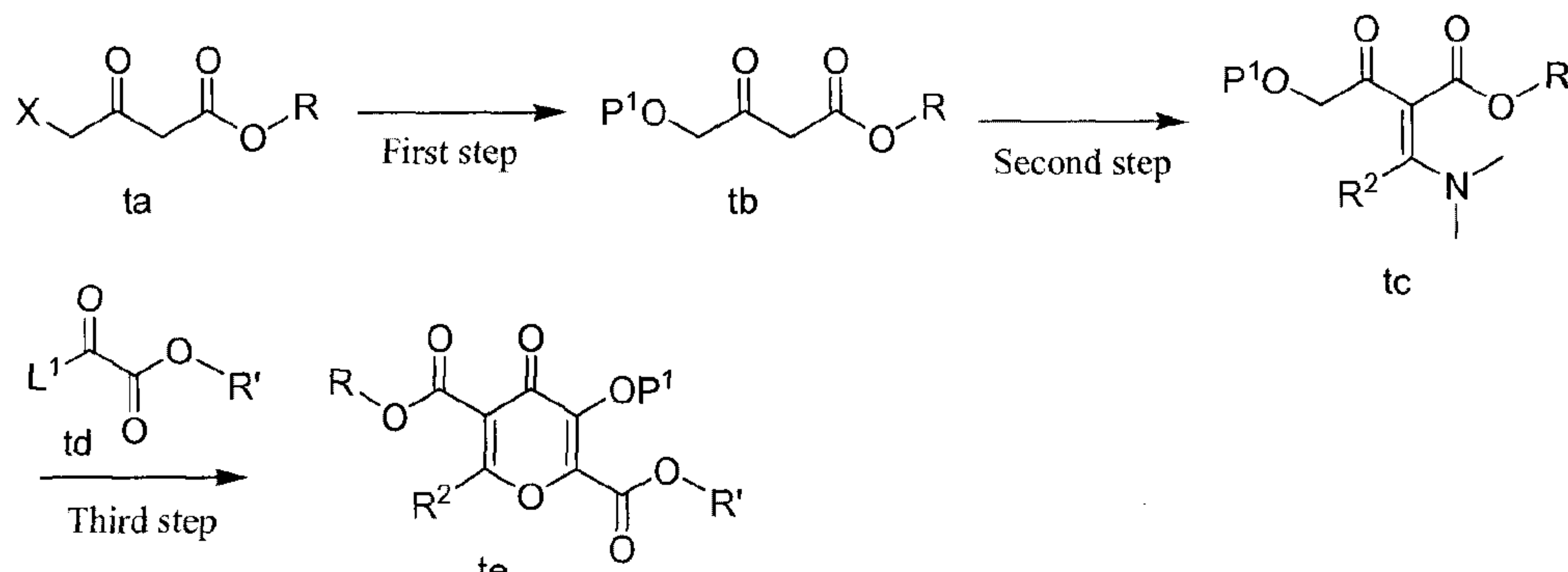
#### Twelfth step

A compound un can be obtained by adding  $R^5-C(=O)-R^6$ , tertiary amine such as, triethylamine, diisopropylethylamine, N-methylmorpholine, etc. and acetic acid, to the compound um in the presence of a solvent such as toluene, DMF, DMA, NMP etc., and performing a reaction at 60°C to 120°C, preferably 80°C to 100°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

[0270]

Synthesis of compound te of Reference example

[Chemical formula 75]



[0271]

(wherein  $R'$  may be a group which can be protected and/or deprotected by the method described in Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) etc. and, for example,  $R'$  is lower alkyl etc.  $X$  is halogen, and other each symbol is same as above)

#### First step

An alcohol ( $P^1-OH$ ) corresponding to an objective substance is added to an organometallic base such as sodium tert-pentoxide, *n*-butyllithium, tert-butyllithium etc. in a solvent such as THF, ether, dichloromethane, DMI, DMF, DMA, etc. or in a mixed solution thereof. A solution of a compound **ta** is added dropwise thereto, and a reaction is performed at  $-20^\circ\text{C}$  to  $40^\circ\text{C}$ , preferably  $0^\circ\text{C}$  to  $30^\circ\text{C}$  for 0.1 hours to 12 hours, preferably 0.5 hours to 6 hours, thereby, a compound **tb** can be obtained.

#### Second step

A compound **tc** can be obtained by adding  $N,N$ -dimethylformamidodimethylacetal to the compound **tb** in a solvent such as THF, dioxane, toluene, ethyl acetate etc. or in a mixed solvent thereof, or without a solvent, and performing a reaction at  $0^\circ\text{C}$  to  $80^\circ\text{C}$ , preferably  $20^\circ\text{C}$  to  $40^\circ\text{C}$  for 0.5 hours to 24

hours, preferably 1 hour to 12 hours.

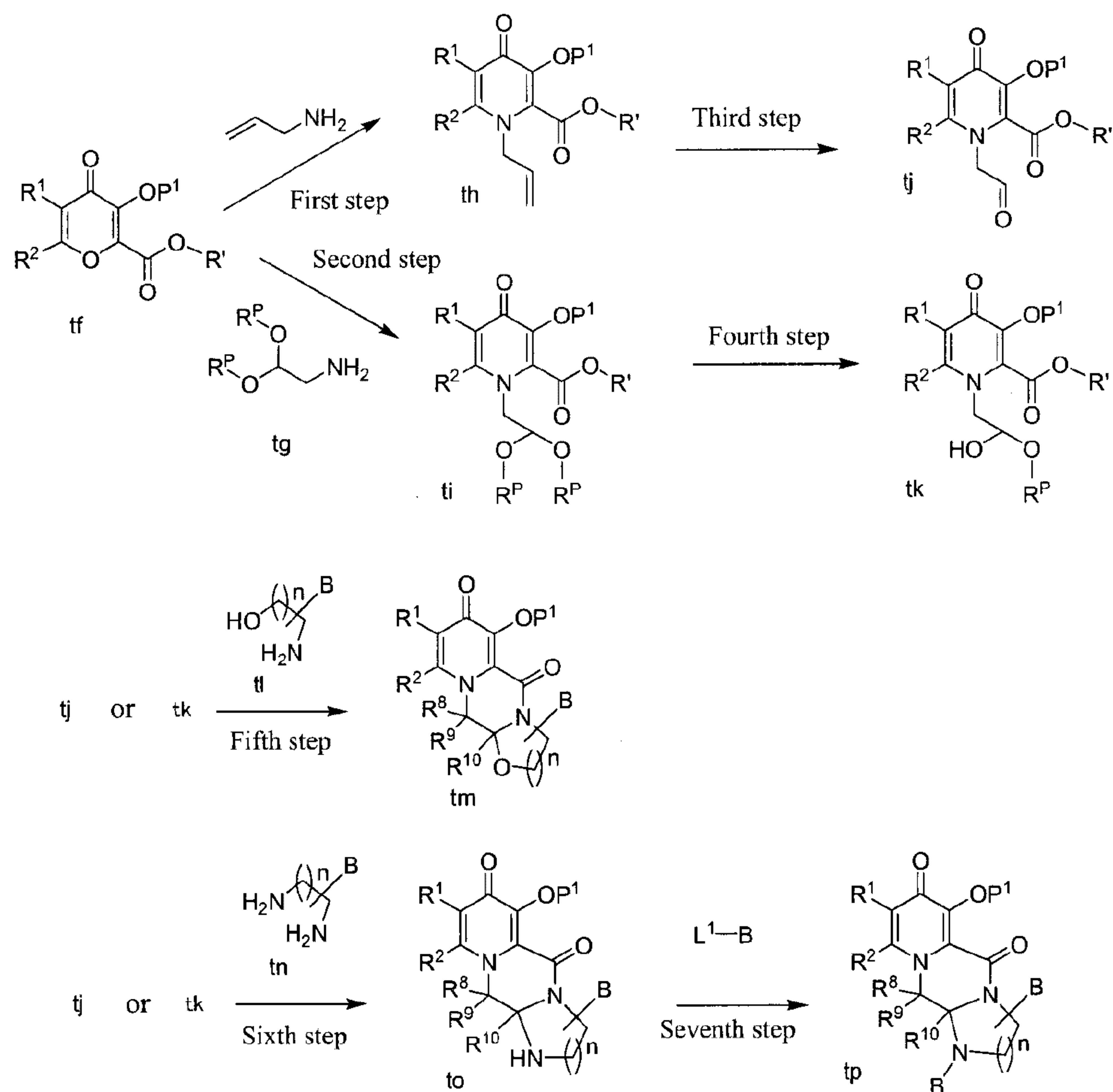
#### Third step

A compound td corresponding to an objective substance is added to an organometallic base such as sodium tert-pentoxide, n-butyllithium, tert-butyllithium, sodium metoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide etc. in a solvent such as THF, ether, DMI, methanol, ethanol, etc. or in a mixed solvent thereof. A solution of the compound tc is added dropwise thereto, a reaction is performed at -20°C to 60°C, preferably 0°C to 30°C for 0.5 hours to 24 hours, preferably 1 hour to 12 hours and, thereafter, an acid such as hydrochloric acid, sulfuric acid etc. is added to perform a reaction at -20°C to 60°C, preferably 0°C to 30°C for 0.5 hours to 24 hours, preferably 1 hour to 12 hours, thereby, a compound te can be obtained.

[0272]

Synthesis of compound tm of Reference example and compound tp of Reference example (see: Reference examples 165, and 169)

[Chemical formula 76]



[0273]

(wherein  $\text{R}^P$  may be an acetal protective group which can protect and/or can be deprotected by the method described in Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) etc. and, for example,  $\text{R}^P$  is lower alkyl etc. Other each symbol is same as above)

First step

A compound **th** can be obtained by adding allylamine to a compound **tf** which can be synthesized by the same method as that of a compound **te** in the presence of a solvent such as ethanol, THF, dioxane, acetonitrile, etc. or in a mixed solvent thereof,

and performing a reaction at 0°C to 80°C, preferably 20°C to 60°C for 0.5 hours to 48 hours, preferably 1 hour to 24 hours.

#### Second step

A compound ti can be obtained by adding a compound tg to a compound tf in the presence of a solvent such as ethanol, THF, dioxane, acetonitrile etc. or in a mixed solvent thereof, and performing a reaction at 0°C to 80°C, preferably 20°C to 60°C for 0.5 hours to 48 hours, preferably 1 hour to 24 hours.

#### Third step

A compound tj can be obtained by adding potassium osmate dihydrate, sodium periodate, and water to the compound th in the presence of a solvent such as THF, ethyl acetate, dioxane, etc. or in a mixed solvent thereof, and performing a reaction at 0°C to 60°C, preferably 10°C to 40°C for 0.5 hours to 24 hours, preferably 1 hour to 12 hours.

Alternatively, a compound tj can be obtained by introducing ozone into the compound th at -10°C to 20°C in the presence of a solvent such as THF, ethyl acetate, dioxane etc. or in a mixed solvent thereof and, subsequent to completion of the reaction, adding zinc-acetic acid, (EtO)<sub>3</sub>P, or dimethyl sulfide.

#### Fourth step

A compound tk can be obtained by adding an acid such as formic acid, trifluoroacetic acid, paratoluenesulfonic acid, etc. to the compound ti in a solvent such as acetone, acetonitrile, ethanol, water, etc. or in a mixed solvent thereof, or adding sulfuric acid in a formic acid solvent, and performing a reaction at 0°C to 90°C, preferably 20°C to 80°C for 0.5 hours to 24 hours, preferably 1 hour to 12 hours.

#### Fifth step

A compound tm can be obtained by adding a compound tl and acetic acid to the compound tj or the compound tk in the presence of a solvent such as chloroform,

dichloromethane, THF, etc., and performing a reaction at 0°C to 40°C, preferably 10°C to 30°C for 0.5 hours to 24 hours, preferably 1 hour to 12 hours.

Sixth step

A compound to can be obtained by adding a compound tn and acetic acid to the compound tj or the compound tk in the presence of a solvent such as chloroform, dichloromethane, THF, etc., and performing a reaction at 0°C to 40°C, preferably 10°C to 30°C for 0.5 hours to 24 hours, preferably 1 hour to 12 hours.

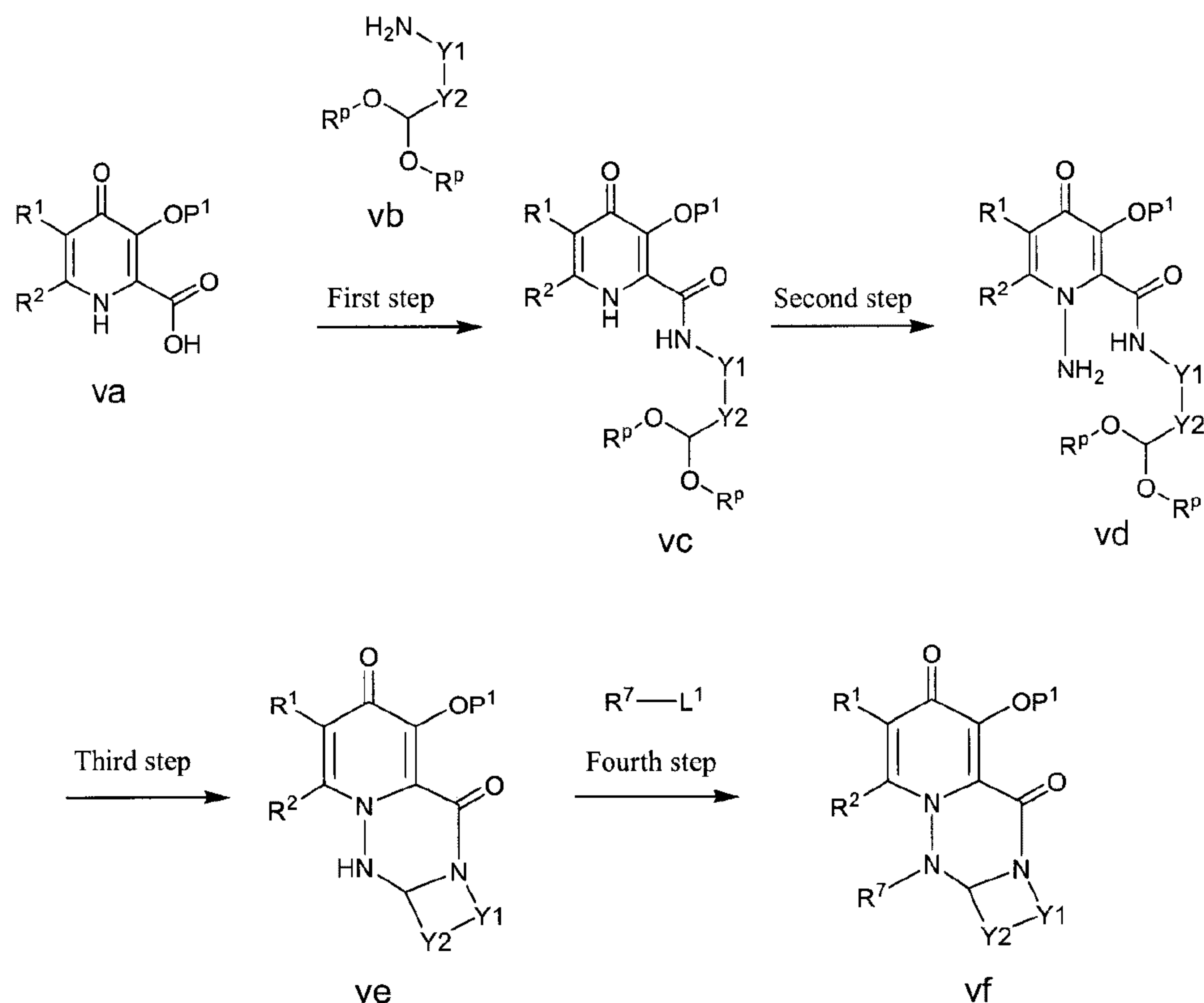
Seventh step

A compound tp can be obtained by adding a compound B-L<sup>1</sup> corresponding to an objective compound to the compound to in the presence of a solvent such as DMF, DMA, NMP, THF, etc. or in a mixed solvent thereof, and performing a reaction at 0°C to 80°C, preferably 20°C to 60°C for 0.5 hours to 12 hours, preferably 1 hour to 6 hours.

[0274]

Synthesis of compound vf of Reference example (see: Reference examples 583, and 584)

[Chemical formula 77]



[0275]

(wherein  $Y_1$  is a substituent corresponding to  $R^{3a}$ , and  $Y_2$  is a substituent corresponding to  $R^{11a}$ . Other each symbol is same as above)

#### First step

A compound **vc** can be obtained by adding a compound **vb** having a substituent corresponding to an objective compound to a compound **va** in the presence of a dehydration-condensation agent such as dicyclohexylcarbodiimide, carbonyldiimidazole, dicyclohexylcarbodiimido-N-hydroxybenzotriazole, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, hexafluorophosphoric acid 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium, WSC·HCl, HATU, etc. in a solvent such as DMF, THF, dichloromethane, acetonitrile

etc. or in a mixed solvent thereof, and performing a reaction at -20°C to 60°C, preferably -10°C to 40°C for 0.1 hours to 24 hours, preferably 1 hour to 12 hours.

Alternatively, a compound vc can be obtained by adding an acylating reagent such as diphenylchlorophosphate, thionyl chloride, oxalyl chloride etc. to a compound va in the presence or absence of a base such as pyridine, triethylamine, diisopropylethylamine, 1-methylimidazole, etc. in the presence of a solvent such as THF, dioxane, dichloromethane, DMF etc., thereby, generating acid chloride, and adding a compound vb having a substituent corresponding to an objective compound, and performing a reaction at -20°C to 60°C, preferably -10°C to 40°C for 0.1 hours to 24 hours, preferably 0.5 hours to 12 hours.

#### Second step

A compound vd can be obtained by adding potassium carbonate, sodium carbonate, and O-(2,4-dinitrophenyl)hydroxylamine to the compound vc in the presence of a solvent such as DMF, DMA, NMP, THF, etc., and performing a reaction at 10°C to 60°C, preferably 20°C to 40°C for 0.1 hours to 48 hours, preferably 1 hour to 24 hours.

#### Third step

A deprotecting reaction of an acetal protective group of the compound vd can be performed by the general method described in Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) etc. Thereafter, a generated aldehyde group is subjected to an intramolecular reaction, thereby, a compound ve can be obtained.

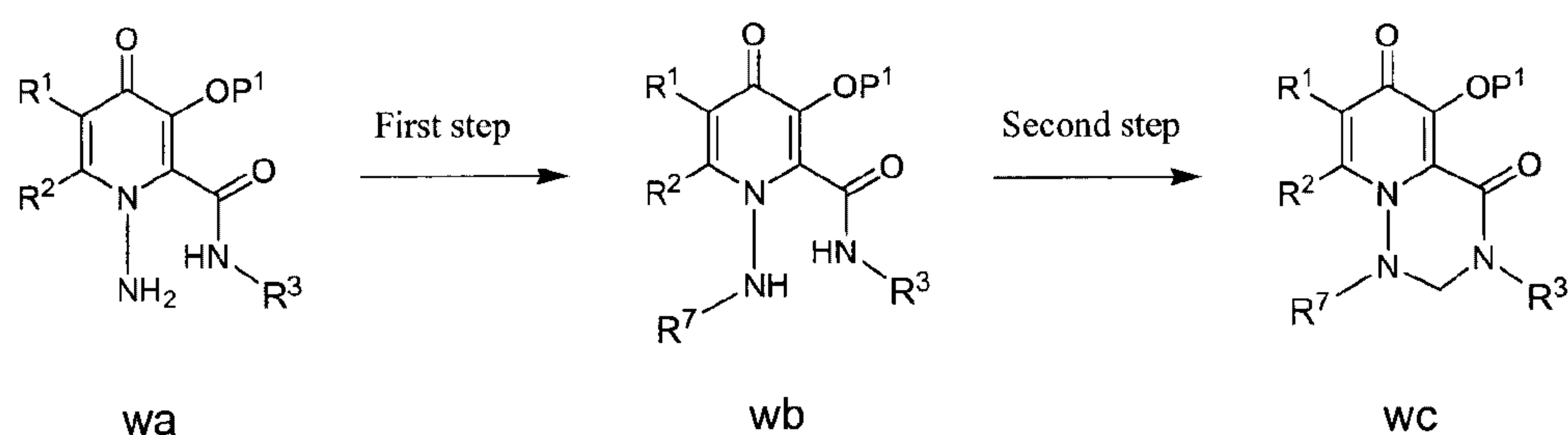
For example, a compound ve can be obtained by adding acetic acid and/or paratoluenesulfonic acid to the compound vd in the presence of a solvent such as DMF, toluene, THF, etc., and performing a reaction at 10°C to 80°C, preferably 30°C to 60°C for 0.5 hours to 12 hours, preferably 1 hour to 6 hours.

## Fourth step

A compound vf can be obtained by adding a compound  $R^7-L^1$  corresponding to an objective substance, and a base such as sodium carbonate, potassium carbonate, cesium carbonate, etc. to the compound ve in the presence of a solvent such as DMF, DMA, NMP, THF, etc. or in a mixed solvent thereof, and performing a reaction at 0°C to 60°C, preferably 10°C to 40°C for 0.1 hours to 48 hours, preferably 1 hour to 24 hours.

[0276]

Synthesis of compound wd of Reference example (see: Reference example 592, etc.)



[0277]

(wherein each symbol is same as above, and  $P^1$  may be a group which can be protected and/or deprotected by the method described in Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) etc. and, for example,  $P^1$  is arylalkyl, etc.)

## First step

A compound **wb** can be obtained by adding a cation-forming reagent (e.g.: dichloroacetic acid) to the compound **wa** in the presence of a solvent such as 1,2-dichloroethane, THF, dioxane, chloroform, etc. and adding a reagent,  $R^7-OH$  corresponding to an objective substance, and performing a reaction at 10°C to 60°C, preferably 20°C to 40°C for 0.1 hours to 24 hours, preferably 0.5 hours to 12 hours.

## Second step

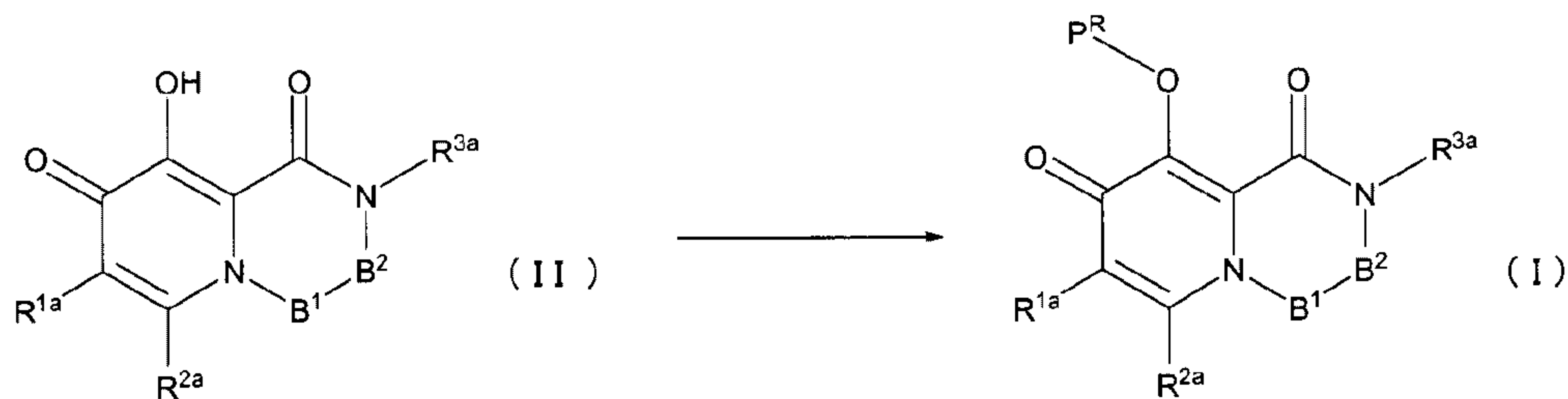
A base (e.g.:

2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) is added to the compound wb in the presence of a solvent such as DMF, DMA, NMP, THF, etc., paraformaldehyde is added, and they are reacted at 0°C to 60°C, preferably 10°C to 40°C for 0.1 hours to 24 hours, preferably 0.5 hours to 12 hours. Next, a compound wc can be obtained by adding a detachment reagent (e.g.: p-toluenesulfonyl chloride), and performing a reaction at 0°C to 60°C, preferably 10°C to 40°C for 0.1 hours to 24 hours, preferably 0.5 hours to 12 hours.

[0278]

Synthesis of compound of Example (prodrug: formula (I)) from compound of Reference example (parent compound: formula (II)) (see: Examples 1, 98, 105, 106, 106, 107, 108, 111, 112, 113, 122, 151, 152, 163, 177, 178, 186, 190, 192, 194, 196, 197, 199, 200, 201, and 203)

[Chemical formula 78]



[0279]

(wherein each substituent is same as in item 1)

A compound of Example can be obtained by the general method including converting a hydroxyl group into an ester group or ether group, using a compound

shown in Reference example as a source.

For example, the method described in Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons), Prog. Med. 5: 2157-2161 (1985), and Supplied by The British Library - "The world's Knowledge", etc. can be utilized.

[0280]

The present invention will be explained in more detail below by way of Examples, Reference examples, Intermediate Synthesis Examples, as well as Test Examples of the present invention, but the present invention is not limited by them.

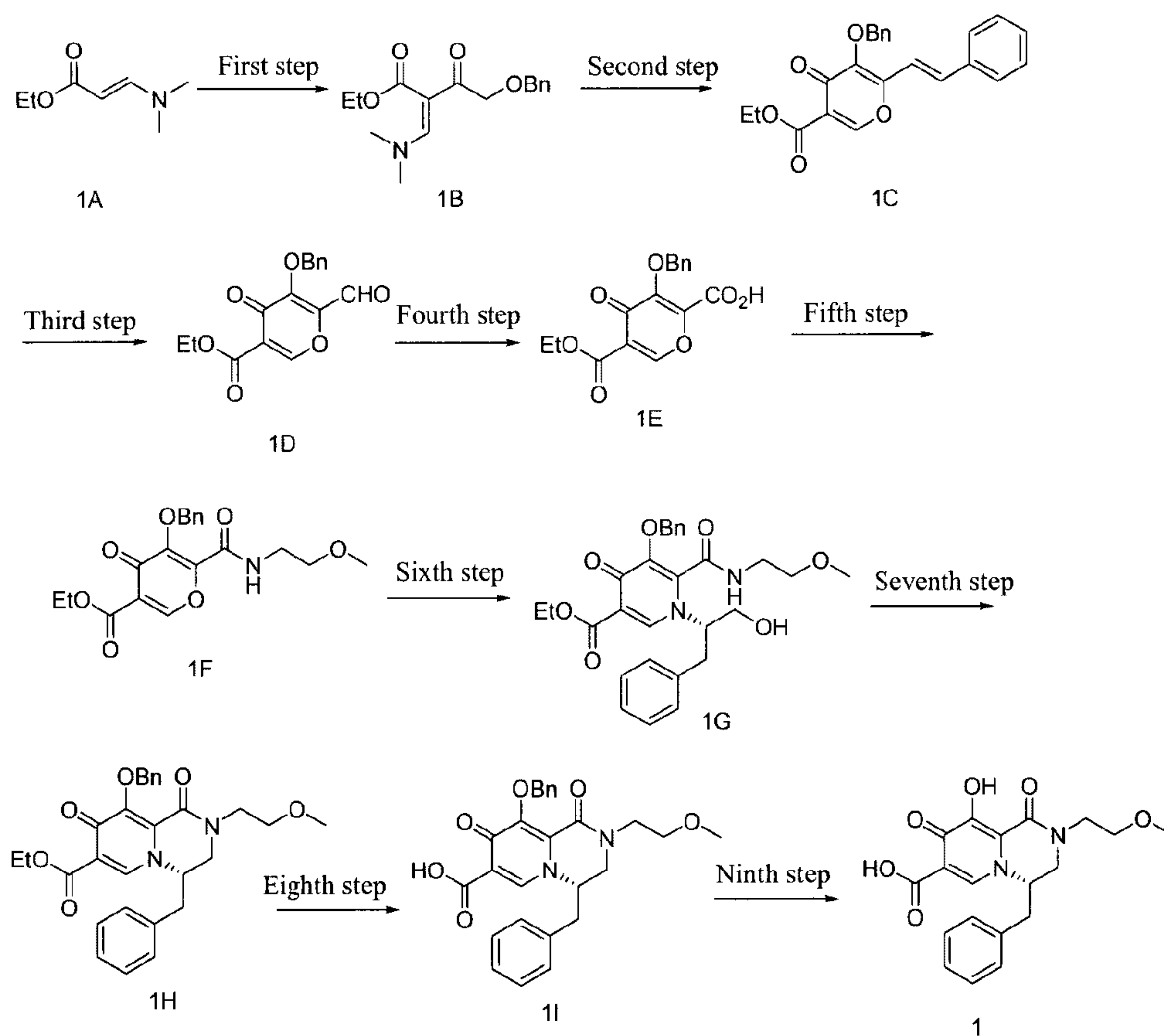
[0281]

Hereinbelow, structural formulae of compounds of Reference examples 1 to 775 that are parent compounds, and Synthesis Examples are shown.

[0282]

Reference example 1

[Chemical formula 79]



[0283]

## First step

A dichloromethane (90 mL) solution of compound 1A (12.8 g, 89.4 mmol) and pyridine (8.50 g, 107 mmol) was cooled to 1 to 3°C, and a dichloromethane (90 mL) solution of benzyloxycarbonyl chloride (19.8 g, 107 mmol) was added dropwise over 50 minutes while the same temperature was retained. After the reaction solution was stirred at the same temperature for 30 minutes, temperature was gradually raised to 15°C over 60 minutes, and ice water was added. The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane once. The combined extracts were washed with water three times, washed with an aqueous

saturated sodium chloride solution, and dried. The solvent was distilled off, and the resulting oil was purified by silica gel column chromatography. The materials were eluted firstly with n-hexane and, then, with n-hexane-ethyl acetate (1 : 1, v/v).

Concentration of objective fraction afforded 22.2 g of compound 1B as an oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.25(3H, t, J = 7.2 Hz), 2.90 (3H, brs), 3.24 (3H, brs), 4.15 (2H, q, J = 7.2 Hz), 4.45 (2H, s), 4.58 (2H, s), 7.25-7.38 (5H, m), 7.72 (1H, s).

#### Second step

A 1N lithiumhexamethyldisilazane THF solution (4.29 ml, 4.29 mmol) was cooled to -78°C, and a THF solution (4 ml) of compound 1B (500 mg, 1.72 mmol) and cinnamoyl chloride (343.2 mg, 2.06 mmol) were added dropwise thereto over 3 minutes while the same temperature was retained. After the reaction solution was stirred at the same temperature for 25 minutes, 2N hydrochloric acid (10 ml) was added, and the mixture was further stirred at room temperature for 10 minutes. To the reaction solution was added ethyl acetate, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate three times. The combined extracts were dried with sodium sulfate. The solvent was distilled off, and the resulting oil was purified by silica gel column chromatography. From fraction eluted with n-hexane-ethyl acetate (1 : 1, v/v), 364.3 mg (yield 56%) of compound 1C was obtained as a solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.40 (3H, t, J = 7.2 Hz), 4.39 (2H, q, J = 7.2 Hz), 5.27 (2H, s), 6.99 (1H, d, J = 16.2 Hz), 7.23 (1H, d, J = 16.2), 7.26-7.48 (10H, m), 8.45 (1H, s).

#### Third step

To a MeCN (5 ml) solution of compound 1C and ruthenium chloride (2.76 mg, 0.0133 mmol) was added dropwise an aqueous solution (8 ml) of sodium periodate (625.8 mg, 2.93 mmol) and 96% sulfuric acid (287.4 mg, 2.93 mmol) over 10 minutes at room temperature under nitrogen stream. After the reaction solution was stirred at

the same temperature for 5 minutes, ethyl acetate was added, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate two times. The combined extracts were dried with sodium sulfate. The solvent was distilled off, and the resulting oil was purified by silica gel column chromatography. From fraction eluted with n-hexane-ethyl acetate (1 : 1, v/v), 303.2 mg (yield 75%) of compound 1D was obtained as an oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.39 (3H, t,  $J = 6.9$  Hz), 4.40 (2H, q,  $J = 6.9$  Hz), 5.54 (2H, s), 7.37 (5H, s), 8.48 (1H, s), 9.85 (1H, s).

#### Fourth step

To a MeCN (15 ml) solution of compound 1D (1.00 g, 3.31 mmol) was added an aqueous solution (10 ml) of 96% sulfuric acid (421.7 mg, 4.30 mmol) and amidosululic acid (642.7 mg, 6.62 mmol) at room temperature, the mixture was stirred, and an aqueous solution (10 ml) of sodium chlorite (388.9 mg, 4.30 mmol) was added dropwise over 5 minutes while the same temperature was retained. After the reaction solution was stirred at the same temperature for 5 minutes, an aqueous saturated sodium chloride solution was added, and the mixture was extracted with ethyl acetate three times. The combined extracts were dried with sodium sulfate. The solvent was distilled off, and the resulting oil was purified by silica gel column chromatography. The materials were eluted firstly with chloroform and, then, with chloroform-MeOH (7 : 3, v/v). Concentration of objective fraction afforded 748.8 mg (yield 71%) of compound 1E as an oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.40 (3H, t,  $J = 7.2$  Hz), 3.93 (1H, brs), 4.40 (2H, q,  $J = 7.2$  Hz), 5.61 (2H, s), 7.38-7.44 (10H, m), 8.52 (1H, s).

#### Fifth step

To a DMF (10 ml) solution of compound 1E (1.00 g, 3.14 mmol) were added

WSC HCl (1.20 g, 6.28 mmol) and HOBt (551.6 mg, 4.08 mmol) at room temperature, and the mixture was stirred at the same temperature for 90 minutes. The reaction solution was cooled to 0°C, and a DMF (2 ml) solution of 2-methoxyethanamine (236.0 mg, 3.14 mmol) was added dropwise over 3 minutes. The reaction solution was stirred at the same temperature for 1 hour, water was added, and the mixture was extracted with ethyl acetate three times. The extract was washed with water three times, and dried with sodium sulfate. The solvent was distilled off, and the resulting oil was purified by silica gel chromatography. The materials were eluted firstly with n-hexane-ethyl acetate (1 : 1, v/v) and, then, with n-hexane-ethyl acetate (1 : 9, v/v). Concentration of objective fraction afforded 928.5 mg (yield 79%) of compound 1F as an oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.39 (3H, t, J = 7.2 Hz), 3.29 (3H, s), 3.41 (2H, t, J = 5.4 Hz), 3.47-3.53 (2H, m), 4.39 (2H, q, J = 7.2 Hz), 5.44 (2H, s), 7.36 (3H, m), 7.44-7.47 (2H, m), 8.07 (1H, brs), 8.54 (1H, s).

#### Sixth step

A xylene (2 ml) solution of compound 1F (500 mg, 1.33 mmol) and (S)-2-amino-3-phenylpropan-1-ol (604.2 mg, 4.0 mmol) was heated to 120°C, and stirred for 30 minutes. After the reaction solution was cooled to room temperature, and the solvent was distilled off, the resulting oil was purified by silica gel chromatography. The materials were eluted firstly with chloroform and, then, with chloroform-MeOH (9 : 1, v/v). Concentration of objective fraction afforded 487 mg (yield 72%) of compound 1G as an oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.41 (3H, t, J = 6.9 Hz), 2.24-2.34 (1H, m), 2.24-3.00 (1H, m), 3.03-3.16 (1H, m), 3.05 (3H, m), 3.25-3.32 (2H, m), 4.13-4.19 (1H, m), 4.17-4.30 (1H, m), 4.36-4.47 (1H, m), 4.51-4.54 (1H, m), 4.55 (1H, d, J = 10.5 Hz), 5.78 (1H, t, J = 6.9 Hz), 7.17-7.26 (4H, m), 7.28-7.35 (5H, m), 7.49 (1H, t, J = 5.4 Hz), 6.32 (1H, s).

## Seventh step

To a THF (6 ml) solution of compound 1G (2.86 g, 5.63 mmol) and triphenylphosphine (2.21 g, 8.45 mmol) was added dropwise a DEAD 40 wt% toluene solution (3.68 g, 8.45 mmol) at room temperature over 3 minutes. The reaction solution was stirred at the same temperature for 30 minutes, the solvent was distilled off, and the resulting oil was purified by silica gel chromatography. From a fraction eluted with ethyl acetate-MeOH (9 : 1, v/v), 1.37 g (yield 50%) of compound 1H was obtained as an oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.31 (3H, t, J = 7.2 Hz), 3.07 (2H, d, J = 6.9 Hz), 3.33 (3H, s), 3.57-3.80 (4H, m), 3.95 (1H, dd, J = 3.0 Hz, 6.6 Hz), 4.01-4.14 (1H, m), 4.16-4.34 (2H, m), 5.24 (1H, d, J = 9.9 Hz), 5.51 (1H, d, J = 9.9 Hz), 7.01-7.03 (2H, m), 7.21-7.37 (5H, m), 7.41-7.58 (1H, m), 7.64-7.69 (2H, m).

## Eighth step

To an EtOH (6 ml) solution of compound 1H (1.0 g, 2.04 mmol) was added a 2N aqueous sodium hydroxide solution (6 ml), and the mixture was stirred at room temperature for 30 minutes. The reaction solution was neutralized with 2N hydrochloric acid, and the precipitated solid was filtered, and dried to obtain 754 mg (yield 80%) of compound 1I.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.10 (2H, d, J = 7.8 Hz), 3.33 (3H, s), 3.57-3.69 (4H, m), 3.82-3.90 (1H, m), 3.95 (1H, dd, J = 3.3 Hz, 13.8 Hz), 4.36 (1H, dd, J = 6.3 Hz, 7.5 Hz), 5.36 (1H, d, J = 10.2 Hz), 5.45 (1H, d, J = 10.2 Hz), 6.98-7.01 (2H, m), 7.28-7.39 (6H, m), 7.59 (2H, dd, J = 1.8 Hz, 8.1 Hz), 7.87 (1H, s).

## Ninth step

Compound 1I (1.0 g, 2.16 mmol) was dissolved in THF (10 ml), 10% Pd-C (200 mg) was added, and the mixture was subjected to a catalytic reduction reaction

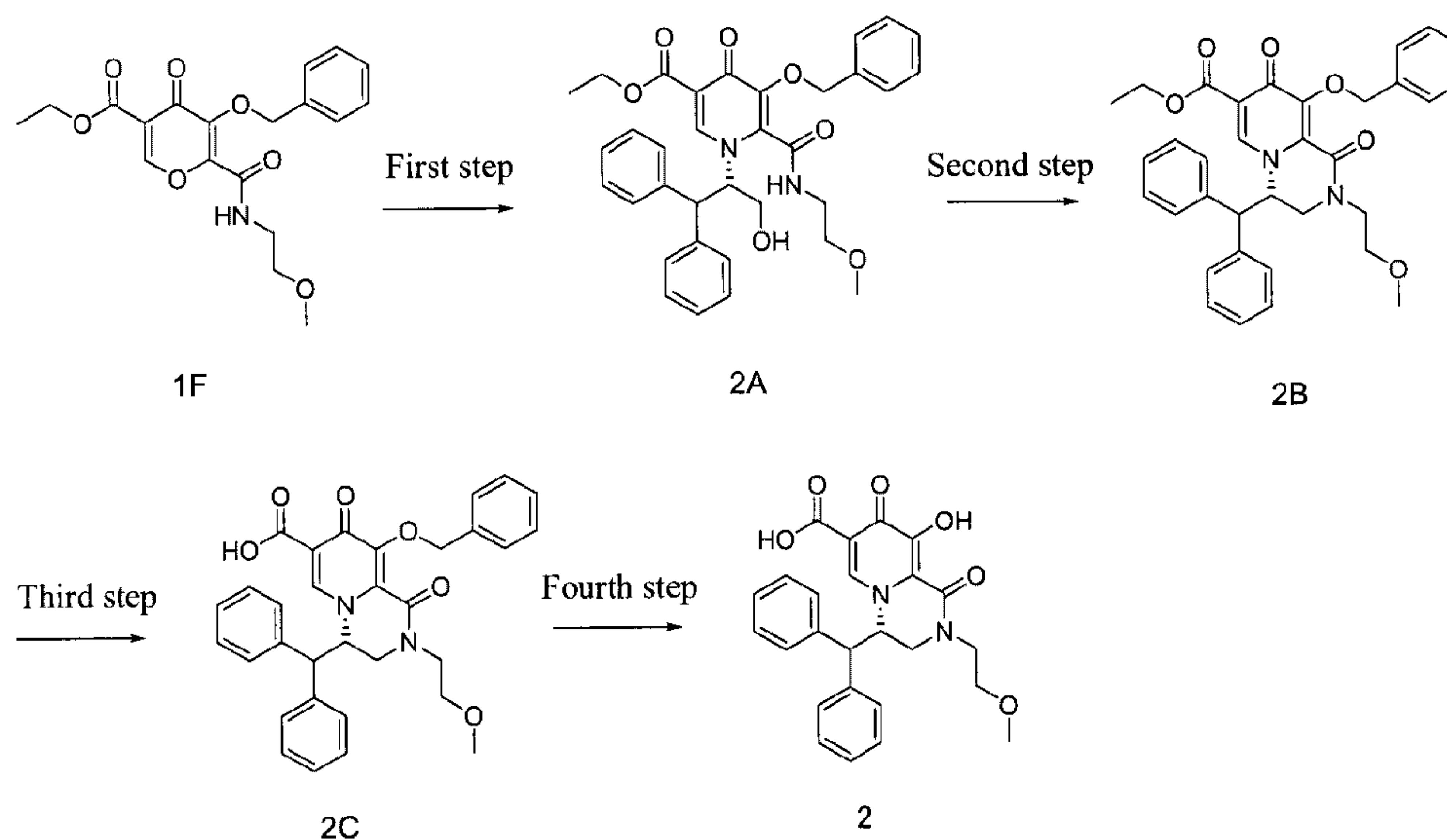
under hydrogen stream. The catalyst was removed by filtration, and the filtrate was concentrated. The resulting residue was washed with ether to obtain 512 mg (yield 64%) of compound 1.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 6.24 (2H, d,  $J = 6.3$  Hz), 3.36 (3H, s), 3.60-3.86 (5H, m), 4.14 (1H, d,  $J = 12.9$  Hz), 4.47 (1H, s), 7.03-7.05 (2H, m), 7.30-7.35 (3H, m), 7.88 (1H, s), 12.68 (1H, s), 14.83 (1H, s).

[0284]

Reference example 2

[Chemical formula 80]



[0285]

First step

To (S)-tert-butyl 3-hydroxy-1,1-diphenylpropan-2-ylcarbamate (5.00 g, 15.3 mmol) was added trifluoroacetic acid (40 ml), and the mixture was stirred for 1 hour under ice-cooling. After trifluoroacetic acid was distilled off, toluene was added, and distilled off again under reduced pressure to obtain crude

(S)-2-amino-3,3-diphenylpropan-1-ol. To the resulting (S)-2-amino-3,3-diphenylpropan-1-ol were added compound 1F (5.73 g, 15.3 mmol), toluene (50 ml), and triethylamine (6.4 ml, 45.8 mmol), the mixture was stirred at 90°C for 1 hour, and cooled to room temperature and, thereafter, the solvent was distilled off. To the resulting residue was added dichloromethane, and the mixture was washed with 2N aqueous hydrochloric acid solution, an aqueous saturated sodium bicarbonate solution, and an aqueous saturated sodium chloride solution. After separation of the organic layer, after magnesium sulfate was added, the mixture was filtered with celite™, and the filtrate was distilled off to obtain candy-like compound 2A (9.12 g).

MS:  $m/z = 585.2 [M + H]^+$ .

#### Second step

The compound 2A (8.60 g, 14.7 mmol) and triphenylphosphine (7.72 g, 29.4 mmol) were dissolved in tetrahydrofuran (90 ml), and a 2.2M toluene solution of diethyl azodicarboxylate (10.0 ml, 22.0 mmol) was added dropwise under ice-cooling. After the mixture was stirred for 2 hours under ice-cooling, and for 18 hours under room temperature, the solvent was distilled off. The resulting residue was purified by silica gel column chromatography to obtain foamy compound 2B (3.88 g, 6.85 mmol).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)  $\delta$ : 1.18 (3H, m), 3.11 (3H, s), 3.16 (1H, m), 3.28 (1H, m), 3.76 (1H, m), 3.97-4.13 (3H, m), 4.31 (1H, d,  $J = 11.3$  Hz), 5.08 (2H, s), 5.52 (1H, d,  $J = 12.0$  Hz), 7.18-7.25 (6H, m), 7.25-7.45 (6H, m), 7.55-7.66 (6H, m).

MS:  $m/z = 567.7 [M + H]^+$ .

#### Third step

To compound 2B (3.4 g, 6.0 mmol) were added ethanol (36 ml), water (12 ml), and a 2N aqueous sodium hydroxide solution (4.5 ml, 9.0 mmol), and the mixture was stirred at room temperature for 40 minutes, thereafter, ethanol (10 ml) and water (10 ml)

were added, and the mixture was further stirred for 30 minutes. Ethanol was distilled off, ethyl acetate and water were added, and the mixture was stirred vigorously and, thereafter, layers were separated. The ethyl acetate layer was washed with 2N sodium hydroxide three times, and the aqueous layers were combined into one aqueous layer. To the aqueous layer was added ethyl acetate, the mixture was neutralized using 2N hydrochloric acid, then the mixture was stirred vigorously and, thereafter, the ethyl acetate layer was separated. To the ethyl acetate layer was added magnesium sulfate, the mixture was filtered with celite, and the filtrate was distilled off. The resulting residue was dissolved in MeOH, and the solvent was distilled off to obtain a solid of compound 2C (3.0 g, 5.64 mmol).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.11 (3H, s), 3.16 (1H, m), 3.25 (1H, m), 3.75 (1H, m), 4.11 (1H, m), 4.36 (1H, d, J = 11.6 Hz), 5.18 (2H, dd, J = 15.7 Hz, 10.4 Hz), 5.71 (1H, d, J = 11.6 Hz), 7.08-7.20 (5H, m), 7.29-7.45 (6H, m), 7.55 (2H, d, J = 6.7 Hz), 7.61 (2H, d, J = 7.5 Hz), 7.98 (1H, s).

MS: m/z = 539.4 [M + H]<sup>+</sup>.

#### Fourth step

To compound 2C (1.50 g, 2.79 mmol) were added methanol (22 ml), and 10% palladium carbon-50% wet (150 mg), and the mixture was stirred for 1 hour under hydrogen atmosphere. Ethyl acetate (44 ml) was added, the mixture was filtered with celite, and the filtrate was distilled off. The resulting residue was dissolved in methanol (20 ml), water (10 ml) was added, and methanol was distilled off. The precipitate was filtered, and dried to obtain compound 2 (1.15 g, 2.56 mmol).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.15 (3H, s), 3.50-3.70 (5H, m), 4.19 (1H, dd, J = 13.8 Hz, 3.1 Hz), 4.49 (1H, d, J = 11.6 Hz), 5.78 (1H, d, J = 9.6 Hz), 7.10-7.27 (6H, m), 7.34 (1H, m), 7.46 (2H, t, J = 7.5 Hz), 7.63 (2H, t, J = 7.7 Hz), 7.94 (1H, s), 12.94 (1H, s), 15.08 (1H,

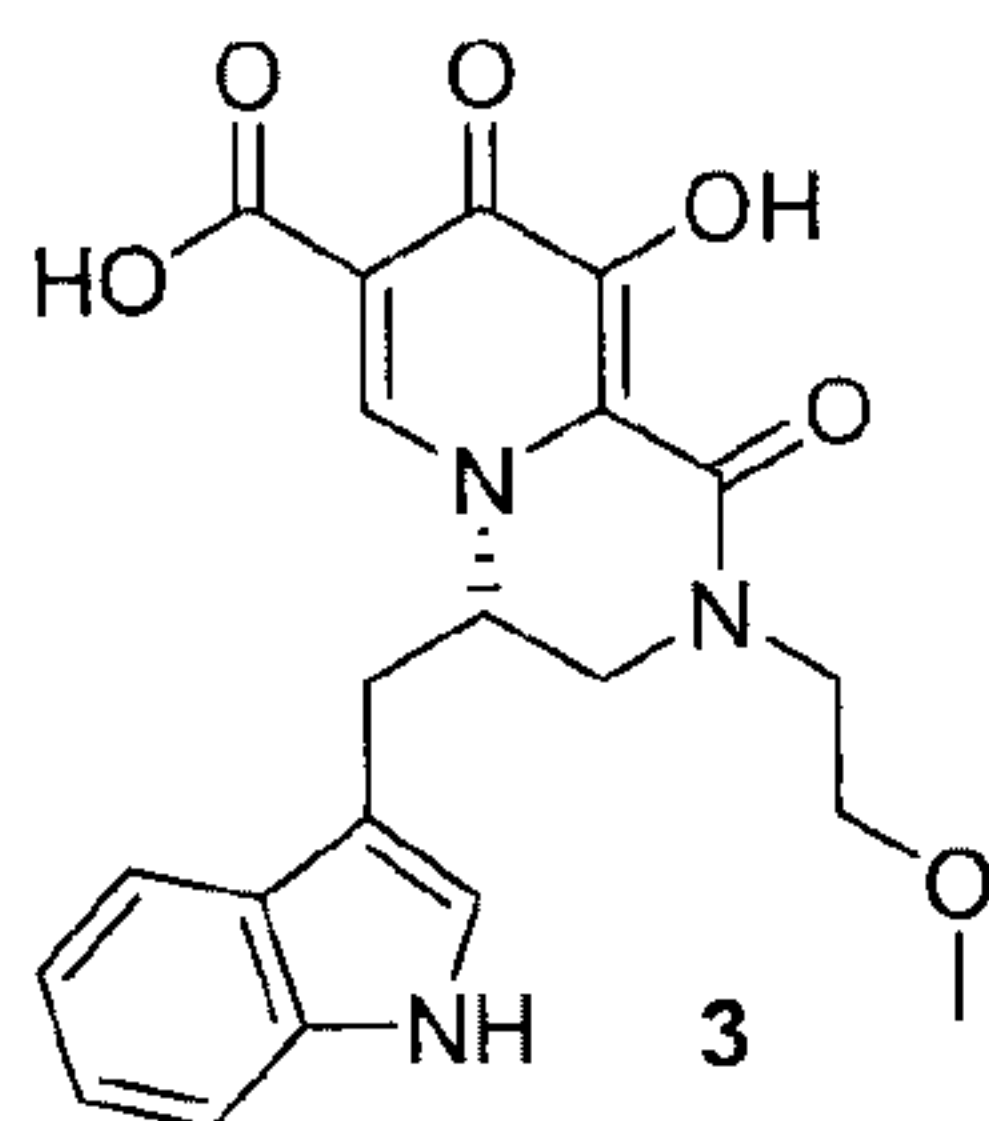
s).

MS:  $m/z = 449.4$   $[M + H]^+$ .

[0286]

Reference example 3

[Chemical formula 81]



[0287]

According to Reference example 2, compound 3 was synthesized by the same procedure.

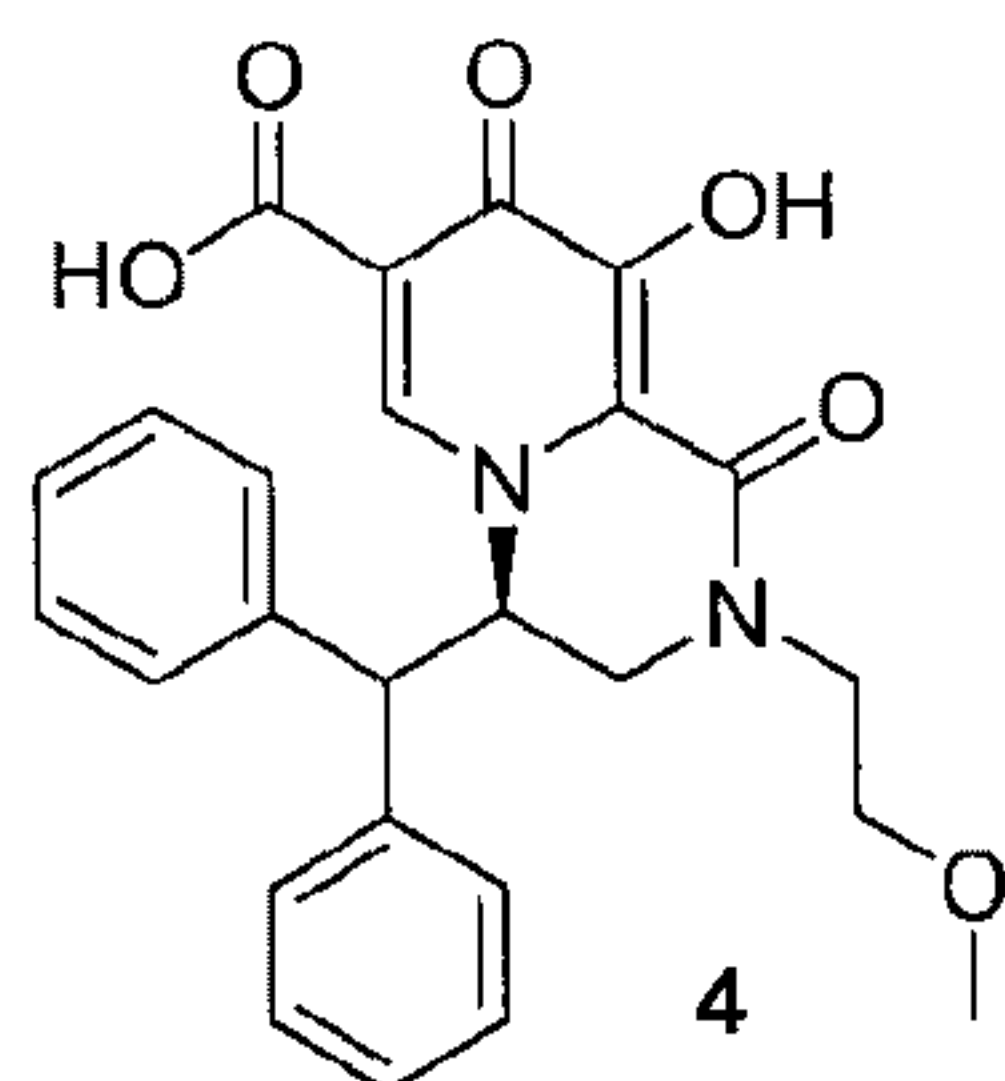
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.15 (1H, m), 3.26 (3H, s), 3.52-3.70 (4H, m), 3.70-3.80 (2H, m), 4.10 (1H, d,  $J = 12.9$  Hz), 4.92 (1H, brs), 6.98 (1H, t,  $J = 7.4$  Hz), 7.03 (1H, brs), 7.08 (1H, t, 7.6 Hz), 7.34 (1H, d,  $J = 7.8$  Hz), 7.47 (1H, d,  $J = 7.3$  Hz), 7.80 (1H, s), 10.94 (1H, brs), 15.38 (1H, brs).

MS:  $m/z = 412.4$   $[M + H]^+$ .

[0288]

Reference example 4

[Chemical formula 82]



[0289]

According to Reference example 2, compound 4 was synthesized by the same procedure.

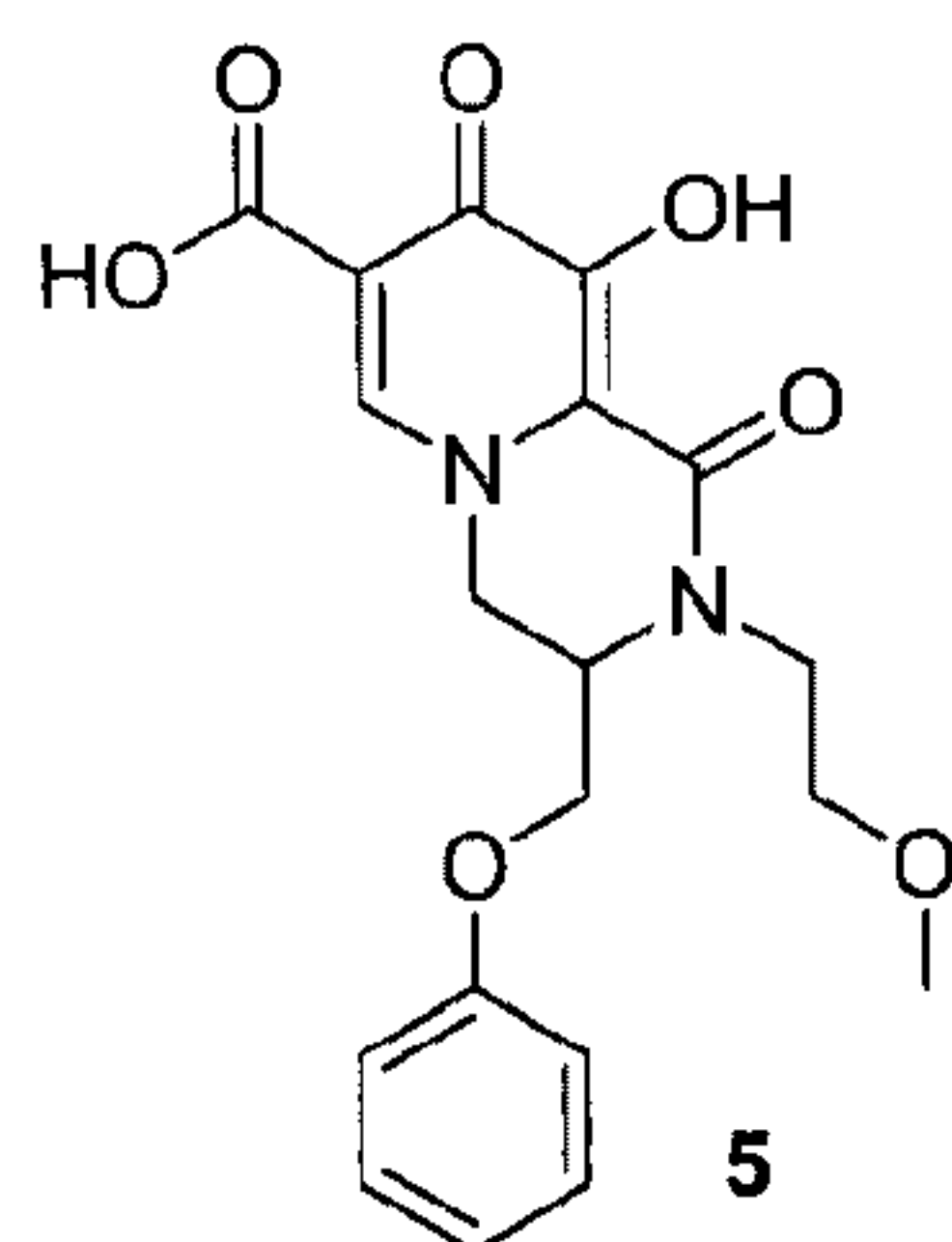
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.13 (3H, s), 3.46-3.72 (5H, m), 4.16 (1H, d,  $J = 12.6$  Hz), 4.48 (1H, d,  $J = 10.9$  Hz), 5.77 (1H, d,  $J = 11.6$  Hz), 7.10-7.27 (6H, m), 7.32 (1H, m), 7.44 (2H, m), 7.61 (2H, m), 7.93 (1H, s), 15.04 (1H, s).

MS:  $m/z = 449.3$   $[\text{M} + \text{H}]^+$ .

[0290]

Reference example 5

[Chemical formula 83]



[0291]

According to Reference example 2, compound 5 was synthesized by the same

procedure.

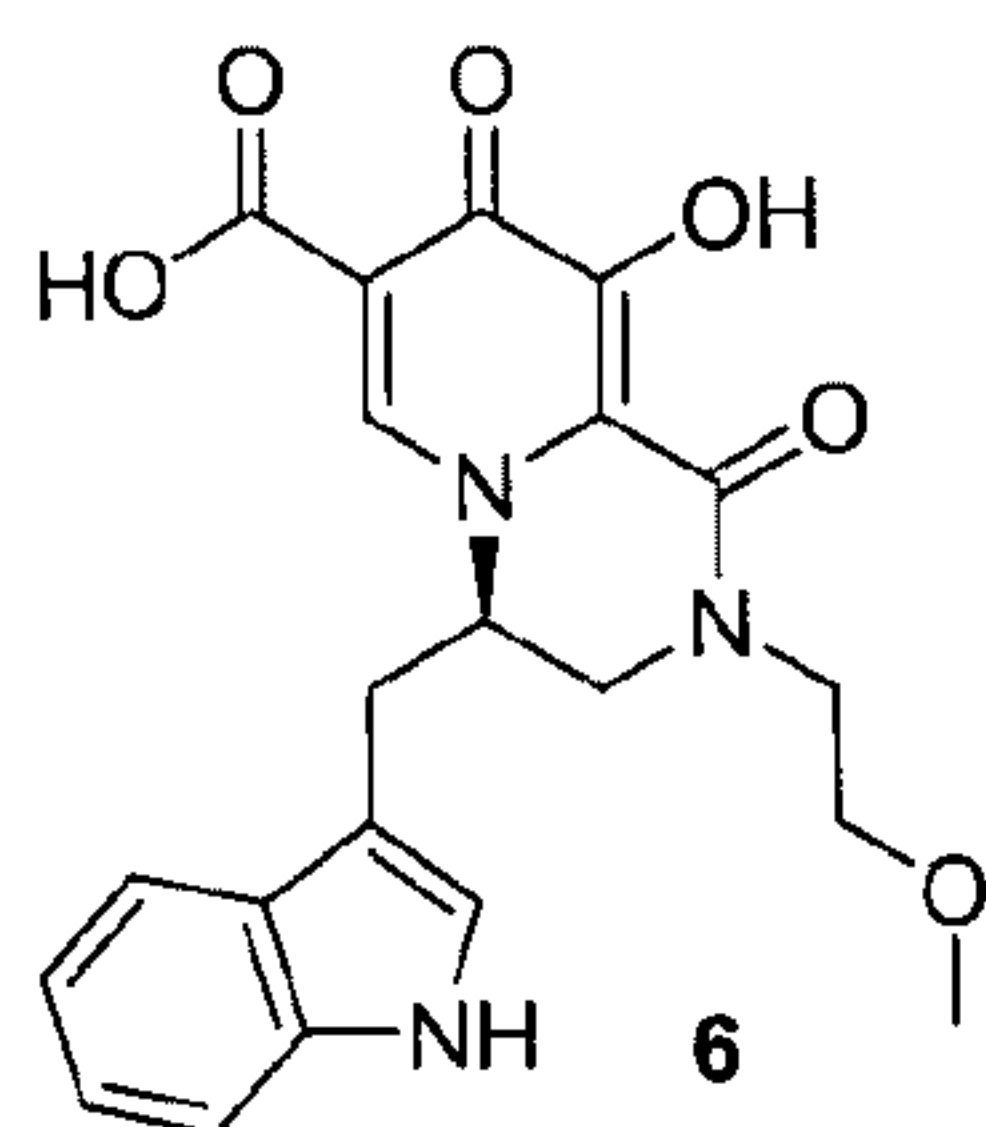
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.28 (3H, s), 3.52-3.68 (4H, m), 4.06 (1H, m), 4.25 (2H, m), 4.41 (1H, brs), 4.56 (1H, d,  $J = 13.6$  Hz), 4.82 (1H, d,  $J = 13.9$  Hz), 6.74 (2H, d,  $J = 7.6$  Hz), 6.92 (1H, t,  $J = 7.20$  Hz), 7.25 (2H, t,  $J = 7.8$  Hz), 8.58 (1H, s), 12.48 (1H, brs), 15.55 (1H, brs).

MS:  $m/z = 389.4$   $[\text{M} + \text{H}]^+$ .

[0292]

Reference example 6

[Chemical formula 84]



[0293]

According to Reference example 2, compound 6 was synthesized by the same procedure.

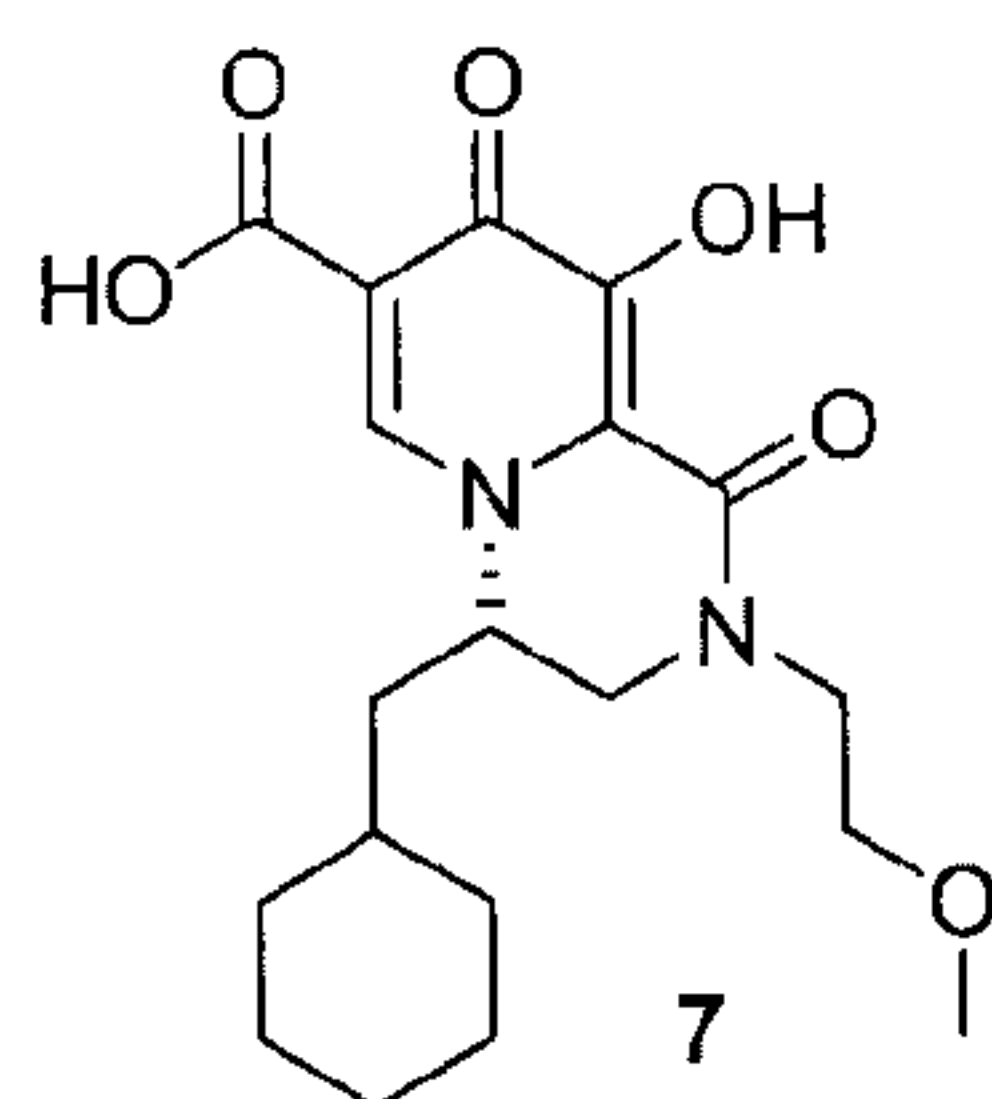
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.16 (1H, m), 3.26 (3H, s), 3.50-3.70 (4H, m), 3.70-3.80 (2H, m), 4.10 (1H, d,  $J = 13.4$  Hz), 4.92 (1H, brs), 6.98 (1H, t,  $J = 7.1$  Hz), 7.03 (1H, brs), 7.08 (1H, t,  $J = 7.3$  Hz), 7.34 (1H, d,  $J = 7.8$  Hz), 7.48 (1H, d,  $J = 7.3$  Hz), 7.81 (1H, s), 12.91 (1H, s), 15.36 (1H, s).

MS:  $m/z = 412.4$   $[\text{M} + \text{H}]^+$ .

[0294]

Reference example 7

[Chemical formula 85]



[0295]

According to Reference example 2, compound 7 was synthesized by the same procedure.

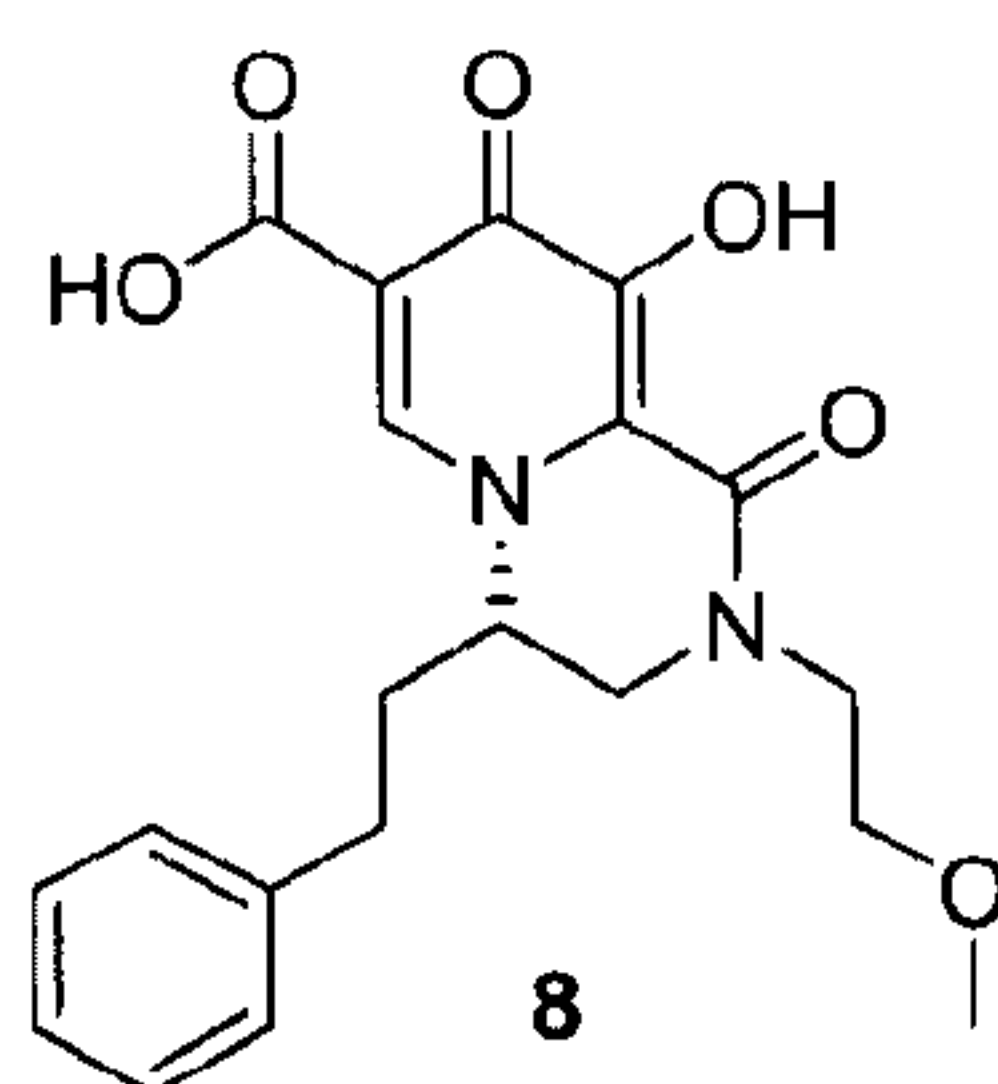
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 0.85-0.95 (2H, m), 1.05-1.25 (5H, m), 1.45-1.80 (8H, m), 3.28 (3H, s), 3.46 (1H, m), 3.58 (1H, m), 3.72 (1H, d,  $J = 13.9$  Hz), 3.93 (1H, m), 4.04 (1H, d,  $J = 13.1$  Hz), 4.88 (1H, s), 8.56 (1H, s), 12.80 (1H, s), 15.51 (1H, s).

MS:  $m/z = 379.3$   $[\text{M} + \text{H}]^+$ .

[0296]

Reference example 8

[Chemical formula 86]



[0297]

According to Reference example 2, compound 8 was synthesized by the same

procedure.

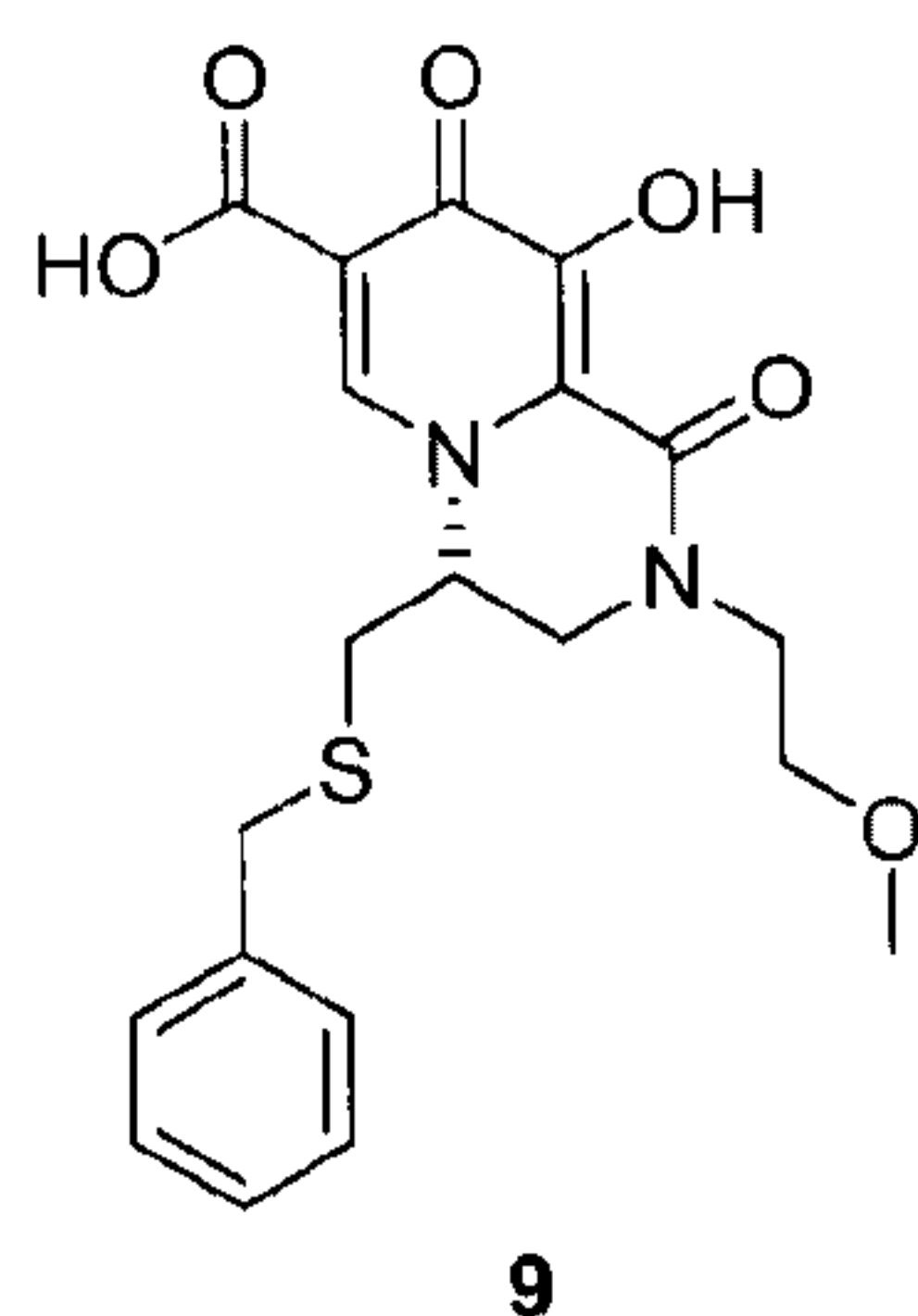
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.07 (2H, m), 2.55 (1H, m), 2.74 (1H, m), 3.17 (1H, s), 3.23 (3H, s), 3.48-3.65 (4H, m), 3.79 (1H, d,  $J = 13.6$  Hz), 3.87 (1H, m), 4.09 (1H, d,  $J = 13.6$  Hz), 4.80 (1H, s), 7.10-7.29 (5H, m), 8.59 (1H, s), 12.77 (1H, s), 15.49 (1H, s).

MS:  $m/z = 387.3$   $[\text{M} + \text{H}]^+$ .

[0298]

Reference example 9

[Chemical formula 87]



**9**

[0299]

According to Reference example 2, compound 9 was synthesized by the same procedure.

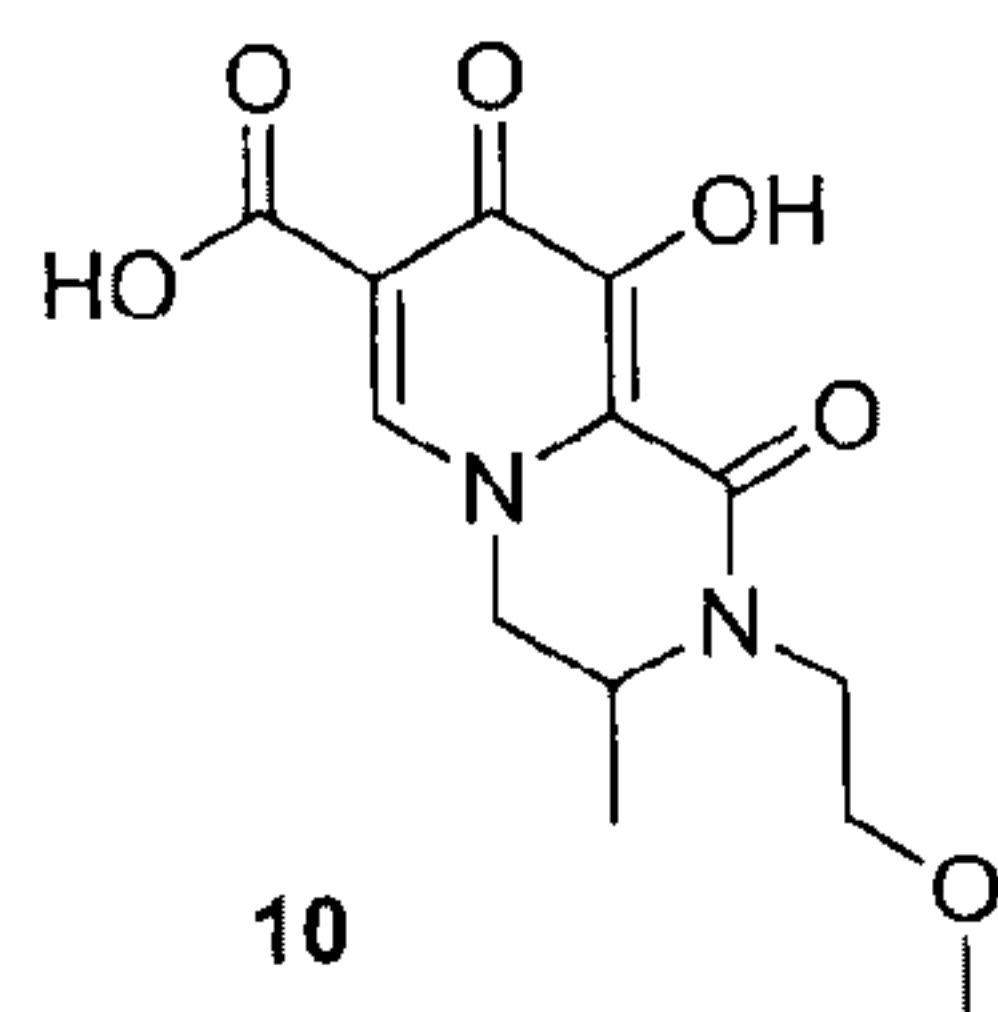
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.80 (1H, dd,  $J = 14.5$  Hz,  $J_2 = 8.5$  Hz), 2.93 (1H, dd,  $J = 14.4$  Hz,  $J_2 = 5.6$  Hz), 3.21 (3H, s), 3.40-3.55 (4H, m), 3.77 (2H, s), 3.82 (1H, d,  $J = 13.1$  Hz), 3.88 (1H, m), 4.13 (1H, d,  $J = 13.6$  Hz), 4.85 (1H, s), 7.20-7.35 (5H, m), 8.61 (1H, s), 12.79 (1H, s), 15.43 (1H, s).

MS:  $m/z = 419.3$   $[\text{M} + \text{H}]^+$ .

[0300]

Reference example 10

[Chemical formula 88]



[0301]

According to Reference example 2, compound 10 was synthesized by the same procedure.

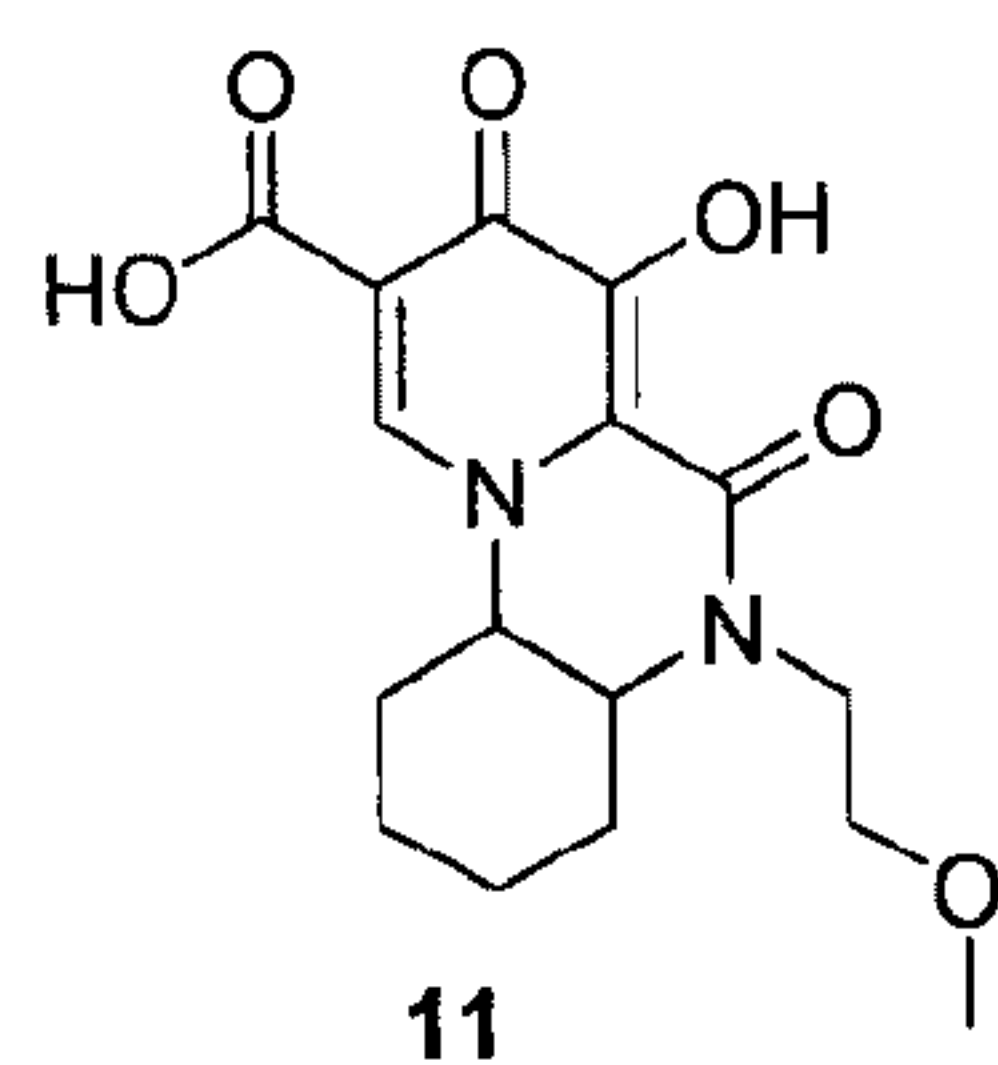
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.22 (3H, d,  $J = 6.2$  Hz), 3.29 (3H, s), 3.43 (1H, m), 3.58 (2H, m), 3.94 (1H, m), 4.12 (1H, brs), 4.41 (1H, d,  $J = 13.6$  Hz), 4.49 (1H, d,  $J = 13.1$  Hz), 8.59 (1H, s), 12.65 (1H, s), 15.53 (1H, s).

MS:  $m/z = 297.2$   $[\text{M} + \text{H}]^+$ .

[0302]

Reference example 11

[Chemical formula 89]



[0303]

According to Reference example 2, compound 11 was synthesized by the same

procedure.

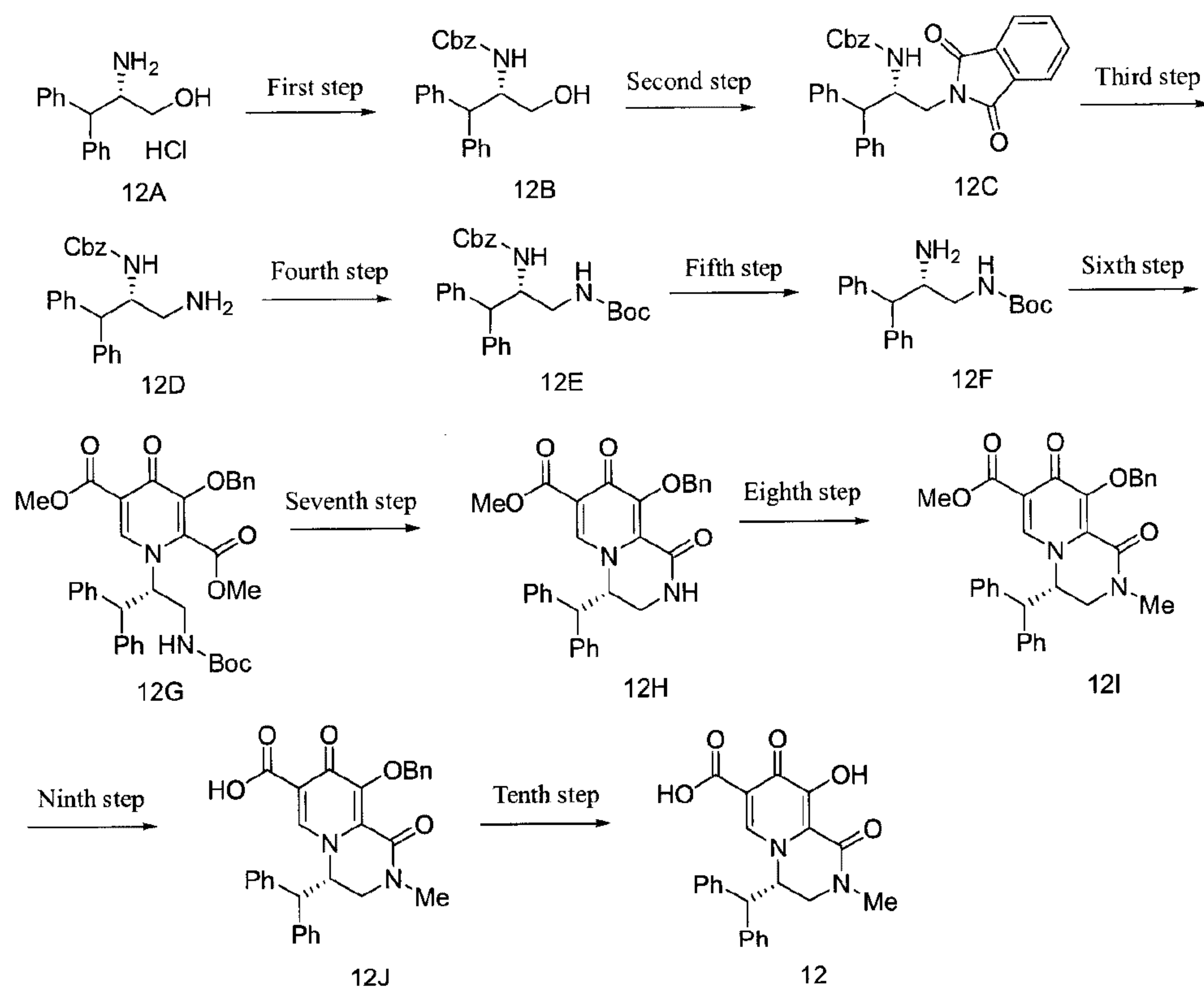
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.46 (4H, brs), 1.76-1.90 (2H, m), 2.22 (1H, brs), 3.27 (3H, s), 3.57 (1H, d,  $J = 5.3$  Hz), 4.07 (1H, m), 4.69 (1H, m), 8.47 (1H, s), 13.04 (1H, s), 15.52 (1H, s).

MS:  $m/z = 337.2$   $[\text{M} + \text{H}]^+$ .

[0304]

Reference example 12

[Chemical formula 90]



[0305]

First step

Compound 12A (1.53 g, 5.80 mmol) were dissolved in THF (6 ml) and water

(6 ml), potassium carbonate (2.41 g, 17.4 mmol) was added, the mixture was stirred, and benzyl chloroformate (1.09 g, 6.38 mmol) was added dropwise at 0°C. After stirring at 0°C for 10 minutes, the mixture was stirred at room temperature for 2 hours. The reaction solution was poured into sodium bicarbonate water, and the mixture was extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid and an aqueous saturated sodium chloride solution, and dried with sodium sulfate. The solvent was distilled off to obtain 2.32 g of compound 12B as a colorless gummy substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.98 (1H, brs), 3.55 (1H, m), 3.75 (1H, m), 4.20 (1H, d, J = 10.5 Hz), 4.58 (1H, m), 4.83 (1H, brs), 5.07 (2H, s), 7.16-7.39 (15H, m).

#### Second step

The compound 12B (1.94 g, 5.37 mmol), triphenylphosphine (2.11 g, 8.05 mmol) and phthalimide (948 mg, 6.44 mmol) were added to THF (20 ml), and diisopropyl azodicarboxylate (2.2M in toluene, 3.66 ml, 8.05 mmol) was added dropwise at room temperature. After stirring at room temperature for 4 hours, the solvent was distilled off under reduced pressure. The resulting crude product was purified by silica gel column chromatography (n-hexane-ethyl acetate, 1 : 1, v/v) to obtain 2.39 g of compound 12C as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.73 (2H, m), 4.05 (1H, d, J = 10.1 Hz), 4.70 (1H, d, J = 9.6 Hz), 4.77 (2H, d, J = 7.2 Hz) 5.02 (1H, m), 7.03-7.42 (15H, m), 7.68 (2H, dd, J = 5.7, 2.1 Hz), 7.78 (2H, dd, J = 5.7, 2.1 Hz).

#### Third step

The compound 12C (2.39 g, 4.87 mmol) was added to THF (20 ml) and methanol (20 ml), hydrazine hydrate (4.88 g, 97.4 mmol) was added, and the mixture was stirred at 50°C for 4 hours. The white precipitate was removed by filtration, and

washed with methanol. After the filtrate was distilled off under reduced pressure, the resulting crude product was purified by amino column chromatography (chloroform-methanol, 99 : 1, v/v) to obtain 1.41 g of compound 12D as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.63 (1H, dd, J = 13.2, 5.8 Hz), 2.86 (1H, d, J = 9.9 Hz), 4.07 (1H, d, J = 10.4 Hz), 4.53 (1H, m), 4.81 (1H, m), 5.00 (2H, d, 8.4 Hz), 7.20-7.36 (10H, m).

#### Fourth step

Compound 12D (1.41 g, 3.91 mmol) was dissolved in THF (15 ml), and Boc2O (896 mg, 4.11 mmol) was added at room temperature. After stirring for 1.5 hours, the solvent was concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (n-hexane-ethyl acetate, 1 : 1, v/v) to obtain 1.77 g of compound 12E as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.41 (9H, s), 3.23 (2H, brm), 3.97 (1H, d, J = 9.8 Hz), 4.58-4.80 (3H, m), 5.00 (2H, d, J = 9.8 Hz), 7.15-7.29 (10H, m).

#### Fifth step

Compound 12E (1.73 g, 3.76 mmol) and palladium-active carbon (10%, wet, 200 mg) were added to methanol (20 ml), and the mixture was stirred at room temperature for 1 hour under hydrogen atmosphere. After filtration with celite, the solvent was concentrated under reduced pressure to obtain 1.01 g of a colorless oily substance 12F.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.44 (9H, s), 2.82 (1H, m), 3.31 (1H, m), 3.73 (2H, d, J = 6.9 Hz), 4.98 (1H, s), 7.18-7.39 (10H, m).

#### Sixth step

Dimethyl 3-(benzyloxy)-4-oxo-4H-pyran-2,5-dicarboxylate (974 mg, 3.06 mmol) obtained by the method shown in Intermediate Synthesis Example 1, and 12F

(999 mg, 3.06 mmol) were added to toluene (10 ml), and the mixture was stirred at 110°C for 5 hours. After the solvent was distilled off under reduced pressure, the resulting crude product was purified by silica gel column chromatography (chloroform-methanol, 98 : 2, v/v) to obtain 1.51 g of compound 12G as a pale yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.36 (9H, s), 3.40 (1H, m), 3.53 (1H, m), 3.82 (3H, s), 3.91 (3H, s), 4.29 (1H, d, J = 11.3 Hz), 4.78 (1H, m), 4.82 (1H, m), 5.11 (1.9H, d, J = 7.5 Hz), 7.10-7.38 (10H, m), 8.27 (1H, s).

#### Seventh step

To compound 12G (1.45 g, 2.31 mmol) was added 4N HCl (ethyl acetate solution, 20 ml), and the mixture was stirred at room temperature for 1.5 hours. After the solvent was distilled off under reduced pressure, sodium bicarbonate water was added, and the mixture was stirred at room temperature for 1.5 hours. This was extracted with chloroform, and dried with sodium sulfate. After the solvent was distilled off under reduced pressure, the resulting crude product was purified by silica gel column chromatography (chloroform-methanol, 95 : 5, v/v) to obtain 1.01 g of compound 12H as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.40 (1H, dd, J = 13.6, 6.6 Hz), 3.78 (3H, s), 3.80 (1H, m), 4.37 (1H, d, J = 11.6 Hz), 4.59 (1H, d, J = 11.0 Hz), 5.43 (2H, d, J = 10.2 Hz), 5.93 (1H, d, J = 5.8 Hz), 7.03-7.21 (5H, m), 7.37 (9H, m), 7.63 (2H, m).

#### Eighth step

Compound 12H (50 mg, 0.10 mmol) was dissolved in DMF (1 ml), and cesium carbonate (165 mg, 0.50 mmol) was added. After stirring at room temperature for 30 minutes, iodomethane (0.032 ml, 0.50 mmol) was added, and the mixture was stirred at room temperature for 3.5 hours. The reaction solution was poured into water, and the

mixture was extracted with ethyl acetate, and dried with sodium sulfate. After the solvent was distilled off under reduced pressure, the resulting crude product was purified by silica gel column chromatography (chloroform-methanol, 95 : 5, v/v) to obtain 49 mg of compound 12I as a colorless solid.

#### Ninth step

Compound 12I (49 mg, 0.096 mmol) was dissolved in THF (0.5 ml) and methanol (0.5 ml), a 2N aqueous sodium hydroxide solution (0.24 ml, 0.48 mmol) was added at room temperature, and the mixture was stirred for 1.5 hours. After 1N hydrochloric acid was added, and the mixture was extracted with ethyl acetate, the extract was dried with sodium sulfate. After the solvent was distilled off under reduced pressure, 54 mg of compound 12J was obtained as a colorless solid.

MS:  $m/z = 481 [M + H]^+$ .

#### Tenth step

To compound 12J obtained in the ninth step was added trifluoroacetic acid (1 ml), and the mixture was stirred at room temperature for 1 hour. After concentration under reduced pressure, pH was adjusted to 3 with sodium bicarbonate water and 2N hydrochloric acid, and the mixture was extracted with chloroform, and dried with sodium sulfate. After the solvent was distilled off under reduced pressure, chloroform-methanol-ethyl ether were added, and the precipitated solid was filtered to obtain 26 mg of compound 12 as a colorless solid.

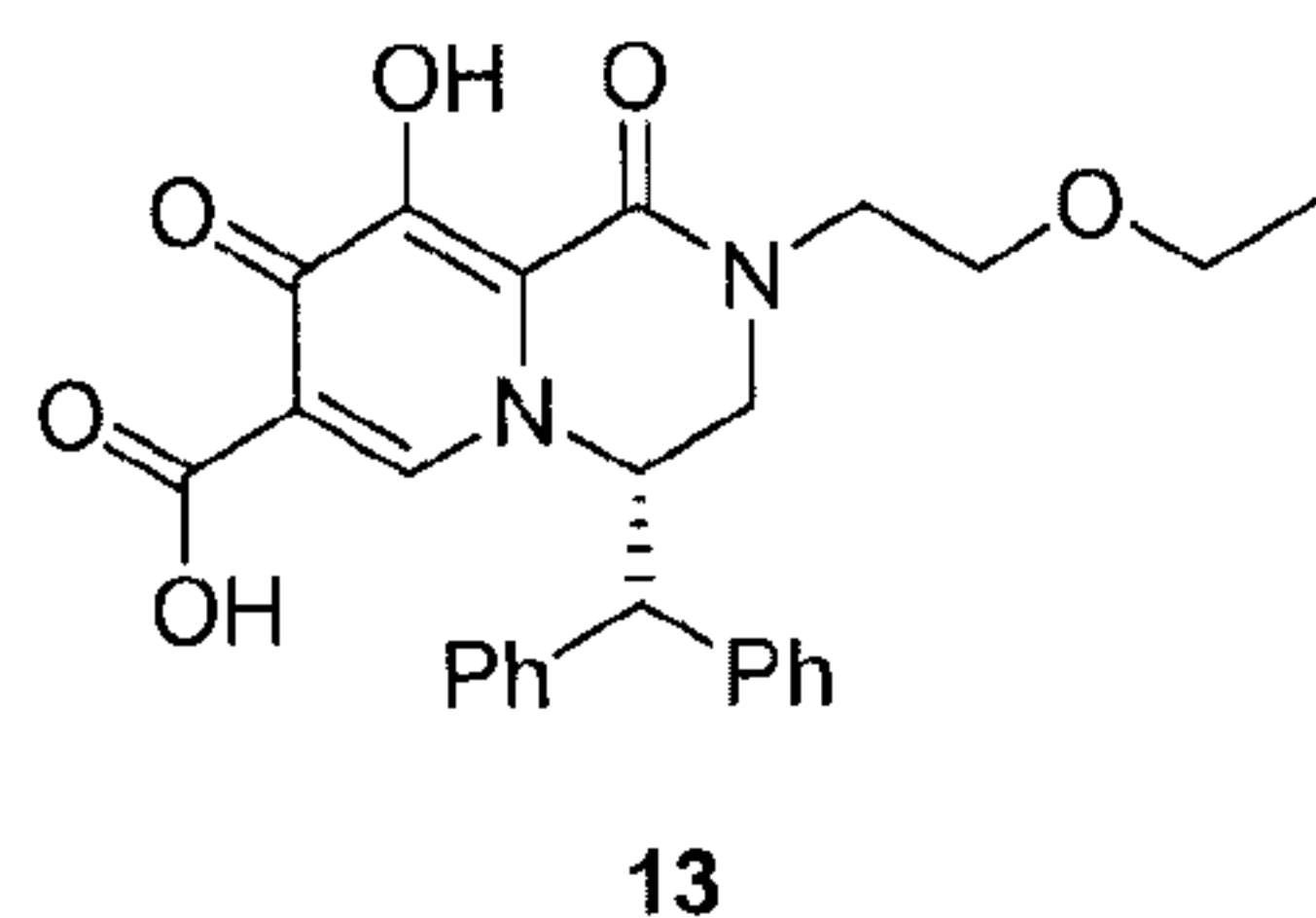
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.01 (3H, s), 3.26 (1H, t,  $J = 14.4$  Hz), 4.23 (1H, dd,  $J = 13.5$ , 3.8 Hz), 4.57 (1H, d,  $J = 11.6$  Hz), 5.78 (1H, d,  $J = 11.3$  Hz), 7.16-7.70 (10H, m), 8.00 (1H, s), 13.00 (1H, s), 15.10 (1H, s).

MS:  $m/z = 405 [M + H]^+$ .

[0306]

## Reference example 13

[Chemical formula 91]



[0307]

According to Reference example 12, compound 13 was synthesized by the same procedure.

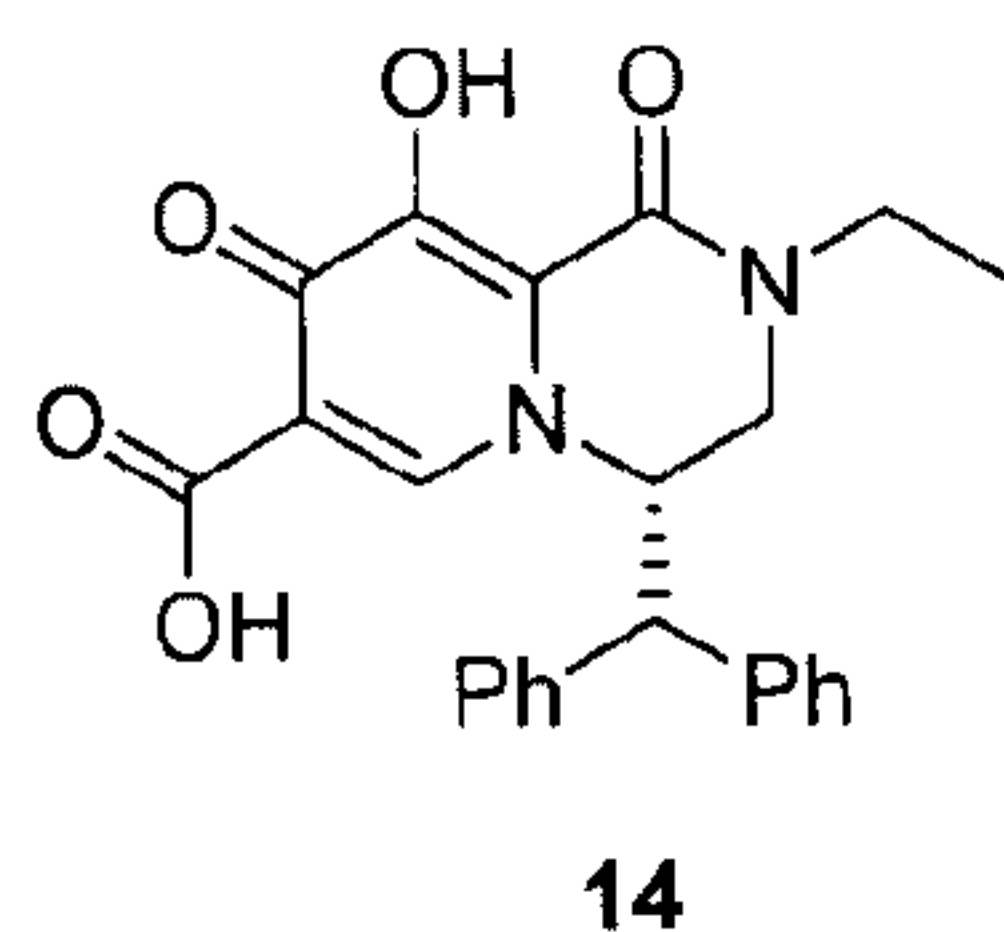
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.05 (3H, t,  $J = 6.9$  Hz), 3.43-3.65 (3H, m), 4.22 (1H, d,  $J = 10.6$  Hz), 4.55 (1H, d,  $J = 11.6$  Hz), 5.81 (1H, d,  $J = 10.1$  Hz), 7.15-7.68 (10H, m), 7.97 (1H, s), 12.96 (1H, s), 15.07 (1H, s).

MS:  $m/z = 463$   $[\text{M} + \text{H}]^+$ .

[0308]

## Reference example 14

[Chemical formula 92]



[0309]

According to Reference example 12, compound 14 was synthesized by the same procedure.

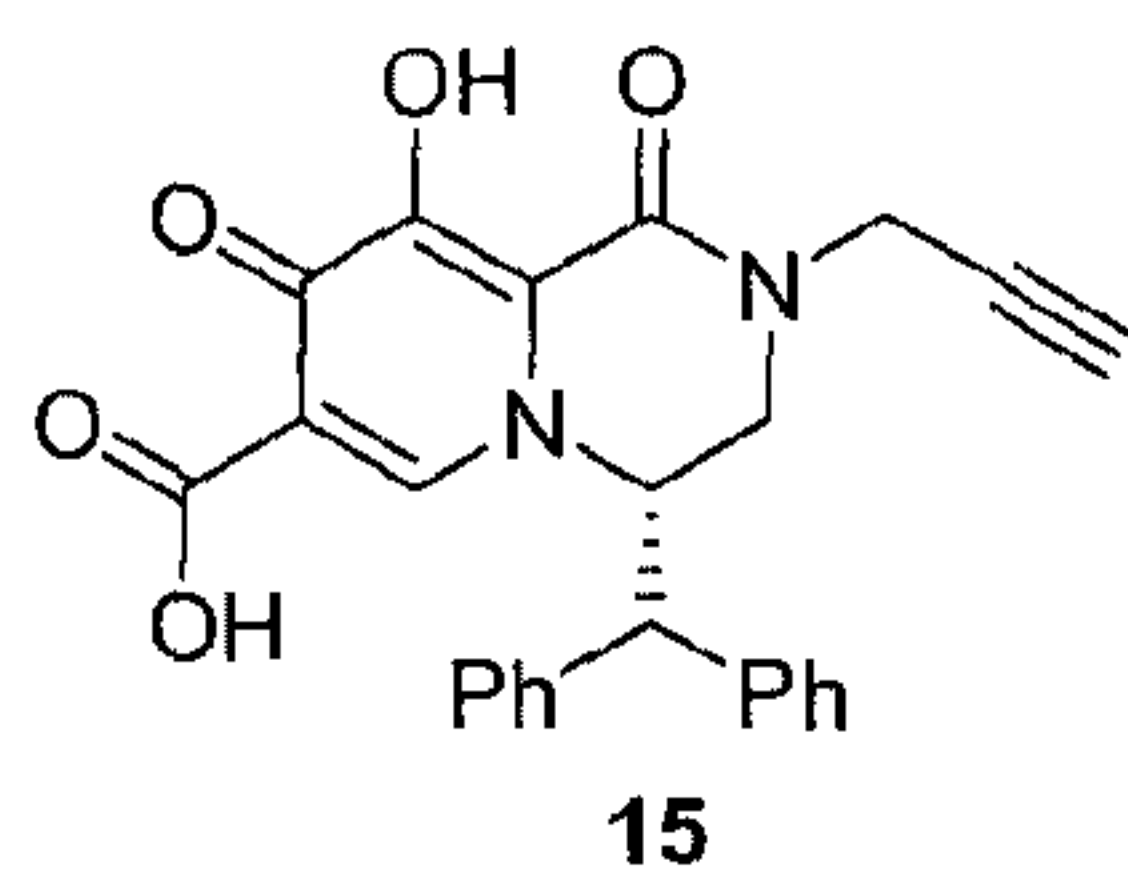
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.98 (3H, t, J = 7.17 Hz), 3.44-3.64 (3H, m), 4.15 (1H, dd, J = 13.7, 3.5 Hz), 4.45 (1H, d, J = 11.6 Hz), 5.79 (1H, d, J = 12.2 Hz), 7.08-7.63 (10H, m), 7.89 (1H, s), 13.01 (1H, s), 15.06 (1H, s).

MS:  $m/z = 419 [M + H]^+$ .

[0310]

### Reference example 15

[Chemical formula 93]



[0311]

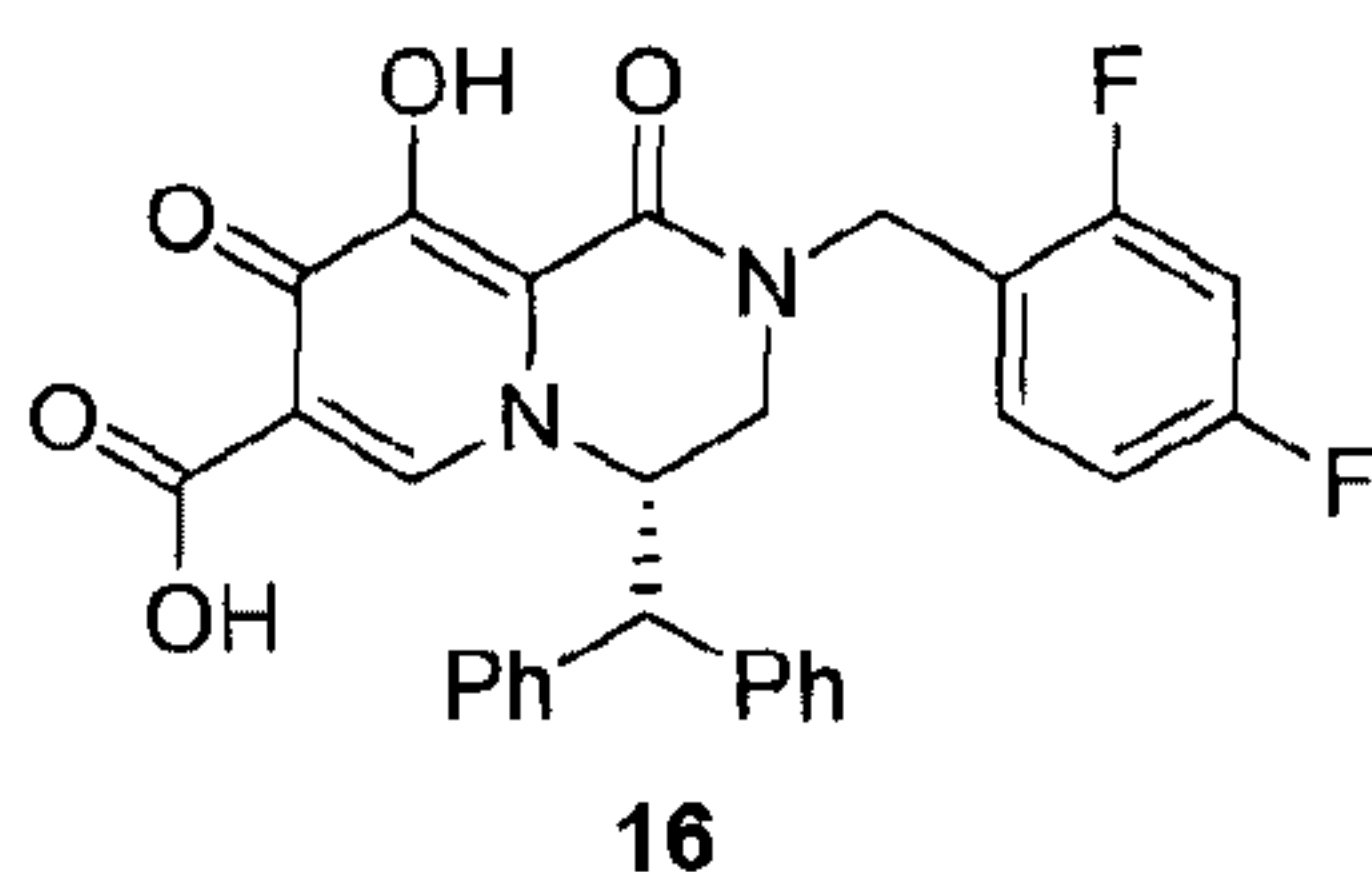
According to Reference example 12, compound 15 was synthesized by the same procedure.

<sup>1</sup> H-NMR (DMSO-d<sub>6</sub>) δ: 3.22 (1H, s), 3.47 (1H, d, J = 13.3 Hz), 4.17 (2H, m), 4.44 (2H, dd, J = 16.7, 3.0 Hz), 5.79 (1H, d, J = 12.2 Hz), 7.10-7.64 (10H, m), 7.98 (1H, s), 12.56 (1H, s), 15.05 (1H, brs).

[0312]

### Reference example 16

[Chemical formula 94]



[0313]

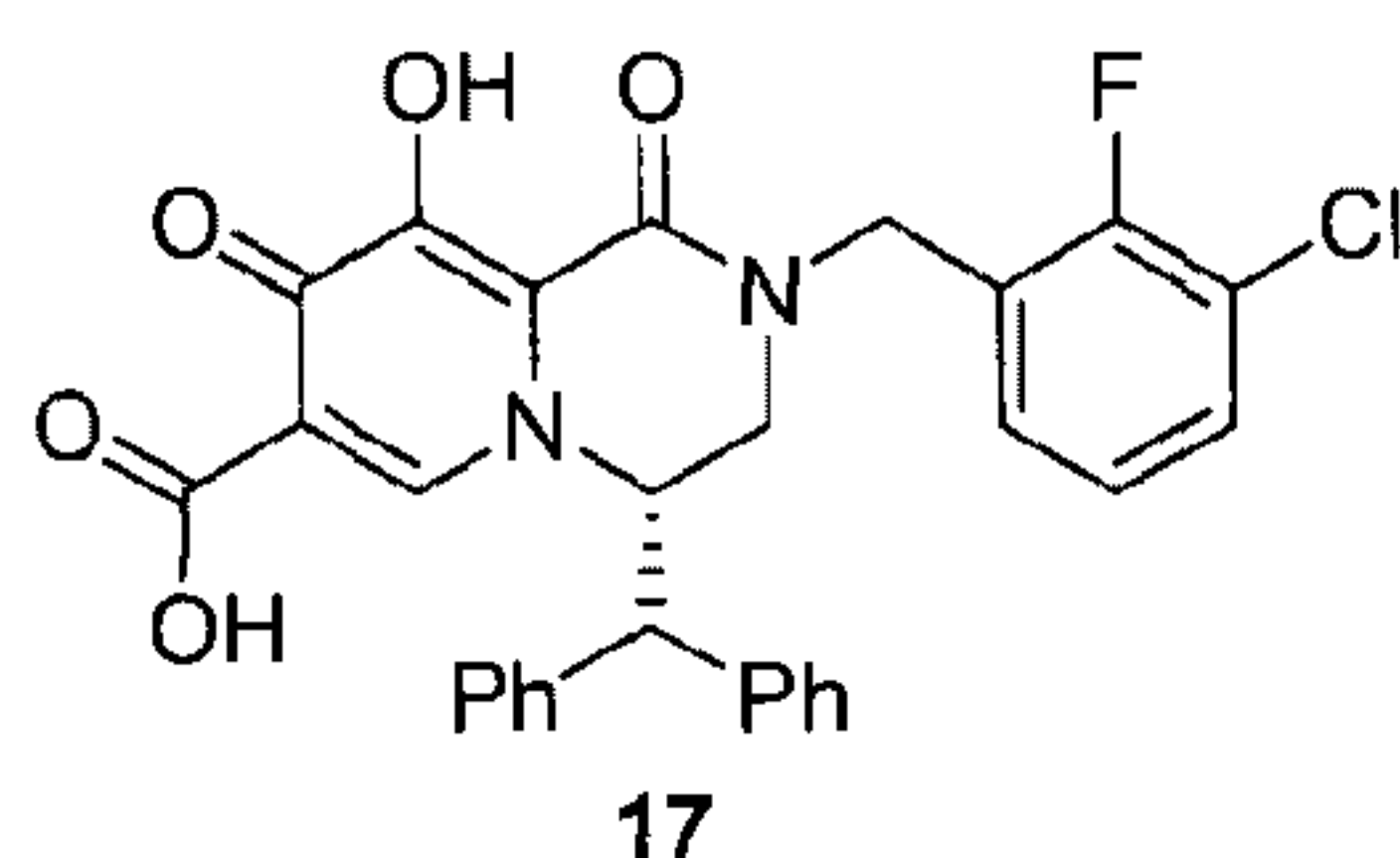
According to Reference example 12, compound 16 was synthesized by the same procedure.

$^1\text{H-NMR}$  (DMSO- $\text{d}_6$ )  $\delta$ : 3.24 (1H, d,  $J = 13.2$  Hz), 4.23 (1H, m), 4.25 (1H, d,  $J = 14.7$  Hz), 4.40 (1H, d,  $J = 14.8$  Hz), 4.92 (1H, d,  $J = 15.4$  Hz), 5.79 (1H, m), 7.03-7.48 (10H, m), 7.93 (1H, s), 12.82 (1H, s), 15.06 (1H, s).

[0314]

Reference example 17

[Chemical formula 95]



[0315]

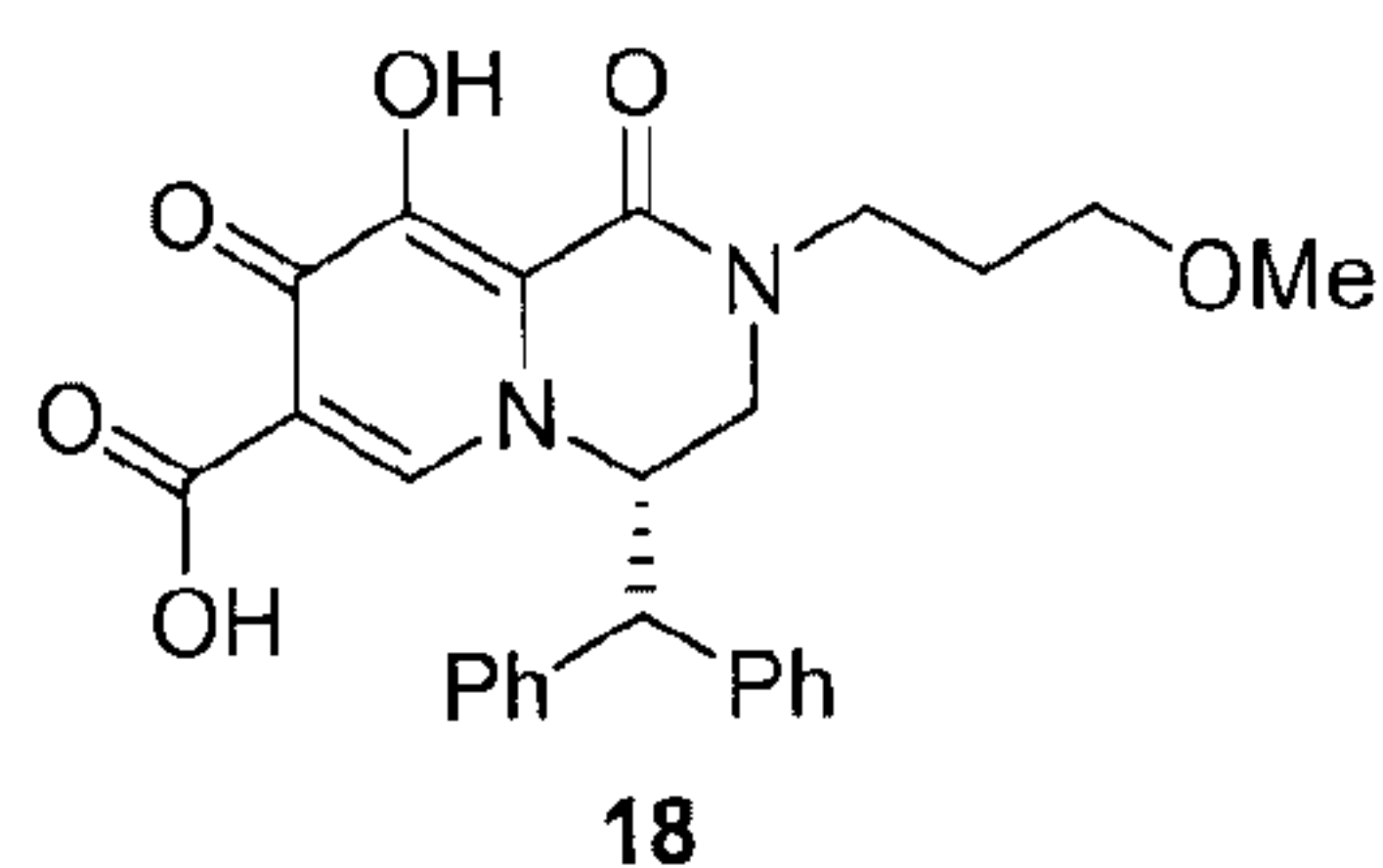
According to Reference example 12, compound 17 was synthesized by the same procedure.

$^1\text{H-NMR}$  (DMSO- $\text{d}_6$ )  $\delta$ : 3.23 (1H, d,  $J = 13.4$  Hz), 4.22 (1H, m), 4.25 (1H, d,  $J = 12.0$  Hz), 4.45 (1H, d,  $J = 14.9$  Hz), 4.93 (1H, d,  $J = 15.3$  Hz), 5.77 (1H, d,  $J = 11.6$  Hz), 7.09-7.56 (10H, m), 7.92 (1H, s), 12.74 (1H, s), 15.06 (1H, s).

[0316]

Reference example 18

[Chemical formula 96]



[0317]

According to Reference example 12, compound 18 was synthesized by the same procedure.

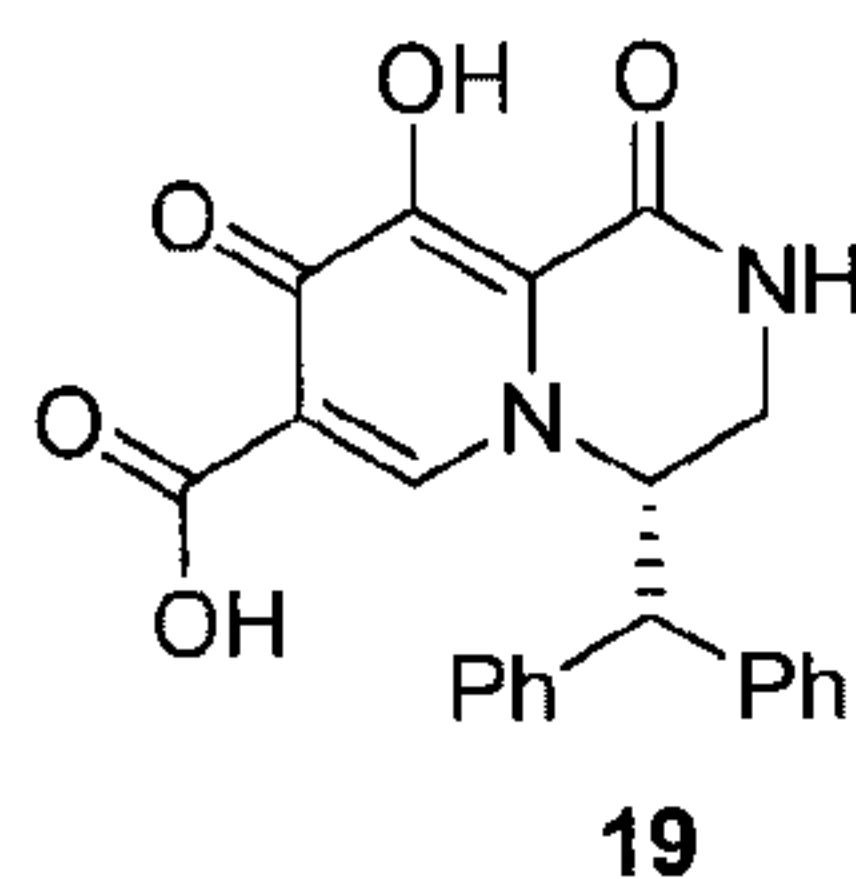
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.63 (2H, m), 3.20 (3H, s), 3.44 (5H, m), 4.19 (1H, d,  $J = 10.2$  Hz), 4.51 (1H, d,  $J = 11.8$  Hz), 5.80 (1H, d,  $J = 11.0$  Hz), 7.13-7.65 (10H, m), 7.93 (1H, s), 13.02 (1H, s).

MS:  $m/z = 463$   $[\text{M} + \text{H}]^+$ .

[0318]

Reference example 19

[Chemical formula 97]



[0319]

According to Reference example 12, compound 19 was synthesized by the same procedure.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.15 (1H, d,  $J = 9.5$  Hz), 3.95 (1H, dd,  $J = 13.5, 3.4$  Hz), 4.51 (1H, d,  $J = 11.6$  Hz), 5.74 (1H, d,  $J = 11.1$  Hz), 7.11-7.62 (10H, m), 7.93 (1H, s), 9.34

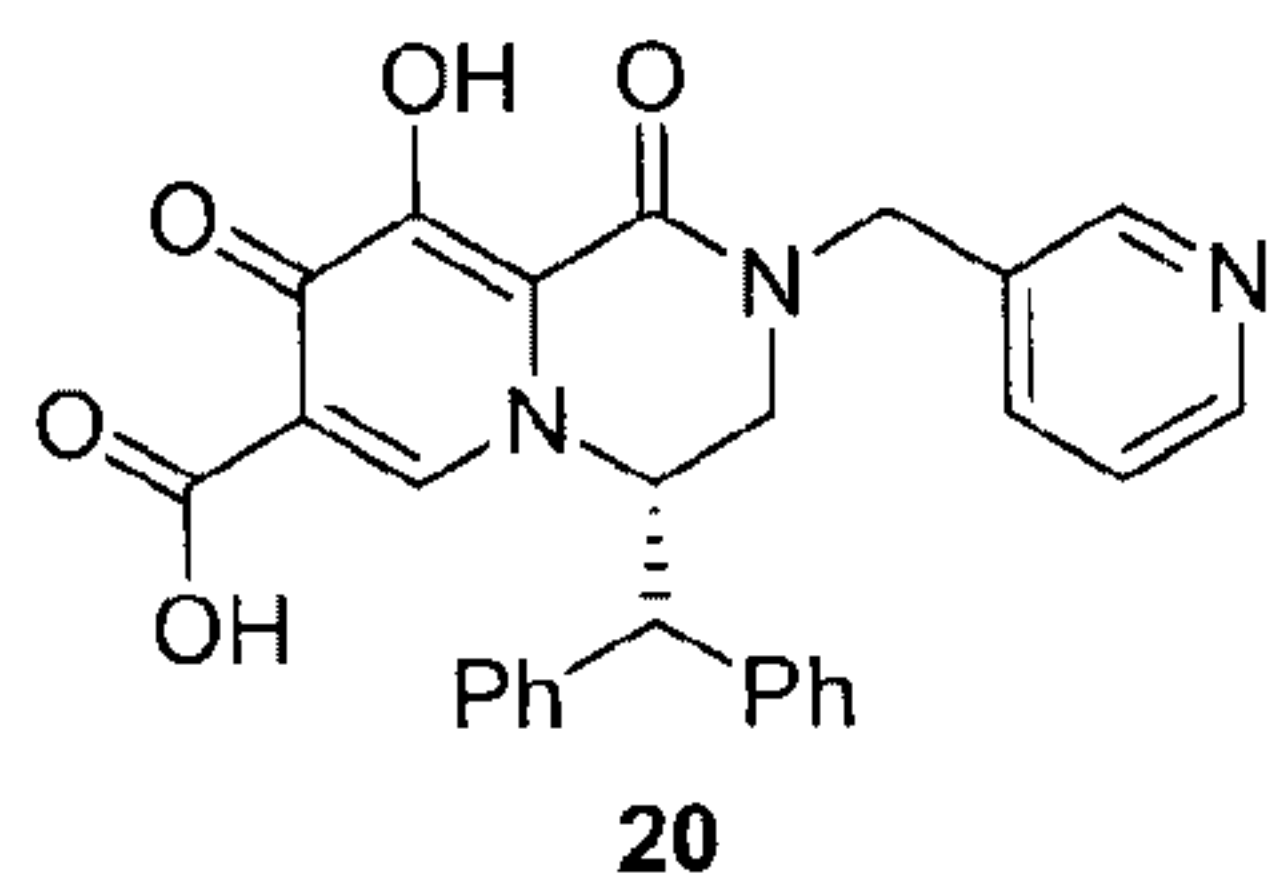
(1H, s), 12.97 (1H, s), 15.07 (1H, brs).

MS:  $m/z = 391 [M + H]^+$ .

[0320]

Reference example 20

[Chemical formula 98]



[0321]

According to Reference example 12, compound 20 was synthesized by the same procedure.

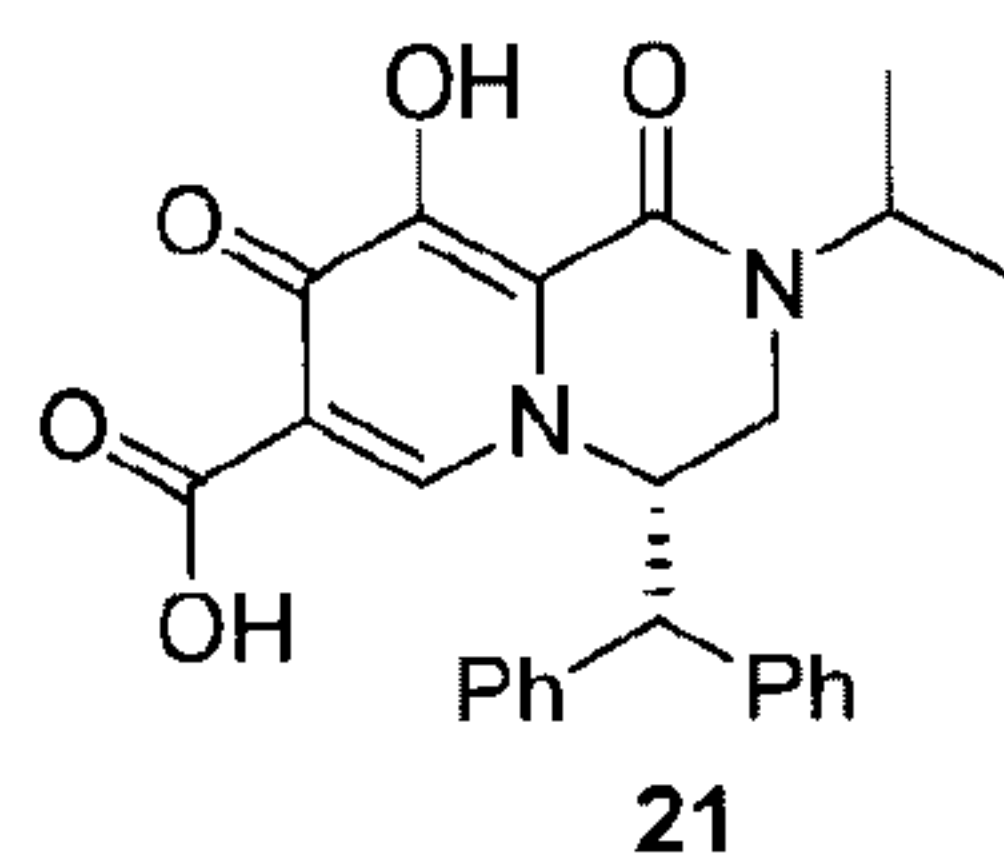
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.26 (1H, m), 4.24 (1H, m), 4.27 (1H, d,  $J = 12.0$  Hz), 4.41 (1H, d,  $J = 14.8$  Hz), 4.87 (1H, d,  $J = 14.9$  Hz), 5.75 (1H, d,  $J = 7.6$  Hz), 7.09-7.77 (12H, m), 7.93 (1H, s), 8.52 (2H, m), 12.79 (1H, s), 15.07 (1H, brs).

MS:  $m/z = 482 [M + H]^+$ .

[0322]

Reference example 21

[Chemical formula 99]



[0323]

According to Reference example 12, compound 21 was synthesized by the same procedure.

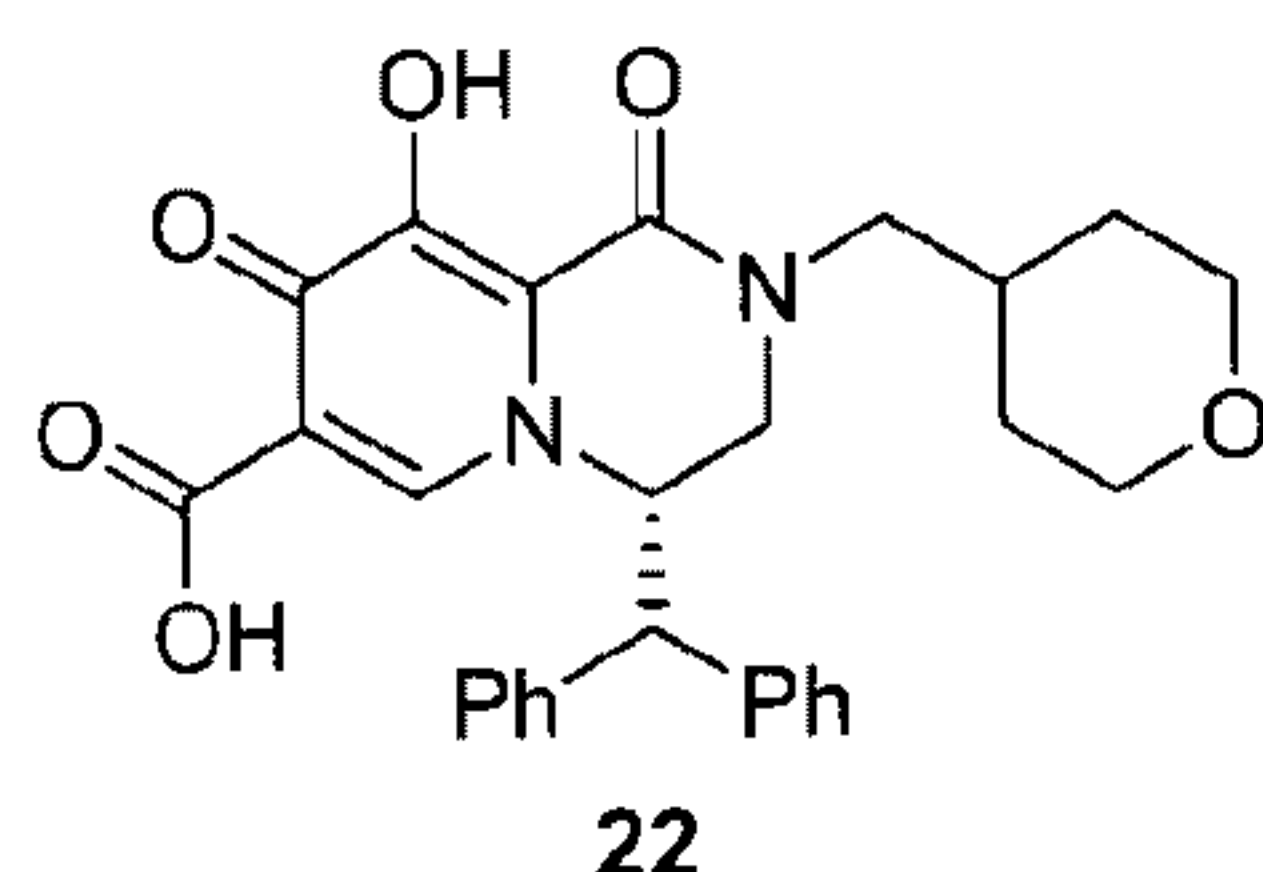
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 0.62 (3H, d,  $J = 6.9$  Hz), 0.82 (3H, d,  $J = 6.6$  Hz), 3.18 (1H, m), 3.75 (1H, d,  $J = 10.2$  Hz), 4.25 (1H, d,  $J = 11.8$  Hz), 4.58 (1H, m), 5.65 (1H, d,  $J = 11.3$  Hz), 6.89-7.43 (10H, m), 7.67 (1H, s), 12.94 (1H, s).

MS:  $m/z = 433$   $[\text{M} + \text{H}]^+$ .

[0324]

Reference example 22

[Chemical formula 100]



[0325]

According to Reference example 12, compound 22 was synthesized by the same procedure.

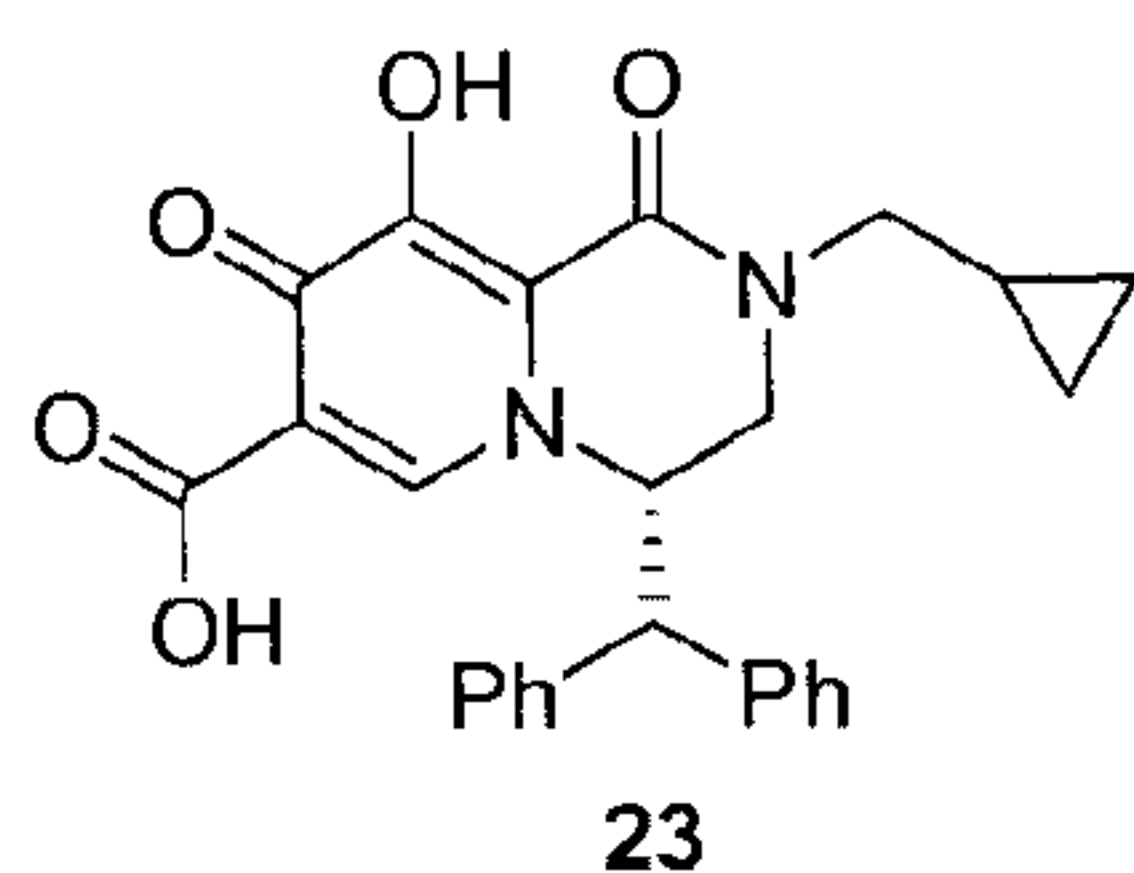
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.07-1.70 (5H, m), 3.04-3.34 (5H, m), 3.82 (2H, dm), 4.18 (1H, d,  $J = 10.2$  Hz), 4.42 (1H, d,  $J = 12.0$  Hz), 5.81 (1H, d,  $J = 11.7$  Hz), 7.11-7.59 (10H, m), 7.86 (1H, s), 12.96 (1H, s), 15.07 (1H, brs).

MS:  $m/z = 489$   $[\text{M} + \text{H}]^+$ .

[0326]

Reference example 23

[Chemical formula 101]



[0327]

According to Reference example 12, compound 23 was synthesized by the same procedure.

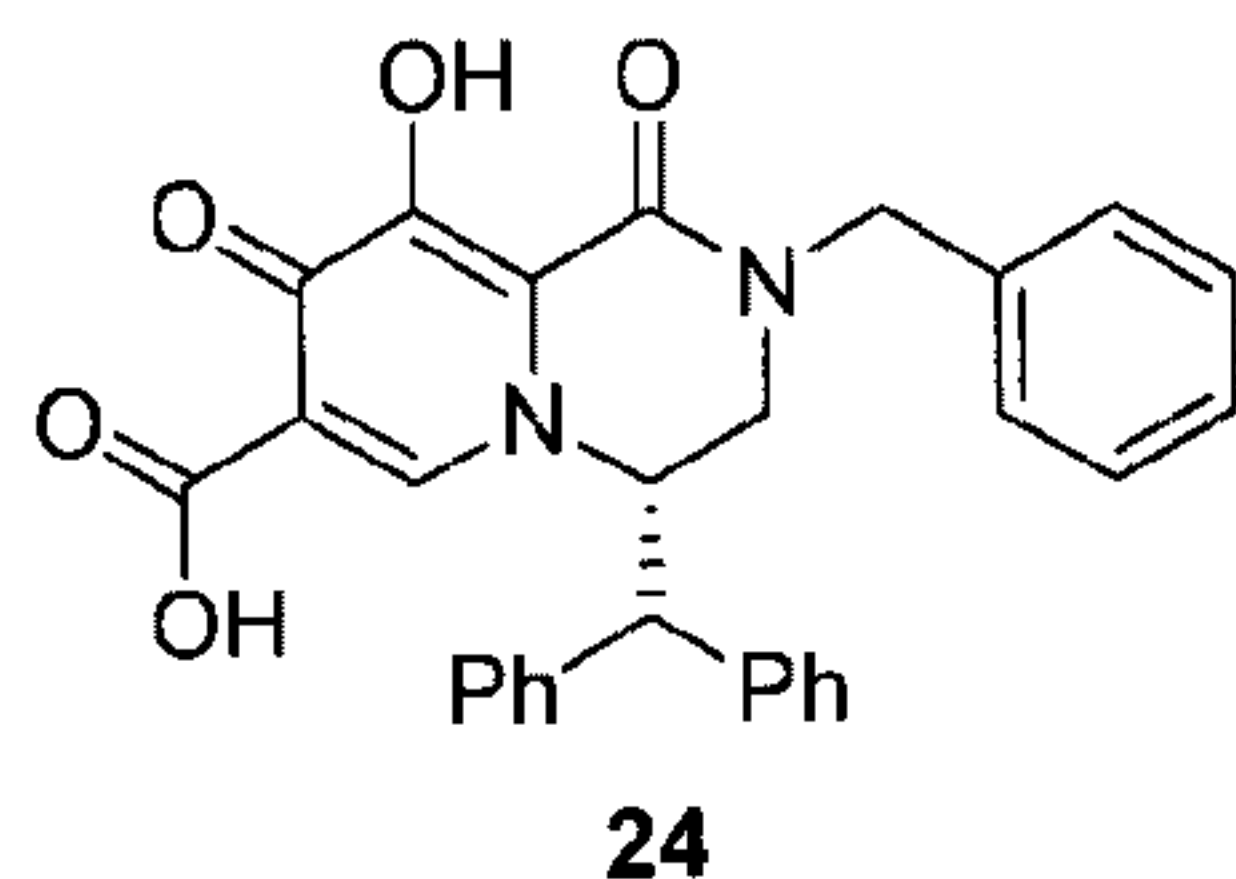
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 0.01-0.79 (5H, m), 3.05 (1H, dd,  $J = 14.1, 7.5$  Hz), 3.49-3.59 (2H, m), 4.16 (1H, dd,  $J = 14.0, 3.3$  Hz), 4.50 (1H, d,  $J = 11.9$  Hz), 5.82 (1H, d,  $J = 11.1$  Hz), 7.11-7.62 (10H, m), 7.89 (1H, s), 12.99 (1H, s), 15.07 (1H, brs).

MS:  $m/z = 445$   $[\text{M} + \text{H}]^+$ .

[0328]

Reference example 24

[Chemical formula 102]



[0329]

According to Reference example 12, compound 24 was synthesized by the same procedure.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.23 (1H, d,  $J = 13.7$  Hz), 4.16 (1H, dd,  $J = 13.2, 3.3$  Hz), 4.19 (2H, d,  $J = 12.0$  Hz), 4.38 (1H, d,  $J = 14.6$  Hz), 4.84 (1H, d,  $J = 14.6$  Hz), 5.72 (1H, d,  $J$

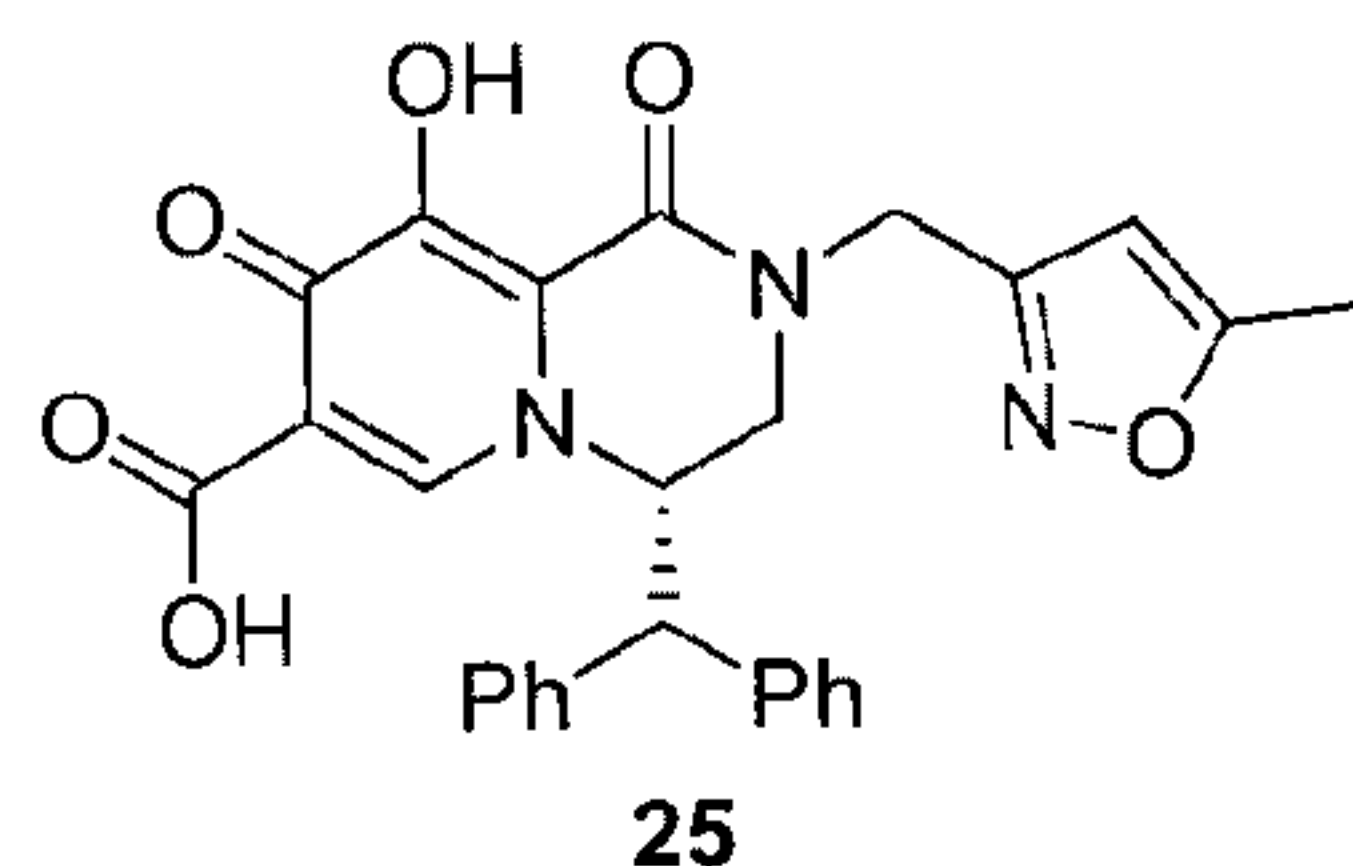
= 11.4 Hz), 7.08-7.33 (15H, m), 7.98 (1H, s), 12.88 (1H, s), 15.07 (1H, s).

MS:  $m/z = 481 [M + H]^+$ .

[0330]

Reference example 25

[Chemical formula 103]



[0331]

According to Reference example 12, compound 25 was synthesized by the same procedure.

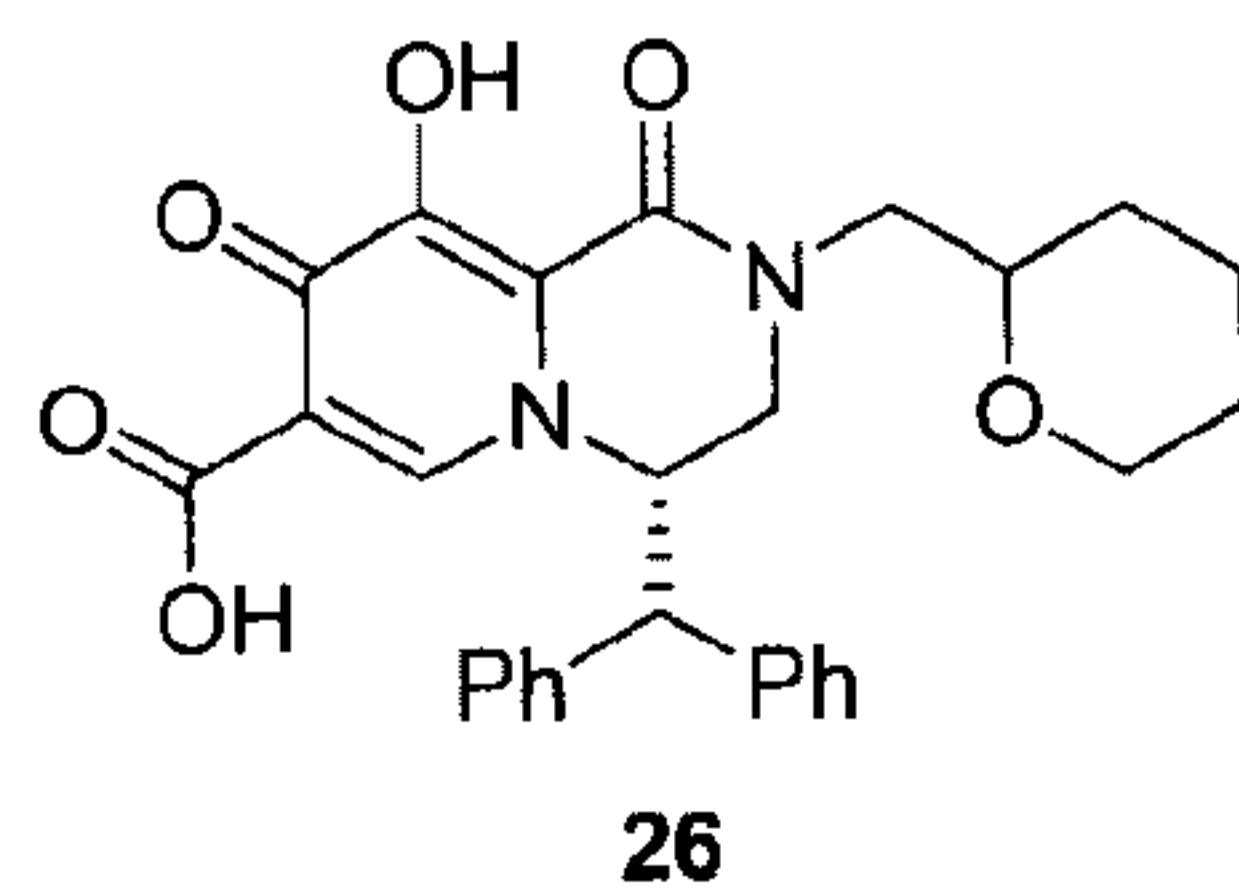
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.39 (3H, s), 3.37 (1H, m), 4.21 (1H, dd,  $J = 14.4, 3.9$  Hz), 4.40 (1H, dd,  $J = 11.7$  Hz), 4.45 (1H, d,  $J = 15.3$  Hz), 4.81 (1H, d,  $J = 15.4$  Hz), 5.78 (1H, d,  $J = 12.0$  Hz), 6.30 (1H, s), 7.09-7.42 (10H, m), 7.95 (1H, s), 12.65 (1H, s), 15.07 (1H, s).

MS:  $m/z = 486 [M + H]^+$ .

[0332]

Reference example 26

[Chemical formula 104]



[0333]

According to Reference example 12, compound 26 was synthesized by the same procedure.

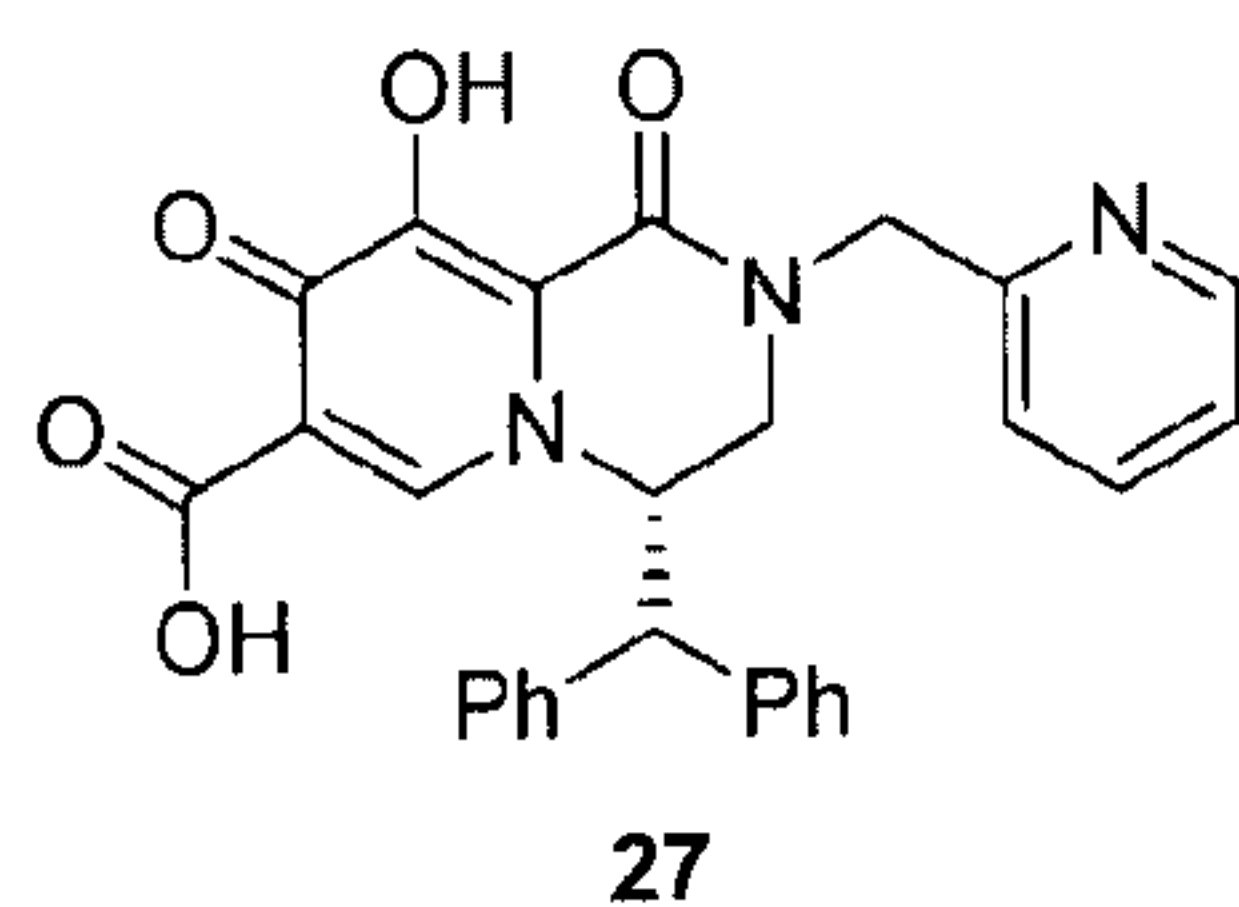
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.20-1.77 (6H, m), 3.11-3.61 (6H, m), 4.21 (1H, d,  $J = 9.9$  Hz), 4.53 (1H, d,  $J = 11.7$  Hz), 5.80 (1H, d,  $J = 11.8$  Hz), 7.14-7.65 (10H, m), 7.95 (1H, s), 12.95 (1H, brs), 15.06 (1H, brs).

MS:  $m/z = 489$   $[\text{M} + \text{H}]^+$ .

[0334]

Reference example 27

[Chemical formula 105]



[0335]

According to Reference example 12, compound 27 was synthesized by the same procedure.

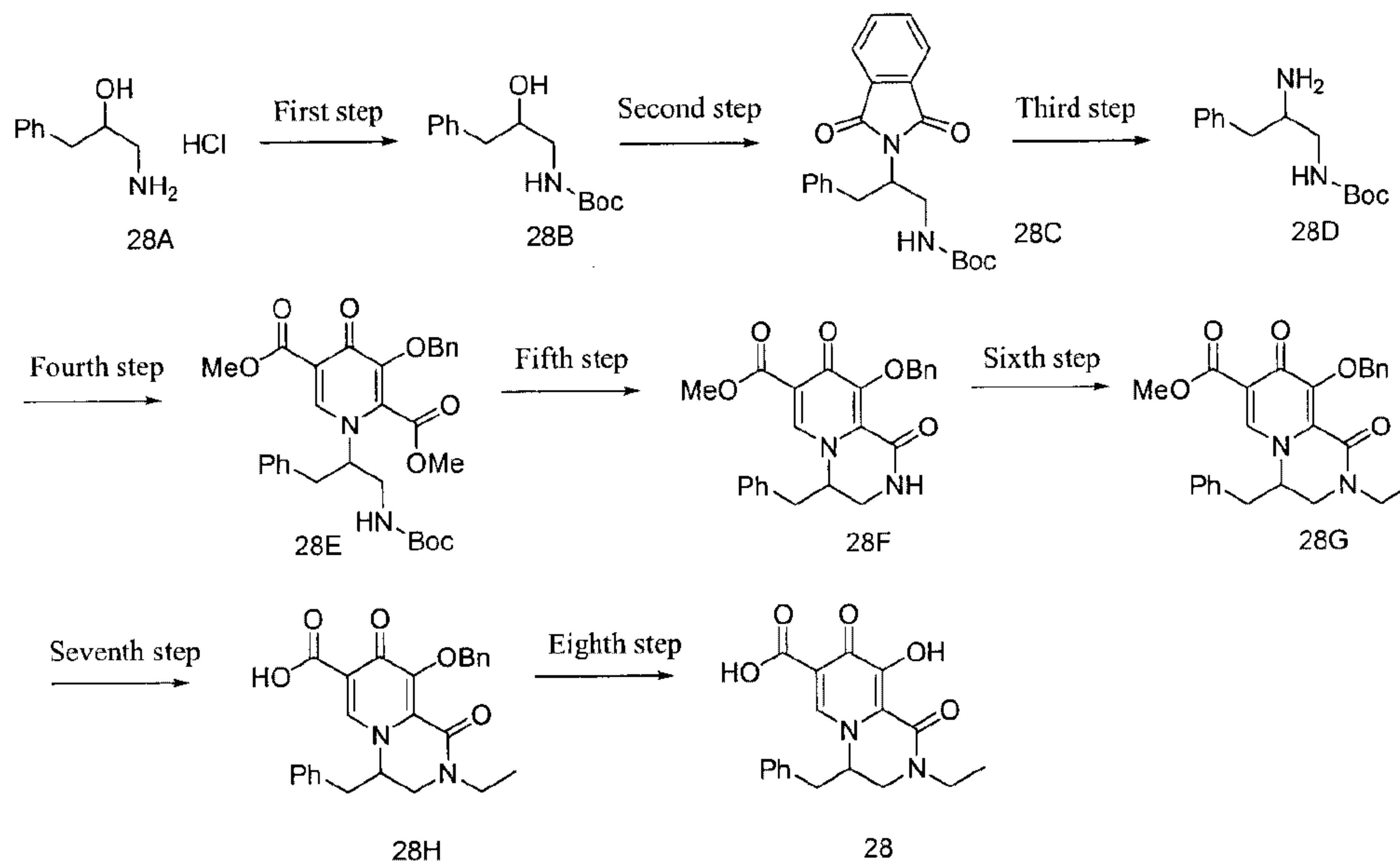
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.36 (1H, m), 4.28 (1H, d,  $J = 12.0$  Hz), 4.54 (1H, d,  $J = 11.4$  Hz), 4.62 (1H, d,  $J = 15.3$  Hz), 4.79 (1H, d,  $J = 15.4$  Hz), 5.77 (1H, d,  $J = 9.9$  Hz), 7.09-7.79 (13H, m), 7.98 (1H, s), 8.46 (1H, d,  $J = 4.6$  Hz), 12.82 (1H, brs), 15.06 (1H, brs).

MS:  $m/z = 482$   $[\text{M} + \text{H}]^+$ .

[0336]

## Reference example 28

[Chemical formula 106]



[0337]

## First step

Compound 28A (3.20 g, 17.1 mmol) was added to THF (20 ml), triethylamine (2.60 ml, 18.8 mmol) was added, and the mixture was stirred at room temperature for 10 minutes. After Boc<sub>2</sub>O (4.09 g, 18.8 mmol) was added at room temperature, the mixture was stirred for 2 hours. The solvent was distilled off under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated sodium chloride solution, and dried with sodium sulfate. The solvent was distilled off under reduced pressure to obtain 5.17 g of compound 28B as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.52 (9H, s), 2.77 (2H, m), 3.03-3.12 (1H, m), 3.38 (1H, m), 3.90-3.98 (1H, m), 4.93 (1H, brs), 7.20-7.35 (5H, m).

### Second step

Compound 28B (4.29 g, 17.1 mmol), triphenylphosphine (5.37 g, 20.5 mmol) and phthalimide (2.76 g, 18.8 mmol) were added to THF (60 ml), and diethyl azodicarboxylate (2.2M in toluene, 11.6 ml, 25.6 mmol) was added dropwise at room temperature. After the mixture was stirred at room temperature for 1 hour, the solvent was distilled off under reduced pressure. The resulting crude product was purified by silica gel column chromatography (n-hexane-ethyl acetate, 2 : 1, v/v) to obtain 6.13 g of compound 28C as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.30 (9H, s), 3.14 (1H, dd,  $J = 13.8, 6.2$  Hz), 3.39 (2H, m), 3.87 (1H, m), 4.67 (1H, m), 4.81 (1H, brs), 7.16-7.19 (5H, m), 7.66 (2H, dd,  $J = 5.3, 3.1$  Hz), 7.75 (2H, dd,  $J = 5.7, 3.0$  Hz).

### Third step

Compound 28C (1.00 g, 2.63 mmol) was added to THF (7 ml) and methanol (7 ml), hydrazine hydrate (2.63 g, 52.6 mmol) was added, and the mixture was stirred at 50°C for 2 hours. The white precipitate was removed by filtration, and washed with methanol. After the filtrate was distilled off under reduced pressure, the resulting crude product was purified by amino column chromatography (chloroform-methanol, 99 : 1, v/v) to obtain 249 mg of compound 28D as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.44 (9H, s), 1.95 (2H, brs), 2.55-3.31 (5H, m), 5.06 (1H, brs), 7.18-7.33 (5H, m).

### Fourth step

Dimethyl 3-(benzyloxy)-4-oxo-4H-pyran-2,5-dicarboxylate (313 mg, 0.983 mmol) and 28D (246 mg, 0.983 mmol) were added to toluene (3 ml), and the mixture was stirred at 100°C for 2.5 hours. After the solvent was distilled off under reduced pressure, the resulting crude product was purified by silica gel column chromatography

(chloroform-methanol, 98 : 2, v/v) to obtain 320 mg of compound 28E as a pale yellow gummy substance.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.42 (9H, s), 3.07 (2H, m), 3.56 (2H, m), 3.68 (3H, s), 3.95 (3H, s), 4.26 (1H, s), 4.86 (1H, s), 5.18 (1H, d,  $J = 10.8$  Hz), 5.22 (1H, d,  $J = 10.8$  Hz), 7.01 (2H, m), 7.24-7.38 (8H, m), 8.22 (1H, s).

MS:  $m/z = 551$   $[\text{M} + \text{H}]^+$ .

#### Fifth step

To compound 28E (315 mg, 0.572 mmol) was added 4N HCl (ethyl acetate solution, 5 ml), and the mixture was stirred at room temperature for 30 minutes. After the solvent was distilled off under reduced pressure, aqueous sodium bicarbonate water was added, and the mixture was extracted with chloroform, and dried with sodium sulfate. After the solvent was distilled off under reduced pressure, the resulting crude product was purified by silica gel column chromatography (chloroform-methanol, 95 : 5, v/v) to obtain 210 mg of compound 28F as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.07-3.15 (2H, m), 3.34 (1H, dd,  $J = 13.2, 6.0$  Hz), 3.74 (2H, m), 3.86 (3H, s), 4.12 (1H, m), 5.27 (1H, d,  $J = 10.1$  Hz), 5.47 (1H, d,  $J = 10.1$  Hz), 6.76 (1H, d,  $J = 6.4$  Hz), 7.04 (2H, m), 7.32 (6H, m), 7.62 (2H, dd,  $J = 7.7, 1.4$  Hz), 7.70 (1H, s).

MS:  $m/z = 419$   $[\text{M} + \text{H}]^+$ .

#### Sixth step

Compound 28F (50 mg, 0.12 mmol) was dissolved in DMF (1 ml), and cesium carbonate (195 mg, 0.597 mmol) was added. After the mixture was stirred at room temperature for 30 minutes, iodoethane (0.048 ml, 0.60 mmol) was added, and the mixture was stirred at room temperature for 3.5 hours. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate, and dried with

sodium sulfate. After the solvent was distilled off under reduced pressure, the resulting crude product was purified by silica gel column chromatography (chloroform-methanol, 95 : 5, v/v) to obtain 47 mg of compound 28G as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.22 (3H, t,  $J = 7.2$  Hz), 3.00-3.15 (2H, m), 3.28 (1H, dd,  $J = 13.6$ , 1.6 Hz), 3.48 (1H, m), 3.75 (1H, m), 3.85 (3H, s), 3.88 (1H, dd,  $J = 13.3$ , 3.2 Hz), 4.15 (1H, m), 5.25 (1H, d,  $J = 9.9$  Hz), 5.50 (1H, d,  $J = 9.9$  Hz), 7.04 (2H, m), 7.29-7.38 (6H, m), 7.60 (1H, s), 7.68 (2H, m).

MS:  $m/z = 447$   $[\text{M} + \text{H}]^+$ .

#### Seventh step

Compound 28G (47 mg, 0.11 mmol) was dissolved in THF (0.5 ml) and methanol (0.5 ml), a 2N aqueous sodium hydroxide solution (0.26 ml, 0.53 mmol) was added at room temperature, and the mixture was stirred for 1 hour. After 1N hydrochloric acid was added, and the mixture was extracted with ethyl acetate, the extract was dried with sodium sulfate. After the solvent was distilled off under reduced pressure, 40 mg of compound 28H was obtained as a colorless solid.

MS:  $m/z = 433$   $[\text{M} + \text{H}]^+$ .

#### Eighth step

To compound 28H obtained in the seventh step was added trifluoroacetic acid (1 ml), and the mixture was stirred at room temperature for 1 hour. After concentration under reduced pressure, pH was adjusted to 3 with sodium bicarbonate water and 2N hydrochloric acid, and the mixture was extracted with chloroform, and dried with sodium sulfate. After the solvent was distilled off under reduced pressure, chloroform-methanol-ethyl ether were added, and the precipitated solid was filtered to obtain 17 mg of compound 28 as a colorless solid.

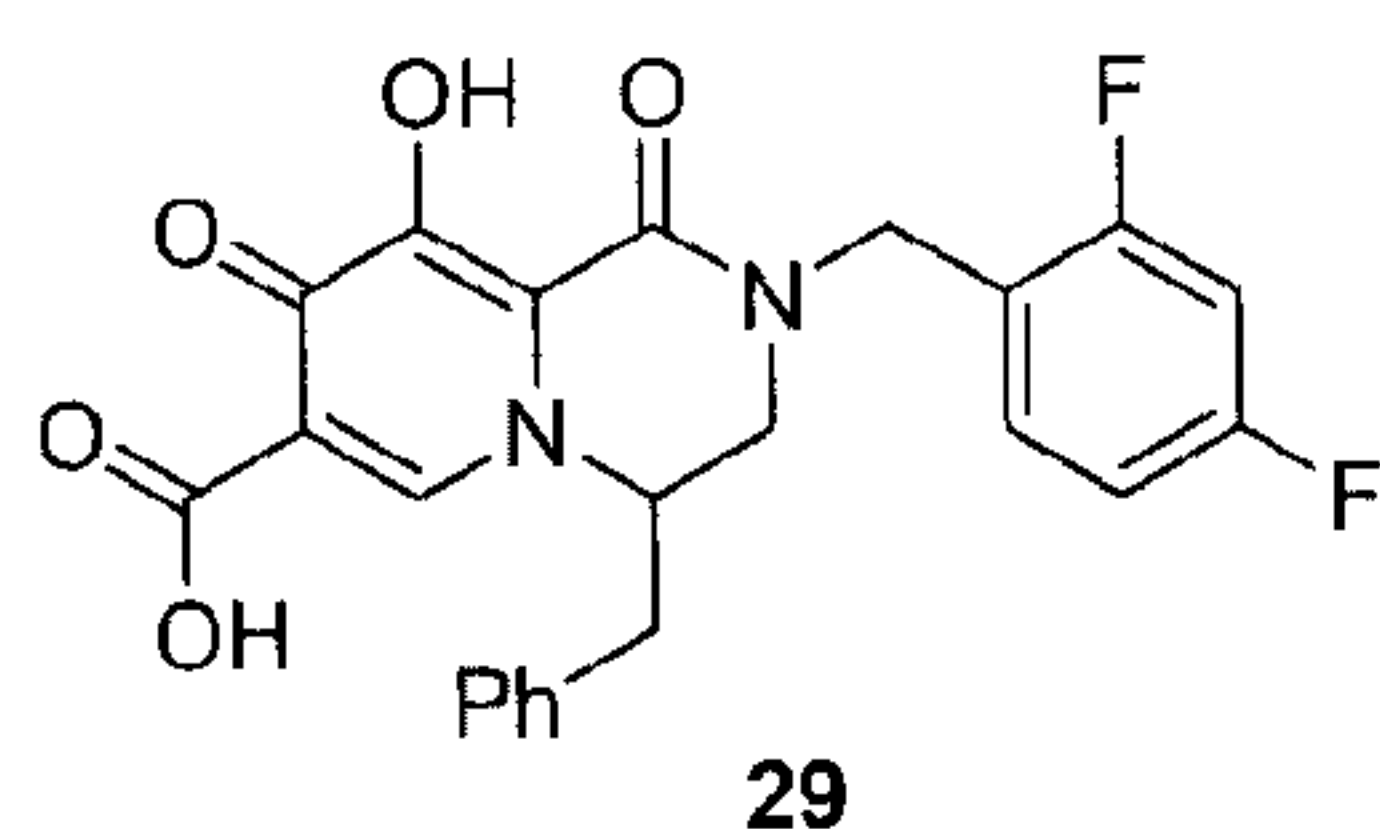
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.17 (3H, t,  $J = 7.2$  Hz), 3.08 (2H, m), 3.51-3.63 (3H, m), 4.08 (1H, dd,  $J = 13.6, 3.9$  Hz), 5.03 (1H, brs), 7.21 (5H, m), 8.07 (1H, s), 12.98 (1H, s), 15.07 (1H, brs).

MS:  $m/z = 343$   $[\text{M} + \text{H}]^+$ .

[0338]

Reference example 29

[Chemical formula 107]



[0339]

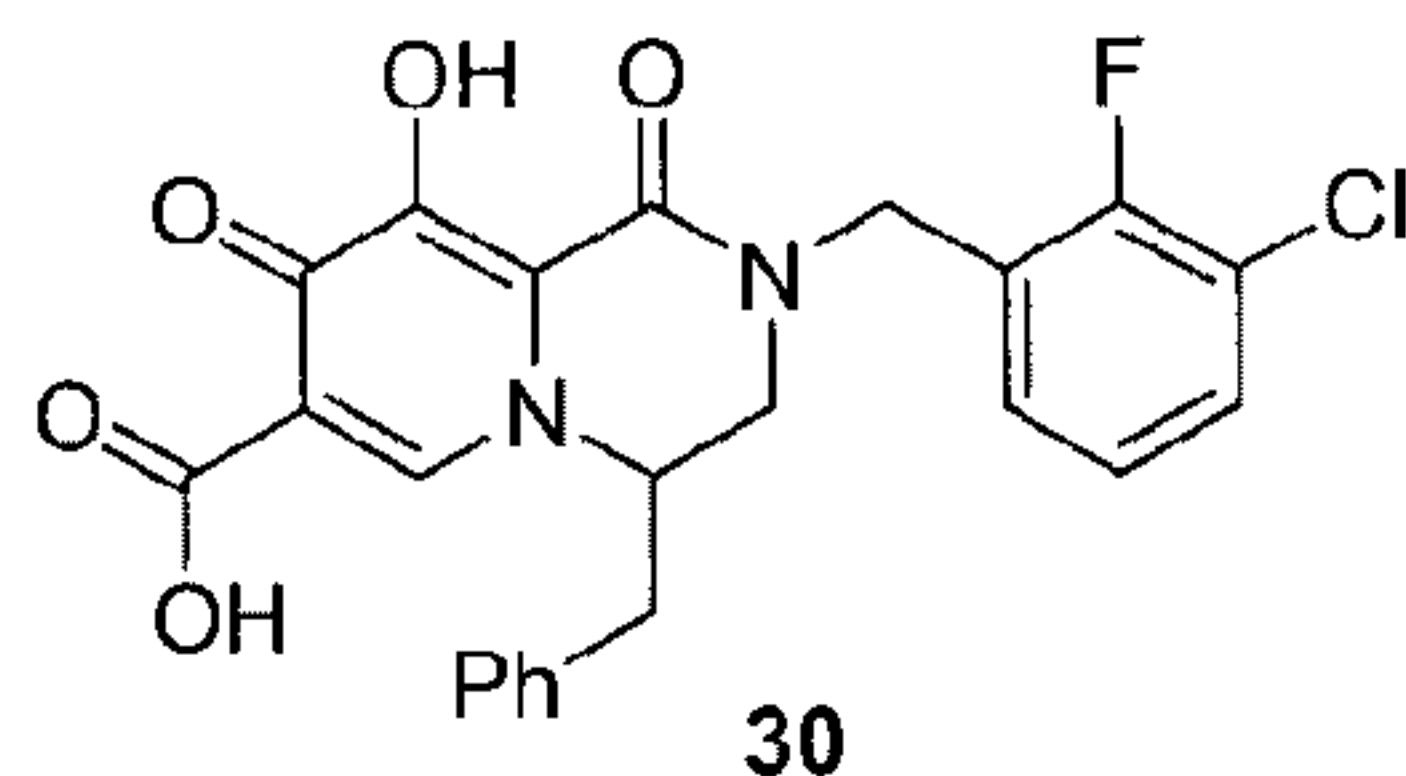
According to Reference example 28, compound 29 was synthesized by the same procedure.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.96 (2H, d,  $J = 7.6$  Hz), 3.46 (1H, d,  $J = 13.3$  Hz), 4.06 (1H, dd,  $J = 13.6, 3.8$  Hz), 4.64 (1H, d,  $J = 14.9$  Hz), 4.89 (1H, d,  $J = 14.6$  Hz), 4.98 (1H, m), 6.97 (2H, m), 7.10-7.37 (5H, m), 7.57 (1H, m), 8.12 (1H, s), 12.75 (1H, s), 15.07 (1H, brs).

[0340]

Reference example 30

[Chemical formula 108]



[0341]

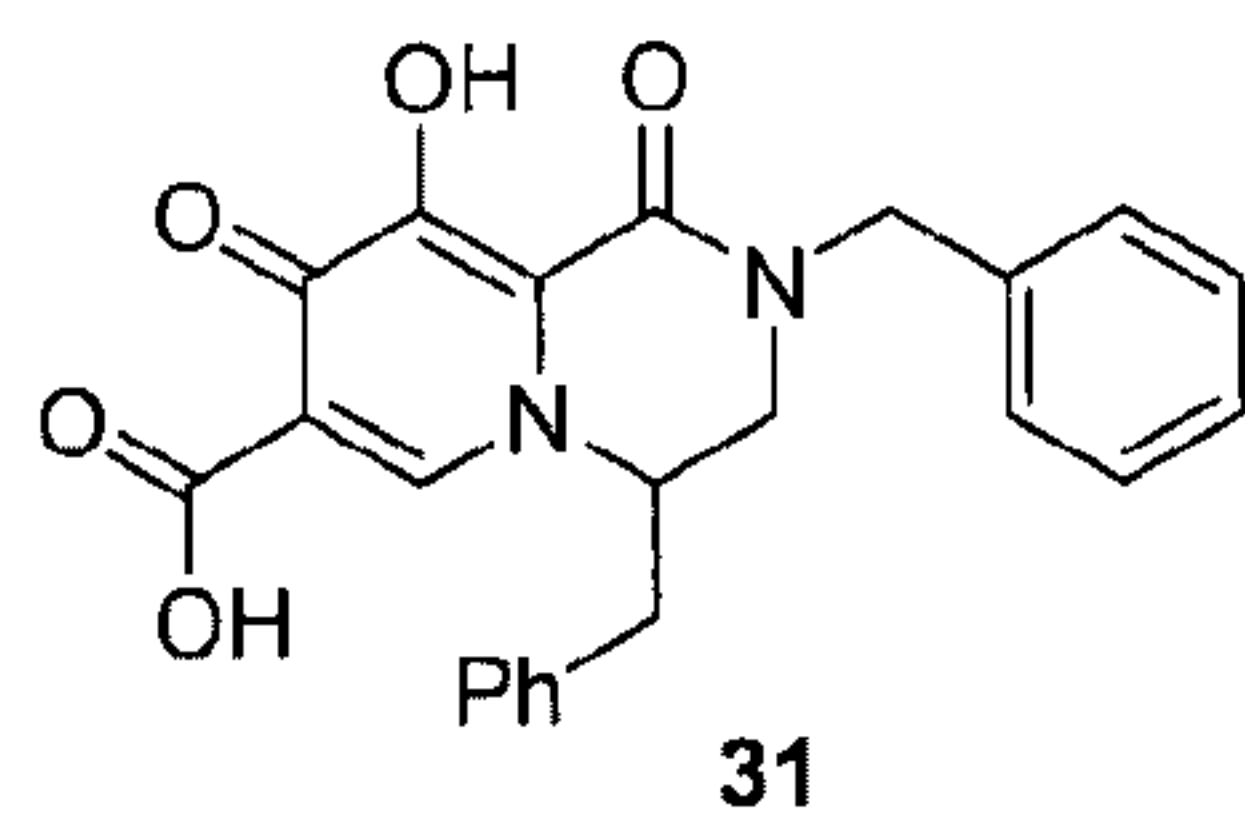
According to Reference example 28, compound 30 was synthesized by the same procedure.

$^1\text{H-NMR}$  (DMSO- $\text{d}_6$ )  $\delta$ : 2.99 (2H, dd,  $J = 7.5, 3.6$  Hz), 3.48 (1H, d,  $J = 13.4$  Hz), 4.09 (1H, dd,  $J = 13.4, 4.0$  Hz), 4.73 (1H, d,  $J = 15.1$  Hz), 4.92 (1H, d,  $J = 15.1$  Hz), 4.99 (1H, m), 6.97 (2H, m), 7.18-7.29 (4H, m), 7.49 (1H, m), 7.61 (1H, m), 8.15 (1H, s), 12.69 (1H, s), 15.06 (1H, brs).

[0342]

Reference example 31

[Chemical formula 109]



[0343]

According to Reference example 28, compound 31 was synthesized by the same procedure.

$^1\text{H-NMR}$  (DMSO- $\text{d}_6$ )  $\delta$ : 2.91 (2H, m), 3.45 (1H, d,  $J = 13.1$  Hz), 4.02 (1H, dd,  $J = 13.6, 4.0$  Hz), 4.57 (1H, d,  $J = 14.6$  Hz), 4.91 (1H, d,  $J = 14.6$  Hz), 4.93 (1H, m), 6.89 (2H, m),

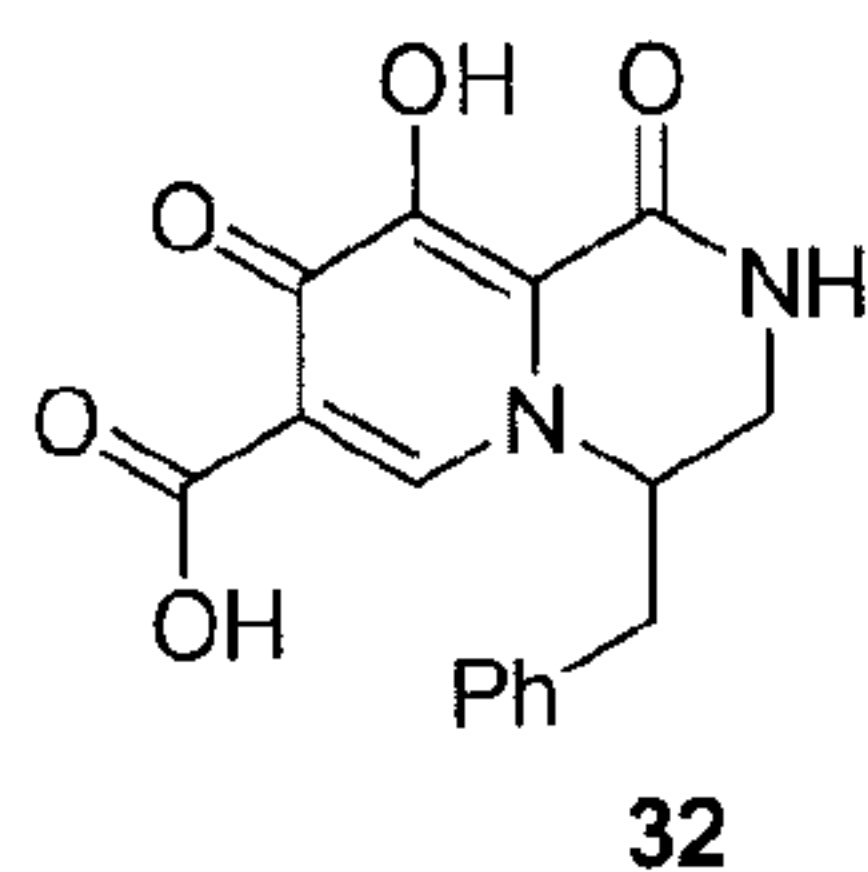
7.18 (3H, m), 7.40 (5H, m), 8.16 (1H, s), 12.86 (1H, brs), 15.06 (1H, brs).

MS:  $m/z = 405 [M + H]^+$ .

[0344]

Reference example 32

[Chemical formula 110]



[0345]

According to Reference example 28, compound 32 was synthesized by the same procedure.

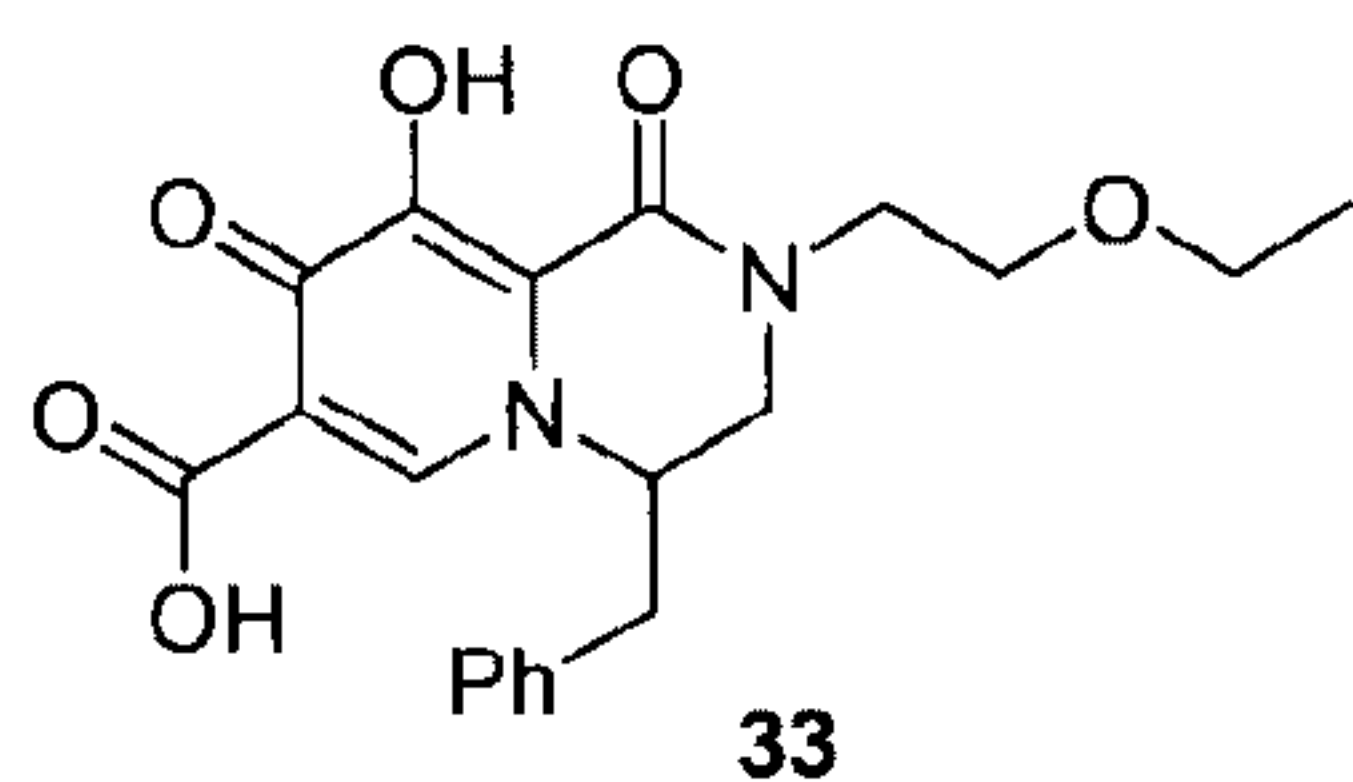
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.10 (2H, m), 3.39 (1H, d,  $J = 13.6$  Hz), 3.84 (1H, dd,  $J = 13.6$ , 4.0 Hz), 4.94 (1H, m), 7.23 (5H, m), 8.19 (1H, s), 9.44 (1H, brs), 12.97 (1H, s), 15.06 (1H, brs).

MS:  $m/z = 315 [M + H]^+$ .

[0346]

Reference example 33

[Chemical formula 111]



[0347]

According to Reference example 28, compound 33 was synthesized by the same procedure.

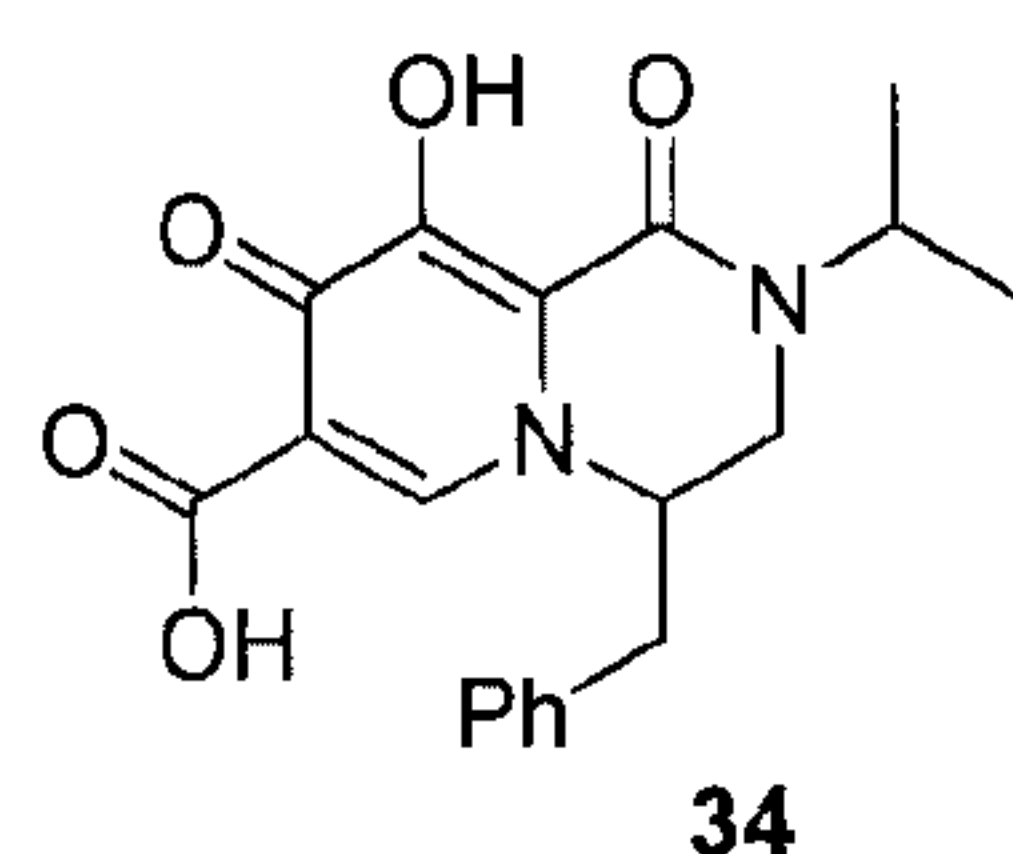
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.09 (3H, t,  $J = 6.9$  Hz), 3.10 (2H, m), 3.42-3.50 (2H, m), 3.71 (5H, m), 4.11 (1H, dd,  $J = 13.6, 3.8$  Hz), 4.99 (1H, brs), 7.11-7.29 (5H, m), 7.99 (1H, s), 12.88 (1H, s), 15.06 (1H, brs).

MS:  $m/z = 387$   $[\text{M} + \text{H}]^+$ .

[0348]

Reference example 34

[Chemical formula 112]



[0349]

According to Reference example 28, compound 34 was synthesized by the same procedure.

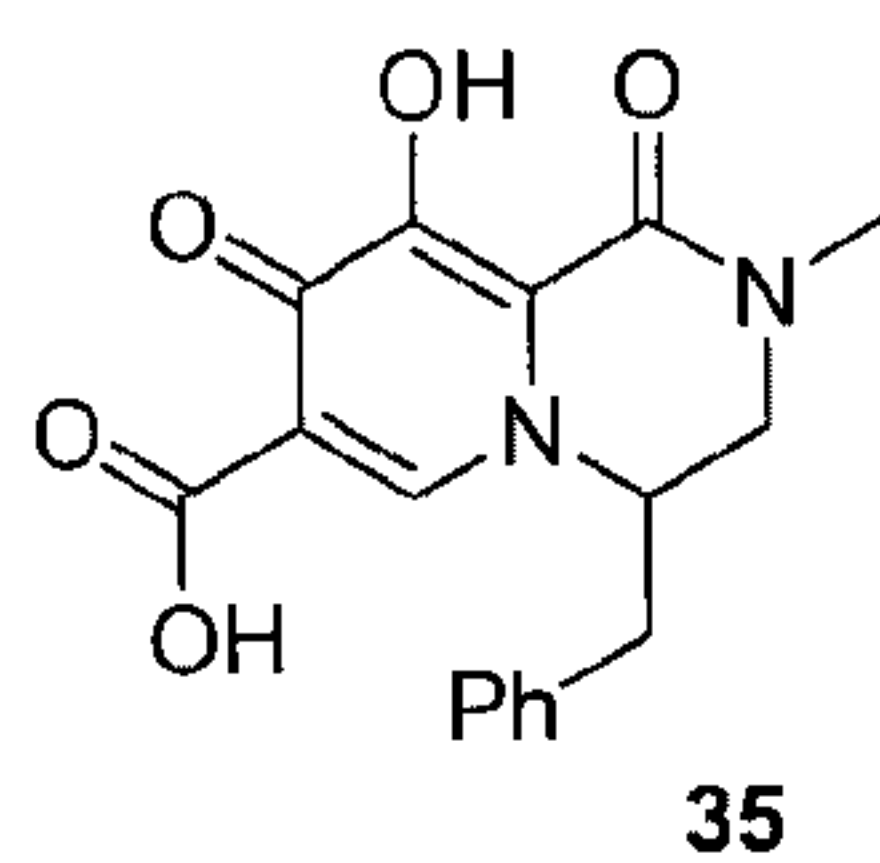
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.16 (3H, d,  $J = 6.9$  Hz), 1.21 (3H, d,  $J = 6.9$  Hz), 2.98 (1H, dd,  $J = 13.6, 9.8$  Hz), 3.13 (1H, dd,  $J = 13.7, 5.8$  Hz), 3.68 (1H, d,  $J = 12.8$  Hz), 3.87 (1H, dd,  $J = 13.6, 3.7$  Hz), 4.83 (1H, quin,  $J = 6.8$  Hz), 5.07 (1H, brs), 7.19 (5H, m), 7.90 (1H, s), 13.09 (1H, s), 15.08 (1H, brs)..

MS:  $m/z = 357$   $[\text{M} + \text{H}]^+$ .

[0350]

Reference example 35

[Chemical formula 113]



[0351]

According to Reference example 28, compound 35 was synthesized by the same procedure.

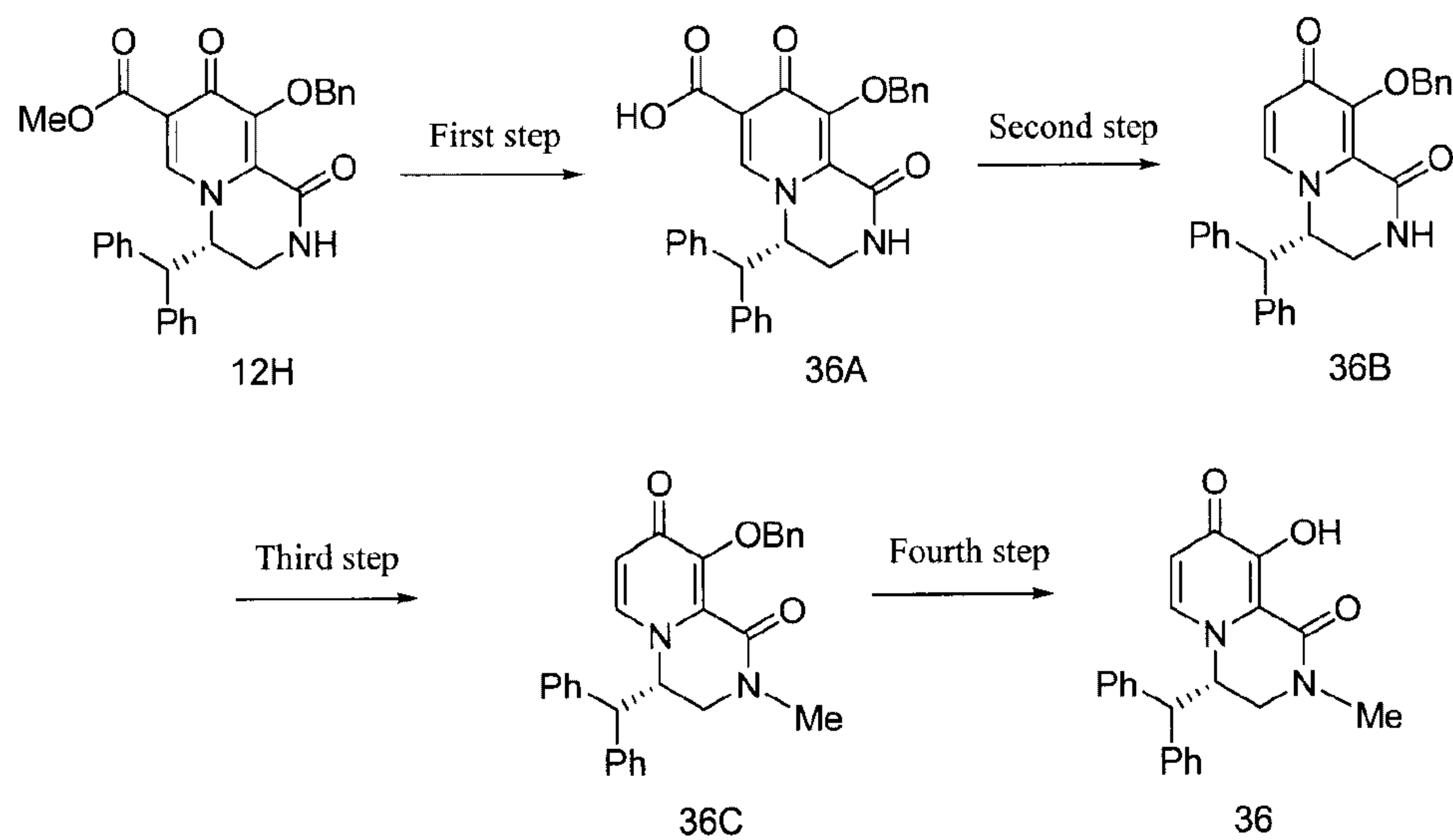
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.07 (3H, s), 3.14 (2H, m), 3.49 (1H, d,  $J = 13.3$  Hz), 4.08 (1H, dd,  $J = 13.7, 4.0$  Hz), 4.99 (1H, m), 7.13-7.31 (5H, m), 8.18 (1H, s), 12.95 (1H, s), 15.06 (1H, brs).

MS:  $m/z = 329$   $[\text{M} + \text{H}]^+$ .

[0352]

Reference example 36

[Chemical formula 114]



[0353]

#### First step

Compound 12H (460 mg, 0.930 mmol) was dissolved in THF (2.5 ml) and methanol (2.5 ml), a 2N aqueous sodium hydroxide solution (2.33 ml, 4.65 mmol) was added at room temperature, and the mixture was stirred for 1.5 hours. After 1N hydrochloric acid was added, and the mixture was extracted with ethyl acetate, the extract was dried with sodium sulfate. After the solvent was distilled off under reduced pressure, 405 mg of compound 36A was obtained as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.45 (1H, ddd, J = 13.8, 6.9, 1.3 Hz), 3.80 (1H, dd, J = 13.5, 2.1 Hz), 4.35 (1H, d, J = 11.6 Hz), 4.77 (1H, d, J = 11.3 Hz), 5.46 (1H, d, J = 10.5 Hz), 5.52 (1H, d, J = 10.5 Hz), 6.11 (1H, d, J = 5.8 Hz), 6.94-6.98 (2H, m), 7.17 (3H, m), 7.31-7.46 (8H, m), 7.58 (3H, m).

#### Second step

Compound 36A (402 mg, 0.837 mmol) was added to diphenyl ether (5 ml), and the mixture was stirred at 245°C for 1 hour under microwave irradiation. The reaction solution was poured into n-hexane, and the precipitated solid was filtered. The resulting crude product was purified by amino column chromatography (chloroform-methanol, 99 : 1, v/v) to obtain 164 mg of compound 36B as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.36 (1H, dd, J = 13.0, 7.0 Hz), 3.72 (1H, d, J = 11.1 Hz), 4.35 (1H, d, J = 11.4 Hz), 4.49 (1H, d, J = 10.2 Hz), 5.38 (1H, d, J = 10.5 Hz), 5.43 (1H, d, J = 10.4 Hz), 5.94 (1H, d, J = 7.2 Hz), 6.29 (1H, d, J = 6.6 Hz), 6.38 (1H, d, J = 7.5 Hz), 6.99 (2H, m), 7.17 (3H, m), 7.36 (8H, m), 7.60 (2H, m).

#### Third step

Compound 36B (40 mg, 0.092 mmol) was dissolved in DMF (1 ml), and

cesium carbonate (179 mg, 0.55 mmol) was added. After stirring at room temperature for 30 minutes, iodomethane (0.029 ml, 0.46 mmol) was added, and the mixture was stirred at room temperature for 3.5 hours. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate, and dried with sodium sulfate. After the solvent was distilled off under reduced pressure, the resulting crude product was purified by silica gel column chromatography (chloroform-methanol, 95 : 5, v/v) to obtain 44 mg of compound 36C as a colorless gummy substance.

#### Fourth step

To compound 36C obtained in the third step was added trifluoroacetic acid (1 ml), and the mixture was stirred at room temperature for 1 hour. After concentration under reduced pressure, pH was adjusted to 6 with sodium bicarbonate water and 2N hydrochloric acid, the mixture was extracted with chloroform, and the extract was dried with sodium sulfate. After the solvent was distilled off under reduced pressure, chloroform-ethyl ether were added, and the precipitated solid was filtered to obtain 24 mg of compound 36 as a colorless solid.

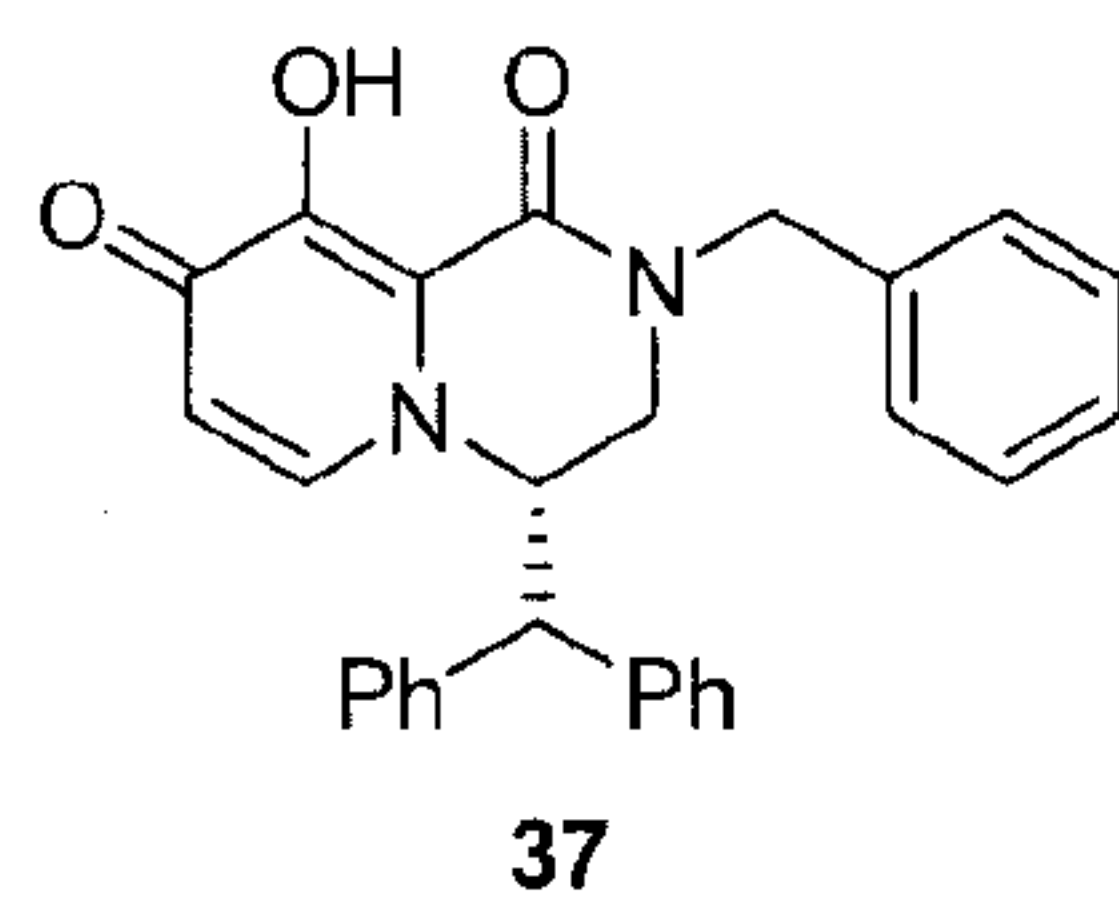
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)  $\delta$ : 2.93 (3H, s), 3.17 (1H, d, J = 13.0 Hz), 4.13 (1H, dd, J = 13.6, 3.4 Hz), 4.47 (1H, d, J = 11.4 Hz), 5.52 (1H, dd, J = 9.3, 3.4 Hz), 5.99 (1H, d, J = 7.3 Hz), 7.18 (4H, m), 7.30 (3H, m), 7.41 (2H, t, J = 7.5 Hz), 7.60 (2H, d, J = 7.2 Hz).

MS: m/z = 361 [M + H]<sup>+</sup>.

[0354]

Reference example 37

[Chemical formula 115]



[0355]

According to Reference example 36, compound 37 was synthesized by the same procedure.

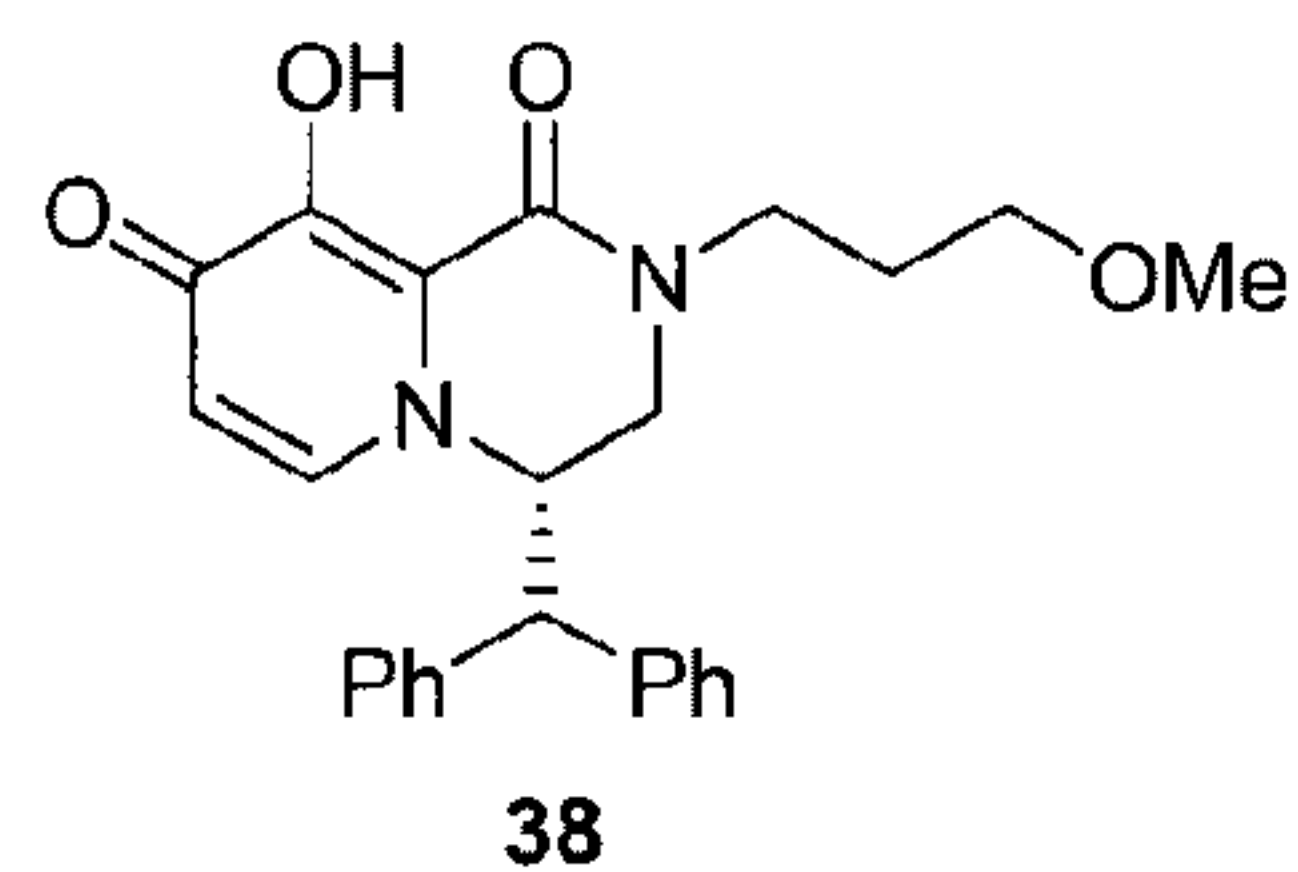
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.16 (2H, d, J = 13.3 Hz), 4.05 (1H, d, J = 10.5 Hz), 4.15 (1H, d, J = 11.7 Hz), 4.38 (1H, d, J = 14.9 Hz), 4.74 (1H, d, J = 14.5 Hz), 5.35 (1H, d, J = 11.4 Hz), 5.65 (1H, d, J = 7.3 Hz), 6.99 (1H, d, J = 7.5 Hz), 7.21 (15H, m).

MS: m/z = 437 [M + H]<sup>+</sup>.

[0356]

Reference example 38

[Chemical formula 116]



[0357]

According to Reference example 36, compound 38 was synthesized by the same procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.57 (2H, m), 3.17 (3H, s), 3.21-3.31 (5H, m), 4.07 (1H, dd, J = 13.5, 3.7 Hz), 4.36 (1H, d, J = 11.6 Hz), 5.42 (1H, d, J = 9.2 Hz), 5.61 (1H, d, J = 7.3

## **DEMANDES OU BREVETS VOLUMINEUX**

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS  
COMPREND PLUS D'UN TOME.**

**CECI EST LE TOME \_\_1\_\_ DE \_\_4\_\_**

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

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## **JUMBO APPLICATIONS / PATENTS**

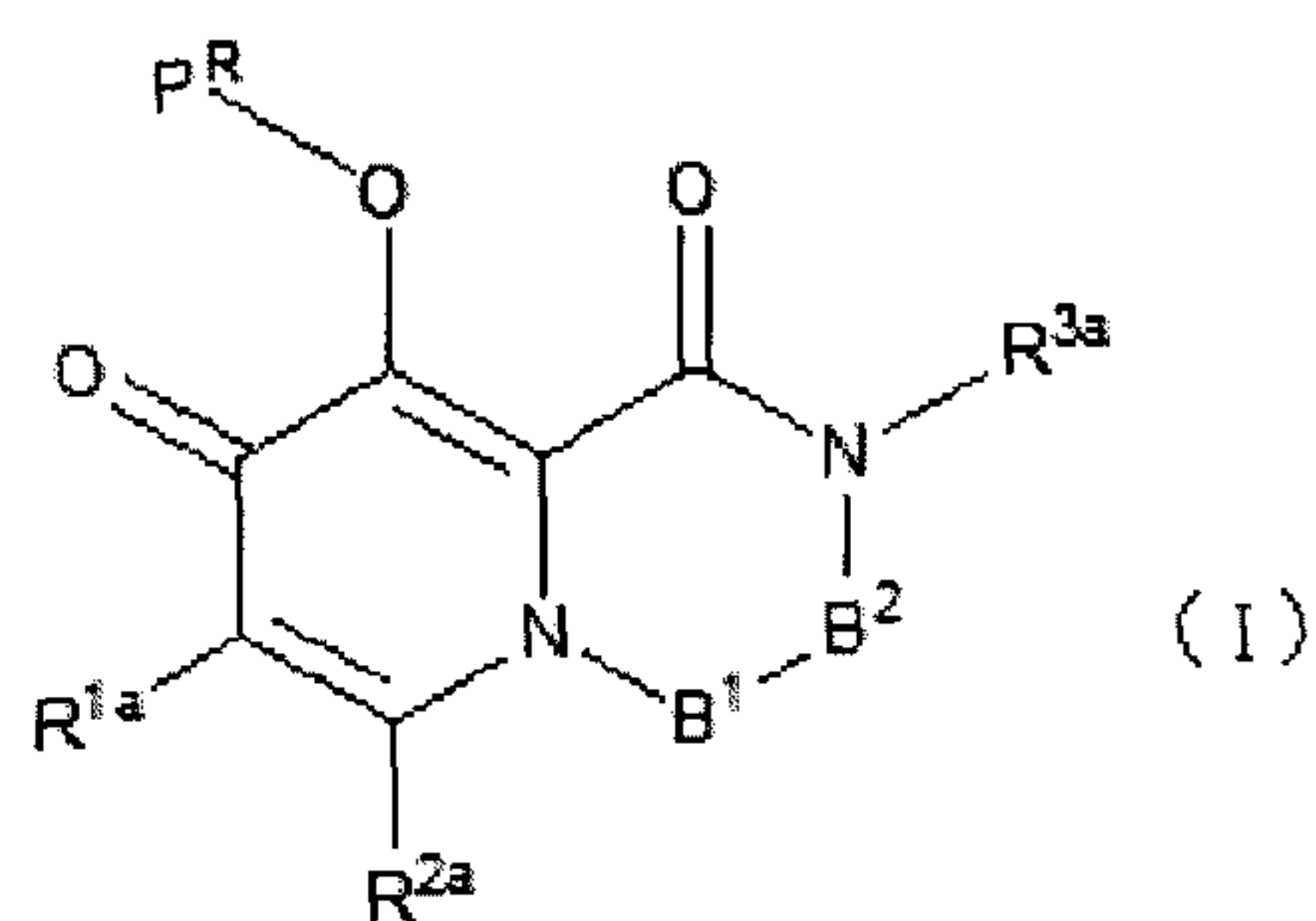
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE  
THAN ONE VOLUME.**

**THIS IS VOLUME \_\_1\_\_ OF \_\_4\_\_**

NOTE: For additional volumes please contact the Canadian Patent Office.

## CLAIMS

1. A compound represented by formula (I):



or a pharmaceutically-acceptable salt or solvate thereof,

wherein:

$P^R$  is a group selected from the following formulas a) to y):

- a)  $-C(=O)-P^{R0}$ ,
- b)  $-C(=O)-P^{R1}$ ,
- c)  $-C(=O)-L-P^{R1}$ ,
- d)  $-C(=O)-L-O-P^{R1}$ ,
- e)  $-C(=O)-L-O-L-O-P^{R1}$ ,
- f)  $-C(=O)-L-O-C(=O)-P^{R1}$ ,
- g)  $-C(=O)-O-P^{R2}$ ,
- h)  $-C(=O)-N(P^{R2})_2$ ,
- i)  $-C(=O)-O-L-O-P^{R2}$ ,
- j)  $-CH_2-O-P^{R3}$ ,
- k)  $-CH_2-O-L-O-P^{R3}$ ,
- l)  $-CH_2-O-C(=O)-P^{R3}$ ,
- m)  $-CH_2-O-C(=O)-O-P^{R3}$ ,

- n)  $-\text{CH}(-\text{CH}_3)-\text{O}-\text{C}(=\text{O})-\text{O}-\text{P}^{\text{R}3}$ ,
- o)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{P}^{\text{R}3}$ ,
- p)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- q)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{N}(\text{P}^{\text{R}3})_2$ ,
- r)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- s)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{N}(-\text{K})-\text{L}-\text{N}(\text{P}^{\text{R}3})_2$ ,
- t)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{O}-\text{L}-\text{O}-\text{P}^{\text{R}3}$ ,
- u)  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{L}-\text{N}(-\text{K})-\text{C}(=\text{O})-\text{P}^{\text{R}3}$ ,
- v)  $-\text{CH}_2-\text{O}-\text{P}(=\text{O})(-\text{OH})_2$ ,
- w)  $-\text{CH}_2-\text{O}-\text{P}(=\text{O})(-\text{OBn})_2$ ,
- x)  $-\text{CH}_2-\text{P}^{\text{R}4}$ , except for a benzyl group, and
- y)  $-\text{C}(=\text{N}^+\text{P}^{\text{R}5}_2)(-\text{NP}^{\text{R}5}_2)$ , wherein:

L is straight or branched lower alkylene, or straight or branched lower alkenylene,

K is hydrogen, or straight or branched lower alkyl,

$\text{P}^{\text{R}0}$  is lower alkyl optionally substituted by substituent group F, or lower alkenyl optionally substituted by substituent group F,

$\text{P}^{\text{R}1}$  is carbocyclic group optionally substituted by substituent group F, heterocyclic group optionally substituted by substituent group F, lower alkyl amino optionally substituted by substituent group F, or lower alkylthio optionally substituted by substituent group F,

$\text{P}^{\text{R}2}$  is lower alkyl optionally substituted by substituent group F, carbocyclic group optionally substituted by substituent group F, or heterocyclic group optionally substituted by substituent group F,

$\text{P}^{\text{R}3}$  is lower alkyl optionally substituted by substituent group F, carbocyclic group optionally substituted by substituent group F, heterocyclic group optionally substituted by substituent group F,

lower alkyl amino optionally substituted by substituent group F, carbocycle lower alkyl optionally substituted by substituent group F, heterocycle lower alkyl optionally substituted by substituent group F, or lower alkylsilyl,

$P^{R^4}$  is carbocyclic group optionally substituted by substituent group F, or heterocyclic group optionally substituted by substituent group F,

$P^{R^5}$  is lower alkyl optionally substituted by substituent group F, and

substituent group F is oxo, lower alkyl, hydroxy lower alkyl, amino, lower alkylamino, carbocycle lower alkyl, lower alkylcarbonyl, halogen, hydroxy, carboxy, lower alkylcarbonylamino, lower alkylcarbonyloxy, lower alkyloxycarbonyl, lower alkyloxy, cyano, and nitro;

$R^{1a}$  is hydrogen, halogen, hydroxy, carboxy, cyano, formyl, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkenyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,

$-Z-N(R^{A1})(R^{A2}),$

$-Z-N(R^{A3})-SO_2-(R^{A4}),$

$-Z-N(R^{A7})-C(=O)-R^{A8},$

-Z-S-R<sup>A9</sup>,

-Z-SO<sub>2</sub>-R<sup>A10</sup>,

-Z-N(R<sup>A12</sup>)-C(=O)-O-R<sup>A13</sup>,

-Z-N(R<sup>A20</sup>)-C(=O)-C(=O)-R<sup>A21</sup>, or

-Z-B(-OR<sup>A22</sup>)(-OR<sup>A23</sup>), wherein:

R<sup>A1</sup>, R<sup>A2</sup>, R<sup>A3</sup>, R<sup>A7</sup>, R<sup>A8</sup>, R<sup>A9</sup>, R<sup>A12</sup>, R<sup>A13</sup>, R<sup>A20</sup>, and R<sup>A21</sup> are each independently selected from a substituent group consisting of hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

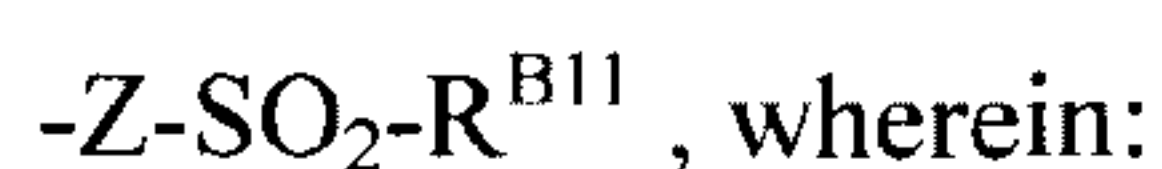
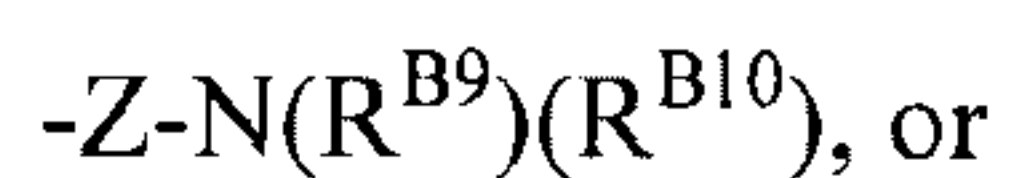
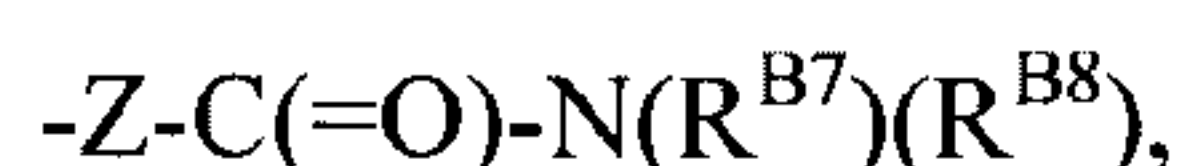
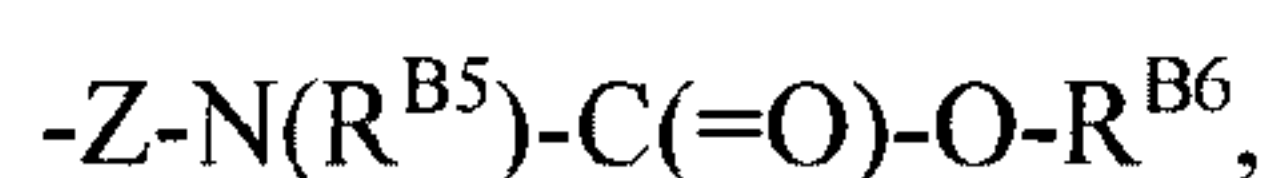
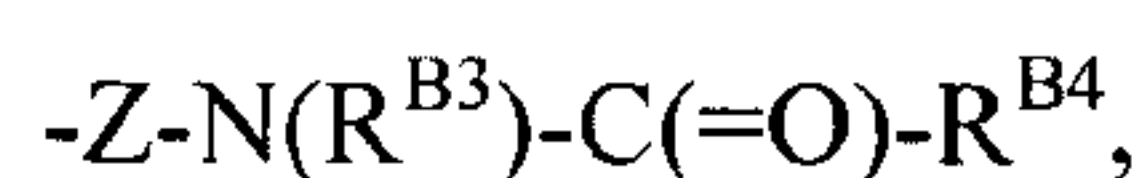
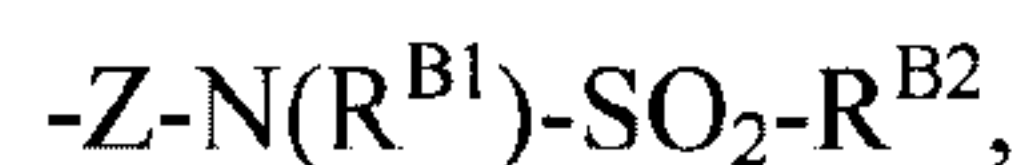
R<sup>A4</sup> and R<sup>A10</sup> are each independently selected from a substituent group consisting of lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

R<sup>A1</sup> and R<sup>A2</sup> may be taken together with an adjacent atom to form heterocycle,

R<sup>A22</sup> and R<sup>A23</sup> are each independently an hydrogen atom, lower alkyl optionally substituted by substituent group C, or R<sup>A22</sup> and R<sup>A23</sup> may be taken together with an adjacent atom to form heterocycle, and

Z is a single bond or straight or branched lower alkylene;

$R^{2a}$  is hydrogen, halogen, carboxy, cyano, formyl, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkenyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C, carbocycleoxy optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxy optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,



$R^{B1}$ ,  $R^{B3}$ ,  $R^{B4}$ ,  $R^{B5}$ ,  $R^{B6}$ ,  $R^{B7}$ ,  $R^{B8}$ ,  $R^{B9}$ , and  $R^{B10}$  are each independently selected from a substituent group consisting of hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by

substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

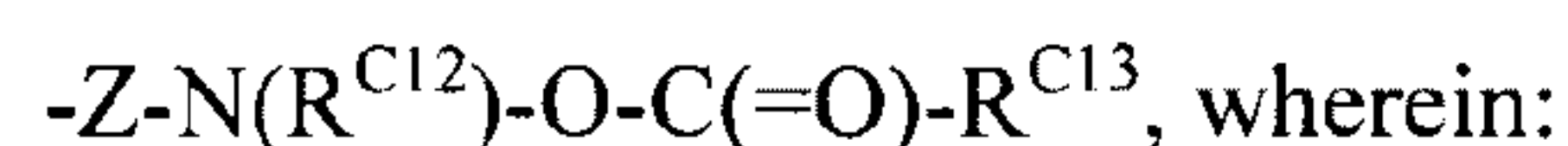
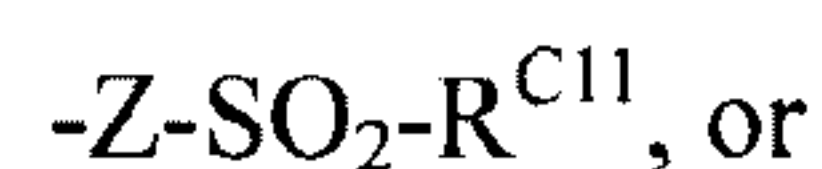
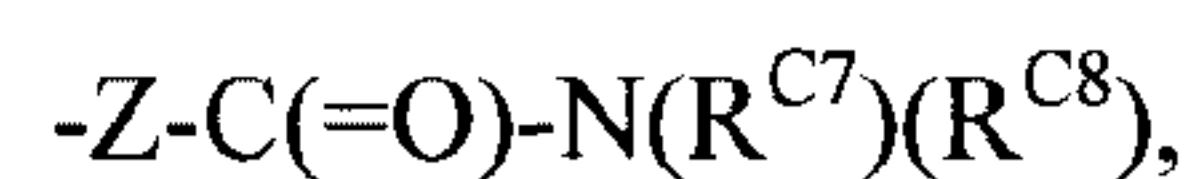
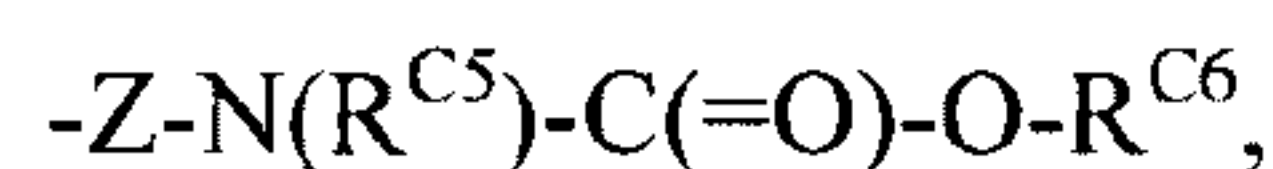
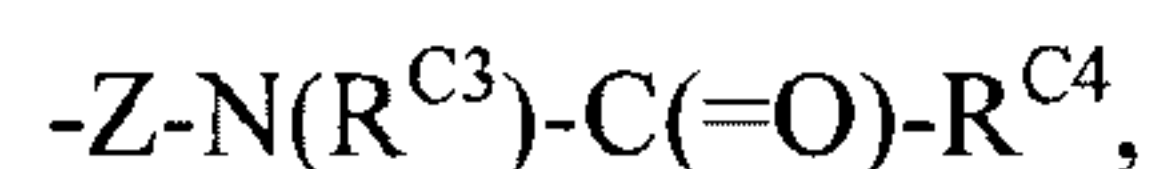
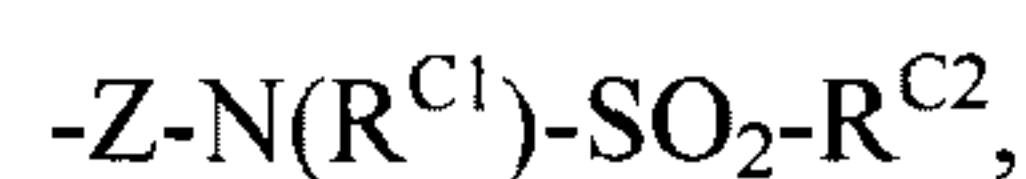
$R^{B2}$  and  $R^{B11}$  are each independently selected from a substituent group consisting of lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{B7}$  and  $R^{B8}$ , and  $R^{B9}$  and  $R^{B10}$  may be taken together with an adjacent atom to form heterocycle, and

Z is a single bond or straight or branched lower alkylene;

$R^{3a}$  is hydrogen, halogen, hydroxy, carboxy, cyano, formyl, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkenyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C, carbocycleoxy optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxy optionally

substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,



$R^{C1}$ ,  $R^{C3}$ ,  $R^{C4}$ ,  $R^{C5}$ ,  $R^{C6}$ ,  $R^{C7}$ ,  $R^{C8}$ ,  $R^{C9}$ ,  $R^{C10}$ ,  $R^{C12}$ , and  $R^{C13}$  are each independently selected from a substituent group consisting of hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{C2}$  and  $R^{C11}$  are each independently selected from a substituent group consisting of lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{C7}$  and  $R^{C8}$ , and  $R^{C9}$  and  $R^{C10}$  each may be taken together with an adjacent atom to form heterocycle, and

Z is a single bond or straight or branched lower alkylene; and

a) either B<sup>1</sup> or B<sup>2</sup> is CR<sup>5a</sup>R<sup>6a</sup>, and the other is NR<sup>7a</sup>, or

b) B<sup>1</sup> is CR<sup>8a</sup>R<sup>9a</sup>, and B<sup>2</sup> is CR<sup>10a</sup>R<sup>11a</sup>;

R<sup>5a</sup>, R<sup>6a</sup>, R<sup>7a</sup>, R<sup>8a</sup>, R<sup>9a</sup>, R<sup>10a</sup>, and R<sup>11a</sup> are each independently selected from a substituent group consisting of hydrogen, carboxy, cyano, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyl carbonyl optionally substituted by substituent group C, lower alkyl oxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,

-Y-S-R<sup>D1</sup>,

-Z-S(=O)-R<sup>D2</sup>,

-Z-SO<sub>2</sub>-R<sup>D3</sup>,

-C(=O)-C(=O)-R<sup>D4</sup>,

-C(=O)-N(R<sup>D5</sup>)(R<sup>D6</sup>),

-Z-C(R<sup>D7</sup>)(R<sup>D8</sup>)(R<sup>D9</sup>),

-Z-CH<sub>2</sub>-R<sup>D10</sup>,

$-Z-N(R^{D11})-C(=O)-O-R^{D12}$ , or

$-Z-N(R^{D13})-C(=O)-R^{D14}$ ,

or

$R^{5a}$  and  $R^{6a}$  may be taken together to form heterocyclic group optionally substituted by substituent group C, wherein:

$R^{D1}$ ,  $R^{D4}$ ,  $R^{D5}$ ,  $R^{D6}$ ,  $R^{D9}$ ,  $R^{D11}$ ,  $R^{D12}$ ,  $R^{D13}$ , and  $R^{D14}$  are each independently selected from a substituent group consisting of hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{D2}$  and  $R^{D3}$  are each independently selected from a substituent group consisting of lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{D7}$ ,  $R^{D8}$ , and  $R^{D10}$  are each independently carbocyclic group optionally substituted by substituent group C, or heterocyclic group optionally substituted by substituent group C,

$R^{D5}$  and  $R^{D6}$  may be taken together with an adjacent atom to form heterocycle,

Y is straight or branched lower alkylene, and

Z is a single bond or straight or branched lower alkylene; and

1) when  $B^1$  is  $CR^{5a}R^{6a}$  and  $B^2$  is  $NR^{7a}$ ,

$R^{3a}$  and  $R^{7a}$  may be taken together with an adjacent atom to form heterocycle optionally substituted by substituent group D,

2) when  $B^1$  is  $NR^{7a}$  and  $B^2$  is  $CR^{5a}R^{6a}$ ,

$R^{3a}$  and  $R^{6a}$  may be taken together with an adjacent atom to form heterocycle optionally substituted by substituent group D, or

3) when  $B^1$  is  $CR^{8a}R^{9a}$ , and  $B^2$  is  $CR^{10a}R^{11a}$ ,

$R^{8a}$  and  $R^{10a}$  may be taken together with an adjacent atom to form carbocycle or heterocycle optionally substituted by substituent group D, or

$R^{3a}$  and  $R^{11a}$  may be taken together with an adjacent atom to form heterocycle optionally substituted by substituent group D;

wherein:

when  $B^1$  is  $CR^{8a}R^{9a}$ , and  $B^2$  is  $CR^{10a}R^{11a}$ , and  $R^{9a}$  is hydrogen, and  $R^{11a}$  is hydrogen,

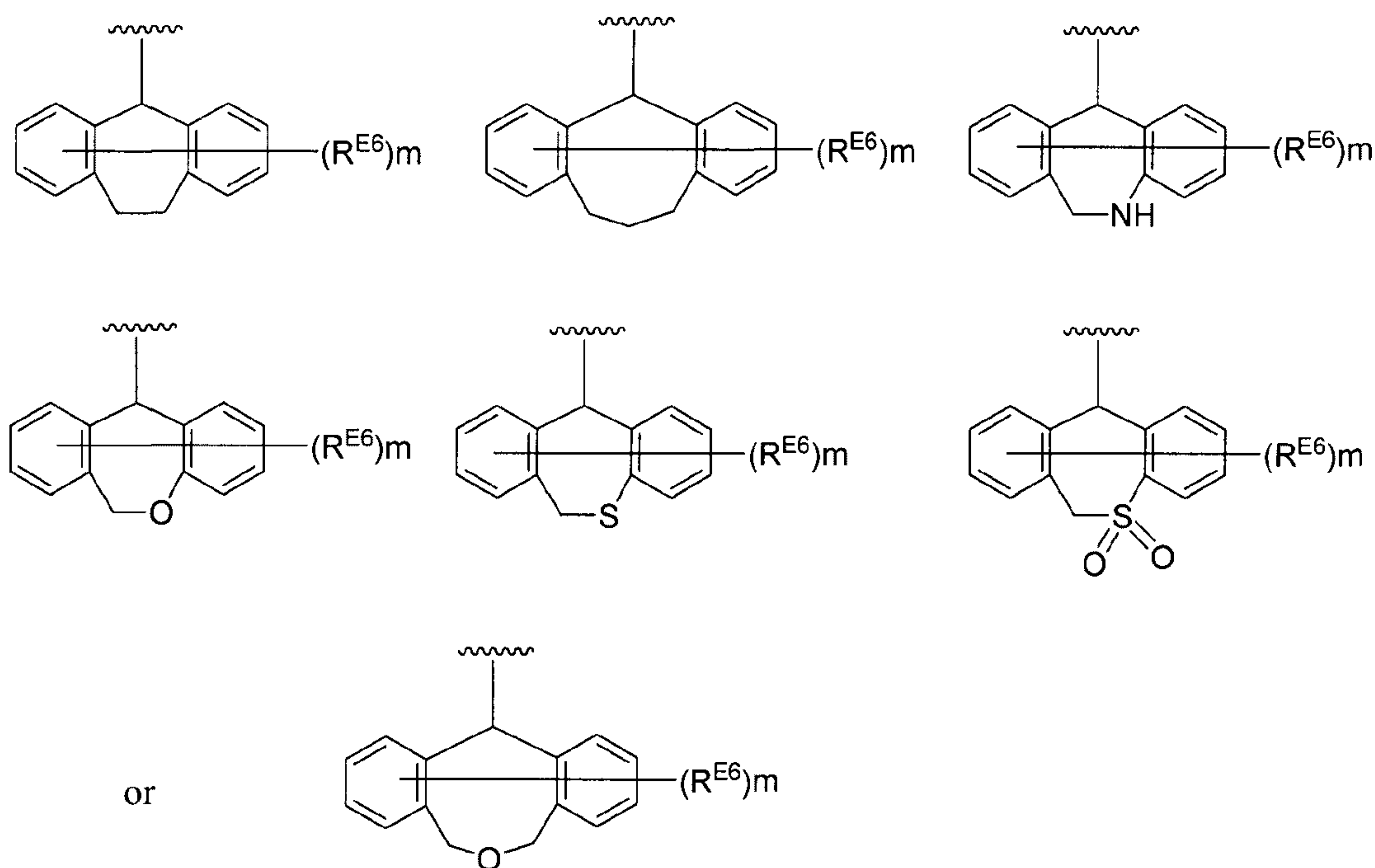
i) either  $R^{8a}$  or  $R^{10a}$  is

$-Z-C(R^{E1})(R^{E2})(R^{E3})$ ,

$-Y-S-R^{E4}$ ,

$-Z-CH_2-R^{E5}$ , or

a group shown below:



, wherein:

$R^{E1}$  and  $R^{E2}$  are each independently, selected from a substituent group consisting of carbocyclic group optionally substituted by substituent group C, and heterocyclic group optionally substituted by substituent group C,

$R^{E3}$  is selected from a substituent group consisting of hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{E4}$  is selected from a substituent group consisting of carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C,

$R^{E5}$  is aromatic heterocyclic group optionally substituted by substituent group C,

$R^{E6}$  is selected from a substituent group C,

m is an integer of 0 or 1 or more, provided that

each  $R^{E6}$  is the same or different groups selected from substituent group C,

Y is straight or branched lower alkylene, and

Z is a single bond or straight or branched lower alkylene; and

ii) the other of  $R^{8a}$  or  $R^{10a}$  is

hydrogen, carboxy, cyano, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,

$-Y-S-R^{F1}$ ,

$-C(=O)-C(=O)-R^{F2}$ , or

$-C(=O)-N(R^{F3})(R^{F4})$ , wherein:

$R^{F1}$ ,  $R^{F2}$ ,  $R^{F3}$ , and  $R^{F4}$  are each independently selected from a substituent group consisting of hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally

substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C, and

Y is straight or branched lower alkylene;

with a proviso that the following c) and d) are excluded:

c)  $R^{5a}$ ,  $R^{6a}$ , and  $R^{7a}$  are all hydrogens,

d)  $R^{8a}$ ,  $R^{9a}$ ,  $R^{10a}$ , and  $R^{11a}$  are all hydrogens;

substituent group C is halogen, cyano, hydroxy, carboxy, formyl, amino, oxo, nitro, lower alkyl, lower alkenyl, lower alkynyl, halogeno lower alkyl, lower alkyloxy, lower alkynyloxy, lower alkylthio, hydroxy lower alkyl, carbocyclic group, heterocyclic group, heterocyclic group substituted by oxo, carbocycle lower alkyloxy, carbocycleoxy lower alkyl, carbocycle lower alkyloxy lower alkyl, heterocycle lower alkyloxy, heterocycleoxy lower alkyl, heterocycle lower alkyloxy lower alkyl, halogeno lower alkyloxy, lower alkyloxy lower alkyl, lower alkyloxy lower alkyloxy, lower alkylcarbonyl, lower alkylcarbonyloxy, lower alkyloxycarbonyl, lower alkylamino, lower alkylcarbonylamino, halogeno lower alkyl carbonylamino, lower alkylaminocarbonyl, lower alkylsulfonyl, lower alkylsulfinyl, and lower alkylsulfonylamino;

substituent group D is halogen, cyano, hydroxy, carboxy, formyl, amino, oxo, nitro, lower alkyl, halogeno lower alkyl, lower alkyloxy, carbocycle lower alkyloxy, heterocycle lower alkyloxy, halogeno lower alkyloxy, lower alkyloxy lower alkyl, lower alkyloxy lower alkyloxy, lower alkylcarbonyl, lower alkyloxycarbonyl, lower alkylamino, lower alkylcarbonylamino, lower alkylaminocarbonyl, lower alkylsulfonyl, lower alkylsulfonylamino, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C,

carbocycle lower alkyl optionally substituted by substituent group C, and heterocycle lower alkyl optionally substituted by substituent group C.

2. The compound according to claim 1, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein:

$R^{1a}$  is hydrogen, halogen, hydroxy, carboxy, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C,

$-Z-N(R^{A1})(R^{A2})$ ,

$-Z-N(R^{A7})-C(=O)-R^{A8}$ ,

$-Z-N(R^{A12})-C(=O)-O-R^{A13}$ , or

$-Z-B(-OR^{A22})(-OR^{A23})$ , wherein:

substituent groups C,  $R^{A1}$ ,  $R^{A2}$ ,  $R^{A7}$ ,  $R^{A8}$ ,  $R^{A12}$ ,  $R^{A13}$ ,  $R^{A22}$ ,  $R^{A23}$ , and Z are the same as those of claim 1.

3. The compound according to claim 1, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein:

$R^{1a}$  is hydrogen, halogen, hydroxy, carboxy, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkyloxy optionally substituted by substituent group C, lower alkylcarbonyl optionally substituted by substituent group C, lower alkyloxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, or

-Z-N(R<sup>A1</sup>)(R<sup>A2</sup>), wherein:

substituent groups C, R<sup>A1</sup>, R<sup>A2</sup>, and Z are the same as those of claim 1.

4. The compound according to claim 1, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein R<sup>1a</sup> is hydrogen or carboxy.

5. The compound according to any one of claims 1 to 4, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein:

R<sup>2a</sup> is hydrogen, lower alkyl optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, or

-Z-N(R<sup>B9</sup>)(R<sup>B10</sup>), wherein:

substituent groups C, R<sup>B9</sup>, R<sup>B10</sup>, and Z are the same as those of claim 1.

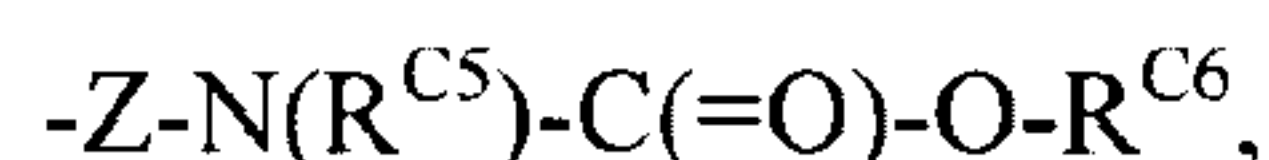
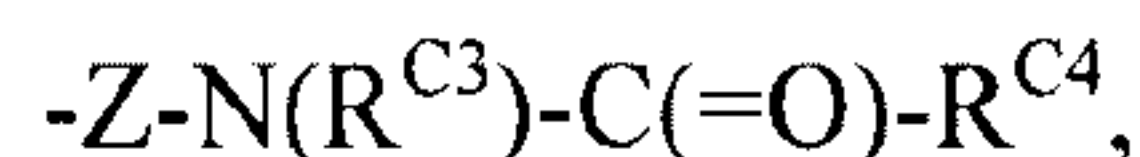
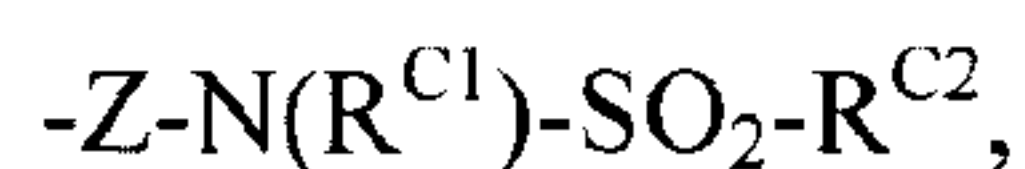
6. The compound according to any one of claims 1 to 4, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein:

R<sup>2a</sup> is hydrogen or lower alkyl optionally substituted by substituent group C, wherein substituent group C is the same as that of claim 1.

7. The compound according to any one of claims 1 to 6, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein:

R<sup>3a</sup> is hydrogen, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl

optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C,



substituent groups C,  $R^{C1}$ ,  $R^{C2}$ ,  $R^{C3}$ ,  $R^{C4}$ ,  $R^{C5}$ ,  $R^{C6}$ ,  $R^{C7}$ ,  $R^{C8}$ ,  $R^{C9}$ ,  $R^{C10}$ , and Z are the same as those of claim 1.

8. The compound according to any one of claims 1 to 6, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein:

$R^{3a}$  is hydrogen, lower alkyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, or carbocycle lower alkyl optionally substituted by substituent group C, wherein substituent group C is the same as that of claim 1.

9. The compound according to any one of claims 1 to 8, or the pharmaceutically-acceptable salt thereof or the solvate thereof,

wherein:

$B^1$  is  $NR^{7a}$ , and  $B^2$  is  $CR^{5a}R^{6a}$ , and

$R^{5a}$ ,  $R^{6a}$  and  $R^{7a}$  are each independently hydrogen, carboxy, cyano, lower alkyl optionally substituted by substituent group C, lower alkenyl optionally substituted by substituent group C, lower alkynyl optionally substituted by substituent group C, lower alkyl carbonyl optionally substituted by

substituent group C, lower alkyl oxycarbonyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, carbocyclecarbonyl optionally substituted by substituent group C, carbocycleoxycarbonyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclecarbonyl optionally substituted by substituent group C, heterocycleoxycarbonyl optionally substituted by substituent group C,

-Y-S-R<sup>D1</sup>,

-Z-S(=O)-R<sup>D2</sup>,

-Z-SO<sub>2</sub>-R<sup>D3</sup>,

-C(=O)-C(=O)-R<sup>D4</sup>,

-C(=O)-N(R<sup>D5</sup>)(R<sup>D6</sup>),

-Z-C(R<sup>D7</sup>)(R<sup>D8</sup>)(R<sup>D9</sup>),

-Z-N(R<sup>D11</sup>)-C(=O)-O-R<sup>D12</sup>, or

-Z-N(R<sup>D13</sup>)-C(=O)-R<sup>D14</sup>, wherein:

substituent groups C, R<sup>D1</sup>, R<sup>D2</sup>, R<sup>D3</sup>, R<sup>D4</sup>, R<sup>D5</sup>, R<sup>D6</sup>, R<sup>D7</sup>, R<sup>D8</sup>, R<sup>D9</sup>, R<sup>D11</sup>, R<sup>D12</sup>, R<sup>D13</sup>, R<sup>D14</sup>, Y,

and Z are the same as those of claim 1.

10. The compound according to any one of claims 1 to 8, or the pharmaceutically-acceptable salt thereof or the solvate thereof,

wherein:

B<sup>1</sup> is NR<sup>7a</sup>, and B<sup>2</sup> is CR<sup>5a</sup>R<sup>6a</sup>,

R<sup>5a</sup> is hydrogen,

$R^{6a}$  is hydrogen, or lower alkyl optionally substituted by substituent group C, and  
 $R^{7a}$  is lower alkyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, or

$-Z-C(R^{D7})(R^{D8})(R^{D9})$ , wherein:

substituent groups C,  $R^{D7}$ ,  $R^{D8}$ ,  $R^{D9}$ , and Z are the same as those of claim 1.

11. The compound according to any one of claims 1 to 8, or the pharmaceutically-acceptable salt thereof or the solvate thereof,

wherein:

$B^1$  is  $CR^{5a}R^{6a}$ , and  $B^2$  is  $NR^{7a}$ ,

$R^{5a}$  is hydrogen,

$R^{6a}$  is hydrogen, or lower alkyl optionally substituted by substituent group C, and

$R^{7a}$  is lower alkyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, or

$-Z-C(R^{D7})(R^{D8})(R^{D9})$ , wherein:

substituent groups C,  $R^{D7}$ ,  $R^{D8}$ ,  $R^{D9}$ , and Z are the same as those of claim 1.

12. The compound according to any one of claims 1 to 6, or the pharmaceutically-

acceptable salt thereof or the solvate thereof,

wherein:

$B^1$  is  $NR^{7a}$ , and  $B^2$  is  $CR^{5a}R^{6a}$ ,

$R^{5a}$  is hydrogen, and

$R^{3a}$  and  $R^{6a}$  are taken together with an adjacent atom to form heterocycle optionally substituted by substituent group D, wherein:

$R^{7a}$  and substituent group D are the same as those of claim 1.

13. The compound according to claim 12, or the pharmaceutically-acceptable salt thereof or the solvate thereof,

wherein:

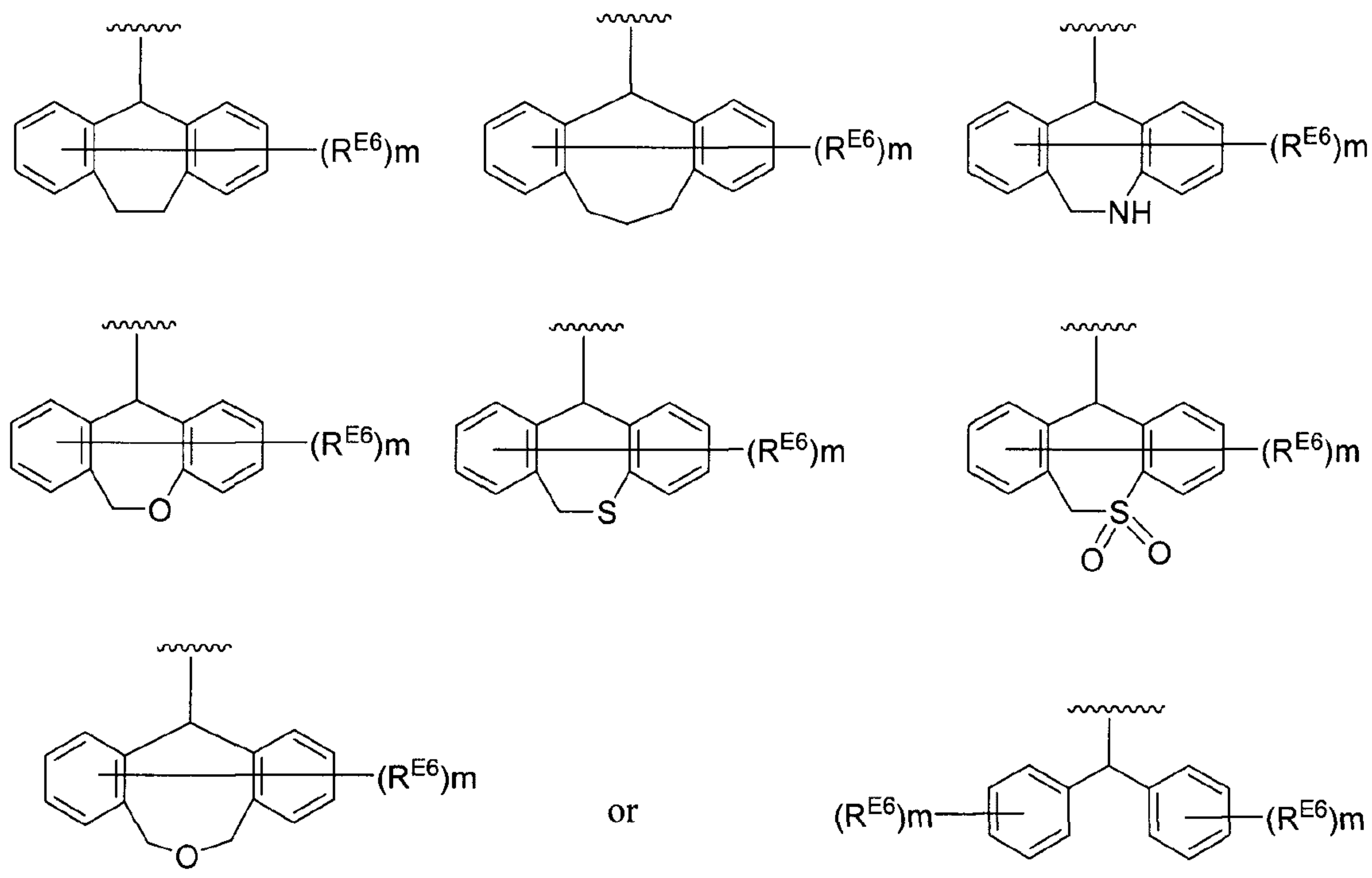
$B^1$  is  $NR^{7a}$ , and  $B^2$  is  $CR^{5a}R^{6a}$ ,

$R^{5a}$  is hydrogen, and

$R^{3a}$  and  $R^{6a}$  are taken together with an adjacent atom to form 5- to 7- membered heterocycle optionally substituted by substituent group D, wherein:

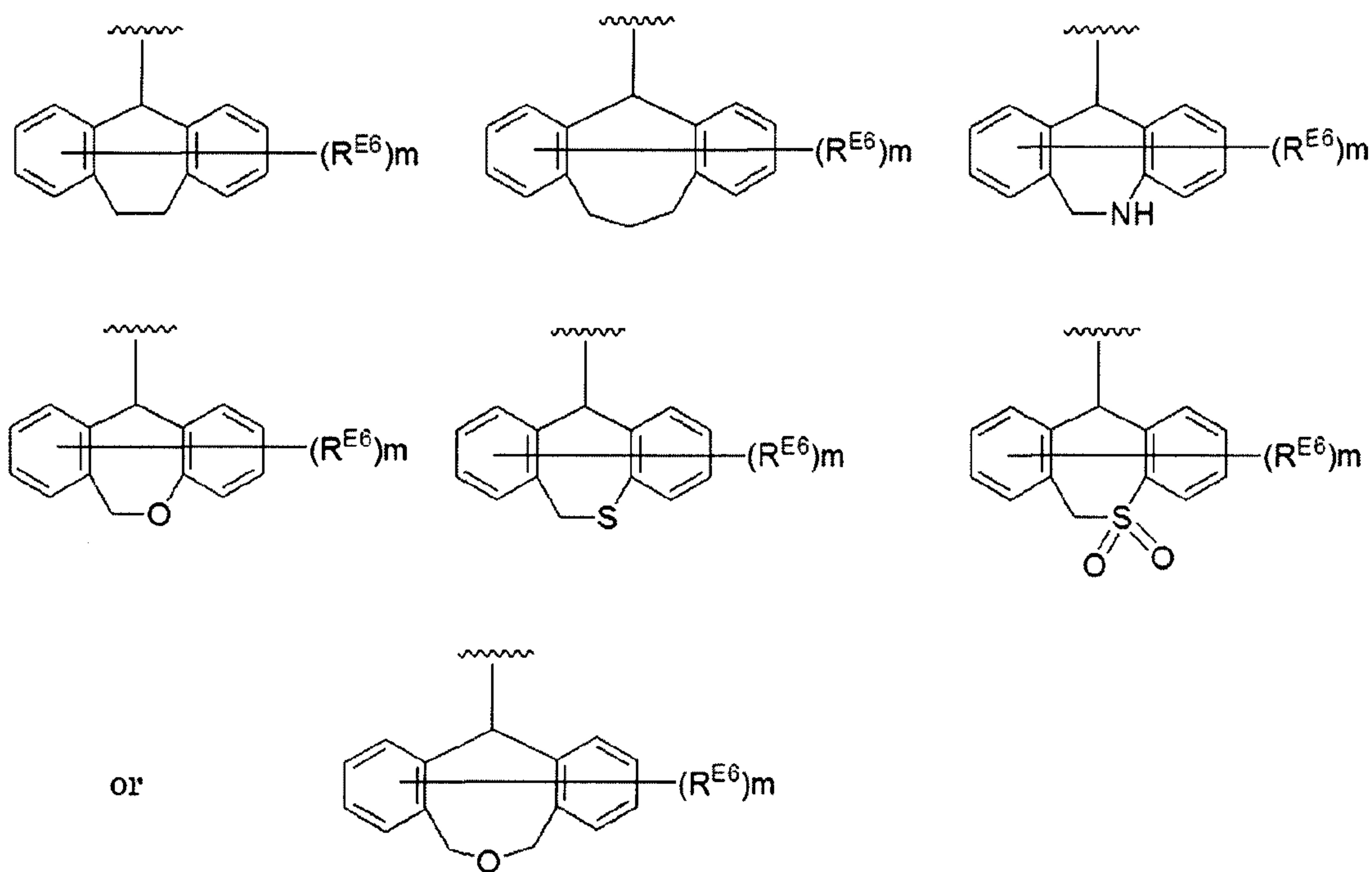
$R^{7a}$  and substituent group D are the same as those of claim 1.

14. The compound according to claim 10 or 11, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein  $R^{7a}$  is a group shown below:



wherein  $R^{E6}$  is selected from a substituent group C and m is an integer of 0 or 1 or more, provided that each  $R^{E6}$  is the same or different groups selected from substituent group C.

15. The compound according to claim 12 or 13, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein  $R^{7a}$  is benzyl, benzhydryl, 4-fluorobenzyl, p-methoxybenzyl, or a group shown below:



wherein  $R^{E6}$  and  $m$  are the same as those of claim 9.

16. The compound according to claim 14 or 15, or the pharmaceutically-acceptable salt thereof or the solvate thereof,

wherein:

each  $R^{E6}$  is independently halogen, cyano, hydroxy, carboxy, amino, oxo, nitro, lower alkyl, halogeno lower alkyl, lower alkyloxy or halogeno lower alkyloxy, and

$m$  is an integer of 0 to 6.

17. The compound according to claim 1, or the pharmaceutically-acceptable salt thereof or the solvate thereof,

wherein:

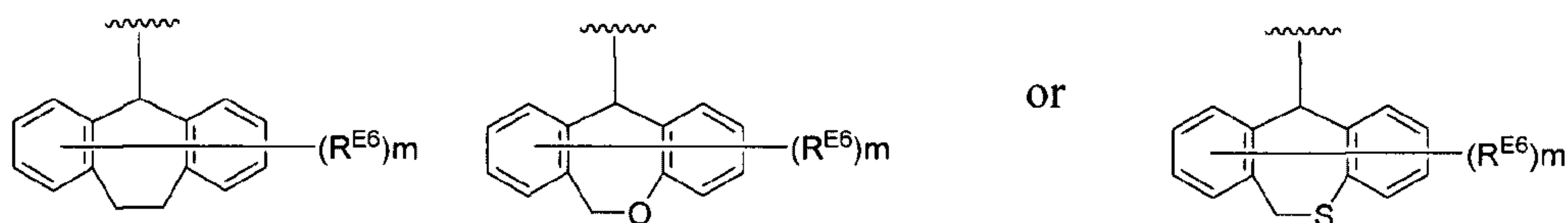
$R^{1a}$  is hydrogen or carboxy,

$R^{2a}$  is hydrogen,

$R^{3a}$  is lower alkyl optionally substituted by substituent group C,

$B^1$  is  $NR^{7a}$ , and  $B^2$  is  $CH_2$ , and

$R^{7a}$  is a group shown below:



wherein substituent group C is the same as those of claim 1, and  $R^{E6}$  and m are the same as those of claim 1.

18. The compound according to any one of claims 1 to 8, or the pharmaceutically-acceptable salt thereof or the solvate thereof,

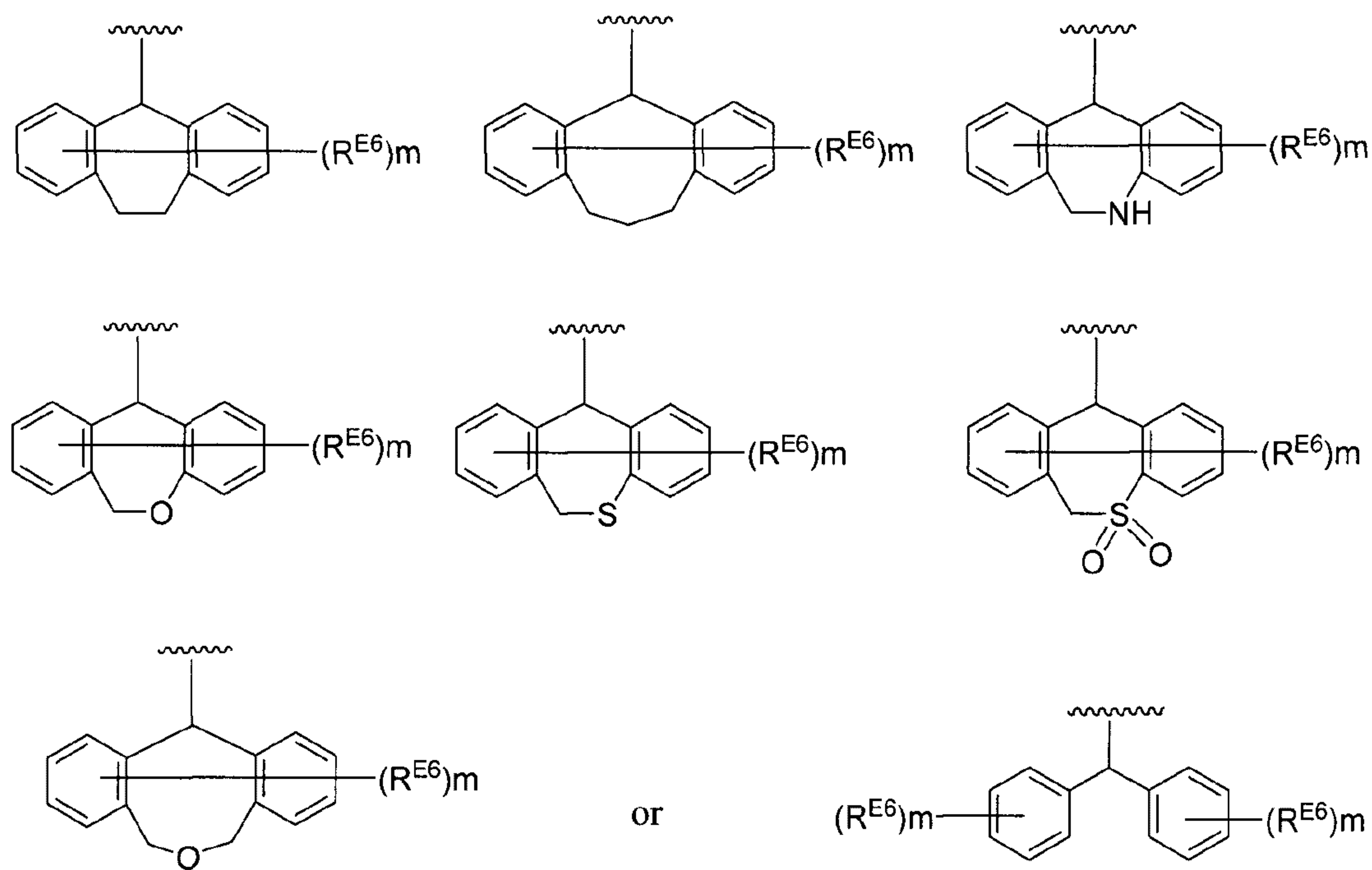
wherein:

$B^1$  is  $CR^{8a}R^{9a}$ , and  $B^2$  is  $CR^{10a}R^{11a}$ ,

$R^{9a}$  is hydrogen, and  $R^{11a}$  is hydrogen, and

i) either  $R^{8a}$  or  $R^{10a}$  is

a group shown below:



wherein  $R^{E6}$  and  $m$  are the same as those of claim 1; and

ii) the other of  $R^{8a}$  or  $R^{10a}$  is hydrogen, or lower alkyl optionally substituted by substituent group C, wherein substituent group C is the same as that of claim 1.

19. The compound according to any one of claims 1 to 6, or the pharmaceutically-acceptable salt thereof or the solvate thereof,

wherein:

$B^1$  is  $CR^{5a}R^{6a}$ , and  $B^2$  is  $NR^{7a}$ ,

$R^{6a}$  is hydrogen,

$R^{3a}$  and  $R^{7a}$  are taken together with an adjacent atom to form heterocycle optionally substituted by substituent group D, and

$R^{5a}$  is hydrogen, lower alkyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by

substituent group C, carbocycloxy lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycloxy lower alkyl optionally substituted by substituent group C,

-Y-S-R<sup>D1</sup>,

-C(=O)-C(=O)-R<sup>D2</sup>, or

-C(=O)-N(R<sup>D3</sup>)(R<sup>D4</sup>), wherein:

R<sup>D1</sup>, R<sup>D2</sup>, R<sup>D3</sup>, R<sup>D4</sup>, Y, substituent group C and substituent group D are the same as those of claim 1.

20. The compound according to claim 19, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein:

R<sup>5a</sup> is hydrogen, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, or heterocycle lower alkyl optionally substituted by substituent group C, wherein substituent group C is the same as that of claim 1.

21. The compound according to any one of claims 1 to 6, or the pharmaceutically-acceptable salt thereof or the solvate thereof,

wherein:

B<sup>1</sup> is CR<sup>8a</sup>R<sup>9a</sup>, and B<sup>2</sup> is CR<sup>10a</sup>R<sup>11a</sup>,

R<sup>9a</sup> is hydrogen, and R<sup>10a</sup> is hydrogen,

R<sup>3a</sup> and R<sup>11a</sup> are taken together with an adjacent atom to form heterocycle optionally substituted by substituent group D, and

$R^{8a}$  is hydrogen, lower alkyl optionally substituted by substituent group C, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, carbocycleoxy lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, heterocycle lower alkyl optionally substituted by substituent group C, heterocycleoxy lower alkyl optionally substituted by substituent group C,

$-Y-S-R^{D1}$ ,

$-C(=O)-C(=O)-R^{D2}$ , or

$-C(=O)-N(R^{D3})(R^{D4})$ , wherein:

$R^{D1}$ ,  $R^{D2}$ ,  $R^{D3}$ ,  $R^{D4}$ , Y, substituent group C, and substituent group D are the same as those of claim 1.

22. The compound according to claim 21, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein:

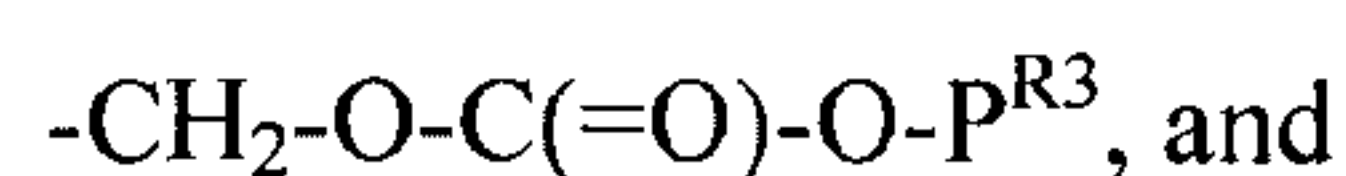
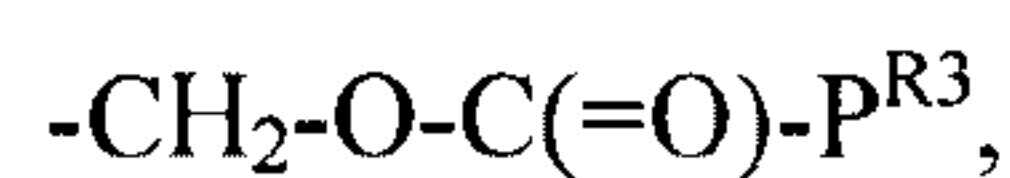
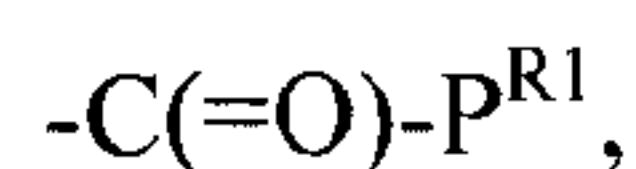
$R^{8a}$  is hydrogen, carbocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, or heterocycle lower alkyl optionally substituted by substituent group C, wherein substituent group C is the same as that of claim 1.

23. The compound according to any one of claims 19 to 22, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein:

substituent group D is carbocyclic group optionally substituted by substituent group C, heterocyclic group optionally substituted by substituent group C, carbocycle lower alkyl optionally substituted by substituent group C, or heterocycle lower alkyl optionally substituted by substituent

group C, wherein substituent group C is the same as that of claim 1.

24. The compound according to any one of claims 1 to 23, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein  $P^R$  is a group selected from the following formulas:



wherein:

$P^{R1}$  is carbocyclic group optionally substituted by substituent group F, heterocyclic group optionally substituted by substituent group F, lower alkyl amino optionally substituted by substituent group F, or lower alkylthio optionally substituted by substituent group F, and

$P^{R3}$  is lower alkyl optionally substituted by substituent group F, carbocyclic group optionally substituted by substituent group F, heterocyclic group optionally substituted by substituent group F, lower alkyl amino optionally substituted by substituent group F, carbocycle lower alkyl optionally substituted by substituent group F, heterocycle lower alkyl optionally substituted by substituent group F, or lower alkylsilyl.

25. The compound according to claim 1, or the pharmaceutically-acceptable salt thereof or the solvate thereof,

wherein:

$R^{1a}$  is hydrogen or carboxy,

$R^{2a}$  is hydrogen,

$R^{3a}$  is lower alkyl optionally substituted by substituent group C,

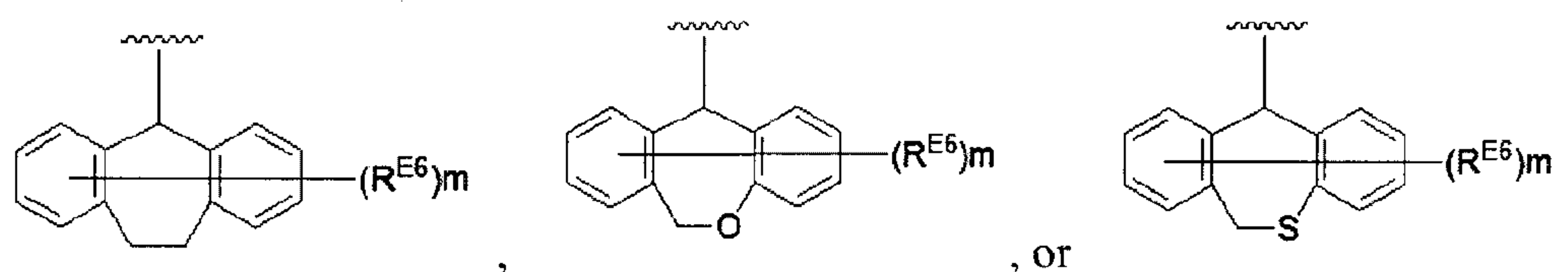
$B^1$  is  $NR^{7a}$ , and  $B^2$  is  $CR^{5a}R^{6a}$ ,

$R^{5a}$  is hydrogen,

$R^{6a}$  is hydrogen, or lower alkyl optionally substituted by substituent group C,

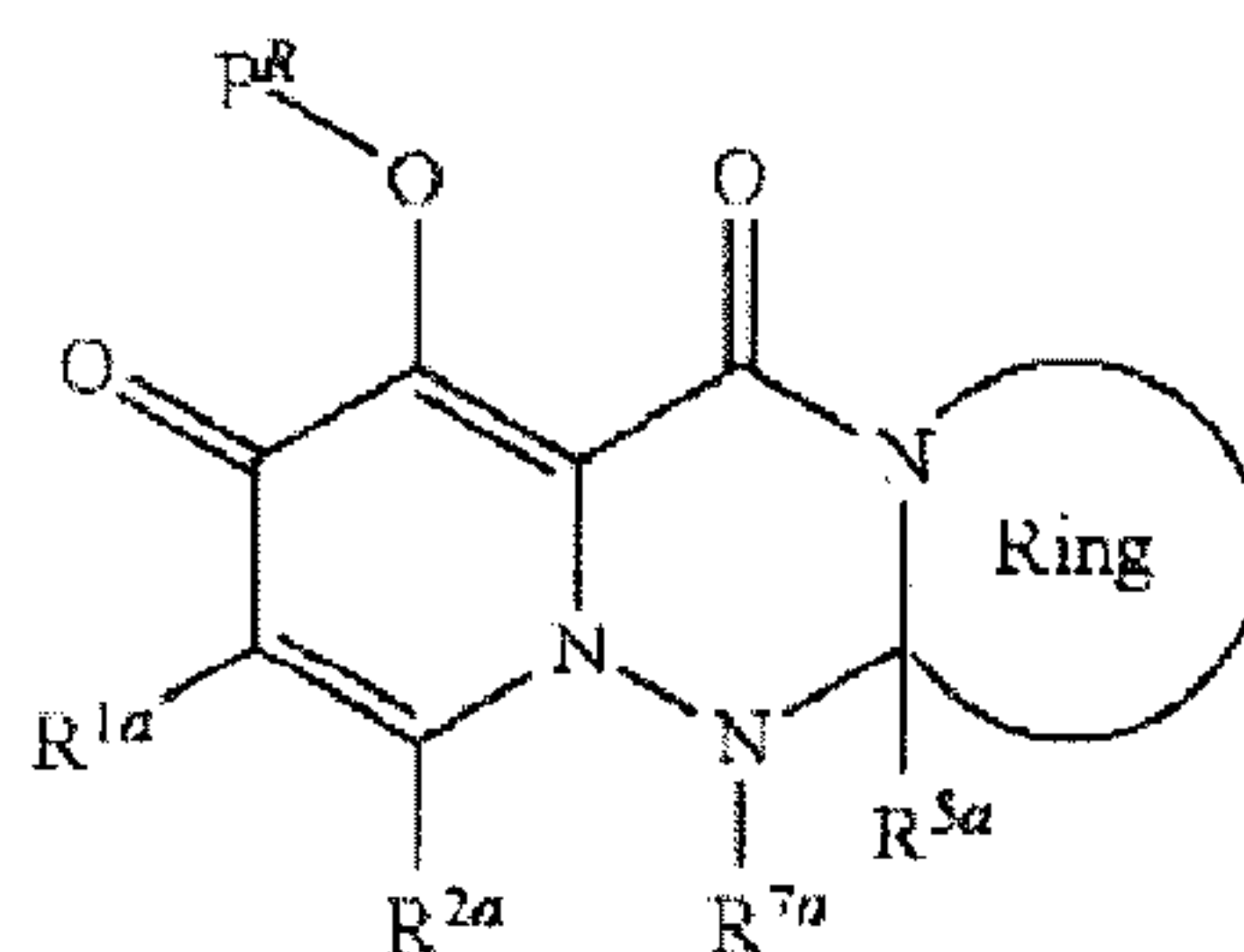
$R^{3a}$  and  $R^{6a}$  are taken together with an adjacent atom to form a 5- to 7-membered heterocycle optionally substituted by substituent group D, and

$R^{7a}$  is:



wherein  $R^{E6}$  and  $m$  are the same as those of claim 1.

26. The compound of claim 1 or 25, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein formula (I) is represented by the following formula:



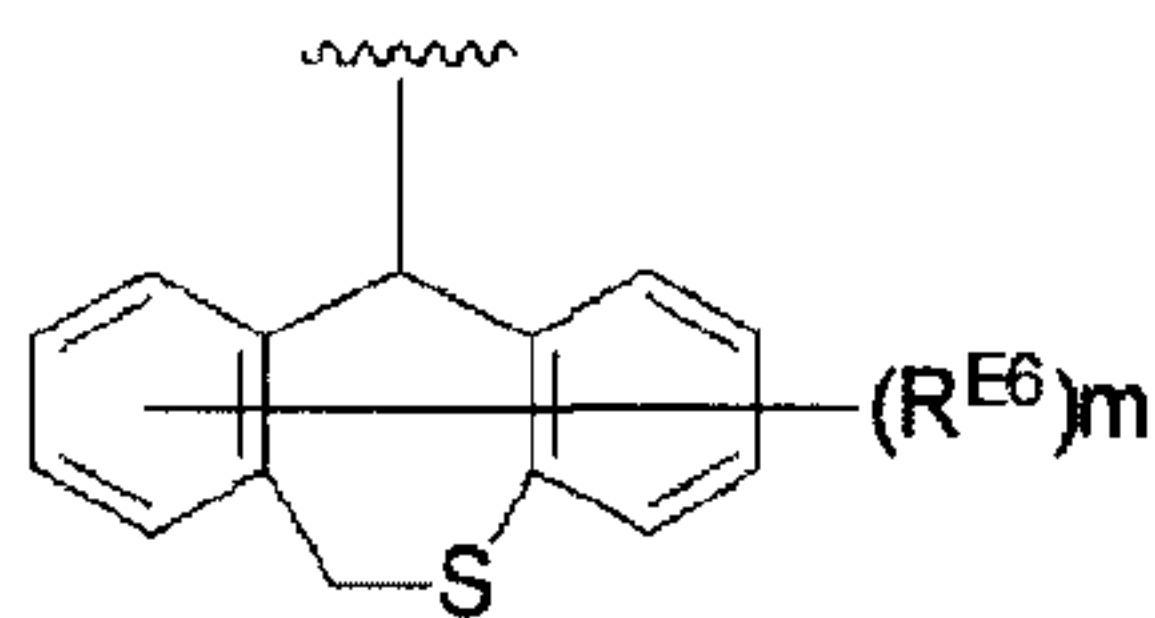
wherein:

Ring is a 6-membered heterocycle,

$P^R$  is  $-CH_2-O-C(=O)-P^{R3}$ ,  $-CH_2-O-C(=O)-O-P^{R3}$ , or  $-CH(-CH_3)-O-C(=O)-O-P^{R3}$ ,

$P^{R3}$  is lower alkyl optionally substituted by substituent group F, and

$R^{7a}$  is:



wherein  $R^{1a}$ ,  $R^{2a}$ , and  $R^{5a}$  are the same as those of claim 25, and  $R^{E6}$  and  $m$  are the same as those of claim 1.

27. The compound of claim 26, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein the 6-membered heterocycle is non-aromatic.

28. The compound of claim 26, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein O is one of the members of the 6-membered heterocycle.

29. The compound of claim 26, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein the 6-membered heterocycle is a morpholinyl ring.

30. The compound of any one of claims 26-29, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein  $P^R$  is  $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-P^{R3}$ , and  $P^{R3}$  is the same as that of claim 26.

31. The compound of claim 30, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein  $P^{R3}$  is methyl, ethyl, or propyl.

32. The compound of any one of claims 26-31, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein  $R^{E6}$  is halogen and  $m$  is 1 or 2.

33. The compound of claim 32, or the pharmaceutically-acceptable salt thereof or the solvate thereof, wherein m is 2 and the two R<sup>E6</sup> groups are positioned adjacent to each other on one of the phenyl rings.

34. A pharmaceutical composition containing a compound according to any one of claims 1 to 33, or a pharmaceutically-acceptable salt thereof or a solvate thereof.

35. The pharmaceutical composition according to claim 34, which exhibits anti-influenza activity.

36. The pharmaceutical composition according to claim 34, which exhibits cap-dependent endonuclease inhibitory activity.

Fig. 1

| Time (hr)         | Transition of Reference example 301 concentration in plasma (ng/ml) |      |      |      |      |
|-------------------|---------------------------------------------------------------------|------|------|------|------|
|                   | 1                                                                   | 2    | 3    | Mean | SD   |
| 0                 | 0                                                                   | 0    | 0    | 0    | 0    |
| 0.25              | 3.0                                                                 | 2.5  | 4.2  | 3.2  | 0.9  |
| 0.5               | 5.1                                                                 | 3.6  | 7.4  | 5.3  | 1.9  |
| 1                 | 5.5                                                                 | 4.4  | 5.9  | 5.2  | 0.8  |
| 2                 | 3.3                                                                 | 2.1  | 3.7  | 3.0  | 0.8  |
| 4                 | 0.9                                                                 | 1.1  | 1.6  | 1.2  | 0.3  |
| 6                 | 1.1                                                                 | 1.1  | 2.8  | 1.7  | 1.0  |
| 8                 | 1.0                                                                 | 2.2  | 3.5  | 2.2  | 1.2  |
| 24                | 0.3                                                                 | 0.2  | 0.2  | 0.2  | 0.1  |
| Cmax (ng/mL)      | 5.5                                                                 | 4.4  | 7.4  | 5.8  | 1.5  |
| Tmax (hr)         | 1.00                                                                | 1.00 | 0.50 | 0.83 | 0.29 |
| AUCall (ng·hr/mL) | 24.7                                                                | 32.6 | 54.1 | 37.2 | 15.2 |
| BA (%)            | 4.51                                                                | 5.95 | 9.87 | 6.78 | 2.77 |

Fig. 2

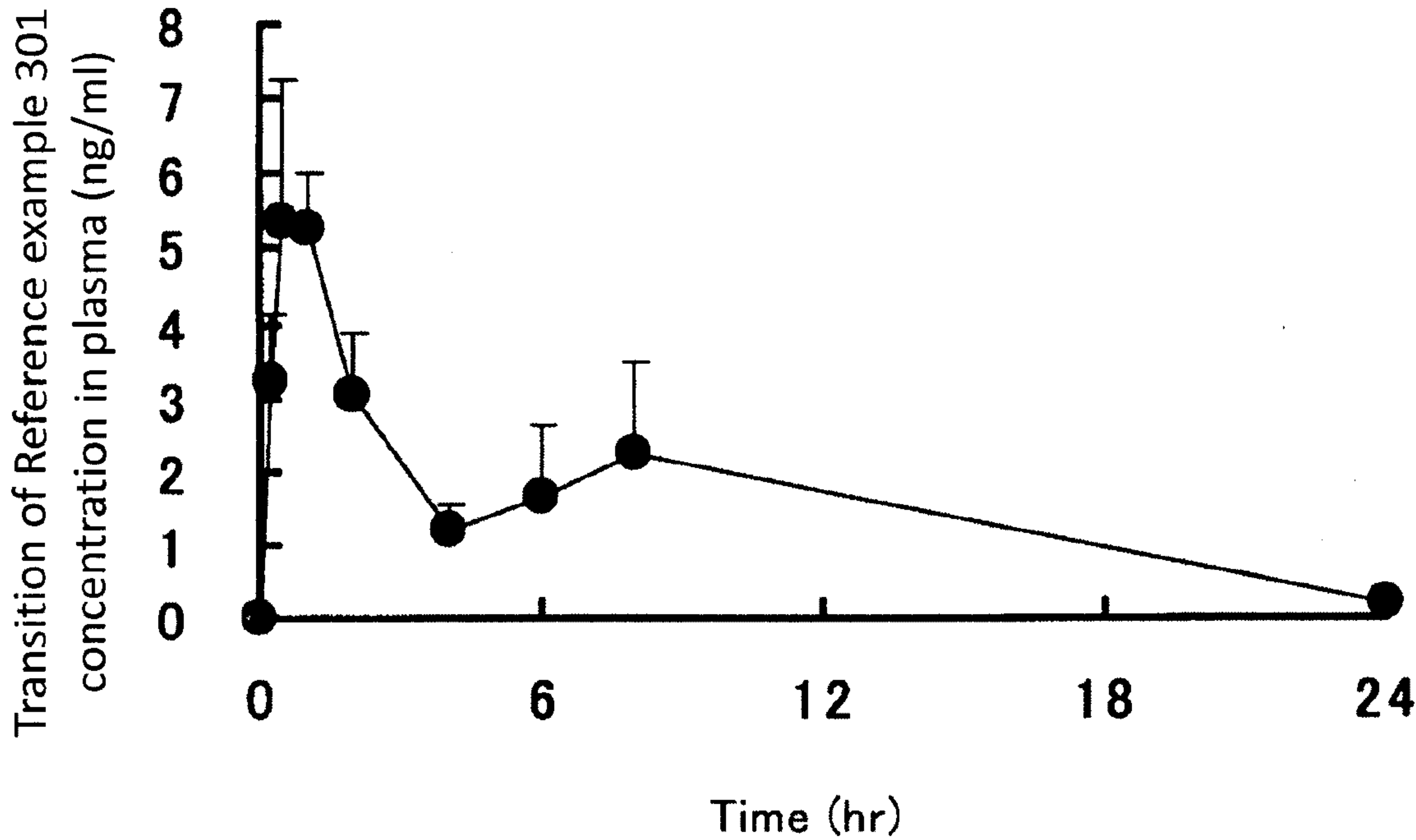


Fig. 3

| Transition of Reference example 301 concentration in plasma (ng/ml) |      |      |      |      |      |
|---------------------------------------------------------------------|------|------|------|------|------|
| Time (hr)                                                           | 1    | 2    | 3    | Mean | SD   |
| 0                                                                   | 0    | 0    | 0    | 0    | 0    |
| 0.25                                                                | 23.7 | 4.4  | 14.6 | 14.2 | 9.6  |
| 0.5                                                                 | 27.5 | 6.0  | 21.9 | 18.5 | 11.1 |
| 1                                                                   | 23.4 | 6.1  | 13.5 | 14.4 | 8.7  |
| 2                                                                   | 11.7 | 4.8  | 7.4  | 8.0  | 3.4  |
| 4                                                                   | 5.8  | 2.2  | 2.6  | 3.5  | 2.0  |
| 6                                                                   | 3.5  | 2.4  | 2.4  | 2.8  | 0.6  |
| 8                                                                   | 2.9  | 1.8  | 3.1  | 2.6  | 0.7  |
| 24                                                                  | 0.8  | 0    | 0    | 0.3  | 0.5  |
| Cmax (ng/mL)                                                        | 27.5 | 6.10 | 21.9 | 18.5 | 11.1 |
| Tmax (hr)                                                           | 0.50 | 1.0  | 0.50 | 0.67 | 0.29 |
| AUCall (ng·hr/mL)                                                   | 102  | 40.5 | 71.0 | 71.3 | 31.0 |
| BA (%)                                                              | 18.7 | 7.40 | 13.0 | 13.0 | 5.6  |

Fig. 4

