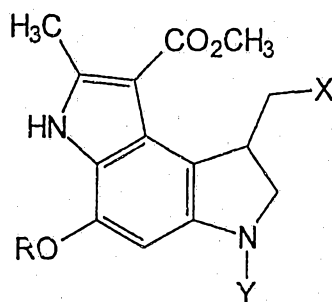




AU9522671

(12) PATENT ABRIDGMENT (11) Document No. AU-B-22671/95
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 685939

- (54) Title
DC-89 DERIVATIVE
- (51)⁶ International Patent Classification(s)
C07D 487/04 A61K 031/40 A61K 031/44 A61K 031/445
A61K 031/495 A61K 031/535
- (21) Application No. : 22671/95 (22) Application Date : 20.04.95
- (87) PCT Publication Number : WO95/29179
- (30) Priority Data
- (31) Number (32) Date (33) Country
6-84714 22.04.94 JP JAPAN
- (43) Publication Date : 16.11.95
- (44) Publication Date of Accepted Application : 29.01.98
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- (56) Prior Art Documents
WO 88/04659
EP 154445
- (57) Claim
1. A DC-89 derivative represented by the formula



wherein:

X represents Cl or Br;

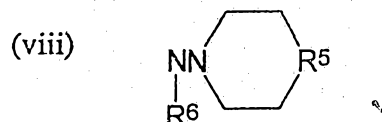
R represents:

- (a) substituted or unsubstituted lower alkyl;
- (b) substituted or unsubstituted aralkyl;
- (c) COR¹ in which R¹ represents;
 - (i) hydrogen;
 - (ii) substituted or unsubstituted lower alkyl
 - (iii) substituted or unsubstituted aryl;
 - (iv) substituted or unsubstituted heterocyclic group selected from the group consisting of pyridyl, pyrazinyl and pyrimidinyl;

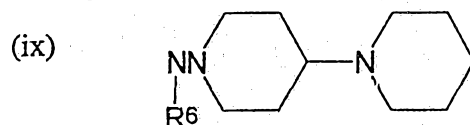
(v) OR^2 (in which R^2 represents substituted or unsubstituted lower alkyl or aryl);

(vi) SR^2 (in which R^2 is the same meaning as defined above);

(vii) NR^3R^4 (in which R^3 and R^4 independently represent hydrogen, substituted lower alkyl, amino, or mono- or di(lower alkyl)amino, provided that R^3 and R^4 are not hydrogen at the same time);

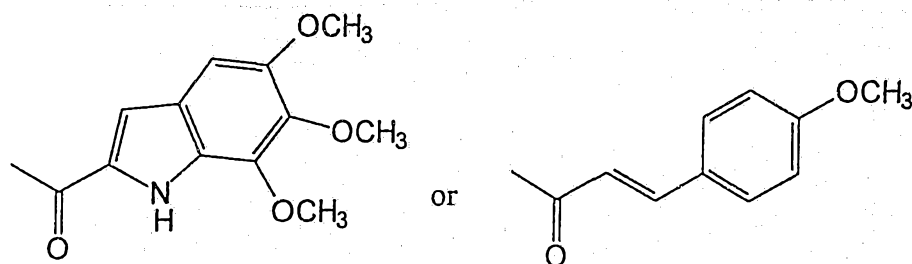


in which R^5 represents NR^7 (in which R^7 represents hydrogen or substituted or unsubstituted lower alkyl) or oxygen, and R^6 represents hydrogen or substituted or unsubstituted lower alkyl, or



(in which R^6 represents hydrogen or substituted or unsubstituted lower alkyl) or SO_2R^8 (in which R^8 represents substituted or unsubstituted lower alkyl or substituted or unsubstituted aryl); and

Y represents



or pharmaceutically acceptable salts thereof.

6. A method for the treatment or prophylaxis of a tumor in a mammal, comprising administering to said mammal an effective amount of a DC-89 derivative according to any one of claims 1 to 3.

OPI DATE 16/11/95 APPLN. ID 22671/95
 AOJP DATE 04/01/96 PCT NUMBER PCT/JP95/00779



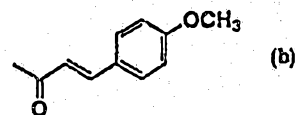
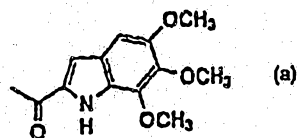
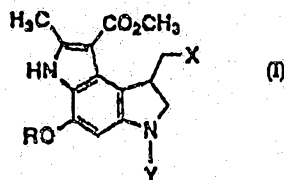
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(51) 国際特許分類6 C07D 487/04 // A61K 31/40, 31/44, 31/495, 31/535, 31/445	A1	(11) 国際公開番号 WO95/29179 (43) 国際公開日 1995年11月2日 (02.11.95)
(21) 国際出願番号 PCT/JP95/00779 (22) 国際出願日 1995年4月20日 (20.04.95) (30) 優先権データ 特願平6/84714 1994年4月22日 (22.04.94) JP (71) 出願人 (米国を除くすべての指定国について) 協和発酵工業株式会社 (KYOWA HAKKO KOGYO CO., LTD.)[JP/JP] 〒100 東京都千代田区大手町一丁目6番1号 Tokyo, (JP) (72) 発明者: および (75) 発明者/出願人 (米国についてのみ) 網城宣善(AMISHIRO, Nobuyoshi)[JP/JP] 岡元晶彦(OKAMOTO, Akihiko)[JP/JP] 〒411 静岡県駿東郡長泉町下土狩1188 Shizuoka, (JP) 長村聡仁(NAGAMURA, Satoru)[JP/JP] 〒747 山口県防府市協和町2-3-105 Yamaguchi, (JP) 斉藤博満(SAITO, Hiromitsu)[JP/JP] 〒214 神奈川県川崎市多摩区西生田4-16-19 Kanagawa, (JP) 小林英二(KOBAYASHI, Eiji)[JP/JP] 〒157 東京都世田谷区粕谷3-18-15 Tokyo, (JP)		五味克成(GOMI, Katsushige)[JP/JP] 〒410-11 静岡県裾野市伊豆島田541-12 Shizuoka, (JP) (81) 指定国 AU, CA, JP, KR, US, 欧州特許(AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). 添付公開書類 国際調査報告書

685939

(54) Title : DC-89 DERIVATIVE

(54) 発明の名称 DC-89誘導体



(57) Abstract

A DC-89 derivative represented by general formula (I) or a pharmacologically acceptable salt thereof, wherein X represents Cl or Br; R represents (un)substituted alkyl, (un)substituted aralkyl, COR¹ or SO₂R²; and Y represents the group (a) or (b). The compound has an excellent antitumor activity and is useful as an antitumor drug.

SPECIFICATION

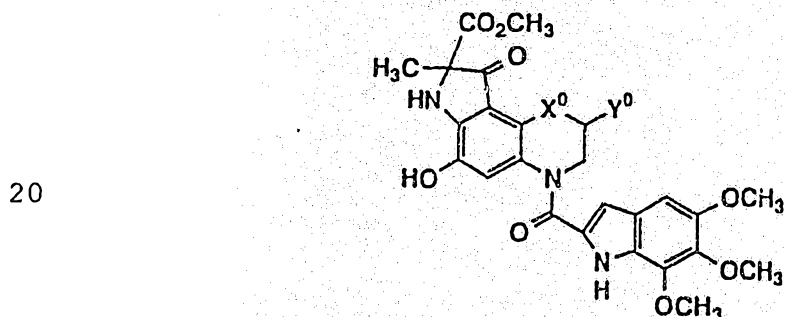
DC-89 DERIVATIVE

5 Technical Field

The present invention relates to DC-89 derivatives. The compounds of the present invention exhibit excellent anti-tumor activity and are useful as anti-tumor agents.

10 Background Art

As compounds related to DC-89 derivatives of the present invention, DC-89A1, DC-89A2, DC-89B1 and DC-89B2 represented by the following structural formula are known, and these compounds exhibit antibacterial activity against various bacteria and also
15 antitumor activity against melanoma B-16, etc.



DC-89A1: X⁰ = -CH₂-, Y⁰ = Cl

25 DC-89A2: X⁰ = single bond, Y⁰ = CH₂Cl

DC-89B1: X⁰ = -CH₂-, Y⁰ = Br

DC-89B2: X⁰ = single bond, Y⁰ = CH₂Br

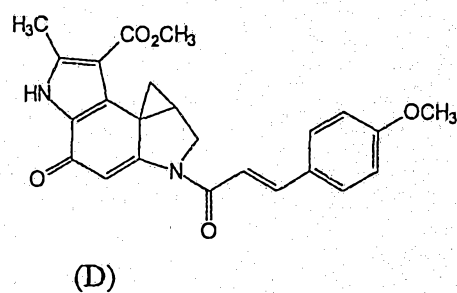
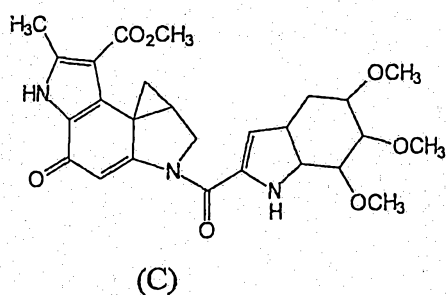
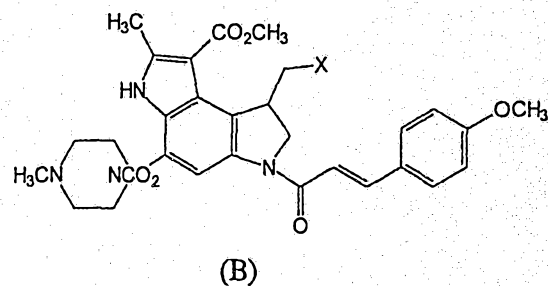
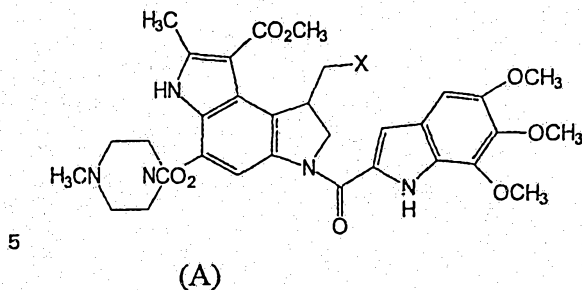
DC-89A1 is disclosed in WO87/06265, and DC-89A2, DC-89B1
30 and DC-89B2 are disclosed in JP,A,2-119787. SF2582A and
SF2582B, which are the same compounds as DC-89A2 and DC-89A1,
are disclosed in JP,A,1-139590. DC-88A and DC113 are disclosed
in WC87/06265 and JP,A,2-177890, respectively. These compounds
exhibit not only antibacterial activity against various bacteria
35 but also anti-tumor activity against melanoma B-16, etc.

DC-88A derivatives and DC-89 derivatives are disclosed in



JP,A,2-288879, JP,A,3-7287, JP,A,3-128379 and JP,A,5-178858.

JP,A,3-128379 discloses Compounds (A) and (C) represented by the following formulae, and JP,A,5-178858 discloses Compounds (B) and (D) represented by the following formulae.

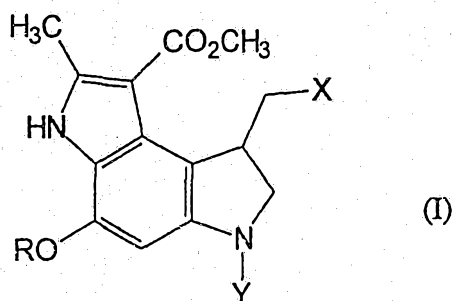


10 Further, CC-1065 and its derivatives are disclosed in JP,A,54-64695, JP,A,60-193989, WO88/04659, EP-359454 and JP,A,3-14581. Related derivatives are disclosed in JP,A,6-116269.

It is an object of the present invention to provide DC-89 derivatives which exhibit excellent anti-tumor activity.

15 Disclosure of the Invention

The present invention provides DC-89 derivatives represented by formula (I)



wherein:

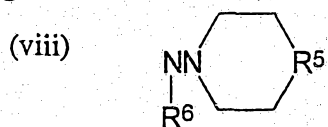
X represents Cl or Br;

20 R represents:

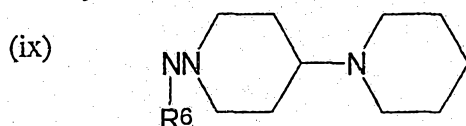
- (a) substituted or unsubstituted lower alkyl;
- (b) substituted or unsubstituted aralkyl;
- (c) COR¹ in which R¹ represents;
 - (i) hydrogen;



- (ii) substituted or unsubstituted lower alkyl
 (iii) substituted or unsubstituted aryl;
 (iv) substituted or unsubstituted heterocyclic group selected from the group consisting of pyridyl, pyrazinyl and pyrimidinyl;
 5 (v) OR^2 (in which R^2 represents substituted or unsubstituted lower alkyl or aryl);
 (vi) SR^2 (in which R^2 is the same meaning as defined above);
 (vii) NR^3R^4 (in which R^3 and R^4 independently represent hydrogen, substituted lower alkyl, amino, or mono- or di(lower alkyl)amino, provided that R^3 and
 10 R^4 are not hydrogen at the same time);

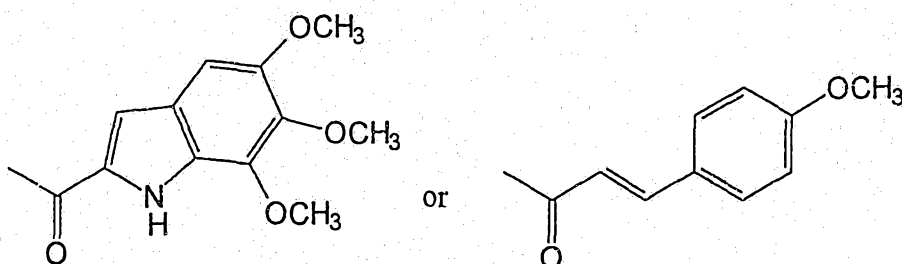


in which R^5 represents NR^7 (in which R^7 represents hydrogen or substituted or unsubstituted lower alkyl) or oxygen, and R^6 represents hydrogen or substituted or unsubstituted lower alkyl, or



15 (in which R^6 represents hydrogen or substituted or unsubstituted lower alkyl) or SO_2R^8 (in which R^8 represents substituted or unsubstituted lower alkyl or substituted or unsubstituted aryl); and

Y represents



20 or pharmaceutically acceptable salts thereof.

The compounds represented by formula (I) are hereinafter referred to as Compounds (I). Similarly, the compounds represented by formulae (I) and (IX) are referred to as Compounds (I) to (IX). Compounds (I)a, (I)b, etc. are intended to be included in
 25 Compounds (I), and Compounds (I)b-1, (I)b-2, etc. are intended to be included in Compounds (I)b.

In the definition of the above-mentioned formula (I), lower alkyl and the alkyl moiety or mono- or di(lower alkyl)amino include linear or branched alkyl groups having 1 to 8 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl,



sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, isohexyl, heptyl, octyl and iso-octyl. Examples of aryl include phenyl and naphthyl. Examples of aralkyl include groups having 7 to 20 carbon atoms such as benzyl, phenethyl, styryl, benzhydryl and trityl. Examples of the heterocyclic group include pyridyl, pyrazinyl and pyrimidinyl. The substituted lower alkyl has 1 to 3 independently-selected substituents such as lower alkoxy, alkylthio optionally substituted by carboxy, carboxy, lower alkoxycarbonyl, benzyloxycarbonyl, amino, mono- or di(lower alkyl)amino, cyclic amino optionally substituted by lower alkyl or cyclic amino, halogen and phenyl, in which examples of the cyclic amino group include pyrrolidino, piperidino, piperazinyl and morpholino, and lower alkyl and the alkyl moiety of lower alkoxy, lower alkylthio, lower alkoxycarbonyl and mono- or di(lower alkyl)amino has the same definition as that of the above-mentioned lower alkyl. Examples of halogen include fluorine, chlorine, bromine and iodine atoms. The substituted aryl, the substituted aralkyl and the substituted heterocyclic group each has 1 to 3 independently-selected substituents such as lower alkyl, substituted alkyl, lower alkoxy, lower alkoxycarbonyl, amino, mono- or di(lower alkyl)amino, pyrrole and halogen, in which lower alkyl and the alkyl moiety of lower alkoxycarbonyl and mono- or di(lower alkyl)amino has the same definition as that of the above-mentioned lower alkyl, and the substituents of substituted lower alkyl and halogen are the same meanings as defined above.

Examples of the pharmaceutically acceptable salts of Compounds (I) include inorganic acid-addition salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate and nitrate, and organic acid-addition salts such as acetate, benzoate, maleate, fumarate, succinate, tartrate, citrate, oxalate, glyoxylate, aspartate and methanesulfonate.

The processes for preparing Compounds (I) are described below.



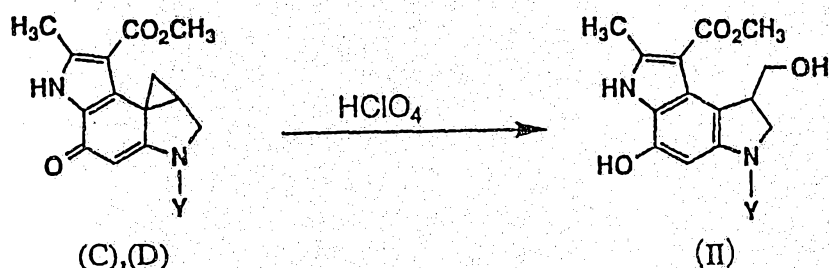
When the defined groups changes under reaction conditions or are inappropriate for conducting the processes, the processes can be easily carried out by using protection/deprotection method for functional groups conventionally employed in organic synthetic chemistry including oxidation, reduction and hydrolysis.

(Process 1)

Compound (I)a, which is Compound (I) wherein R is substituted or unsubstituted lower alkyl or substituted or unsubstituted aralkyl, can be prepared by the following process.

(Process 1-1)

Compound (II) can be prepared by treating Compound (C) or Compound (D) with perchloric acid in an inert solvent.



In the formulae, Y is the same meaning as defined above.

Perchloric acid is usually used in an amount of 1 to 20 equivalents based on Compound (C) or (D).

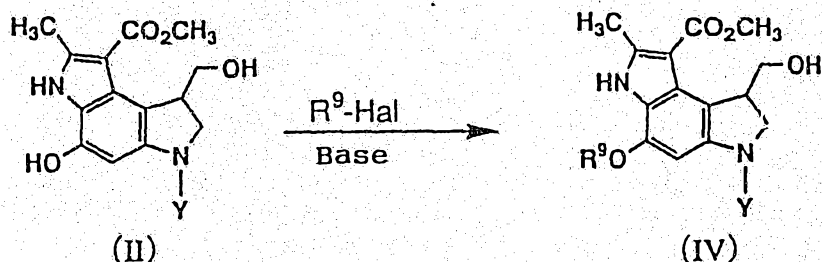
As the inert solvent, water, dimethylformamide, tetrahydrofuran, toluene, dioxane, acetonitrile, etc. may be used singly or in combination. The reaction is usually conducted at -20°C to 50°C for 10 minutes to 10 hours.

(Process 1-2)

Compound (IV) can be prepared by reacting Compound (II), in the presence of a base in an inert solvent, with



wherein R^9 is substituted or unsubstituted lower alkyl or substituted or unsubstituted aralkyl in the definition of R, and Hal is a chlorine, bromine or iodine atom.

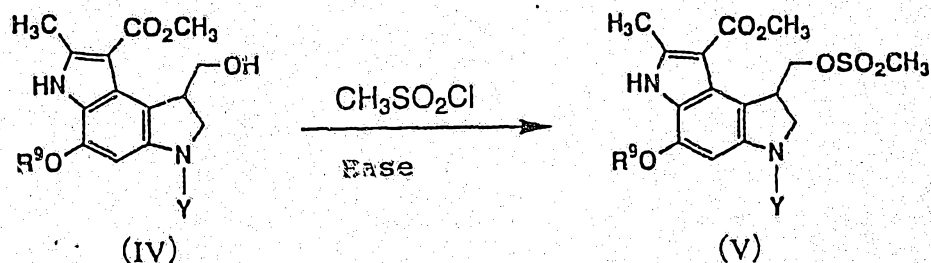


In the formulae, R^9 and Y are the same meanings as defined above.

Compound (III) is usually used in an amount of 1 to 10 equivalents based on Compound (II). Examples of the base include potassium carbonate, sodium hydrogen carbonate, potassium tert-butoxide, triethylamine, pyridine and 4-dimethylaminopyridine. The base is usually used in an amount of 1 to 10 equivalents based on Compound (II). As the inert solvent, dimethylformamide, acetone, tetrahydrofuran, toluene, dioxane, acetonitrile, etc. may be used singly or in combination. The reaction is usually conducted at -20°C to 80°C for 1 hour to 3 days.

(Process 1-3)

Compound (V) can be prepared by reacting Compound (IV) with methanesulfonyl chloride in the presence of a base in an inert solvent.



In the formulae, R^9 and Y are the same meanings as defined above.



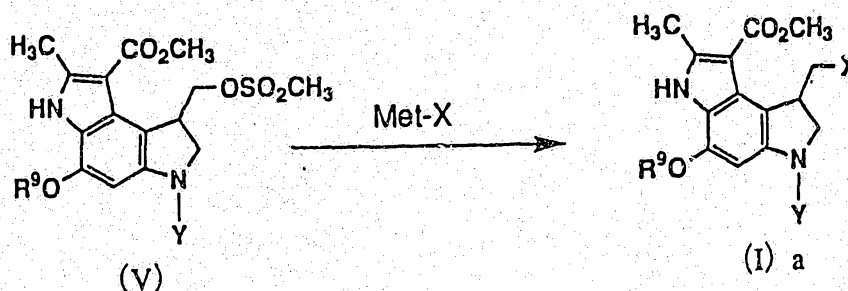
Methanesulfonyl chloride is usually used in an amount of 1 to 5 equivalents based on Compound (IV). Examples of the base include potassium tert-butoxide, triethylamine, pyridine and 4-dimethylaminopyridine. The base is usually used in an amount of 1 to 5 equivalents based on Compound (IV). However, when the base serves also as a solvent, it is used in large excess. As the inert solvent, pyridine, methylene chloride, chloroform, dimethylformamide, tetrahydrofuran, toluene, dioxane, etc. may be used singly or in combination. The reaction is usually conducted at -80°C to 50°C for 30 minutes to 1 day.

(Process 1-4)

Compound (I)a can be prepared by reacting Compound (V) in an inert solvent, with

Met-X (VI)

wherein Met is an alkali metal such as lithium, sodium and potassium, and X is the same meaning as defined above.



In the formulae, R⁹, Met, X and Y are the same meanings as defined above.

Compound (VI) is usually used in an amount of 1 to 20 equivalents based on Compound (V). As the inert solvent, dimethylformamide, dimethylsulfoxide, tetrahydrofuran, toluene, dioxane, acetonitrile, etc. may be used singly or in combination. The reaction is usually conducted at 0°C to 100°C for 30 minutes to 2 days.

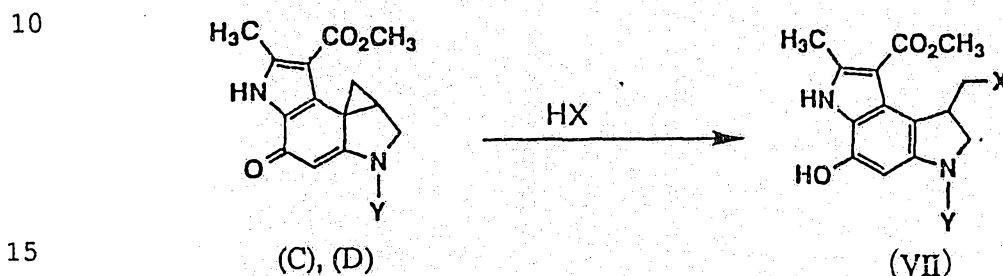


(Process 2)

Compound (I)b, which is Compound (I) wherein R is COR¹ in which R¹ is the same meaning as defined above, can be prepared by the following process.

(Process 2-1)

Compound (VII) can be prepared by treating Compound (C) or Compound (D) with hydrochloric acid or hydrobromic acid in an inert solvent.



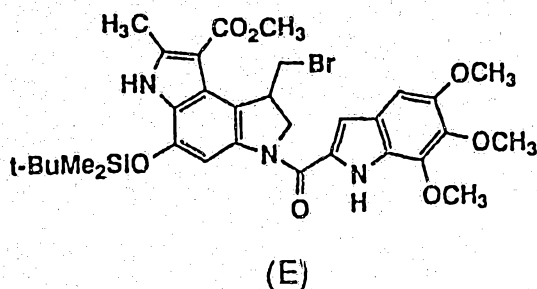
In the formulae, X and Y are the same meanings as defined above.

20 Hydrochloric acid or hydrobromic acid is usually used in an amount of 1 to 20 equivalents based on Compound (C) or (D). As the inert solvent, water, dimethylformamide, tetrahydrofuran, dioxane, acetonitrile, etc. may be used singly or in combination. The reaction is usually conducted at -30°C to 50°C for 10 minutes to 5 hours.

25

Compound (C) can be prepared from Compound (E) having the following structure, which is a precursor of Compound (C), by the process disclosed in JP,A,3-128379. Compound (C) thus obtained also may be used without isolation in the above

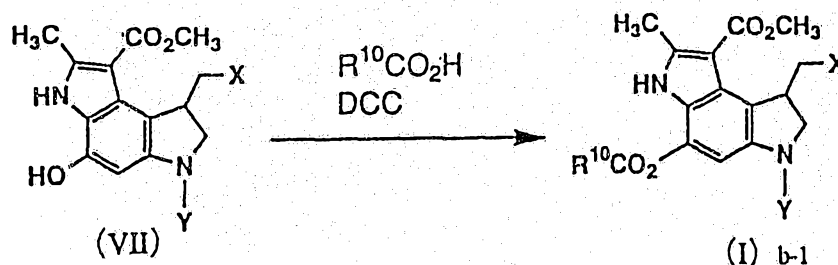
30 process.



In the formula, Me represents a methyl group, and t-Bu represents a tert-butyl group.

(Process 2-2-1)

Compound (I)b-1, which is Compound (I)b wherein R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heterocyclic group, can be prepared by reacting Compound (VII), in an inert solvent, with a condensation agent such as dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine and $R^{10}CO_2H$ (in which R^{10} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heterocyclic group in the definition of R^1).



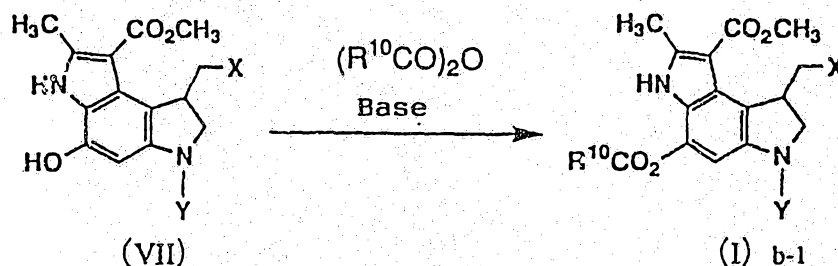
In the formulae, R^{10} , X and Y are the same meanings as defined above.

$R^{10}CO_2H$, DCC and 4-dimethylaminopyridine are usually used in amounts of 1 to 10 equivalents based on Compound (VII). As the inert solvent, methylene chloride, chloroform, dimethylformamide, tetrahydrofuran, toluene, dioxane, acetonitrile, etc. may be used singly or in combination. The reaction is usually conducted at $-20^\circ C$ to $50^\circ C$ for 1 hour to 1 day.

(Process 2-2-2)

Compound (I)b-1 can be prepared by reacting Compound (VII) with an acid anhydride represented by the formula $(R^{10}CO)_2O$ in which R^{10} is the same meaning as defined above in the presence of a base in an inert solvent.





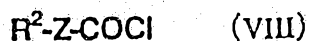
In the formulae, R^{10} , X and Y are the same meanings as defined above.

10 The acid anhydride is usually used in an amount of 1 to 10 equivalents based on Compound (VII). Examples of the base include triethylamine, pyridine and 4-dimethylaminopyridine. The base is usually used in an amount of 1 to 10 equivalents based on Compound (VII). However, when the base serves also as a solvent, it is used in large excess. As the inert solvent, methylene chloride, chloroform, dimethylformamide, tetrahydrofuran, toluene, dioxane, pyridine, etc. may be used singly or in combination. The reaction is usually conducted at

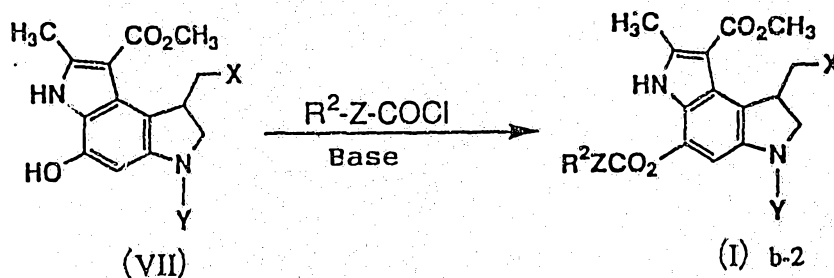
20 -20°C to 50°C for 30 minutes to 1 day.

(Process 2-3)

Compound (I)b-2, which is Compound (I)b wherein R^1 is OR^2 or SR^2 in which R^2 is the same meaning as defined above, can be prepared by reacting Compound (VII) with



wherein Z is oxygen or sulfur, and R^2 is the same meaning as defined above in the presence of a base in an inert solvent.



35 In the formulae, X, Y, Z and R^2 are the same meanings as defined above.



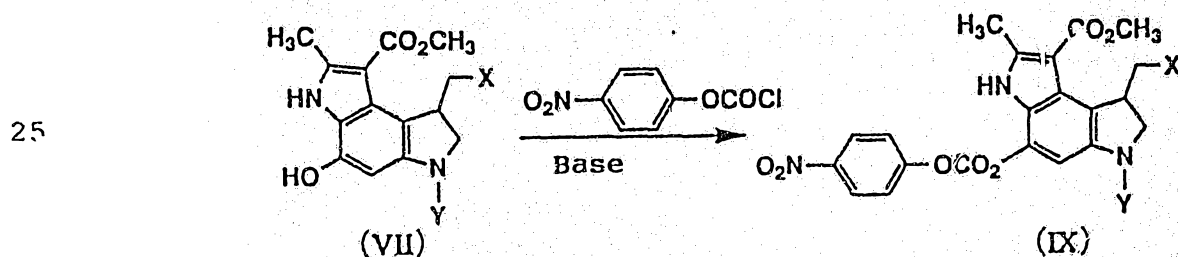
Compound (VIII) is usually used in an amount of 1 to 10 equivalents based on Compound (VII). Examples of the base include potassium tert-butoxide, triethylamine, pyridine and 4-dimethylaminopyridine. The base is usually used in an amount of 1 to 10 equivalents based on Compound (VII). However, when the base serves also as a solvent, it is used in large excess. As the inert solvent, methylene chloride, chloroform, dimethylformamide, tetrahydrofuran, toluene, dioxane, pyridine, etc. may be used singly or in combination. The reaction is usually conducted at -80°C to 50°C for 30 minutes to 1 day.

(Process 2-4)

Compound (I)b-3, which is Compound (I)b wherein R¹ is NR^{3a}R^{4a} wherein R^{3a} and R^{4a} independently represent hydrogen or substituted or unsubstituted lower alkyl in the definition of R³ and R⁴, can be prepared by the following process.

(Process 2-4-1)

Compound (IX) can be prepared by reacting Compound (VII) with p-nitrophenyl chloroformate in the presence of a base in an inert solvent.



In the formulae, X and Y are the same meanings as defined above.

30

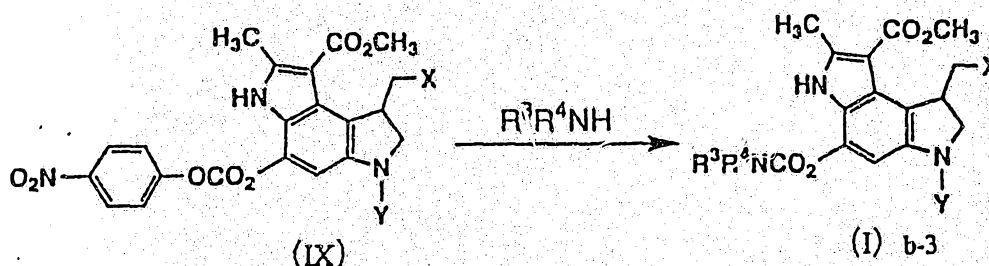
p-Nitrophenyl chloroformate is usually used in an amount of 1 to 5 equivalents based on Compound (VII). Examples of the base include potassium tert-butoxide, triethylamine, pyridine and 4-dimethylaminopyridine. The base is usually used in an amount of 1 to 5 equivalents based on Compound (VII). However, when the base serves also as a solvent, it is used in large excess. As the inert solvent, methylene chloride, chloroform,



pyridine, dimethylformamide, tetrahydrofuran, toluene, dioxane, etc. may be used singly or in combination. The reaction is usually conducted at -80°C to 30°C for 30 minutes to 10 hours.

5 (Process 2-4-2)

Compound (I)b-3 can be prepared by reacting Compound (IX) with R^3R^4NH (in which R^3 and R^4 are the same meanings as defined above) in the presence of a base in an inert solvent.

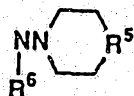


In the formulae X, Y, R^3 and R^4 are the same meanings as defined above.

R^3R^4NH is usually used in an amount of 1 to 5 equivalents based on Compound (IX). Examples of the base include triethylamine, pyridine and 4-dimethylaminopyridine. The base is usually used in an amount of 1 to 5 equivalents based on Compound (IX). However, when the base serves also as a solvent, it is used in large excess. As the inert solvent, methylene chloride, chloroform, dimethylformamide, tetrahydrofuran, toluene, dioxane, etc. may be used singly or in combination. The reaction is usually conducted at -80°C to 80°C for 30 minutes to 1 day.

30 (Process 2-5)

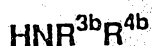
Compound (I)b-4, which is Compound (I)b wherein R^1 is $NR^{3b}R^{4b}$ (in which R^{3b} and R^{4b} independently represent hydrogen, amino or mono- or di(lower alkyl)amino in the definition of R^3 and R^4) or



(in which R^5 and R^6 are the same meanings as defined above), can

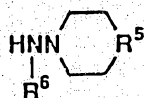


be prepared by reacting Compound (IX), in the presence of a base in an inert solvent, with



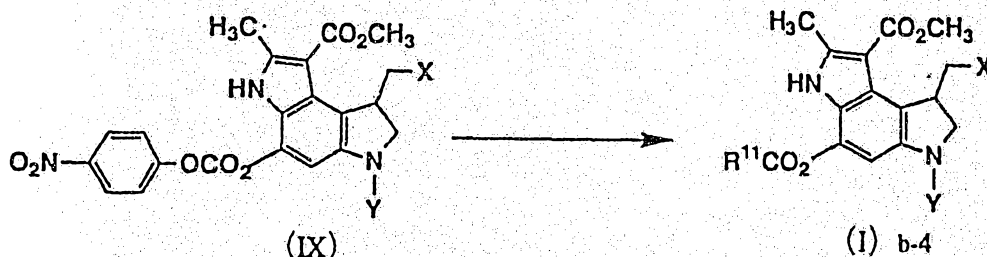
(X) a

or

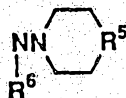


(X) b

wherein R^{3b} , R^{4b} , R^5 and R^6 are the same meanings as defined above.



In the formulae, R^{11} is $\text{NR}^{3b}\text{R}^{4b}$ (in which R^{3b} and R^{4b} are the same meanings as defined above) or



(in which R^5 and R^6 are the same meanings as defined above) in the definition of R^1 , and X and Y are the same meanings as defined above.

Compound (X) is usually used in an amount of 1 to 5 equivalents based on Compound (IX). Examples of the base include triethylamine, pyridine and 4-dimethylaminopyridine. The base is usually used in an amount of 1 to 5 equivalents based on Compound (IX). However, when the base serves also as a solvent, it is used in large excess. As the inert solvent, methylene chloride, chloroform, dimethylformamide, tetrahydrofuran, toluene, dioxane, etc. may be used singly or in combination. The reaction is usually conducted at -80°C to 50°C for 30 minutes to 1 day.

(Process 3)

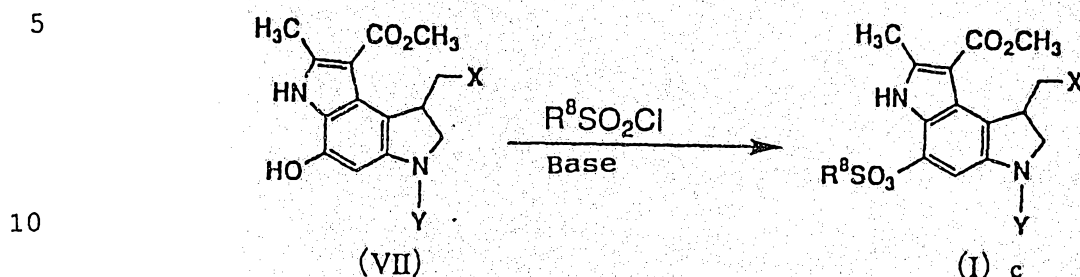
Compound (I)c, which is Compound (I) wherein R is SO_2R^8 (in which R^8 is the same meaning as defined above), can be prepared



by reacting Compound (VII), in the presence of a base in an inert solvent, with Compound (XI) represented by the formula



wherein R^{B} is the same meaning as defined above.



In the formulae, R^{B} , X and Y are the same meanings as defined above.

15 Compound (XI) is usually used in an amount of 1 to 10 equivalents based on Compound (VII). Examples of the base include potassium tert-butoxide, triethylamine, pyridine and 4-dimethylaminopyridine. The base is usually used in an amount of 1 to 5 equivalents based on Compound (VII). However, when the

20 base serves also as a solvent, it is used in large excess. As the inert solvent, methylene chloride, chloroform, dimethylformamide, pyridine, tetrahydrofuran, toluene, dioxane, etc. may be used singly or in combination. The reaction is usually conducted at -80°C to 50°C for 30 minutes to 20 hours.

25 After the completion of the reaction of each process, water, acid, buffer, an aqueous solution of sodium hydrogen carbonate, etc. are added to the reaction mixture, if necessary, and the mixture is extracted with an organic solvent such as ethyl acetate, chloroform and ether. The extract is washed with

30 water, an aqueous solution of sodium hydrogen carbonate, an aqueous solution of sodium chloride, etc. and dried over anhydrous sodium sulfate, etc. After the solvent is evaporated, the resulting residue is purified by silica-gel column chromatography, thin-layer chromatography, high-performance

35 preparative liquid chromatography, recrystallization, etc.

In the case where a salt of Compound (I) is desired and it is obtained in the form of the desired salt, it can be subjected



to purification as such. In the case where Compound (I) is obtained in the free state and its salt is desired, the desired salt can be obtained by dissolving or suspending Compound (I) in a suitable solvent and adding a suitable acid to the solution or suspension.

The reaction intermediates may be directly used in the subsequent step without isolation or purification. Compounds (I) and its pharmaceutically acceptable salts may be in the form of adducts with water or various solvents, which are also within the scope of the present invention. Further, all possible isomers of Compounds (I) including optical isomers and mixtures thereof also fall within the scope of the present invention.

The structures and compound numbers of representative compounds which fall under Compounds (I) are shown in Table 1. The structures and compound numbers of the synthetic intermediates of Compound (I) are shown in Table 2.

20

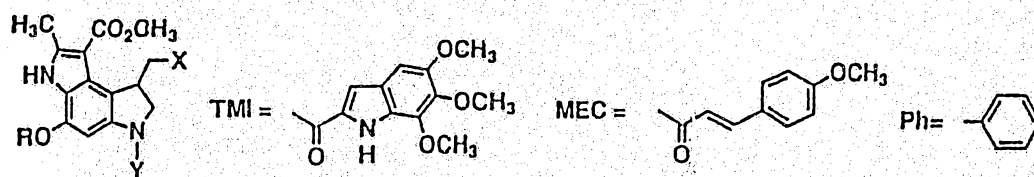
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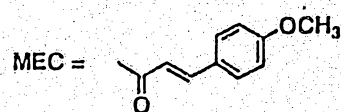
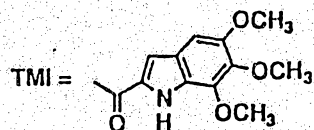
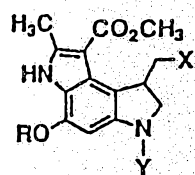
Table 1



	Compound No.	R	X	Y
10	1	CH ₂ Ph	Br	TMI
	2	CH ₃	Br	TMI
	3	CH ₃	Cl	TMI
	4	SO ₂ CH ₃	Br	TMI
15	5	SO ₂ CF ₃	Br	TMI
	6	COCH ₃	Br	TMI
	7	CO ₂ CH ₃	Br	TMI
	8	CO ₂ Ph	Br	TMI
20	9	CONHCH ₂ CO ₂ CH ₂ Ph	Br	TMI
	10	CONHCH ₂ CO ₂ H	Br	TMI
	11	CONHCH(CH ₂ Ph)CO ₂ H	Br	TMI
	12	CO ₂ CH ₃	Br	MEC
	13	CONHCH ₂ CO ₂ H	Br	MEC
25	14	COCH ₃	Br	MEC
	15	COSCH ₃	Br	MEC
	16	CO-	Br	MEC
	17	CO-	Br	MEC
30	18	CONHN-	Br	MEC
	19	CONHN-	Br	MEC
	20	CONHN-	Br	MEC
	21	CO-	Br	MEC
35	22	CO-	Br	MEC
	23	CO-	Br	MEC



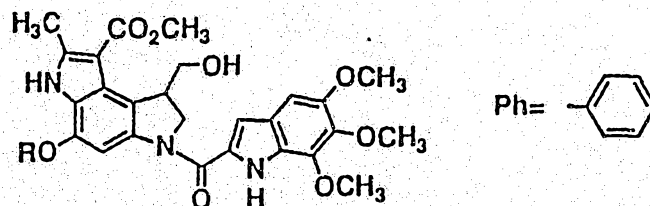
Table 1 (continued)



Compound No.	R	X	Y
24		Br	MEC
25		Br	MEC
26		Br	MEC
27		Br	MEC
28		Br	MEC
29	CONHN(CH ₃) ₂	Br	MEC
30	CON(CH ₃)NH ₂	Br	MEC
31		Br	MEC
32		Br	MEC
33	COCH ₂ SCH ₂ CO ₂ H	Br	MEC
34		Br	MEC
35		Br	MEC
36		Br	MEC
37		Br	MEC
38	CON(CH ₃)NHCH ₃	Br	MEC
39		Br	MEC
40		Br	MEC



Table 2



Compound No.	R
a	H
b	CH ₂ Ph
c	CH ₃

The pharmacological activity of representative Compounds (I) is shown in Test Examples.

20 Test Example

1. Growth Inhibitory Effect Against HeLaS₃ cells

HeLaS₃ cells were suspended in MEM medium containing 10% fetal calf serum and 2 mM glutamine to a concentration of 2.67×10^4 cells/ml. The cell suspension thus prepared was put into wells of a 24-well culture plate in an amount of 0.75 ml per well. After the cells were incubated in a CO₂ incubator overnight at 37°C, Compound (I) which had been appropriately diluted with a culture medium was added to each well in an amount of 0.25 ml.

The cells were further incubated in the CO₂ incubator for 72 hours, and the culture supernatant was removed. Then, the cells were dispersed in a solution of trypsin and EDTA, and recovered. The number of the cells was counted using a cell counter. The concentration of Compound (I) at which the growth of the cells is inhibited by 50% was calculated by comparing the number of untreated cells with the number of the cells



treated with Compound (I) at known concentrations, and the value was defined as IC_{50} .

The result is shown in Table 3.

5 2. Therapeutic Effect on Sarcoma 180 Tumor

Five male ddY-strain mice each weighing 18-20 g were used for each group as test animals, and 5×10^5 Sarcoma 180 tumor cells were implanted at the axilla subcutaneously. One day after the implantation, 0.2 ml of a physiological saline containing
10 Compound (I) at the concentration shown in Table 3 was intravenously administered to each mouse. T/C [T: average tumor volume (mm^3) of the group treated with the test compound, C: average tumor volume (mm^3) of the control group (to which 0.2 ml of a physiological saline was intravenously administered)] was
15 determined seven days after the implantation.

The result is shown in Table 3.

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Table 3

	Compound No.	I C ₅₀ (nM)	Dose (mg/kg)	T/C
5	1	5.1	8.0	0.19
	2	6.3	8.0	0.27
	4	4.0	16	0.20
	6	0.13	0.50	0.18
	7	0.082	0.50	0.10
	8	0.051	0.50	0.090
10	10	0.23	4.0	0.10
	11	0.17	4.0	0.07
	13	0.98	12	0.33
	14	0.31	4.0	0.22
	15	0.43	1.0	0.36
	16	0.40	2.0	0.33
	18	0.54	8.0	0.18
15	19	0.53	4.0	0.26
	20	6.7		
	21	0.38		
	22	2.7		
	24	0.43	2.0	0.31
	25	13	2.0	0.14
	26	1.7	2.0	0.15
20	28	0.83	2.0	0.21
	29	0.43	2.0	0.18
	30	0.94	2.0	0.22
	32	0.80	8.0	0.10
	33	0.33	2.0	0.17
	34	0.52	2.0	0.28
	36	1.0	4.0	0.35
25	37	0.91	8.0	0.27
	38	1.5	4.0	0.14
	39	0.36		
	40	0.29		

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3. Acute toxicity

Compound (I) was intravenously administered to ddY-strain male mice each weighing 20 ± 1 g. MLD (minimum lethal dose) was determined by observing the mortality at 14 days after administration. The result is shown in Table 4.

Table 4

	Compound No.	MLD (mg/kg)
10	6	0.25
	7	0.50
	8	0.50
	10	>4.0
	11	>4.0
	13	2.0
	14	2.0
15	19	>8.0
	25	2.0
	26	2.0
	28	2.0
	29	2.0
	30	2.0
	32	>8.0
20	33	2.0
	37	>8.0
	38	4.0
	39	4.0
	40	2.0

25

Compounds (I) and pharmaceutically acceptable salts thereof can be used as anti-tumor compositions singly or in combination with at least one pharmaceutically acceptable auxiliary. For example, Compounds (I) or salts thereof are dissolved in a physiological saline or in an aqueous solution of glucose, lactose, mannitol, etc. to prepare a pharmaceutical composition suitable for injection. Alternatively, Compounds (I) or salts thereof are freeze-dried in a conventional manner and mixed with sodium chloride to prepare a powder injection. If necessary, the pharmaceutical composition of the present invention may contain additives which are known in the art of medical



preparation, for example, pharmaceutically acceptable salts.

Although the dose of the composition of the present invention varies depending on the age, condition, etc. of a patient, Compound (I) is administered to mammals including human beings at a dose of 0.01 to 60 mg/kg/day. Administration may be conducted, for example, once a day (single administration or consecutive administrations) or intermittently 1 to 3 times a week or once every 2 to 3 weeks, intravenously. If desired, intraarterial administration, intraperitoneal administration, intrathoracic administration, etc. are also possible at a similar dose and in a similar manner. Further, if desired, the composition may also be administered orally, in a similar dose and in a similar manner. Forms for oral administration include tablets, capsules, powders, granules and ampoules, which contain pharmaceutical auxiliaries well known in the art of medical preparation.

The present invention is illustrated by referring to the following Examples. The physicochemical properties shown in the following Examples were determined with the following equipment.

20

NMR	JEOL, Ltd.	FX-100 (100 MHz)
		JNM-GX270 (270 MHz)
		JNM-EA270 (270 MHz)
	Bruker	AM-400 (400 MHz)
		AM-500 (500 MHz)
MS	Hitachi Ltd.	M-80B
	Shimadzu	QP-1000
	JEOL, Ltd.	JMS-D300
		JMS-SX102
IR	Japan Spectral Co., Ltd.	IR-810
	HORIBA	FT200

25

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In thin-layer chromatography, a silica-gel plate (Silica gel 60F_{254s} 0.5 mm 20 x 20 cm) manufactured by Merck Co. was used. As the silica gel, Wakogel C-200 manufactured by Wako Pure Chemical Industries, Ltd. was used.



Best Mode for Carrying Out the Invention

Example 1 Synthesis of Compound 1

Compound b (17 mg, 0.028 mmol) obtained in Reference Example 2 was dissolved in 1 ml of pyridine, and 0.0065 ml (0.084 mmol) of methanesulfonyl chloride was added thereto. The mixture was stirred at room temperature for 2 hours. To the reaction mixture was added a 0.01 M phosphate buffer (pH 7), and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 1 ml of N,N-dimethylformamide, and 7.3 mg (0.084 mmol) of lithium bromide was added thereto. The mixture was stirred at 80°C for 2 hours. To the resulting reaction mixture was added a 0.01 M phosphate buffer (pH 7), and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel column chromatography (20 ml of silica gel, n-hexane: ethyl acetate=2:1) to give 12 mg of Compound 1 (yield: 64%).

The physicochemical properties of Compound 1 are as follows.

¹H-NMR (400MHz, CDCl₃) δ(ppm); 9.38 (1H, br s), 8.62 (1H, br s), 8.16 (1H, s), 7.51-7.36 (5H, m), 7.01 (1H, d, J=2.3Hz), 6.90 (1H, s), 5.27 (1H, d, J=11.0Hz), 5.22 (1H, d, J=11.0Hz), 4.75 (1H, br d, J=8.9Hz), 4.56 (2H, m), 4.08 (3H, s), 3.97 (3H, s), 3.95 (3H, s), 3.93 (3H, s), 3.82 (1H, dd, J=8.1, 2.1Hz), 3.22 (1H, dd, J=8.1, 8.1Hz), 2.72 (3H, s)
IR (KBr) ν (cm⁻¹); 1697, 1605, 1525, 1494, 1415, 1214, 1112, 1088
SIMS (m/z); 664, 662 (M+H)⁺, 430, 428, 234



Example 2 Synthesis of Compound 2

Compound c (52 mg, 0.089 mmol) obtained in Reference Example 3 was dissolved in 2.6 ml of pyridine, and 0.014 ml (0.181 mmol) of methanesulfonyl chloride was added thereto. The mixture was stirred at room temperature for 2 hours. To the reaction mixture was added a 0.01 M phosphate buffer (pH 7), and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 2.6 ml of N,N-dimethylformamide, and 15.5 mg (0.178 mmol) of lithium bromide was added thereto. The mixture was stirred at 80°C for 3 hours. To the resulting reaction mixture was added a 0.01 M phosphate buffer (pH 7), and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel column chromatography (20 ml of silica gel, n-hexane: ethyl acetate=1:1) to give 48 mg of Compound 2 (yield: 92%).

The physicochemical properties of Compound 2 are as follows.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ (ppm); 9.38 (1H, br s), 8.59 (1H, br s), 8.02 (1H, s), 7.01 (1H, d, $J=2.3\text{Hz}$), 6.90 (1H, s), 4.74 (1H, br d, $J=8.9\text{Hz}$), 4.54 (2H, m), 4.08 (3H, s), 4.01 (3H, s), 3.97 (3H, s), 3.95 (3H, s), 3.92 (3H, s), 3.82 (1H, dd, $J=9.8, 3.9\text{Hz}$), 3.21 (1H, dd, $J=9.9, 9.9\text{Hz}$), 2.73 (3H, s)
 $\text{IR}(\text{KBr}) \nu(\text{cm}^{-1})$; 1697, 1584, 1492, 1411, 1312, 1215, 1112
 $\text{SIMS}(m/z)$; 588, 586 ($\text{M}+\text{H}$)⁺, 354, 352, 234

Example 3 Synthesis of Compound 3

Compound c (25 mg, 0.048 mmol) obtained in Reference Example 3 was dissolved in 2.0 ml of pyridine, and 0.019 ml (0.25 mmol) of methanesulfonyl chloride was added thereto. The mixture was stirred at room temperature for 24 hours. To the



reaction mixture was added 1 N hydrochloric acid, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 2.0 ml of N,N-dimethylformamide, and 11.0 mg (0.259 mmol) of lithium chloride was added thereto. The mixture was stirred at 80°C for 3 hours. To the resulting reaction mixture was added a 0.01 M phosphate buffer (pH 7), and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel column chromatography (20 ml of silica gel, n-hexane: ethyl acetate=3:1) to give 19 mg of Compound 3 (yield: 73%).

The physicochemical properties of Compound 3 are as follows.

¹H-NMR (400MHz, CDCl₃) δ(ppm); 9.42 (1H, s), 8.70 (1H, s), 8.03 (1H, s), 7.00 (1H, d, J=2.3Hz), 6.89 (1H, s), 4.75 (1H, br d, J=9.5 Hz), 4.52 (1H, dd, J=9.5, 8.4Hz), 4.47 (1H, m), 4.07 (3H, s), 4.00 (3H, s), 3.95 (3H, s), 3.95 (3H, s), 3.94 (1H, m), 3.92 (3H, s), 3.33 (1H, dd, J=10.1, 9.9Hz), 2.73 (3H, s)
IR (KBr) ν (cm⁻¹); 1685, 1631, 1521, 1457, 1405, 1313, 1220, 1113
SIMS (m/z); 542 (M+H)⁺, 234

Example 4 Synthesis of Compound 4

Compound E (30 mg, 0.044 mmol) was dissolved in 1.5 ml of tetrahydrofuran (THF), and 1.5 ml of a 1 N hydrobromic acid aqueous solution was added thereto. The mixture was stirred at room temperature for 24 hours. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate, and concentrated under



reduced pressure. The obtained crude product was dissolved in 2 ml of methylene chloride. Then, 0.016 ml (0.21 mmol) of methanesulfonyl chloride and 0.029 ml (0.21 mmol) of triethylamine were added thereto. The mixture was stirred at -78°C for 2 hours. To the reaction mixture was added phosphate buffer (pH 7), and the mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel column chromatography (30 ml of silica gel, chloroform:methanol=100:1) to give 25 mg of Compound 4 (yield: 87%).

The physicochemical properties of Compound 4 are as follows.

¹H-NMR (400MHz, CDCl₃) δ(ppm); 9.36(1H, br s), 9.00(1H, br s), 8.31(1H, s), 7.01(1H, d, J=2.2Hz), 6.90(1H, s), 4.77(1H, dd, J=10.5, 1.0Hz), 4.68(1H, m), 4.57(1H, dd, J=10.4, 9.6Hz), 4.08 (3H, s), 3.98(3H, s), 3.95(3H, s), 3.92(3H, s), 3.81(1H, dd, J=10.1, 2.5Hz), 3.33(1H, s), 3.26(1H, dd, J=9.9, 9.9Hz), 2.75(3H, s)
IR(KBr) ν(cm⁻¹); 1698, 1522, 1410, 1364, 1217, 1177, 1106
SIMS(m/z); 652, 650(M+1)⁺, 418, 416, 234

Example 5 Synthesis of Compound 5

Compound E (100mg, 0.15 mmol) was dissolved in 5 ml of tetrahydrofuran, and 0.220 ml (0.22 mmol) of a tetrahydrofuran solution (1.0 M) of tetra-n-butylammonium fluoride was added thereto. The mixture was stirred at room temperature for 1 hour. To the reaction mixture was added a 0.2 M phosphate buffer (pH 7), and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. To the reaction mixture were added 5 ml of acetonitrile and 0.5 ml of 48% hydrobromic acid, and the mixture was stirred for 1 hour.



To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product
5 was dissolved in 5 ml of methylene chloride, and 0.075 ml (0.45 mmol) of trifluoromethanesulfonic anhydride and 0.063 ml (0.45 mmol) of triethylamine were added thereto at -78°C . The mixture was stirred at -78°C for 2 hours. To the reaction mixture was added phosphate buffer (pH 7), and the mixture was extracted
10 with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel column chromatography (30 ml of silica gel, hexane:ethyl
15 acetate=3:1) to give 77 mg of Compound 5 (yield: 73%).

The physicochemical properties of Compound 5 are as follows.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ (ppm); 9.39 (1H, s), 8.74 (1H, s),
20 8.45 (1H, s), 7.00 (1H, d, $J=2.3\text{Hz}$), 6.89 (1H, s),
4.78 (1H, dd, $J=10.5, 1.3\text{Hz}$), 4.69 (1H, m), 4.58 (1H, dd, $J=10.2, 9.2\text{Hz}$),
4.08 (3H, s), 3.99 (3H, s), 3.95 (3H, s), 3.92 (3H, s),
3.79 (1H, dd, $J=10.1, 2.4\text{Hz}$), 3.26 (1H, dd, $J=10.0, 10.0\text{Hz}$),
2.78 (3H, s)
25 IR (KBr) ν (cm^{-1}); 1697, 1611, 1522, 1412, 1311, 1213, 1137,
1114
SIMS (m/z); 706, 704 ($\text{M}+\text{H}$)⁺, 234

Example 6 Synthesis of Compound 6

30 Compound E (40 mg, 0.058 mmol) was dissolved in 4 ml of tetrahydrofuran, and 0.087 ml (0.087 mmol) of a tetrahydrofuran solution (1.0 M) of tetra-*n*-butylammonium fluoride was added thereto. The mixture was stirred at room temperature for 1 hour. To the reaction mixture was added a 0.2 M phosphate
35 buffer (pH 7), and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous



solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. To the reaction mixture were added 4 ml of acetonitrile and 2 ml of 48% hydrobromic acid, and the mixture was stirred for 1 hour. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 4 ml of methylene chloride, and 0.020 ml (0.21 mmol) of acetic anhydride and 25 mg (0.20 mmol) of dimethylaminopyridine were added thereto at 0°C. The mixture was stirred at 0°C for 2 hours. To the reaction mixture was added phosphate buffer (pH 7), and the mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel column chromatography (30 ml of silica gel, chloroform:methanol=50:1) to give 23 mg of Compound 6 (yield: 65%).

The physicochemical properties of Compound 6 are as follows.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ (ppm): 9.35 (1H, br s), 8.45 (1H, s), 8.20 (1H, s), 6.99 (1H, d, $J=2.2\text{Hz}$), 6.89 (1H, s), 4.75 (1H, br d, $J=9.6\text{Hz}$), 4.62 (1H, m), 4.55 (1H, br d, $J=9.8\text{Hz}$), 4.08 (3H, s), 3.96 (3H, s), 3.95 (3H, s), 3.92 (3H, s), 3.81 (1H, dd, $J=10.0, 2.4\text{Hz}$), 3.24 (1H, dd, $J=10.0, 10.0\text{Hz}$), 2.72 (3H, s), 2.41 (3H, s)
 IR (KBr) ν (cm^{-1}): 1686, 1654, 1559, 1507, 1457, 1314, 1189
 SIMS (m/z): 616, 614 ($M+H$) $^+$, 234

Example 7 Synthesis of Compound 7

Compound E (40 mg, 0.058 mmol) was dissolved in 4 ml of tetrahydrofuran, and 0.088 ml (0.088 mmol) of a tetrahydrofuran solution (1.0 M) of tetra-*n*-butylammonium fluoride was added



thereto. The mixture was stirred at room temperature for 1 hour. To the reaction mixture was added a 0.2 M phosphate buffer of pH 7, and the mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous

5 solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. To the obtained crude product were added 4 ml of acetonitrile and 2 ml of 48% hydrobromic acid, and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added a 1 N
10 hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 2.5 ml of methylene chloride, and 0.014 ml (0.18 mmol) of methyl
15 chloroformate and 0.025 ml (0.18 mmol) of triethylamine were added thereto at -78°C. The mixture was stirred at -78°C to 0°C for 2 hours. To the reaction mixture was added a 0.2 M phosphate buffer (pH 7), and the mixture was extracted with chloroform. The chloroform layer was washed with a saturated
20 aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel column chromatography (30 ml of silica gel, n-hexane:ethyl acetate=2:1) to give 32 mg of Compound 7 (yield: 87%).

25 The physicochemical properties of Compound 7 are as follows.

¹H-NMR (270MHz, CDCl₃) δ (ppm); 9.39 (1H, s), 8.74 (1H, s),
8.33 (1H, s), 7.00 (1H, d, J=2.0Hz), 6.90 (1H, s), 4.75 (1H, br d,
30 J=9.4Hz), 4.58 (2H, m), 4.08 (3H, s), 3.97 (3H, s), 3.96 (3H, s),
3.95 (3H, s), 3.92 (3H, s), 3.72 (1H, m), 3.24 (1H, dd, J=9.9, 9.4Hz),
2.72 (3H, s)

IR (KBr) ν (cm⁻¹); 1768, 1696, 1617, 1495, 1442, 1315, 1263,
1219, 1111

35 FABMS (m/z); 632, 630 (M+H)⁺, 234



Example 8 Synthesis of Compound 8

Compound E (50 mg, 0.07 mmol) was dissolved in 5 ml of tetrahydrofuran, and 0.11 ml (0.11 mmol) of a tetrahydrofuran solution (1.0 M) of tetra-n-butylammonium fluoride was added thereto. The mixture was stirred at room temperature for 1 hour. To the reaction mixture was added a 0.2 M phosphate buffer of pH 7, and the mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. To the obtained crude product were added 5 ml of acetonitrile and 2.5 ml of 48% hydrobromic acid, and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 3 ml of methylene chloride, and 0.027 ml (0.22 mmol) of phenyl chloroformate and 0.030 mg (0.22 mmol) of triethylamine were added thereto at -78°C. The mixture was stirred at -78°C to 0°C for 1 hour. To the reaction mixture was added a 0.2 M phosphate buffer (pH 7), and the mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel column chromatography (30 ml of silica gel, n-hexane:ethyl acetate=2:1) to give 40 mg of Compound 8 (yield: 82%).

The physicochemical properties of Compound 8 are as follows.

$^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 9.39(1H, s), 8.84(1H, s), 8.45(1H, s), 7.46-7.29(5H, m), 7.00(1H, d, $J=1.9\text{Hz}$), 6.90(1H, s), 4.76(1H, br d, $J=9.4\text{Hz}$), 4.59(2H, m), 4.08(3H, s), 3.98(3H, s), 3.95(3H, s), 3.92(3H, s), 3.72(1H, m), 3.24(1H, d, $J=9.9, 9.4\text{Hz}$), 2.75(3H, s)



IR(KBr) ν (cm⁻¹); 1780, 1614, 1493, 1464, 1414, 1313, 1221, 1188, 1111

FABMS(m/z); 694, 692(M+H)⁺, 234

5 Example 9 Synthesis of Compound 9

Compound E (20 mg, 0.03 mmol) was dissolved in 1 ml of tetrahydrofuran, and 0.045 ml (0.045 mmol) of a tetrahydrofuran solution (1.0 M) of tetra-n-butylammonium fluoride was added thereto. The mixture was stirred at room temperature for 1
10 hour. To the reaction mixture was added a 0.2 M phosphate buffer of pH 7, and the mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. To the
15 obtained crude product were added 1 ml of acetonitrile and 0.5 ml of 48% hydrobromic acid, and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was dried
20 over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 1 ml of methylene chloride, and 19 mg (0.09 mmol) of p-nitrophenyl chloroformate and 0.013 mg (0.09 mmol) of triethylamine were added thereto at -78°C. The mixture was stirred for 30 minutes.
25 To the reaction mixture were added 36 mg (0.11 mmol) of glycine benzyl ester p-toluenesulfonate and 0.015 ml (0.11 mmol) of triethylamine, and the mixture was stirred at -78°C to 0°C for 2 hours. To the reaction mixture was added a saturated aqueous solution of sodium hydrogen carbonate, and the resulting mixture
30 was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel column chromatography (20 ml of silica gel, chloroform:methanol=
35 50:1) to give 15 mg of Compound 9 (yield: 65%).



The physicochemical properties of Compound 9 are as follows.

$^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 9.34 (1H, br), 9.31 (1H, s),
5 8.10 (1H, br), 7.28-7.18 (5H, m), 6.91 (1H, d, $J=2.0\text{Hz}$),
6.81 (1H, s), 5.82 (1H, t, $J=5.6\text{Hz}$), 5.09 (2H, s),
4.99 (2H, t, $J=5.5\text{Hz}$), 4.65 (1H, br d, $J=10.0\text{Hz}$), 4.47 (2H, m),
4.00 (3H, s), 3.95 (3H, s), 3.86 (3H, s), 3.84 (3H, s), 3.71 (1H,
br d, $J=7.2\text{Hz}$), 3.14 (1H, dd, $J=9.9, 9.6\text{Hz}$), 2.57 (3H, s)
10 IR (KBr) ν (cm^{-1}); 1741, 1583, 1495, 1456, 1414, 1290, 1213,
1190
FABMS (m/z); 765, 763 ($M+H$)⁺, 234

Example 10 Synthesis of Compound 10

15 Compound 9 (15 mg, 0.02 mmol) obtained in Example 9 was
dissolved in a mixture of 0.5 ml of ethanol, 0.1 ml of methanol
and 0.1 ml of a 1 N hydrobromic acid aqueous solution, and 4 mg
of 10% Pd/C was added thereto. The mixture was stirred in a
hydrogen atmosphere at room temperature for 2 hours. The
20 reaction mixture was filtered, and the filtrate was concentrated
under reduced pressure. Water was added to the obtained crude
product, and the mixture was extracted with chloroform. The
chloroform layer was washed with a saturated aqueous solution of
sodium chloride, dried over anhydrous sodium sulfate, and
25 concentrated under reduced pressure. The obtained crude product
was purified by silica-gel column chromatography (20 ml of
silica gel, chloroform:methanol:acetic acid=100:10:2) to give 12
mg of Compound 10 (yield: 89%).

The physicochemical properties of Compound 10 are as
30 follows.

$^1\text{H-NMR}$ (270 MHz, acetone- d_6 + trifluoroacetic acid) δ (ppm);
8.04 (1H, s), 6.98 (1H, s), 6.87 (1H, s), 5.40 (1H, br), 4.54 (2H, m),
3.91 (3H, s), 3.78 (3H, s), 3.77 (1H, m), 3.75 (3H, s), 3.74 (3H, s),
35 3.74 (1H, m), 2.57 (3H, s)



IR(KBr) ν (cm⁻¹); 1697, 1601, 1444, 1416, 1219, 1109, 1088

FABMS(m/z); 675, 673(M+H)⁺, 234

Example 11 Synthesis of Compound 11

- 5 Compound E (20 mg, 0.03 mmol) was dissolved in 1 ml of tetrahydrofuran, and 0.045 ml (0.045 mmol) of a tetrahydrofuran solution (1.0 M) of tetra-n-butylammonium fluoride was added thereto. The mixture was stirred at room temperature for 1 hour. To the reaction mixture was added a 0.2 M phosphate
- 10 buffer of pH 7, and the mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. To the obtained crude product were added 1 ml of acetonitrile and 0.5
- 15 ml of 48% hydrobromic acid, and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate, and concentrated under reduced
- 20 pressure. The obtained crude product was dissolved in 1 ml of methylene chloride, and 19 mg (0.09 mmol) of p-nitrophenyl chloroformate and 0.013 ml (0.09 mmol) of triethylamine were added thereto at -78°C. The mixture was stirred for 30 minutes. To the reaction mixture were added 18 mg (0.11 mmol) of
- 25 phenylalanine and 0.013 ml (0.09 mmol) of triethylamine, and the mixture was stirred at -78°C to room temperature for 24 hours. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated
- 30 aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel column chromatography (20 ml of silica gel, chloroform:methanol:acetic acid=100:5:1) to give 8 mg of Compound 11 (yield: 35%).
- 35 The physicochemical properties of Compound 11 are as follows.



¹H-NMR (270MHz, DMSO-d₆) δ(ppm); 12.35 (1H, br), 11.38 (1H, br s),
7.81 (2H, s), 7.27-7.16 (5H, m), 6.95 (1H, d, J=2.2Hz),
6.93 (1H, s), 4.58 (1H, m), 4.41 (3H, m), 4.15 (1H, m), 3.88 (3H, s),
3.79 (3H, s), 3.77 (3H, s), 3.74 (3H, s), 3.54 (3H, m), 2.98 (1H, m),
5 2.62 (3H, s)
IR (KBr) ν (cm⁻¹); 1699, 1525, 1416, 1313, 1217, 1111
FABMS (m/z); 765, 763 (M+H)⁺, 573, 571, 234

Example 12 Synthesis of Compound 12

10 Acetonitrile (1.5 ml) and 0.135 ml of 48% hydrobromic acid
were added to 33 mg (0.079 mmol) of Compound D, and the mixture
was stirred at room temperature for 1 hour. To the reaction
mixture was added a 1 N hydrobromic acid aqueous solution, and
the mixture was extracted with chloroform. The chloroform layer
15 was dried over anhydrous sodium sulfate, and concentrated under
reduced pressure. The obtained crude product was dissolved in
3.5 ml of methylene chloride, and 0.019 ml (0.25 mmol) of methyl
chloroformate and 0.033 ml (0.24 mmol) of triethylamine were
added thereto at -78°C. The mixture was stirred for 3 hours.
20 To the reaction mixture was added a 0.2 M phosphate buffer of pH
7, and the resulting mixture was extracted with chloroform. The
chloroform layer was washed with a saturated aqueous solution of
sodium chloride, dried over anhydrous sodium sulfate, and
concentrated under reduced pressure. The obtained crude product
25 was purified by silica-gel column chromatography (30 ml of
silica gel, chloroform:methanol=50:1) to give 40 mg of Compound
12 (yield: 72%).

The physicochemical properties of Compound 12 are as
follows.

30

¹H-NMR (270MHz, CDCl₃) δ(ppm); 8.86 (1H, br), 8.40 (1H, br),
7.80 (1H, d, J=15.1Hz), 7.57 (1H, d, J=8.9Hz), 6.93 (1H, d, J=8.8Hz),
6.80 (1H, d, J=15.2Hz), 6.79 (1H, br s), 4.54 (1H, m), 4.47 (1H,
br d, J=10.9Hz), 4.31 (1H, dd, J=9.6, 9.6Hz), 3.96 (3H, s),
35 3.93 (3H, s), 3.86 (3H, s), 3.79 (1H, br d, J=10.5Hz),
3.22 (1H, dd, J=10.5, 10.5Hz), 2.67 (3H, s)



IR(KBr) ν (cm⁻¹); 1768, 1697, 1645, 1512, 1437, 1412, 1252, 1217, 1095

FABMS(m/z); 559, 557(M)⁺

5 Example 13 Synthesis of Compound 13

Acetonitrile (3.5 ml) and 0.29 ml of 48% hydrobromic acid were added to 70 mg (0.17 mmol) of Compound D, and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and
10 the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was dissolved in 7 ml of methylene chloride, and 103 mg (0.51 mmol) of p-nitrophenyl chloroformate and 0.071 ml (0.51 mmol) of triethylamine were
15 added thereto at -78°C. The mixture was stirred for 30 minutes. To the reaction mixture were added 100 mg (0.58 mmol) of glycine tert-butyl ester hydrochloride and 0.083 ml (0.60 mmol) of triethylamine, and the mixture was stirred at -78°C to room temperature for 9 hours. To the reaction mixture was added a
20 0.2 M phosphate buffer of pH 7, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel
25 column chromatography (30 ml of silica gel, chloroform:methanol=20:1) to give 110 mg of a tert-butyl ester of Compound 13 (yield: 85%). Ethylene dichloride (8ml) was added to the tert-butyl ester of Compound 13 (80 mg, 0.10 mmol), and 0.18 ml of 48% hydrobromic acid was added thereto. The
30 mixture was stirred at 50°C for 4 hours. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by
35 silica-gel chromatography (preparative T.L.C., chloroform: methanol:acetic acid=50:10:1) to give 23 mg of Compound 13



(yield: 32%).

The physicochemical properties of Compound 13 are as follows.

- 5 $^1\text{N-NMR}$ (270 MHz, acetone d_6 + trifluoroacetic acid- d) δ (ppm);
8.17 (1H, br), 7.68 (1H, d, $J=15.5\text{Hz}$), 7.60 (2H, d, $J=8.9\text{Hz}$),
7.03 (1H, d, $J=15.4\text{Hz}$), 6.89 (2H, d, $J=8.9\text{Hz}$), 4.49 (2H, m),
3.96 (2H, s), 3.93 (1H, m), 3.83 (3H, s), 3.78 (1H, m), 3.76 (3H, s),
3.37 (1H, m), 2.61 (3H, s)
10 IR (KBr) ν (cm^{-1}); 1700, 1647, 1572, 1560, 1412, 1221, 1109
FABMS (m/z); 708, 706 (M) $^+$

Example 14 Synthesis of Compound 14

- Acetonitrile (1.3 ml) and 0.27 ml of 48% hydrobromic acid
15 were added to 13 mg (0.031 mmol) of Compound D, and the mixture
was stirred at room temperature for 1 hour. To the reaction
mixture was added a 1 N hydrobromic acid aqueous solution, and
the resulting mixture was extracted with chloroform. The
chloroform layer was dried over anhydrous sodium sulfate, and
20 concentrated under reduced pressure. The obtained crude product
was dissolved in 1 ml of methylene chloride, and 0.009 ml (0.25
mmol) of acetic anhydride and 12 mg (0.098 mmol) of
dimethylaminopyridine were added thereto at 0°C. The mixture
was stirred for 3 hours. To the reaction mixture was added a
25 0.2 M phosphate buffer of pH 7, and the resulting mixture was
extracted with chloroform. The chloroform layer was washed with
a saturated aqueous solution of sodium chloride, dried over
anhydrous sodium sulfate, and concentrated under reduced
pressure. The obtained crude product was purified by silica-gel
30 column chromatography (20 ml of silica gel, chloroform:methanol=
100:1) to give 16 mg of Compound 14 (yield: 95%).

The physicochemical properties of Compound 14 are as follows.

- 35 $^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 8.43 (1H, br), 8.31 (1H, br),
7.80 (1H, d, $J=15.6\text{Hz}$), 7.57 (2H, d, $J=8.6\text{Hz}$), 6.94 (2H, d, $J=8.6\text{Hz}$),

6.79 (2H, d, J=15.5Hz), 4.57 (1H, m), 4.48 (1H, br d, J=10.3Hz),
4.31 (1H, dd, J=9.5, 9.5Hz), 3.97 (3H, s), 3.86 (3H, s),
3.80 (1H, dd, J=10.5, 2.3Hz), 3.24 (1H, dd, J=10.4, 10.4Hz),
2.71 (3H, s), 2.40 (3H, s)
5 IR(KBr) ν (cm⁻¹); 1701, 1691, 1637, 1602, 1490, 1458, 1203
FABMS (m/z); 543, 541 (M)⁺

Example 15 Synthesis of Compound 15

Acetonitrile (0.61 ml) and 5.4 μ l of 48% hydrobromic acid
10 were added to 10.0 mg (0.0239 mmol) of Compound D, and the
mixture was stirred at room temperature for 40 minutes. The
reaction mixture was concentrated under reduced pressure. The
obtained crude product was dissolved in 0.61 ml of methylene
chloride, and 6.4 μ l (0.074 mmol) of methyl chlorotriolformate
15 and 10.0 μ l (0.072 mmol) of triethylamine were added thereto at
-78°C. The mixture was stirred at -78°C for 80 minutes. To the
reaction mixture was added a saturated aqueous solution of
sodium hydrogen carbonate, and the resulting mixture was
extracted with chloroform. The chloroform layer was washed with
20 a saturated aqueous solution of sodium chloride, dried over
anhydrous sodium sulfate, and concentrated under reduced
pressure. The obtained crude product was purified by thin-layer
chromatography (chloroform:methanol=15:1) to give 11.5 mg of
Compound 15 (yield: 84%).

25 The physicochemical properties of Compound 15 are as
follows.

¹H-NMR (270MHz, CDCl₃) δ (ppm); 8.80 (1H, s), 8.37 (1H, brs),
7.80 (1H, d, J=15.2Hz), 7.56 (2H, d, J=8.6Hz), 6.93 (2H, d, J=8.9Hz),
30 6.79 (1H, d, J=15.2Hz), 4.50-4.59 (1H, m), 4.47 (1H, d, J=10.6Hz),
4.30 (1H, dd, J=9.2, 9.2Hz), 3.95 (3H, s), 3.85 (3H, s),
3.79 (1H, dd, J=10.2, 3.4Hz), 3.22 (1H, dd, J=10.2, 10.2Hz),
2.68 (3H, s), 2.44 (3H, s)
FABMS (m/z); 575, 573 (M+H)⁺
35 IR(KBr) ν (cm⁻¹); 1701, 1610, 1506, 1404, 1294, 1265, 1234,
1196, 1176, 1111

Example 16 Synthesis of Compound 16

Acetonitrile (1.16 ml) and 10.8 μ l of 48% hydrobromic acid were added to 20.0 mg (0.0478 mmol) of Compound D, and the mixture was stirred at room temperature for 50 minutes. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 0.75 ml of methylene chloride, and 0.30 ml of methylene chloride containing 17.7 mg (0.143 mmol) of nicotinic acid and 29.6 mg (0.143 mmol) of dicyclohexylcarbodiimide was added thereto at -20°C . The mixture was stirred for 5 minutes. Subsequently, to the mixture was added 17.5 mg (0.143 mmol) of 4-dimethylaminopyridine, and the mixture was stirred at -20°C to room temperature for 18.5 hours. To the reaction mixture was added a saturated aqueous solution of sodium hydrogen carbonate, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by thin-layer chromatography (chloroform:methanol=30:1) to give 18.8 mg of Compound 16 (yield: 65%).

The physicochemical properties of Compound 16 are as follows.

$^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 10.89 (1H, brs),
9.34 (1H, d, $J=1.7\text{Hz}$), 8.75 (1H, dd, $J=5.0, 1.7\text{Hz}$), 8.35 (1H, brs),
8.27 (1H, dt, $J=7.9, 1.7\text{Hz}$), 7.77 (1H, d, $J=15.2\text{Hz}$),
7.56 (2H, d, $J=8.6\text{Hz}$), 7.36 (1H, dd, $J=7.9, 5.0\text{Hz}$), 6.93 (2H, d, $J=8.6\text{Hz}$),
6.79 (1H, d, $J=15.2\text{Hz}$), 4.58-4.69 (1H, m),
4.49 (1H, d, $J=10.6\text{Hz}$), 4.33 (1H, dd, $J=10.2, 8.9\text{Hz}$), 3.98 (3H, s),
3.85 (4H, s), 3.27 (1H, dd, $J=10.2, 9.9\text{Hz}$), 2.73 (3H, s)
 FABMS (m/z); 606, 604 ($\text{M}+\text{H}$)⁺

IR(KBr) ν (cm^{-1}); 1747, 1697, 1649, 1595, 1512, 1408, 1294, 1265, 1217, 1173, 1093

Example 17 Synthesis of Compound 17

5 Anhydrous ethyl acetate (1.59 ml) was added to 19.8 mg (0.0328 mmol) of Compound 16 obtained in Example 16, and 9.56 μl of 6.86 N hydrogen chloride in ethanol was added thereto. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure to give
10 19.9 mg of Compound 17.

The physicochemical properties of Compound 17 are as follows.

$^1\text{H-NMR}$ (270MHz, DMSO- d_6) δ (ppm); 12.14 (1H, brs), 9.37 (1H, s),
15 8.96 (1H, brd, $J=4.0\text{Hz}$), 8.58 (1H, dt, $J=7.9, 2.0\text{Hz}$), 8.23 (1H, s),
7.75 (2H, d, $J=8.6\text{Hz}$), 7.71-7.74 (1H, m), 7.60 (1H, d, $J=15.5\text{Hz}$),
7.07 (1H, d, $J=15.5\text{Hz}$), 7.00 (2H, d, $J=8.6\text{Hz}$), 4.41-4.59 (3H, m),
3.86 (4H, s), 3.81 (3H, s), 2.64 (3H, s)
IR(KBr) ν (cm^{-1}); 1697, 1645, 1601, 1512, 1408, 1284, 1252,
20 1217, 1174, 1097

Example 18 Synthesis of Compound 18

Acetonitrile (1.74 ml) and 41 μl of 48% hydrobromic acid were added to 30.0 mg (0.0717 mmol) of Compound D, and the
25 mixture was stirred at room temperature for 2 hours. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium
30 sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 1.74 ml of methylene chloride, and 43.4 mg (0.215 mmol) of p-nitrophenyl chloroformate and 30 μl (0.215 mmol) of triethylamine were added thereto at -78°C . The mixture was stirred for 10 minutes. Subsequently, to the
35 mixture was added 43 μl (0.359 mmol) of 1-amino-4-methylpiperazine, and the mixture was stirred at -78°C to 0°C

f , hours. To the reaction mixture was added a saturated aqueous solution of sodium hydrogen carbonate, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by thin-layer chromatography (chloroform:methanol=9:1) to give 20.4 mg of Compound 18 (yield: 44%).

10 The physicochemical properties of Compound 18 are as follows.

$^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 9.85 (1H, brs), 8.25 (1H, brs), 7.79 (1H, d, $J=15.5\text{Hz}$), 7.55 (2H, d, $J=8.6\text{Hz}$), 7.07 (1H, br), 15 6.92 (2H, d, $J=8.6\text{Hz}$), 6.78 (1H, d, $J=15.2\text{Hz}$), 4.46-4.56 (1H, m), 4.42 (1H, d, $J=10.2\text{Hz}$), 4.26 (1H, dd, $J=9.9, 8.6\text{Hz}$), 3.91 (3H, s), 3.85 (3H, s), 3.75 (1H, dd, $J=9.9, 2.3\text{Hz}$), 3.18 (1H, dd, $J=9.9, 9.9\text{Hz}$), 2.95 (4H, br), 2.56 (3H, s), 2.52 (4H, br), 2.25 (3H, s)
20 FABMS (m/z); 642, 640 ($M+H$)⁺
IR (KBr) ν (cm^{-1}); 1741, 1697, 1650, 1512, 1433, 1410, 1252, 1215, 1173, 1090

Example 19 Synthesis of Compound 19

25 Ethanol (0.86 ml) and 0.43 ml of methanol were added to 20.4 mg (0.0318 mmol) of Compound 18 obtained in Example 18, and 13.9 μl of 6.86 N hydrogen chloride in ethanol was added thereto. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced 30 pressure to give 20.9 mg of Compound 19.

The physicochemical properties of Compound 19 are as follows.

$^1\text{H-NMR}$ (270MHz, $\text{DMSO}-d_6$) δ (ppm); 12.12 (1H, brs), 10.20 (1H, br), 35 9.49 (1H, brs), 8.03 (1H, s), 7.75 (2H, d, $J=8.3\text{Hz}$), 7.59 (1H, d, $J=15.2\text{Hz}$), 7.06 (1H, d, $J=15.2\text{Hz}$),



7.00 (2H, d, J=8.6Hz), 4.41-4.55 (3H, br), 3.84 (3H, s),
3.81 (3H, s), 3.78 (1H, br), 3.11-3.20 (7H, m), 2.79 (3H, s),
2.65 (3H, s)
IR(KBr) ν (cm⁻¹); 1749, 1697, 1647, 1512, 1437, 1414, 1250, 1219,
5 1188, 1093

Example 20 Synthesis of Compound 20

Acetonitrile (1.74 ml) and 40.6 μ l of 48% hydrobromic acid
were added to 30.0 mg (0.0717 mmol) of Compound D, and the
10 mixture was stirred at room temperature for 40 minutes. To the
reaction mixture was added a 1 N hydrobromic acid aqueous
solution, and the resulting mixture was extracted with
chloroform. The chloroform layer was washed with a saturated
aqueous solution of sodium chloride, dried over anhydrous sodium
15 sulfate, and concentrated under reduced pressure. The obtained
crude product was dissolved in 1.74 ml of methylene chloride,
and 43.4 mg (0.215 mmol) of p-nitrophenyl chloroformate and 30
 μ l (0.215 mmol) of triethylamine were added thereto at -78°C.
The mixture was stirred for 35 minutes. Subsequently, to the
20 mixture was added 34.6 μ l (0.359 mmol) of 4-aminomorpholine, and
the mixture was stirred at -78°C to room temperature for 23
hours. To the reaction mixture was added a saturated aqueous
solution of sodium hydrogen carbonate, and the resulting mixture
was extracted with chloroform. The chloroform layer was washed
25 with a saturated aqueous solution of sodium hydrogen carbonate
and with a saturated aqueous solution of sodium chloride, dried
over anhydrous sodium sulfate, and concentrated under reduced
pressure. The obtained crude product was purified by thin-layer
chromatography (chloroform:methanol=9:1) to give 25.9 mg of
30 Compound 20 (yield: 58%).

The physicochemical properties of Compound 20 are as
follows.

¹H-NMR (270MHz, CDCl₃) δ (ppm): 9.96 (1H, brs), 8.25 (1H, s),
35 7.81 (1H, d, J=15.2Hz), 7.54 (2H, d, J=8.9Hz), 7.42 (1H, brs),
6.91 (2H, d, J=8.9Hz), 6.77 (1H, d, J=15.2Hz), 4.42-4.56 (1H, m),



4.40 (1H, d, J=10.2Hz), 4.26 (1H, dd, J=9.2, 9.2Hz), 3.89 (3H, s),
3.84 (3H, s), 3.75 (1H, brd, J=8.3Hz), 3.65 (4H, br),
3.22 (1H, dd, J=9.6, 9.2Hz), 2.84 (4H, br), 2.52 (3H, s)
FABMS (m/z); 629, 627 (M+H) +
5 IR (KBr) ν (cm⁻¹); 1697, 1647, 1603, 1512, 1435, 1414, 1252, 1215,
1111, 1090

Example 21 Synthesis of Compound 21

Acetonitrile (1.45 ml) and 34 μ l of 48% hydrobromic acid
10 were added to 25.0 mg (0.0597 mmol) of Compound D, and the
mixture was stirred at room temperature for 50 minutes. To the
reaction mixture was then added a 1 N hydrobromic acid aqueous
solution, and the resulting mixture was extracted with
chloroform. The chloroform layer was washed with a saturated
15 aqueous solution of sodium chloride, dried over anhydrous sodium
sulfate, and concentrated under reduced pressure. The obtained
crude product was dissolved in 1.31 ml of methylene chloride,
and 24.9 mg (0.179 mmol) of 3-aminopyrazine-2-carboxylic acid
and 37 mg (0.179 mmol) of dicyclohexylcarbodiimide were added
20 thereto at -20°C. The mixture was stirred for 5 minutes.
Subsequently, to the mixture was added 21.9 mg (0.179 mmol) of
4-dimethylaminopyridine, and the mixture was stirred at -20°C to
room temperature for 18.5 hours. To the reaction mixture was
added a saturated aqueous solution of sodium hydrogen carbonate,
25 and the resulting mixture was extracted with chloroform. The
chloroform layer was washed with a saturated aqueous solution of
sodium hydrogen carbonate and with a saturated aqueous solution
of sodium chloride, dried over anhydrous sodium sulfate, and
concentrated under reduced pressure. The obtained crude product
30 was purified by thin-layer chromatography (chloroform:methanol=
20:1) to give 24.1 mg of Compound 21 (yield: 64%).

The physicochemical properties of Compound 21 are as
follows.

35 ¹H-NMR (270MHz, CDCl₃+CD₃OD) δ (ppm); 8.54 (1H, s),
8.29 (1H, d, J=2.0Hz), 7.92 (1H, d, J=2.0Hz), 7.73 (1H, d, J=15.5Hz),

7.53 (2H, d, J=8.6Hz), 6.89 (2H, d, J=8.9Hz), 6.76 (1H, d, J=14.8Hz),
4.48-4.59 (1H, m), 4.44 (1H, d, J=10.2Hz),
4.29 (1H, dd, J=9.9, 8.6Hz), 3.91 (3H, s), 3.81 (3H, s),
3.79 (1H, dd, J=8.6, 2.0Hz), 3.21 (1H, dd, J=10.2, 9.9Hz),
5 2.65 (3H, s)

FABMS (m/z); 622, 620 (M+H) ⁺

IR (KBr) ν (cm⁻¹); 1716, 1697, 1647, 1597, 1512, 1408, 1296,
1248, 1174, 1092

10 Example 22 Synthesis of Compound 22

Acetonitrile (1.45 ml) and 34 μ l of 48% hydrobromic acid
were added to 25.0 mg (0.0597 mmol) of Compound D, and the
mixture was stirred at room temperature for 60 minutes. To the
reaction mixture was then added a 1 N hydrobromic acid aqueous
15 solution, and the resulting mixture was extracted with
chloroform. The chloroform layer was washed with a saturated
aqueous solution of sodium chloride, dried over anhydrous sodium
sulfate, and concentrated under reduced pressure. The obtained
crude product was dissolved in 1.45 ml of methylene chloride,
20 and 27 mg (0.179 mmol) of 3,4-diaminobenzoic acid and 37 mg
(0.179 mmol) of dicyclohexylcarbodiimide were added thereto at
-20°C. The mixture was stirred for 10 minutes. Subsequently, to
the mixture was added 21.9 mg (0.179 mmol) of 4-
dimethylaminopyridine, and the mixture was stirred at -20°C to
25 room temperature for 16 hours. To the reaction mixture was
added a saturated aqueous solution of sodium hydrogen carbonate,
and the resulting mixture was extracted with chloroform. The
chloroform layer was washed with a saturated aqueous solution of
sodium hydrogen carbonate and with a saturated aqueous solution
30 of sodium chloride, dried over anhydrous sodium sulfate, and
concentrated under reduced pressure. The obtained crude product
was purified by thin-layer chromatography (chloroform:methanol=
9:1) to give 13.7 mg of Compound 22 (yield: 36%).

The physicochemical properties of Compound 22 are as
35 follows.

¹H-NMR (270MHz, DMSO-d₆) δ(ppm); 12.06(1H, brs), 8.07(1H, brs),
7.75(2H, d, J=8.6Hz), 7.59(1H, d, J=15.5Hz), 7.37(1H, s),
7.35(1H, dd, J=8.2, 2.0Hz), 7.06(1H, d, J=15.5Hz),
6.99(2H, d, J=8.6Hz), 6.63(1H, d, J=7.9Hz), 5.51(2H, brs),
5 4.82(2H, br), 4.39-4.57(3H, m), 3.85(3H, s),
3.83(1H, brd, J=11.2Hz), 3.81(3H, s), 3.45(1H, dd, J=8.9, 8.9Hz),
2.62(3H, s)
FABMS(m/z); 635, 633(M+H)⁺
IR(KBr) ν(cm⁻¹); 1701, 1693, 1645, 1593, 1512, 1410, 1306, 1250,
10 1205, 1092

Example 23 Synthesis of Compound 23

Acetonitrile (1.45 ml) and 33.8 μl of 48% hydrobromic acid were added to 25.0 mg (0.0597 mmol) of Compound D, and the
15 mixture was stirred at room temperature for 50 minutes. To the reaction mixture was further added 13.5 μl of 48% hydrobromic acid, and the mixture was stirred for 20 minutes. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with
20 chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 0.94 ml of methylene chloride, and 0.37 ml of methylene chloride containing 29.6 mg (0.179
25 mmol) of 4-dimethylaminobenzoic acid and 37 mg (0.179 mmol) of dicyclohexylcarbodiimide was added thereto at -20°C. The mixture was stirred for 5 minutes. Subsequently, to the mixture was added 21.9 mg (0.179 mmol) of 4-dimethylaminopyridine, and the mixture was stirred at -20°C to room temperature for 18
30 hours. To the reaction mixture was added a saturated aqueous solution of sodium hydrogen carbonate, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, dried
35 over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by thin-layer



chromatography (chloroform:methanol=80:1) to give 22.3 mg of Compound 23 (yield: 58%).

The physicochemical properties of Compound 23 are as follows.

- 5 $^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 9.44 (1H, brs), 8.28 (1H, brs),
7.92 (2H, d, $J=8.9\text{Hz}$), 7.75 (1H, d, $J=15.2\text{Hz}$), 7.54 (2H, d, $J=8.6\text{Hz}$),
6.92 (2H, d, $J=8.2\text{Hz}$), 6.77 (1H, d, $J=15.5\text{Hz}$), 6.51 (2H, d, $J=8.6\text{Hz}$),
4.47-4.58 (1H, m), 4.43 (1H, d, $J=10.2\text{Hz}$),
4.25 (1H, dd, $J=9.2, 8.2\text{Hz}$), 3.94 (3H, s), 3.84 (3H, s),
10 3.82 (1H, brd, $J=10.6\text{Hz}$), 3.19 (1H, dd, $J=10.2, 9.9\text{Hz}$), 3.01 (6H, s),
2.50 (3H, s)
FABMS (m/z); 648, 646 (M+H) $^+$
IR (KBr) ν (cm^{-1}); 1697, 1647, 1603, 1512, 1406, 1267, 1174, 1155,
1088

15 Example 24 Synthesis of Compound 24

- Acetonitrile (2.32 ml) and 54.1 μl of 48% hydrobromic acid
were added to 40.0 mg (0.0956 mmol) of Compound D, and the
mixture was stirred at room temperature for 40 minutes. To the
reaction mixture was added a 1 N hydrobromic acid aqueous
20 solution, and the resulting mixture was extracted with
chloroform. The chloroform layer was washed with a saturated
aqueous solution of sodium chloride, dried over anhydrous sodium
sulfate, and concentrated under reduced pressure. The obtained
crude product was dissolved in 2.32 ml of methylene chloride,
25 and 47.4 mg (0.287 mmol) of 3-dimethylaminobenzoic acid and 59.2
mg (0.287 mmol) of dicyclohexylcarbodiimide were added thereto
at -20°C . The mixture was stirred for 5 minutes. Subsequently,
to the mixture was added 35 mg (0.287 mmol) of 4-
dimethylaminopyridine, and the mixture was stirred at -20°C to
30 room temperature for 17.5 hours. To the reaction mixture was
added a saturated aqueous solution of sodium hydrogen carbonate,
and the resulting mixture was extracted with chloroform. The
chloroform layer was washed with a saturated aqueous solution of
sodium hydrogen carbonate and with a saturated aqueous solution
35 of sodium chloride, dried over anhydrous sodium sulfate, and
concentrated under reduced pressure. The obtained crude product



was purified by thin-layer chromatography (chloroform) to give 43.8 mg of a crude product. Then, the crude product was purified by high-performance preparative liquid chromatography (acetonitrile:water=90:10) to give 31.6 mg of Compound 24 (yield: 51%).

The physicochemical properties of Compound 24 are as follows.

$^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 9.57 (1H, brs), 8.30 (1H, brs), 7.73 (1H, d, $J=15.2\text{Hz}$), 7.53 (2H, d, $J=8.6\text{Hz}$), 7.42 (1H, d, $J=7.9\text{Hz}$), 7.34 (1H, brs), 7.18 (1H, dd, $J=7.9, 7.9\text{Hz}$), 6.92 (2H, d, $J=8.6\text{Hz}$), 6.83 (1H, dd, $J=7.9, 2.6\text{Hz}$), 6.72 (1H, d, $J=15.2\text{Hz}$), 4.45-4.58 (1H, m), 4.40 (1H, d, $J=10.2\text{Hz}$), 4.25 (1H, dd, $J=9.2, 8.2\text{Hz}$), 3.95 (3H, s), 3.84 (3H, s), 3.80 (1H, dd, $J=9.6, 2.0\text{Hz}$), 3.18 (1H, dd, $J=10.2, 9.9\text{Hz}$), 2.87 (6H, s), 2.56 (3H, s)
 FABMS (m/z); 648, 646 ($M+H$)⁺
 IR (KBr) ν (cm^{-1}); 1734, 1697, 1653, 1603, 1512, 1458, 1406, 1250, 1173, 1093

Example 25 Synthesis of Compound 25

Acetonitrile (2.32 ml) and 54.1 μl of 48% hydrobromic acid were added to 40.0 mg (0.0956 mmol) of Compound D, and the mixture was stirred at room temperature for 40 minutes. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 2.32 ml of methylene chloride, and 55.4 mg (0.287 mmol) of 4-diethylaminobenzoic acid and 59.2 mg (0.287 mmol) of dicyclohexylcarbodiimide were added thereto at -20°C . The mixture was stirred for 5 minutes. Subsequently, to the mixture was added 35 mg (0.287 mmol) of 4-dimethylaminopyridine, and the mixture was stirred at -20°C to room temperature for 21.5 hours. To the reaction mixture was



added a saturated aqueous solution of sodium hydrogen carbonate, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by column chromatography (chloroform) to give 65.3 mg of a crude product. Then, the crude product was purified by thin-layer chromatography (chloroform:methanol=80:1) to give 43.4 mg of Compound 25 (yield: 67%).

The physicochemical properties of Compound 25 are as follows.

$^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 8.97 (1H, brs), 8.33 (1H, brs), 7.99 (2H, d, $J=9.2\text{Hz}$), 7.78 (1H, d, $J=15.2\text{Hz}$), 7.56 (2H, d, $J=8.6\text{Hz}$), 6.93 (2H, d, $J=8.9\text{Hz}$), 6.80 (1H, d, $J=15.2\text{Hz}$), 6.61 (2H, d, $J=8.9\text{Hz}$), 4.50-4.63 (1H, m), 4.46 (1H, d, $J=10.6\text{Hz}$), 4.29 (1H, dd, $J=9.9, 8.3\text{Hz}$), 3.96 (3H, s), 3.85 (3H, s), 3.83 (1H, dd, $J=11.6, 2.2\text{Hz}$), 3.43 (4H, q, $J=6.9\text{Hz}$), 3.22 (1H, dd, $J=10.2, 9.9\text{Hz}$), 2.59 (3H, s), 1.21 (6H, t, $J=6.9\text{Hz}$)
FABMS (m/z); 676, 674 (M+H) $^+$
IR (KBr) ν (cm^{-1}); 1716, 1697, 1653, 1603, 1512, 1408, 1261, 1182, 1155, 1090

Example 26 Synthesis of Compound 26

Acetonitrile (1.74 ml) and 40.6 μl of 48% hydrobromic acid were added to 30.0 mg (0.0717 mmol) of Compound D, and the mixture was stirred at room temperature for 40 minutes. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 2.32 ml of methylene chloride, and 40.3 mg (0.215 mmol) of 4-(1H-pyrrol-1-yl)benzoic acid and 44.4 mg (0.215 mmol) of dicyclohexylcarbodiimide were added thereto at -20°C . The mixture was stirred for 5 minutes. Subsequently, to the mixture was added 26.3 mg (0.215 mmol) of



4-dimethylaminopyridine, and the mixture was stirred at -20°C to room temperature for 17 hours and 15 minutes. To the reaction mixture was added a saturated aqueous solution of sodium hydrogen carbonate, and the resulting mixture was extracted with
5 chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by column
10 chromatography (chloroform) to give 29.3 mg of a crude product. Then, the crude product was purified by high-performance preparative liquid chromatography (acetonitrile:water=90:10) to give 20.2 mg of Compound 24 (yield: 42%).

The physicochemical properties of Compound 26 are as
15 follows.

$^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 10.24 (1H, brs), 8.28 (1H, s),
8.03 (2H, d, $J=7.9\text{Hz}$), 7.71 (1H, d, $J=15.2\text{Hz}$), 7.52 (2H, d, $J=8.6\text{Hz}$),
7.13 (2H, d, $J=7.3\text{Hz}$), 6.93 (2H, brs), 6.91 (2H, d, $J=8.2\text{Hz}$),
20 6.67 (1H, d, $J=15.2\text{Hz}$), 6.29 (2H, brs), 4.20-4.48 (1H, br),
4.29 (1H, d, $J=10.9\text{Hz}$), 3.99-4.15 (1H, m), 3.92 (3H, s),
3.84 (3H, s), 3.67 (1H, brd, $J=9.2\text{Hz}$), 3.02 (1H, dd, $J=10.2, 9.6\text{Hz}$),
2.56 (3H, s)

FABMS(m/z); 670, 668 (M+H) $^+$

25 IR(KBr) ν (cm^{-1}); 1699, 1653, 1606, 1512, 1473, 1408, 1335, 1261,
1182, 1092

Example 27 Synthesis of Compound 27

Acetonitrile (1.16 ml) and 27 μl of 48% hydrobromic acid
30 were added to 20.0 mg (0.0478 mmol) of Compound D, and the mixture was stirred at room temperature for 40 minutes. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with
chloroform. The chloroform layer was washed with a saturated
35 aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained



crude product was dissolved in 1.16 ml of methylene chloride, and 33.6 mg (0.143 mmol) of 4-(4-methylpiperazinylmethyl)benzoic acid and 29.6 mg (0.143 mmol) of dicyclohexylcarbodiimide were added thereto at -20°C. The mixture was stirred for 5 minutes. Subsequently, to the mixture was added 17.5 mg (0.143 mmol) of 4-dimethylaminopyridine, and the mixture was stirred at -20°C to room temperature for 21 hours and 15 minutes. To the reaction mixture was added a saturated aqueous solution of sodium hydrogen carbonate, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by thin-layer chromatography (chloroform:methanol=9:1) to give 20.9 mg of Compound 27 (yield: 61%).

The physicochemical properties of Compound 27 are as follows.

¹H-NMR (270MHz, CDCl₃) δ(ppm); 9.16-9.28 (1H, br), 8.33 (1H, brs), 8.08 (2H, d, J=7.9Hz), 7.75 (1H, d, J=15.2Hz), 7.54 (2H, d, J=8.3Hz), 7.40 (2H, d, J=7.9Hz), 6.92 (2H, d, J=8.6Hz), 6.76 (1H, d, J=15.5Hz), 4.51-4.61 (1H, m), 4.44 (1H, d, J=9.9Hz), 4.28 (1H, dd, J=8.9, 7.6Hz), 3.95 (3H, s), 3.84 (3H, s), 3.80 (1H, brd, J=8.5Hz), 3.55 (2H, s), 3.21 (1H, dd, J=10.2, 9.9Hz), 2.61 (3H, s), 2.49 (8H, brs), 2.31 (3H, s)
FABMS (m/z); 717, 715 (M+H)⁺
IR (KBr) ν (cm⁻¹); 1697, 1653, 1647, 1601, 1512, 1408, 1250, 1217, 1173, 1090

Example 28 Synthesis of Compound 28

Anhydrous ethyl acetate (1.81 ml) was added to 12.7 mg (0.0177 mmol) of Compound 27 obtained in Example 27, and 172 mg of 5% hydrobromic acid in methanol was added thereto. The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated under reduced pressure to give



16.0 mg of Compound 28.

The physicochemical properties of Compound 28 are as follows.

5 $^1\text{H-NMR}$ (270MHz, DMSO- d_6) δ (ppm); 12.14 (1H, s), 9.40-9.80 (1H, br),
8.24 (2H, d, $J=8.3\text{Hz}$), 8.17 (1H, s), 7.76 (2H, d, $J=8.6\text{Hz}$),
7.67 (2H, d, $J=7.3\text{Hz}$), 7.59 (1H, d, $J=15.5\text{Hz}$),
7.08 (1H, d, $J=15.2\text{Hz}$), 7.00 (2H, d, $J=8.6\text{Hz}$), 4.44-4.54 (3H, m),
3.86 (3H, s), 3.81 (3H, s), 3.49 (2H, d, $J=6.6\text{Hz}$), 3.06-3.21 (3H, m),
10 2.84 (3H, s), 2.63 (3H, s)
IR (KBr) ν (cm^{-1}); 1734, 1697, 1653, 1601, 1512, 1437, 1412,
1252, 1217, 1174, 1093

Example 29 Synthesis of Compound 29

15 Acetonitrile (1.74 ml) and 41 μl of 48% hydrobromic acid
were added to 30.0 mg (0.0717 mmol) of Compound D, and the
mixture was stirred at room temperature for 1 hour. To the
reaction mixture was added a 1 N hydrobromic acid aqueous
solution, and the resulting mixture was extracted with
20 chloroform. The chloroform layer was washed with a saturated
aqueous solution of sodium chloride, dried over anhydrous sodium
sulfate, and concentrated under reduced pressure. The obtained
crude product was dissolved in 1.74 ml of methylene chloride,
and 43.4 mg (0.215 mmol) of p-nitrophenyl chloroformate and 30
25 μl (0.215 mmol) of triethylamine were added thereto at -78°C .
The mixture was stirred for 1.5 hours. Subsequently, to the
mixture was further added 14.5 mg (0.0717 mmol) of p-nitrophenyl
chloroformate, and the mixture was stirred for 30 minutes.
Then, 27.2 μl (0.359 mmol) of 1,1-dimethylhydrazine was added
30 thereto, and the mixture was stirred at -78° to -20°C for 24
hours. To the reaction mixture was added a saturated aqueous
solution of sodium hydrogen carbonate, and the resulting mixture
was extracted with chloroform. The chloroform layer was washed
with a saturated aqueous solution of sodium hydrogen carbonate
35 and with a saturated aqueous solution of sodium chloride, dried
over anhydrous sodium sulfate, and concentrated under reduced

pressure. The obtained crude product was purified by thin-layer chromatography (chloroform:methanol=20:1) to give 18.9 mg of Compound 29 (yield: 45%).

5 The physicochemical properties of Compound 29 are as follows.

$^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 9.76 (1H, brs), 8.23 (1H, brs),
7.80 (1H, d, $J=15.5\text{Hz}$), 7.56 (2H, d, $J=8.6\text{Hz}$), 7.03 (1H, brs),
6.92 (2H, d, $J=8.9\text{Hz}$), 6.79 (1H, d, $J=15.2\text{Hz}$), 4.43-4.51 (1H, m),
10 4.40 (1H, d, $J=10.9\text{Hz}$), 4.23 (1H, dd, $J=9.6, 9.2\text{Hz}$), 3.89 (3H, s),
3.84 (3H, s), 3.71 (1H, dd, $J=7.3, 2.3\text{Hz}$),
3.15 (1H, dd, $J=9.6, 9.6\text{Hz}$), 2.65 (6H, s), 2.53 (3H, s)
FABMS (m/z); 587, 585 ($M+H$)⁺
IR (KBr) ν (cm^{-1}); 2953, 1695, 1647, 1603, 1512, 1421, 1410,
15 1250, 1215, 1173, 1093

Example 30 Synthesis of Compound 30

Acetonitrile (0.87 ml) and 20.3 μl of 48% hydrobromic acid were added to 15.0 mg (0.0358 mmol) of Compound D, and the
20 mixture was stirred at room temperature for 50 minutes. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium
25 sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 0.87 ml of methylene chloride, and 21.6 mg (0.107 mmol) of p-nitrophenyl chloroformate and 15 μl (0.107 mmol) of triethylamine were added thereto at -78°C . The mixture was stirred for 40 minutes. Subsequently, to the
30 mixture was added 9.5 μl (0.179 mmol) of 1-methylhydrazine, and the mixture was stirred at -78°C to 0°C for 100 minutes. To the reaction mixture was added a saturated aqueous solution of sodium hydrogen carbonate, and the resulting mixture was
35 extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, dried over

anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by thin-layer chromatography (chloroform:methanol=12:1) to give 14.6 mg of Compound 30 (yield: 71%).

5 The physicochemical properties of Compound 30 are as follows.

$^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 9.81-10.21 (1H, br), 8.24 (1H, brs),
7.81 (1H, d, $J=15.2\text{Hz}$), 7.57 (2H, d, $J=8.3\text{Hz}$),
10 6.93 (2H, d, $J=8.6\text{Hz}$), 6.82 (1H, d, $J=15.5\text{Hz}$), 4.47-4.55 (1H, br),
4.46 (1H, d, $J=10.2\text{Hz}$), 4.33 (1H, dd, $J=9.2, 8.9\text{Hz}$), 3.94 (3H, s),
3.85 (3H, s), 3.77 (1H, dd, $J=9.4, 2.1\text{Hz}$), 3.29 (3H, brs),
3.19 (1H, dd, $J=9.9, 9.9\text{Hz}$), 2.32 (3H, s)
FABMS (m/z); 573, 571 (M^+H^+)
15 IR (KBr) (cm^{-1}); 1697, 1647, 1599, 1512, 1433, 1410, 1248, 1217,
1173, 1111

Example 31 Synthesis of Compound 31

Acetonitrile (3.78 ml) and 89.4 μl of 48% hydrobromic acid
20 were added to 66.1 mg (0.158 mmol) of Compound D, and the
mixture was stirred at room temperature for 50 minutes. To the
reaction mixture was added a 1 N hydrobromic acid aqueous
solution, and the resulting mixture was extracted with
chloroform. The chloroform layer was washed with an aqueous
25 solution of sodium chloride, dried over anhydrous sodium
sulfate, and concentrated under reduced pressure. The obtained
crude product was dissolved in 3.0 ml of methylene chloride, and
95.5 mg (0.474 mmol) of p-nitrophenyl chloroformate and 66 μl
(0.474 mmol) of triethylamine were added thereto at -78°C , and
30 the mixture was stirred for 45 minutes. To the mixture was
added 0.78 ml of a dichloromethane solution containing 101 mg
(0.553 mmol) of 1-amino-4-piperidinopiperidine, and the mixture
was stirred at 0°C to room temperature for 23.5 hours. To the
reaction mixture was added a saturated aqueous solution of
35 sodium hydrogen carbonate, and the resulting mixture was
extracted with chloroform. The chloroform layer was washed with

a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by thin-layer chromatography (chloroform:methanol:triethylamine=9:1:0.2) to give 48.5 mg of Compound 31 (yield: 43%).

The physicochemical properties of Compound 31 are as follows.

¹H-NMR (270MHz, CDCl₃) δ(ppm); 9.85 (1H, brs), 8.27 (1H, brs), 7.78 (1H, d, J=15.2Hz), 7.55 (2H, d, J=8.6Hz), 7.01 (1H, br), 6.92 (2H, d, J=8.9Hz), 6.79 (1H, d, J=14.9Hz), 4.48-4.51 (1H, m), 4.43 (1H, d, J=9.9Hz), 4.28 (1H, dd, J=9.6, 8.6Hz), 3.32 (3H, s), 3.85 (3H, s), 3.78 (1H, dd, J=9.4, 2.5Hz), 3.29 (2H, br), 3.20 (1H, dd, J=10.2, 10.2Hz), 2.64 (3H, s), 2.59 (9H, br), 1.84 (3H, br), 1.65 (3H, br), 1.45 (2H, br)
FABMS (m/z); 710, 708 (M+H)⁺
IR (KBr) ν (cm⁻¹), 1697, 1645, 1601, 1512, 1433, 1410, 1252, 1215, 1173, 1107

20 Example 32 Synthesis of Compound 32

Anhydrous ethyl acetate (2.5 ml) was added to 30.6 mg (0.0432 mmol) of Compound 31 obtained in Example 31, and 210 mg of 5% hydrobromic acid in methanol was added thereto. The mixture was stirred at -20°C for 40 minutes. The reaction mixture was concentrated under reduced pressure to give 35.6 mg of Compound 32.

The physicochemical properties of Compound 32 are as follows.

¹H-NMR (270MHz, DMSO-d₆) δ(ppm); 12.04 (1H, brs), 9.25 (1H, s), 9.00 (1H, br), 8.02 (1H, s), 7.75 (2H, d, J=8.6Hz), 7.59 (1H, d, J=15.2Hz), 7.06 (1H, d, J=15.2Hz), 7.00 (2H, d, J=8.9Hz), 4.36-4.53 (3H, m), 3.85 (3H, s), 3.82 (3H, s), 3.78 (1H, m), 3.17-3.27 (2H, m), 2.86-3.04 (1H, m), 2.69-2.79 (2H, m), 2.65 (3H, s), 1.99-2.07 (2H, br), 1.60-1.91 (9H, m), 1.34-1.49 (2H, m)

IR(KBr) ν (cm⁻¹); 1749, 1695, 1645, 1601, 1512, 1456, 1412, 1250, 1217, 1174

Example 33 Synthesis of Compound 33

5 Acetonitrile (1.45 ml) and 33.8 μ l of 48% hydrobromic acid were added to 25.0 mg (0.0597 mmol) of Compound D, and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with
10 chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 1.45 ml of methylene chloride, and 24.5 mg (0.185 mmol) of thiodiglycolic anhydride and 23.3 mg
15 (0.191 mmol) of 4-dimethylaminopyridine were added thereto at 0°C. The mixture was stirred at 0°C for 3 hours. To the reaction mixture was added a 0.01 M phosphate buffer of pH 7 and a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was
20 washed with a saturated aqueous solution of sodium hydrogencarbonate and with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by thin-layer chromatography (chloroform:methanol:acetic
25 acid=4:1:0.1) to give 25.9 mg of Compound 33 (yield: 69%).

The physicochemical properties of Compound 33 are as follows.

¹H-NMR (270MHz, CDCl₃) δ (ppm); 10.40 (1H, brs), 8.02 (1H, s),
30 7.66 (1H, d, J=15.2Hz), 7.49 (2H, d, J=8.3Hz), 6.88 (2H, d, J=8.3Hz), 6.63 (1H, d, J=15.5Hz), 4.36-4.46 (1H, m), 4.29 (1H, d, J=10.6Hz), 4.11 (H, dd, J=9.9, 9.2Hz), 3.89 (3H, s), 3.82 (3H, s), 3.64 (1H, dd, J=9.9, 2.3Hz), 3.59 (2H, s), 3.40 (1H, d, J=14.8Hz), 3.33 (1H, d, J=14.8Hz), 3.07 (1H, dd, J=10.2, 9.9Hz), 2.50 (3H, s)
35 FABMS (m/z); 633, 631 (M+H)⁺
IR(KBr) ν (cm⁻¹); 1697, 1637, 1603, 1512, 1437, 1416, 1252, 1219,

1174, 1105

Example 34 Synthesis of Compound 34

Acetonitrile (1.74 ml) and 40.6 μ l of 48% hydrobromic acid
5 were added to 30.0 mg (0.0717 mmol) of Compound D, and the
mixture was stirred at room temperature for 60 minutes. To the
reaction mixture was added a 1 N hydrobromic acid aqueous
solution, and the resulting mixture was extracted with
chloroform. The chloroform layer was washed with a saturated
10 aqueous solution of sodium chloride, dried over anhydrous sodium
sulfate, and concentrated under reduced pressure. The obtained
crude product was dissolved in 1.74 ml of methylene chloride,
and 54.1 mg (0.215 mmol) of 4-(tert-
15 butoxycarbonylaminomethyl)benzoic acid and 44.4 mg (0.215 mmol)
of dicyclohexylcarbodiimide were added thereto at -20°C . The
mixture was stirred for 5 minutes. Subsequently, to the mixture
was added 26.3 mg (0.215 mmol) of 4-dimethylaminopyridine, and
the mixture was stirred at -20°C to room temperature for 5.5
20 hours. To the reaction mixture was added a 0.01 M phosphate
buffer of pH 7, and the resulting mixture was extracted with
chloroform. The chloroform layer was washed with a saturated
aqueous solution of sodium chloride, dried over anhydrous sodium
sulfate, and concentrated under reduced pressure. The obtained
crude product was purified by column chromatography (chloroform
25 and methanol:30:1) to give 44.3 mg of a crude product.
Subsequently, the crude product was purified by high-performance
liquid chromatography (acetonitrile:water=80:20) to give 28.5 mg
of Compound 34 (yield: 54%).

30 The physicochemical properties of Compound 34 are as
follows.

$^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 9.44-9.76 (1H, brs), 8.30 (1H, brs),
8.00 (2H, d, $J=7.3\text{Hz}$), 7.75 (1H, d, $J=15.2\text{Hz}$), 7.55 (2H, d, $J=8.6\text{Hz}$),
7.22 (2H, d, $J=7.3\text{Hz}$), 6.92 (2H, d, $J=8.9\text{Hz}$), 6.76 (1H, d, $J=15.2\text{Hz}$),
35 5.25 (1H, brs), 4.47-4.59 (1H, m), 4.43 (1H, d, $J=10.9\text{Hz}$),
4.21-4.38 (3H, m), 3.94 (3H, s), 3.84 (3H, s),

3.81 (1H, brd, J=10.9Hz), 3.20 (1H, dd, J=10.2, 10.2Hz), 1.45 (9H, s)
FABMS (m/z); 734, 732 (M+H)⁺
IR (KBr) ν (cm⁻¹); 1705, 1695, 1645, 1512, 1410, 1261, 1217, 1173,
1090, 1016

5

Example 35 Synthesis of Compound 35

1,2-Dichloromethane (2.0 ml) and 1.445 g (0.893 mmol) of 5% hydrobromic acid in methanol were added to 65.4 mg (0.0717 mmol) of the crude product obtained in Example 34, and the mixture was
10 stirred at 60°C for 5 hours and 45 minutes. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and with a
15 saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by thin-layer chromatography (chloroform and methanol:4:1) to obtain 84.5 mg of a crude product. Subsequently, the crude product was
20 purified by column chromatography (chloroform:methanol=10:1) to give 15.1 mg of Compound 35 (yield: 33%).

The physicochemical properties of Compound 35 are as follows.

25 ¹H-NMR (270MHz, CDCl₃+CD₃OD) δ (ppm); 8.25 (1H, brs),
8.13 (2H, d, J=7.9Hz), 7.70 (1H, d, J=15.2Hz), 7.51 (2H, d, J=8.6Hz),
7.37 (2H, d, J=8.2Hz), 6.88 (2H, d, J=8.6Hz), 6.75 (1H, d, J=15.5Hz),
4.47-4.58 (1H, m), 4.42 (1H, d, J=10.6Hz),
4.26 (1H, dd, J=9.6, 8.9Hz), 3.91 (3H, s), 3.89 (2H, s),
30 3.81 (3H, s), 3.78 (1H, brd, J=8.4Hz), 3.19 (1H, dd, J=9.9, 9.9Hz),
2.61 (3H, s)
FABMS (m/z); 634, 632 (M+H)⁺
IR (KBr) ν (cm⁻¹); 1732, 1695, 1647, 1601, 1512, 1410, 1259, 1219,
1174, 1092

35



Example 36 . Synthesis of Compound 36

Anhydrous ethyl acetate (1.17 ml) was added to 11.1 mg (0.0175 mmol) of compound 35 obtained in Example 35, and 85 mg of 5% hydrobromic acid in methanol was added thereto. The mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to give 14.6 mg of Compound 36.

The physicochemical properties of Compound 36 are as follows.

10

$^1\text{H-NMR}$ (270MHz, DMSO- d_6) δ (ppm); 12.15 (1H, brs), 8.32 (2H, br), 8.27 (2H, d, $J=8.2\text{Hz}$), 8.18 (1H, brs), 7.75 (2H, d, $J=8.3\text{Hz}$), 7.72 (2H, d, $J=7.6\text{Hz}$), 7.58 (1H, d, $J=15.5\text{Hz}$), 7.08 (1H, d, $J=15.2\text{Hz}$), 7.00 (2H, d, $J=8.6\text{Hz}$), 4.50-4.60 (1H, m), 4.41-4.48 (2H, br), 4.21-4.23 (2H, m), 3.86 (3H, s), 3.83 (1H, brd), 3.81 (3H, s), 2.63 (3H, s)
IR (KBr) ν (cm^{-1}); 1734, 1697, 1635, 1601, 1514, 1437, 1417, 1259, 1174, 1093

15

20 Example 37 Synthesis of Compound 37

Anhydrous ethyl acetate (1.25 ml) was added to 19.6 mg (0.0306 mmol) of compound 18 obtained in Example 18, and 149 mg of 5% hydrobromic acid in methanol was added thereto. The mixture was stirred at 0°C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 23 mg of Compound 37.

25

The physicochemical properties of Compound 37 are as follows.

30

$^1\text{H-NMR}$ (270MHz, DMSO- d_6) δ (ppm); 12.07 (1H, brs), 9.49 (2H, brs), 8.04 (1H, brs), 7.76 (2H, d, $J=8.3\text{Hz}$), 7.59 (1H, d, $J=15.2\text{Hz}$), 7.07 (1H, d, $J=15.5\text{Hz}$), 7.00 (2H, d, $J=7.3\text{Hz}$), 4.38-4.56 (3H, br), 3.85 (3H, s), 3.82 (3H, s), 3.77 (1H, br), 3.02-3.30 (5H, m), 2.82 (3H, s), 2.66 (3H, s)
IR (KBr) ν (cm^{-1}); 1697, 1647, 1601, 1512, 1437, 1412, 1250, 1217, 1174, 1093

35



Example 38 Synthesis of Compound 38

Acetonitrile (1.2 ml) and 27 μ l of 48% hydrobromic acid were added to 20.0 mg (0.0478 mmol) of Compound D, and the mixture was stirred at room temperature for 40 minutes. To the reaction mixture was then added a 1 N hydrobromic acid aqueous solution, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was dissolved in 1.1 ml of methylene chloride, and 28.9 mg (0.143 mmol) of p-nitrophenyl chloroformate and 20 μ l (0.143 mmol) of triethylamine were added thereto at -78°C . The mixture was stirred for 45 minutes. Then, to the mixture was added a solution of 31.8 mg (0.239 mmol) of 1,2-dimethylhydrazine dihydrochloride and 67 μ l (0.478 mmol) of triethylamine in 0.31 ml of chloroform. The mixture was stirred at -20°C for 2 hours and 25 minutes. To the reaction mixture was added a saturated aqueous solution of sodium hydrogen carbonate, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by thin-layer chromatography (chloroform:methanol=20:1) to give 12.9 mg of Compound 38 (yield: 46%).

The physicochemical properties of Compound 38 are as follows.

$^1\text{H-NMR}$ (270MHz, CDCl_3) δ (ppm); 9.65 (1H, brs), 9.39 (1H, brs), 8.24 (1H, s), 7.80 (1H, d, $J=15.2\text{Hz}$), 7.57 (2H, d, $J=8.9\text{Hz}$), 6.94 (2H, d, $J=8.9\text{Hz}$), 6.81 (1H, d, $J=15.5\text{Hz}$), 4.50-4.57 (1H, m), 4.46 (1H, d, $J=10.2\text{Hz}$), 4.31 (1H, dd, $J=9.6, 8.9\text{Hz}$), 3.94 (3H, s), 3.86 (3H, s), 3.78 (1H, dd, $J=9.7, 2.5\text{Hz}$), 3.27 (3H, brs), 3.20 (1H, dd, $J=10.2, 9.9\text{Hz}$), 2.71 (3H, brs), 2.44 (3H, brs)
FABMS (m/z); 587, 585 (M+H) $^{+}$



IR(KBr) ν (cm⁻¹); 1716, 1697, 1686, 1647, 1601, 1512, 1410, 1252, 1219, 1173, 1159, 1109

Example 39 Synthesis of Compound 39

5 Acetonitrile (1.58 ml) and 348 mg of 5% hydrobromic acid in methanol were added to 30.0 mg (0.0717 mmol) of Compound D, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure. The obtained crude product was dissolved in 1.58 ml of methylene
10 chloride, and 49.7 mg (0.215 mmol) of 2-(4-methylpiperazinyl)acetic acid dihydrochloride and 41.1 mg (0.215 mmol) of N-ethyl-N'-3-dimethylaminopropylcarbodiimide hydrochloride were added thereto at -20°C. The mixture was stirred for 5 minutes. To the reaction mixture was then added
15 52.6 mg (0.430 mmol) of 4-dimethylaminopyridine, and the mixture was stirred at -20°C for 4 hours and 10 minutes. To the reaction mixture was added a saturated aqueous solution of sodium hydrogen carbonate, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with
20 a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. Trifluoroacetic acid was then added thereto, and the mixture was concentrated under reduced pressure. To the obtained crude product were added 2.00 ml of
25 anhydrous ethyl acetate and 355 mg of 5% hydrobromic acid in methanol, and the mixture was stirred at -20°C for 1 hour. The precipitated crystals were collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give 14.4 mg of Compound 39 (yield 25%).

30 The physicochemical properties of Compound 39 are as follows.

¹H-NMR (270MHz, DMSO-d₆) δ (ppm); 12.06(1H, s), 9.45(1H, brs), 8.10(1H, s), 7.75(2H, d, J=8.6Hz), 7.59(1H, d, J=15.5Hz),
35 7.70(1H, d, J=15.2Hz), 7.00(2H, d, J=8.9Hz), 4.36-4.58(3H, br), 3.89(2H, s), 3.85(3H, s), 3.81(3H, s), 3.80(1H, brd, J=9.9Hz),



3.38-3.50(3H,m), 3.03-3.20(4H,m), 2.82(5H,br), 2.66(3H,s)
IR(KBr) ν (cm⁻¹); 1647, 1637, 1601, 1512, 1458, 1437, 1410,
1250, 1207, 1174

5 Example 40 Synthesis of Compound 40

Acetonitrile (1.58 ml) and 348 mg of 5% hydrobromic acid in methanol were added to 30.0 mg (0.0717 mmol) of Compound D, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure. The
10 obtained crude product was dissolved in 1.58 ml of methylene chloride, and 64.4 mg (0.215 mmol) of 2-(4-piperidinopiperidinyl)acetic acid dihydrochloride and 41.1 mg (0.215 mmol) of N-ethyl-N'-3-dimethylaminopropylcarbodiimide hydrochloride were added thereto at -20°C. The mixture was
15 stirred for 5 minutes. Subsequently, 52.6 mg (0.430 mmol) of 4-dimethylaminopyridine was added to the mixture, and the mixture was stirred at -20°C to room temperature for 7 hours. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, and the resulting mixture was
20 extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. Trifluoroacetic acid was added thereto, and the mixture was concentrated under reduced
25 pressure. Anhydrous ethyl acetate (2.00 ml) and 580 mg of 5% hydrobromic acid in methanol were added to the obtained crude product, and the mixture was stirred at -20°C for 1 hour. The precipitated crystals were collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give 48.1 mg
30 of Compound 40 (yield: 77%).

The physicochemical properties of Compound 40 are as follows.

¹H-NMR(270MHz,DMSO-d₆) δ (ppm); 12.19(1H,s), 9.38(1H,brs),
8.20(1H,s), 7.76(2H,d,J=8.6Hz), 7.59(1H,d,J=15.2Hz),
35 7.08(1H,d,J=15.6Hz), 7.00(2H,d,J=8.6Hz), 4.38-4.60(3H,m),
4.41(1H,br), 3.85(3H,s), 3.82(3H,s), 3.79 (1H,m),

3.37-3.73 (5H, m), 2.86-3.23 (4H, m), 2.68 (3H, s), 2.25 (2H, br),
1.64-2.16 (7H, m), 1.44 (1H, br)
IR (KBr) ν (cm⁻¹); 1695, 1686, 1645, 1601, 1512, 1437, 1410, 1250,
1176, 1109

5

Reference Example 1 Synthesis of Compound a

Compound E (705 mg, 1.03 mmol) was dissolved in 36 ml of tetrahydrofuran, and 1.55 ml of a 1 M tetrahydrofuran solution of tetra-n-butylammonium fluoride was added thereto. The
10 mixture was stirred at room temperature for 1 hour. Phosphate buffer (pH 7) was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and
15 concentrated under reduced pressure. The obtained crude product was dissolved in 53 ml of N,N-dimethylformamide, and 11 ml of 70% perchloric acid and 21 ml of water were added thereto at 0°C. The mixture was stirred at 0°C to room temperature for 2 hours. A saturated aqueous solution of sodium hydrogen
20 carbonate was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified
25 by silica-gel column chromatography (160 ml of silica gel, chloroform:methanol=30:1) to give 385 mg of Compound a (yield: 73%).

The physicochemical properties of Compound a are as follows.

30

¹H-NMR (400MHz, DMSO-d₆) δ (ppm); 11.36 (1H, br s), 9.52 (1H, s),
7.82 (1H, br s), 6.97 (1H, d, J=2.2Hz), 6.87 (1H, s), 4.67 (1H, br
d, J=9.8Hz), 4.47 (1H, dd, J=5.3, 5.3Hz),
4.39 (1H, dd, J=10.1, 8.4Hz), 4.18 (1H, m), 4.05 (3H, s), 3.89 (3H, s),
35 3.88 (3H, s), 3.86 (3H, s), 3.73 (1H, dd, J=10.5, 5.0Hz),
2.66 (3H, s)

IR(KBr) ν (cm⁻¹); 1595, 1490, 1442, 1320, 1223, 1161

SIMS(m/z); 510(M)⁺, 234

Reference Example 2 Synthesis of Compound b

- 5 Compound a (50 mg, 0.098 mmol) was dissolved in 3 ml of N,N-dimethylformamide, and 20 mg (0.14 mmol) of potassium carbonate and 22 ml (0.19 mmol) of benzyl bromide were added thereto. The mixture was stirred at room temperature for 48 hours. Phosphate buffer (pH 7) was added to the reaction
- 10 mixture, and the resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel column chromatography
- 15 (20 ml of silica gel, chloroform:methanol=100:1) to give 40 mg of Compound b (yield: 68%).

The physicochemical properties of Compound b are as follows.

- 20 ¹H-NMR(400MHz,CDCl₃) δ (ppm); 9.39(1H,br s), 8.63(1H,br s), 8.18(1H,s), 7.50-7.37(5H,m), 6.99(1H,d,J=2.3Hz), 6.86(1H,s), 5.24(2H,d,J=11.0Hz), 4.66(1H,dd,J=10.1,1.2Hz), 4.52(1H,dd,J=10.0,8.5Hz), 4.38(1H,m), 4.07(3H,s), 3.94(3H,s), 3.91(3H,s), 3.90(3H,s), 3.85(1H,dd,J=10.5,4.7Hz),
- 25 3.58(1H,dd,J=10.5,6.5Hz), 2.68(3H,s)
- IR(KBr) ν (cm⁻¹); 1671, 1636, 1597, 1492, 1443, 1417, 1313, 1219, 1113
- EIMS(m/z); 599(M+1)⁺, 234

30 Reference Example 3 Synthesis of Compound c

- Compound a (100 mg, 0.195 mmol) was dissolved in 5 ml of N,N-dimethylformamide, and 41 mg (0.30 mmol) of potassium carbonate and 0.019 ml (0.31 mmol) of methyl iodide were added thereto. The mixture was stirred at room temperature for 24
- 35 hours. Then, 0.01 M phosphate buffer (pH 7) was added to the reaction mixture, and the resulting mixture was extracted with

ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica-gel column chromatography (20 ml of silica gel, chloroform:methanol=80:1) to give 52 mg of Compound c (yield: 51%).

The physicochemical properties of Compound c are as follows.

¹H-NMR (400MHz, CDCl₃) δ(ppm); 9.39(1H, br s), 8.26(1H, br s), 8.05(1H, s), 6.99(1H, d, J=2.3Hz), 6.86(1H, s), 4.66(1H, dd, J=10.2, 1.2Hz), 4.52(1H, dd, J=10.1, 10.1Hz), 4.37(1H, m), 4.07(3H, s), 4.00(3H, s), 3.94(3H, s), 3.91(3H, s), 3.90(3H, s), 3.85(1H, dd, J=10.4, 4.7Hz), 3.59(1H, dd, J=10.5, 7.4Hz), 2.69(3H, s)
IR (KBr) ν(cm⁻¹); 1670, 1634, 1521, 1446, 1411, 1313, 1221, 1113
SIMS (m/z); 524 (M+H)⁺, 234

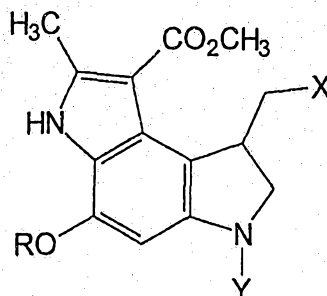
20 Industrial Availability

The present invention relates to DC-89 derivatives. The compounds of the present invention exhibit excellent anti-tumor activity and are useful as anti-tumor agents.



The claims defining the invention are as follows:

1. A DC-89 derivative represented by the formula

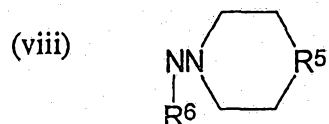


wherein:

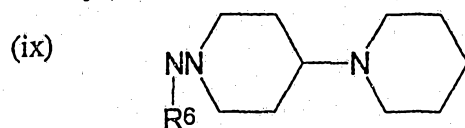
5 X represents Cl or Br;

R represents:

- (a) substituted or unsubstituted lower alkyl;
 (b) substituted or unsubstituted aralkyl;
 (c) COR¹ in which R¹ represents;
 10 (i) hydrogen;
 (ii) substituted or unsubstituted lower alkyl
 (iii) substituted or unsubstituted aryl;
 (iv) substituted or unsubstituted heterocyclic group selected from the
 group consisting of pyridyl, pyrazinyl and pyrimidinyl;
 15 (v) OR² (in which R² represents substituted or unsubstituted lower
 alkyl or aryl);
 (vi) SR² (in which R² is the same meaning as defined above);
 (vii) NR³R⁴ (in which R³ and R⁴ independently represent hydrogen,
 substituted lower alkyl, amino, or mono- or di(lower alkyl)amino, provided that R³ and
 20 R⁴ are not hydrogen at the same time);



in which R⁵ represents NR⁷ (in which R⁷ represents hydrogen or substituted or
 unsubstituted lower alkyl) or oxygen, and R⁶ represents hydrogen or substituted or
 unsubstituted lower alkyl, or



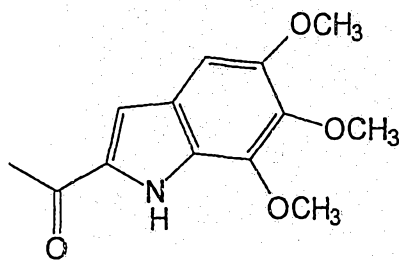
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(in which R⁶ represents hydrogen or substituted or unsubstituted lower alkyl) or SO₂R⁸
 (in which R⁸ represents substituted or unsubstituted lower alkyl or substituted or
 unsubstituted aryl); and

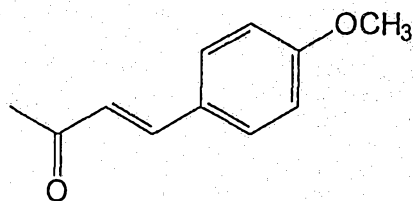
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or



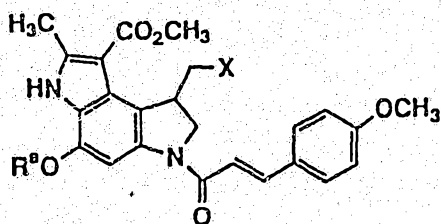
or pharmaceutically acceptable salts thereof.

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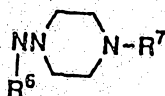
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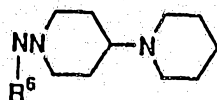
2. A DC-89 derivative represented by the formula



wherein X represents Cl or Br; and R^a represents COR^1 (in which R^1 represents substituted or unsubstituted aryl, NR^3R^4 (in which R^3 and R^4 independently represent hydrogen, substituted lower alkyl, amino or mono- or di(lower alkyl)amino, provided that R^3 and R^4 are not hydrogen atoms at the same time),

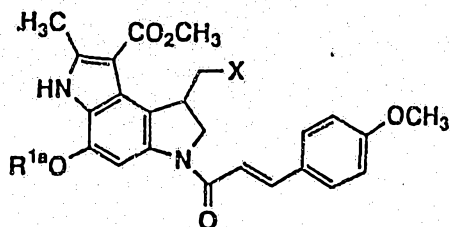


(in which R^6 and R^7 independently represent hydrogen or substituted or unsubstituted lower alkyl), or

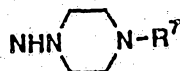


(in which R^6 is the same meaning as defined above)), and pharmaceutically acceptable salts thereof.

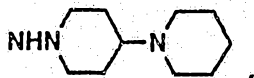
3. A DC-89 derivative represented by the formula



wherein X represents Cl or Br; and R^{1a} represents



(in which R^7 represents hydrogen or substituted or unsubstituted lower alkyl), or



and pharmaceutically acceptable salts thereof.

4. A DC-89 derivative, substantially as hereinbefore described with reference to any one of the Examples.

5. A process of preparing a DC-89 derivative, which process is substantially as hereinbefore described with reference to any one of the Examples.

5 6. A method for the treatment or prophylaxis of a tumor in a mammal, comprising administering to said mammal an effective amount of a DC-89 derivative according to any one of claims 1 to 3.

Dated 18 January, 1996
Kyowa Hakko Kogyo Co., Ltd.

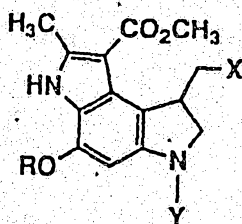
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Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

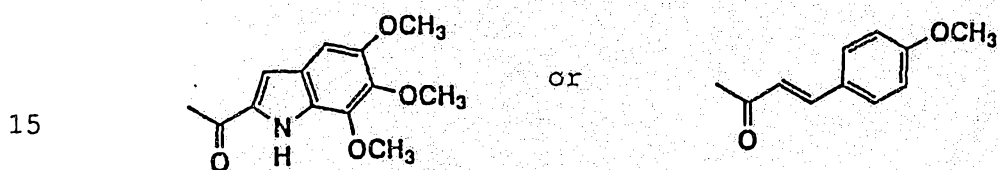


ABSTRACT

DC-89 derivatives represented by the formula



10 wherein X represents Cl or Br; R represents substituted or unsubstituted alkyl, substituted or unsubstituted aralkyl, COR¹ or S₂OR¹; and Y represents



and pharmaceutically acceptable salts thereof.

20 The compounds of the present invention exhibit excellent anti-tumor activity and are useful as anti-tumor agents.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP95/00779

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl⁶ C07D487/04 // A61K31/40, 31/44, 31/495, 31/535, 31/445
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl⁶ C07D487/04, A61K31/40, 31/44, 31/495, 31/535, 31/445

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, 2-502005, T (The Upjohn Co.), July 5, 1990 (05. 07. 90) & WO, 8804659, A	1 - 3
Y	EP, 154445, A (The Upjohn Co.), February 20, 1985 (20. 02. 85) & US, 4912227, A	1 - 3

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date
"L" document, which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed.

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

May 29, 1995 (29. 05. 95)

Date of mailing of the international search report

June 20, 1995 (20. 06. 95)

Name and mailing address of the ISA/

Japanese Patent Office

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Authorized officer

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