The present invention relates to a tetracyclic fused heterocyclic compound represented by the following formula [I]

```
R1

R2

R3

R4

X

Y

Z
```

wherein each symbol is as defined in the specification, or a pharmaceutically acceptable salt thereof, and a hepatitis C virus (HCV) polymerase inhibitor and a therapeutic agent for hepatitis C containing this compound. The compound of the present invention shows an anti-HCV activity based on the HCV polymerase inhibitory activity, and useful as an agent for the prophylaxis or treatment of hepatitis C.
TETRACYCLIC FUSED HETEROCYCLIC COMPOUND AND USE THEREOF AS HCV POLYMERASE INHIBITOR

TECHNICAL FIELD

[0001] The present invention relates to a tetracyclic fused heterocyclic compound or a pharmaceutically acceptable salt thereof, which shows anti-hepatitis C virus (HCV) activity, particularly anti-HCV activity based on an RNA-dependent RNA polymerase inhibitory activity. In addition, the present invention relates to a hepatitis C virus polymerase inhibitor, an anti-hepatitis C virus agent and a therapeutic agent for hepatitis C containing said tetracyclic fused heterocyclic compound or a pharmaceutically acceptable salt thereof.

BACKGROUND ART

[0002] In 1989, a main causative virus of non-A non-B posttransfusion hepatitis was found and named hepatitis C virus (HCV). Since then, several types of hepatitis viruses have been found besides type A, type D and type C, wherein hepatitis caused by HCV is called hepatitis C.

[0003] The patients infected with HCV are considered to involve several percent of the world population, and the infection with HCV characteristically becomes chronic.

[0004] HCV is an envelope RNA virus, wherein the genome is a single strand plus-strand RNA, and belongs to the genus Flavivirus of Flaviviridae (from The International Committee on Taxonomy of Viruses, International Union of Microbiological Societies). Of the same hepatitis viruses, for example, hepatitis B virus (HBV), which is a DNA virus, is eliminated by the immune system and the infection with this virus ends in an acute infection except for neonates and infants having yet immature immunological competence. In contrast, HCV somehow avoids the immune system of the host due to an unknown mechanism. Once infected with this virus, even an adult having a mature immune system frequently develops persistent infection. When chronic hepatitis is associated with the persistent infection with HCV, it advances to cirrhosis or hepatic cancer in a high rate. Emaciation of tumor by operation does not help much, because the patient often develops recurrent hepatic cancer due to the sequela inflammation in non-cancerous parts. In addition, there is a report on the involvement of HCV infection in dermatosis such as chronic urticaria, lichen planus, cryoglobulinemic purpura and the like (The Japanese Journal of Dermatology, Vol. 111, No. 7, pages 1075-1081, 2001).

[0005] Thus, an effective therapeutic method of hepatitis C is desired. Apart from the symptomatic therapy to suppress inflammation with an anti-inflammatory agent, the development of a therapeutic agent that reduces HCV to a low level free from inflammation and that eradicates HCV has been strongly demanded.

[0006] At present, a treatment with interferon is the only effective method known for the eradication of HCV. However, interferon can eradicate the virus only in about one-third of the patient population. For the rest of the patients, it has no effect or provides only a temporary effect. In recent years, polyethylene glycolated interferon has been put to practical use, and enhanced effects and reduced side effects have been achieved. However, complete response rate still remains at a low level, and therefore, an anti-HCV drug to be used in the place of or concurrently with interferon is awaited in great expectation.

[0007] In recent years, Ribavirin (1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide) has become commercially available as a therapeutic agent for hepatitis C, which is to be used concurrently with interferon. It enhances the efficacy of interferon but only to a low efficacy rate, and a different novel therapeutic agent for hepatitis C is desired.

[0008] Also, an attempt has been made to potentiate the immunocompetence of the patient with an interferon agonist, an interleukin-12 agonist and the like, thereby to eradicate the virus, but an effective pharmaceutical agent has not been found yet.

[0009] In addition, the inhibition of HCV growth, wherein HCV-specific protein is targeted, has been drawing attention these days.

[0010] The gene of HCV encodes a protein such as serine protease, RNA helicase, RNA-dependent RNA polymerase and the like. These proteins function as a specific protein essential for the growth of HCV.

[0011] One of the specific proteins, RNA-dependent RNA polymerase (hereinafter to be also briefly referred to as an HCV polymerase), is an enzyme essential for the growth of the virus. The gene replication of HCV having a plus-strand RNA gene is considered to involve synthesis of a complementary minus-strand RNA by the use of the plus-strand RNA as a template and using the obtained minus-strand RNA as a template, amplifying the plus-strand RNA. The portion called NS5B of a protein precursor, that HCV codes for, has been found to show an RNA-dependent RNA polymerase activity (EMBO J., Vol. 15, pages 12-22, 1996), and is considered to play a central role in the HCV gene replication.

[0012] Therefore, an HCV polymerase inhibitor can be a target in the development of an anti-HCV drug, and the development thereof is eagerly awaited. However, an effective HCV polymerase inhibitor has not been developed yet, like in other attempts to develop an anti-HCV drug based on other action mechanisms. As the situation stands, no pharmaceutical agent can treat hepatitis C satisfactorily.

[0013] The following describes known compounds comparatively similar to the present invention.

[0014] WO03/099824 discloses the following compound etc. as anti-HCV agents, and teaches that this compound shows an HCV polymerase inhibitory action (WO03/099824, Example 4 (page 32, line 10-page 35), Table 1 (page 20)).

[0015] However, the compound of the present invention is not disclosed therein and no description suggestive thereof is found in the specification.

[0016] On the other hand, as known tetracyclic fused heterocyclic compounds, whose pharmaceutical use is known, the following can be mentioned.
EP226508 discloses that the following compound b etc. show an anticancerous action (EP226508, Example 2 (page 4, last line—page 6, line 2), formula VII of claim 5 (page 31)).

Other reference describes following compound c etc. and synthetic methods of compounds usable as central nervous system agents (Bollettino Chimico Farmaceutico, Vol. 120, No. 2, pages 102-107, 1981).

However, none of these references discloses the compound of the present invention, not to mention disclosure of use of the compounds of these references as antiviral agents or description suggestive thereof.

As the compounds comparatively similar to the compound of the present invention, relating to use other than a pharmaceutical agent, the following can be mentioned.

JP-A-4-329547 discloses the following compound d known as an electronic photographic-sensitized material (JP-A-4-329547, formula 52 (page 7, lower right column)).

A different reference discloses the following compound e etc., wherein its synthetic method is described (J. Org. Chem., Vol. 66, No. 2, pages 412-420, 2001, Table 3 No. 19 (page 415)).

A yet different reference discloses the following compound f etc., wherein its synthetic method is described (Organic Letters, Vol. 4, No. 8, pages 1355-1358, 2002, Table 1 No. 17 (page 1357), Scheme 4 (page 1356)).

Another different reference discloses the following compound g etc., wherein its synthetic method is described (J. Org. Chem., Vol. 31, No. 6, pages 2009-2011, 1966, Scheme 1 (page 2010)).
[0025] However, none of these references discloses the compound of the present invention, not to mention disclosure of use of the compounds of these references as an antiviral agents or description suggestive thereof.

[0026] As a therapeutic agent for hepatitis C having an indole skeleton, WO03/010140 is known (WO03/010140, Example Nos. 1 (page 41), 10 (page 51), 14 (page 57), 18 (page 60), 20 (page 63), 22 (page 64), compound No. 149 (page 79)).

[0027] In this publication, as an anti-HCV agent having a polymerase inhibitory activity, the following indole compounds A, B, C, D etc. are described.

![compound A (Ex. 1)]
![compound B (Ex. 14)]
![compound C (Ex. 10)]
![compound D (Compound# 149)]

wherein Ex. means Example No. in the publication.

[0028] In this publication, as compounds having other skeleton, the following compounds E, F, G etc. are described.

![compound E (Ex. 22)]
![compound F (Ex. 18)]
![compound G (Ex. 20)]

[0029] In WO03/010141, as a synthetic intermediate for an anti-HCV agent having a polymerase inhibitory activity, the above-mentioned compounds etc. are described (WO03/010141, page 92, page 101, page 108, page 112, page 115, page 116).

This publication also describes the following compound J etc. as compounds having other skeletons.

The above-mentioned WO03/000254 further describes the following benzimidazole compounds K, L, M, N, O etc.

In addition, WO02/04425 describes the following benzimidazole compound P etc. as anti-HCV agents having a polymerase inhibitory activity (WO02/04425, entry No.
In this publication, the following compounds Q, R etc. are described as compounds having other skeletons.

[0034] WO03/026587 also discloses the following compounds S, T etc. as anti-HCV agents having a polymerase inhibitory activity (WO03/026587, Example Nos. 12 (page 56), 65 (page 65)).

[0035] As therapeutic agents for hepatitis C having a benzimidazole skeleton, the compounds described in WO97/36866, JP-T-2000-511989 (EP006097) and WO99/51619 are also known.

[0036] WO03/007945 also describes benzimidazole compounds etc. as synthetic intermediates for anti-HCV agents having a polymerase inhibitory activity.

[0037] Furthermore, WO99/09007 and U.S. Pat. No. 5,932,743 describe the following indole compound U etc. as chemical library compounds that can be used for screening of pharmaceutical products (see WO99/09007, Example 12 (page 25); U.S. Pat. No. 5,932,743).

DISCLOSURE OF INVENTION

[0039] Based on the findings from the preceding studies, it has been elucidated that a pharmaceutical agent having an anti-HCV activity is effective for the prophylaxis and treatment of hepatitis C, and particularly an anti-HCV agent having an inhibitory activity on RNA-dependent RNA polymerase of HCV can be a prophylactic and therapeutic agent effective against hepatitis C and a prophylactic and therapeutic agent for the disease caused by hepatitis C.

[0040] Accordingly, the present invention provides a compound having an anti-HCV activity, particularly a compound having an RNA-dependent RNA polymerase inhibitory activity.

[0041] The present inventors have made an in-depth study of compounds having an anti-HCV activity, particularly RNA-dependent RNA polymerase inhibitory activity, and completed the present invention.
Thus, the present invention provides the following 1 to 70. A compound represented by the following formula I or a pharmaceutically acceptable salt thereof:

![Chemical Structure](image)

wherein

G^0 is a carbon atom or a nitrogen atom, a broken line in ring A shows a single bond or a double bond,

R^1 is

(1) a carboxyl group,

(2) a carboxylic acid equivalent,

(3) —CONR^11R^12

(wherein R^11 and R^12 are each independently

[0062] (1) a hydrogen atom,

[0063] (2') a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from the following group E,

[0064] (3') a C_{2-5} alkenyl group optionally substituted by 1 to 3 substituents selected from the following group E,

[0065] (4') a C_{6-14} aryl group optionally substituted by 1 to 5 substituents selected from the following group E,

[0066] (5') a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group E

(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),

[0067] (6') a C_{3-10} cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group E,

[0068] (7') —NR_{131}R_{132},

[0069] (8') —NHCOOR_{133},

[0070] (9') —NHCOR_{134},

(wherein R_{131}, R_{132}, R_{133} and R_{134} are each independently a hydrogen atom or a group selected from the following group F),

[0071] (10') —CR_{135}R_{136}—CH=CH—,

[0072] (11') —CR_{135}R_{136}—L—CONR_{130}—R_{137},

(12') —CR_{138}R_{139}—L_{102}—CONR_{140}—L_{103}—D^3,

(13') —CR_{138}R_{139}—L_{102}—CONR_{140}—L_{104}—CONR_{141}—L_{105}—D^3,

or

(14')

L_{105}—D^4—L_{106}—D^5
(wherein R₁⁴² is a hydrogen atom or a group selected from the following group F)

0078 (3") —CONR¹⁴³R¹⁴⁴
(whence R¹⁴³ and R¹⁴⁴ are each independently a hydrogen atom, a C₁₋₆ alkyl group or a group selected from the following group F)

0079 (4") a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the following group A,

0080 (5") a C₂₋₆ alkenyl group optionally substituted by 1 to 3 substituents selected from the following group A,

0081 (6") a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from the following group B,

0082 (7") a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group B
(whence said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),

0083 (8") a C₅₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group B,

0084 (9") a C₆₋₁₄ aryl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from the following group B,

0085 (10") a heterocyclic C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from the following group B and

0086 (11") a C₅₋₁₀ cycloalkyl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from the following group B or
R¹³⁵ and R¹³⁶, or, R¹³⁸ and R¹³⁹ are bonded to each other, and optionally form, together with the carbon atom bonded thereto,

0087 (1") a C₅₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group B or

0088 (2") a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group B
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),

R¹³⁷ is

0089 (1") a hydrogen atom,

0090 (2") a carboxylic group,

0091 (3") a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the following group E,

0092 (4") a C₂₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the following group E,

0093 (5") a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from the following group E,

0094 (6") a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group E
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom) or

0095 (7") a C₅₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group E,

R¹⁴⁰ and R¹⁴¹ are each independently

0096 (1") a hydrogen atom or

0097 (2") a C₁₋₆ alkyl group,

L¹⁰⁰ is

0098 (1") a bond,

0099 (2") —CO—,

0100 (3") —CH₂O—,

0101 (4") —CH₃NH—,

0102 (5") —CH₃NHCO—,

0103 (6") a C₁₋₆ alkylene optionally substituted by hydroxyl group or

0104 (7") a C₂₋₆ alkenylene,

L¹⁰¹ and L¹⁰² are each independently

0105 (1") a bond,

0106 (2") —CO—,

0107 (3") a C₁₋₆ alkylene optionally substituted by hydroxyl group or

0108 (4") a C₂₋₆ alkenylene,

L¹⁰³ is

0109 (1") a bond or

0110 (2") a C₁₋₆ alkylene,

L¹⁰⁴ is a C₁₋₆ alkylene,

L¹⁰⁵ is

0111 (1") a bond or

0112 (2") a C₁₋₆ alkylene,

L¹⁰⁶ is

0113 (1") a bond,

0114 (2") a C₁₋₆ alkylene,

0115 (3") —NH—,

0116 (4") —NH—CH₂— or

0117 (5") —CH₂—CONH—,

ring D¹, ring D² and ring D³ are each independently

0118 (1") a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from the following group E,
(2') a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group E or

(3') a heterocycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group E

(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom))

(4) —COOR

(5) CO—D' or

(6) CO—D'—O—D'

(wherein ring D is a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group E

(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom)

ring D is a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from the following group E

R² may substitute at a substitutable position on carbon atom or nitrogen atom constituting Q and is

(1) a hydrogen atom,

(2) a group selected from the following group E,

(3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the following group E,

(4) a C₂₋₆ alkenyl group optionally substituted by 1 to 3 substituents selected from the following group E,

(5) L²—D'—L¹—D'

(6) L¹—D'

(7) L¹—CH₂—L¹—D'

(8) L¹—(CH₂)n—L¹—(CH₂)m—D'

(wherein L¹ and L² are each independently

(1') a bond,

(2') C₃₋₆ alkyne,

(3') C₂₋₆ alkenylene,

(4') —(CH₂)n—O—(CH₂)m—

(5') —(CH₂)n—S—(CH₂)m—

(6') —(CH₂)n—NR(1—L)—(CH₂)m—

(7') —(CH₂)n—CO—(CH₂)m—

(8') —(CH₂)n—CONR(1—L)—(CH₂)m—

(9') —(CH₂)n—NR(1—L)₂CO₂—(CH₂)m—

(10') —(CH₂)n—NR(1—L)₂CONR(1—L)—(CH₂)m—

(11') —(CH₂)n—NR(1—L)₂CO—(CH₂)m—

(12') —(CH₂)n—NR(1—L)₂SO₂—(CH₂)m—

(13') —(CH₂)n—SO₂—(CH₂)m—

(14') —(CH₂)n—SO₂NR(1—L)₂—(CH₂)m—

(15') —(CH₂)n—N⁺R¹⁻₂R²⁻₃—(CH₂)m—

(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom)
R³ is
(1) a hydrogen atom,
(2) a halogen atom,
(3) a C₃₋₆ alkanoyl group,
(4) a carboxyl group,
(5) a cyano group,
(6) a nitro group,
(7) a C₃₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the following group A,
(8) —OR¹⁰¹
(wherein R¹⁰¹ is a hydrogen atom or a group selected from the following group C),
(9) —NR¹⁰²R¹¹⁹
(wherein R¹⁰² and R¹¹⁹ are each independently a hydrogen atom, a C₃₋₆ alkanoyl group or a C₃₋₆ alkylsulfonyl group),
(10) —COOR¹⁰³
(wherein R¹⁰³ is a group selected from the following group C or a glucuronic acid residue),
(11) —CONR¹⁰⁴R¹⁰⁵
(wherein R¹⁰⁴ and R¹⁰⁵ are each independently a hydrogen atom, a hydroxyl group, a cyano group, a C₃₋₆ alkoxy group or a C₃₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the following group A),
(12) —SO₂R¹⁰⁶
(wherein R¹⁰⁶ is a hydroxyl group, an amino group, a C₃₋₆ alkyl group or a C₃₋₆ alkyamino group),
(13) —NHCOR¹⁰⁷
(wherein R¹⁰⁷ is an amino group or a C₃₋₆ alkyamino group),
(14) —C(==NR¹⁰₈)—NH₂
(wherein R¹⁰₈ is a hydrogen atom, a C₃₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the following group A, a hydroxyl group or a C₃₋₆ alkoxy group),
(15) —P(==O)(OR¹⁰⁹),
(wherein R¹⁰⁹ are each independently a hydrogen atom or a group selected from the following group C),
(16) —P(==O)(OR¹¹⁰)NR¹¹¹R¹¹²
(wherein R¹¹⁰, R¹¹¹ and R¹¹² are each independently a hydrogen atom or a group selected from the following group C),
(17) —CONHCO—R¹¹³
(wherein R¹¹³ is a group selected from the following group C),
(18) —CONHSO₂—R¹¹⁴
(wherein R¹¹⁴ is a group selected from the following group C),
(19) —SO₂NHCO—R¹¹⁵
(wherein R¹¹⁵ is a group selected from the following group C) or
(20) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group B
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),
R⁴ may substitute at a substitutable position on carbon atom or nitrogen atom constituting Q and each is independently
(1) a halogen atom,
(2) a C₃₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the following group A,
(3) —OR¹¹⁶
(wherein R¹¹⁶ is a hydrogen atom or a group selected from the following group C),
(4) —NR¹¹⁷R¹¹⁸
(wherein R¹¹⁷ and R¹¹⁸ are each independently a hydrogen atom, a C₃₋₆ alkanoyl group or a group selected from the following group C),
(5) a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from the following group B or
(6) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group B
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),
a is 0, 1 or 2.
R³ and R⁴ are each independently
(1) a hydrogen atom,
(2) a halogen atom,
(3) a C₃₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the following group A,
(4) —OR¹²⁰
(wherein R¹²⁰ is a hydrogen atom or a group selected from the following group C) or
(5) —NR¹²¹R¹²²
(wherein R¹²¹ and R¹²² are each independently a hydrogen atom, a C₃₋₆ alkanoyl group or a group selected from the following group C),
ring Cy is
(1) a C₅₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group B,
(2) a C₅₋₁₀ cycloalkenyl group optionally substituted by 1 to 5 substituents selected from the following group B or
(3) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group B
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),
X is
(1) a group selected from the following group D,

\[ \text{[0152]} \quad (2) \text{ a } C_{2-5} \text{ alkyl group optionally substituted by 1 to 3 substituents selected from the following group A or } \]

\[ \text{[0153]} \quad (3) \text{ a heterocyclic group comprising 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom, each } Z \text{ is independently } \]

\[ \text{[0154]} \quad (1') \text{ a } C_{6-14} \text{ aryl group, } \]
\[ \text{[0155]} \quad (2') \text{ a } C_{3-10} \text{ cycloalkyl group or } \]
\[ \text{[0156]} \quad (3') \text{ a heterocyclic group comprising 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom, each } Z \text{ is independently } \]

\[ \text{[0157]} \quad (1') \text{ a group selected from the following group D, } \]
\[ \text{[0158]} \quad (2') \text{ a } C_{6-14} \text{ aryl group optionally substituted by 1 to 5 substituents selected from the following group D, } \]
\[ \text{[0159]} \quad (3') \text{ a } C_{3-10} \text{ cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group D, } \]
\[ \text{[0160]} \quad (4') \text{ a } C_{6-14} \text{ aryl } C_{1-5} \text{ alkyl group optionally substituted by 1 to 5 substituents selected from the following group D, } \]

\[ \text{[0161]} \quad (5') \text{ a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group D (wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom) or } \]

\[ \text{[0162]} \quad (6') \text{ a heterocyclic } C_{1-5} \text{ alkyl group optionally substituted by 1 to 5 substituents selected from the following group D (wherein said heterocyclic cycle } C_{1-5} \text{ alkyl group is a } C_{1-5} \text{ alkyl group substituted by } \text{a heterocyclic group optionally substituted by 1 to 5 substituents selected from group D as defined above), } \]

\[ \text{[0163]} \quad \text{w is an integer of 1 to 3, } \]
\[ \text{Y is } \]

\[ \text{(a) } C_{1-6} \text{ alkyne, } \]
\[ \text{(b) } C_{2-6} \text{ alkenylene or } \]
\[ \text{(c) } -Y'\text{-}(CH}_{2m}\text{=}Y''\text{-}(CH}_{2n}\text{=} \]

\[ \text{[0164]} \quad \text{wherein m and n are each independently 0 or an integer of 1 to 6, } \]
\[ \text{[0165]} \quad \text{Y' and Y'' are each independently } \]

\[ \text{[0166]} \quad (1) \text{ a bond, } \]
\[ \text{[0167]} \quad (2) \text{ -O-, } \]
\[ \text{[0168]} \quad (3) \text{ -NR''-, } \]
\[ \text{[0169]} \quad (4) \text{ -S-, } \]
\[ \text{[0170]} \quad (5) \text{ -CO-, } \]
\[ \text{[0171]} \quad (6) \text{ -SO-, } \]
\[ \text{[0172]} \quad (7) \text{ -SO}_{2}-, \]
\[ \text{[0173]} \quad (8) \text{ -CO}_{2}-, \]
\[ \text{[0174]} \quad (9) \text{ -OCO-, } \]
\[ \text{[0175]} \quad (10) \text{ -CONR}-, \]
\[ \text{[0176]} \quad (11) \text{ -NR''CO-, } \]
\[ \text{[0177]} \quad (12) \text{ -SO}_{2}NR''-, \]
\[ \text{[0178]} \quad (13) \text{ -NR''SO}_{2}-, \]
\[ \text{[0179]} \quad (14) \text{ -NR''CO}_{2}-, \]
\[ \text{[0180]} \quad (15) \text{ -OCONR''-, } \]
\[ \text{[0181]} \quad (16) \text{ -NR''CO}_{2}-, \]
\[ \text{[0182]} \quad (17) \text{ -CR''R''- or } \]
\[ \text{[0183]} \quad (18) \text{ -CH}==\text{CH-} \]

\[ \text{[0184]} \quad \text{wherein } R'' \text{ is } \]

\[ \text{[0185]} \quad (1') \text{ a hydrogen atom, } \]
\[ \text{[0186]} \quad (2') \text{ a group selected from the following group C, } \]
\[ \text{[0187]} \quad (3') \text{ -}(	ext{CH}_{2})_{m}-\text{COOR''} \]
\[ \text{[0188]} \quad (4') \text{ -}(	ext{CH}_{2})_{m}-\text{CONR''} \]
\[ \text{[0189]} \quad (5') \text{ -}(	ext{CH}_{2})_{m}-\text{COR''} \]
\[ \text{[0190]} \quad (6') \text{ -}(	ext{CH}_{2})_{m}-\text{SO}_{2}R'' \]

\[ \text{[0191]} \quad \text{wherein } R'' \text{ is an integer of 1 to 6, } R'' \text{ and } R'' \text{ are each independently a hydrogen atom or a group selected from the following group C, } R'' \text{ is a group selected from the following group C, } R'' \text{ are each independently } \]
\[ \text{[0192]} \quad (1') \text{ a hydrogen atom, } \]
\[ \text{[0193]} \quad (2') \text{ a group selected from the following group F, } \]
\[ \text{[0194]} \quad (3') \text{ -}(	ext{CH}_{2})_{m}-\text{OR''} \]
\[ \text{[0195]} \quad (4') \text{ -}(	ext{CH}_{2})_{m}-\text{NHR''} \]
\[ \text{[0196]} \quad (5') \text{ -}(	ext{CH}_{2})_{m}-\text{PO} \]

\[ \text{[0197]} \quad \text{wherein } R'' \text{ is a group selected from the following group C, } R'' \text{ is a hydrogen atom, a } C_{1-6} \text{ alkyl group, a } C_{1-6} \text{ alkanoyl group, a } C_{6-14} \text{ aryl } C_{1-5} \text{ alkoxy group or a } C_{1-6} \text{ alkoxy group )}} \]

\[ \text{[0198]} \quad \text{wherein } R'' \text{ is a group selected from the following group C, } R'' \text{ is a hydrogen atom, a } C_{1-6} \text{ alkyl group, a } C_{1-6} \text{ alkanoyl group, a } C_{6-14} \text{ aryl } C_{1-5} \text{ alkoxy group or a } C_{1-6} \text{ alkoxy group )}} \]

\[ \text{[0199]} \quad \text{group A: } \]

\[ \text{(1) a halogen atom, } \]
\[ \text{(2) a } C_{1-6} \text{ alkoxy } C_{1-6} \text{ alkoxy group, } \]
\[ \text{(3) a cyano group, } \]
\[ \text{(4) -OR''} \]

\[ \text{[0200]} \quad \text{wherein } R'' \text{ is a group selected from the following group C, } R'' \text{ is a hydrogen atom, a } C_{1-6} \text{ alkyl group, a } C_{1-6} \text{ alkanoyl group, a } C_{6-14} \text{ aryl } C_{1-5} \text{ alkoxy group or a } C_{1-6} \text{ alkoxy group )}} \]

\[ \text{[0201]} \quad \text{group B: } \]

\[ \text{(1) a halogen atom, } \]
\[ \text{(2) a } C_{1-6} \text{ alkoxy } C_{1-6} \text{ alkoxy group, } \]
\[ \text{(3) a cyano group, } \]
\[ \text{(4) -OR''} \]
(5) —SR,R',
(6) —NR,R',
(7) —COOR,R',
(8) —CONR,R',
(9) —SO,H,
(10) —SO,NR,R',
(11) —NHCOR,R',
(12) —NHSO,R,R',
(13) —NHCOR,R',
(14) —COR,R',
(15) —N*R,R',

(wherein R and R' are each a hydrogen atom, a C-alkyl group or a benzyl group, R is a C-alkyl group and R' is a C-alkyl group)

[0196] group B:
(1) a halogen atom,
(2) a cyano group,
(3) a nitro group,
(4) a C1-6 alkyl group,
(5) a C2-6 alkyl group optionally substituted by carboxyl group,
(6) a halogenated C1-6 alkyl group,
(7) —(CH2)n—OR,.
(8) —(CH2)n—SR,.
(9) —(CH2)n—NR,.
(10) —(CH2)n—COOR,.
(11) —(CH2)n—CONR,.
(12) —(CH2)n—COR,.
(13) —(CH2)n—NR—COR,.
(14) —(CH2)n—NR—SO,R,.
(15) —(CH2)n—SO,R,.
(16) —(CH2)n—SO2NR,.
(17) —(CH2)n—CONR—SO,R,.
(18) —(CH2)n—SO2NR—COR,.
(19) —(CH2)n—NR—CONR,.
(20) —(CH2)n—CONR—CONR,.
(21) —O—(CH2)n—COOR.
(22) —CO—(CH2)n—R,.

(wherein R, R', and R'' are each independently a hydrogen atom or a C1-6 alkyl group, R is a C1-6 alkyl group, R' is a heterocyclic group and r is 0 or an integer of 1 to 6)

[0197] group C:
(1) a C1-6 alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
(2) a C6-14 aryl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,
(3) a C6-14 aryl C1-6 alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,
(4) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the aforementioned group B and
(5) a heterocyclic C1-6 alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B

[0198] group D:
(a) a hydrogen atom,
(b) a halogen atom,
(c) a cyano group,
(d) a nitro group,
(e) a C1-6 alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
(f) —(CH2)n—OR,.

(wherein R is
(1) a hydrogen atom,
(2) a group selected from the following group F,
(3) a C2-6 alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A or
(4) a C2-6 alkynyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,

hereinafter each t is independently 0 or an integer of 1 to 6,
(g) —(CH2)n—S(O),—R,.

(wherein R is
(1) a hydrogen atom or
(2) a group selected from the following group F,
q is 0, 1, 2 or 3,
(h) —(CH2)n—NR—R,.

(wherein R and R are each independently
(1) a hydrogen atom or
(2) a group selected from the following group F,
(i) —(CH2)n—COOR,.

(wherein R is
(1) a hydrogen atom or
(2) a group selected from the following group F,
(j) —(CH2)n—CONR,.

(wherein R and R are each independently
(1) a hydrogen atom,
(2) a hydroxyl group,
(3) a group selected from the following group F or
(4) a C1-6 alkoxy group,
(k) \(-\text{CH}_2\text{CO}\) 

wherein \(R^{28}\) is

(1) a hydrogen atom or

(2) a group selected from the following group F,

(l) \(-\text{CH}_2\text{NR}^\text{d10}\text{CO} \text{R}^{\text{d10}}\),

wherein \(R^{\text{d10}}\) is

(1) a hydrogen atom,

(2) a \(C_{1,6}\) alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A or

(3) a \(C_{1,6}\) alkanoyl group,

\(R^{\text{d10}}\) is

(1) an amino group,

(2) a \(C_{1,6}\) alkylamino group or

(3) a group selected from the following group F,

(m) \(-\text{CH}_2\text{NR}^\text{d11}\text{SO}_2 \text{R}^{\text{d12}}\),

wherein \(R^{\text{d11}}\) is

(1) a hydrogen atom,

(2) a \(C_{1,6}\) alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A or

(3) a \(C_{1,6}\) alkanoyl group,

\(R^{\text{d12}}\) is

(1) a hydrogen atom or

(2) a group selected from the following group F,

(n) \(-\text{CH}_2\text{SO}_2\text{NR}^\text{d13}\text{R}^{\text{d14}}\),

wherein \(R^{\text{d13}}\) and \(R^{\text{d14}}\) are each independently

(1) a hydrogen atom or

(2) a group selected from the following group F,

(o) \(-\text{CH}_2\text{CONR}^\text{d15}\text{SO}_2\text{R}^{\text{d16}}\),

wherein \(R^{\text{d15}}\) and \(R^{\text{d16}}\) are each independently

(1) a hydrogen atom or

(2) a group selected from the following group F,

(p) \(-\text{CH}_2\text{SO}_{2\text{NR}^\text{d17}}\text{COR}^{\text{d18}}\),

wherein \(R^{\text{d17}}\) is

(1) a hydrogen atom or

(2) a group selected from the following group F,

(q) \(-\text{CH}_2\text{NR}^{\text{d19}}\text{COOR}^{\text{d20}}\),

wherein \(R^{\text{d19}}\) and \(R^{\text{d20}}\) are each independently

(1) a hydrogen atom or

(2) a group selected from the following group F,

(r) \(-\text{CH}_2\text{NR}^{\text{d21}}\text{CONR}^{\text{d22}}\text{R}^{\text{d23}}\),

wherein \(R^{\text{d21}}\), \(R^{\text{d22}}\) and \(R^{\text{d23}}\) are each independently

(1) a hydrogen atom or

(2) a group selected from the following group F,

(s) \(-\text{CH}_2\text{C}(-\text{NR}^{\text{d24}})\text{NH}_2\),

wherein \(R^{\text{d24}}\) is

(1) a hydrogen atom,

(2) a hydroxyl group,

(3) a \(C_{1,6}\) alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A or

(4) \(C_{1,6}\) alkoxy group,

(t) \(-\text{CH}_2\text{O}\text{COR}^{\text{d25}}\),

wherein \(R^{\text{d25}}\) is

(1) an amino group,

(2) a \(C_{1,6}\) alkyamino group or

(3) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the aforementioned group B, \(p\) is 0 or an integer of 1 to 6,

(u) \(-\text{CH}_2\text{O}\text{COR}^{\text{d26}}\text{R}^{\text{d27}}\),

wherein \(R^{\text{d26}}\) and \(R^{\text{d27}}\) are each independently

(1) a hydrogen atom or

(2) a \(C_{1,6}\) alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A, \(p\) is 0 or an integer of 1 to 6,

(v) \(-\text{CH}_2\text{O}\text{COOR}^{\text{d28}}\),

wherein \(R^{\text{d28}}\) is

(1) a hydrogen atom or

(2) a group selected from the following group F, and

(w) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the aforementioned group B

(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom)

\[\text{[O199]}\text{ group E:}\]

(a) a halogen atom,

(b) a cyano group,

(c) a nitro group,

(d) an azido group,

(e) \(-\text{OP}(\equiv\text{O})(\text{OH})_2\),

(f) \(-\text{OR}^{\text{e1}}\),

wherein \(R^{\text{e1}}\) is

(1) a hydrogen atom,

(2) a group selected from the following group F,

(3) a \(C_{2,6}\) alkenyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A or

(4) \(C_{2,6}\) alkynyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
(g) \(-\text{SO}_2-\text{R}^{e2}\)
wherein \(\text{R}^{e2}\) is

(1) a hydrogen atom or
(2) a group selected from the following group F,
q is 0, 1, 2 or 3,
(h) \(-\text{NR}^{e3}\text{R}^{e4}\),
wherein \(\text{R}^{e3}\) and \(\text{R}^{e4}\) are each independently

(1) a hydrogen atom,
(2) a cyano group or
(3) a group selected from the following group F,
(i) \(-\text{COOR}^{e5}\),
wherein \(\text{R}^{e5}\) is

(1) a hydrogen atom or
(2) a hydroxyl group,
(3) a group selected from the following group F or
(4) a \(\text{C}_{1-6}\) alkoxy group,
(k) \(-\text{COR}^{e8}\),
wherein \(\text{R}^{e8}\) is a group selected from the following group F,
(l) \(-\text{NR}^{e9}\text{CO}-\text{R}^{e10}\),
wherein \(\text{R}^{e9}\) is

(1) a hydrogen atom,
(2) a \(\text{C}_{1-6}\) alkyl group or
(3) a \(\text{C}_{1-6}\) alkanoyl group,
\(\text{R}^{e10}\) is

(1) a hydrogen atom,
(2) an amino group,
(3) a \(\text{C}_{1-6}\) alkylamino group,
(4) a \(\text{C}_{2-6}\) alkenyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A or
(5) a group selected from the following group F,
(m) \(-\text{NR}^{e11}\text{SO}_2-\text{R}^{e12}\),
wherein \(\text{R}^{e11}\) is

(1) a hydrogen atom,
(2) a \(\text{C}_{1-6}\) alkyl group or
(3) a \(\text{C}_{1-6}\) alkanoyl group,
\(\text{R}^{e12}\) is

(1) a hydrogen atom or
(2) a group selected from the following group F,
(n) \(-\text{SO}_2-\text{NR}^{e13}\text{R}^{e14}\),
wherein \(\text{R}^{e13}\) and \(\text{R}^{e14}\) are each independently

(1) a hydrogen atom or
(2) a group selected from the following group F,
(o) \(-\text{CONR}^{e15}-\text{SO}_2\text{R}^{e16}\),
wherein \(\text{R}^{e15}\) and \(\text{R}^{e16}\) are each independently

(1) a hydrogen atom or
(2) a group selected from the following group F,
(p) \(-\text{SO}_2\text{NR}^{e17}-\text{COR}^{e18}\),
wherein \(\text{R}^{e17}\) is

(1) a hydrogen atom or
(2) a group selected from the following group F,
\(\text{R}^{e18}\) is a group selected from the following group F,
(q) \(-\text{NR}^{e19}-\text{COOR}^{e20}\),
wherein \(\text{R}^{e19}\) and \(\text{R}^{e20}\) are each independently

(1) a hydrogen atom or
(2) a group selected from the following group F,
(r) \(-\text{NR}^{e21}-\text{CONR}^{e22}\text{R}^{e23}\)
wherein \(\text{R}^{e21}\), \(\text{R}^{e22}\) and \(\text{R}^{e23}\) are each independently

(1) a hydrogen atom or
(2) a group selected from the following group F,
(s) \(-\text{NHCO}-\text{COOR}^{e24}\)
wherein \(\text{R}^{e24}\) is

(1) a hydrogen atom or
(2) a group selected from the following group F,
(t) \(-\text{NHCO}-\text{CONR}^{e25}\text{R}^{e26}\)
wherein \(\text{R}^{e25}\) and \(\text{R}^{e26}\) are each independently

(1) a hydrogen atom,
(2) a hydroxyl group or
(3) a group selected from the following group F,

(v) \(-\text{NH}-\text{COOR}^{e27}\)

(w) \(-\text{NH}-\text{COOR}^{e28}\)
(y) a C₅₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,
(z) a C₂₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,
(aa) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the aforementioned group B
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),
(bb) a C₂₋₁₀ cycloalkylidene group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,
(cc) a heterocycle ylidene group optionally substituted by 1 to 5 substituents selected from the aforementioned group B
(wherein said heterocycle ylidene group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),

when group E is a substituent on a C₅₋₁₄ aryl group, a C₂₋₁₀ cycloalkyl group or a heterocyclic group, it may be
(dd) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
(ee) a C₂₋₅ alkenyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
(ff) a C₂₋₆ alkynyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
(gg) C₁₋₆ alkylidene group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
(hh) a C₅₋₁₄ aryl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,
(ii) a C₂₋₁₀ cycloalkyl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,
or
(jj) a heterocycle C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B

[0210] group F:
(1) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
(2) a C₅₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,
(3) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the aforementioned group B
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),

(4) a C₅₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,
(5) a C₅₋₁₄ aryl C₅₋₁₆ alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,
(6) a heterocycle C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B
(wherein said heterocyclic group is a C₁₋₆ alkyl group substituted by "a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B" as defined above) and
(7) a C₅₋₁₀ cycloalkyl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B.

[0202] The compound of [1], wherein, in the formula [1],

\[ G_1 \cdots G_i \]

is N═C═C, or a pharmaceutically acceptable salt thereof.

[3] The compound of [1], wherein, in the formula [1], the moiety

\[ R^1, R^2, R^3, R^4 \]

is a fused ring selected from the group consisting of

\[ R^1, R^2, R^3, R^4 \]
[4] The compound of [3], wherein, in the formula [1], the moiety

[5] The compound of [4], wherein, in the formula [1], the moiety is a fused ring selected from the group consisting of

or a pharmaceutically acceptable salt thereof.

or a pharmaceutically acceptable salt thereof.
or a pharmaceutically acceptable salt thereof.

[6] The compound of [5], wherein, in the formula [1], the moiety

or a pharmaceutically acceptable salt thereof.

[7] The compound of [1], wherein G², G³ and G⁴ are carbon atoms,
or a pharmaceutically acceptable salt thereof.

[8] The compound of [1], wherein Q¹ is —O—, —NH—, —S— or —CONH—,
or a pharmaceutically acceptable salt thereof.

[9] The compound of [8], wherein Q¹ is —NH—, or a pharmaceutically acceptable salt thereof.

[10] The compound of [8], wherein b is an integer of 1 to 3, c is an integer of 1 to 3 and d is 0, or a pharmaceutically acceptable salt thereof.

[11] The compound of [1], wherein Q is —(CH₂)₂—O— or —(CH₂)₂—NH—, or a pharmaceutically acceptable salt thereof.

[12] The compound of [1], wherein R¹ is a carboxyl group or —CONR¹⁻¹², or a pharmaceutically acceptable salt thereof.

[13] The compound of [12], wherein R¹ is a carboxyl group, or a pharmaceutically acceptable salt thereof.

[14] The compound of [12], wherein R¹ is —CONR¹⁻¹², or a pharmaceutically acceptable salt thereof.

[15] The compound of [14], wherein R¹¹ is a hydrogen atom, and

R² is

——CR¹⁵⁵R¹⁵⁶L¹⁰⁰⁻¹³⁷,
——CR¹⁵⁵R¹⁵⁶L¹⁰¹⁻¹⁴⁰⁻¹³⁷,
——CR¹⁵⁵R¹⁵⁶L¹⁰²⁻¹⁴⁰⁻¹⁰³⁻¹⁰⁴⁻¹⁰⁵⁻¹⁰⁶—or

——CR¹⁵⁵R¹⁵⁶L¹⁰⁰⁻¹⁰³⁻¹⁰⁴⁻¹⁰⁵⁻¹⁰⁶—or

or a pharmaceutically acceptable salt thereof.

[16] The compound of [15], wherein R¹² is —CR¹⁵⁵R¹⁵⁶L¹⁰⁰⁻¹³⁷, or a pharmaceutically acceptable salt thereof.

[17] The compound of [16], wherein L¹⁰⁰ is a bond, and
R¹³⁷ is a C₆⁻aryl group optionally substituted by 1 to 5 substituents selected from group E or
a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),
or a pharmaceutically acceptable salt thereof.

[18] The compound of [17], wherein R¹³⁵ and R¹³⁶ are each independently a group selected from group G, or, R¹³⁵ and R¹³⁶ are bonded to each other, and form, together with the carbon atom bonded thereto, a C₆⁻cycloalkyl group optionally substituted by 1 to 5 substituents selected from group B, or a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B, or a pharmaceutically acceptable salt thereof.

[19] The compound of [16], wherein L¹⁰⁰ is methylene, and
R¹³⁷ is a C₆⁻aryl group optionally substituted by 1 to 5 substituents selected from group E or
a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),
or a pharmaceutically acceptable salt thereof.

[20] The compound of [19], wherein R¹³⁵ is a group selected from group G, and R¹³⁶ is a hydrogen atom, or a pharmaceutically acceptable salt thereof.

[21] The compound of [15], wherein R¹² is —CR¹⁵⁵R¹⁵⁶L¹⁰¹⁻¹⁴⁰⁻¹⁰³⁻¹⁰⁴⁻¹⁰⁵⁻¹⁰⁶, or a pharmaceutically acceptable salt thereof.

[22] The compound of [21], wherein L¹⁰¹ is a bond, or a pharmaceutically acceptable salt thereof.

[23] The compound of [22], wherein R¹³⁵ and R¹³⁶ are each independently a group selected from group G, or, R¹³⁵ and R¹³⁶ are bonded to each other, and form, together with the carbon atom bonded thereto, a C₃⁻cycloalkyl group
optionally substituted by 1 to 5 substituents selected from group B, or a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B, or a pharmaceutically acceptable salt thereof.

[24] The compound of [23], wherein R1\textsuperscript{40} is a hydrogen atom, and

R1\textsuperscript{37} is a C\textsubscript{6}-aryl group optionally substituted by 1 to 5 substituents selected from group E or

a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E

(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),
or a pharmaceutically acceptable salt thereof.

[25] The compound of [15], wherein R1\textsuperscript{12} is

\[
-\text{CR}^{38}\text{R}^{39}-\text{L}^{102}-\text{CONR}^{40}\text{L}^{101}-\text{D}^{1}\n\]
or a pharmaceutically acceptable salt thereof.

[26] The compound of [15], wherein R1\textsuperscript{12} is

\[
-\text{CR}^{38}\text{R}^{39}-\text{L}^{102}-\text{CONR}^{40}-\text{L}^{104}-\text{CONR}^{41}-\text{L}^{103}-\text{D}^{1}\n\]
or a pharmaceutically acceptable salt thereof.

[27] The compound of [25] or [26], wherein L1\textsuperscript{102} is a bond, or a pharmaceutically acceptable salt thereof.

[28] The compound of [27], wherein R1\textsuperscript{38} and R1\textsuperscript{39} are each independently a group selected from group G, or, R1\textsuperscript{38} and R1\textsuperscript{39} are bonded to each other, and form, together with the carbon atom bonded thereto, a C\textsubscript{3} to C\textsubscript{10} cycloalkyl group optionally substituted by 1 to 5 substituents selected from group B, or a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B, or a pharmaceutically acceptable salt thereof.

[29] The compound of [28], wherein L1\textsuperscript{102} is a bond, ring D\textsuperscript{1} is a C\textsubscript{6}-aryl group optionally substituted by 1 to 5 substituents selected from group E or

a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E

(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom), and

R1\textsuperscript{40} and R1\textsuperscript{41} are each independently a hydrogen atom, or a pharmaceutically acceptable salt thereof.

[30] The compound of [1], wherein R2\textsuperscript{2} is a hydrogen atom, a group selected from group E, a C\textsubscript{1}-alkyl group optionally substituted by 1 to 3 substituents selected from group E, or

\[
-\text{L}^{1}-\text{D}^{1}-\text{L}^{1}-\text{D}^{1} \quad \text{or} \quad -\text{L}^{1}-\text{D}^{1}\n\]

wherein each symbol is as defined in [1], or a pharmaceutically acceptable salt thereof.

[31] The compound of [30], wherein R2\textsuperscript{2} is a C\textsubscript{1}-alkyl group optionally substituted by 1 to 3 substituents selected from group E or

\[
-\text{L}^{1}-\text{D}^{1}\n\]

wherein each symbol is as defined in [1], or a pharmaceutically acceptable salt thereof.

[32] The compound of [31], wherein R2\textsuperscript{2} is

\[
-\text{L}^{1}-\text{D}^{1}\n\]

wherein each symbol is as defined in [1], or a pharmaceutically acceptable salt thereof.

[33] The compound of [30], wherein L\textsuperscript{1} and L\textsuperscript{2} are each independently a bond, a C\textsubscript{6}-aryl group, a CH3 group, a CH2 group, or a pharmaceutically acceptable salt thereof.

[35] The compound of [33], wherein u1 and v1 are each independently 0 or an integer of 1 to 3, or a pharmaceutically acceptable salt thereof.

[36] The compound of [30], wherein ring D\textsuperscript{1} and ring D\textsuperscript{2} are each independently a C\textsubscript{6}-aryl group optionally substituted by 1 to 5 substituents selected from group E or a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E, or a pharmaceutically acceptable salt thereof.

[37] The compound of [1], wherein R2\textsuperscript{2} is a hydrogen atom, a halogen atom, a C\textsubscript{1}-alkyl group optionally substituted by 1 to 3 substituents selected from group A or —OR\textsuperscript{101} (wherein R1\textsuperscript{101} is a hydrogen atom or a group selected from group C), or a pharmaceutically acceptable salt thereof.

[38] The compound of [1], wherein R2\textsuperscript{2} and R6\textsuperscript{2} are each independently a hydrogen atom, a halogen atom, a C\textsubscript{1}-alkyl group optionally substituted by 1 to 3 substituents selected from group A or —OR\textsuperscript{120} (wherein R1\textsuperscript{120} is a hydrogen atom or a group selected from group C), or a pharmaceutically acceptable salt thereof.

[39] The compound of [1], wherein ring A is benzene or a 5- or 6-membered heterocycle comprising 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom, or a pharmaceutically acceptable salt thereof.
[40] The compound of [39], wherein ring A is benzene, or a pharmaceutically acceptable salt thereof.

[41] The compound of [1], wherein ring Cy is a C₃₋₁₀ cycloalkyl group or a C₃₋₁₀ cycloalkenyl group, or a pharmaceutically acceptable salt thereof.

[42] The compound of [41], wherein ring Cy is a cyclohexyl group, or a pharmaceutically acceptable salt thereof.

[43] The compound of [1], wherein X is a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A, —(CH₂)ₗ—OR', —(CH₂)ₗ—S(O)ₗ—R', —(CH₂)ₗ—NR'R' or (CH₂)ₗ—NR₃₊R₄⁴, or

![I-A]

wherein each symbol is as defined in [1], or a pharmaceutically acceptable salt thereof.

[44] The compound of [43], wherein Y is —(CH₂)ₘ—OR —(CH₂)ₙ—OR' or —NR'R', wherein each symbol is as defined in [1], or a pharmaceutically acceptable salt thereof.

[45] The compound of [43], wherein Y is —O—CH₂— or —O—, or a pharmaceutically acceptable salt thereof.

[46] The compound of [43], wherein Y is —NR'R', wherein each symbol is as defined in [1], or a pharmaceutically acceptable salt thereof.

[47] The compound of [43], wherein ring B is a C₆₋₁₄ aryl group or a heterocyclic group comprising 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom, or a pharmaceutically acceptable salt thereof.

[48] The compound of [47], wherein ring B is a phenyl group, a pyridyl group, a pyrrolidinyl group, a piperazinyl group, a morpholinyl group, a azepanyl group, a 1,4-oxazepanyl group, an isoxazolyl group, a thiazolyl group or a 2-oxooxazolidinyl group, or a pharmaceutically acceptable salt thereof.

[49] The compound of [43], wherein Z is 1 to 3 substituents selected from

(1) a hydrogen atom,
(2) a halogen atom,
(3) a nitro group,
(4) a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group D,
(5) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from group D,
(6) a heterocyclic group optionally substituted by 1 to 5 substituents selected from group D,
(7) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
(8) —(CH₂)ₗ—OR'₉,
(9) —(CH₂)ₗ—S(O)ₗ—R',
(10) —(CH₂)ₗ—NR₃₊R₄⁴,
(11) —(CH₂)ₗ—COOR'₉,
(12) —(CH₂)ₗ—CONR₃₊₅¹,Rₗ²,
(13) —(CH₂)ₗ—COR₉,
(14) —(CH₂)ₗ—NR₃₊CO₉,Rₗ¹₋₅₁,
(15) —(CH₂)ₗ—NR₃₊SO₉,Rₗ¹₋₅₂ and
(16) —(CH₂)ₗ—NR₃₊COOR₉

wherein each symbol is as defined in [1], or a pharmaceutically acceptable salt thereof.

[50] The compound of [1], which is represented by the following formula [I-A], or a pharmaceutically acceptable salt thereof:

![I-A]

wherein X' is a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A or —OR', and other symbols are as defined in [1].

[51] The compound of [1], which is represented by the following formula [I-B], or a pharmaceutically acceptable salt thereof:

![I-B]

wherein Q'² is —O— or —NH—, and other symbols are as defined in [1].

[52] The compound of [1], which is represented by the following formula [I-C], or a pharmaceutically acceptable salt thereof:

![I-C]
wherein \( Q^{2} \) is \(-\text{O}^{-} \) or \(-\text{NR}^{2}^{-} \), \( X \) is a hydrogen atom, a halogen atom, a \( C_{1-6} \) alkyl group optionally substituted by 1 to 3 substituents selected from group A or \(-\text{OR}^{3} \), and other symbols are as defined in [1].

[53] A pharmaceutical composition comprising a compound of any of [1] to [52], or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[54] A hepatitis C virus polymerase inhibitor comprising a compound of any of [1] to [52] or a pharmaceutically acceptable salt thereof as an active ingredient.


[56] A therapeutic agent for hepatitis C, which comprises a compound of any of [1] to [52] or a pharmaceutically acceptable salt thereof as an active ingredient.

[57] A therapeutic agent for hepatitis C, which comprises (a) a hepatitis C virus polymerase inhibitor of [54] and (b) at least one pharmaceutical agent selected from the group consisting of a different antiviral agent, an antiinflammatory agent and an immunostimulant.

[58] A therapeutic agent for hepatitis C, which comprises (a) a hepatitis C virus polymerase inhibitor of [54] and (b) interferon.

[59] An anti-hepatitis C virus agent, which comprises (a) an antihepatitis C virus agent of [55] and (b) at least one pharmaceutical agent selected from the group consisting of a different antiviral agent, an antiinflammatory agent and an immunostimulant.

[60] An anti-hepatitis C virus agent comprising (a) an antihepatitis C virus agent of [55] and (b) interferon.

[61] A pharmaceutical composition comprising (a) a compound of any of [1] to [52] or a pharmaceutically acceptable salt thereof, and (b) at least one pharmaceutical agent selected from the group consisting of a different antiviral agent, an antiinflammatory agent and an immunostimulant.

[62] A pharmaceutical composition comprising (a) a compound of any of [1] to [52] or a pharmaceutically acceptable salt thereof, and (b) interferon.

[63] Use of a compound of any of [1] to [52] or a pharmaceutically acceptable salt thereof for the production of a pharmaceutical agent for treating hepatitis C.


[66] The method of [65], further comprising administering an effective amount of at least one pharmaceutical agent selected from the group consisting of a different antiviral agent, an antiinflammatory agent and an immunostimulant to the mammal.

[67] The method of [65], further comprising administering an effective amount of interferon to the mammal.

[68] A method for inhibiting hepatitis C virus polymerase, which comprises administering an effective amount of a compound of any of [1] to [52] or a pharmaceutically acceptable salt thereof to a mammal.

[69] The method of [68], further comprising administering an effective amount of at least one pharmaceutical agent selected from the group consisting of a different antiviral agent, an antiinflammatory agent and an immunostimulant to the mammal.

[70] The method of [68], further comprising administering an effective amount of interferon to the mammal.

**DETAILED DESCRIPTION OF THE INVENTION**

[0203] The definitions of respective substituents and moieties used in the present specification are as follows.

[0204] The “halogen atom” is a fluorine atom, chlorine atom, bromine atom or iodine atom, preferably fluorine atom, chlorine atom or bromine atom.

[0205] The “C\(_{1-6}\) alkyl group” is a linear or branched chain alkyl group having 1 to 6 carbon atoms, preferably a linear or branched chain alkyl group having 1 to 4 carbon atoms. Specifically, methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, tert-pentyl group, hexyl group and the like can be mentioned.

[0206] The “C\(_{2-6}\) alkenyl group” is a linear or branched chain alkenyl group having 2 to 6 carbon atoms. Specifically, vinyl group, allyl group, 1-propenyl group, isopropenyl group, 1-butynyl group, 2-butenyl group, 1,3-butadienyl group, 2-isopentenyl group, 3-isohexenyl group, 4-methyl-3-pentenyl group and the like can be mentioned.

[0207] The “C\(_{2-6}\) alkynyl group” is a linear or branched chain alkenyl group having 2 to 6 carbon atoms. Specifically, ethynyl group, 1-propynyl group, 2-propynyl group, 3-butylnyl group and the like can be mentioned.

[0208] The “halogenated C\(_{1-6}\) alkyl group” is the above-defined “C\(_{1-6}\) alkyl group” substituted by the above-defined “halogen atom”, which is preferably a halogenated alkyl group wherein the alkyl moiety is a linear or branched chain alkyl group having 1 to 4 carbon atoms. Specifically, fluoromethyl group, difluoromethyl group, trifluoromethyl group, bromomethyl group, chloromethyl group, 1,2-dichloroethyl group, 2,2-dichloroethyl group, 2,2,2-trifluoroethyl group and the like can be mentioned.

[0209] The “C\(_{1-6}\) alkenylene” is a straight chain alkenylene having 1 to 6 carbon atoms, and methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and the like can be mentioned.

[0210] The “C\(_{2-6}\) alkenylene” is a straight chain alkenylene having 2 to 6 carbon atoms, and vinylene, propylene, 1-butenylene, 1,3-butadiene and the like can be mentioned.

[0211] The “C\(_{1-6}\) alkoxy group” is an alkyl-oxy group wherein the alkyl moiety is the above-defined “C\(_{1-6}\) alkyl group”, preferably an alkoxy group wherein the alkyl moiety is a linear or branched chain alkyl group having 1 to 4 carbon atoms. Specifically, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group and the like can be mentioned.
group, tert-butyloxy group, pentyloxy group, hexyloxy group and the like can be mentioned.

[0212] The “C<sub>n</sub>-alkoxy C<sub>m</sub>-alkoxy group” is an alkyl-oxy-alkyl-oxy group wherein the above-defined “C<sub>n</sub>-alkoxy group” is substituted by the above-defined “C<sub>m</sub>-alkoxy group”, preferably that wherein the alkyl moiety is a linear or branched chain alkyl group having 1 to 4 carbon atoms. Specifically, methoxymethoxy group, ethoxymethoxy group, 1-(methoxy)ethoxy group, 2-(methoxy)ethoxy group, methoxypropoxy group, isopropoxyethoxy group and the like can be mentioned.

[0213] The “C<sub>n</sub>-alkanoyl group” is an alkyl-carbonyl group wherein the alkyl moiety is the above-defined “C<sub>n</sub>-alkyl group”, preferably an alkyl-carbonyl group wherein the alkyl moiety is a linear or branched chain alkyl group having 1 to 4 carbon atoms. Specifically, acetyl group, propionyl group, butyryl group, isobutyryl group, pivaloyl group and the like can be mentioned.

[0214] The “C<sub>1</sub>-alkoxy carbonyl group” is an alkyl-oxy-carbonyl group wherein the carbonyl group is the above-defined “C<sub>1</sub>-alkoxy group”, preferably an alkyl-oxy-carbonyl group wherein the alkyl moiety is a linear or branched chain alkyl group having 1 to 4 carbon atoms. Specifically, methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, butyloxycarbonyl group, isobutyloxycarbonyl group, tert-butyloxycarbonyl group, pentyloxycarbonyl group, hexyloxycarbonyl group and the like can be mentioned.

[0215] The “C<sub>1</sub>-alkylamino group” is an alkyl-amino group or a dialkyl-amino group wherein the alkyl moiety is the above-defined “C<sub>1</sub>-alkyl group”, preferably an alkyl-amino group or a dialkyl-amino group wherein the alkyl moiety is a linear or branched chain alkyl group having 1 to 4 carbon atoms. Specifically, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, hexylamino group, dimethylamino group, diethylamino group, N-ethyl-N-methylamino group, N-isobutyl-N-isopropylamino group and the like can be mentioned.

[0216] The “C<sub>1</sub>-alkanoylamino group” is an alkyl-carbonyl-amino group wherein the alkyl moiety is the above-defined “C<sub>1</sub>-alkanoyl group”, preferably an alkyl-carbonyl-amino group wherein the alkyl moiety is a linear or branched chain alkyl group having 1 to 4 carbon atoms. Specifically, acetylaminogroup, propionylamino group, butyrylamino group, isobutyrylamino group, pivaloylamino group and the like can be mentioned.

[0217] The “C<sub>1</sub>-alkylsulfonyl group” is an alkyl-sulfonyl group wherein the alkyl moiety is the above-defined “C<sub>1</sub>-alkyl group”, preferably an alkyl-sulfonyl group wherein the alkyl moiety is a linear or branched chain alkyl group having 1 to 4 carbon atoms. Specifically, methanesulfonyl group, ethylsulfonyl group, propylsulfonyl group, isopropylsulfonyl group, butylsulfonyl group, isobutylsulfonyl group, tert-butyalsulfonyl group, pentylsulfonyl group, hexylsulfonyl group and the like can be mentioned.

[0218] The “C<sub>6</sub>-aryl group” is an aromatic hydrocarbon group having 6 to 14 carbon atoms. Specifically, phenyl group, naphthyl group, anthryl group, indenyl group, azulenyl group, fluorenyl group, phenanthryl group and the like can be mentioned, with preference given to phenyl group.

[0219] The C<sub>2</sub>-<sub>10</sub> cycloalkyl group is a saturated cycloalkyl group having 3 to 10, preferably 3 to 8, more preferably 5 to 7, carbon atoms, and includes monocyclic fused ring. Specifically, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, adamantyl group and the like can be mentioned.

[0220] The C<sub>2</sub>-<sub>10</sub> cycloalkenyl group is a cycloalkenyl group having 3 to 10, preferably 3 to 8, more preferably 5 to 7, carbon atoms, and includes at least one, preferably 1 or 2, double bonds. Specifically, cyclopentenyl group, cyclohexenyl group, cycloheptenyl group, 1,2-cyclohexadien-1-yl group, 1,2-cyclohexadien-1-yl group, cycloheptenyl group, cyclooctenyl group and the like can be mentioned. It does not include aryl group such as phenyl group and completely saturated cycloalkyl group.

[0221] The C<sub>3</sub>-<sub>14</sub> aryl C<sub>1</sub>-<sub>6</sub> alkoxy carbonyl group is an aryl-alkyl-oxy-carbonyl group wherein the alkyl moiety is the above-defined “C<sub>n</sub>-alkyl group”, and the aryl moiety is the above-defined “C<sub>1</sub>-<sub>14</sub> aryl group”. Preferred is an aryl-alkyl-oxy-carbonyl group wherein the alkyl moiety is a straight or branched chain alkyl group having 1 to 4 carbon atoms and the aryl moiety is a phenyl group. Specifically, benzoxycarbonyl group, phenethoxycarbonyl group, 3-phenylpropoxycarbonyl group, 2-phenylpropoxycarbonyl group, 4-phenylbutoxycarbonyl group and the like can be mentioned.

[0222] The “bond” means a direct connection. For example, when O<sup>L</sup> is a “bond” in —O-L<sup>L</sup>-Ph, it means —O-Ph.

[0223] The “glucuronic acid residue” is a group remaining after removing any hydroxyl group from glucuronic acid, and preferably substitutes at the 1-position of β-D-glucuronic acid.

[0224] The “heterocyclic group” and “heterocyclic group comprising 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom” has, as a ring-constituting atom, 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom besides carbon atom, wherein the number of atom constituting the ring is 3 to 14, includes saturated ring and unsaturated ring, monocyclic and fused ring, and may be a spiro ring.

[0225] As the monocyclic heterocyclic group, specifically, pyridyl group, pyrazinyl group, pyrimidinyl group, pyridazinyl group, 1,3,5-triazinyl group, pyrrol group, pyrazol group, imidazolyl group, triazolyl group, 1,2,4-triazolyl group, tetrazolyl group, thienyl group, furyl group, oxazolyl group, isoxazolyl group, thiadiazolyl group, isothiazolyl group, oxadiazolyl group, 1,3,4-oxadiazole group, 1,2,5-oxadiazole group, thiadiazolyl group, 1,2,4-thiadiazolyl group, 1,3,4-thiadiazolyl group, 1,2,5-thiadiazolyl group, pyrrolyl group, pyridinyl group, 4,5-dihydro-1H-imidazolyl group, 4,5-dihydro-1H-imidazolyl group, 4,5-dihydro-1H-imidazolyl group, 4,5-dihydro-1H-imidazolyl group, azetidinyl group, piperidyl group, piperazinyl group, 1,2,3,6-tetrahydropyridyl group, morpholinyl group, thiomorpholinyl group,
3,6-dihydro-2H-pyranyl group, tetrahydropyranyl group, tetrahydrofuranyl group, azepanyl group (e.g., azepan-1-yl group), azocanyl group (e.g., azocan-1-yl group), azonanyl group (e.g., azonan-1-yl group), 1,4-diazepanyl group (e.g., 1,4-diazepan-1-yl group), 1,4-oxazepanyl group (e.g., 1,4-oxazepan-4-yl group) and the like can be mentioned.

[0226] This heterocyclic group includes the groups represented by the following formulas.

\[
\begin{align*}
&\text{\begin{tikzpicture}
\draw (0,0) circle (1cm);
\fill (0,0) circle (0.1cm);
\node at (0,0) {N};
\end{tikzpicture}}\quad \text{\begin{tikzpicture}
\draw (0,0) circle (1cm);
\fill (0,0) circle (0.1cm);
\node at (0,0) {N};
\end{tikzpicture}}
\end{align*}
\]

wherein \( \text{E}^1 \) is an oxygen atom, a sulfur atom or NH, \( \text{E}^2 \) is an oxygen atom, \( \text{CH}_2 \) or NH, \( \text{E}^3 \) is an oxygen atom or a sulfur atom, wherein \( i \) is an integer of 1 to 3, \( h \) and \( h' \) are the same or different and each is an integer of 1 to 3.

[0227] Specifically,

\[
\begin{align*}
&\text{\begin{tikzpicture}
\draw (0,0) circle (1cm);
\fill (0,0) circle (0.1cm);
\node at (0,0) {N};
\end{tikzpicture}}\quad \text{\begin{tikzpicture}
\draw (0,0) circle (1cm);
\fill (0,0) circle (0.1cm);
\node at (0,0) {N};
\end{tikzpicture}}
\end{align*}
\]
and the like can be mentioned.

[0228] As a fused heterocyclic group, specifically, quinolyl group, isoquinolyl group, quinazolinyl group, quinoxalinyll group, phthalazinyl group, cinnolinyl group, naphthyridinyl group, 1,2,3,4-tetrahydroquinolinyl group, 5,6,7,8-tetrahydroquinolinyl group, 1,2,3,4-tetrahydroisoquinolinyl group, 5,6,7,8-tetrahydroisoquinolinyl group, indolyl group, benzimidazolyl group, 2,3-dihydrobenzimidazolyl group, 2,3-dihydro-2-oxobenzimidazolyl group, indolinyll group, isoindolinyl group, octahydroindolyl group, octahydroindinyl group, benzofuranyl group, benzothienyl group, benzoxazolyl group, benzothiazolyl group, 3,4-dihydro-2H-benzof[1,4]oxazinyl group, 3-oxo-3,4-dihydro-2H-benzof[1,4]oxazinyl group, octahydrocyclopenta[c]pyrrolyl group, 2-oxo-2H-cromenyl group, benzo[1,3]dioxanoyl group, 4-oxo-1H-quinolinyl group, 2-oxohexahydrothieno[3,4-d]imidazolyl group, 7-azabicyclo[2.2.1]heptyl group.

[0229] As a Spiro heterocyclic group, specifically,

wherein h" is an integer of 1 to 6

and the like can be mentioned.

[0230] The “5- or 6-membered heterocycle comprising 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom” is a 5-membered or 6-membered saturated or unsaturated ring containing G°, which contains, besides carbon atom, 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom, wherein G° is a nitrogen atom or a carbon atom, and a broken line in ring A is a single bond or a double bond.

[0231] Preferably, it is a heterocycle containing 1 or 2, more preferably 1, heteroatom selected from oxygen atom, nitrogen atom and sulfur atom, besides carbon atom, wherein the heteroatom is preferably a nitrogen atom.

[0232] As the ring A, specifically, benzene, cyclopentane, cyclohexane, cyclopentene, cyclohexene, pyridine, pyrazine, pyrimidine, pyridazine, 1,3,5-triazine, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiophene, furan, oxazole, isoxazole, thiazole, isothiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 2,3-dihydro-1H-pyrrrole, 2,5-dihydro-1H-pyrrrole, pyrrolidine, imidazolidine, piperidine, pipirazine, morpholine, thiomorpholine, tetrahydropyran, oxazolidine, 1,2,3,4-tetrahydropyridine, 1,2,3,6-tetrahydropyridine.
and the like can be mentioned.

[0233] As the mode of binding of the

and the like can be mentioned.

[0234] The “group A” means the substituent groups of the following (1) to (15).

(R^1 and R^2 are each independently a hydrogen atom, the above-defined “C_{1-6} alkyl group” or a benzyl group, R^3 is the above-defined “C_{1-6} alkyl group” and R^4 is the above-defined “C_{1-6} alkyl group”)

(1) the above-defined “halogen atom”,
(2) the above-defined “C_{1-6} alkoxy C_{1-6} alkoxy group”,
(3) a cyano group,
(4) —OR^2 (e.g., hydroxy group, methoxy group, ethoxy group, isopropoxy group, tert-butoxy group, benzyl oxy group etc.),
(5) —SR^2 (e.g., mercapto group, methylsulfanyl group etc.),
(6) —NR^2R^3 (e.g., amino group, methylamino group, ethylamino group, isopropylamino group, dimethylamino group, diethylamino group, disopropylamino group, di-tert-butylamino group, N-ethyl-N-methylamino group etc.),
(7) —COOR^2 (e.g., carboxyl group, methoxycarbonyl group, ethoxycarbonyl group, isopropylcarbonyl group, tert-butoxy carbonyl group etc.),

[0235] (8) —CONR^2R^3 (e.g., carbamoyl group, methylcarbamoyl group, ethylcarbamoyl group, isopropylcarbamoyl group, dimethylcarbamoyl group, diethylcarbamoyl group, diisopropylcarbamoyl group, di-tert-butylcarbamoyl group, N-ethyl-N-methylcarbamoyl group etc.),
(9) —SO_3H,

[0236] (10) —SO_2NR^2R^3 (e.g., sulfamoyl group, methylsulfamoyl group, ethylsulfamoyl group, isopropylsulfamoyl group, dimethylsulfamoyl group, diethylsulfamoyl group, diisopropylsulfamoyl group, di-tert-buty1sulfamoyl group, N-ethyl-N-methylsulfamoyl group etc.),
(11) —NHCOR^2 (e.g., formylamino group, acetylamino group, propionylamino group, isobutyrylamino group, piv- aloylamino group etc.).
(12) — NH$_2$SO$_3$R$^{55}$ (e.g., methanesulfonylamino group, ethylsulfonylamino group, isopropylsulfonylamino group, tert-butylsulfonylamino group etc.),

(13) — NHCO$_2$R$^{54}$ (e.g., tert-butoxycarbonylamino group etc.),

(14) — COR$^{51}$ (e.g., formyl group, acetyl group, propionyl group, isobutyryl group, pivaloyl group etc.) and

(15) — N$^+$R$^{51}$R$^{52}$R$^{53}$ (e.g., trimethylammonio group, triethylammonio group etc.).

[0237] The “group B” means the substituent groups of the following (1) to (22).

[0238] (the following R$^{51}$, R$^{52}$ and R$^{54}$ are each independently a hydrogen atom or the above-defined “C$_{1-6}$ alkyl group”, R$^{53}$ is the above-defined “C$_{1-6}$ alkyl group”, R$^{55}$ is the above-defined “heterocyclic group” and r is 0 or an integer of 1 to 6)

(1) the above-defined “halogen atom”;

(2) a cyano group,

(3) a nitro group,

(4) the above-defined “C$_{1-6}$ alkyl group”,

[0239] (5) the above-defined “C$_{2-6}$ alkenyl group” optionally substituted by carboxyl group (e.g., vinyl group, allyl group, 1-propenyl group, isopropenyl group, 1-butenyl group, 2-butenyl group, 1,3-butadienyl group, 2-isopentenyl group, 3-isohexenyl group, 4-methyl-3-pentenyl group, 2-carboxyethyl group etc.),

(6) the above-defined “halogenated C$_{1-6}$ alkyl group”,

(7) — (CH$_2$)$_3$-OR$^{51}$ (e.g., hydroxyl group, methoxy group, ethoxy group, isopropoxy group, tert-butoxy group, hydroxymethyl group, methoxymethyl group, 2-(methoxymethyl) group etc.),

(8) — (CH$_2$)$_3$-SR$^{51}$ (e.g., mercapto group, methylsulfanyl group, mercaptomethyl group, 2-(methylsulfanyl)ethyl group etc.),

[0240] (9) — (CH$_2$)$_3$-NR$^{51}$R$^{52}$ (e.g., amino group, methylamino group, ethylamino group, isopropylamino group, dimethylamino group, diethylamino group, disopropylamino group, di-tert-butylamino group, N-ethyl-N-methylamino group, dimethoxymethyl group, 2-(methylamino)ethyl group etc.),

(10) — (CH$_2$)$_3$-COOR$^{51}$ (e.g., carboxyl group, methoxy carbonyl group, ethoxycarbonyl group, isopropoxy carbonyl group, tert-butoxycarbonyl group, carboxymethyl group, 2-(carboxyethyl) group etc.),

[0241] (11) — (CH$_2$)$_3$-CONR$^{51}$R$^{52}$ (e.g., carbamoyl group, methylcarbamoyl group, ethylcarbamoyl group, isopropylcarbamoyl group, dimethylcarbamoyl group, diethylcarbamoyl group, di-tert-butyldiaminogroup, N-ethyl-N-methylcarbamoyl group, carboxamidomethyl group, dimethylaminocarbamoylmethyl group, 2-(methylicarbamoyl)ethyl group etc.),

(12) — (CH$_2$)$_3$-COR$^{51}$ (e.g., formyl group, acetyl group, propionyl group, isobutyryl group, pivaloyl group, acetyl methyl group, 2-pivaloyl ethyl group etc.),

[0242] (13) — (CH$_2$)$_3$-NR$^{51}$-COR$^{52}$ (e.g., formy lamino group, propionylamino group, isobutyrylamino group, pivaloylamino group, N-ethyl-N-methylamino group, acetylaminomethyl group, 2-isobutyryl ethyl group etc.),

[0243] (14) — (CH$_2$)$_3$-NR$^{51}$-SO$_2$R$^{53}$ (e.g., methanesulfonylamino group, ethylsulfonylamino group, isopropylsulfonylamino group, tert-butylsulfonylamino group, N-ethyl-N-methanesulfonylamino group, methanesulfonylaminomethyl group, 2-(tert-butylsulfonyl)ethyl group etc.),

(15) — (CH$_2$)$_3$-SO$_2$R$^{53}$ (e.g., methanesulfonyl group, ethylsulfonyl group, tert-butylsulfonyl group, methanesulfonylmethyl group, 2-(ethylsulfonyl)ethyl group etc.),

[0244] (16) — (CH$_2$)$_3$-SO$_2$NR$^{51}$R$^{52}$ (e.g., sulfamoyl group, methylsulfinamoyl group, ethylsulfinamoyl group, isopropysulfinamoyl group, dimethylsulfinamoyl group, diethylsulfinamoyl group, di-isopropylsulfinamoyl group, di-tert-butylsulfinamoyl group, N-ethyl-N-methylsulfinamoyl group, sulfinamoylmethyl group, 2-(methylsulfinamoyl)ethyl group etc.),

[0245] (17) — (CH$_2$)$_3$-CONR$^{51}$-SO$_2$R$^{53}$ (e.g., methanesulfinycarbamoyl group, ethylsulfinycarbamoyl group, isopropylsulfinycarbamoyl group, tert-butylsulfinycarbamoyl group, N-ethyl-N-methanesulfinycarbamoyl group, methanesulfinycarbamoylmethyl group, 2-(ethylsulfinycarbamoyl)ethyl group etc.),

[0246] (18) — (CH$_2$)$_3$-SO$_2$NR$^{51}$-COR$^{52}$ (e.g., acetylsulfinamoyl group, propionylsulfinamoyl group, isobutyrylsulfinamoyl group, pivaloylsulfinamoyl group, N-acetyl-N-methylsulfinamoyl group, acetylaminosulfinamoylmethyl group, 2-(pivaloylsulfinamoyl)ethyl group etc.),

[0247] (19) — (CH$_2$)$_3$-NR$^{51}$-COOR$^{53}$ (e.g., methoxy carbamino group, ethoxycarbonylamino group, isopropylcarbonylamino group, tert-butoxycarbonylamino group, methoxycarbonylamino methyl group, 2-(tert-butoxycarbamino)ethyl group etc.),

[0248] (20) — (CH$_2$)$_3$-NR$^{51}$-CONR$^{52}$R$^{54}$ (e.g., ureido group, 3-methylureido group, 3-ethylureido group, 3-isopropylureido group, 3,3-dimethylureido group, 3,3-diisopropylureido group, 3,3-di-tert-butylureido group, 3-ethyl-3-methylureido group, 1,3-dimethylureido group, trimethylureido group, ureidomethyl group, 2-(3,3-dimethylureido)ethyl group),

(21) — O—(CH$_2$)$_3$-COOR$^{53}$ (e.g., carboxymethoxy group, 2-carboxyethoxymethyl group, 3-carboxypropoxy group, 4-carboxybutoxy group, 5-carboxypentoxyl group, methoxycarbonylmethoxy group, 2-ethoxycarbonyl ethoxymethyl group etc.) and

[0222] — CO—(CH$_2$)$_3$-R$^{55}$ (e.g., 1-oxo-5-(2-oXOoxheXyhydrOimino)3,4-dimiazol-6-yl)pentyl group etc.).

[0249] The “C$_{1-6}$ alkyl group optionally substituted by 1 to 3 substituents selected from group A” is a group wherein the above-defined “C$_{1-6}$ alkyl group” is optionally substituted by 1 to 3 substituents selected from the above-defined “group A”, which includes non-substituted alkyl group.

[0250] Specifically, methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-
butyl group, tert-butyl group, pentyl group, isopentyl group, tert-pentyl group, neopentyl group, 1-ethylpropl group, hexyl group, trifluoromethyl group, hydroxymethyl group, 2-hydroxyethyl group, 3-hydroxypropyl group, 4-hydroxybutyl group, 1-hydroxy-1-methylthyl group, 1-hydroxypropan-2-yl group, 1,3-dihydroxypropan-2-yl group, 1-hy-
droxy-2-methylpropan-2-yl group, carboxymethyl group, ethoxycarbonylmethyl group, 2-carboxyethyl group, meth-
oxymethyl group, methoxymethyl group, ethoxymethyl group, ethoxycarbonylmethyl group, ethoxycarbonyl-
methyl group, 2-ethoxycarbonylmethyl group, 2-dimethylaminomethyl group, carboxamomethyl group, cyclo-
alkylamomethyl group, sulfamoylmethyl group, 2-sulfamoylmethyl group, methylsulfamoylmethyl group and the like can be mentioned.

[0258] Specifically, vinyl group, allyl group, 1-propenyl group, isopropenyl group, 1-butenyl group, 2-butenyl group, 1,3-butadienyl group, 2-isopentenyl group, 3-isohexenyl group, 4-methyl-3-pentenyl group, 2-carboxyethenyl group and the like can be mentioned.

[0259] The “C_{3-10} cycloalkyl group optionally substituted by 1 to 5 substituents selected from group B” is the above-defined “C_{3-10} cycloalkyl group” optionally substituted by 1 to 5 substituents selected from the above-defined “group B”, which includes non-substituted cycloalkenyl group.

[0259] Specifically, cyclopropenyl group, cyclobutenyl group, cyclopentenyl group, cyclopen
tadienyl group, cyclohexenyl group (cyclohex-1-enyl group, cyclohex-2-enyl group), cyclohex-3-enyl group, 3-methylcyclohex-3-enyl group, 3-methylcyclohex-3-enyl group, 5-acetylaminocyclohex-3-enyl group, 2,4-cyclohexadien-1-yl group, 2,5-cyclohexadien-1-yl group, cycloheptenyl group and cyclooctenyl group and the like can be mentioned.

[0261] The “heterocyclic group optionally substituted by 1 to 5 substituents selected from group B” is the above-defined “heterocyclic group” optionally substituted by 1 to 5 substituents selected from the above-defined “group B”, which includes non-substituted heterocyclic group.

[0262] Specifically, 2-pyrindyl group, 3-pyrindyl group, 4-pyridyl group, 3-fluoropyridin-4-yl group, 3-chloropyridin-4-yl group, 4-chloropyridin-3-yl group, pyrazinyl group, pyrimidinyl group, pyridazinyl group, 1,3,5-triazinyl group, pyrrolyl group, pyrazolyl group, imidazolyl group, 1,2,4-
triazolyl group, tetrazolyl group, 2-thienyl group, 3-thienyl group, furyl group, oxazolyl group, 2-methylthiazol-4-yl group, isoxazolyl group, isothiazolyl group, 3-thiazolyl group, 2-methylthiazol-4-yl group, 2,5-dimethylthiazol-4-yl group, 2,4-dimethylthiazol-5-yl group, isothiazolyl group, thiadiazolyl group, pyr
rolinyl group, pyridinyl group, 3-hydroxyprolidinyl group, imidazolidinyl group, azetidinyl group, piperidyl group, 3-hydroxypropenidino group, 4-hydroxypropenidino group, 3,4-dihydroxypropenidino group, 4-methoxyprop
dino group, 4-carboxypropenidino group, 4-hydroxymethyl
pyrpidinidino group, 2,2,6,6-tetramethyl-4-hydroxypropenidino group, N-
methylpyrpidinidino-4-yl group, N-(2-butoxybarylopyrpidinidino-4-yl group, N-acetylpiperidin-4-yl group, N-methylsulfonylpir
peridin-4-yl group, N-methylpiperazinyl group, 4-methylsulfonylpir
peridin-4-yl group, N-methylsulfonylpiperazinyl group, morpholinyl group, thiomorpholinyl group, 1-oxothiomorpholin-4-yl group, 1,1-dioxoorthiomorpholin-4-yl group, tetrahydropryna
yl group, tetrahydrofuranyl group, azepanyl group, azoca
nyl group, azonanoyl group, 1,4-diazepanoyl group, 1,4-ox
azepanoyl group, quinolyl group, isoquinolyl group, quinazolinyl group, quinoxalinyl group, phthalazinyl group, cinnolinyl group, naphthridinyl group, 1,2,3,4-tetrahydroqu
quinol group, 5,6,7,8-tetrahydroquinolinyl group, 1,2,3,4-
tetrahydroisoquinolinyl group, 5,6,7,8-tetrahydroisoquinolinyl group, indolyl group, benzimidazolyl group, indoliny
l group, isoindolinyl group, octahydroindolyl group, octah
drosoindolyl group, benzoquinanyl group, benzothienyl group, benzoxazolyl group, benzoazolyl group, octahy
drocyclopenta[c]pyrrolyl group,
and the like can be mentioned.

[0263] For ring Cy, preferable "heterocyclic group optionally substituted by 1 to 5 substituents selected from group B" is

wherein E' is an oxygen atom, a sulfur atom, CH2 or NH, wherein R1 to R5 is a hydrogen atom or a C1-C4 alkyl group, and e and e' are each independently an integer of 1 to 3.

[0264] Specifically, pyrrolidinyl group, imidazolidinyl group, piperidyl group, piperazinyl group, morpholinyl group, thiomorpholinyl group, tetrahydropyranyl group, tetrahydrothiopyranyl group, 1-oxotetrahydrothiopyranyl group, 1,1-dioxotetrahydrothiopyranyl group and the like can be mentioned.

[0265] The "C6-C14 aryl C1-C4 alkyl group optionally substituted by 1 to 5 substituents selected from group B" is the
above-defined “C₃₋₁₀ alkyl group” substituted by the above-defined “C₃₋₁₀ aryl group optionally substituted by 1 to 5 substituents selected from group B”.

[0266] Specifically, benzyl group, 1-naphthylmethyl group, 2-naphthylmethyl group, phenethyl group, 3-phenylpropyl group, 2-phenylpropyl group, 3-fluorobenzyl group, 4-fluorobenzyl group, 3,5-dichlorobenzyl group, 4-chlorobenzyl group, 2,4-dichlorobenzyl group, 3,5-dichlorobenzyl group, pentafluorobenzyl group, 4-methylbenzyl group, 4-tert-butybenzyl group, 2-trifluoromethylbenzyl group, 4-trifluoromethylbenzyl group, 4-nitrobenzyl group, 4-cyanobenzyl group, 4-acetylbenezyl group, 4-carboxybenzyl group, 4-carbamoylbenzyl group, 4-amino benzyl group, 4-dimethylaminobenzyl group, 4-acetylaminobenzyl group, 4-(methyloxoyl)aminobenzyl group, 4-methoxybenzyl group, 3,4,5-trimethoxybenzyl group, 4-methylthiobenzyl group, 4-methylylfoxybenzyl group, 4-aminosulfonylbenzyl group, 3-nitro-4-methoxybenzyl group, 4-nitro-3-methoxybenzyl group and the like can be mentioned.

[0267] The “heterocyclic C₃₋₅ alkyl group optionally substituted by 1 to 5 substituents selected from group B” is the above-defined “C₃₋₅ alkyl group” selected from the above-defined “heterocyclic group optionally substituted by 1 to 5 substituents selected from group B”.

[0268] Specifically, 2-pyridylmethyl group, 3-pyridinylethyl group, 2-chloropyridin-4-ylmethyl group, 4-pyridinylethyl group, pyrrolylmethyl group, imidazolylmethyl group, 2-thienylmethyl group, 3-thienylmethyl group, 2-furanyl group, 2-oxazolylmethyl group, 5-isoxazolylmethyl group, 2-methylloxazol-4-ylmethyl group, 2-thiazolylmethyl group, 4-thiazolylmethyl group, 5-thiazolylmethyl group, 2-methylthiazol-4-ylmethyl group, 2-methylthiazol-5-ylmethyl group, 2,5-dimethyloxazol-4-ylmethyl group, 4-methylthiazol-2-ylmethyl group, 2,4-dimethyloxazol-5-ylmethyl group, 2-isoxazolylmethyl group, 2-pyrrolinylmethyl group, pyrrolidinylmethyl group, piperidinylmethyl group, 4-piperidinylmethyl group, 1-methylpyperidin-4-ylmethyl group, 4-hydroxyperiperonidinomethyl group, 3-hydroxyprolidinylmethyl group, 2-(4-hydroxyperiperdino) ethyl group, 1-(tert-butoxybenzylperiperdino-4-ylmethyl group, 1-acetylpiperidin-4-ylmethyl group, 1-methyloxoylperiperdin-4-ylmethyl group, piprazinylmethyl group, morpholinylmethyl group, thiomorpholinylmethyl group, 1-tetralinylmethyl group, 2-quinolinylmethyl group, 1-isouquinolinylmethyl group and the like can be mentioned.

[0269] The “C₃₋₁₀ cycloalkylidene group optionally substituted by 1 to 5 substituents selected from group B” is the above-defined “C₃₋₅ alkyl group” substituted by the above-defined “C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from group B”.

[0270] Specifically, cyclopropylmethyl group, cyclobutylmethyl group, cyclopentylmethyl group, cyclohexylmethyl group, 2-(cyclopentyl)ethyl group, 2-(cyclohexyl)ethyl group, cycloheptenylmethyl group, 2-methylocycloheptenyl group, 3-methylocyclohexylmethyl group, 4-methylocyclohexylmethyl group, 3,5-dimethylocyclohexylmethyl group, 4,4-dimethylocyclohexylmethyl group, 3,5-dimethylocyclohexylmethyl group, 4-tert-butylocyclohexylmethyl group, 4-hydroxylocyclohexylmethyl group, 4-methylocyclohexylmethyl group, 2,3,4,5,6-pentafluorocyclohexylmethyl group, 1-adamantylmethyl group and the like can be mentioned.

[0271] The “C₃₋₁₀ cycloalkylidene group optionally substituted by 1 to 5 substituents selected from group B)” is such group wherein C₃₋₁₀ cycloalkylidene group is optionally substituted by 1 to 5 substituents selected from the above-defined “group B”, which includes non-substituted cycloalkylidene group.

[0272] Specifically, cyclopropylene group, cyclobutylene group, cyclohexylene group, cycloheptylene group, 4-fluorocyclohexylene group, 2-methylocyclohexylene group, 3-methylocyclohexylene group, 4-methylocyclohexylene group, 4-ethylcyclohexylene group, 4,4-dimethylocyclohexylene group, 3,5-dimethylocyclohexylene group, 4,4-dimethylocyclohexylene group, 3,5-dimethylocyclohexylene group, 4-tert-butylocyclohexylene group, 4-hydroxylocyclohexylene group, 4-methoxylocyclohexylene group, 4-methoxycarbonylocyclohexylene group, 2,3,4,5,6-pentafluorocyclohexylene group and the like can be mentioned.

[0273] In addition, a group wherein the cyclopentenyldiene group or cyclohexyldiene group is substituted by fluorine atom, chlorine atom, bromine atom, nitro group, methyl group, ethyl group, isopropyl group, tert-butyl group, carbonyl group, methoxy carbonyl group, acetyl group, trifluoromethyl group, hydroxymethyl group, methoxymethyl group, 2-carboxyethyl group, methoxy group, carbamoyl group, methylthio group, dimethylaminocarbonyl group, methyloxoyl group or acetylamino group can be mentioned.

[0274] For group E for R₂, it is preferably a cyclohexyldiene group.

[0275] The “heterocyclic ylidene group optionally substituted by 1 to 5 substituents selected from group B” is such group wherein the heterocyclic ylidene group is optionally substituted by 1 to 5 substituents selected from the above-defined “group B”, which includes non-substituted heterocycle ylidene group.

[0276] The heterocyclic ylidene group contains, as ring constituting atom, 1 to 4 heteroatom selected from oxygen atom, nitrogen atom and sulfur atom, wherein the number of atom constituting the ring is 3 to 14, which includes saturated ring and unsaturated ring, monocycle and fused ring.

[0277] As the “heterocycle ylidene group optionally substituted by 1 to 5 substituents selected from group B”, specifically, dihydrofuran-3-ylidene group, pyrrolidin-3-ylidene group, tetrahydrofuran-4-ylidene group, piperidin-3-ylidene group, piperidin-4-ylidene group, 1-methympyperidin-4-ylidene group, 1-ethylperiperdin-4-ylidene group, 1-isopropilperiperdin-4-ylidene group, 1-tert-butylpiperidin-4-ylidene group, 1-acetylpiperidin-4-ylidene group, 1-methylsulfonilperiperdin-4-ylidene group, 1-methoxybenzylperiperdin-4-ylidene group, 1-tetralindioxybenzylperiperdin-4-ylidene group, 1,3-dihydro-1H-indolin-4-ylidene group, 4-oxocyclohexyldiene group and the like can be mentioned.

[0278] For group E for R₂, it is preferably 1-methylpyperidin-4-ylidene group, 1-ethylperiperdin-4-ylidene group, 1-acetylpiperidin-4-ylidene group, 1-methanesulfonilperiperdin-4-ylidene group, 1-methoxybenzylperiperdin-4-ylidene group, 1,3-dihydro-1H-indolin-4-ylidene group, 4-oxocyclohexyldiene group and the like can be mentioned.

[0279] The “C₃₋₅ alkylidene group optionally substituted by 1 to 3 substituents selected from group A” is such group
wherein a linear or branched chain having 1 to 6 carbon atoms, preferably having 1 to 4 carbon atoms, preferably a branched chain alkylidene group, is optionally substituted by 1 to 3 substituents selected from the above-defined "group A", which includes non-substituted alkylidene group.

[0280] Specifically, methylidene group, ethyldiene group, propyldiene group, isopropyldiene group, butyldiene group, pentyldiene group, dimethylaminomethyldiene group, methoxy carbonylimethyldiene group, 2-methoxyethylidene group, diaminomethyldiene group and the like can be mentioned.

[0281] For group E for R², it is preferably an isopropyldiene group.

[0282] The "group C" means the substituent groups of the following (1) to (5).

(1) the above-defined "C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A”,
(2) the above-defined “C₅₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group B”;
(3) the above-defined “C₅₋₁₄ aryl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group B”;
(4) the above-defined “heterocyclic group optionally substituted by 1 to 5 substituents selected from group B” and
(5) the above-defined “heterocycle C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group B”.

[0283] The "group F" means the substituent groups of the following (1) to (7).

(1) the above-defined “C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A”,
(2) the above-defined “C₅₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group B”,
(3) the above-defined “heterocyclic group optionally substituted by 1 to 5 substituents selected from group B”,
(4) the above-defined “C₄₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from group B”,
(5) the above-defined “C₅₋₁₄ aryl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group B”,
(6) the above-defined “heterocycle C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group B” and
(7) the above-defined “C₄₋₁₀ cycloalkyl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group B”.

[0284] The “group D’” means the substituent groups of the following (a) to (w).

(in the following, each t independently means 0 or an integer of 1 to 6)
(a) a hydrogen atom,
(b) the above-defined “halogen atom”,
(c) a cyano group,
(d) a nitro group,
(e) the above-defined “C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A”,
(f) \((\text{CH}_2)_n - \text{OR}^t\), wherein \(\text{R}^t\) is
   (1) a hydrogen atom,
   (2) the above-defined “group selected from group F”,
   (3) the above-defined “C₂₋₆ alkenyl group optionally substituted by 1 to 3 substituents selected from group A” or
   (4) the above-defined “C₃₋₆ alkylnyl group optionally substituted by 1 to 3 substituents selected from group A”,
   (e) substituent exemplified for “—(CH₂)₃—OR₃^m” in group B, trithiophenemethyl group, methoxythiophenemethyl, phenoxy group, benzyloxy group, 4-pyridyldimethyl group, 4-carboxybenzyl group, vinyl group, ethyl, propyl group, etc.)
   (f) \((\text{CH}_2)_n - \text{Si(O)}(\text{OR})^t\), wherein \(\text{R}^t\) is
   (1) a hydrogen atom or
   (2) the above-defined “group selected from group F”,
   (g) \((\text{CH}_2)_n - \text{NR}^t\), wherein \(\text{R}^t\) is each independently
   (1) a hydrogen atom or
   (2) the above-defined “group selected from group F”,
   (h) \((\text{CH}_2)_n - \text{NR}^t\text{R}^t\), wherein \(\text{R}^t\) and \(\text{R}^t\) are each independently
   (1) a hydrogen atom or
   (2) the above-defined “group selected from group F”,
   (i) \((\text{CH}_2)_n - \text{COR}^t\), wherein \(\text{R}^t\) is
   (1) a hydrogen atom or
   (2) a hydroxyl group,
   (3) the above-defined “group selected from group F” or
   (4) the above-defined “C₁₋₆ alkoxy group”, (e.g., substituent exemplified for “—(CH₂)ₙ—CONR²(OR)²”, in group B, hydroxycarbonyl group, methoxycarbonyl group, phenylcarbamoyl group, benzylcarbamoyl group,
2-morpholinoethylcarbamoyl group, 2-(dimethylamino)ethylcarbamoyl group, methoxymethylcarbamoyl group etc.

(k) —(CH₂)₂—COR³¹

[0290] wherein R³⁸ is the above-defined “group selected from group F”, (e.g., substituent exemplified for “—(CH₂)₅COR³¹” in group B, trifluoroacetyl group, methoxycarbonyl group, hydroxymethyl group, benzyl group, phenylacetyl group, 3-(dimethylamino)propionyl group, 3-morpholinopropanoyl group etc.)

(l) —(CH₂)₁—NR⁶¹SO₂—R⁶¹²

wherein R⁶¹⁰ is

(1) a hydrogen atom,

(2) the above-defined “C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A” or

(3) the above-defined “C₁₋₆ alkanoyl group”,

(1) an amino group,

(2) the above-defined “C₁₋₆ alkylamino group” or

[0291] (3) the above-defined “group selected from group F”, (e.g., substituent exemplified for “—(CH₂)₅—NR⁶¹—COR³²” in group B, uracil group, 3-methylureido group, 3-ethylureido group, 3-isopropylureido group, 3,3-dimethylureido group, 3,3-diethylureido group, 3,3-diisopropylureido group, 3,3-di-tert-butylureido group, 3-ethyl-3-methylureido group, 1,3-dimethylureido group, trimethylureido group, 2-(3,3-dimethylureido)ethyl group, benzoylamo group, phenylacetamido group, trifluoroacetamido group, methylnitromethylenamido group, N-acetyl-N-methylamino group, N-isopropyl-N-pivaloylamino group, dimethylacetamido group, N-(dimethylaminocarbonyl)-N-methylamino group, morpholinoacetamido group, N-methyl-N-(morpholinoacetamido) group etc.)

(m) —(CH₂)₁—NR⁶¹¹SO₂—R⁶¹²

wherein R⁶¹¹ is

(1) a hydrogen atom,

(2) the above-defined “C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A” or

(3) the above-defined “C₁₋₆ alkanoyl group”,

R⁶¹² is

(1) a hydrogen atom or

[0292] (2) the above-defined “group selected from group F”, (e.g., substituent exemplified for “—(CH₂)₅—NR⁶¹—SO₂R³¹²” in group B, trifluoromethylsulfonylamino group, phenylsulfonylamino group, benzylsulfonylamino group, 2-(dimethylamino)ethylsulfonylamino group, 2-morpholinoethylsulfonylamino group, 2-acetyl-N-methanesulfonylamino group, N-benzyl-N-methanesulfonylamino group etc.)

(n) —(CH₂)₁—SO₂—NR⁶¹³R⁶¹⁴

wherein R⁶¹³ and R⁶¹⁴ are each independently

(1) a hydrogen atom or

[0293] (2) the above-defined “group selected from group F”, (e.g., substituent exemplified for “—(CH₂)₅—SO₂NR³¹⁵R³¹⁶— in group B, trifluoromethylsulfonylamino group, 2-(dimethylamino)ethylsulfonylamino group, phenylsulfonylamino group, benzylsulfonylamino group, 2-morpholinoethylsulfonylamino group etc.)

(o) —(CH₂)₁—CONR³¹⁵—SO₂R³¹⁶

wherein R³¹⁵ and R³¹⁶ are each independently

(1) a hydrogen atom or
(t) \(-(CH_2)_n-\text{O}-(CH_2)_n-\text{COR}^{225}\),
wherein \(R^{225}\) is
(1) an amino group,
(2) the above-defined “\(C_{1-6}\) alkylamino group” or
(3) the above-defined “heterocyclic group optionally substituted by 1 to 5 substituents selected from group B”,

\[\text{p} \geq 0 \text{ or an integer of 1 to 6 (e.g., carbamoyl-methoxy group, methylcarbamoylmethoxy group, 2-(dimethylcarbamoyl)ethoxy group, 2-(pyridin-2-yl)-2-oxoethoxy group, 2-piperidin-1-yl-2-oxoethoxy group, 2-piperazin-1-yl-2-oxoethoxy group, 2-pyridolin-1-yl-2-oxoethoxy group, 2-morpholin-4-yl-2-oxoethoxy group etc.)}\]

wherein \(R^{226}\) and \(R^{227}\) are each independently
(1) a hydrogen atom or
(2) the above-defined “\(C_{1-6}\) alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A”;

\[\text{p} \geq 0 \text{ or an integer of 1 to 6, (e.g., 2-(hydroxyethylamino)ethoxy group, 2-(2-aminoethoxyamino)ethoxy group etc.)}\]

\[(u) -\text{(CH}_2\text{)}_n-\text{O}-(\text{CH}_2\text{)}_n-\text{NR}^{226}\text{R}^{227},\]

wherein \(R^{226}\) and \(R^{227}\) are each independently
(1) a hydrogen atom or
(2) the above-defined “group selected from group F”, (e.g., amino group, ethylamino group, isopropylamino group, dimethylamino group, diethylamino group, disopropylamino group, di-tert-butylamino group, N-ethyl-N-methylamino group, phenylamino group, benzylamino group, methoxymethylamino group, N-ethyl-N-(carbamoyl)methylamino group, N-ethyl-N-[2- (acetyl)ethyl]amino group, N-[2-amino-2-(dimethyl- carbamoyl)ethyl]-N-ethylamino group, N,N-bis(amino-ethyl)amino group etc.)

\[(i) -\text{COOR}^{28}\]

wherein \(R^{28}\) is
(1) a hydrogen atom or
(2) a cyano group or

\[(k) -\text{COR}^{28}\]

wherein \(R^{28}\) is
(1) a hydrogen atom or
(2) a hydroxyl group,

(3) the above-defined “group selected from group F” or

\[(j) -\text{CONR}^{28}\text{R}^{27},\]

wherein \(R^{28}\) and \(R^{27}\) are each independently
(1) a hydrogen atom,
(2) a hydroxyl group,

(3) the above-defined “group selected from group F” or

\[(g) -\text{S(O)}_{\text{p}}-\text{R}^{22},\]

wherein \(R^{22}\) is
(1) a hydrogen atom or
(2) the above-defined “group selected from group F”,

\[(f) -\text{OR}^{31}\]

wherein \(R^{31}\) is
(1) a hydrogen atom,
(2) the above-defined “group selected from group F”,
(3) the above-defined “\(C_{3-6}\) alkynyl group optionally substituted by 1 to 3 substituents selected from group A”, (e.g., hydroxyl group, methoxy group, ethoxy group, isopropoxy group, tert-butyl group, trifluoromethoxy group, methoxymethoxy group, phenox group, benzoxyl group, 4-pyridinmethoxy group, 4-carboxybenzoxyl group, viynyl group, ethynyloxy group etc.)

\[(e) -\text{OP(=O)(OH)}_{\text{2}},\]

\[(d) -\text{azido group},\]

(3) the above-defined “\(C_{3-6}\) alkynyl group optionally substituted by 1 to 3 substituents selected from group A” or

\[(b) -\text{azido group},\]

(2) the above-defined “\(C_{3-6}\) alkynyl group optionally substituted by 1 to 3 substituents selected from group A” or

\[(a) -\text{halogen atom},\]

(1) a hydrogen atom,

group, phenylacetyl group, 3-(dimethylamino)propionyl group, 3-morpholinopropionyl group etc.)

(l) —NR²⁰⁰CO—R²¹⁰,

wherein R²⁰⁰ is

(1) a hydrogen atom,
(2) the above-defined “C₁₋₆ alkyl group” or
(3) the above-defined “C₁₋₆ alkanoyl group”,
R²¹⁰ is

(1) a hydrogen atom,
(2) an amino group,
(3) the above-defined “C₁₋₆ alkylamino group”,
(4) the above-defined “C₂₋₆ alkenyl group optionally substituted by 1 to 3 substituents selected from group A” or

(m) —NR²¹¹SO₂—R²¹²,

wherein R²¹¹ is

(1) a hydrogen atom,
(2) the above-defined “C₁₋₆ alkyl group” or
(3) the above-defined “C₁₋₆ alkanoyl group”, R²¹² is

(1) a hydrogen atom or

(n) —SO₂—NR²¹³R²¹⁴,

wherein R²¹³ and R²¹⁴ are each independently

(1) a hydrogen atom or

(o) —CONR²¹⁵—SO₂R²¹⁶,

wherein R²¹⁵ and R²¹⁶ are each independently

(1) a hydrogen atom or

(0) (2) the above-defined “group selected from group F”, (e.g., methanesulfonylcarbamoyl group, ethylsulfonylcarbamoyl group, isopropylsulfonylcarbamoyl group, tert-butylsulfonylcarbamoyl group, N-methyl-N-(methanesulfonyl)carbamoyl group, trifluoromethylsulfonylcarbamoyl group, 2-(dimethylamino)ethylsulfonylcarbamoyl group, phenylsulfonylcarbamoyl group, benzylsulfonylcarbamoyl group, 2-morpholinooethylsulfonylcarbamoyl group, N-benzyl-N-(methanesulfonyl)carbamoyl group etc.)

(p) —SO₂NR²¹⁷—COR²¹⁸,

wherein R²¹⁷ is

(1) a hydrogen atom or

(q) —NR²¹⁹—COOR²²⁰,

wherein R²¹⁹ and R²²⁰ are each independently

(1) a hydrogen atom or

(r) —NR²²¹—CONR²²²R²²³,

wherein R²²¹, R²²² and R²²³ are each independently

(1) a hydrogen atom or

(s) —NHCO—COOR²²⁴,

wherein R²²⁴ is

(1) a hydrogen atom or

(t) —NHCO—CONR²²⁵R²²⁶,

wherein R²²⁵ and R²²⁶ are each independently

(1) a hydrogen atom,
(2) a hydroxyl group or

(2) the above-defined “group selected from group F”, (e.g., ureido group, 3-methylureido group, 3-ethylureido group, 3-isopropylureido group, 3,3-dimethylureido group, 3,3-dimethylureido group, 3,3-diisopropylureido group, 3,3-di-tert-butylureido group, 3-ethyl-3-methylureido group, trimethylureido group, benzoylamino group, phenacylamino group, 3-phenacylamino group, N-acetyl-N-methylamino group, N-isopropyl-N-pivaloylamino group, 3-carboxy-3-butenoylamino group etc.)
(3) the above-defined “group selected from group F”, (e.g., —NHCO—CONH₂, —NHCO—CONHCH₃, —NHCO—CONHOH etc.)

(y) the above-defined “C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group B”,

(z) the above-defined “C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from group B”,

(aa) the above-defined “heterocyclic group optionally substituted by 1 to 5 substituents selected from group B”,

(bb) the above-defined “C₃₋₁₀ cycloalkylidene group optionally substituted by 1 to 5 substituents selected from group B”, and

(cc) the above-defined “heterocyclic ylidene group optionally substituted by 1 to 5 substituents selected from group B”,

when group E is a substituent on a C₆₋₁₄ aryl group, a C₃₋₁₀ cycloalkyl group or a heterocyclic group, it may be

(dd) the above-defined “C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A”,

(ee) the above-defined “C₂₋₆ alkenyl group optionally substituted by 1 to 3 substituents selected from group A”,

(ff) the above-defined “C₂₋₆ alkynyl group optionally substituted by 1 to 3 substituents selected from group A”,

(gg) the above-defined “C₁₋₆ alkylidene group optionally substituted by 1 to 3 substituents selected from group A”,

(hh) the above-defined “C₆₋₁₄ aryl C₁₋₆ alky group optionally substituted by 1 to 5 substituents selected from group B”,

(i) the above-defined “C₆₋₁₀ cycloalkyl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group B”, or

(jj) the above-defined “heterocycle C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group B”.

[0313] The “C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group D)” is the above-defined “C₆₋₁₄ aryl group” optionally substituted by 1 to 5 substituents selected from the above-defined “group D”, which includes non-substituted aryl group.

[0314] Specifically, phenyl group, naphthyl group, anthryl group, indenyl group, azulenyl group, fluorenyl group, phenanthryl group, 3-fluorophenyl group, 4-fluorophenyl group, 3-chlorophenyl group, 4-chlorophenyl group, 2,4-dichlorophenyl group, 3,5-dichlorophenyl group, 4-bromophenyl group, 4-nitrophenyl group, pentafluorophenyl group, 4-methylphenyl group, 4-tert-butylphenyl group, 2-trifluoromethylphenyl group, 4-trifluoromethylphenyl group, 4-(hydroxy)methylphenyl group, 4-(methoxymethyl)phenyl group, 4-(2-carboxethyl)phenyl group, 3-carboxyphenyl group, 4-carboxyphenyl group, 4-methoxyphenyl group, 3,4,5-trimethoxyphenyl group, 4-carbamoylphenyl group, 4-methylthiophenyl group, 4-(dimethylaminocarbonyl)phenyl group, 4-methylsulfonylphenyl group, 4-acetylamino phenyl group, 4-cyanophenyl group, 4-acetylphenyl group, 4-aminophenyl group, 4-dimethylaminophenyl group, 4-(methylsulfonylamino)phenyl group, 4-methylsulfonylphenyl group, 4-aminosulfonylphenyl group, 3-nitro-4-methoxyphenyl group, 4-nitro-3-methoxyphenyl group, 4-(tetrazol-5-yl)phenyl group and the like can be mentioned.

[0315] The “C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from group D)” is the above-defined “C₃₋₁₀ cycloalkyl group” optionally substituted by 1 to 5 substituents selected from the above-defined “group D”, which includes non-substituted cycloalkyl group.

[0316] Specifically, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, 4-fluorocyclohexyl group, 2-methylcyclohexyl group, 3-methylcyclohexyl group, 4-methylcyclohexyl group, 4,4-dimethylcyclohexyl group, 3,5-dimethylcyclohexyl group, 4-tert-butylcyclohexyl group, 4-hydroxycyclohexyl group, 4-methoxycyclohexyl group, 2,3,4,5,6-pentafluorocyclohexyl group, 1-adamantylmethyl group and the like can be mentioned.

[0317] In addition, such group wherein cyclopentyl group or cyclohexyl group is substituted by fluorine atom, chlorine atom, bromine atom, nitro group, methyl group, tert-butyl group, carboxyl group, trifluoromethyl group, hydroxethyl group, methoxymethyl group, 2-carboxyethyl group, methoxy group, carbamoyl group, methylthio group, dimethylaminocarbonyl group, methysulfonamyl group or acetylamino group can be mentioned.

[0318] The “heterocyclic group optionally substituted by 1 to 5 substituents selected from group D)” is the above-defined “heterocyclic group” optionally substituted by 1 to 5 substituents selected from the above-defined “group D”, which includes non-substituted heterocyclic group.

[0319] Specifically, 2-pyridyl group, 3-pyridyl group, 4-pyridyl group, 3-fluoropyridin-4-yl group, 3-chloropyridin-4-yl group, 4-chloropyridin-3-yl group, pyrazinyl group, pyrimidinyl group, pyridazinyl group, 1,3,5-triazinyl group,
pyrrolyl group, pyrazolyl group, imidazolyl group, 1,2,4-triazolyl group, tetrazolyl group, 2-thienyl group, 3-thienyl group, furyl group, oxazolyl group, 2-methyloxazol-4-yl group, isoxazolyl group, thiazolyl group, 2-methylthiazol-4-yl group, 2,5-dimethylthiazol-4-yl group, 2,4-dimethylthiazol-5-yl group, isothiazolyl group, thiadiazolyl group, pyrrolinyl group, pyrrolidinyl group, imidazolidinyl group, piperidyl group, N-methylpiperidin-4-yl group, N-(tert-butoxycarbonyl)piperidin-4-yl group, N-acetyl-piperidin-4-yl group, N-methylsulfonylpiperidin-4-yl group, piperazinyl group, 4-ethylpiperazin-1-yl group, 4-methanesulfonylpiperazin-1-yl group, 4-dimethylcarbamoylpiperazin-1-yl group, morpholinyl group, thiomorpholinyl group, tetrahydropranyl group, quinolyl group, isoquinolyl group, quinazolinyl group, quinoxalinyl group, phthalazinyl group, ciinoliny group, napthyridinyl group, 5,6,7,8-tetrahydroquinolyl group, indolyl group, benzimidazolyl group, indoliny group, benzofuranyl group, benzothienyl group, benzoxazolyl group, benzothiazolyl group.

[0320] In addition, such group wherein the 3, 4, 5 or 6-position of 2-pyridyl group, 2, 4, 5 or 6-position of 3-pyridyl group, 2, 3, 5 or 6-position of 4-pyridyl group, 3, 4 or 5-position of 2-thienyl group, and 2, 4 or 5-position of 3-thienyl group are substituted by fluorine atom, chlorine atom, bromine atom, nitro group, methyl group, tert-butyl group, carboxyl group, trifluoromethyl group, hydroxymethyl group, methoxymethyl group, 2-carboxyethyl group, methoxy group, carbanoyl group, methylthio group, dimethylaminocarbonyl group, methylsulfonyl group, amino group or acetylaminogroup can be mentioned.

[0321] The "C₆₋₁₄ aryl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group D" is the above-defined "C₁₋₆ alkyl group" substituted by the above-defined "C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group D".

[0322] Specifically, benzyl group, 1-naphthylmethyl group, 2-naphthylmethyl group, phenethyl group, 3-phenylpropyl group, 2-phenylpropyl group, 3-fluorobenzyl group, 4-fluorobenzyl group, 3-chlorobenzyl group, 4-chlorobenzyl group, 2,4-dichlorobenzyl group, 2,3,4-trichlorobenzyl group, 4-bromobenzyl group, 4-nitrobenzyl group, pentafluorobenzyl group, 4-methylbenzyl group, 4-tert-butylbenzyl group, 2-trifluoromethylbenzyl group, 4-trifluoromethylbenzyl group, 4-(hydroxymethyl)benzyl group, 4-(methoxymethyl)benzyl group, 4-(2-carboxyethyl)benzyl group, 3-carboxybenzyl group, 4-carboxybenzyl group, 4-methoxybenzyl group, 3,4,5-trimethoxybenzyl group, 4-carbamoylbenzyl group, 4-methylthiobenzyl group, 4-dimethylaminocarbonylbenzyl group, 4-methanesulfonylbenzyl group, 4-acetylamino)benzyl group, 4-cyanobenzyl group, 4-acetylbenzyl group, 4-aminobenzyl group, 4-dimethylaminobenzyl group, 4-(methylsulfonfonyl)benzyl group, 4-methylsulfinylbenzyl group, 4-aminosulfonylbenzyl group, 4-nitro-3-methoxyphenylmethyl group and the like can be mentioned.

[0323] The “heterocycle C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group D” is the above-defined “C₁₋₆ alkyl group” substituted by the above-defined “heterocyclic group optionally substituted by 1 to 5 substituents selected from group D”.

[0324] Specifically, 2-pyridylmethyl group, 3-pyridylmethyl group, 2-chloropyridin-4-ylmethyl group, 4-pyridylmethyl group, pyrrolidinemethyl group, imidazolylmethyl group, 2-thienylmethyl group, 3-thienylmethyl group, 2-furymethyl group, 2-oxazolylmethyl group, 2-isothiazolylmethyl group, 2-methylthiazol-4-ylmethyl group, 2-thiazolylmethyl group, 5-thiazolylmethyl group, 2-methylthiazol-4-ylmethyl group, 2-methylthiazol-5-ylmethyl group, 2,5-dimethylthiazol-4-ylmethyl group, 4-methylthiazol-2-ylmethyl group, 2,4-dimethylthiazol-5-ylmethyl group, 2-isothiazolylmethyl group, 2-pyrrolinylmethyl group, pyrrolidinemethyl group, piperidinemethyl group, 4-piperidinemethyl group, 1-methylpiperidin-4-ylmethyl group, 4-hydroxypiperidinemethyl group, 2-(4-hydroxypiperidin)ethyl group, 1-(tert-butoxycarbonyl)piperidin-4-ylmethyl group, 1-acetyl piperidin-4-ylmethyl group, 1-methylsulfonylpiperidin-4-ylmethyl group, piperazinylmethyl group, morpholinomethyl group, thiomorpholinomethyl group, 1-tetrahydropranyl)methyl group, 2-quinozolylmethyl group, 1-isquinolyl)methyl group and the like can be mentioned.
The "C_{14} alkyl group optionally substituted by 1 to 3 substituents selected from group E" is the above-defined "C_{14} alkyl group" optionally substituted by 1 to 3 substituents selected from the above-defined "group E" which includes non-substituted alkyl group.

Specifically, methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, tert-pentyl group, neopentyl group, 1-ethylpropyl group, hexyl group, trithioalkyl group, hydroxyethyl group, 2-hydroxyethyl group, 3-hydroxypropyl group, 4-hydroxybutyl group, 1-hydroxy-1-methylethyl group, 1-hydroxypropan-2-yl group, 1,3-dihydroxypropan-2-yl group, 1-hydroxy-2-methylpropan-2-yl group, 1,1-dimethyl-2-hydroxyethyl group, carboxyethyl group, ethoxyethyl group, methoxyethyl group, methoxyethyl group, ethoxyethylcarbamoylmethyl group, ethoxyethylcarbamoylmethyl group, 2-dimethylaminomethyl group, carbamoylmethyl group, methacrylamoinomethyl group, sulfoethyl group, sulfamoylmethyl group, 2-sulfamoylthethyl group, methylsulfamoylmethyl group and the like can be mentioned.

The "C_{2,5} alkenyl group optionally substituted by 1 to 3 substituents selected from group E" is the above-defined "C_{2,5} alkenyl group" optionally substituted by 1 to 3 substituents selected from the above-defined "group E" which includes non-substituted alkenyl group.

Specifically, vinyl group, allyl group, 1-propenyl group, isopropenyl group, 1-butenyl group, 2-butenyl group, 1,3-butadienyl group, 2-isopentenyl group, 3-isopropenyl group, 4-methyl-3-pentenyl group and the like can be mentioned.

The "C_{3,14} aryl group optionally substituted by 1 to 5 substituents selected from group E" is the above-defined "C_{3,14} aryl group" optionally substituted by 1 to 5 substituents selected from the above-defined "group E" which includes non-substituted aryl group.

Specifically, phenyl group, naphthyl group, anthryl group, indenyl group, azulenyl group, fluorenyl group, phenanthryl group, 3-fluorophenyl group, 4-fluorophenyl group, 3-chlorophenyl group, 4-chlorophenyl group, 2,4-dichlorophenyl group, 3,5-dichlorophenyl group, 2-bromophenyl group, 4-nitrophenyl group, pentfluorophenyl group, 4-methylphenyl group, 4-tert-butylphenyl group, 2-trifluoromethylphenyl group, 4-trifluoromethylphenyl group, 4-(hydroxy)methyphenyl group, 4-(methoxymethyl)phenyl group, 4-(2-carboxyethyl)phenyl group, 3-carboxyphenyl group, 4-carboxyphenyl group, 4-methoxyphenyl group, 3,4,5-trimethoxyphenyl group, 4-carbamoylphenyl group, 4-methylthiophenyl group, 4-methylaminocarboxyphenyl group, 4-methylaminocarboxyphenyl group, 4-acetylamino phenyl group, 4-cyanophenyl group, 4-acylphenyl group, 4-aminophenyl group, 4-dimethylaminophenyl group, 4-(methylsulfonilamino)phenyl group, 4-methylsulfonilphenyl group, 4-aminoisoflonylphenyl group, 3-nitro-4-methoxyphenyl group, 4-nitro-3-methoxyphenyl group, 4-(tetrazol-5-yl)phenyl group and the like can be mentioned.

The "C_{3,10} cycloalkyl group optionally substituted by 1 to 5 substituents selected from group E" is the above-defined "C_{3,10} cycloalkyl group" optionally substituted by 1 to 5 substituents selected from the above-defined "group E", which includes non-substituted cycloalkyl group.

Specifically, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, 1-adamantyl group, 4-fluorocyclohexyl group, 2-methylcyclohexyl group, 3-methylcyclohexyl group, 4-methylcyclohexyl group, 4,4-dimethylcyclohexyl group, 3,5-dimethylcyclohexyl group, 4-tert-butylcyclohexyl group, 4-hydroxycyclohexyl group, 4-methoxycyclohexyl group, 2,3,4,5,6-pentfluorocyclohexyl group and the like can be mentioned.

In addition, such group wherein the cyclopentyl group or cyclohexyl group is substituted by fluorine atom, chlorine atom, bromine atom, nitro group, methyl group, tert-butyl group, carboxyl group, trifluoromethyl group, hydroxymethyl group, methoxyethyl group, 2-carboxyethyl group, methoxy group, carboxy group, methythio group, dimethylaminocarbonyl group, methylsulfonyl group or acetylaminogroup can be mentioned.

The "heterocyclic group optionally substituted by 1 to 5 substituents selected from group E" is the above-defined "heterocyclic group" optionally substituted by 1 to 5 substituents selected from the above-defined "group E", which includes non-substituted heterocyclic group.

Specifically, 2-pyridyl group, 3-pyridyl group, 4-pyridyl group, 3-fluoropyridin-4-yl group, 3-chloropyridin-4-yl group, 4-chloropyridin-3-yl group, pyrazinyl group, pyrimidinyl group, pyridazinyl group, 1,3,5-triazinyl group, pyrrol group, pyrazolyl group, imidazolyl group, 2-methylimidazol-1-yl group, 1,2,4-triazolyl group, tetrazolyl group, 2-thienyl group, 3-thienyl group, furf group, oxazolyl group, 2-methyloxazol-4-yl group, isoxazolyl group, thiadiazolyl group, 2-methylthiazol-4-yl group, 2,5-dimethylthiazol-4-yl group, 2,4-dimethylthiazol-5-yl group, 2-(dimethylaminothiazol-4-yl group), isothiazolyl group, thiadiazolyl group, pyrrolinyl group, pyrrolidinyl group, 1-methylpyrrolidin-3-yl group, 1-acetylpyrrolidin-3-yl group, 1-methanesulfonlpyrrolidin-3-yl group, 1-methoxy carbonylpyrrolidin-3-yl group, imidazolindinyl group, piperidyl group, 4-methylpiperidin-1-yl group, 2-methylpiperidin-1-yl group, 3-methylpiperidin-1-yl group, 4-ethylpiperidin-1-yl group, 4-propylpiperidin-1-yl group, 4-isopropylpiperidin-1-yl group, 4,4-dimethylpiperidin-1-yl group, 2,2,6,6-tetramethylpiperidin-1-yl group, 4-trifluoromethylpiperidin-1-yl group, 4-hydroxypiperidin-1-yl group, 3-hydroxypiperidin-1-yl group, 4-methoxypiperidin-1-yl group, 3-methoxypiperidin-1-yl group, 4-dimethylamin piperidin-1-yl group, 4-methylenepiperidin-1-yl group, 4-ethylidenepiperidin-1-yl group, 4-isopropylidene piperidin-1-yl group, 1-methylpiperidin-4-yl group, 1-ethyl piperidin-4-yl group, 1-methoxypiperidin-4-yl group, 1-methoxycarbonylpiperidin-4-yl group, 1-(2-tert-butoxycarbonyl)piperidin-4-yl group, 1-acyl piperidin-4-yl group, 1-methanesulfonfylpiperidin-4-yl group, 1-methylpiperidin-3-yl group, 1-ethylpiperidin-3-yl group, 1-methoxycarbonylpiperidin-3-yl group, 1-methoxycarbonylpiperidin-3-yl group, 1-methylpiperidin-2-yl group, 1-ethylpiperidin-2-yl group, 1-acyl piperidin-2-yl group, 1-methanesulfonfylpiperidin-2-yl group, 1-methoxypiperidin-2-yl group, 1-methoxycarbonylpiperidin-2-yl group, piperazinyl group, 4-methylpiperazin-1-yl group, 4-ethylpiperazin-1-yl group,
4-isopropylpiperazin-1-yl group, 4-methoxypiperazin-1-yl group, 4-phenylpiperazin-1-yl group, 4-benzylpiperazin-1-yl group, 4-ethoxycarbonylpiperazin-1-yl group, 4-(tert-butyloxycarbonyl)piperazin-1-yl group, 4-cyclopentylcarbonylpiperazin-1-yl group, 4-acetyl)piperazin-1-yl group, 4-isobutyrylpiperazin-1-yl group, 4-benzoylpiperazin-1-yl group, 4-(2-methoxycarbonylpiperazin-1-yl group, 4-methylcarbamoylepiperazin-1-yl group, 4-dimethylcarbamoylpiperazin-1-yl group, 4-methanesulfonylpiperazin-1-yl group, 1,2,3,6-tetrahydrodropyrindyl group, morpholinyl group, thiomorpholinyl group, tetrahydropyranyl group, tetrahydrofuranyl group, azepanyl group, azocanyl group, azonanyl group, 1,4-diazepanyl group, 4-methyl-1,4-diazepan-4-yl group, 4-ethyl-1,4-diazepan-4-yl group, 1,4-oxazepanyl group, quinolyl group, isoquinolyl group, quinazolinyl group, phthalazinyl group, cinnolinyl group, napththrydindyl group, 1,2,3,4-tetrahydroquinolyl group, 5,6,7,8-tetrahydroquinolyl group, 1,2,3,4-tetrahydroisoquinolyl group, 5,6,7,8-tetrahydroisoquinolyl group, indolyl group, benzimidazolyl group, indolyl group, isoindolyl group, octahydroindolyl group, octahydrosoindolyl group, benzofuranyl group, benzothienyl group, benzoxazolyl group, benzothiazolyl group, octahydrocyclopent[c]pyrrolyl group,

and the like can be mentioned.

[0336] In addition, such group wherein the 3, 4, 5 or 6-position of 2-pyridyl group, 2, 4, 5 or 6-position of 3-pyridyl group, 2, 3, 5 or 6-position of 4-pyridyl group, 3, 4 or 5-position of 2-thienyl group, and 2, 4 or 5-position of 3-thienyl group are substituted by fluorine atom, chlorine atom, bromine atom, nitro group, methyl group, tert-butyl group, carboxyl group, trifluoromethyl group, hydroxymethyl group, methoxymethyl group, 2-carboxyethyl group, methoxy group, carbamoyl group, methylthio group, dimethylaminocarbonyl group, methylsulfonfyl group, amino group or acetylamino group can be mentioned.

[0337] The “carboxylic acid equivalent” means a bioisostere and may only be a substituent having a similar polar effect as carboxylic acid. Specifically, a chain substituent such as —CONHR\(^{108}\)

(wherein R\(^{108}\) is a hydroxyl group, a cyano group, a C\(_{1-6}\) alkoxy group or a C\(_{6-14}\) arylxylo group),

—SO\(_2\)R\(^{108}\)

(wherein R\(^{108}\) is a hydroxyl group, an amino group or a C\(_{1-6}\) alkylamino group),

—HNCO\(^{107}\)

(wherein R\(^{107}\) is an amino group or a C\(_{1-6}\) alkylamino group),

—P\((\equiv O)(OH)(OR)^{109}\)

(wherein R\(^{109}\) is a hydrogen atom or a substituent selected from the above-mentioned group C),

—P\((\equiv O)(OH)NR^{111}(R)^{112}\)

(wherein R\(^{111}\) and R\(^{112}\) are each independently a hydrogen atom or a substituent selected from the above-mentioned group C).
CONHCO—R$^{113}$

(wherein R$^{113}$ is a substituent selected from the above-mentioned group C),

CONHSO$_2$—R$^{114}$

(wherein R$^{114}$ is a substituent selected from the above-mentioned group C),

SO$_2$NHC0—R$^{115}$

[0338] (wherein R$^{115}$ is a substituent selected from the above-mentioned group C) and the like, or a cyclic substituent such as a heterocyclic group having a hydrogen atom donor such as

(wherein E$^{h1}$ is an oxygen atom, a sulfur atom or N(—R$^{h1}$), R$^{h1}$ is a hydrogen atom or a C$_1$-6 alkyl group, E$^{h3}$ is an oxygen atom or a sulfur atom, R$^{k2}$ is a C$_1$-6 alkyl group, R$^{k3}$ is an electron-withdrawing group such as a halogen atom, a cyano group, a C$_1$-6 alkyl group, a trifluromethyl group, a formyl group, a chlorocarbonyl group, a nitro group, an acetyl group, an ethoxycarbonyl group, a carbamoyl group and the like) and the like, and said heterocyclic group substituted by an electron-withdrawing group and the like can be mentioned.

[0339] More specifically,

—CONHCN, —CONHOH, —CONHOMe,
—CONHOT-Bu, —CONHOBn,
—SO$_2$H, —SO$_2$NH$_2$, —SO$_2$NHMe,
—NHCONH$_2$, —NHCON(Me)$_2$,
—P(O)(OH)$_2$, —P(O)(OH)(OEt),
—P(O)(OH)NH, —P(O)(OH)NHMe,
—CONHCOMe, —CONHCOBn.

[0340] —CONHSO$_2$Me, —CONHSO$_2$Pr, —CONHSO$_2$Ph,

—SO$_2$NHC0Me, —SO$_2$NHCOPh

wherein Me is a methyl group, Et is an ethyl group, Pr is a propyl group, t-Bu is a tert-butyl group, Ph is a phenyl group and Bn is a benzyl group, and
[0341] As the carboxylic acid equivalent, preferred are 
—CONHOBu, —CONHOBn, —SO₂H, —CONHSO₂Me, 
—CONHSO₂Pr, —CONHSO₂Ph,

[0342] In the formula [I], as a

moiety, N—C=NC is preferable, as a

moiety, preferred is a fused ring selected from the group consisting of

and the like can be mentioned.
more preferably, a fused ring selected from the group consisting of

\[ \begin{align*}
R^1 & \quad \text{and} \\
R^2 & 
\end{align*} \]

particularly preferably,

\[ \begin{align*}
R^1 & \\
R^2 & 
\end{align*} \]

[0343] For \( G^2, G^4 \) or \( G^3 \), preferred is a carbon atom, when pharmacological activity is not markedly degraded, it may be a nitrogen atom, which may be substituted by \( R^3 \).

\( Q \) is \((CH_2)_n - (CH_2)_{m} - (CH_2)_{p} - \), wherein the bond on the left side is joined with \( G^2 \), and the bond on the right side is joined with \( G^3 \).

[0344] \( Q^1 \) is \( -O-, -NH-, -S-, -OCO-, -OCONH-, -CO-, -SO-, -SO2-, -NCO-, -NHSO2-, -NHCOO-, -COO-, -CONH-, -SO2NH-, -NHSO2NH-, -CH=CH- or -CH=N-, wherein the bond on the left side is joined with \((CH_2)_n - (CH_2)_{m} - (CH_2)_{p} - \), and the bond on the right side is joined with \((CH_2)_n - (CH_2)_{m} - (CH_2)_{p} - \).

[0345] For \( Q^1 \), preferred are \( -O-, -NH-, -S- \) or \(-CONH-\), more preferred are \(-O-, -NH-\) and \(-CONH-\), particularly preferred is \(-NH-\).

[0346] For \( b \), preferred is an integer of 1 to 3, particularly preferably 1 or 3.

[0347] For \( c \), preferred is an integer of 1 to 3, particularly preferred is 2.

[0348] For \( d \), preferred is 0.

[0349] For \( Q \), preferred are \(-(CH_2)_n - (CH_2)_{m} - (CH_2)_{p} - \) or \(-O-\) and \(-NH-\).

[0350] For \( R^1 \), preferred is a carboxyl group, \(-CONR^{11}R^{12}, -COOR^{13,14} \),

\[ \begin{align*}
\text{or} \\
\text{or} 
\end{align*} \]

more preferably a carboxyl group or \(-CONR^{11}R^{12}, -COOR^{13,14} \).

[0351] For \( R^{11} \), preferred is a hydrogen atom or a \( C_{1-6} \) alkyl group.

[0352] For \( R^{12} \), preferred is a hydrogen atom, \( a C_{1-6} \) alkyl group optionally substituted by 1 to 3 substituents selected from group E, \( a C_{6-14} \) aryl group optionally substituted by 1 to 5 substituents selected from group E, \( a \) heterocyclic group optionally substituted by 1 to 5 substituents selected from group E, \( a C_{3-10} \) cycloalkyl group optionally substituents.
tuted by 1 to 5 substituents selected from group E', —NR₁₃R₁₄, —NHCOR₁₃, —NHCOR₁₄, —CR₁₅R₁₆-L₁₀₀-R₁₇,

--- CR₁₈R₁₉-L₁₀₂-CONR₁₄₀-L₁₆₃—Dₕ ,

--- CR₁₈R₁₉-L₁₀₂-CONR₁₄₀-L₁₆₃—CONR₁₄₁-L₁₆₃ —Dₗ or

--- L₁₆₅ —Dₖ —L₁₆₆—Dₗ .

[0353] For R₁₀₃, preferred is “a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A”, “a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group B” or “a C₆₋₁₄ aryl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group B”.

[0354] As the “heterocyclic group” of “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E” for ring D₅, preferred is a pyridinyl group, a pyrrolidinyl group, a piperidinyl group, a piperazinyl group, a 2,6-dioxopiperazinyl group or a 2,3,4,9-tetrahydro-1H-p-carbolinyl group.

[0355] As the “C₆₋₁₄ aryl group” of “a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group E” for ring D₅, preferred is a phenyl group.

[0356] For group E in ring D₅ and ring D₇, preferred is a hydroxyl group, a carboxyl group or a C₂₋₆ alkenyl group optionally substituted by carboxyl group.

[0357] For R₁₃₁, R₁₃₂, R₁₃₃ and R₁₃₄, preferred for each independently is a hydrogen atom, “a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A”, “a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group B” or “a C₆₋₁₄ aryl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group B”.

[0358] More preferably, R₁₃₁ and R₁₃₂ are each a C₁₋₆ alkyl group, R₁₃₃ is a C₆₋₁₄ aryl C₁₋₆ alkyl group, R₁₃₄ is a C₆₋₁₄ aryl group optionally substituted by carboxyl group.

[0359] For R₁₃₅ and R₁₃₆, preferred for each independently is a hydrogen atom, —COOR₁₄₂, —CONR₁₄₃—R₁₄₄, “a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A” or “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B”, or R₁₃₅ and R₁₃₆ are bonded to each other, and form, together with the carbon atom bonded thereto, “a C₅₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from group B”.

[0360] For R₁₄₂, preferred is a hydrogen atom or “a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A”. More preferably, R₁₄₂ is a hydrogen atom or a C₁₋₆ alkyl group.

[0361] For R₁₄₃ and R₁₄₄, preferred for each independently is a hydrogen atom, a C₁₋₆ alkoxy group, “a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A”, “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B” or “a heterocyclic C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group B”. More preferably, R₁₄₃ is a hydrogen atom, R₁₄₄ is a hydrogen atom, “a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A”, “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B” or “a heterocyclic C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group B”. For “a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A” represented by R₁₄₄, preferred is a C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from a hydroxyl group and —NR₁₄₅—R₁₄₆ (wherein R₁₄₁ and R₁₄₂ are each independently a hydrogen atom or a C₁₋₆ alkyl group). For the “heterocyclic group” of “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B” represented by R₁₄₄, preferred is any pyridyl group. For the “heterocyclic” moiety of “a heterocyclic C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from a pyridyl group and —NR₁₄₅—R₁₄₆ (wherein R₁₄₁ and R₁₄₂ are each independently a hydrogen atom or a C₁₋₆ alkyl group). For the “heterocyclic group” of “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B” represented by R₁₄₄, preferred is a morpholino group, pyrrolidinyl group or a pyridyl group.

[0362] For the “heterocyclic group” of “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B” represented by R₁₃₅ and R₁₃₆, preferred is a thiazolyl group or a pyridyl group.

[0363] For the “C₅₋₁₀ cycloalkyl group” of “a C₅₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from group B” which is formed by R₁₃₅ and R₁₃₆ bonded to each other, together with the carbon atom bonded thereto, preferred is “a C₅₋₁₀ cycloalkyl group”, more preferably a cyclopropyl group, a cyclobutyl group, a cyclopentyl group or a cyclohexyl group.

[0364] For L₁₀₀, preferred is a bond, —CO—, —CH₂—O—, —CH₂—NH—, —CH₂—NHCO— or methylene, more preferably a bond or methylene.

[0365] For L₁₀₁, preferred is a bond or methylene.

[0366] For R₁₃₇, preferred is “a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group E” or “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E”.

[0367] For the “C₆₋₁₄ aryl group” of “a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group E” represented by R₁₃₇, preferred is a phenyl group.

[0368] For the “heterocyclic group” of “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E” represented by R₁₃₇, preferred is an indolyl group, a 2-oxo-2H-chromenyl group, a benzo[1,3]thiazolinyl group, a benzimidazolyl group, a benzo[1,2]oxazinyl group, a benzothienyl group, a benzothiazolyl group, a pyridyl group, a pyrimidinyl group, a pyrazolyl group, a 4-oxo-1H-quinoxalinyl group, a furyl group, a thienyl group, an oxazolyl group or a thiazolyl group, more preferably, an indolyl group, a benzimidazolyl group, a benzo[1,2]oxazinyl group or a benzothienyl group, and particularly preferably, an indolyl group.

[0369] For R₁₃₈ and R₁₃₉, preferred for each independently is a hydrogen atom or “a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A”, or R₁₃₈ and R₁₃₉ are bonded to each other, and form, together with the carbon atom bonded thereto, “a C₅₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from group B” or “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B”.
For the “C₃₋₁₀ cycloalkyl group” of “a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from group B”, which is formed by R¹³⁸ and R¹³⁹ bonded to each other, together with the carbon atom bonded thereto, preferred is “a C₃₋₇ cycloalkyl group”, more preferably is a cyclopropyl group, a cyclobutyl group, a cyclopentyl group or a cyclohexyl group.

For the “heterocyclic group” of “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B”, which is formed by R¹³⁸ and R¹³⁹ bonded to each other, together with the carbon atom bonded thereto, preferred is a “4-, 5- or 6-membered heterocyclic group comprising 1 to 3 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom”, more preferably, a piperidyl group, a pyrrolidinyl group, a tetrahydropyranyl group or a tetrahydrothiophenyl group.

Particularly preferably, R¹³⁸ and R¹³⁹ are each independently a hydrogen atom or a C₁₋₆ alkyl group, or R¹ and R¹² are bonded to each other, and form, together with the carbon atom bonded thereto, a cyclobutyl group or a cyclopentyl group.

For R¹⁴⁰ and R¹⁴¹, preferred is a hydrogen atom.

For L¹⁰², preferred is a bond or vinylene.

For L¹⁰³, preferred is a bond.

For L¹⁰⁴, preferred is propylene.

For ring D⁵, preferred is “a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group E² or “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E²”.

For the “C₆₋₁₄ aryl group” of “a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group E²” represented by ring D⁵, preferred is a phenyl group.

For the “heterocyclic group” of “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E²” represented by ring D⁵, preferred is an indolyl group, a 2-oxo-2H-chromenyl group, a benzol[1,3]dioxolanylnyl group, a benzimidazolyl group, a benzofuranyl group, a benzothienyl group, a benzoazolyl group, a pyridyl group, a pyrimidinyl group, a pyrazolyl group, a 4-oxo-1H-quinolinyl group, a furyl group, a thienyl group, an oxazolyl group or a thiazolyl group, more preferably, an indolyl group, a benzimidazolyl group, a benzofuranyl group or a benzothienyl group, particularly preferably, an indolyl group.

For ring D⁵, preferred is “a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from group E² or “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E²”.

For ring D⁵, preferred is “a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group E²”.

For the “C₃₋₁₀ cycloalkyl group” of “a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from group E²” represented by ring D⁴ and ring D⁵, preferred is a cyclohexyl group.

For the “heterocyclic group” of “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E²” represented by ring D⁴ and ring D⁵, preferred is a piperidyl group or a pyrrolidinyl group.

For the “C₆₋₁₄ aryl group” of “a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group E²” represented by ring D⁴ and ring D⁵, preferred is a phenyl group.

For the group E in R¹³⁷, ring D⁵, ring D⁴ and ring D⁵, preferred is a halogen atom, a cyano group, a nitro group, an azido group, —OP(=O)(OH)₂, —OR¹¹, —S(O)₂R²¹, —NR²²R²³, —COOR²¹, —CONR²²R²³, —COR²⁴, —NR²⁵CO—R²⁶, —NR²⁶SO₂—R²⁷, —NR²²¹CONR²²²R²²³, ——NHCO—COOR²¹, ——NHCO—CONR²²²R²²³, —CONH—COOH.

“a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group B”, “a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from group B”, “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B”, “a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A”, “a C₂₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A”, “a C₂₋₆ alkynyl group optionally substituted by 1 to 3 substituents selected from group A” or “a C₆₋₁₄ aryl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from group B”, more preferably, a carboxyl group, —OR¹¹ (wherein R¹¹ is a hydrogen atom or a C₁₋₆ alkyl group substituted by carboxyl group), a C₁₋₆ alkyl group substituted by carboxyl group or a C₂₋₆ alkynyl group substituted by carboxyl group, particularly preferably, a carboxyl group, a hydroxyl group, —OCH₂COOH, —CH=CH—COOH or —CH₂CH₂COOH.

Preferably, R¹¹ is
wherein R' is preferably selected from a hydrogen atom, a 5- to 10-membered heterocyclic group comprising 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom.

(wherein the heterocyclic group is optionally substituted by 1 to 4 substituents selected from the group consisting of —CH₃, —CF₃, —OH, —CH₂COOH, —COOH, —NHCH(CH₂)₂, —NHCOC(OH)CH₂, —NH₂, —NHCH₃ and —N(CH₃)₂, —COOH, —COO(C(1-6 alkyl)), —CONH₂, —COCH₃, —(CH₂)₄COOH

(wherein p₁ is an integer of 1 to 4), benzyloxy, —CH —(C₁₋₄ aryl)-COOH, pyridylcarbamoyl, pyridylmethylcarbamoyl and —CONH —(C₂₋₄ alkyl)-N(CH₃)₂.

More preferably, R' is COOR₁₂₋₂₀, CONHR₁₂₋₂₀ O or

More preferably, R⁻₁₂ is preferably a hydrogen atom, a C₁₋₄ alkyl group, an amino group, —NH(C₁₋₄ alkyl), —N(C₁₋₄ alkyl)₂ or —NHCO(C₁₋₄ alkyl).

Preferably, R⁻₁₂ is a hydrogen atom, a heterocycle C₁₋₄ alkyl group (wherein the heterocycle is selected from morpholinyl, pyrrolidinyl and N-methylpyrrolidinyl), —(C₁₋₄ alkyl)-N(CH₃)₂, —(C₁₋₄ alkyl)-OH, —CH(CH₂OH)₂ or —CH₂CH(OH)CH₂OH. More preferably, R⁻₁₂ is a hydrogen atom.

Preferably, R⁻₂ is a hydrogen atom or a C₁₋₄ alkyl group. More preferably, R⁻₂ is a hydrogen atom or —CH₃.

Preferably, R⁻₂ is selected from a hydrogen atom, a hydroxyl group, an amino group, a 5- to 10-membered heterocyclic group comprising 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom, sulfur atom (wherein the heterocyclic group is optionally substituted by hydroxyl group), —COOH, —CH₃, —CF₃, —CH₂COOH, —O(C₁₋₄ alkyl)-COOH, —NHCCO(OH), —NHSO₃CH₃, —NHSO₂CF₃,

More preferably, R⁻₂ is —OCH₂COOH or a hydroxyl group.

Preferably, R⁻₂ is selected from a hydrogen atom, a C₁₋₄ alkyl group and —(CH₂)₃COOH (wherein p₁ is an integer of 1 to 4). More preferably, R⁻₂ is a hydrogen atom, —CH₃ or —CH₂COOH.

Preferably, R⁻₂ is a hydrogen atom or a C₁₋₄ alkyl group. More preferably, R⁻₂ is a hydrogen atom or —CH₃. Still more preferably, R⁻₂ is a hydrogen atom.

Preferably, R'' is selected from a hydrogen atom, C₁₋₄ alkyl group, —NH(C₁₋₄ alkyl), —N(C₁₋₄ alkyl)₂ or —NHCO(C₁₋₄ alkyl).

Preferably, R'' is a hydrogen atom or —CH₃. Still more preferably, R'' is a hydrogen atom. Alternatively, R'' is preferably pentafluorophenyl.

Preferably, R'' is a C₁₋₄ alkoxy group, a hydroxyl group, —O(C₁₋₄ alkyl)-COOH, a C₁₋₄ alkyl group, a halogen atom, —OC₃₋₄ alkynyl)-COOH, —(C₁₋₄ alkyl)-OH, —COOH or an azido group.

Preferably, R'' is a hydroxyl group, —(CH₂)₃COOH (wherein p₁ is an integer of 1 to 4), an amino group, a C₁₋₄ alkyl group, —NHCCO(OH), —NH(C₅₋₇ alkyl)-COOH, —O(C₁₋₄ alkyl)-COOH, —COOH, a 5- or 6-membered heterocyclic group comprising 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom.

Preferably, m₁ is 0 or an integer of 1 to 4. More preferably, m₁ is 1.

More preferably, R⁻₁₂ is —O(C₁₋₄ alkyl)-COOH, a C₁₋₄ alkyl group or a halogen atom.

Preferably, m₁ is —O(C₁₋₄ alkyl)-COOH, a C₁₋₄ alkyl group or a halogen atom.
Alternatively, \( R^{12} \) is preferably a hydroxyl group or \(-\text{O}(\text{C}_{1-6}\text{alkyl})-\text{COOH}\).

Alternatively, \( R^{12} \) is preferably a hydrogen atom, a halogen atom or an amino group.

Alternatively, \( R^{12} \) is more preferably a hydrogen atom, a halogen atom or an amino group.

Alternatively, \( R^{12} \) is preferably a hydroxyl group or a \(-\text{O}(\text{C}_{1-6}\text{alkyl})-\text{COOH}\).

Alternatively, \( R^{12} \) is preferably a hydroxyl group or an amino group.

Alternatively, \( R^{12} \) is more preferably a hydroxyl group or an amino group.

Alternatively, \( R^{12} \) is preferably a hydroxyl group or an amino group.

Alternatively, \( R^{12} \) is more preferably a hydroxyl group or an amino group.

Alternatively, \( R^{12} \) is preferably a hydroxyl group or a hydroxyl group.

Alternatively, \( R^{12} \) is preferably a hydroxyl group or a hydroxyl group.

Alternatively, \( R^{12} \) is preferably a hydroxyl group or a hydroxyl group.

Alternatively, \( R^{12} \) is preferably a hydroxyl group or a hydroxyl group.

Alternatively, \( R^{12} \) is more preferably a hydroxyl group or a hydroxyl group.

Alternatively, \( R^{12} \) is more preferably a hydroxyl group or a hydroxyl group.

Alternatively, \( R^{12} \) is preferably a hydroxyl group or a hydroxyl group.

Alternatively, \( R^{12} \) is more preferably a hydroxyl group or a hydroxyl group.

Alternatively, \( R^{12} \) is preferably a hydroxyl group or a hydroxyl group.

Alternatively, \( R^{12} \) is more preferably a hydroxyl group or a hydroxyl group.
group optionally substituted by 1 to 5 substituents selected
from group B", "a C₆₋₁₄ aryl C₁₋₆ alkyl group optionally
substituted by 1 to 5 substituents selected from group B", "a
heterocycle C₁₋₆ alkyl group optionally substituted by 1 to 5
substituents selected from group B" or "a C₃₋₁₀ cycloalkyl
C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents
selected from group B"; or R³⁻¹³ and R⁵⁻¹³ are bonded to each
other and optionally form, together with the carbon atom
bonded thereto, "a C₃₋₁₀ cycloalkyl group optionally substi-
tuted by 1 to 5 substituents selected from group B" or "a
heterocyclic group optionally substituted by 1 to 5 substitu-
ts selected from group B".

[0410] Here, as the substituent selected from group A, preferred
are 1 to 3 substituents selected from a halogen atom, —OR¹,—NR¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻¹⁻�
R_{12} is

\[ \text{CR}^{135}_R \text{CR}^{136}_R \text{L}^{100}_R \text{CR}^{137}_R, \]

[0418]  

\[ \text{CR}^{135}_R \text{CR}^{136}_R \text{L}^{101}_R \text{CONR}^{140}_R \text{L}^{103}_R \]  

\[ \text{D}^2 \]

or

\[ \text{CR}^{135}_R \text{CR}^{136}_R \text{L}^{102}_R \text{CONR}^{140}_R \text{L}^{104}_R \text{CONR}^{141}_R \text{L}^{103}_R \text{D}^2 \]

[0419] When R_{12} is \( \text{CR}^{135}_R \text{CR}^{136}_R \text{L}^{100}_R \text{CR}^{137}_R \), preferably, L is a bond, and R^{137} is a C_{6,14} aryl group optionally substituted by 1 to 5 substituents selected from group E or a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E (wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom).

[0420] More preferably, R^{135} and R^{136} are each independently a group selected from group G, or R^{135} and R^{136} are bonded to each other, and form, together with the carbon atom bonded thereto, a C_{3,10} cyclealkyl group optionally substituted by 1 to 5 substituents selected from group B, or a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B.

[0421] In a different preferable embodiment wherein R_{12} is \( \text{CR}^{135}_R \text{CR}^{136}_R \text{L}^{100}_R \text{CR}^{137}_R \), \( \text{L}^{100}_R \) is methylene, and R^{137} is a C_{6,14} aryl group optionally substituted by 1 to 5 substituents selected from group E or a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E (wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom).

[0422] More preferably, R^{135} is a group selected from group G and R^{136} is a hydrogen atom.

[0423] When R_{12} is \( \text{CR}^{135}_R \text{CR}^{136}_R \text{L}^{101}_R \text{CONR}^{140}_R \text{L}^{103}_R \), L is preferably a bond.

[0424] More preferably, R^{135} and R^{136} are each independently a group selected from group G, or R^{135} and R^{136} are bonded to each other, and form, together with the carbon atom bonded thereto, a C_{3,10} cyclealkyl group optionally substituted by 1 to 5 substituents selected from group B, or a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B.

[0425] Still more preferably, R^{140} is a hydrogen atom and R^{137} is a C_{6,14} aryl group optionally substituted by 1 to 5 substituents selected from group E or a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E (wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom).

[0426] When R_{12} is

\[ \text{CR}^{135}_R \text{CR}^{136}_R \text{L}^{102}_R \text{CONR}^{140}_R \text{L}^{103}_R \text{D}^2 \]

or

\[ \text{CR}^{135}_R \text{CR}^{136}_R \text{L}^{102}_R \text{CONR}^{140}_R \text{L}^{104}_R \text{CONR}^{141}_R \text{L}^{103}_R \text{D}^2 \]

L_{102} is preferably a bond.

[0427] More preferably, R^{138} and R^{139} are each independently a group selected from group E, or R^{138} and R^{139} are bonded to each other, and form, together with the carbon atom bonded thereto, a C_{3,10} cycloalkyl group optionally substituted by 1 to 5 substituents selected from group B, or a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B.

[0428] Still more preferably, L_{103} is a bond, ring D^3 is a C_{6,14} aryl group optionally substituted by 1 to 5 substituents selected from group E or a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E (wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom), and R^{140} and R^{141} are each a hydrogen atom.

[0429] R^1 is specifically a carboxylic group, a methoxycarbonyl group, an ethoxycarbonyl group, a phenoxy carbonyl group, a benzyloxy carbonyl group, a car bamoyl group, a methyl carbamoyl group, a (2-hydroxyethyl) carbamoyl group, a (1,1-dimethyl-2-hydroxyethyl) carbamoyl group, a carboxymethyl carbamoyl group, an N-carboxymethyl-N-methyl carbamoyl group, a (1-carboxy-3-methylbutyl) carbamoyl group, a (1-carboxy-2-methoxycarbonyl) carbamoyl group, a (1-carboxy-2-methylthioethyl) carbamoyl group, a (1-carboxy-2-methyl) carbamoyl group, a (1-carboxy-2-2,2-dimethylpropyl) carbamoyl group, a [2-(2-hydroxy ethoxy)ethyl] carbamoyl group or a tert-butyl carbamoyl group, particularly preferably a carboxyl group.

[0430] R^1 may be a “carboxylic acid equivalent” which is a substitutent biologically equivalent to a carboxyl group, and as a specific “carboxylic acid equivalent”, the aforementioned substituent and the like can be mentioned.

[0431] Moreover, an example of R^1 is a group represented by

\[
\begin{align*}
\text{O} & \quad \text{R}^{12} \\
\text{H} & \quad \text{R}^{12}
\end{align*}
\]

wherein R^{12} is selected from the following formulas, can be mentioned.

\[
\begin{align*}
\text{O} & \quad \text{OH} \\
\text{X} & \quad \text{CH}_3
\end{align*}
\]
Furthermore, as other examples of $R^1$, the groups selected from the following formulae can be mentioned.
[0434] Preferably, L₁ and L₂ are each independently a bond, C₁₋₆ alkylene, \((\text{CH}_2)_n\), \(\text{NR}^{1-3}\), \(\text{CONR}^{1-3}\), \(\text{CO}-(\text{CH}_2)_n\), or \((\text{CH}_2)_n\) alkylene, more preferably \(\text{C}_1-6\) alkylene.

[0435] Preferably, u, v, u₁ and v₁ are each independently 0 or an integer of 1 to 3, more preferably 0 or 1, particularly preferably 1.

[0436] For R¹⁻¹, preferably is a hydrogen atom, preferably, ring D¹ and ring D² are each independently “a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group E” or “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group E”.

[0437] As the “C₆₋₁₄ aryl group” of “a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group E” for ring D¹ and ring D², preferred is a phenyl group.

[0438] As the “heterocyclic group” of the “heterocyclic group optionally substituted by 1 to 5 substituents selected from group E” for ring D¹ and ring D², preferred is a 5- to 10-membered saturated or unsaturated monocyclic or fused heterocyclic group having 1 or 2 nitrogen atoms and optionally further having an oxygen atom or a sulfur atom, such as pyrrolidinyl group, 2-oxopyrrolidinyl group, pyridyl group, piperidyl group, piperazinyl group, morpholinyl group, thiomorpholinyl group, 1,1-dioxomorpholinyl group, azepanyl group, 4-oxazepanyl group” “1,4-diazepanyl group, 5-oxo-1,4-diazepanyl group, 1,4-oxazepanyl group, azocanlyl group, azonanlyl group, thiazolyl group.

[0433] For R², preferred are a hydrogen atom, “a group selected from group E”, “a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group E”,

- \(L^1 \rightarrow D^1 \) and \(L^2 \rightarrow D^2 \),

more preferred are “a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group E” and

- \(L^1 \rightarrow D^1 \),

and the like. More preferred is a 5- to 7-membered saturated or unsaturated monocyclic heterocyclic group having 1 or 2
nitrogen atoms and optionally further having an oxygen atom or a sulfur atom, and particularly preferably, pyrroldinyl group, 2-oxopyrrolidinyl group, pyridyl group, piperidyl group, piperazinyl group, morpholyl group, thiomorpholyl group, 1,1-dioxomorpholyl group, azepanyl group, 1,4-diazepanyl group and 1,4-oxazeplan group can be mentioned.

[0439] As the group E in R², preferred are --OR⁵⁺, "-S(O)₂R⁶⁻, "-NR³⁶⁻, "-COR⁷⁺, "-CONR³⁵⁻R⁷⁺, "-COR⁸⁺ and "a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group B², when group E is a substituent on ring D¹ or ring D², it may be "a C₁₋₅ alkyl group optionally substituted by 1 to 3 substituents selected from group A".

[0440] As the "group selected from group E" represented by R², preferred are "-CONR³⁵⁻R⁷⁺" and "-COR⁸⁺.

[0441] As the "C₁₋₅ alkyl group optionally substituted by 1 to 3 substituents selected from group E" represented by R², preferred are a C₁₋₅ alkyl group optionally substituted by 1 to 3 substituents selected from "-OR⁵⁺, "-NR³⁶⁻, "-COR⁷⁺, "-CONR³⁵⁻R⁷⁺ and "-COR⁸⁺.

[0442] With regard to group E in R², preferred for R⁴⁺ is a hydrogen atom or a C₁₋₅ alkyl group, preferred for R⁵⁺ is a hydrogen atom or a C₁₋₅ alkyl group, preferably R⁶⁻ and R⁷⁺ are each independently a hydrogen atom or a C₁₋₅ alkyl group, preferred for R⁸⁻ is a hydrogen atom or a C₁₋₅ alkyl group, preferably R⁷⁺ and R⁸⁻ are each independently a hydrogen atom, a hydroxyl group, a C₁₋₅ alkyl group optionally substituted by 1 to 3 substituents selected from group A, a C₁₋₅ alkoxy group or C₁₋₅ alkoxy group, preferred for R⁹⁺ is a C₁₋₅ alkyl group or a C₁₋₅ aryl group, preferred for "C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from group B²" is a C₆₋₁₄ aryl group, when group E is a substituent on ring D¹ or ring D², "a C₁₋₅ alkyl group optionally substituted by 1 to 3 substituents selected from group A" is preferably a C₁₋₅ alkyl group.

[0443] For R², hydrogen atom, phenylsulfonyl group, benzoyloxy carbonyl group, dimethylcarbamoyl group, acetyl group, alky group, methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, cyclohexyl group, 2,2,2-trifluoroethyl group, cyclohexyl group, 2-nitromethyl group, 2-(methoxyethoxy)ethyl group, pivaloylmethyl group, ethoxycarbonyl methyl group, 3-(3-methylethylidene)propyl group, 2-(methylcarbamoxy)ethyl group, 2-(methylsulfinyl)ethyl group, 2-(methanesulfonyl)ethyl group, 2-(methylsulfonyl)ethyl group, 2-hydroxy-2-methylpropyl group, methanesulfonylcarbamoyl methyl group, 3-(dimethylamino)-2-hydroxoy propyl group, carbamoxy methyl group, methy carbamoyl methyl group, isopropyl carbamoylmethyl group, dimethylcarbamoyl methyl group, dimethylcarbamoyl propyl group, isobutyl carbamoylmethyl group, (1-ethylpropyl) carbamoylmethyl group, (2,2-dimethylpropyl) carbamoylmethyl group, (3,3-dimethylbutyl) carbamoylmethyl group, tert-butyl carbamoylmethyl group, (2,2,2-trifluoroethyl) carbamoylmethyl group, methoxy carbamoylmethyl group, 2-methoxyethyl carbamoylmethyl group, 3-methoxy propyl carbamoylmethyl group, 2-(methylsulfinyl)ethyl carbamoylmethyl group, carboxymethyl carbamoylmethyl group, 2-carboxyethyl carbamoylmethyl group, 3-carboxypropyl carbamoylmethyl group, carboxamyl carbamoylmethyl group, 2-(dimethylamino)ethyl carbamoylmethyl group, N-[2-(dimethylamino)ethyl]-N-methyl carbamoylmethyl group, N-(2-methoxyethyl)-N-methyl carbamoylmethyl group, 3-(dimethylamino) propyl carbamoylmethyl group, 2-(acetamido)ethyl carbamoylmethyl group, 2-hydroxyethyl group, 3-hydroxypropyl group, 2-methoxyethyl group, 2-(dimethylamino)ethyl group, carboxymethyl group, 2-(acetamido)ethyl group, 3-(acetamido)propyl group, 2-(methanesulfonyl)amino)ethyl group, 3-(methanesulfonyl)amino)propyl group, [2-(N-(methanesulfonyl))-N-methylamino]ethyl group, 3-(acetylsulfonyl)amino]propyl group, 2-(3-methyl-2-butenyloxy)ethyl group, 2-(2-methoxy ethoxy)ethyl carbamoylmethyl group, 2-(2-ethyl hydroxy)2-xyloxyethyl group, 2-(4-methyl phenoxy)ethyl group, 2-(3-methylthiazol-2-ylamino)ethyl group, cyclopropyl carbamoylmethyl group, cyclobutyl carbamoylmethyl group, cyclopentyl carbamoylmethyl group, cyclohexyl carbamoylmethyl group, phenyl carbamoylmethyl group, benzyl carbamoylmethyl group, phenethy carbamoylmethyl group, N-benzyl-N-methyl carbamoylmethyl group, 3-phenylpropyl carbamoylmethyl group, 4-phenylbutyl carbamoylmethyl group, 2-(3-chlorobenzyloxy)ethyl group, 3-(4-methylbenzylsulfonyl)propyl group, 2-(phenylacetyl) amino)ethyl group, 2-(pyridyl) ethyl carbamoylmethyl group, 3-(pyridyl) ethyl carbamoylmethyl group, 2-(pyridyl)-3-ethyl carbamoylmethyl group, 2-(pyridyl)-4-ethyl carbamoylmethyl group, 2-(pyridyl)-5-ethyl carbamoylmethyl group, 2-(pyridyl)-6-ethyl carbamoylmethyl group, N-methyl-N-(pyridyl)-2-ethyl carbamoylmethyl group, N-methyl-N-(pyridyl)-3-ethyl carbamoylmethyl group, N-methyl-N-(pyridyl)-4-ethyl carbamoylmethyl group, N-methyl-N-(pyridyl)-5-ethyl carbamoylmethyl group, benzoylmethyl group, 2-(2,4-dimethylthiazol-5-yl)-2-oxoethyl group, 2-(3-methylisoxazol-4-yl)-2-oxoethyl group, 2-oxo-2-(pyrrolidin-1-yl)ethyl group, 2-(3-methoxy pyrrolidin-1-yl)-2-oxoethyl group, 2-(2-carboxypyrrolidin-1-yl)-2-oxoethyl group, 2-(2-carboxypyridin-1-yl)-2-oxoethyl group, 2-oxo-2-piperidinoethyl group, 2-morpholin-2-2-oxoethyl group, 2-(4-methyl pyrrolidin-1-yl)-2-oxoethyl group, 2-(4-ethyl pyrrolidin-1-yl)-2-oxoethyl group, 2-(3-methyl pyrrolidin-1-yl)-2-oxoethyl group, 2-(4-hydroxy propylidin-1-yl)-2-oxoethyl group, 2-(4-methyl pyrrolidin-1-yl)-2-oxoethyl group, 2-(4-methyl pyrrolidin-1-yl)-2-oxoethyl group, 2-(4-ethyl pyrrolidin-1-yl)-2-oxoethyl group, 2-(4-acetyl pyrrolidin-1-yl)-2-oxoethyl group, 2-(4-isopropyli pyrrolidin-1-yl)-2-oxoethyl group, 2-(4-ethyl py rrolidin-1-yl)-2-oxoethyl group, 2-(4-phenyl pyrrolidin-1-yl)-2-oxoethyl group, 2-(4-acetyl pyrrolidin-1-yl)-2-oxoethyl group, 2-(4-carboxy pyrrolidin-1-yl)-2-oxoethyl group, 2-(4-ethoxy carbonyl pyrrolidin-1-yl)-2-oxoethyl group, 2-(4-methanesulfonyl pyrrolidin-1-yl)-2-oxoethyl group, 2-oxo-2-thiomorpholin-4-yl)ethyl group, 2-(4,1-dioxothio morpholin-4-yl)-2-oxoethyl group, 2-(azaepan-1-yl)-2-oxoethyl group, 2-(1,4-oxazepan-4-yl)-2-oxoethyl group, 2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl group, 4-morpholino-4-oxo butyl group, 4-(4-ethyl pyrrolidin-1-yl)-4-oxoethyl group, 2-(thiophen-2-ylcarbonyl-
noethyl group, 2-piperidinoethylcarbamoylmethyl group, 2-morpholinoethylcarbamoylmethyl group, 2-(1-methylpyrrolidin-2-yl)ethylcarbamoylmethyl group, 3-(2-oxopyrrolidin-1-yl)propylcarbamoylmethyl group and 2-(1-benzylpiperidin-4-yl)ethylcarbamoylmethyl group can be specifically mentioned.

[0444] For R², benzyl group, phenethyl group, 3-phenylpropyl group, 2-methoxybenzyl group, 2-(dimethylaminobenzyl) group, 3-methoxybenzyl group, 3-(dimethylamino)benzyl group, 3-phenooxybenzyl group, 4-fluorobenzyl group, 4-chlorobenzyl group, 4-methylbenzyl group, 4-hydroxybenzyl group, 4-methoxybenzyl group, 4-ethylbenzyl group, 4-(diethylaminobenzyl) group, 2-pyrrolidinylmethyl group, 2-pyridinylmethyl group, 2-pyrindinylmethyl group, 2-amino-pyrindin-3-ylmethyl group, 2-acetylaminopyrindin-3-ylmethyl group, 2-(pyrrolidin-1-yl)ethyl group, 2-(2-oxopyrrolidin-1-yl)ethyl group, 2-piperidinoethyl group, 2-(piperazin-1-yl)ethyl group, 2-(4-methylpiperidin-1-yl)ethyl group, 2-(4-ethylpiperidin-1-yl)ethyl group, 2-(1-ethylpiperidin-4-yl)ethyl group, 2-(4-hydroxypiperidin-1-yl)ethyl group, 2-(4-methoxy-piperidin-1-yl)ethyl group, 2-(4-phenoxy-piperidin-1-yl)ethyl group, 2-[4-(dimethylamino)piperidin-1-yl]ethyl group, 2-(1-acetylpirperidin-4-yl)ethyl group, 2-[1-(tert-butoxycarbonyl)piperidin-4-yl]ethyl group, 2-[1-(methanesulfonyl)piperidin-4-yl]ethyl group, 2-[4-(dimethylamino)piperazin-1-yl]ethyl group, 2-[4-(4-methylpiperazin-1-yl)ethyl group, 2-[4-(4-ethylpiperazin-1-yl)ethyl group, 2-[4-(4-isopropylpiperazin-1-yl)ethyl group, 2-[4-(2-[1-(tert-butoxycarbonyl)piperidin-4-yl]ethyl group, 2-[4-(4-benzoylpiperazin-1-yl)ethyl group, 2-[4-(2-dimethylcarboxyl)pyrperazin-1-yl)ethyl group, 2-[4-(4-methanesulfonylpiperazin-1-yl)ethyl group, 2-[4-(2-morpholinocarbonyl)pyrperazin-1-yl)ethyl group, 2-[4-(2-dimethylcarboxyl)pyrperazin-1-yl)ethyl group, 2-[4-(2-morpholinocarbonyl)pyrperazin-1-yl)ethyl group, 2-[4-(4-methanesulfonylpiperazin-1-yl)ethyl group, 3-[1-(2-[1-(4-methoxyethyl)oxy)piperidin-4-yl]ethyl group, 2-[4-(2-morpholinocarbonyl)pyrperazin-1-yl)ethyl group, 2-[4-(4-methanesulfonylpiperazin-1-yl)ethyl group and 2-[4-(2-methoxyethyl)-N-methylamino]ethyl group can be specifically mentioned.

[0447] In addition, for R²,

[0448] 3-oxo-3-piperidinopropyl group,

[0449] 3-morpholino-3-oxopropyl group,

[0450] 3-(4-methylpiperazin-1-yl)-3-oxopropyl group,

[0451] 3-(4-ethylpiperazin-1-yl)-3-oxopropyl group,

[0452] 3-(4-acetyl-piperazin-1-yl)-3-oxopropyl group,

[0453] 3-(4-methoxypiperazin-1-yl)-3-oxopropyl group,

[0454] 3-piperidinopropyl group,

[0455] 3-(4-methylpiperazin-1-yl)-propyl group,

[0456] 3-(4-ethylpiperazin-1-yl)-propyl group,

[0457] 3-(4-acetyl-piperazin-1-yl)-propyl group,

[0458] 3-(4-methanesulfonylpiperazin-1-yl)-propyl group,

[0459] 3-(4-methoxypiperazin-1-yl)-propyl group,

[0460] 3-(3-methoxycarbonylpiperazin-1-yl)-propyl group,

[0461] (tetrahydropryan-4-yl)methyl group,

[0462] 2-(tetrahydropryan-4-yl)ethyl group,

[0463] 2-(1-methylpiperidin-4-yl)ethyl group,

[0464] 2-(1-ethylpiperidin-4-yl)ethyl group,

[0465] 2-(1-acetyl-piperidin-4-yl)ethyl group,

[0466] 2-(1-methanesulfonyl-piperidin-4-yl)ethyl group,

[0467] 2-(1-methoxypiperidin-4-yl)ethyl group,

[0468] 2-(1-methoxycarbonylpiperidin-4-yl)ethyl group,

[0469] 2-(4-methylpiperidin-1-yl)-propyl group,

[0470] 2-(1-methylpiperidin-3-yl)ethyl group,

[0471] 2-(1-ethylpiperidin-3-yl)ethyl group,

[0472] 2-(1-acetyl-piperidin-3-yl)ethyl group,

[0473] 2-(1-methanesulfonyl-piperidin-3-yl)ethyl group,

[0474] 2-(1-methoxypiperidin-3-yl)ethyl group,

[0475] 2-(1-methoxycarbonylpiperidin-3-yl)ethyl group,

[0476] (tetrahydropryan-3-yl)methyl group,

[0477] (1-methylpiperidin-3-yl)methyl group,

[0478] (1-ethylpiperidin-3-yl)methyl group,

[0479] (1-acetyl-piperidin-3-yl)methyl group,

[0480] (1-methanesulfonylpiperidin-3-yl)methyl group,

[0481] (1-methoxypiperidin-3-yl)methyl group,
(1-methoxy carbonyl piperidin-3-yl)methyl group,
2-(tetrahydro pyran-2-yl)ethyl group,
2-(1-methyl piperidin-2-yl)ethyl group,
2-(1-ethyl piperidin-2-yl)ethyl group,
2-(1-acetyl piperidin-2-yl)ethyl group,
2-(1-methanesulfonyl piperidin-2-yl)ethyl group,
2-(1-methoxy piperidin-2-yl)ethyl group,
2-(1-methoxy carbonyl piperidin-2-yl)ethyl group,
2-(tetrahydro pyran-2-yl) methyl group,
(1-methyl piperidin-2-yl) methyl group,
(1-ethyl piperidin-2-yl) methyl group,
(1-(acetyl piperidin-2-yl)methyl group,
(1-methanesulfonyl piperidin-2-yl)methyl group,
(1-methoxy piperidin-2-yl)methyl group,
(1-methoxy carbonyl piperidin-2-yl)methyl group,
2-(2-oxopiperidin-1-yl)ethyl group,
2-(3-oxomorpholin-4-yl)ethyl group,
2-(4-methyl-2-oxopiperazin-1-yl)ethyl group,
2-(4-ethyl-2-oxopiperazin-1-yl)ethyl group,
2-(4-acetyl-2-oxopiperazin-1-yl)ethyl group,
2-(4-methanesulfonyl-2-oxopiperazin-1-yl)ethyl group,
2-(4-methoxy-2-oxopiperazin-1-yl)ethyl group,
3-(4-methoxy carbonyl-2-oxopiperazin-1-yl)ethyl group,
2-(4-ethylidenepiperidin-1-yl)ethyl group,
2-(4-methylenepiperidin-1-yl)ethyl group,
2-(4-isopropylidenepiperidin-1-yl)ethyl group,
2-(1-methyl piperidin-4-ylidene)ethyl group,
2-(1-ethyl piperidin-4-ylidene)ethyl group,
2-(1-acetyl piperidin-4-ylidene)ethyl group,
2-(1-methanesulfonyl piperidin-4-ylidene)ethyl group,
2-(1-methoxy piperidin-4-ylidene)ethyl group,
2-(1-methoxy carbonyl piperidin-4-ylidene)ethyl group,
2-(1-methoxy piperidin-4-yl)oxy)ethyl group,
2-(3-methylpiperidin-1-yl)ethyl group,
2-(azocan-1-yl)ethyl group,
2-(azonan-1-yl)ethyl group,
2-(1,2,3,4-tetrahydroquinolin-1-yl)ethyl group,
2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl group,
2-(octahydrocyclopenta[c]pyrrol-2-yl)ethyl group,
2-(4-trifluoromethylpiperidin-1-yl)ethyl group,
2-(4-propylpiperidin-1-yl)ethyl group,
2-(4-isopropylpiperidin-1-yl)ethyl group,
2-(4,4-dimethylpiperidin-1-yl)ethyl group,
2-(2,2,6,6-tetramethylpiperidin-1-yl)ethyl group,
2-(1,2,3,6-tetrahydropyridin-1-yl)ethyl group,
2-(isoindolin-2-yl)ethyl group,
2-(octahydroisoindol-2-yl)ethyl group,
2-(1-adamantylamino)ethyl group,
2-(2-methylpiperidin-1-yl)ethyl group,
2-(2-dimethylamino)ethyl group,
2-(diethylamino)ethyl group,
2-(diisopropylamino)ethyl group,
2-(4-methoxycarbonylpiperazin-1-yl)-2-oxoethyl group,
2-(4-methylcarbamoylpiperazin-1-yl)-2-oxoethyl group,
2-(3-(2-methoxyacetyl)piperazin-1-yl)-2-oxoethyl group,
2-(4-cyclopentoxycarbonylpiperazin-1-yl)-2-oxoethyl group,
2-(4-benzylpiperazin-1-yl)-2-oxoethyl group,
2-(4-isobutyrylpiperazin-1-yl)-2-oxoethyl group,
2-(4-methoxycarbonylpiperazin-1-yl)ethyl group,
2-(4-methylcarbamoylpiperazin-1-yl)ethyl group,
2-(4-(2-methoxyacetyl)piperazin-1-yl)ethyl group,
2-(4-cyclopentoxycarbonylpiperazin-1-yl)ethyl group,
2-(4-benzylpiperazin-1-yl)ethyl group,
2-(4-isobutyrylpiperazin-1-yl)ethyl group,
methylcarbamoyl group,
tert-butylcarbamoyl group,
N-tert-butyl-N-methylcarbamoyl group,
cyclohexylcarbamoyl group,
tetrahydropryan-4-yl)carbamoyl group,
(1-methylpiperidin-4-yl)carbamoyl group,
(1-acetyl)piperidin-4-yl)carbamoyl group,
(1-methanesulfonylpiperidin-4-yl)carbamoyl group,
(1-methoxycarbonylpiperidin-4-yl)carbamoyl group,
cyclopentylcarbamoyl group,
(tetrahydrofuran-3-yl)carbamoyl group,
(1-methylpyrrolidin-3-yl)carbamoyl group,
(1-acetyl)pyrrolidin-3-yl)carbamoyl group,
(1-methanesulfonylpyrrolidin-3-yl)carbamoyl group,
(1-methoxycarbonylpyrrolidin-3-yl)carbamoyl group,
N-cyclohexyl-N-methylcarbamoyl group,
N-methyl-N-(tetrahydropryan-4-yl)carbamoyl group,
N-methyl-N-(1-methylpiperidin-4-yl)carbamoyl group,
(1-acetyl)piperidin-4-yl)-N-methylcarbamoyl group,
(1-methanesulfonylpiperidin-4-yl)-N-methylcarbamoyl group,
(1-methoxycarbonylpiperidin-4-yl)-N-methylcarbamoyl group,
N-cyclopentyl-N-methylcarbamoyl group,
N-methyl-N-(tetrahydrofuran-3-yl)carbamoyl group,
N-methyl-N-(1-methylpyrrolidin-3-yl)carbamoyl group,
N-(1-acetyl)pyrrolidin-3-yl)-N-methylcarbamoyl group,
(1-methanesulfonylpyrrolidin-3-yl)-N-methylcarbamoyl group,
(1-methoxycarbonylpyrrolidin-3-yl)-N-methylcarbamoyl group,
N-(N-tert-butyl-N-methylcarbamoyl group,
N-(3-(2-methoxyacetyl)piperidin-1-yl)-N-methylcarbamoyl group,
(1-methanesulfonylpyrrolidin-3-yl)-N-methylcarbamoyl group,
(1-methoxycarbonylpyrrolidin-3-yl)-N-methylcarbamoyl group,
(2-(N-acetyl-N-methylamino)ethyl group,
(2-(N-methyl-N-propionylamino)ethyl group,
(2-(N-cyclohexanecarbonyl-N-methylamino)ethyl group,
(2-(N-methyl-N-(tetrahydropryan-4-carbonyl)-l-amino)ethyl group,
(2-(N-methyl-N-(1-methylpiperidine-4-carbonyl)-l-amino)ethyl group,
(2-(N-1-acetyl)piperidine-4-carbonyl)-N-methylamino)ethyl group,
(2-(N-1-methanesulfonylpiperidine-4-carbonyl)-N-methylamino)ethyl group,
(2-(N-1-methoxycarbonylpiperidine-4-carbonyl)-N-methylamino)ethyl group,
(2-(N-cyclopentanecarbonyl-N-methylamino)ethyl group,
[0626] 2-(N-methyl-N-(1-methylpyrrolidine-3-carbonylamino)ethyl group,
[0627] 2-(N-(1-acetylpyrrolidine-3-carbonyl)-N-methylamino)ethyl group,
[0628] 2-(N-(1-methanesulfonyl)pyrrolidine-3-carbonyl)-N-methylamino)ethyl group,
[0629] 2-(N-(1-methoxy)carbonylpyrrolidine-3-carbonyl)-N-methylamino)ethyl group,
[0630] 2-(N-methanesulfonyl-N-methylamino)ethyl group,
[0631] 2-(N-methoxycarbonyl-N-methylamino)ethyl group,
[0632] 2-(N-ethoxycarbonyl-N-methylamino)ethyl group,
[0633] 2-(N-cyclohexyloxycarbonyl-N-methylamino)ethyl group,
[0634] 2-(N-methyl-N-(tetrahydropryan-4-yloxy)carbonylamino)ethyl group,
[0635] 2-(N-methyl-N-(1-methylpiperidin-4-yloxy)carbonylamino)ethyl group,
[0636] 2-(N-(1-acetyl piperidin-4-yloxy)carbonyl)-N-methylamino)ethyl group,
[0637] 2-(N-(1-methanesulfonyl)piperidin-4-yloxy carbonyl)-N-methylamino)ethyl group,
[0638] 2-(N-(1-methoxy) carbonylpiperidin-4-yloxy carbonyl)-N-methylamino)ethyl group,
[0639] 2-(N-cyclopentyl oxycarbonyl-N-methylamino)ethyl group,
[0640] 2-(N-methyl-N-(tetrahydrofuran-3-yloxy)carbonylamino)ethyl group,
[0641] 2-(N-methyl-N-(1-methylpyrrolidin-3-yloxy)carbonylamino)ethyl group,
[0642] 2-(N-(1-acetylpyrrolidin-3-yloxy)carbonyl)-N-methylamino)ethyl group,
[0643] 2-(N-(1-methanesulfonyl)pyrrolidin-3-yloxy)carbonyl)-N-methylamino)ethyl group, and
[0644] 2-(N-(1-methoxy)carbonylpiperidin-3-yloxy)carbonyl)-N-methylamino)ethyl group can be mentioned.

[0645] As specific examples of R², the following groups can be mentioned.
[0646] 2-(4-acetyl piperazin-1-yl)ethyl group,
[0647] 3-(tetrahydropryan-2-yloxy)propyl group,
[0648] 2-(1-isopropyl piperidin-4-yl)ethyl group,
[0649] 2-(3,6-dihydro-2H-pyridin-1-yl)-2-oxoethyl group,
[0650] 2-(octahydroquinolinin-1-yl)-2-oxoethyl group,
[0651] 2-(1,3-dihydroisoindol-2-yl)-2-oxoethyl group,
[0652] 2-(octahydroquinolinin-2-yl)-2-oxoethyl group,
[0653] 2-(octahydroquinolinin-1-yl)ethyl group,
[0654] 2-(1,3-dihydroisoindol-2-yl)ethyl group,
[0655] 2-(octahydroisoquinolinin-2-yl)ethyl group,
[0656] 3-dimethylaminopropyl group,
[0657] 1-tert-butoxycarbonylpiperidin-3-ylmethyl group
[0658] 2-(1-cyclopropyl piperidin-4-yl)ethyl group,
[0659] 2-(1-tert-butoxycarbonylpiperidin-2-yl)ethyl group,
[0660] 2-(piperidin-3-yl)ethyl group,
[0661] 1-tert-butoxycarbonylpiperidin-3-yl)ethyl group,
[0662] 2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl group,
[0663] 2-(1-propyl piperidin-4-yl)ethyl group,
[0664] 2-(4,4-difluoropiperidin-1-yl)ethyl group,
[0665] 2-(1-ethyl piperidin-4-ylidene)-2-fluoropropyl group,
[0666] cis-2-(octahydroisoindol-2-yl)ethyl group,
[0667] 2-(8-azaspiro[4,5]decan-8-yl)ethyl group,
[0668] 2-(3,5-dimethyl piperidin-1-yl)-2-oxoethyl group,
[0669] 2-(3-ethyl piperidin-1-yl)ethyl group,
[0670] 2-(cis-2,6-dimethyl piperidin-1-yl)ethyl group,
[0671] 3-azepan-1-yl)propyl group,
[0672] 2-(4-methoxymethyl piperidin-1-yl)ethyl group,
[0673] 2-(N-methyl-N-propylamino)ethy group,
[0674] 2-(3-methoxymethyl piperidin-1-yl)ethyl group,
[0675] 2-(1-isopropyl piperidin-3-yl)ethyl group,
[0676] 2-(3,6-dihydro-2H-pyridin-1-yl)ethyl group,
[0677] 2-((S)-2-methoxymethylpyrrolidin-1-yl)ethyl group,
[0678] 2-(2-methylpyrrolidin-1-yl)ethyl group,
[0679] 2-(N-isobutyl-N-methylamino)ethyl group,
[0680] 2-(N-isopropyl-N-methylamino)ethyl group,
[0681] 2-(N-(2-dimethylaminoethyl)-N-methylamino)ethyl group,
[0682] 2-(4-ethanesulfonylpiperazin-1-yl)ethyl group,
[0683] 2-(4-propionyl piperazin-1-yl)ethyl group,
[0684] 2-(4-isopropoxycarbonylpiperazin-1-yl)ethyl group,
[0685] 2-(1-propyl piperidin-3-yl)ethyl group,
[0686] 2-(N-cyclohexyl-N-methylamino)ethyl group,
[0687] 2-(4-methanesulfonyl-1,4-diazepan-1-yl)ethyl group,
[0688] 2-(4-methoxycarbonyl-1,4-diazepan-1-yl)ethyl group,
[0689] 2-(3-methylpyrrolidin-1-yl)ethyl group,
[0690] 2-(3-methoxypyrrolidin-1-yl)ethyl group,
[0691] 2-(piperidin-4-yl)ethyl group,
[0692] 2-(1-methyl piperidin-4-yl)ethyl group,
[0639] 2-[N-(1-methoxy carbonyl)pyrrolidin-3-yl]-N-methylamino]ethyl group,
[0649] 2-[N-(1-acetyl pyrrolidin-3-yl)-N-methylamino]ethyl group,
[0659] 2-[N-(1-methanesulfonyl)pyrrolidin-3-yl]-N-methylamino]ethyl group,
[0669] 2-(2-methylmorpholin-4-yl)ethyl group,
[0679] 2-(2-ethylmorpholin-4-yl)ethyl group,
[0689] 2-(3-ethyl morpholin-4-yl)ethyl group,
[0699] 2-(1-isobutylpiperidin-3-yl)ethyl group,
[0700] 2-(1-cyclo pentylpiperidin-3-yl)ethyl group,
[0701] 2-(3-propylpiperidin-1-yl)ethyl group,
[0702] 3-[pyrrolidin-1-yl]propyl group,
[0703] 3-[1,4-oxazepan-4-yl]propyl group,
[0704] 2-(2-methoxymethylpiperidin-1-yl)ethyl group,
[0705] 2-[N-(1-acetyl piperidin-4-yl)-N-methylamino]ethyl group,
[0706] 2-[N-(1-methanesulfonyl)piperidin-4-yl]-N-methylamino]ethyl group,
[0707] 2-[N-(1-methoxy carbonyl)piperidin-4-yl]-N-methylamino]ethyl group,
[0708] 2-[N-methyl-N-(1-methyl piperidin-4-yl)amino]ethyl group,
[0709] 2-[N-methyl-N-(tetrahydropran-4-yl)amino]ethyl group,
[0710] 2-[N-methyl-N-(1-methyl pyrrolidin-3-yl)amino]ethyl group,
[0711] 2-[N-methyl-N-(pyrrolidin-3-yl)amino]ethyl group,
[0712] 3-diethylaminopropyl group,
[0713] 2-[3-(2-methoxyethyl)piperidin-1-yl]ethyl group,
[0714] 2-[(R)-2-methoxymethylpyrro lidin-1-yl]ethyl group,
[0715] 2-[1-isopropylpiperidin-4-yl]oxyxy]ethyl group,
[0716] 2-(N-cyclopentyl-N-methylamino)ethyl group,
[0717] 3-(3-methylpiperidin-1-yl)propyl group,
[0718] 2-[N-methyl-(tetrahydrofur an-3-yl)amino]ethyl group,
[0719] 3-[2-methylpiperidin-1-yl]propyl group,
[0720] 2-[N,N-dimethy l-(5-methylisoxazol-3-yl)m amino]ethyl group,
[0721] 3-(2-methoxymethylpiperidin-1-yl)propyl group,
[0722] 2-(2-ethylpiperidin-1-yl)ethyl group,
[0723] 2-((S)-3-ethylpiperidin-1-yl)ethyl group,
[0724] 2-((R)-3-ethylpiperidin-1-yl)ethyl group,
[0725] 2-(1-cyclo propylpiperidin-3-yl)ethyl group,
[0726] 3-[3-methoxymethylpiperidin-1-yl]propyl group,
2-\{(S)-3-\text{phenoxy}methylpiperidin-1-yl\}ethyl group,
2\{(S)-3-\text{phenoxy}methylpiperidin-1-yl\}ethyl group,
2\{(7-benzyl-7-azabicyclo[2.2.1]hept-1-yl\}ethyl group,
2\{(7-azabicyclo[2.2.1]hept-1-yl\}ethyl group,
2\{(7-carboxymethyl-7-azabicyclo[2.2.1]hept-1-yl\}ethyl group,
2-\text{cyclohexylethyl} group,
2\{(S)-3-\text{2-hydroxy}ethylpiperidin-1-yl\}ethyl group,
2\{(S)-3-\text{2-hydroxy}ethylpiperidin-1-yl\}ethyl group,
2\{(R)-3-\text{phenoxy}methylpiperidin-1-yl\}ethyl group,
2\{(4-2-methoxyethyl)piperidin-1-yl\}ethyl group,
3\text{diethylamino}-2-\text{hydroxypropyl} group,
2\{(4-acetyl-1,4-diazepan-1-yl\}ethyl group,
2\{(S)-3-\text{2-ethoxy}ethylpiperidin-1-yl\}ethyl group,
2\{(5-oxo-1,4-diazepan-1-yl\}ethyl group,
2\{(4-methoxyazepan-1-yl\}ethyl group,
2\{(4-methyl-5-oxo-1,4-diazepan-1-yl\}ethyl group,
2\{(S)-3-\text{N-dimethylcarbamoylmethyl}piperidin-1-y}l\}ethyl group,
2\{(R)-3-\text{2-methoxyethyl}piperidin-1-yl\}ethyl group,
2\{(S)-3-\text{2-hydroxy}2-\text{methylpropyl}piperidin-1-yl\}ethyl group,
2\{(N-ethyl-N-(3-methoxypropyl)amino\}ethyl group,
2\{(6-methyl-1,4-oxazepan-4-yl\}ethyl group,
2\{(R)-3-\text{1-hydroxy}-1-\text{methylthyl}piperidin-1-yl\}ethyl group,
2\{(1-2-methoxyethyl)piperidin-3-yl\}ethyl group,
2\{(4-oxazepan-1-yl\}ethyl group,
2\{(S)-3-\text{2-dimethylcarbamoylethyl}piperidin-1-yl\}ethyl group,
2\{(4-hydroxyazepan-1-yl\}ethyl group,
2\{(N-ethyl-N-(4-methoxybutyl)amino\}ethyl group,
2\{(S)-3-\text{2-methoxypropyl}piperidin-1-yl\}ethyl group,
2\{(R)-3-\text{1-methoxy}-1-\text{methylthyl}piperidin-1-yl\}ethyl group,
2\{(3-dimethylcarbamoylpiperidin-1-yl\}ethyl group,
2\{(R)-3-\text{2-methoxyethoxy}piperidin-1-yl\}ethyl group,
2\{(3-methoxyethylazepan-1-yl\}ethyl group,
2\{(S)-3-\text{2-(N-acetyl-N-methylamino)ethyl}piperidin-1-yl\}ethyl group,
wherein each symbol is as defined above, more preferred are a hydrogen atom, a halogen atom, “a \( C_{1,6} \) alkyl group optionally substituted by 1 to 3 substituents selected from group A”, “—(CH\(_2\))\(_n\)—OR\(^{d1}\)”, “—(CH\(_2\))\(_n\)—S(O)\(_n\)=—R\(^{d2}\)” and

![Diagram](image)

wherein each symbol is as defined above.

0815 For Y, preferred is —(CH\(_2\))\(_n\)—O—(CH\(_2\))\(_n\)— (wherein each symbol is as defined above), more preferred are —O—CH\(_2\)— and —O—, still more preferably is —O—CH\(_2\)—.

0816 Other preferable embodiment of Y is —NR\(^{d1}\)—(CH\(_2\))\(_n\)—Y\(^{d2}\)—, more preferably, —NR\(^{d1}\)—CH\(_2\)—CO— or —NR\(^{d1}\)—(CH\(_2\))\(_n\)—.

0817 For R\(^{d1}\), preferred is “a heterocycle \( C_{1,6} \) alkyl group optionally substituted by 1 to 5 substituents selected from group B” or —(CH\(_2\))\(_n\)—COR\(^{d1}\). For R\(^{d1}\), preferred is “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group B”.

0818 For ring B, preferred are a \( C_{6,14} \) aryl group and “a heterocyclic group comprising 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom”, more preferred are phenyl group, pyridyl group, piperidyl group, pyrrolidinyl group, pyridazinyl group, piperazinyl group, morpholinyl group, azepanyl group, 1,4-oxazepanyl group, isoazolyl group, thiazolyl group and 2-oxoazolidinyl group, more preferred are phenyl group, pyridyl group and piperidyl group, and still more preferred is phenyl group.

0819 For Z, preferred are 1 to 3 substituents selected from

(1) a hydrogen atom,
(2) a halogen atom,
(3) a nitro group,
(4) a \( C_{6,14} \) aryl group optionally substituted by 1 to 5 substituents selected from group D,
(5) a \( C_{3,10} \) cycloalkyl group optionally substituted by 1 to 5 substituents selected from group D,
(6) a heterocyclic group optionally substituted by 1 to 5 substituents selected from group D,
(7) a \( C_{1,6} \) alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,

—(CH\(_2\))\(_n\)—OR\(^{d1}\),

—(CH\(_2\))\(_n\)—S(O)\(_n\)=—R\(^{d2}\),

—(CH\(_2\))\(_n\)—NR\(^{d1}\)R\(^{d4}\),

(8) —(CH\(_2\))\(_n\)—COOR\(^{d5}\),

(9) —(CH\(_2\))\(_n\)—CONR\(^{d6}\)R\(^{d7}\),

(10) —(CH\(_2\))\(_n\)—COR\(^{d8}\),

(11) —(CH\(_2\))\(_n\)—NR\(^{d1}\)CO—R\(^{d10}\),

(12) —(CH\(_2\))\(_n\)—NR\(^{d1}\)SO\(_2\)—R\(^{d12}\) and

(13) —(CH\(_2\))\(_n\)—NR\(^{d1}\)SO\(_2\)—R\(^{d12}\) and

(14) —(CH\(_2\))\(_n\)—NR\(^{d1}\)CO—R\(^{d10}\),

(15) —(CH\(_2\))\(_n\)—NR\(^{d1}\)SO\(_2\)—R\(^{d12}\) and

(16) —(CH\(_2\))\(_n\)—NR\(^{d1}\)COOR\(^{d20}\)

(wherein each symbol is as defined above), more preferably, 1 to 3 substituents selected from

(1) a hydrogen atom,
(2) a halogen atom,
(3) a \( C_{6,14} \) aryl group optionally substituted by 1 to 5 substituents selected from group D,
(4) a heterocyclic group optionally substituted by 1 to 5 substituents selected from group D,
(5) —(CH\(_2\))\(_n\)—OR\(^{d1}\),

—(CH\(_2\))\(_n\)—S(O)\(_n\)=—R\(^{d2}\),

—(CH\(_2\))\(_n\)—NR\(^{d1}\)R\(^{d4}\),

—(CH\(_2\))\(_n\)—COOR\(^{d5}\),

—(CH\(_2\))\(_n\)—NR\(^{d1}\)CO—R\(^{d10}\),

—(CH\(_2\))\(_n\)—NR\(^{d1}\)SO\(_2\)—R\(^{d12}\),

—(CH\(_2\))\(_n\)—NR\(^{d1}\)SO\(_2\)—R\(^{d12}\), and

—(CH\(_2\))\(_n\)—NR\(^{d1}\)COOR\(^{d20}\)

(wherein each symbol is as defined above).

0820 The “\( C_{6,14} \) ary1 group” of the “\( C_{6,14} \) ary1 group optionally substituted by 1 to 5 substituents selected from group D” for Z is preferably a phenyl group.

0821 The “heterocyclic group” of the “heterocyclic group optionally substituted by 1 to 5 substituents selected from group D” for Z is preferably a pyrroldinyl group, a 2-oxopyrroldinyl group, a piperidinyl group, a piperazinyl group or a morpholinyl group.

0822 When Z is “a \( C_{6,14} \) aryl group optionally substituted by 1 to 5 substituents selected from group D” or “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group D”, the group D is preferably a hydrogen atom, “\( C_{1,6} \) alkyl group optionally substituted by 1 to 3 substituents selected from A”, “—(CH\(_2\))\(_n\)—S(O)\(_n\)=—R\(^{d2}\)” or “—(CH\(_2\))\(_n\)—CONR\(^{d6}\)R\(^{d7}\)”.

0823 With regard to group D in Z,

for R\(^{d1}\), preferred are a hydrogen atom and a \( C_{1,6} \) alkyl group,

for R\(^{d2}\), preferred are a hydrogen atom and a \( C_{1,6} \) alkyl group,

preferably, R\(^{d3}\) and R\(^{d4}\) are each independently a hydrogen atom or a \( C_{1,6} \) alkyl group,

for R\(^{d5}\), preferred are a hydrogen atom and a \( C_{1,6} \) alkyl group,

for R\(^{d6}\), preferred are a hydrogen atom, a \( C_{1,6} \) alkyl group and a \( C_{1,6} \) alkenyl group,

for R\(^{d7}\), preferred are a \( C_{1,6} \) alkyl group optionally substituted by —NR\(^{d6}\)R\(^{d2}\) and a heterocycle \( C_{1,6} \) alkyl group (wherein the heterocycle \( C_{1,6} \) alkyl group is preferably a morpholinomethyl group),
for R°12, preferred are a hydrogen atom, a C₁₋₆ alkyl group and a C₁₋₆ alkanoyl group,
for R°12, preferred are a hydrogen atom and a C₁₋₆ alkyl group,
for the "C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from A", preferred is a C₁₋₆ alkyl group.

[0824] X is specifically hydrogen atom, methyl group, ethyl group, propyl group, isopropyl group, tert-butyl group, fluoromentic, chlorine atom, bromine atom, trifluoromethyl group, hydroxyl group, methoxy group, ethoxy group, isoprogoxy group, methylsulfanly group, trifluoromethoxy group, cyano group, nitro group, amino group, dimethylamino group, phenyl group, pyridyl group (2-pyridyl group, 3-pyridyl group, 4-pyridyl group), carboxyl group, carboxyl group, 2-methoxyethoxy group, 2-(2-hydroxyethylamino)ethoxy group, 2-dimethylaminoethoxy group, carboxymethoxy group, methoxycarboxyloxy group and the like can be mentioned.
X is more specifically
-continued

-continued

-continued

-continued
-continued

-continued
and the like can be mentioned.

[0825] In the formula [I], moreover, a compound represented by the following formula [I-A], [I-B] or [I-C] is particularly preferable.
wherein X is a hydrogen atom, a halogen atom, "a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from group A" or "—OR_{3-6}", and other symbols are as defined above.

wherein Q is —O— or —NH—, and other symbols are as defined above.

wherein Q is —O— or —NR—, X is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from group A or —OR_{3-6}, and other symbols are as defined above.

The "carboxyl-protecting group" only needs to be suitable for reaction conditions, and is capable of protecting and deprotecting the group, for example, methyl; substituted methyl group such as methoxymethyl, methythiomethyl, 2-tetrahydropranyl, methoxyethoxymethyl, benzoxymethyl, phenacyl, diaclyamethyln, phthaliamidomethyl etc.; ethyl; substituted ethyl group such as 2,2,2-trichloroethy1, 2-chloroethyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 2-(p-toluenesulfonyl)ethyl, t-butyl etc.; benzyl; substituted benzyl group such as diphenylmethyl, triphenylmethyl, p-nitrobenzyl, 4-picolyl, p-methoxybenzyl, 2-(9,10-dioxoanthrylmethyl) ethyl etc.; silyl group such as trimethylsilyl, t-butyldimethylsilyl, phena(dimethylethylsilyl; and the like.

The "pharmaceutically acceptable salt" may be any as long as it forms a non-toxic salt with a compound of the above-mentioned formula [1]. Such salt can be obtained by reacting the compound with an inorganic acid, such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; or an organic acid, such as oxalic acid, malonic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid, trifluoroacetic acid, gluconic acid, ascorbic acid, methylsulfonic acid, benzenesulfonic acid, meglumine acid and the like; or an inorganic base, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonium hydroxide and the like; or an organic base, such as methylamine, diethylamine, triethylamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)methylamine, guanidine, choline, cinchonine and the like; with an amino acid, such as lysine, arginine, alanine and the like. The present invention encompasses water-retaining product, hydrate and solvate of each compound.

The present invention also encompasses a prodrug and a metabolite of each compound.

A "prodrug" means a derivative of the compound of the present invention, which is capable of chemical or metabolic decomposition, which shows inherent efficacy by reverting to the original compound after administration to a body, and which includes salts and complexes without a covalent bond.

A prodrug is utilized for, for example, improving absorption by oral administration, or targeting of a target site.

As the modification moiety, a functional group having high reactivity in the compound of the present invention can be mentioned such as hydroxyl group, carboxyl group, amino group, thiol group and the like.

As preferable embodiments of the compound of the present invention, a compound having fine pharmacological activity (e.g., a compound having strong polymerase inhibitory activity, a compound having strong inhibitory activity on enzyme complex comprising polymerase, a compound having strong HCV replicon-inhibitory activity, a compound having high anti-HCV activity in HCV infected cells and the like), a compound having fine bioavailability (e.g., a compound showing high oral absorbability, a compound having high cell-permeability, a compound stable to metabolic enzyme, a compound with low binding ability to protein and the like), a highly safe compound (e.g., a compound free of immunogenicity or showing low allergic response, a compound free of or low in increase in bilirubin value, a
compound showing low P450 (CYP)-inhibitory activity and the like) and the like can be mentioned.

[0834] When the inventive compound is used as a pharmaceutical preparation, the inventive compound is generally admixed with pharmaceutically acceptable carriers, excipients, diluents, binders, disintegrants, preservatives, buffers, emulsifiers, aromatics, coloring agents, sweeteners, thickeners, correctives, solubilizers known per se, and other additives such as water, vegetable oil, alcohol such as ethanol, benzyl alcohol and the like, polyethylene glycol, glycerol trisaceta, gelatin, lactose, carbohydrate such as starch and the like, magnesium stearate, talc, lanolin, petrolatum and the like, and prepared into a dosage form of tablets, pills, powders, granules, suppositories, injections, eye drops, liquids, capsules, troches, aerosols, elixirs, suspensions, emulsions, syrups and the like, which can be administered systemically or topically and orally or parenterally.

[0835] While the dose varies depending on the age, body weight, general condition, treatment effect, administration route and the like, it is from 0.01 mg to 3 g for an adult per dose, which is given one to several times a day.

[0836] The “prophylaxis of hepatitis C” means, for example, administration of a pharmaceutical agent to an individual found to carry an HCV by a test and the like but without a symptom of hepatitis C, or to an individual who shows an improved disease state of hepatitis after a treatment of hepatitis C, but who still carries an HCV and is associated with a risk of recurrence of hepatitis.

[0837] The therapeutic agent for hepatitis C of the present invention is expected to provide a synergistic effect when concurrently used with other antiviral agents, antiinflammatory agents or immunostimulants.

[0838] The medicaments with the prospect of synergistic effect include, for example, interferon-α, interferon-β, interferon-γ, interleukin-2, interleukin-8, interleukin-10, interleukin-12, TNF-α, recombinant or modified products thereof, agonists, antibodies, vaccines, ribozymes, antisense nucleotides and the like.

[0839] As evidenced in the combination therapy of anti-HIV agents, which is also called a cocktail therapy, the combined use of various anti-virus agents against viruses showing frequent genetic mutations is expected to show effect for suppressing emergence and increase of drug tolerant viruses. For example, 2 or 3 agents from HCV-RES inhibitors, HCV-NS3 protease inhibitors, HCV-NS2/NS3 protease inhibitors, HCV-NS5A inhibitors and HCV polymerase inhibitors may be used in combination. Specifically, the combined use with Ribavirin(R), interferon-α (IFN-α), Reoften(R), Intron A(R), Sumiferon(R), Multiferon(R), interferon(R), Ornferon(R), Pegásys(R), PEG-Intron A(R)), interferon-β (Fron(R), Rebi(R), AvoneX(R), IFNβMOCHIDA(R)), interferon-α, 1β-L-ribofuransosyl-1H-1,2,4-triazole-3-carboxamide, 16α-bromo-3β-hydroxy-5α-androstan-17-one, 11β-imidazol-4-ethanamine dihydrochloride, HCV ribozyme Pehtazyme(R), polyclonal antibody Civa(O(R), lactoferrin GPX-400, (1S,2R,8R,8αR)-1,2,8-trihydroxyoctahydroindolizidin chloride, HCV vaccine (MTH-68/B, Innivax C(R), Lingex(R)), anti-sense oligonucleotide SIS-14803, HCV-RNA transcriptase inhibitor VP-50406, tetrachlorodecaoxide (high concentration Oxoferrin(R)), tetrahydrofurunit-3-y1 (S)-N-3-[3-(3-methoxy-4-oxazol-5-ylphenyl)ureido]benzylcarbamate, 4-amino-2-ethoxyethyl-α,-α-dimethyl-1H-imidazol[4,5-c] quinoline-1-ethanol, interleukin-2 (Proleukin(R)), thyro- alan and the like is exemplified, wherein (R) shows product names.


[0841] In the case of combined administration, the compound of the present invention can be administered simultaneously with a pharmaceutical agent to be used in combination (hereinafter combination drug) or administered at certain time intervals. In the case of combined administration, a pharmaceutical composition containing the compound of the present invention and a combination drug can be administered. Alternatively, a pharmaceutical composition containing the compound of the present invention and a pharmaceutical composition containing a combination drug may be administered separately. The administration route of the compound of the present invention and that of the combination drug may be the same or different.

[0842] In the case of a combined administration, the compound of the present invention can be administered once a day or several times a day in a single dose of 0.1 mg to 1 g, or may be administered at a smaller dose. The combination drug can be administered at a dose generally used for the prevention or treatment of hepatitis C, for example, at a single dose of 0.2 mg to 0.8 mg. Alternatively, it may be administered at a smaller dose.

[0843] Inasmuch as HCV is known to be a virus associated with many genetic mutations, a compound effective for many genotypes is one of the preferable modes. If a compound ensures high blood concentration and sustentation thereof when administered as a pharmaceutical agent to an animal infected with HCV, it is also one of the preferable modes. From these aspects, a compound having high inhibitory activity on both HCV type 1a and type 1b and high blood concentration is particularly preferable.

[0844] Examples of the Production Method of the compound to be used for the practice of the present invention are
given in the following. However, the Production Method of
the compound of the present invention is not limited to these
examples.

[0845] Even if no directly corresponding disclosure is
found in the following Production Methods, the steps may
be modified for efficient production of the compound, such
as introduction of a protecting group into a functional group
with deprotection in a subsequent step, and changing the
order of Production Methods and steps.

[0846] The treatment after reaction in each step may be
conventional ones, for which typical methods, such as
isolation and purification, crystallization, recrystallization,
silica gel chromatography, preparative HPLC and the like,
can be appropriately selected and combined.

REFERENCE EXAMPLE 1

[0847]

\[ \text{wherein } Q^{10} \text{ is, for example, } O \text{ or } NH, R^4 \text{ is a leaving group such as bromine atom, iodine atom, } -OTF \text{ (trifluorometh}

ylsulfonyloxy group) and the like, } -B(OR^{11})(OR^{12}) \text{ is } -B(OH)_{2}, \]

4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl group, ring A' is ring A wherein G^{5} is carbon atom, and other
symbols are as defined above.

[0848] Compound [2] can be obtained from commercially
available compound [1] or compound [1] obtained by a
conventional method and a boric acid ester.

[0849] As the boric acid ester, pinacolborane, bis(pinacolato)diboron and the like can be mentioned.

[0850] As a catalyst, palladium catalysts such as
Pd(PPh\_3)\_4, Pd(dppb)Cl\_2, PdCl\_2(dppf)CH\_2Cl\_2,
PdCl\_2(PPh\_3)_2, Pd(OAc)_2, PdCl\_2, palladium black, palladium
carbon and the like can be mentioned.

[0851] As a base, strong bases such as ethylenediamine,
sodium carbonate, barium hydroxide, potassium phosphate,
cesium carbonate, sodium hydrogen carbonate, sodium tert-
butoxide, potassium tert-butoxide, triethylamine, potassium
acetate and the like are generally preferable. As the ligand,
triphenylphosphine, tri(2-tolyl)phosphine, (2-biphenyl)di-
cyclohexylphosphate and the like may be added.

[0852] In addition, compound [1] may be reacted with a
boric acid ester such as triisopropyl borate, trimethyl borate
and the like in the presence of n-butyllithium. Where
necessary, a protecting group may be introduced into -Q^{10}H
and the protected compound may be subjected to the reaction.

[0853] As a solvent, 1,4-dioxane, THF (tetrahydrofuran),
toluene, dimethoxyethane, water and the like can be men-
tioned.

REFERENCE EXAMPLE 2

[0854]

WHEREIN [4] IS, FOR EXAMPLE, A COMPOUND WHEREIN
cycloalkyl group having 3 to 10 carbon atoms is substituted
by oxo group, such as cyclopentanone, cyclohexanone and
the like.

Step 1

[0855] Compound [5] can be obtained by reacting com-
by a conventional method with compound [4] in the
presence of a base, or under aldol reaction conditions.

[0856] As a base, preferably, sodium methoxide, sodium
ethoxide, lithium diisopropylamide, sodium hydroxide,
potassium hydroxide, sodium hydride and the like can be
mentioned.

[0857] As a solvent, alcohol solvent such as methanol,
ethanolo and the like, THF, 1,4-dioxane, DMF (dimethylform-
amide), DMSO (dimethyl sulfoxide), DMA (dimethylac-
etaimide), water and a mixed solvent thereof and the like can
be mentioned.

[0858] As the reaction temperature, -20°C to 120°C is
preferable.

[0859] In addition, for a reaction under acidic conditions,
in a mixed solvent of acetic acid and phosphoric acid, they
may be treated at a reaction temperature of from 15°C to
20°C.

Step 2

[0860] Compound [6] can be obtained by hydrogenation
of compound [5] in a solvent such as methanol, ethanol,
THF, ethyl acetate, acetic acid, formic acid, water and the
like, in the presence of a catalyst such as palladium carbon,
palladium hydroxide, palladium hydroxide on carbon, plat-
innium oxide, Raney-nickel and the like, at room temperature
or under heating.
wherein $R^{e4}$ is carboxyl-protecting group such as methyl group, ethyl group, tert-butyl group, benzyl group and the like, $Hal^1$ is halogen atom such as bromine atom, iodine atom and the like, and other symbols are as defined above.

Step 1

[0862] Compound [8] can be obtained by introducing a protecting group into a carboxyl group of compound [7] obtained by a conventional method or in the same manner as in Reference Example 2.

[0863] Where necessary, a protecting group may be introduced into a nitrogen atom of indole.

Step 2


[0865] As the halogenating agent, bromine, N-bromosuccinimide, pyridine tribromide, dibromohydantoin, pyridinium hydrobromide perbromide, an iodide thereof and the like can be mentioned.

[0866] As a solvent, halogen solvents (dichloromethane, chloroform, carbon tetrachloride etc.), hydrocarbon solvents (toluene etc.), ether solvents (1,4-dioxane, DME (1,2-dimethoxyethane), THF etc.), acetic acid, ethyl acetate, isopropyl alcohol or a mixed solvent thereof and the like can be mentioned.

[0867] As the reaction temperature, from $-40^\circ$ C. to $100^\circ$ C. is preferable.

Production Method 1
-continued

![Chemical structures and reactions](image)
wherein c' is an integer of 1 to 4,

\[
\begin{align*}
Q^{11} & \text{ is } -O-, -S-, -OCO-, -OCONH-, -NHCO-, -NHSO_2-, -NHCOO-, -COO-, -CONH-, -SO_2NH-, -NHCONH-, -NH_2NH-, -CH=CH-, -CH=\text{N} & \text{ or } -N=CH-, \\
R^{15} & \text{ is } -OH, -SH, -NH_2, -COOH, -SO_2NH_2, \text{ a protected group thereof or } -CHO, \\
R^{16} & \text{ is } -OH, -SH, -NH_2, -COOH, -SO_2NH_2 \text{ or } -CHO, \\
R^{17} & \text{ is a leaving group such as Hal}^2 \text{ (wherein Hal}^2 \text{ is halogen atom such as chlorine atom, bromine atom and the like), } -OMs \text{ (mesityloxy group), } -OTs \text{ (tosylxy group), } -OTf \text{ and the like or a protected OH group,} \\
R^{18} & \text{ is } -OH, -NH_2, -COOH, -CHO, -COHal^2, -OCOHal^2, -SO_2Hal^2, -NHSO_2Hal^2, -OC(=\text{NH})C(Hal), \text{ (wherein Hal is halogen atom such as fluorine atom, chlorine atom and the like), } -NCO, \text{ Hal}^2 \text{ or } -P(\text{Ph})_3, \\
R^{19} & \text{ is a leaving group such as Hal}^2, -OMs \text{ or } -OTs \text{ and the like, compound [11] is a metal compound, wherein the metal moiety M includes boron, zinc, tin, magnesium, lithium and the like, for example, phenylboronic acid derivative, and other symbols are as defined above.}
\end{align*}
\]

Step 1

[0868] Compound [12] can be obtained by reacting compound [10] obtained by a conventional method or in the same manner as in Reference Example 3 with compound [11] obtained by a conventional method or in the same manner as in Reference Example 1.

Step 2

[0869] When R^{15} is a protected group, deprotection is conducted by a conventional method to give compound [13] from compound [12].

Step 3


[0871] For example, when a desired Q^{11} is -OCO-, Compound [15] can be obtained by esterification of compound [14] wherein R^{18} is -OH and compound [13] wherein R^{19} is HOOC— by a conventional method.

[0872] In the following, examples of reaction for each desired Q^{11} are shown in the form of a Table.

<table>
<thead>
<tr>
<th>Desired Q^{11}</th>
<th>R^{18}</th>
<th>R^{16}</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>-OCO-</td>
<td>-OH</td>
<td>HOOC-</td>
<td>esterification or amidation by reaction in the presence of condensing agent or reaction as acid halide, Mitsunobu reaction and the like.</td>
</tr>
<tr>
<td>-COO-</td>
<td>-COOH</td>
<td>HO-</td>
<td></td>
</tr>
<tr>
<td>-CONH-</td>
<td>-CONHHal^2</td>
<td>HO-</td>
<td></td>
</tr>
<tr>
<td>-NHCO-</td>
<td>-NH_2</td>
<td>HOOC-</td>
<td></td>
</tr>
<tr>
<td>-OCOHal^2</td>
<td>-OCOHal^2</td>
<td>HOOC-</td>
<td></td>
</tr>
<tr>
<td>-SO_2Hal^2</td>
<td>-SO_2Hal^2</td>
<td>HOOC-</td>
<td></td>
</tr>
<tr>
<td>-NHSO_2Hal^2</td>
<td>-NHSO_2Hal^2</td>
<td>HOOC-</td>
<td></td>
</tr>
</tbody>
</table>

Step 4

[0873] When R^{17} is a protected OH group, deprotection is conducted by a conventional method, after which halogenation, mesylation or tosylation is conducted to give compound [16] from compound [15].

Step 5

[0874] Compound [1-1] can be obtained by condensation cyclization of compound [16] by a conventional method.

Step 6

[0875] When Q^{11} is -CONH- or -NHCO-, compounds [1-2] and [1-3] can be respectively obtained by reduction of compound [1-1] by a conventional method.

Step 7

[0876] When Q^{11} is -S-, compounds [1-4] and [1-5] can be obtained by oxidation of compound [1-1] by a conventional method.

Production Method 1-1

![Diagram]

[18]
wherein each symbol is as defined above.

[0877] Compound [19] can be obtained by reacting compound [17] obtained by a conventional method or in the same manner as in Reference Example 3 with compound [18] obtained by a conventional method or in the same manner as in Reference Example 1 using a Suzuki reaction.

[0878] For example, Compound [19] can be obtained by a reaction in a solvent such as DME, acetonitrile, alcohol solvents (methanol, ethanol etc.), DME, THF, toluene, water, or a mixed solvent thereof and the like in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium, bis(triphenylphosphine)palladium(II) dichloride, palladium acetate—triphenylphosphine and the like, a nickel catalyst such as nickel chloride, 1,3-bis(diphenylphosphino)propane nickel(II) chloride and the like and a base such as sodium carbonate, potassium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, potassium phosphate, triethylamine, potassium fluoride, cesium fluoride, sodium hydrogenphosphate, cesium carbonate and the like, at room temperature or under heating.

[0879] The reactivity may be increased by adding lithium chloride and the like.

[0880] In addition, the following compounds may be used instead of the above-mentioned compounds [17] and [18].

wherein R_{110} is halogen atom such as chlorine atom, bromine atom and the like or hydroxyl group, and other symbols are as defined above.

Step 1


such as DMF, acetonitrile, THF, chloroform, ethyl acetate, methylene chloride, toluene and the like by adding a condensing agent such as dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diphenylphosphoryl azide and the like and, where necessary, N-hydroxysuccinimide, 1-hydroxybenzotriazole and the like to give amide compound [22]. Alternatively, amide Compound [22] can be obtained from compound [21] as follows. The carboxylic acid compound [21] is converted to an acid halide with thionyl chloride, oxalyl chloride and the like (a catalyst amount of DMF may be added), or to an active ester of carboxylic acid compound [21] (e.g., converting to a mixed acid anhydride with ethyl chlororcarbonate and the like), which is then reacted with compound [20] in the presence of a base, such as triethylamine, potassium carbonate, pyridine and the like, or in an amine solvent such as pyridine and the like, to give amide compound [22]. For the reaction of active ester with compound [20], dimethylaminopyridine may be added.

When R"10" is halogen atom such as chlorine atom, bromine atom and the like, compound [21] is reacted with compound [20] in the presence of a base such as triethylamine, potassium carbonate, pyridine and the like, or in an amine solvent such as pyridine and the like to give amide compound [22].

To increase selectivity of reaction with amino group, acetic acid and sodium acetate may be added at an equivalent ratio.

Step 2

Compound [1-6] can be obtained by condensation cyclization of compound [22] in a solvent such as ethanol, DMF, DMA, DMSO, acetone, acetonitrile, 1,4-dioxane, THF, toluene, water and the like, in the presence or absence of a base such as potassium hydroxide, sodium hydroxide, potassium carbonate, triethylamine, sodium ethoxide, potassium tert-butoxide and the like, under cooling to under heating.

Step 3

Compound [1-7] can be obtained by reducing compound [1-6] by a conventional method.

For example, reduction is carried out using a borohydride (e.g., sodium borohydride, sodium triacetoxyborohydride and the like), borane-THF complex and the like as a reducing agent. In this case, an acid such as acetic acid, hydrochloric acid and the like may be added.

As a preferable solvent, ether solvents (1,4-dioxane, THF etc.), alcohol solvents (methanol, ethanol etc.), polar solvents (DMF, DMSO, acetonitrile etc.), halogen solvents (dichloromethane, chloroform etc.), hydrocarbon solvents (benzene, toluene etc.), ester solvents (ethyl acetate, butyl acetate etc.), water, or a mixed solvent thereof and the like can be mentioned.

Production Method 2
wherein $Q^{12}$ is $-O-$, $-S-$, $-OCO-$, $-OCONH-$, $-NHCO-$, $-NHISO_2-$, $-NHCOO-$, $-COO-$, $-CONH-$, $-NHCONH-$, $-NHISO_2NH-$, $-CH=NH-$ or $-N\equiv CH-$,

$R^{11}$ is $-OH$, $-NH_2$, $-COOH$, a protected group thereof, $-CHO$, $-Hal^2$, $-OMs$ or $-OTs$,

$R^{12}$ is $-OH$, $-NH_2$, $-COOH$, $-CHO$, $-Hal^2$, $-OMs$ or $-OTs$, and other symbols are as defined above.

Step 1

[0893] In the following, examples of reaction for each desired $Q^{12}$ are shown in the form of a Table.

<table>
<thead>
<tr>
<th>Desired $Q^{12}$</th>
<th>$-R^{12}$</th>
<th>$-R^{6}$</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-OCO-$</td>
<td>$-OH$</td>
<td>$HOOC-$</td>
<td>esterification or condensation</td>
</tr>
<tr>
<td>$-COO-$</td>
<td>$-COOH$</td>
<td>$HO-$</td>
<td>amidation by a carboxylic acid</td>
</tr>
<tr>
<td>$-CONH-$</td>
<td>$-COOH$</td>
<td>$H_2N-$</td>
<td>amidation with carbodiimide</td>
</tr>
<tr>
<td>$-NHCO-$</td>
<td>$-NH_2$</td>
<td>$HOOC-$</td>
<td>amidation with $SOCl_2$</td>
</tr>
<tr>
<td>$-NHISO_2H-$</td>
<td>$-NH_2$</td>
<td>$H_2N-$</td>
<td>amidation with $SOCl_2$</td>
</tr>
<tr>
<td>$-NHCONH-$</td>
<td>$-OH$</td>
<td>$H_2O$</td>
<td>amidation with $SOCl_2$</td>
</tr>
<tr>
<td>$-NHISO_2NH-$</td>
<td>$-NH_2$</td>
<td>$H_2N-$</td>
<td>amidation with $SOCl_2$</td>
</tr>
<tr>
<td>$-O-$</td>
<td>$-OH$</td>
<td>$HS-$</td>
<td>amidation with $SOCl_2$</td>
</tr>
<tr>
<td>$-S-$</td>
<td>$-OH$</td>
<td>$HS-$</td>
<td>amidation with $SOCl_2$</td>
</tr>
<tr>
<td>$-Hal^2$</td>
<td>$-OH$</td>
<td>$HO-$</td>
<td>amidation with $SOCl_2$</td>
</tr>
<tr>
<td>$-OMs$</td>
<td>$-OH$</td>
<td>$HO-$</td>
<td>amidation with $SOCl_2$</td>
</tr>
<tr>
<td>$-OTs$</td>
<td>$-OH$</td>
<td>$HO-$</td>
<td>amidation with $SOCl_2$</td>
</tr>
<tr>
<td>$-CH=NH-$</td>
<td>$-CHO$</td>
<td>$H_2N-$</td>
<td>amidation with $SOCl_2$</td>
</tr>
<tr>
<td>$-N\equiv CH-$</td>
<td>$-NH_2$</td>
<td>$HOC-$</td>
<td>amidation with $SOCl_2$</td>
</tr>
</tbody>
</table>

Step 2

[0894] Compounds [1-2], [1-3], [1-4] and [1-5] can be obtained from compound [1-8] in the same manner as in Production Method 1, Step 6 or Step 7.

Step 3

[0895] For example, when desired $Q^{12}$ is $-O-$, Compound [1-8] can be obtained by etherification of compound [25] wherein $R^{12}$ is $-OH$ and $R^{6}$ is $HO-$ using Mitsunobu reaction.
wherein R\(^{13}\) and R\(^{14}\) are the same or different and each is hydroxyl-protecting group, and other symbols are as defined above.

Step 1

[0895] Compound [27] can be obtained by reacting compound [10] with commercially available compound [26] or compound [26] obtained by a conventional method, in the same manner as in Production Method 1-2, Step 2.

Step 2

[0896] Compound [29] can be obtained by reacting compound [27] with compound [28] obtained by a conventional method or in the same manner as in Reference Example 1, in the same manner as in Production Method 1-1.

Step 3


Step 4

[0898] Compound [29] can be obtained by reacting compound [30] with compound [26], in the same manner as in Production Method 1-2, Step 2.

Step 5

[0899] Compound [31] can be obtained by removing hydroxyl-protecting group of compound [29] by a conventional method.

[0900] As the hydroxyl-protecting group, tert-butyldimethylsilyl group, acetyl group, benzyl group, methoxymethyl group, methoxyethoxymethyl group, 2-tetrahydropyranyl group and the like can be mentioned.

[0901] For example, when R\(^{13}\) and R\(^{14}\) are methoxyethoxymethyl group or 2-tetrahydropyranyl group, deprotection is conducted by a method such as treatment with hydrochloric acid at room temperature in a mixed solvent of tetrahydrofuran and methanol and the like.

[0902] In addition, when R\(^{13}\) and R\(^{14}\) are benzyl groups, deprotection is conducted by a method such as treatment with a palladium catalyst at room temperature in a mixed solvent of tetrahydrofuran and methanol under a hydrogen atmosphere, treatment under acidic conditions of hydrobromide/acetic acid and the like, or reaction with an acid such as hydrochloric acid, sulfuric acid, hydrobromic acid and the like in an acetic acid solvent, and the like.

Step 6

[0903] Compound [1-9] can be obtained by Mitsunobu reaction using compound [31] in a solvent such as DMF, acetonitrile, THF and the like, using triphenylphosphine-diethyl azodicarboxylate, triphenylphosphine-diisopropyl azodicarboxylate and the like.

[0904] In addition, compound [1-9] can also be obtained by mesylation, tosylation, trifluoromethylsulfonylation of hydroxyl group of compound [31] followed by reaction in the presence of a strong base such as sodium hydride, potassium hydride and the like.
wherein \( Q^{13} \) is \(-\text{OCO}\), \(-\text{OCNH}\), \(-\text{NHCO}\), 
\(-\text{NHCOO}\), \(-\text{NHCONH}\) or \(-\text{NHISO}_2\text{NH}\),

\( R^{15} \) is \(-\text{NH}_2 \) or \(-\text{OH}\),

\( R^{16} \) is \(-\text{OH}, -\text{NH}_2\), \(-\text{COOH}\) or a protected group thereof,

\( R^{17} \) is \(-\text{OH}, -\text{NH}_2 \) or \(-\text{COOH}\),

\( d' \) is an integer of 1 to 4, and other symbols are as defined above.

Step 1


Step 2

[0907] Compound [34] can be obtained by reacting compound [32] with compound [33] in the same manner as in Production Method 1-1.

Step 3

[0908] When \( R^{16} \) is a protected group, Compound [35] can be obtained from compound [34] by deprotection by a conventional method.

Step 4

[0909] When \( R^{17} \) is \(-\text{OH}, \text{Compound } [36] \) can be obtained by halogenation by a conventional method.

Step 5

[0910] Compound [1-10] can be obtained by intramolecular cyclization of compound [36] in the same manner as in Production Method 1-2, Step 2.

Step 6

[0911] Compound [1-11] can be obtained by intramolecular cyclization of compound [35].

[0912] For example, when desired \( Q^{13} \) is \(-\text{OCO}\), Compound [1-11] can be obtained from compound [35], wherein \( R^{15} \) is \(-\text{OH} \) and \( R^{17} \) is \( \text{HOOC} \), by esterification by a conventional method.

[0913] In the following, examples of reaction for each desired \( Q^{13} \) are shown in the form of a Table.

<table>
<thead>
<tr>
<th>Desired ( Q^{13} )</th>
<th>(-R^{13})</th>
<th>(-R^{17})</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-\text{OCO})</td>
<td>(-\text{OH})</td>
<td>(\text{HOOC})</td>
<td>esterification or amidation by reaction in the presence of condensing agent, reaction an acid halide, Mitsunobu reaction and the like.</td>
</tr>
<tr>
<td>(-\text{NHCO})</td>
<td>(-\text{NH}_2)</td>
<td>(\text{HO})</td>
<td>carbamoylation with carbodiimide, COCl₂.</td>
</tr>
<tr>
<td>(-\text{OCNH})</td>
<td>(-\text{OH})</td>
<td>(\text{H}_2\text{N})</td>
<td>reaction with SO₂Cl₂.</td>
</tr>
<tr>
<td>(-\text{NHCO NH})</td>
<td>(-\text{NH}_2)</td>
<td>(\text{H}_2\text{N})</td>
<td></td>
</tr>
</tbody>
</table>

Step 7

[0914] When \( Q^{13} \) is \(-\text{NHCO}\), Compound [1-12] can be obtained by reducing compound [1-11] by a conventional method.
wherein $R^{18}$ is $-\text{OH}$, $-\text{NH}_2$ or $-\text{SH}$, $Q^{14}$ is $-\text{O}-$, $-\text{NH}-$ or $-\text{S}-$, and other symbols are as defined above.

Step 1

[0915] Compound [I-14] can be obtained by reacting compound [37] obtained in the same manner as in Production Method 1-1 with compound [38] in a solvent such as ethanol, DMF, DMA, acetone, acetonitrile, THF, toluene, water and the like, in the presence of a base.

[0916] Here, Hal is preferably bromine atom.

[0917] As a base, a weak base such as sodium carbonate, potassium carbonate and the like is preferable.

Step 2

[0918] Compound [40] can be obtained by reacting compound [37] with compound [39] in a solvent such as ethanol, DMF, DMA, acetone, acetonitrile, THF, toluene, water and the like, in the presence of a base.

[0919] Here, Hal and Hal$^2$ are each preferably bromine atom and chlorine atom.

[0920] As a base, a weak base such as sodium carbonate, potassium carbonate and the like is preferable.

Step 3

[0921] Compound [I-14] can be obtained by cyclization of compound [40] in the same manner as in Production Method 1-2, Step 2.

[0922] As a base, a strong base such as sodium hydride, potassium hydroxide, potassium tert-butoxide and the like is preferable.

Step 4

[0923] When $Q^{14}$ is $-\text{S}-$, compounds [I-15] and [I-16] can be obtained by oxidation of compound [I-14] by a conventional method.
Production Method 5

Step 1

Step 2

Step 3

Step 4

Step 5

Step 6
wherein each symbol is as defined above.

Step 1

[0924] Compound [42] can be obtained by reacting compound [41] obtained by a conventional method or in the same manner as in Reference Example 2 with compound [23] obtained by a conventional method.

Step 2

[0925] Compound [43] can be obtained by halogenation of compound [42] by a conventional method.

Step 3


Step 4-Step 7

[0927] Compounds [1-8], [1-2], [1-3], [1-4] and [1-5] can be obtained from compound [24] in the same manner as in Production Method 2.

Production Method 5-1

wherein each symbol is as defined above.
Step 1

(0928) Compound [44] can be obtained by reacting compound [41] and compound [21] in the same manner as in Production Method 1-2, Step 2.

Step 2

(0929) Compound [45] can be obtained by halogenation of compound [44] in the same manner as in Reference Example 3, Step 2.

Step 3

(0930) Compound [1-17] can be obtained by reacting compound [45] with compound [46] in the same manner as in Production Method 1-1.

Step 4

(0931) Compound [1-18] can be obtained by reducing compound [1-17] in the same manner as in Production Method 1-2, Step 3.

Production Method 5-2

\[
\begin{align*}
\text{Step 1:} & \quad \text{Hal}^2 \rightarrow (\text{CH}_2)_n \rightarrow \text{CO} \rightarrow \text{R}^{10} \\
\text{Step 2:} & \quad \text{Hal}^1 \rightarrow \text{N}^1 \\
\text{Step 3:} & \quad \text{NH}_2 \\
\end{align*}
\]

wherein each symbol is as defined above.

Step 1


Step 2

(0933) Compound [1-17] can be obtained by reacting compound [45] with compound [46] in the same manner as in Production Method 1-1.

Step 3

(0934) Compound [1-18] can be obtained by reducing compound [1-17] in the same manner as in Production Method 1-2, Step 3.

Production Method 6

\[
\begin{align*}
\text{Step 1:} & \quad \text{Hal}^9 \rightarrow (\text{CH}_2)_n \rightarrow \text{R}^9 \\
\text{Step 2:} & \quad \text{Hal}^9 \rightarrow (\text{CH}_2)_n \rightarrow \text{Q}^{15} \rightarrow (\text{CH}_2)_n \\
\text{Step 3:} & \quad \text{Hal}^9 \rightarrow (\text{CH}_2)_n \\
\end{align*}
\]

wherein each symbol is as defined above.
wherein, when \( d \) is 0, \( Q^{15} \) is \(-S-, -SO-, -OCo-, -OCNH-, -NHCO-, -NHSO-, -HNCO-, -COO-, -CONH-, -SO\( _2 \)NH-, -NHCONH-, -NHSO\( _2 \)NH-, -CH\( \equiv \)CH- or -CO-,
when \( d \) is an integer of 1 to 4, \( Q^{15} \) is, in addition to the above-mentioned, -O- or -NH-
\( Q^{16} \) is -CO-, -SO\( _2 \)-, -COO-, -CONH- or -SO\( _2 \)NH-
\( b' \) is an integer of 1 to 4, and other symbols are as defined above.

Step 1

Compounds [50], [51] and [52] can be obtained by reacting compound [41] with compounds [47], [48] and [49] obtained by a conventional method, respectively, in the same manner as in Production Method 1-2, Step 2.

Step 2

Compounds [I-19], [I-20] and [I-21] can be obtained by reacting compounds [50], [51] and [52], respectively, in a solvent such as DME, DMF, DMA, 1,4-dioxane and the like, in the presence of a base such as sodium carbonate, potassium acetate, sodium acetate and the like and a palladium catalyst such as tetrakis(triphenylphosphine)palladium, bis(triphenylphosphine)palladium(II) dichloride, palladium acetate-triphenylphosphine and the like, at room temperature or under heating.
wherein $R^{e2}$ is a group selected from group F, and other symbols are as defined above.

Step 1

[0937] Compounds [53] and [54] can be obtained by treating compounds [I-22] and [I-23] obtained by the above-mentioned Production Method, respectively, with $P_2S_5$ or a Lawesson reagent.

Step 2

[0938] Compounds [I-24] and [I-25] can be obtained by reacting compounds [55] with compounds [53] and [54], respectively.

Step 3

[0939] Compounds [I-26] and [I-27] can be obtained by reacting compound [56] with compounds [I-24] and [I-25], respectively.
wherein \( R^{19} \) is amino-protecting group, ring \( A'' \) is ring A wherein \( G^3 \) is nitrogen atom, and other symbols are as defined above.
Step 1

[0948] Compound [63] can be obtained by introducing cyano group into compound [62] obtained by a conventional method or the method described in WO03/010140, by a conventional method.

[0949] For example, Compound [63] can be obtained by reacting compound [62] with trimethylsilyl cyanide under heating in a solvent such as acetonitrile, in the presence of a base such as triethylamine and the like.

Step 2

[0950] Compound [64] can be obtained by reacting compound [63] with compound [26] in the same manner as in Production Method 1-2, Step 2.

Step 3

[0951] Compound [65] can be obtained by reacting cyano group of compound [64] using acid chloride such as acetyl chloride and the like in an alcohol solvent (R^4=--OH) that becomes a source of R^6, such as ethanol and the like under reflux.

Step 4

[0952] Compound [66] can be obtained by halogenation of compound [65] in the same manner as in Reference Example 3, Step 2.

Step 5

[0953] Compound [67] can be obtained by reacting compound [63] with compound [21] in the same manner as in Production Method 1-2, Step 2.

Step 6

[0954] Compound [68] can be obtained from compound [67] in the same manner as in the above-mentioned Step 3.

Step 7

[0955] Compound [69] can be obtained by halogenation of compound [68] in the same manner as in Reference Example 3, Step 2.

[0956] Compounds [66] and [69] obtained in this Production Method can be used in the above-mentioned Production Methods to give the final compound.

Production Method 9

wherein each symbol is as defined above.
wherein each symbol is as defined above.

Step 1

[0957] Compound [71] can be obtained by reacting commercially available compound [70] or compound [70] obtained by a conventional method with compound [4] in a mixed solvent of THF-acetic acid, in the presence of a reducing agent such as a borohydride (e.g., sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride and the like) and the like.

Step 2

[0958] Compound [73] can be obtained by treating compound [72] obtained in the same manner as in Step 1, with sodium nitrite in a mixed solvent of acetic acid-water.

Step 3

[0959] Compound [74] can be obtained by reducing compound [73] by a conventional method.

Step 4


Production Method 10
wherein R² is C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group E and the like, R²⁻¹⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻.nasa

Step 1

[0961] Compound [I-30] can be obtained by reacting compound [76] obtained by the above-mentioned Production Method with compound [77] in a solvent such as DMF, DMSO, acetonitrile, ethanol, THF, or a mixed solvent thereof, in the presence of a base such as sodium hydride, potassium carbonate, sodium ethoxide, potassium tert-butoxide and the like, under ice-cooling to under heating. In addition, potassium iodide or tetrabutylammonium iodide may be used to increase reactivity.

Step 2

[0962] In this Production Method, R² may be any group as long as it is bonded to nitrogen atom of fused ring via carbon atom, wherein C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group E as well as, for example, L²⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻･･ awards dock
Production Method 11

Step 1

[0969] Compound [I-35] can be obtained by deprotection of carboxyl-protecting group R^{20} of compound [I-34] obtained by the above-mentioned Production Method, by a conventional method.

[0970] Here, a reaction under conditions free from deprotection of R^{20} is preferable. For example, when R^{20} is methyl group or ethyl group and R^{25} is tert-butyl group, deprotection can be conducted by treatment with trifluoroacetic acid in a solvent such as methylene chloride, chloroform and the like.

Step 2

[0971] Compounds [I-36] and [I-37] can be obtained by reacting compound [I-35] with compounds [81] and [80], respectively, in the same manner as in Production Method 1-2, Step 1.

Production Method 12

Step 2

[0972] Compound [I-39] can be obtained by hydrolysis of compound [I-38] obtained in the same manner as in the above-mentioned Production Methods, in a solvent such as methanol, ethanol, THF, dioxane, water and the like, or a mixed solvent thereof under basic conditions of sodium.

wherein each symbol is as defined above.

wherein ring D^y is that containing NH as a component constituting a ring such as piperidine, piperazine, pyrrolidine and the like, and each symbol is as defined above.
hydroxide, potassium hydroxide, potassium carbonate, lithium hydroxide and the like or acidic conditions of hydrochloric acid, sulfuric acid and the like.

Step 2

[0973] Compounds [I-40], [I-78] and [I-79] can be obtained by reacting compound [I-39] with compounds [82], [124] and [125], respectively, in the same manner as in Production Method 1-2, Step 1.

[0974] For compounds [82], [124] and [125], commercially available products or compounds obtained by conventional methods or compounds obtained by the methods described in WO02/04425, WO03/007945 and WO03/010141 can be used.

Production Method 13

[0975] In this Production Method, conversion of the substituents R¹ and R² on the fused ring is shown. This Production Method is applicable irrespective of the position of substitution.

Production Method 13-1

[0976] Conversion of cyano group to substituted amidino group

[0977] The compound [I-41] obtained in the same manner as in the above-mentioned Production Method is reacted with hydroxylamine in a solvent such as water, methanol, ethanol, THF, DMF and the like to give compound [I-42]. When a salt of hydroxylamine such as hydrochloride and the like is used, the reaction is carried out in the presence of a base such as sodium hydrogen carbonate, sodium hydroxide, triethylamine and the like.

Production Method 13-2

[0978] Conversion of sulfonic ester moiety to sulfonic acid

Producing Method 14

[0979] The compound [I-43] obtained in the same manner as in the above-mentioned Production Method is reacted with iodide salt such as sodium iodide, lithium iodide and the like, bromide salt such as sodium bromide, tetrabutylammonium bromide and the like, amine such as pyridine, trimethylamine, triazole and the like, phosphine such as triphenylphosphine and the like in a solvent such as DMF, DMSO, acetonitrile, methanol, ethanol, water and the like with heating to give compound [I-44].

Production Method 14-1

[0980] This Production Method relates to conversion of the substituent X on the ring A.

Conversion of hydroxyl group to ether

[0981] Conversion of hydroxyl group to ether
wherein R^{22} is hydroxyl-protecting group such as acetyl, benzyl and the like, R^{23} is halogen atom such as chlorine atom, bromine atom and the like, hydroxy or leaving group such as sulfonate (e.g., mesyloxy, tosylxy and the like), —B(OR^{23})(OR^{23}) and the like, R^{24} is alkyl optionally substituted by 1 to 3 substituents selected from group A corresponding to R^{11}. J^1 is a bond, C_{1-6} alkenylene, C_{2-6} alkenylene or *—(CH}_{2}_{m}–Y^2–(CH}_2}_{n}=*, wherein * shows the side to be bonded to R^{23}, m is an integer of 1 to 6, and other symbols are as defined above.

Step 1

[0982] Compound [1-46] can be obtained by deprotection of compound [1-45] obtained in the same manner as in the above-mentioned Production Method, by a conventional method.

[0983] For example, when R^{22} is acetyl group, compound [1-45] is hydrolyzed, in a solvent such as methanol, ethanol, THF, 1,4-dioxane and the like, or a mixed solvent thereof, or a mixed solvent of such solvent and water, under basic conditions of sodium hydroxide, potassium hydroxide, potassium carbonate, lithium hydroxide, sodium methoxide, sodium ethoxide and the like or acidic conditions of hydrochloric acid, sulfuric acid and the like to give compound [1-46].

[0984] When R^{22} is benzyl group, compound [1-45] is subjected to catalytic reduction in a solvent such as methanol, ethanol, THF, ethyl acetate, acetic acid, water and the like in the presence of palladium carbon, or by reacting with an acid such as hydrobromic acid and the like in a solvent such as acetic acid to give compound [1-46].

Step 2

[0985] When R^{23} of compound [83] is halogen atom, —OMs or —OTs, compound [1-46] is reacted with compound [83] in a solvent such as DMF, DMSO, acetonitrile, ethanol, THF and the like in the presence of a base such as sodium hydride, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium ethoxide, potassium t-butoxide and the like at room temperature or with heating to give compound [1-47]. The reaction may be accelerated by adding sodium iodide or potassium iodide.

[0986] When R^{23} of compound [83] is hydroxyl group, the hydroxyl group of compound [83] is converted to halogen atom with thionyl chloride, phosphorus trichloride, phosphorus tribromide, carbon tetrabromide-triphenyl phosphine, N-bromosuccinimide and the like and reacted with compound [1-46] by the aforementioned method to give compound [1-47]. In this case, compound [1-46] may be subjected to Mitsunobu reaction with compound [83] in a solvent such as DMF, acetonitrile, THF and the like using triphenylphosphine-diethyl azodicarboxylate and the like to give compound [1-47].

[0987] For example, when J^1 is a bond and R^{23} is —B(OR^{23})(OR^{23}), compound [1-46] is reacted with compound [83] in a solvent such as chloroform, methylene chloride, THF, toluene, 1,4-dioxane and the like in the presence of a base such as copper acetate, pyridine, triethylamine and the like to give compound [1-47].

[0988] The Compound [1-48] can be obtained in the same manner as above from compound [1-46] and compound [84].

Production Method 14-2

[0989] Conversion of nitro to substituted amino group
Step 1

[0990] The compound [1-49] obtained in the same manner as the above-mentioned Production Method, is hydrogenated in a solvent such as methanol, ethanol, THF, ethyl acetate, acetic acid, water and the like in the presence of a catalyst such as palladium carbon, palladium hydroxide, platinum oxide, Raney nickel and the like at room temperature or with heating to give compound [1-50]. In addition, compound [1-49] is reduced with a reducing agent such as zinc, iron, tin(II) chloride, sodium sulfite and the like, or reacted with hydrazine in the presence of iron(III) chloride to give compound [1-50]. The compound [1-50] can be also obtained by reacting compound [1-49] with sodium hydrosulfite under alkaline conditions.

Step 2

[0991] The compound [1-50] is alkylated with compound [85] in the same manner as in Step 2 of Production Method 14-1 to give compound [1-51].

Step 3

[0992] When J° of compound [86] is \(-\text{CO}-(\text{CH}_2)_n-Y^2-(\text{CH}_2)_n-\), \(-\text{CONR}^3-(\text{CH}_2)_m-Y^2-(\text{CH}_2)_n-\), \(-\text{CO}-(\text{CH}_2)_n-\), \(-\text{CO}_2-(\text{CH}_2)_n-\) or \(-\text{CONR}^3-(\text{CH}_2)_n-\), compound [1-50] is reacted with compound [86] in a solvent such as DMF, acetonitrile, THF, chloroform, ethyl acetate, methylene chloride, toluene and the like using a condensing agent such as dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, hydrochloride, diphenylphosphoryl azide and the like and, where necessary, adding N-hydroxysuccinimide, 1-hydroxybenzotriazole and the like to give amide compound [1-55]. Alternatively, amide compound [1-55] can be obtained from compound [1-54] as follows. The carboxylic acid compound [1-54] is converted to an acid halide with thionyl chloride, oxalyl chloride and the like, or to an active ester of carboxylic acid compound [1-54] (e.g., converting to a mixed acid anhydride with ethyl chlorocarbonate and the like), which is then reacted with amine compound [88] in the presence of a base such as triethylamine, potassium carbonate, pyridine and the like to give amide compound [1-55].

[0993] When J° of compound [86] is \(-\text{SO}_2-(\text{CH}_2)_n-Y^2-(\text{CH}_2)_n-\) or \(-\text{SO}_2-(\text{CH}_2)_n-\), compound [1-50] is sulfonylated with compound [86] in the same manner as above to give compound [1-52].

[0994] The compound [1-50] is acylated with compound [87] in the same manner as above to give compound [1-53].

[0995] This Production Method is applied in the same manner as above to give disubstituted compounds (tertiary amine) of compound [1-51], compound [1-52] and compound [1-53].

Production Method 14-3

[0996] Conversion of carboxylic acid ester moiety to amide

Step continued

wherein \(J^\circ\) is \(-\text{(CH}_2)_n-Y^2-(\text{CH}_2)_n-\) and \(\#-(\text{CH}_2)_m-Y^2-(\text{CH}_2)_n-\) wherein \(\#\) shows the side to be bonded to amine, and other symbols are as defined above.

[0997] The carboxylic acid compound [1-54] obtained in the same manner as in the above-mentioned Production Method is condensed with amine compound [88] in a solvent such as DMF, acetonitrile, THF, chloroform, ethyl acetate, methylene chloride, toluene and the like using a condensing agent such as dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diphenylphosphoryl azide and the like and, where necessary, adding N-hydroxysuccinimide, 1-hydroxybenzotriazole and the like to give amide compound [1-55]. Alternatively, amide compound [1-55] can be obtained from compound [1-54] as follows. The carboxylic acid compound [1-54] is converted to an acid halide with thionyl chloride, oxalyl chloride and the like, or to an active ester of carboxylic acid compound [1-54] (e.g., converting to a mixed acid anhydride with ethyl chlorocarbonate and the like), which is then reacted with amine compound [88] in the presence of a base such as triethylamine, potassium carbonate, pyridine, 4-(dimethylamino)pyridine and the like, to give amide compound [1-55].

[0998] Compound [1-56] can be obtained by reacting carboxylic acid compound [1-54] with amine compound [89] in the same manner as above.

Production Method 15

[0999] In this Production Method, additional substituent(s) is(are) introduced into ring B.

Production Method 15-1

[1000] Direct bonding of ring Z'' to ring B
wherein ring \( Z'' \)-M is aryl metal compound, ring \( Z'' \) moiety is optionally substituted \( C_{n,1-6} \) aryl or optionally substituted heterocyclic group corresponding to substituent \( Z \), and the metal moiety contains boron, zinc, tin, magnesium and the like, such as phenylboronic acid and 4-chlorophenylboronic acid, \( w' \) is 0, 1 or 2, and other symbols are as defined above.

[1001] The compound [1-57] obtained in the same manner as in the above-mentioned Production Method is reacted with aryl metal compound [90] in a solvent such as DMF, acetonitrile, 1,2-dimethoxyethane, THF, toluene, water and the like in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)-palladium, bis(triphenylphosphine)palladium(II) dichloride, palladium acetate-triphenylphosphine and the like, a nickel catalyst such as nickel chloride, 1,3-bis(diphenylphosphino)propane nickel(II) chloride and the like, and a base such as potassium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, potassium phosphate, triethylamine, potassium fluoride, sodium hydrogen phosphate, cesium carbonate and the like at room temperature or with heating, to give compound [1-58].

Production Method 15-2

[1002] Conversion of hydroxyl group to ether

wherein \( R^{23} \) leaving group such as chlorine atom, bromine atom, iodine atom, trifluoromethanesulfonyloxy, \( p \)-toluenesulfonyloxy, methanesulfonyloxy and the like, \( R^{27} \) is formyl, carboxyl or carboxylic acid ester such as methoxy-carbonyl, ethoxy-carbonyl, tert-butoxy-carbonyl and the like, and other symbols are as defined above.

[1003] The compound [1-59] obtained in the same manner as in the above-mentioned Production Method is reacted with compound [91] in the same manner as in Step 2 of Production Method 14-1 to give compound [1-60].

Production Method 15-3

[1004] Synthesis in advance of ring B part such as compound [83] in Production Method 14-1

[1005] Commercially available compound [92] or compound [92] obtained by a conventional method is reacted
with aryl metal compound [90] in the same manner as in Production Method 15-1 to give compound [93].

Step 2

[1006] The compound [93] obtained in the same manner as in the above-mentioned Production Method is reduced according to a conventional method to give compound [94].

[1007] For example, compound [93] is reacted in a solvent such as methanol, ethanol, THF and the like in the presence of a reducing agent such as lithium aluminum hydride, sodium borohydride and the like under cooling to heating to give compound [94].

Step 3

[1008] The compound [94] obtained in the same manner as in the above-mentioned Production Method is reacted in a solvent such as 1,4-dioxane, diethyl ether, THF, methylene chloride, chloroform, toluene and the like with a halogenating agent, such as phosphorus halides (e.g., phosphorus pentachloride, phosphorus tribromide and the like), thionyl chloride and the like, to give compound [95]. For an accelerated reaction, the reaction may be carried out in the presence of a tertiary amine such as triethylamine, DMF, pyridine and the like, or under heating.

Step 4

[1009] The compound [94] or [95] obtained in the same manner as in the above-mentioned Production Method is reacted with compound [1-46] in the same manner as in Step 2 of Production Method 14-1 to give compound [1-61].

Production Method 15-4

[1011] For example, when M' is magnesium, magnesium is reacted with compound [96] in a solvent such as THF, diethyl ether, benzene, toluene and the like, preferably THF, from cooling to heating, preferably at −100°C to 100°C, to give compound [97].

Step 2

[1012] The compound [97] obtained in the same manner as in the above-mentioned Production Method is reacted with compound [98] to give compound [99].

[1013] The compound [97] is reacted with compound [98] in a solvent such as diethyl ether, benzene, toluene, THF and the like, preferably THF, from cooling to room temperature, preferably at −100°C to 30°C, to give compound [99].

Step 3

[1014] The compound [99] obtained in the same manner as in the above-mentioned Production Method is halogenated in the same manner as in Step 3 of Production Method 15-3 to give compound [100].

[1015] The compound [99] is reacted with thionyl chloride and pyridine preferably in toluene solvent to give compound [100].

[1016] When compound [100] is symmetric, namely, when the ring B-(Z)w moiety and the ring B’-(Z)w’ moiety are the same, compound [97] is reacted with formate such as methyl formate, ethyl formate and the like, preferably ethyl formate, in a solvent such as diethyl ether, benzene, toluene, THF and the like, preferably THF, from cooling to room temperature, preferably at −100°C to 30°C, to give compound [100].

Production Method 15-5

[1017] Method including steps to introduce a protecting group into a functional group

wherein M' is a metal such as magnesium, lithium, zinc and the like, and other symbols are as defined above.

Step 1

[1010] Commercially available compound [96] or compound [96] obtained by a conventional method is converted to aryl metal reagent by a conventional method to give compound [97].
oxalyl chloride and the like in a solvent such as THF, chloroform, methylene chloride, toluene and the like, and reacted with potassium tert-butoxide or di-tert-butyl dicarbonate to give compound [102].

Step 2

[1020] The methyl group of compound [102] obtained in the same manner as in the above-mentioned Production Method is converted to bromomethyl with N-bromosuccinimide and N,N'-azobisisobutyronitrile and reacted with compound [I-62] in the same manner as in Step 2 of Production Method 14-1 to give compound [I-63].

Step 3

[1021] The compound [I-63] obtained in the same manner as in the above-mentioned Production Method is reacted with aryl metal compound [90] in the same manner as in Production Method 15-1 to give compound [I-64].

Step 4

[1022] The R^5o fragment of the compound [I-64] obtained in the same manner as in the above-mentioned Production Method is removed by a conventional method to give compound [I-65].

[1023] The carboxyl-protecting group can be removed by a conventional deprotection method according to the protecting group. In this Step, the conditions free from reaction of R^4 are preferable. For example, when R^5o is tert-butyl, compound [I-64] is treated with trifluoroacetic acid in a solvent such as methylene chloride, chloroform and the like to give compound [I-65]. In addition, compound [I-64] may be treated with hydrogen chloride or hydrochloric acid in a solvent such as ethyl acetate, dioxane, alcohol and the like to give compound [I-65].

Step 5

[1024] The compound [I-65] obtained in the same manner as in the above-mentioned Production Method is subjected to amide condensation with compound [103] in the same manner as in Production Method 14-3 to give compound [I-66].

Step 6

[1025] The compound [I-66] obtained in the same manner as in the above-mentioned Production Method is deprotected in the same manner as in Step 1 of Production Method 12 to give compound [I-67].

[1026] As used herein, R^4 is preferably a protecting group that does not react during the Step 1 through Step 5 but removed in this Step.

[1027] For example, when R^4 is methyl, compound [I-66] is reacted in an alcohol solvent such as methanol, ethanol, n-propanol, isopropanol and the like or a mixed solvent of alcohol solvent and water in the presence of a base such as potassium carbonate, sodium carbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide and the like from cooling to heating for deprotection, followed by acidifying the reaction solution to give compound [I-67].
Production Method 15-6

wherein g is an integer of 1 to 5, and other symbols are as defined above.

Step 1

The compound [1-62] obtained by the above-mentioned Production Method is reacted with toluene derivative [104] in the same manner as in Step 2 of Production Method 15-5 to give compound [1-68].

Step 2

The compound [1-68] obtained by the above-mentioned Production Method is reacted with aryl metal compound [90] in the same manner as in Production Method 15-1 to give compound [1-69].

Step 3

The compound [1-69] obtained by the above-mentioned Production Method is reduced in the same manner as in Step 1 of Production Method 14-2 to give compound [1-70].

Step 4

The compound [1-70] obtained by the above-mentioned Production Method is amide condensed with compound [105] in the same manner as in Production Method 14-3, which is then subjected to cyclization in a solvent such as DMF, acetonitrile, THF, toluene and the like in the presence or absence of a base such as potassium carbonate, triethylamine, potassium tert-butoxide and the like at room temperature or with heating, to give compound [1-71].

Step 5

The compound [1-71] obtained by the above-mentioned Production Method is deprotected in the same manner as in Step 1 of Production Method 12 to give compound [1-72].

Production Method 15-7
wherein each symbol is as defined above.

Step 1

[1033] Commercially available compound [106] or compound [106] obtained by a conventional method is reacted with compound [90] in the same manner as in Production Method 15-1 to give compound [107].

Step 2

[1034] The compound [107] obtained in the same manner as in the above-mentioned Production Method is reduced in the same manner as in Step 1 of Production Method 14-2 to give compound [108].

Step 3

[1035] The compound [108] obtained in the same manner as in the above-mentioned Production Method is reduced in the same manner as in Step 2 of Production Method 15-3 to give compound [109].

Step 4

[1036] The compound [109] obtained in the same manner as in the above-mentioned Production Method is reacted with compound [105] in a solvent such as DMF, acetonitrile, THF, chloroform, ethyl acetate, methylene chloride, toluene and the like to give compound [110]. To enhance the reaction selectivity for amino group, acetic acid and sodium acetate may be added in an equivalent ratio.

Step 5

[1037] The compound [110] obtained in the same manner as in the above-mentioned Production Method is subjected to cyclization in a solvent such as ethanol, DMF, acetonitrile, THF, toluene, water and the like in the presence or absence of a base such as potassium hydroxide, potassium carbonate, triethylamine, potassium tert-butoxide and the like at room temperature or with heating, to give compound [111].

Step 6

[1038] The compound [111] obtained in the same manner as in the above-mentioned Production Method is halogenated in the same manner as in Step 3 of Production Method 15-3 to give compound [112].

Step 7

[1039] The compound [112] obtained in the same manner as in the above-mentioned Production Method is reacted in the same manner as in Step 2 of Production Method 14-1 with compound [1-62] obtained in the same manner as in the above-mentioned Production Method to give compound [1-71].
Step 8

The compound [1-71] obtained in the same manner as in the above-mentioned Production Method is deprotected in the same manner as in Step 1 of Production Method 12 to give compound [1-72].

Production Method 15-8

wherein R^N1 and R^N2 are the same or different and each is hydrogen atom or a group selected from group F, or R^N1 and R^N2 are linked to form a heterocycle containing NH such as piperidino group, 1-piperazinyl group, morpholino group and the like, R^610, is a group selected from group F, R^611 is a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from group A, and other symbols are as defined above.

Step 1

The compound [1-68] obtained in the same manner as in the above-mentioned Production Method is reacted with amine compound [113] in a solvent such as DMSO, DMF, acetonitrile, THF, toluene and the like in the presence or absence of a base such as potassium carbonate, triethylamine, potassium tert-butoxide and the like at room temperature or with heating, to give compound [1-73].

Step 2

The compound [1-73] is reduced in the same manner as in Step 1 of Production Method 14-2 to give compound [1-74].

Step 3

The compound [1-74] is reacted with carboxylic acid compound [114] in the same manner as in Production Method 14-3 to give compound [1-75].

Step 4

The compound [1-75] is alkylated with compound [115] in the same manner as in Step 2 of Production Method 14-1 to give compound [1-76].

Step 5

The compound [1-76] is deprotected in the same manner as in Step 1 of Production Method 12 to give compound [1-77].
Production Method 15-9

Step 1
[1046] Commercially available compound [106] or compound [106] obtained by a conventional method is reacted with amine compound [113] in the same manner as in Step 1 of Production Method 15-8 to give compound [116].

Step 2
[1047] The compound [116] is reduced in the same manner as in Step 1 of Production Method 14-2 to give compound [117].
Step 3

[1048] The compound [117] is reduced in the same manner as in Step 2 of Production Method 15-3 to give compound [118].

Step 4

[1049] The hydroxyl group of the compound [118] is protected by a conventional method to give compound [119].

[1050] For protection, for example, when R<sup>22</sup> is acetyl group, the compound [118] is reacted with acetic anhydride in the presence of pyridine or tertiary amine at room temperature to heating, when R<sup>22</sup> is benzyl group, the compound [118] is heated under reflux with benzyl chloride or benzyl bromide in benzene, toluene, acetone, THF, chloroform and the like in the presence of a base such as potassium hydroxide, potassium carbonate and the like, when R<sup>22</sup> is tert-butyldiphenylylsilyl group, the compound [118] is treated with tert-butyldiphenylylsilyl chloride and imidazole at room temperature in DMF, and the like.

[1051] In addition, desired R<sup>416</sup>—CO group may be introduced as a hydroxyl-protecting group in the next Step 5 without going through this step.

Step 5

[1052] The compound [119] is reacted with carboxylic acid compound [114] in the same manner as in Production Method 14-3 to give compound [120].

Step 6

[1053] The compound [120] is alkylated with compound [115] in the same manner as in Step 2 of Production Method 14-1 to give compound [121].

Step 7

[1054] The compound [121] is deprotected in the same manner as in Step 1 of Production Method 14-1 to give compound [122].

Step 8

[1055] The compound [122] is halogenated in the same manner as in Step 3 of Production Method 15-3 to give compound [123].

Step 9

[1056] The compound [123] is reacted in the same manner as in Step 2 of Production Method 14-1 with compound [1-62] obtained in the same manner as in the above-mentioned Production Method to give compound [1-76].

Step 10

[1057] The compound [1-76] is deprotected in the same manner as in Step 1 of Production Method 12 to give compound [1-77].

Production Method 16

[1058] A compound wherein Q is (CH<sub>2</sub>)<sub>x</sub>Q<sup>1</sup>(CH<sub>2</sub>)<sub>y</sub>—, Q<sup>1</sup> is —CO—, and c=d=0 can be obtained by a method similar to the method described in Tetrahedron Lett., 32, 3317-3320, 1991.

G:G

[1059] A compound wherein Q is (CH<sub>2</sub>)<sub>x</sub>Q<sup>1</sup>(CH<sub>2</sub>)<sub>y</sub>—, Q<sup>1</sup> is —CONH—, c=d=0, and

G:G

is C—C—N can be obtained by a method similar to the method described in EP226508.

G:G

[1060] A compound wherein Q is (CH<sub>2</sub>)<sub>x</sub>Q<sup>1</sup>(CH<sub>2</sub>)<sub>y</sub>—, Q<sup>1</sup> is —CH═CH—, c=d=0, and

G:G

is C—C—N can be obtained by a method similar to the method described in Tetrahedron Lett., 39, 8725-8728, 1998.

G:G

[1061] A compound wherein Q is (CH<sub>2</sub>)<sub>x</sub>Q<sup>1</sup>(CH<sub>2</sub>)<sub>y</sub>—, Q<sup>1</sup> is —CH═N—, c=d=0, and

G:G

is C—C—N can be obtained by a method similar to the method described in EP226508 and Organic Lett., 4, 1355-1358, 2002.

G:G

[1062] A compound wherein Q is (CH<sub>2</sub>)<sub>x</sub>Q<sup>1</sup>(CH<sub>2</sub>)<sub>y</sub>—, Q<sup>1</sup> is —N═CH—, c=d=0, and

G:G

is C—C—N can be obtained by a method similar to the method described in J. Heterocycl. Chem., 30(3), 603-609, 1993.

REFERENCE EXAMPLE 5

[1063]
wherein each symbol is as defined above.

Step 1

[1064] Compound [202] can be obtained by introducing a nitro group into compound [201] by a conventional method.

Step 2


[1066] For example, compound [82] is added to a solvent such as acetonitrile, THF, chloroform, ethyl acetate, methylene chloride, toluene, pyridine, triethylamine and the like, under cooling and allowed to react at room temperature to under heating.

Step 3

[1067] Compound [204] can be obtained by reacting compound [203] with N,N-dimethylformamide dimethyl acetal under heating.

Step 4

[1068] Compound [205] can be obtained by reducing and cyclizing compound [204] by a conventional method.

Step 5


Step 6

[1070] Compound [207] can be obtained by hydrogenating compound [206] in the same manner as in Reference Example 2, Step 2.

Step 7

[1071] Compound [208] can be obtained by halogenating compound [207] in the same manner as in Reference Example 3, Step 2.

Production Method 17
wherein each symbol is as defined above.

Step 1

[1072] Compound [210] can be obtained by introducing a protecting group into a hydroxyl group of compound [209] by a conventional method.

[1073] For example, when R^{13} is a tetrahydropryn-2-yl group, 3,4-dihydro-2H-pyran is reacted with compound [209] in a non-alcoholic solvent such as chloroform, dichloromethane, diethyl ether and the like, in the presence of an acid such as p-toluenesulphonic acid, hydrochloric acid, phosphorus oxychloride and the like.

Step 2

[1074] Compound [211] can be obtained by reacting compound [210] with boric acid ester in the same manner as in Reference Example 1.

Step 3


Step 4

[1076] Compound [213] can be obtained by eliminating a hydroxyl-protecting group of compound [212] by a conventional method.

Step 5

[1077] Compound [214] can be obtained by converting a hydroxyl group of compound [213] to a leaving group by halogen substitution, mesylation or tosylation by a conventional method.

Step 6

[1078] Compound [1-101] can be obtained by subjecting compound [214] to condensation cyclization in the same manner as in Production Method 1-2, Step 2.

Step 7

[1079] Compound [1-102] can be obtained by hydrolysis of compound [1-101] in the same manner as in Production Method 12, Step 1.

Production Method 18

wherein Q^{17} is —O— or —S—, and other symbols are as defined above.

Step 1


Step 2

Step 3

Compound [218] can be obtained by eliminating a hydroxyl-protecting group of compound [217] by a conventional method.

Step 4

Compound [I-103] can be obtained converting a hydroxyl group of compound [218] to a leaving group by halogen substitution, mesylation or tosylation by a conventional method, and subjecting the compound to condensation cyclization in the same manner as in Production Method 1-2, Step 2.

Furthermore, a carboxylic acid form can be also obtained by eliminating a carboxyl-protecting group of compound [I-103] by a conventional method. Production Method 18-1
wherein \( R^{m} \) is a group selected from group C, \( m' \) is 0 or an integer of 1 to 5, and other symbols are as defined above.

Step 1

[1085] Compound [220] can be obtained by reacting compound [219] with compound [9\(^7\)] in the same manner as in Production Method 1-1.

Step 2

[1086] Compound [1-135] can be obtained by eliminating the hydroxyl-protecting group of compound [220], then converting the hydroxyl group to a leaving group by halogen substitution, mesylation or tosylation by a conventional method, and then subjecting the compound to condensation cyclization in the same manner as in Production Method 1-2, Step 2.

Step 3

[1087] Compound [1-136] can be obtained by reducing the nitro group of compound [1-135] by a conventional method.

Step 4


[1089] In this case, a compound wherein amino group is dissubstituted by compound [223] may also be obtained. In this event, compound [1-104] isolated then can be used in the next step.

Step 5


[1091] Here, the corresponding substituent can be also introduced by reacting compound [1-104] with an aldehyde compound or a ketone compound instead of compound [224] in the presence of a reducing agent.

[1092] As the reducing agent, borohydrides such as sodium borohydride, sodium cyanoborohydride, sodium triacetoxymethyldride and the like can be mentioned.

[1093] As a solvent, THF, 1,4-dioxane, dichloromethane, chloroform, methanol, ethanol, toluene, acetic acid and the like can be mentioned. Acetic acid may be added.

Step 6


Step 7

[1095] Compound [1-107] can be obtained by hydrolyzing compound [1-106] in the same manner as in Production Method 12, Step 1.

Production Method 19

wherein each symbol is as defined above.

Step 1


Step 2

[1097] Compound [1-108] can be obtained by cyclizing compound [226] in the same manner as in Production Method 6, Step 2.
Production Method 19-1

[221] \xrightarrow{\text{Hal}} [26] \xrightarrow{\text{OR}} [227] 

\[
\begin{align*}
\text{Step 1} & \quad \text{Step 2} \\
\text{Step 3} & \quad \text{Step 4} \\
\text{Step 5} & \quad \text{Step 6} \\
\text{Step 7} & \quad \text{Step 8} \\
\text{Step 9} & \quad 
\end{align*}
\]

[9] 

[I-109] 

[I-110] 

[I-112] 

[I-113]
wherein each symbol is as defined above.

Step 1

[1098] Compound [227] can be obtained by reacting compound [221] with compound [26] in the same manner as in Production Method 14-1, Step 2.

Step 2

[1099] Compound [228] can be obtained by deprotecting the hydroxyl group of compound [227] by a conventional method. Here, conditions for deprotecting R^{13} without affecting R^{14} are preferable, as R^{13} preferred are tetrahydro-2-yl group, tert-butyl group, acetyl group and the like, and as R^{14}, preferred are benzyl group, methyl group and the like.

Step 3

[1100] Compound [229] can be obtained by converting the hydroxyl group of compound [228] to a leaving group by halogen substitution, mesylation or tosylation by a conventional method.

Step 4


Step 5

[1102] Compound [I-109] can be obtained cyclizing compound [230] in the same manner as in Production Method 6, Step 2.

Step 6

[1103] Compound [I-110] can be obtained by eliminating the hydroxyl-protecting group of compound [I-109] by a conventional method.

Step 7

[1104] Compound [I-112] can be obtained by reacting compound [I-110] with compound [223] in the same manner as in Production Method 14-1, Step 2.

Step 8

[1105] Compound [I-113] can be obtained by reducing carbonyl of compound [I-112] by a conventional method.

Step 9

[1106] Compound [I-114] can be obtained by hydrolyzing compound [I-113] in the same manner as in Production Method 12, Step 1.
Step 1


Step 2

[1108] Compound [232] can be obtained by eliminating the hydroxyl-protecting group of compound [231] and then converting the hydroxyl group to a leaving group by halogen substitution, mesylation or tosylation by a conventional method.

Step 3

[1109] Compound [233] can be obtained by reacting compound [232] with potassium phthalimide in DMF solvent in the presence of a base such as potassium carbonate and the like at room temperature or under heating.

Step 4

[1110] Compound [234] can be obtained by reacting compound [233] in the presence of hydrazine in a solvent such as methanol, ethanol, THF and the like at room temperature or under heating.

Step 5

[1111] Compound [235] can be obtained by introducing a protecting group into the amino group of compound [234] by a conventional method.

Step 6


Step 7

[1113] Compound [238] can be obtained by hydrogenating the formyl group of compound [237] to give hydroxymethyl group by a conventional method.

Step 8

[1114] Compound [239] can be obtained by converting the hydroxyl group of compound [238] to a leaving group by halogen substitution, mesylation or tosylation by a conventional method.

Step 9

[1115] Compound [1-115] can be obtained by subjecting compound [239] to condensation cyclization in the same manner as in Production Method 1-2, Step 2.

Production Method 20-1

...
wherein each symbol is as defined above.

Step 1

[1116] Compound [242] can be obtained by amide condensation of compound [240] with compound [241] in the same manner as in Production Method 1-2, Step 1.

Step 2


Step 3

[1118] Compound [244] can be obtained by reducing the carbonyl of compound [243] and then introducing a protecting group into the nitrogen atom of reduced compound [243] by a conventional method.

Step 4

[1119] Compound [245] can be obtained by converting the hydroxyl group of compound [244] to a leaving group by halogen substitution, mesylation or tosylation by a conventional method.
Step 5

[1120] Compound [I-115] can be obtained by subjecting compound [245] to condensation cyclization in the same manner as in Production Method 1-2, Step 2.

Step 6

[1121] Compound [I-116] can be obtained by eliminating, by a conventional method, the amino-protecting group of compound [I-115] obtained in the previous step or in the same manner as in Production Method 20.

Step 7

[1122] Compound [I-117] can be obtained by reacting compound [I-116] with compound [77] in the same manner as in Production Method 10, Step 1.

[1123] The substituent can be introduced into the nitrogen atom in the same manner using compound [78] described in Production Method 10, compound [246] described in Production Method 21 and the like instead of compound [77].

[1124] The substituent may be also introduced in the same manner as in Production Method 18-1, Step 5, using an aldehyde compound or a ketone compound.

Step 8

[1125] Compound [I-118] can be obtained by hydrolyzing compound [I-117] in the same manner as in Production Method 12, Step 1.

Production Method 21
wherein each symbol is as defined above.

Step 1

[1126] Compound [248] can be obtained by introducing a hydroxyl-protecting group into compound [247] by a conventional method.

Step 2

[1127] Compound [249] can be obtained by reducing the nitro group of compound [248] by a conventional method.

Step 3

[1128] Compound [250] can be obtained by reacting compound [249] with boric acid ester in the same manner as in Reference Example 1.

Step 4


Step 5

[1130] Compound [252] can be obtained by reacting compound [251] with compound [21] in the same manner as in Production Method 1-2, Step 1.

Step 6

[1131] Compound [I-119] can be obtained by subjecting compound [252] to condensation cyclization in the same manner as in Production Method 1-2, Step 2.

Step 7

[1132] Compound [I-120] can be obtained by reacting compound [I-119] with compound [246] in the same manner as in Production Method 10, Step 1.

Step 8

[1133] Compound [I-121] can be obtained by eliminating the hydroxyl-protecting group of compound [I-120] by a conventional method.

Step 9

[1134] Compound [I-122] can be obtained by reacting compound [I-121] with compound [83] in the same manner as in Production Method 14-1, Step 2.

Step 10

[1135] Compound [I-123] can be obtained by reducing carbonyl of compound [I-122] by a conventional method.

Step 11

[1136] Compound [I-124] can be obtained by hydrolyzing compound [I-123] in the same manner as in Production Method 12, Step 1.

Production Method 22-1
wherein each symbol is as defined above.

Step 1


[1138] In general, compound [254], wherein a protecting group has been introduced into an amino group, is used, and after reaction of Step 1, compound [255] obtained by eliminating the amino-protecting group can be used in the next step.

Step 2

[1139] Compound [I-126] can be obtained by reacting compound [I-38] with compound [255] in the same manner as in Production Method 1-2, Step 1.

[1140] Compound [I-38] can be used for this Step after hydrolyzing the carboxyl-protecting group in the same manner as in Production Method 12, Step 1.

Step 3

[1141] Compound [I-125] can be obtained by reacting compound [I-38] with compound [254] in the same manner as in Production Method 1-2, Step 1.

[1142] Compound [I-38] can be used for this Step after hydrolyzing the carboxyl-protecting group in the same manner as in Production Method 12, Step 1.

[1143] In general, compound [254], wherein a protecting group has been introduced into carboxylic acid, is used, and after reaction of Step 3, compound [I-125] obtained by eliminating the carboxyl-protecting group can be used in the next step.

Step 4

[1144] Compound [I-126] can be obtained by reacting compound [I-125] with compound [253] in the same manner as in Production Method 1-2, Step 1.

Production Method 22-2
wherein each symbol is as defined above.

[1145] Compounds [257] and [I-127] can be obtained in the same manner as in Production Method 22-1, using compound [256] instead of compound [253].

Production Method 22-3
wherein each symbol is as defined above.

Step 1

[1146] Compound [I-129] can be obtained by subjecting compound [I-128], obtained in the same manner as in Production Method 22-1 or Production Method 22-2, to condensation cyclization in a solvent such as an alcohol solvent, acetic acid and the like at room temperature or under heating.

Step 2

[1147] Compound [I-130] can be obtained by hydrolyzing compound [I-129] in the same manner as in Production Method 12, Step 1.

Step 3

[1148] Compound [I-131] can be obtained by reacting compound [I-130] with compound [258] in the same manner as in Production Method 1-2, Step 1.

Production Method 23
wherein \( R^1 \) is a \( C_{1-6} \) alkyl group optionally substituted by 1 to 3 substituents selected from group \( \Lambda \), a \( C_{6-14} \) aryl group optionally substituted by 1 to 5 substituents selected from group \( B \) or a heterocyclic group optionally substituted by 1 to 5 substituents selected from group \( B \), and each symbol is as defined above.

Step 1


Step 2

[1150] Compound [261] can be obtained by reacting compound [222] with compound [46] in the same manner as in Production Method 1-1.

Step 3


[1152] As the reducing agent, borohydrides such as sodium borohydride, sodium cyanoborohydride, sodium triacetoxilyborohydride and the like can be mentioned.

[1153] As the solvent, THF, 1,4-dioxane, dichloromethane, chloroform, methanol, ethanol, toluene, acetic acid and the like can be mentioned. Acetic acid may be added.

Step 4


Step 5

[1155] Compound [1-134] can be obtained by hydrolyzing compound [1-133] in the same manner as in Production Method 12, Step 1.

[1156] In the above-mentioned Production Method, substituents \( R^8 \) and/or \( R^7 \) may be present on -Q-, as long as the reaction is not adversely affected.

[1157] In the compounds of the formula [I], a desired heterocyclic group (including carboxylic acid equivalent) can be formed according to a method similar to the methods disclosed in known publications. Examples of such heterocyclic group and reference publications are recited in the following.

[1158] 5-oxo-\( \Delta^2 \)-1,2,4-oxadiazolin-3-yl (or 2,5-dihydro-5-oxo-\( \Delta^1 \)-1,2,4-oxadiazolin-3-yl), 5-oxo-\( \Delta^2 \)-1,2,4-thiadiazolin-3-yl (or 2,5-dihydro-5-oxo-\( \Delta^1 \)-1,2,4-thiadiazolin-3-yl), 2-oxo-\( \Delta^2 \)-1,2,3,5-oxathiadiazolin-4-yl (or 2-oxo-\( \Delta^2 \)-1,2,3,5-oxathiazolidin-4-yl); Journal of Medicinal Chemistry, 39(26), 5228-35, 1996, based on compound [1-42], for example, 5-oxo-\( \Delta^2 \)-1,2,4-oxadiazolin-3-yl, 5-thioxo-\( \Delta^1 \)-1,2,4-oxadiazolin-3-yl can be formed.

[1159] 5-oxo-\( \Delta^2 \)-1,2,4-triazolin-3-yl: J Org Chem, 61(24), 8397-8401, 1996.

[1160] 1-oxo-\( \Delta^3 \)-1,2,3,5-thiatrazolin-4-yl: Liebig's Ann Chem, 37(6), 1980.

[1161] 3-oxo-\( \Delta^4 \)-1,2,4-oxadiazolin-5-yl: EP145095.


[1163] 5-oxo-\( \Delta^3 \)-1,2,4-dioxazolin-3-yl: J Prakt Chem, 314, 145, 1972.


[1165] 5-oxo-\( \Delta^3 \)-1,2,4-dithiazolin-3-yl: J Org Chem, 61(19), 6639-6645, 1996.

[1166] 2-oxo-\( \Delta^4 \)-1,3,4-dioxazolin-5-yl: J Org Chem, 39, 2472, 1974.


[1173] 2,5-dioxoisoxazolidin-4-yl: Heterocycles, 43(1), 49-52, 1996.


[1175] 2,4-dioxoisoxazolin-5-yl: J Am Chem Soc, 73, 4752, 1951.


EXAMPLES

[1179] The tetracyclic fused heterocyclic compounds of the formula [1] and production methods thereof of the present invention are explained in detail in the following by way of Examples. It is needless to say that the present invention is not limited by these Examples. In the Examples, Me means methyl group, Et means ethyl group, tBu means tert-butyl group, Ac means acetyl group, Bn means benzyl group, Boc means tert-butoxycarbonyl group, THP means 2-tetrahydropyranyl group, and Tf means trifluoromethanesulfonil group.

Example 1-1

Production of methyl 6-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6]1,4]diazepine[7,1-a]indole-10-carboxylate

Step 1: Production of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine

[1180]

To a solution of 2-bromoaniline (1.0 g, 5.81 mmol) in 1,4-dioxane (15 ml) were added triethylamine (3.24 ml, 23.2 mmol) and 1,1-bis(diphenylphosphino)ferrocene dichloropalladium(II) dichloromethane complex (PdCl₂(dppf)CH₂Cl₂) (243 mg, 0.30 mmol) at room temperature. To the reaction mixture was added dropwise pina-colaborane (2.53 ml, 17.4 mmol), and the reaction mixture was heated to 100°C and stirred for 3 hr. The reaction mixture was cooled to room temperature and saturated aqueous ammonium chloride solution was added. The mixture was extracted with diethyl ether. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=5:1) to give 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine (810 mg, yield 63%).

[1181]

[1182] ¹H-NMR(400 MHz, CDCl₃): (ppm) 7.59(1H, dd, J=7.2, 1.6 Hz), 7.20(1H, dd, J=15.2, 7.2, 2.0 Hz), 6.66(1H, t, J=7.4 Hz), 6.58(1H, d, J=8.0 Hz), 4.72(2H, brs), 1.33(12H, s).

[1183] To a suspension of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (6.50 g, 19.3 mmol) obtained in the same manner as in the method described in WO03/010140 and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine (5.08 g, 23.2 mmol) in 1,2-dimethoxyethane (90 ml) and water (45 ml) were added sodium hydrogen carbonate (4.81 g, 57.9 mmol) and tetrakis(triphenylphosphine)palladium (1.12 mg, 0.965 mmol), and the mixture was heated under reflux for 9 hr. The mixture was allowed to cool to room temperature, and water was added to the reaction mixture. The mixture was extracted with ethyl acetate and the organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane:ethyl acetate=4:1:3:1) to give methyl 2-(2-amino-naphenyl)-3-cyclohexyl-1H-indole-6-carboxylate (6.48 g, yield 96%).

[1184] ¹H-NMR(400 MHz, DMSO-δ₆): δ(ppm) 11.30(1H, s), 7.95(1H, d, J=1.2 Hz), 7.78(1H, d, J=8.4 Hz), 7.58(1H, dd, J=8.4, 1.2 Hz), 7.14 (1H, d, J=8.0, 0.8 Hz), 7.04(1H, dd, J=7.6, 1.6 Hz), 6.79(1H, dd, J=8.0, 0.8 Hz), 6.65(1H, brs, J=7.2, 0.4 Hz), 4.81(2H, brs), 3.84(3H, s), 2.53-2.63(1H, m), 1.63-1.94(7H, m), 1.16-1.37(3H, m).
Step 3: Production of methyl 2-([2-(2-chloroacetylamo)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate

[1186]

MeOOC
\begin{align*}
\text{H}_2\text{N} & \quad \text{H}_2\text{O} \\
\text{Cl} & \quad \text{Cl} \\
\text{MeOOC} & \\
\end{align*}

Step 4: Production of methyl 13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1189]

MeOOC
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{MeOOC} & \\
\end{align*}

[1187] To a suspension of methyl 2-([2-(aminophenyl)-3-cyclohexyl-1H-indole-6-carboxylate (6.48 g, 18.6 mmol), sodium acetate (1.68 g, 20.5 mmol) and acetic acid (1.17 ml, 20.5 mmol) in tetrahydrofuran (60 ml) was added dropwise chloroacetyl chloride (1.63 ml, 20.5 mmol), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 2-([2-(chloroacetylamo)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate (7.90 g, yield 100%).

[1188] £1-H-NMR(400 MHz, DMSO-d$_6$): $\delta$(ppm) 11.44(1H, s), 9.38(1H, s), 7.98(1H, d, J=12 Hz), 7.90(1H, d, J=8.0 Hz), 7.82(1H, d, J=8.4 Hz), 7.60(1H, dd, J=8.0, 1.2 Hz), 7.47(1H, td, J=8.4, 0.8 Hz), 7.36(1H, dd, J=7.6, 1.6 Hz), 7.30(1H, td, J=7.6, 0.6 Hz), 4.15(2H, s), 3.85(3H, s), 2.42-2.50(1H, m), 1.61-1.91(7H, m), 1.11-1.34(3H, m).

[1190] To a solution of methyl 2-([2-(2-chloroacetylamo)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate (7.90 g, 18.6 mmol) in N,N-dimethylformamide (170 ml) was added sodium hydride (1.64 g, 40.9 mmol) under ice-cooling and the mixture was stirred for 2 hr. 1N Hydrochloric acid (45 ml) and water (200 ml) were added to the reaction mixture and the precipitated solid was collected by filtration. After washing successively with water and hexane, the solid was dried in vacuo to give methyl 13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (6.72 g, yield 93%).

[1191] £1-H-NMR(400 MHz, DMSO-d$_6$): $\delta$(ppm) 10.34(1H, s), 8.27(1H, d, J=1.2 Hz), 7.96(1H, d, J=8.4 Hz), 7.68(1H, dd, J=8.4, 1.6 Hz), 7.49-7.53(2H, m), 7.38(1H, t, J=7.6 Hz), 7.28(1H, d, J=8.0 Hz), 5.07(1H, d, J=15.6 Hz), 4.52(1H, d, J=14.8 Hz), 3.89(3H, s), 2.81-2.91(1H, m), 1.98-2.11(3H, m), 1.84-1.94(1H, m), 1.66-1.78(2H, m), 1.34-1.56(3H, m), 1.10-1.27(1H, m).
**Example 1-2**

Production of methyl 13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

![Chemical structure](image1)

**Example 1-3**

Production of 13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride

![Chemical structure](image2)

[1192]

[1193] To a suspension of methyl 13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (6.72 g, 17.3 mmol) in tetrahydrofuran (13 ml) was added 1M BH₃ THF complex tetrahydrofuran solution (67 ml) under ice-cooling, and the mixture was stirred at room temperature for 4 hr. 2N Hydrochloric acid (40 ml) was added to the reaction mixture at room temperature and the mixture was stirred at 70°C for 1 hr. The mixture was allowed to cool to room temperature and 2N aqueous sodium hydroxide solution (40 ml) was added to the reaction mixture. The mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (6.08 g, yield 94%).

[1194] ¹H-NMR(400 MHz, DMSO-d₆); δ (ppm) 8.13(1H, d, J=1.6 Hz), 7.86(1H, d, J=8.8 Hz), 7.63(1H, d, J=8.8, 1.6 Hz), 7.17-7.21(2H, m), 6.91(1H, d, J=8.4, 1.2 Hz), 6.83(1H, t, J=7.4 Hz), 5.80(1H, t, J=4.0 Hz), 4.41(2H, brs), 3.86(3H, s), 3.45-3.52(2H, m), 2.80-2.89(1H, m), 1.97-2.10(2H, m), 1.68-1.85(5H, m), 1.21-1.46(3H, m).

[1196] To a solution of methyl 13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (60 mg, 0.16 mmol) in tetrahydrofuran (2 ml) and methanol (1 ml) was added 4N aqueous sodium hydroxide solution (1 ml), and the mixture was stirred for 3 hr. 1N Hydrochloric acid (4 ml) was added to adjust to pH 7, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the residue in tetrahydrofuran (2 ml) was added 4N HCl-ethyl acetate solution (1 ml), and the solvent was evaporated under reduced pressure. Diethyl ether was added to the residue and the precipitated solid was collected by filtration, washed with diethyl ether and dried in vacuo to give 13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (48 mg, yield 76.4%).

[1197] ¹H-NMR(300 MHz, DMSO-d₆); (ppm) 8.18(1H, s), 7.89(1H, d, J=8.4 Hz), 7.65(1H, d, J=9.9 Hz), 7.18-7.44(4H, brm), 3.46-4.47(4H, brm), 2.81-2.91(1H, m), 1.96-2.11(2H, m), 1.68-1.86(5H, m), 1.22-1.45(3H, m).

[1198] MS 361(M+).
Example 1-4

Production of methyl 5-tert-butoxycarbonylmethyl-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1199]

Example 1-5

Production of (13-cyclohexyl-10-methoxycarbonyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indol-5-yl)acetic acid

[1203]

[1200] To a solution of methyl 13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (2.00 g, 5.34 mmol) obtained in Example 1-2 in N,N-dimethylformamide (16 ml) were added potassium carbonate (1.85 g, 13.4 mmol), sodium iodide (800 mg, 5.34 mmol) and tert-butyl bromoacetate (1.18 ml, 8.01 mmol), and the mixture was stirred at 90°C for 12 hr. The mixture was allowed to cool to room temperature, and water (40 ml) was added. The precipitated solid was collected by filtration, washed successively with water and hexane and dried in vacuo to give methyl 5-tert-butoxycarbonylmethyl-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (2.47 g, yield 95%).

[1201] 1H-NMR(400 MHz, DMSO-d$_6$): δ(ppm) 8.18(1H, d, J=1.2 Hz), 7.88(1H, d, J=8.8 Hz), 7.62(1H, dd, J=8.0, 1.2 Hz), 7.38(1H, t, J=7.8 Hz), 7.28(1H, d, J=7.6 Hz), 7.14(1H, t, J=7.4 Hz), 7.02(1H, d, J=8.0 Hz), 3.87(5H, s), 3.51(2H, brs), 2.75-2.85(1H, m), 1.95-2.09(2H, m), 1.66-1.86(5H, m), 1.17-1.45(3H, m), 1.29(9H, s).

[1202] MS 489(M+1).

[1204] To a solution of methyl 5-tert-butoxycarbonylmethyl-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (2.47 g, 5.05 mmol) in chloroform (17 ml) was added trifluoroacetic acid (17 ml) and the mixture was stirred at room temperature for 5 hr. The reaction mixture was evaporated under reduced pressure and the residue was purified by silica gel chromatography (chloroform:methanol=30:1:15:1) to give (13-cyclohexyl-10-methoxycarbonyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indol-5-yl)acetic acid (1.34 g, yield 61%).

[1205] 1H-NMR(400 MHz, DMSO-d$_6$): δ(ppm) 12.60(1H, brs), 8.18(1H, d, J=1.2 Hz), 7.87(1H, d, J=8.4 Hz), 7.62(1H, dd, J=8.8, 1.6 Hz), 7.37(1H, td, J=8.0, 0.8 Hz), 7.27(1H, dd, J=7.6, 1.6 Hz), 7.11(1H, t, J=7.4 Hz), 7.05(1H, d, J=8.0 Hz), 4.40(2H, brs), 3.88(2H, brs), 3.87(3H, s), 3.58(2H, t, J=5.4 Hz), 2.76-2.86(1H, m), 1.94-2.07(2H, m), 1.66-1.86(5H, m), 1.20-1.45(3H, m).

[1206] MS 433(M+1).
Example 1-6

Production of methyl 13-cyclohexyl-5-[2-oxo-2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1207]

Example 1-7

Production of 13-cyclohexyl-5-[2-oxo-2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride

[1210]

To a solution of (13-cyclohexyl-10-methoxycarbonyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-5-yl)acetic acid (400 mg, 0.46 mmol) in N,N-dimethylformamide (2 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide monohydrochloride (105 mg, 0.54 mmol), 1-hydroxybenzotriazole monohydrate (75 mg, 0.55 mmol) and thiomorpholine (0.05 ml, 0.49 mmol) and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:2:3) to give methyl 13-cyclohexyl-5-[2-oxo-2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (149 mg, yield 62.6%).

[1209] MS 518(M+1).

To a solution of methyl 13-cyclohexyl-5-[2-oxo-2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (114 mg, 0.22 mmol) in tetrahydrofuran (1 ml) and methanol (1 ml) was added 4N aqueous sodium hydroxide solution (1 ml) and the mixture was stirred at 70°C for 2 hr. The mixture was allowed to cool to room temperature and 1N hydrochloric acid (4 ml) was added to adjust to pH 7. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the residue in ethyl acetate (1 ml) was added 4N HCl-ethyl acetate solution (1 ml) and the solvent was evaporated under reduced pressure. Hexane was added to the residue and the precipitated solid was collected by filtration, washed with hexane, and dried in vacuo to give 13-cyclohexyl-5-[2-oxo-2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (68 mg, yield 57.6%).

[1212] MS 504(M+1).
Example 1-8

Production of methyl 13-cyclohexyl-5-[2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1213]

To a solution of methyl 13-cyclohexyl-5-[2-oxo-2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (149 mg, 0.28 mmol) obtained in Example 1-6 in tetrahydrofuran (1 ml) was added 1M BH₃ THF complex tetrahydrofuran solution (2 ml) with stirring under ice-cooling, and the mixture was stirred at room temperature for 4 hr. 2N Hydrochloric acid was added to the reaction mixture at room temperature and the mixture was stirred at 70°C for 2 hr. To the reaction mixture was added 4N aqueous sodium hydroxide solution to adjust to pH 8 and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the residue in ethyl acetate (1 ml) was added 4N HCl-ethyl acetate solution (1 ml) and the solvent was evaporated under reduced pressure. Ethyl acetate was added to the residue and the precipitated solid was collected by filtration, washed with hexane and dried in vacuo to give methyl 13-cyclohexyl-5-[2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (88 mg, yield 61%).

[1215] MS 504(M+1).

Example 1-9

Production of 13-cyclohexyl-5-[2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride

[1216]

To a solution of methyl 13-cyclohexyl-5-[2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (88 mg, 0.17 mmol) in tetrahydrofuran (1 ml) and methanol (1 ml) was added 4N aqueous sodium hydroxide solution (1 ml) and the mixture was stirred at room temperature for 20 hr. To the reaction mixture was added 1N hydrochloric acid to adjust to pH 7. The mixture was extracted with ethyl acetate and the organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the residue in ethyl acetate (1 ml) was added 4N HCl-ethyl acetate solution (1 ml) and the solvent was evaporated under reduced pressure. Ethyl acetate was added to the residue and the precipitated solid was collected by filtration, washed with hexane and dried in vacuo to give 13-cyclohexyl-5-[2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (44 mg, yield 44.9%).

[1218] MS 490(M+1).
Example 1-10

Production of methyl 3-chloro-13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

Step 1: Production of 5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine

Step 2: Production of methyl 2-(2-amino-4-chlorophenyl)-3-cyclohexyl-1H-indole-6-carboxylate

[1220] To a solution of 2-bromo-5-chloroaniline (20.0 g, 96.9 mmol) in 1,4-dioxane (200 ml) were added triethylamine (54.0 ml, 487 mmol) and [1,1-bis(diphenylphosphine)ferrocene]dichloropalladium(II) dichloromethane complex (3.96 g, 4.84 mmol), and under a nitrogen stream, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (42.3 ml, 290 mmol) was added dropwise. The mixture was stirred at 100°C for 10.5 hr. The mixture was allowed to cool to room temperature and filtered through celite. To the filtrate was added dropwise methanol (25 ml) at 0°C. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=20:1) to give 5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine (16.5 g, yield 65%).

[1221] 3H-NMR(400 MHz, DMSO-d6); (ppm) 7.28(1H, d, J=6.0 Hz), 6.59(1H, d, J=1.2 Hz), 6.43(1H, dd, J=6.3, 1.5 Hz), 5.70(2H, s), 1.24(12H, s).

[1222] To a suspension of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (5.20 g, 15.4 mmol) obtained in the same manner as in the method described in WO03/010140 and 5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine (4.11 g, 16.2 mmol) in 1,2-dimethoxyethane (20 ml) and water (10 ml) were added sodium hydrogen carbonate (4.10 g, 48.6 mmol) and tetrakis(triphenylphosphine)palladium (1.87 g, 1.62 mmol) and the mixture was heated under reflux for 12 hr. The mixture was allowed to cool to room temperature, and water was added to the reaction mixture. The mixture was extracted with ethyl acetate and the organic layer was washed successively with saturated aqeous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane:ethyl acetate=5:1) to give methyl 2-(2-amino-4-chlorophenyl)-3-cyclohexyl-1H-indole-6-carboxylate (6.17 g, yield 100%).

[1224] 1H-NMR(400 MHz, DMSO-d6); (ppm) 11.33(1H, br), 7.95(1H, d, J=1.2 Hz), 7.79(1H, d, J=8.4 Hz), 7.58(1H, dd, J=8.0, 1.6 Hz), 7.02(1H, d, J=8.0 Hz), 6.83(1H, d, J=2.0 Hz), 6.65(1H, dd, J=8.0, 2.4 Hz), 5.17(2H, br), 3.84(3H, s), 2.55-2.55(1H, m), 1.64-1.91(6H, m), 1.20-1.37(4H, m).
Step 3: Production of methyl 2-[4-chloro-2-(2-chloroacetylamino)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate

[1225]

Step 4: Production of methyl 3-chloro-13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1227]

[1226] To a suspension of methyl 2-(2-amino-4-chlorophenyl)-3-cyclohexyl-1H-indole-6-carboxylate (6.17 g, 16.1 mmol), sodium acetate (1.39 g, 17.0 mmol) and acetic acid (0.98 ml, 17.0 mmol) in tetrahydrofuran (50 ml) was added dropwise chloroacetyl chloride (1.35 ml, 17.0 mmol), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure and water was added. The precipitate was collected by filtration, washed with water and dried in vacuo to give methyl 2-[4-chloro-2-(2-chloroacetylamino)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate (6.71 g, yield 95%).

[1228] To a solution of methyl 2-[4-chloro-2-(2-chloroacetylamino)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate (6.71 g, 14.6 mmol) in N,N-dimethylformamide (40 ml) and tetrahydrofuran (10 ml) was added sodium hydride (1.29 g, 3.21 mmol) under ice-cooling, and the mixture was stirred for 2 hr. The reaction mixture was concentrated under reduced pressure and water was added. The precipitate was collected by filtration, washed successively with water and hexane and dried in vacuo to give methyl 3-chloro-13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (6.97 g, yield 100%).

[1229] $^1$H-NMR (400 MHz, DMSO-d$_6$): (ppm) 8.28 (1H, d, $J$=1.2 Hz), 7.96 (1H, d, $J$=8.4 Hz), 7.68 (1H, d, $J$=8.4, 1.6 Hz), 7.52 (1H, d, $J$=8.4 Hz), 7.44 (1H, d, $J$=8.4, 2.0 Hz), 7.31 (1H, d, $J$=2.0 Hz), 5.10 (1H, d, $J$=14.4 Hz), 4.58 (1H, d, $J$=14.8 Hz), 3.89 (3H, s), 2.81-2.81 (1H, m), 1.67-2.10 (5H, m), 1.37-1.56 (2H, m), 1.13-1.29 (3H, m).
Example 1-11
Production of methyl 3-chloro-13-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

Example 1-12
Production of methyl 3-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1230]

[1231] A suspension of methyl 3-chloro-13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (2.00 g, 4.73 mmol), 1-(2-chloroacetyl)piperidine (1.15 g, 7.09 mmol) and potassium carbonate (1.31 g, 9.46 mmol) in N,N-dimethylformamide (20 ml) was stirred at 90° C. for 24 hr. The reaction mixture was concentrated under reduced pressure and water was added. The precipitate was collected by filtration, washed with water and dried in vacuo. A crude product was washed with a mixed solvent of hexane (45 ml) and diethyl ether (15 ml) and dried in vacuo to give methyl 3-chloro-13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (2.16 g, yield 83%).

[1232] ^1H-NMR(400 MHz, DMSO-d$_6$): δ(ppm) 8.29(1H, d, J=1.6 Hz), 7.95(1H, d, J=8.8 Hz), 7.68(1H, dd, J=8.8, 1.6 Hz), 7.51-7.57(3H, m), 5.22(1H, d, J=14.8 Hz), 4.71(1H, d, J=16.8 Hz), 4.56(1H, d, J=14.8 Hz), 4.50(1H, d, J=16.8 Hz), 3.89(3H, s), 3.29-3.43(4H,m), 2.83-2.83(1H, m), 1.33-2.08(16H, m).

[1234] To a solution of methyl 3-chloro-13-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (3.80 g, 6.94 mmol) in tetrahydrofuran (10 ml) was added 1M BH$_3$ THF complex tetrahydrofuran solution (50 ml) under ice-cooling, and the mixture was stirred at room temperature for 4 hr. 2N Hydrochloric acid (40 ml) was added to the reaction mixture under ice-cooling, and the mixture was stirred at 70° C. for 12 hr. The reaction mixture was allowed to cool to room temperature, neutralized with saturated aqueous sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (ethyl acetate:methanol=50:1) to give methyl 3-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (2.30 g, yield 64%).

[1235] ^1H-NMR(400 MHz, DMSO-d$_6$): δ(ppm) 8.15(1H, d, J=1.6 Hz), 7.84(1H, d, J=8.8 Hz), 7.59(1H, dd, J=8.4, 1.2 Hz), 7.30(1H, d, J=2.0 Hz), 7.24(1H, d, J=8.0 Hz), 7.15(1H, dd, J=8.4, 2.4 Hz), 3.86-4.75(4H, m), 3.84(3H, s), 3.12-3.51(4H, m), 2.74-2.74(1H, m), 1.60-2.35(12H, m), 1.09-1.40(8H, m).
Example 1-13

Production of 3-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid

[1236]

Example 1-14

Production of 3-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride

[1240]

To a suspension of methyl 3-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (1.21 g, 2.32 mmol) in tetrahydrofuran (10 ml) and methanol (10 ml) was added 4N aqueous sodium hydroxide solution (3 ml), and the mixture was stirred at 90°C for 8 hr. 1N Hydrochloric acid (12 ml) was added to adjust to pH 7, and the mixture was extracted with a mixed solvent of ethyl acetate and tetrahydrofuran. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and crude crystals were washed with methanol, collected by filtration and dried in vacuo to give 3-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (884 mg, yield 72%).

[1238] 1H-NMR(400 MHz, DMSO-d6): (ppm) 11.64 (1H, br), 8.14 (1H, d, J=1.2 Hz), 7.83 (1H, d, J=8.4 Hz), 7.60 (1H, dd, J=8.4, 1.2 Hz), 7.32 (1H, d, J=2.0 Hz), 7.26 (1H, d, J=8.0 Hz), 7.17 (1H, dd, J=8.4, 2.0 Hz), 3.03-3.93 (8H, m), 2.76-2.76 (1H, m), 1.59-2.34 (12H, m), 1.19-1.47 (8H, m).

[1239] MS 506(M+1:Cl35), 508(M+1:Cl37).

To a solution of 3-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (1.86 g, 3.67 mmol) in ethyl acetate (20 ml) was added 4N HCl-ethyl acetate solution (7 ml) at room temperature, and the mixture was stirred for 30 min. The reaction mixture was concentrated under reduced pressure. Diethyl ether was added to the crude crystals and the crystals were collected by filtration and washed with diethyl ether. The crystals were dried in vacuo to give 3-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (2.13 g, yield 92%).

[1242] 1H-NMR(400 MHz, DMSO-d6): (ppm) 10.23 (1H, br), 8.18 (1H, d, J=1.2 Hz), 7.85 (1H, d, J=8.4 Hz), 7.60 (1H, dd, J=8.4, 1.2 Hz), 7.35-7.38 (2H, m), 7.32 (1H, dd, J=8.0, 1.6 Hz), 2.88-4.98 (6H, m), 2.79-2.79 (1H, m), 2.52-2.61 (2H, m), 0.98-2.07 (20H, d).

[1243] MS 506(M+1).
Example 1-15

Production of methyl 13-cyclohexyl-2-fluoro-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]
indole-10-carboxylate

Step 1: Production of 4-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine

[1244]

[1245] To a solution of 2-bromo-4-fluorophenol (5.0 g, 26.3 mmol) in 1,4-dioxane (50 mL) were added triethylamine (18.5 mL, 132.7 mmol) and [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (PdCl2(dppf)CH2Cl2) (1.07 g, 1.3 mmol) at room temperature. To the mixture was added dropwise pinacolborane (11.5 mL, 79.2 mmol) at room temperature and the mixture was stirred at 100°C for 27 hr. Saturated aqueous ammonium chloride solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (toluene) to give 4-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl amine (2.0 g, yield 32.0%).

[1246] 1H-NMR(400 MHz, CDCl3): δ(ppm) 7.28(1H, d, J=3.2 Hz), 6.91(1H, d, J=8.8, 8.8, 3.2 Hz), 6.53(1H, dd, J=8.8, 3.6 Hz), 4.45(2H, brs), 1.34(12H, s).

[1247] MS 238(M+1)

Step 2: Production of methyl 2-(2-amino-5-fluorophenyl)-3-cyclohexyl-1H-indole-6-carboxylate

[1248]

[1249] To a suspension of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (2.35 g, 6.98 mmol) obtained in the same manner as in the method described in WO03/010140 and 4-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine (1.99 g, 8.38 mmol) in 1,2-dimethoxyethane (24 mL) and water (12 mL) were added sodium hydrogen carbonate (2.00 g, 24.0 mmol) and tetakis(triphenylphosphine)palladium (400 mg, 0.34 mmol), and the mixture was heated under reflux for 14 hr. The mixture was allowed to cool to room temperature, and water was added to the reaction mixture. The mixture was extracted with ethyl acetate and the organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane:ethyl acetate=4:1-3:1) to give methyl 2-(2-amino-5-fluorophenyl)-3-cyclohexyl-1H-indole-6-carboxylate (2.44 g, yield 95.7%).

[1250] 1H-NMR(300 MHz, CDCl3): δ(ppm) 8.22(1H, brs), 8.09(1H, brs), 7.82(1H, d, J=6.0 Hz), 5.37-7.49(1H, m), 7.17(1H, brd, J=6.6 Hz), 6.89-7.03(1H, m), 6.74(1H, dd, J=8.1, 4.8 Hz), 3.94(3H, s), 3.66(2H, brs), 2.63-2.78(1H, m), 1.70-2.01(7H, m), 1.23-1.50(3H, m).

Step 3: Production of methyl 2-[2-(2-chloroacetyl-amino)-5-fluorophenyl]-3-cyclohexyl-1H-indole-6-carboxylate

[1251]
To a suspension of methyl 2-(2-amino-5-fluorophenyl)-3-cyclohexyl-1H-indole-6-carboxylate (2.44 g, 6.68 mmol), sodium acetate (602 mg, 7.3 mmol) and acetic acid (0.45 ml, 7.86 mmol) in tetrahydrofuran (20 ml) was added dropwise chloroacetyl chloride (0.60 ml, 7.55 mmol), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium carbonate solution and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and a mixed solvent of hexane:ethyl acetate (4:1) was added to the residue. The precipitated solid was collected by filtration to give methyl 2-[2-(2-chloroacetylamino)-5-fluorophenyl]-3-cyclohexyl-1H-indole-6-carboxylate (2.5 g, yield 84.7%).

$^1$H-NMR(400 MHz, DMSO-d$_6$): $\delta$(ppm) 10.33(1H, s), 8.29(1H, d, J=1.2 Hz), 7.98(1H, d, J=8.4 Hz), 7.68(1H, dd, J=8.4, 1.6 Hz), 7.41(1H, d, J=8.4, 2.8 Hz), 7.30(1H, dd, J=8.8, 5.6 Hz), 7.26(1H, dd, J=9.2, 3.2 Hz), 7.50(1H, d, J=14.8 Hz), 4.57(1H, d, J=14.8 Hz), 3.89(3H, s), 2.79-2.90(1H, m), 1.98-2.12(3H, m), 1.86-1.94(1H, m), 1.67-1.78(2H, m), 1.48-1.57(1H, m), 1.34-1.45(2H, m), 1.16-1.28(1H, m).

Example 1-16

Production of methyl 13-cyclohexyl-2-fluoro-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

$^1$H-NMR(400 MHz, DMSO-d$_6$): $\delta$(ppm) 11.50(1H, s), 9.49(1H, s), 8.99(1H, d, J=1.6 Hz), 7.85(1H, dd, J=4.8, 4.8 Hz), 7.83(1H, d, J=8.8 Hz), 7.60(1H, dd, J=8.4, 2.8 Hz), 7.34(1H, dd, J=8.4, 2.8 Hz), 7.21(1H, dd, J=9.2, 3.2 Hz), 4.18(2H, s), 3.85(3H, s), 2.41-2.48(1H, m), 1.78-1.92(2H, m), 1.61-1.77(5H, m), 1.21-1.34(3H, m).

$^1$H-NMR(400 MHz, DMSO-d$_6$): $\delta$(ppm) 15.22(1H, s), 9.52(1H, s), 8.98(1H, d, J=1.6 Hz), 7.84(1H, dd, J=4.8, 4.8 Hz), 7.82(1H, d, J=8.8 Hz), 7.60(1H, dd, J=8.8, 2.8 Hz), 7.33(1H, dd, J=8.4, 2.8 Hz), 7.20(1H, dd, J=9.2, 3.2 Hz), 4.18(2H, s), 3.85(3H, s), 2.41-2.48(1H, m), 1.78-1.92(2H, m), 1.61-1.77(5H, m), 1.21-1.34(3H, m).


[1255] To a solution of methyl 2-[2-(2-chloroacetylamino)-5-fluorophenyl]-3-cyclohexyl-1H-indole-6-carboxylate (2.5 g, 5.6 mmol) in N,N-dimethylformamide was added sodium hydride (250 mg, 6.25 mmol) under ice cooling, and the mixture was stirred for 2 hr. To the reaction mixture was added 1N hydrochloric acid and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane:ethyl acetate=3:2:2:3) to give methyl 13-cyclohexyl-2-fluoro-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (1.81 g, yield 79.7%).

[1256] $^1$H-NMR(400 MHz, DMSO-d$_6$): $\delta$(ppm) 10.35(1H, s), 8.29(1H, d, J=1.2 Hz), 7.98(1H, d, J=8.4 Hz), 7.68(1H, dd, J=8.4, 1.6 Hz), 7.41(1H, dd, J=8.4, 2.8 Hz), 7.30(1H, dd, J=8.8, 5.6 Hz), 7.26(1H, dd, J=9.2, 3.2 Hz), 5.10(1H, d, J=14.8 Hz), 4.57(1H, d, J=14.8 Hz), 3.89(3H, s), 2.79-2.90(1H, m), 1.98-2.12(3H, m), 1.86-1.94(1H, m), 1.67-1.78(2H, m), 1.48-1.57(1H, m), 1.34-1.45(2H, m), 1.16-1.28(1H, m).

[1257]
[1258] To a solution of methyl 13-cyclohexyl-2-fluoro-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (150 mg, 0.37 mmol) and 1-(2-chloroacetyl)piperidine (90 mg, 0.55 mmol) in N,N-dimethylformamide (2 ml) were added potassium carbonate (102 mg, 0.73 mmol) and potassium iodide (5 mg, 0.03 mmol) and the mixture was stirred at 90°C for 3 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane:ethyl acetate=1:1:1:2) to give methyl 13-cyclohexyl-2-fluoro-6-oxo-5-[2-oxo-2-(piperidine-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (137 mg, yield 69.9%).

[1259] 1H-NMR(400 MHz, CDCl3): δ(ppm) 8.22(1H, brs), 7.89(1H, d, J=8.4 Hz), 7.79(1H, d, J=8.4, 1.2 Hz), 7.61(1H, dd, J=9.6, 5.2 Hz), 7.13-7.20(2H, m), 5.00(1H, d, J=14.4 Hz), 4.80(1H, d, J=16.4 Hz), 4.55(1H, d, J=14.4 Hz), 3.95(1H, d, J=16.0 Hz), 3.95(3H, s), 3.66-3.74(1H, m), 3.49-3.58(1H, m), 3.43-3.42(1H, m), 3.22-3.31(1H, m), 2.88-2.99(1H, m), 1.92-2.17(4H, m), 1.76-1.87(2H, m), 1.23-1.72(10H, m).

Example 1-17

Production of methyl 13-cyclohexyl-2-fluoro-5-[2-(piperidine-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1260]

[1261] To a solution of methyl 13-cyclohexyl-2-fluoro-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (137 mg, 0.25 mmol) in tetrahydrofuran (1.0 ml) was added 1M BH3·THF complex tetrahydrofuran solution (2.0 ml) under ice-cooling stirred, and the mixture was stirred at room temperature for 3 hr. 2N Hydrochloric acid was added to the reaction mixture, and the mixture was stirred at 70°C for 5 hr. 4N Aqueous sodium hydroxide solution was added to adjust to pH 8 and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (chloroform:methanol=30:1-10:1) to give methyl 13-cyclohexyl-2-fluoro-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (91 mg, yield 70.5%).

[1262] MS 504(M+1).

Example 1-18

Production of 13-cyclohexyl-2-fluoro-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride

[1263]
[1264] To a solution of methyl 13-cyclohexyl-2-fluoro-5-[2-piperidin-1-ylthethyl]-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid (91 mg, 0.18 mmol) in tetrahydrofuran (1.0 ml) and methanol (1.0 ml) was added 4N aqueous sodium hydroxide solution (1.0 ml), and the mixture was stirred at 60°C for 3 hr. 1N Hydrochloric acid was added to the reaction mixture to adjust to pH 7 and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the residue in tetrahydrofuran (1.0 ml) was added 4N HCl-ethyl acetate solution (1 ml) and the solvent was evaporated under reduced pressure. Hexane was added and the precipitated solid was collected by filtration. The solid was washed with hexane and dried in vacuo to give 13-cyclohexyl-2-fluoro-5-[2-piperidin-1-ylthethyl]-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (64 mg, yield 63.4%).

[1265] MS 490.2(M+1).

[1266] The compounds of Examples 1-19 to 1-95 were produced by the same method as in Examples 1-1 to 1-18 or a method similar thereto, and where necessary, employing other conventional methods. Chemical structural formulas are shown in Tables 2-20.

[1267] 5-acetyl-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid (Example 1-19),

[1268] 13-cyclohexyl-5-methyl-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid (Example 1-20),

[1269] 13-cyclohexyl-5-dimethylcarbamoylmethyl-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid (Example 1-21),

[1270] 5-benzyl-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid (Example 1-22),

[1271] 13-cyclohexyl-5-isopropyl-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-23),

[1272] 13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid (Example 1-24),

[1273] 5-(benzylcarbamoylmethyl)-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid (Example 1-25),

[1274] 13-cyclohexyl-5-[2-(morpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid (Example 1-26),

[1275] 13-cyclohexyl-5-[2-(morpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-27),

[1276] 13-cyclohexyl-5-dimethylcarbamoylmethyl-3-methoxy-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid (Example 1-28),

[1277] 13-cyclohexyl-5-[2-oxo-2-(piperidin-1-ylthethyl)]-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid (Example 1-29),

[1278] 13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-30),

[1279] 13-cyclohexyl-5-dimethylcarbamoylmethyl-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid (Example 1-31),

[1280] 13-cyclohexyl-5-[2-(piperidin-1-ylthethyl)-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-32),

[1281] 13-cyclohexyl-5-[2-(pyridin-2-ylmethyl)carbamoylmethyl]-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-33),

[1282] 13-cyclohexyl-5-[2-[(pyridin-2-ylmethyl)amino]ethyl]-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid trihydrochloride (Example 1-34),

[1283] 13-cyclohexyl-5-[2-(4-hydroxy-piperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-35),

[1284] 13-cyclohexyl-5-[2-(4-methoxy-piperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-36),


[1286] 13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-38),

[1287] 13-cyclohexyl-5-[2-(4-methoxy-piperazin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6]1,4-diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-39),


[1290] 13-cyclohexyl-5-[2-(4-hydroxypiperidin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid dihydrochloride (Example 1-42).

[1291] 13-cyclohexyl-5-[2-(4-dimethylaminopiperidin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid dihydrochloride (Example 1-43).

[1292] 13-cyclohexyl-5-[2-(4-dimethylaminopiperidin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid trihydrochloride (Example 1-44).

[1293] 13-cyclohexyl-5-[2-(1,1-dioxothiomorpholin-4-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monohydrochloride (Example 1-45).

[1294] 13-cyclohexyl-5-[2-(4-ethoxyxarbolypiperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monohydrochloride (Example 1-46).

[1295] 13-cyclohexyl-5-[2-(4-isopropylpiperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid dihydrochloride (Example 1-47).

[1296] 13-cyclohexyl-5-[2-(4-isopropylpiperazin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid trihydrochloride (Example 1-48).

[1297] 13-cyclohexyl-5-[2-(1,4-oxazepan-4-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monochloride (Example 1-49).

[1298] 13-cyclohexyl-5-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid dihydrochloride (Example 1-50).

[1299] 5-[2-(4-acylpiperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monochloride (Example 1-51).

[1300] 13-cyclohexyl-5-[2-(4-methylpiperazin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid trihydrochloride (Example 1-52).

[1301] 13-cyclohexyl-5-[2-(4-methyl-1,4-diazepan-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid trihydrochloride (Example 1-53).

[1302] 13-cyclohexyl-5-[2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid dihydrochloride (Example 1-54).

[1303] 13-cyclohexyl-5-[2-(4-ethypiperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxamide (Example 1-55).

[1304] 13-cyclohexyl-5-[2-oxo-2-(pyrrolidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monohydrochloride (Example 1-56).

[1305] 13-cyclohexyl-5-[2-(pyrrolidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid dihydrochloride (Example 1-57).

[1306] 13-cyclohexyl-5-[2-(morpholin-4-yl)-2-oxoethyl]-7-phenyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monohydrochloride (Example 1-58).

[1307] 13-cyclohexyl-7-phenyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monohydrochloride (Example 1-59).

[1308] 3-chloro-13-cyclohexyl-5-[2-(morpholin-4-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monohydrochloride (Example 1-60).

[1309] 13-cyclohexyl-5-[4-(morpholin-4-yl)-4-oxobuty]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monochloride (Example 1-61).

[1310] 13-cyclohexyl-5-[4-(4-ethylpiperazin-1-yl)-4-oxobuty]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid dihydrochloride (Example 1-62).

[1311] 13-cyclohexyl-3-methyl-5-[2-(morpholin-4-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monochloride (Example 1-63).

[1312] 13-cyclohexyl-3-methoxy-5-[2-(morpholin-4-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monochloride (Example 1-64).

[1313] 13-cyclohexyl-3-methoxy-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monohydrochloride (Example 1-65).

[1314] 13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-3-methoxy-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid dihydrochloride (Example 1-66).

[1315] 13-cyclohexyl-3-methoxy-5-[2-(morpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid dihydrochloride (Example 1-67).

[1316] 13-cyclohexyl-3-methyl-5-[2-(morpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid dihydrochloride (Example 1-68).

[1317] 13-cyclohexyl-5-[2-(1,4-oxazepan-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid dihydrochloride (Example 1-69).

[1318] 13-cyclohexyl-5-[2-(4-methanesulfonylpiperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monochloride (Example 1-70).

[1319] 13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin-7,1-a-jindole-10-carboxylic acid monochloride (Example 1-71).
13-cyclohexyl-5-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid monohydrochloride (Example 1-72),

13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-73),

13-cyclohexyl-3-methoxy-5-[2-(piperazin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-74),

13-cyclohexyl-5-[2-(4-methylpiperazin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid monohydrochloride (Example 1-75),

3-chloro-13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)ethyl]-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-76),

3-chloro-13-cyclohexyl-5-[2-oxo-2-(piperazin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid monohydrochloride (Example 1-77),

5-[2-(azepan-1-yl)-2-oxoethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid monohydrochloride (Example 1-78),

3-chloro-13-cyclohexyl-5-[2-(methyl-4-y1)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-79),

13-cyclohexyl-5-[4-(morpholin-4-yl)butyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-80),

13-cyclohexyl-5-[2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-81),

13-cyclohexyl-5-[2-(4-phenylpiperazin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-82),

5-[2-(azepan-1-yl)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-83),

13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-N-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxamide (Example 1-84),

13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-N-(2-hydroxyethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxamide (Example 1-85),

13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-N-(2-hydroxy-1,1-dimethylethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxamide (Example 1-86),

13-cyclohexyl-5-[2-(4-dimethylcarbamoylpiperazin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-87),

5-[2-(4-benzoylpiperazin-1-yl)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-88),

5-[2-(4-(1-tert-butoxy carbonylpiperidin-4-y1)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid (Example 1-89),

13-cyclohexyl-5-[2-(2-oxonorbornidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid monohydrochloride (Example 1-90),

13-cyclohexyl-5-[2-(4-methanesulfonylpiperazin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-91),

5-[2-(1-acetyl piperidin-4-yl)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid monohydrochloride (Example 1-92),

13-cyclohexyl-5-[2-(1-ethylpiperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-93),

13-cyclohexyl-5-[2-(1-methylpiperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid monohydrochloride (Example 1-94),

5-[2-(4-(2-tetrahydro car barren piperazin-1-yl)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid dihydrochloride (Example 1-95).

Example 1-168

Production of 13-cyclohexyl-3-methyl-5-[2-(1,4-oxazepan-4-y1)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]jindole-10-carboxylic acid

Step 1: Production of N-chloroacetyl-1,4-oxazepane

\[ \text{HCl} \quad \text{O} \quad \text{Cl} \]

\[ \text{Cl} \quad \text{O} \quad \text{N} \quad \text{Cl} \]

\[ \text{O} \quad \text{N} \quad \text{Cl} \]

\[ \text{Cl} \quad \text{O} \quad \text{N} \quad \text{Cl} \]

A suspension of 1,4-oxazepane hydrochloride (24.80 g, 180 mmol), sodium acetate (29.60 g, 360 mmol) and acetic acid (20.6 ml, 360 mmol) in tetrahydrofuran (400 ml) was stirred for 1 hr. a solution of chloroacetyl chloride (14.3 ml, 180 mmol) in tetrahydrofuran (100 ml) was added dropwise under ice-cooling, and the mixture was stirred overnight at room temperature. To the reaction mixture was added sodium hydrogen carbonate (65.7 g, 792 mmol), and the mixture was stirred for 1 hr. The insoluble material was...
filtered, and the filtrate was concentrated. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=2:1-1:2) to give N-chloroacetyl-1,4-oxazepane (29.8 g, yield 93%).

[1346] $^1$H-NMR(400 MHz, DMSO-d$_6$): $\delta$(ppm) 4.42(1H, s), 4.39(1H, s), 3.70-3.72(1H, m), 3.54-3.65(7H, m), 1.82-1.88(1H, m), 1.72-1.78(1H, m).

Step 2: Production of methyl 13-cyclohexyl-3-methyl-5-[2-(1,4-oxazepan-4-yl)-2-oxoethyl]-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1347]

A suspension of methyl 13-cyclohexyl-3-methyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (2.53 g, 6.30 mmol), N-chloroacetyl-1,4-oxazepane (1.23 g, 6.92 mmol) and potassium carbonate (1.73 g, 12.6 mmol) in N,N-dimethylformamide (13 ml) was stirred at 90°C for 3 hr. To the reaction mixture was added 2N hydrochloric acid (13 ml), and the precipitated solid was collected by filtration. After washing with water, the solid was dried in vacuo and suspended in methanol. The suspension was stirred for 1 hr, and the obtained crystals were collected by filtration. The crystals were washed with methanol and dried in vacuo to give methyl 13-cyclohexyl-3-methyl-5-[2-(1,4-oxazepan-4-yl)-2-oxoethyl]-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (2.85 g, yield 83%).

[1349] $^1$H-NMR(400 MHz, DMSO-d$_6$): $\delta$(ppm) 8.28(1H, s), 7.95(1H, d, J=8.8 Hz), 7.68(1H, dd, J=8.0, 1.2 Hz), 7.42(1H, d, J=7.6 Hz), 7.29-7.33(2H, m), 5.20(1H, d, J=14.4 Hz), 4.68(1H, dd, J=16.8, 9.6 Hz), 4.48(1H, d, J=14.4 Hz), 4.40(1H, d, J=18.0 Hz), 3.89(3H, s), 3.38-3.71(8H, m), 2.82-2.93(1H, m), 2.41(3H, s), 1.67-2.09(8H, m), 1.53-1.61(1H, m), 1.34-1.48(2H, m), 1.12-1.26(1H, m).

Step 3: Production of methyl 13-cyclohexyl-3-methyl-5-[2-(1,4-oxazepan-4-yl)-2-methylphenyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1350]

[1351] To a solution of methyl 13-cyclohexyl-3-methyl-5-[2-(1,4-oxazepan-4-yl)-2-methylphenyl]-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (2.70 g, 4.97 mmol) in tetrahydrofuran (8 ml) was added a solution (20 ml) of 1M BH$_4$ THF complex in tetrahydrofuran, and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added 4N hydrochloric acid (14 ml), and the mixture was stirred at 70°C for 4 hr. The reaction mixture was allowed to cool to room temperature, neutralized with 4N aqueous sodium hydroxide solution and saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was crystallized from methanol (10 ml) and collected by filtration. After washing with methanol, the crystals were dried in vacuo to give methyl 13-cyclohexyl-3-methyl-5-[2-(1,4-oxazepan-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (2.27 g, yield 89%)

[1352] $^1$H-NMR(400 MHz, DMSO-d$_6$): $\delta$(ppm) 8.17(1H, d, J=1.2 Hz), 7.85(1H, d, J=8.8 Hz), 7.61(1H, dd, J=8.4, 1.2 Hz), 7.19(1H, d, J=7.6 Hz), 7.07(1H, s), 6.98(1H, d, J=7.6 Hz), 5.87(3H, s), 3.42(2H, t, J=6.0 Hz), 3.26-3.29(2H, m),
2.76-2.85 (1H, m), 2.42-2.48 (4H, m), 2.38 (3H, s), 1.91-2.06 (2H, m), 1.63-1.86 (5H, m), 1.49-1.54 (2H, m), 1.19-1.44 (5H, m).

Step 4: Production of 13-cyclohexyl-3-methyl-5-[2-(1,4-oxazepan-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid

[1353]

Example 1-413

Production of 13-cyclohexyl-5-[2-(S)-3-(2-methoxyethyl)piperidin-1-yl][ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride

Step 1: Production of (3S)-2-[1-(tert-butoxycarbonyl)piperidin-3-yl]ethanol

[1357]

[1358] To a suspension of lithium aluminum hydride (11.90 g, 313 mmol) in tetrahydrofuran (250 ml) was added a solution of (3S)-ethyl-2-[1-(tert-butoxycarbonyl)piperidin-3-yl]acetate (85.0 g, 313 mmol), obtained in the same manner as in the method described in WO97/25041, in tetrahydrofuran (600 ml) over 2 hr under ice-cooling, and the mixture was further stirred for 3 hr. To the reaction mixture were successively added water (12 ml), 4N aqueous sodium hydroxide solution (36 ml), water (12 ml) and anhydrous magnesium sulfate, and the mixture was stirred at room temperature for 1 hr. Insoluble material was filtered off, and the solvent was evaporated under reduced pressure to give (3S)-2-[1-(tert-butoxycarbonyl)piperidin-3-yl]ethanol (58.10 g, yield 97.6%).

[1359] 1H-NMR(400 MHz, CDCl3): δ/ppm 3.84(1H, m), 3.71(3H, m), 2.80(1H, m), 2.53(1H, br), 1.82(2H, m), 1.60(2H, m), 1.46(3H, m), 1.43(9H, s), 1.12(1H, m).

Step 2: Production of tert-butyl (S)-3-(2-methoxyethyl)piperidine-1-carboxylate

[1360]

[1361] To a suspension of sodium hydride (13.00 g, 325 mmol) in tetrahydrofuran (60 ml) and N,N-dimethylformamide (350 ml) was added a solution of (3S)-2-[1-(tert-butoxycarbonyl)piperidin-3-yl]ethanol (62.00 g, 270 mmol) in N,N-dimethylformamide (200 ml) at room temperature, and the mixture was stirred for 15 min. To the reaction mixture was added methyl iodide (18.5 ml, 297 mmol) at room temperature, and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried

[1362] MS 502.3(M+1).
over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give tert-butyl (S)-3-(2-methoxyethyl)piperidine-1-carboxylate (65.0 g, yield 98%).

[1362] $^1$H-NMR(300 MHz, CDCl$_3$): $\delta$(ppm) 3.85-3.88(1H, m), 3.40(2H, t, J=6.6 Hz), 3.31(3H, s), 2.77-2.77(1H, m), 1.80-1.80(2H, m), 1.48-1.63(4H, m), 1.43(9H, s), 1.10-1.10(1H, m), 0.84-0.84(1H, m).

Step 3: Production of (S)-3-(2-methoxyethyl)piperidine hydrochloride

[1363]

[1364] To a solution of tert-butyl (S)-3-(2-methoxyethyl)piperidine-1-carboxylate (64 g, 263 mmol) in ethyl acetate (100 ml) was added 4N HCl-ethyl acetate solution (320 ml), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure to give (S)-3-(2-methoxyethyl)piperidine hydrochloride as a crude product (46.7 g, yield 98%). The obtained crude product was used for Step 4 without further purification.

[1365] $^1$H-NMR(400 MHz, CDCl$_3$): $\delta$(ppm) 9.59(1H, br), 9.26(1H, br), 3.35-3.45(4H, m), 3.28(3H, s), 2.67-2.80(1H, m), 2.48-2.60(1H, m), 2.05-2.14(1H, m), 1.80-1.99(3H, m), 1.45-1.59(2H, m), 1.09-1.21(1H, m).

Step 4: Production of (S)-3-(2-methoxyethyl)-N-(chloroacetyl)piperidine

[1366]

[1367] To a suspension of (S)-3-(2-methoxyethyl)piperidine hydrochloride (46.7 g, 260 mmol), sodium acetate (46.90 g, 572 mmol) and acetic acid (33.1 ml, 572 mmol) in tetrahydrofuran (470 ml) was added dropwise chloroacetyl chloride (28.3 ml, 7.53 mmol) under ice-cooling, and the mixture was stirred overnight at temperature. To the reaction mixture was added saturated aqueous sodium hydroxide carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydroxide carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1) to give (S)-3-(2-methoxyethyl)-N-(chloroacetyl)piperidine (45.0 g, yield 78.8%).

[1368] $^1$H-NMR(400 MHz, CDCl$_3$): $\delta$(ppm) 4.28-4.37(1H, m), 3.69-3.81(1H, m), 3.37-3.46(2H, m), 3.32(1.5H, s), 3.00(1.5H, s), 2.75-2.81(0.5H, m), 2.23-2.70(0.5H, m), 2.45-2.51(0.5H, m), 1.83-1.91(1H, m), 1.40-1.77(5H, m), 1.14-1.23(1H, m).

Step 5: Production of 2-iodo-5-methylphenylamine hydrochloride

[1369]

[1370] To a solution of 1-iodo-4-methyl-2-nitrobenzene (5.00 g, 19 mmol) in tetrahydrofuran (12.5 ml), methanol (25 ml) and water (6.3 ml) were added sodium acetate (5.30 g, 95 mmol) and ammonium chloride (6.10 g, 114 mmol), and the mixture was stirred overnight at 70° C. The reaction mixture was allowed to cool to room temperature, tetrahydrofuran (50 ml) was added to the reaction mixture. After filtration through celite, the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the residue in ethyl acetate (20 ml) was added 4N HCl-ethyl acetate solution (10 ml). The precipitated solid was collected by filtration, washed with ethyl acetate, and dried in vacuo to give 2-iodo-5-methylphenylamine hydrochloride (2.56 g, yield 50%).

[1371] $^1$H-NMR(300 MHz, DMSO-d$_6$): $\delta$(ppm) 8.34(2H, brs), 7.56(1H, d, J=8.1 Hz), 6.93(1H, s), 6.51(1H, d, J=7.8 Hz), 2.20(3H, s).
Step 6: Production of 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine

[1372]

[1373] To a solution of 2-iodo-5-methylphenylamine hydrochloride (1.00 g, 3.7 mmol) in 1,4-dioxane (15 ml) were added triethylamine (2.6 ml, 18.6 mmol) and PdCl2(dppf)CH2Cl2 (151 mg, 0.19 mmol) at room temperature. To the mixture was added dropwise pinacolborane (1.62 ml, 11.1 mmol) at room temperature, and the mixture was stirred at 100°C for 4 hr. To the reaction mixture was added saturated aqueous ammonium chloride solution, and the mixture was extracted with diethyl ether. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=5:1) to give 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine (570 mg, yield 66%).

[1374] 1H-NMR(400 MHz, CDCl3): δ(ppm) 7.48 (1H, d, J=6.0 Hz), 6.49 (1H, d, J=6.0 Hz), 6.41 (1H, s), 4.66 (2H, brs), 2.24 (3H, s), 1.32 (12H, s).

Step 7: Production of methyl 2-(2-amino-4-methylphenyl)-3-cyclohexyl-1H-indole-6-carboxylate hydrochloride

[1375]

[1376] To a suspension of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (656 mg, 2.0 mmol), obtained in the same manner as in the method described in WO03/010140, and 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine (570 mg, 2.4 mmol) in 1,2-dimethoxyethane (13 ml) and water (6.5 ml) were added sodium hydrogen carbonate (508 mg, 7.1 mmol) and tetrais(triphenylphosphine)palladium (118 mg, 0.10 mmol), and the mixture was stirred at 80°C for 3 hr. The reaction mixture was allowed to cool to room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the residue in ethyl acetate (2 ml) was added 4N HCl-ethyl acetate solution (2 ml). The precipitated solid was collected by filtration, washed with diethyl ether, and dried in vacuo. The obtained crude product (638 mg) was used for Step 8 without further purification.

Step 8: Production of methyl 2-[2-(2-chloroacetylamino)-4-methylphenyl]-3-cyclohexyl-1H-indole-6-carboxylate

[1377]
boxylate (640 mg, 1.5 mmol) in N,N-dimethylformamide (10 mL) was added sodium hydride (141 mg, 3.5 mmol) under ice-cooling, and the mixture was stirred for 5 hr. 1N Hydrochloric acid (5 mL) was added to the reaction mixture, and the mixture was diluted with water. The precipitated solid was collected by filtration, washed with water and hexane, and dried in vacuo to give methyl 13-cyclohexyl-3-methyl-6-oxo-6,7-dihydro-5H-benza[5,6][1,4]diazepino [7,1-a]indole-10-carboxylate (614 mg, yield 95%).

1381] 'H-NMR(300 MHz, DMSO-d_6): δ(ppm) 10.28(1H, s), 8.26(1H, s), 7.95(1H, d, J=8.4 Hz), 7.68(1H, dd, J=9.0, 1.5 Hz), 7.43(1H, d, J=8.1 Hz), 7.22(1H, d, J=7.8 Hz), 7.09(1H, s), 5.06(1H, d, J=15.0 Hz), 4.50(1H, d, J=14.4 Hz), 3.89(3H, s), 2.80-2.89(1H, m), 2.40(3H, s), 1.98-2.08(3H, m), 1.86-1.93(1H, m), 1.68-1.79(2H, m), 1.36-1.55(3H, m), 1.13-1.25(1H, m).

Step 10: Production of methyl 13-cyclohexyl-5-[2-[(S)-3-[2-(methoxyethyl)piperidin-1-yl]-2-oxoethyl]-3-methyl-6-oxo-6,7-dihydro-5H-benza[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1378] To a suspension of methyl 2-(2-amino-4-methylphenyl)-3-cyclohexyl-1H-indole-6-carboxylate (638 mg, 1.6 mmol), sodium acetate (289 mg, 3.5 mmol) and acetic acid (0.10 mL, 1.8 mmol) in tetrahydrofuran (7 mL) was added dropwise chloroacetyl chloride (0.14 mL, 1.8 mmol), and the mixture was stirred at room temperature for 12 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The obtained crude product (640 mg) was used for Step 9 without further purification.

Step 9: Production of methyl 13-cyclohexyl-3-methyl-6-oxo-6,7-dihydro-5H-benza[5,6][1,4]diazepino [7,1-a]indole-10-carboxylate

[1379]

[1380] To a solution of methyl 2-[2-(2-chloroacetyl-lamino)-4-methylphenyl]-3-cyclohexyl-1H-indole-6-carboxylate (640 mg, 1.5 mmol) in N,N-dimethylformamide (10 mL) was added sodium hydride (141 mg, 3.5 mmol) under ice-cooling, and the mixture was stirred for 5 hr. 1N Hydrochloric acid (5 mL) was added to the reaction mixture, and the mixture was diluted with water. The precipitated solid was collected by filtration, washed with water and hexane, and dried in vacuo to give methyl 13-cyclohexyl-3-methyl-6-oxo-6,7-dihydro-5H-benza[5,6][1,4]diazepino [7,1-a]indole-10-carboxylate (614 mg, yield 95%).

[1381] 'H-NMR(300 MHz, DMSO-d_6): δ(ppm) 10.28(1H, s), 8.26(1H, s), 7.95(1H, d, J=8.4 Hz), 7.68(1H, dd, J=9.0, 1.5 Hz), 7.43(1H, d, J=8.1 Hz), 7.22(1H, d, J=7.8 Hz), 7.09(1H, s), 5.06(1H, d, J=15.0 Hz), 4.50(1H, d, J=14.4 Hz), 3.89(3H, s), 2.80-2.89(1H, m), 2.40(3H, s), 1.98-2.08(3H, m), 1.86-1.93(1H, m), 1.68-1.79(2H, m), 1.36-1.55(3H, m), 1.13-1.25(1H, m).

Step 10: Production of methyl 13-cyclohexyl-5-[2-[(S)-3-[2-(methoxyethyl)piperidin-1-yl]-2-oxoethyl]-3-methyl-6-oxo-6,7-dihydro-5H-benza[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1382]
dole-10-carboxylate (1.00 g, 2.48 mmol), (S)-3-(2-methoxyethyl)-N-(chloroacetyl)piperidine (819 mg, 3.72 mmol) and potassium carbonate (606 mg, 4.46 mmol) in N,N-dimethylformamide (20 ml) was stirred at 80° C. for 3 hr. The reaction mixture was allowed to cool to room temperature. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=1:1) to give methyl 13-cyclohexyl-5-[2-[(S)-3-(2-methoxyethyl)piperidin-1-yl]-2-oxoethyl]-3-methyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (967 mg, yield 67%).

[1384] 1H-NMR(400 MHz, DMSO-d6): δ (ppm) 8.24 (1H, s), 7.91 (1H, d, J=6.0 Hz), 7.65 (1H, dd, J=6.3, 1.2 Hz), 7.38 (1H, d, J=6.0 Hz), 7.24-7.28 (2H, m), 7.15 (1H, d, J=10.8 Hz), 4.56-4.66 (1H, m), 4.34-4.47 (2H, m), 3.93-4.00 (1H, m), 3.86 (3H, s), 3.51-3.67 (1H, m), 3.21-3.31 (1H, m), 3.09-3.18 (3H, m), 2.80-3.02 (2H, m), 2.55-2.68 (1H, m), 2.38 (3H, s), 1.93-2.03 (3H, m), 1.84-1.88 (1H, m), 1.66-1.75 (3H, m), 1.52-1.59 (2H, m, 1.05-1.45 (9H, m).

Step 11: Production of methyl 13-cyclohexyl-5-[2-[(S)-3-(2-methoxyethyl)piperidin-1-yl]-2-oxoethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1385]

[1386] To a solution of methyl 13-cyclohexyl-5-[2-[(S)-3-(2-methoxyethyl)piperidin-1-yl]-2-oxoethyl]-3-methyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (967 mg, 1.6 mmol) in tetrahydrofuran (3 ml) was added a solution (15 ml) of 1.0 M BH₃THF complex in tetrahydrofuran, and the mixture was stirred at room temperature for 1 hr. 5N Hydrochloric acid (18 ml) was added to the reaction mixture, and the mixture was stirred at 60° C. for 5 hr. The reaction mixture was allowed to cool to room temperature, and the reaction mixture was neutralized with 1N aqueous sodium hydroxide solution and saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=10:1) to give methyl 13-cyclohexyl-5-[2-[(S)-3-(2-methoxyethyl)piperidin-1-yl]-2-oxoethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (820 mg, yield 89%).

[1387] 1H-NMR(400 MHz, DMSO-d6): δ (ppm) 8.13 (1H, d, J=0.9 Hz), 7.81 (1H, d, J=6.3 Hz), 7.57 (1H, dd, J=6.6, 1.5 Hz), 7.15 (1H, d, J=5.7 Hz), 7.04 (1H, s), 6.94 (1H, d, J=6.0 Hz), 3.83 (3H, s), 3.05-3.40 (8H, m), 2.75-2.82 (1H, m), 2.48-2.62 (5H, m), 2.22-2.39 (5H, m), 1.88-2.01 (3H, m), 1.62-1.81 (5H, m), 1.41-1.54 (2H, m), 1.06-1.38 (8H, m), 0.60-0.71 (1H, m).

Step 12: Production of 13-cyclohexyl-5-[2-[(S)-3-(2-methoxyethyl)piperidin-1-yl]ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride

[1388]

[1389] To a solution of methyl 13-cyclohexyl-5-[2-[(S)-3-(2-methoxyethyl)piperidin-1-yl]ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (820 mg, 1.47 mmol) in tetrahydrofuran (16 ml) and methanol (8 ml) was added 4N aqueous sodium hydrox-
ide solution (8 ml), and the mixture was stirred at 60° C. for 5 hr. The reaction mixture was adjusted to pH 7 with 1N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the residue in ethyl acetate (10 ml) was added 4N HCl-ethyl acetate solution (5 ml). The solvent was evaporated under reduced pressure and diethyl ether was added. The precipitated solid was collected by filtration, washed with diethyl ether, and dried in vacuo to give 13-cyclohexyl-5-[2-[(S)-3-(2-methoxyethyl) piperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6]1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (535 mg, yield 59%).

[1390] 1H-NMR(400 MHz, DMSO-d6): δ (ppm) 10.26 (1H, brs), 8.12 (1H, s), 7.78 (1H, d, J=6.3 Hz), 7.56 (1H, d, J=6.3, 0.9 Hz), 7.21 (1H, d, J=5.7 Hz), 7.13 (1H, d, J=6.4 Hz), 7.04 (1H, d, J=6.4 Hz), 2.76-2.84 (4H, m), 2.37 (3H, s), 1.89-2.00 (2H, m), 1.64-1.84 (3H, m), 1.42-1.57 (1H, m), 1.18-1.37 (2H, m), 0.86-0.95 (1H, m).

[1391] MS 544.3(M+1).

Example 1-416

Production of 13-cyclohexyl-5-[2-[(R)-3-methoxyethyl)piperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6]1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride

Step 1: Production of tert-butyl 3-ethyl (R)-piperidine-1,3-dicarboxylate

[1392]

[1393] To a solution of ethyl (R)-piperidine-3-carboxylate (10.00 g, 63.6 mmol) in diethyl ether (100 ml) was added dropwise di-tert-butyl dicarbonate (16.00 g, 73.2 mmol) under ice-cooling, and the mixture was stirred for 40 min. The solvent was evaporated under reduced pressure to give 1-tert-butyl 3-ethyl (R)-piperidine-1,3-dicarboxylate (16.80 g). The obtained compound was used for Step 2 without purification.

[1394] 1H-NMR(300 MHz, CDCl3): δ (ppm) 4.00-4.30 (1H, m), 4.14 (2H, q, J=7.2 Hz), 3.84-3.98 (1H, m), 2.88-3.17 (1H, m), 2.75-2.87 (1H, m), 2.35-2.51 (1H, m), 1.98-2.10 (1H, m), 1.57-1.78 (2H, m), 1.37-1.51 (1H, m), 1.46 (9H, s), 1.27 (3H, t, J=7.2 Hz).

Step 2: Production of tert-butyl (R)-3-hydroxymethylpiperidine-1-carboxylate

[1395]

[1396] To a suspension of lithium aluminum hydride (2.90 g, 76.3 mmol) in tetrahydrofuran (100 ml) was added a solution of 1-tert-butyl 3-ethyl (R)-piperidine-1,3-dicarboxylate (16.30 g, 63.6 mmol) in tetrahydrofuran (60 ml) over 20 min under ice-cooling, and the mixture was further stirred for 20 min. The reaction mixture was successively added water (2.9 ml), 4N aqueous sodium hydroxide solution (2.9 ml), water (8.7 ml) and anhydrous sodium sulfate, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was filtered, and the solvent was evaporated under reduced pressure to give tert-butyl (R)-3-hydroxymethylpiperidine-1-carboxylate (13.00 g, yield 95.0%).

[1397] 1H-NMR(300 MHz, CDCl3): δ (ppm) 3.39-3.95 (2H, m), 3.51 (2H, d, J=6.8 Hz), 2.72-3.20 (2H, m), 1.52-1.94 (4H, m), 1.35-1.50 (1H, m), 1.46 (9H, s), 1.15-1.34 (1H, m).

Step 3: Production of tert-butyl (R)-3-methoxymethylpiperidine-1-carboxylate

[1398]

[1399] To a solution of tert-butyl (R)-3-hydroxymethylpiperidine-1-carboxylate (11.50 g, 53.7 mmol) in N,N-dimethylformamide (110 ml) was added sodium hydride (3.22 g, 80.6 mmol) under ice-cooling, and the mixture was stirred at room temperature for 20 min. To the reaction mixture was added methyl iodide (4.35 ml, 69.9 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the obtained residue was puri-
fied by silica gel column chromatography (hexane:ethyl acetate=1:1) to give tert-butyl (R)-3-methoxymethylpiperidine-1-carboxylate (13.00 g, yield 100%).

[1400] ¹H-NMR(300 MHz, CDCl₃): δ(ppm) 3.84-4.05(2H, m), 3.32(3H, s), 3.24(2H, d, J=6.0 Hz), 2.75-2.89(1H, m), 2.52-2.71(1H, m), 1.70-1.86(2H, m), 1.57-1.69(1H, m), 1.36-1.52(1H, m), 1.46(9H, s), 1.15-1.28(1H, m).

Step 4: Production of (R)-3-methoxymethylpiperidine hydrochloride

[1401]

[1402] To a solution of tert-butyl (R)-3-methoxymethylpiperidine-1-carboxylate (13.00 g, 56.6 mmol) in ethyl acetate (26 ml) was added 4N HCl-ethyl acetate solution (26 ml), and the mixture was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure to give (R)-3-methoxymethylpiperidine hydrochloride as a crude product. A mixed solvent (100 ml) of hexane:ethyl acetate=1:4 was added to the obtained solid, and the mixture was stirred. The solid was collected by filtration to give (R)-3-methoxymethylpiperidine hydrochloride (7.82 g, yield 84%).

[1403] ¹H-NMR(300 MHz, CDCl₃): δ(ppm) 9.11(2H, br), 3.37-3.53(2H, m), 3.22-3.37(2H, m), 3.31(3H, s), 2.62-2.88(2H, m), 2.19-2.38(1H, m), 1.72-2.11(3H, m), 1.21-1.44(1H, m).

Step 5: Production of (R)-3-methoxymethyl-N-(chloroacetyl)piperidine

[1404]

[1405] To a suspension of (R)-3-methoxymethylpiperidine hydrochloride (6.00 g, 36.3 mmol), sodium acetate (6.55 g, 79.9 mmol) and acetic acid (4.57 ml, 79.9 mmol) in tetrahydrofuran (120 ml) was added dropwise chloroacetyl chloride (3.18 ml, 39.9 mmol) under ice-cooling, and the mixture was stirred overnight at room temperature. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:4) to give (R)-3-methoxymethyl-N-(chloroacetyl)piperidine (6.00 g, yield 80%).

[1406] ¹H-NMR(400 MHz, CDCl₃): δ(ppm) 4.32-4.43(0.4H, m), 4.02-4.23(2.6H, m), 3.67-3.85(1H, m), 3.29-3.39(5H, m), 3.07-3.18(0.4H, m), 3.03(0.6H, dd, J=7.0, 10.1 Hz), 2.87-2.99(0.6H, m), 2.62(0.4H, dd, J=7.7, 9.7 Hz), 1.20-2.02(5H, m).

Step 6: Production of methyl 13-cyclohexyl-5-[2-((R)-3-methoxymethylpiperidin-1-yl)-2-oxoethyl]-3-methyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1407]

[1408] A suspension of methyl 13-cyclohexyl-3-methyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (1.00 g, 2.48 mmol), (R)-3-methoxymethyl-N-(chloroacetyl)piperidine (613 mg, 2.98 mmol) and potassium carbonate (687 mg, 4.97 mmol) in N,N-dimethylformamide (15 ml) was stirred at 80°C for 2 hr. The reaction mixture was allowed to cool to room temperature and water was added to the reaction mixture. The precipitate
was collected by filtration, washed with water, and dried in vacuo to give methyl 13-cyclohexyl-5-[2-((R)-3-methoxymethylpiperidin-1-yl)-2-oxoethyl]-3-methyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (1.45 g) as a crude product. The obtained crude product was used for Step 7 without further purification.

[1409] 1H-NMR(300 MHz, DMSO-d6): δ(ppm) 8.27(1H, s), 7.94(1H, d, J=8.3 Hz), 7.68(1H, d, J=8.7 Hz), 7.42(1H, d, J=7.9 Hz), 7.25-7.36(2H, m), 5.18(1H, d, J=14.3 Hz), 4.58-4.73(1H, m), 4.33-4.55(2H, m), 4.05-4.19(0.5H, m), 3.78-3.94(0.5H, m), 3.89(3H, s), 3.49-3.69(1H, m), 3.20(3H, s), 3.17(2H, d, J=10.2 Hz), 2.79-3.01(2H, m), 2.41(3H, s), 1.06-2.15(16H, m).

Step 7: Production of methyl 13-cyclohexyl-5-[2-((R)-3-methoxymethylpiperidin-1-yl)ethy]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate

[1410]

[1411] To a solution of methyl 13-cyclohexyl-5-[2-((R)-3-methoxymethylpiperidin-1-yl)-2-oxoethyl]-3-methyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (1.40 g, 2.45 mmol) in tetrahydrofuran (5.6 ml) was added a solution (14 ml) of 1.07M BH4 in THF complex in tetrahydrofuran under ice-cooling, and the mixture was stirred at room temperature for 16 hr. 5N Hydrochloric acid (5 ml) was added to the reaction mixture under ice-cooling, and the mixture was stirred at 70°C for 4 hr. The reaction mixture was allowed to cool to room temperature, and the reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=9:1) to give methyl 13-cyclohexyl-5-[2-((R)-3-methoxymethylpiperidin-1-yl)ethy]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (1.19 g, yield 83%).

[1412] 1H-NMR(300 MHz, DMSO-d6): δ(ppm) 8.15(1H, d, J=1.6 Hz), 7.84(1H, d, J=8.8 Hz), 7.59(1H, d, J=8.4 Hz), 7.30(1H, d, J=2.0 Hz), 7.24(1H, d, J=8.0 Hz), 7.15(1H, dd, J=8.4, 2.4 Hz), 3.86-4.75(4H, m), 3.84(3H, s), 3.12-3.51(4H, m), 2.74-2.74(1H, m), 1.60-2.33(12H, m), 1.09-1.40(8H, m).

Step 8: Production of 13-cyclohexyl-5-[2-((R)-3-methoxymethylpiperidin-1-yl)ethyl]-2-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride

[1413]

[1414] To a solution of methyl 13-cyclohexyl-5-[2-((R)-3-methoxymethylpiperidin-1-yl)ethyl]-2-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (1.19 g, 2.18 mmol) in tetrahydrofuran (20 ml) and methanol (15 ml) was added 4N aqueous sodium hydroxide solution (10 ml), and the mixture was stirred at 55°C for 3 hr. The reaction mixture was adjusted to pH 6.5 with 2N hydrochloric acid (20 ml), and extracted with a mixed solvent of ethyl acetate and tetrahydrofuran. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure to give 13-cyclohexyl-5-[2-((R)-3-methoxymethylpiperidin-1-yl)ethyl]-2-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid as a crude product. To a solution of the obtained crude product in ethyl acetate (5 ml) was added 4N HCl-ethyl acetate solution (10 ml) at room temperature, and the mixture was stirred for 30 min. The reaction mixture was concentrated under reduced pressure, diethyl ether was
added to the obtained solid, and the solid was collected by filtration and dried in vacuo to give 13-cyclohexyl-5-[(R)-3-methoxymethylpiperidin-1-yl]ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6,11]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (705 mg, yield 61.3%).

[1415] 1H-NMR(300 MHz, DMSO-d₆): δ (ppm) 10.64-11.09 (1H, m), 8.16 (1H, s), 7.84 (1H, d, J=8.7 Hz), 7.61 (1H, d, J=7.9 Hz), 7.25 (1H, d, J=7.9 Hz), 7.19 (1H, s), 7.08 (1H, d, J=7.5 Hz), 4.08-5.02 (2H, m), 3.30-3.96 (2H, m), 3.10-3.25 (2H, m), 2.93-3.09 (2H, m), 3.04 (3H, s), 2.57-2.92 (4H, m), 2.22-2.48 (2H, m), 2.41 (3H, s), 1.90-2.12 (4H, m), 1.45-1.89 (7H, m), 1.21-1.43 (5H, m).

[1416] MS 530.3(M+1)

[1417] The compounds of Examples 1-96 to 1-445 were produced by the same methods as in Examples 1-1 to 1-18, 1-168, 1-413 and 1-416 or methods similar thereto, and where necessary, employing other preferred methods. The chemical structural formulas are shown in Tables 20-100.

Example 2-1

Production of methyl 12-cyclohexyl-3-hydroxy-6,7-dihydro-5-oxa-7-azaazabenzo[a,e]azulene-9-carboxylate

Step 1: Production of 1-bromo-2,4-bismethoxymethoxybenzene

[1418]

To a solution of 4-bromoresorcinol (30 g, 159 mmol) in acetone (300 ml) were added potassium carbonate (66 g, 471 mmol) and chloromethyl methyl ether (30 ml, 397 mmol) under ice-cooling and the mixture was stirred at room temperature for 22 hr. The reaction mixture was concentrated and water was added. The mixture was extracted with ethyl acetate and the organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give 1-bromo-2,4-bismethoxymethoxybenzene as a crude product. The obtained compound was used in Step 2 without further purification.

[1419] 1H-NMR(400 MHz, CDCl₃): δ (ppm) 7.95 (1H, d, J=8.4 Hz), 6.85 (1H, d, J=2.8 Hz), 6.61 (1H, dd, J=8.8, 2.8 Hz), 5.22 (2H, s), 5.13 (2H, s), 5.31 (3H, s), 3.46 (3H, s).

Step 2: Production of 2,4-bismethoxymethoxyphenylboronic acid

[1421]

Step 3: Production of methyl 2-(2,4-bismethoxymethoxyphenyl)-3-cyclohexyl-1H-indole-6-carboxylate

[1424]
[1425] To a suspension of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (14.5 g, 43.2 mmol), obtained in the same manner as in the method described in WO03/010140, and 2,4-bismethoxymethoxyphenylboronic acid (13.6 g, 56.2 mmol) in 1,2-dimethoxyethane (140 ml) and water (70 ml) were added lithium chloride (5.5 g, 129 mmol), sodium carbonate (13.7 g, 129 mmol) and tetrakis(triphenylphosphine)palladium (5.0 g, 4.3 mmol), and the mixture was stirred at 90°C for 22 hr. The mixture was allowed to cool to room temperature, and filtered through celite. The filtrate was extracted with ethyl acetate and the organic layer was washed successively with saturated aqueous ammonium chloride solution and saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel chromatography (hexane/ethyl acetate=3:1) to give methyl 2-(2,4-bismethoxymethoxyphenyl)-3-cyclohexyl-1H-indole-6-carboxylate (16.9 g, yield 86%).

[1426] 1H-NMR(400 MHz, CDCl3): δ(ppm) 8.38(1H, s), 7.82(1H, d, J=8.4 Hz), 7.74(1H, dd, J=8.4, 1.2 Hz), 6.96(1H, d, J=2.4 Hz), 6.83(1H, dd, J=8.4, 8.4 Hz), 5.22(2H, s), 5.12(2H, s), 3.92(3H, s), 3.53(3H, s), 3.35(3H, s), 2.73-2.86(1H, m), 1.92-2.07(2H, m), 1.71-1.88(5H, m), 1.26-1.41(3H, m).

[1427] MS 454(M+1).

Step 4: Production of methyl 2-(2,4-bis-methoxymethoxyphenyl)-3-cyclohexyl-1-[2-(tetrahydropran-2-yloxyethyl)-1H-indole-6-carboxylate

[1428]

[1429] To a solution of methyl 2-(2,4-bismethoxymethoxyphenyl)-3-cyclohexyl-1H-indole-6-carboxylate (16.9 g, 37.3 mmol) in N,N-dimethylformamide (120 ml) was added sodium hydride (2.1 g, 52.2 mmol) under ice-cooling, and the mixture was stirred for 20 min. To the reaction mixture was added 2-(2-bromomethoxy)tetrahydro-2H-pyran (8.5 ml, 55.9 mmol), and the mixture was stirred at room temperature for 4 hr. To the reaction mixture was added saturated aqueous sodium hydroxide solution and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 2-(2,4-bismethoxymethoxyphenyl)-3-cyclohexyl-1-[2-(tetrahydropran-2-yloxyethyl)-1H-indole-6-carboxylate as a crude product. The obtained compound was used in Step 5 without further purification.

[1430] 1H-NMR(400 MHz, CDCl3): δ(ppm) 8.21(1H, d, J=5.2 Hz), 7.70-7.78(2H, m), 7.11(1H, dd, J=8.4, 1.6 Hz), 6.95(1H, t, J=2.2 Hz), 6.78(1H, dd, J=8.4, 2.4 Hz), 5.23(2H, s), 5.03(2H, ddd, J=15.6, 5.4, 1.5 Hz), 4.33-4.40(2H, m), 3.97-4.24(3H, m), 3.92(3H, s), 3.69-3.83(2H, m), 3.54(3H, s), 3.42-3.53(2H, m), 2.44-2.54(1H, m), 1.22-1.90(16H, m).

[1431] MS 582(M+1).

Step 5: Production of methyl 3-cyclohexyl-2-(2,4-dihydroxyphenyl)-1-(2-hydroxyethyl)-1H-indole-6-carboxylate

[1432]
[1433] To a solution of methyl 2-(2,4-bismethoxymethoxyphenyl)-3-cyclohexyl-1-[2-(tetrahydro-5-2-oxoxyethyl]-1H-indole-6-carboxylate in methanol (525 ml) and tetrahydrofuran (30 ml) was added 6N hydrochloric acid (105 ml) and the mixture was stirred for 10 hr. The reaction mixture was concentrated and water was added. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=1:1) to give methyl 3-cyclohexyl-2-(2,4-dihydroxyphenyl)-1-(2-hydroxyethyl)-1H-indole-6-carboxylate (10.3 g, yield 68%).

[1434] 1H-NMR(400 MHz, CDCl3): δ(ppm) 8.12(1H, s), 7.76-7.83(2H, m), 7.00(1H, d, J=8.0 Hz), 6.49-6.55(2H, m), 5.67(1H, brs), 5.18(1H, s), 4.06-4.15(2H, m), 3.94(3H, s), 3.87-3.93(1H, m), 3.73-3.81(1H, m), 2.45-2.56(1H, m), 1.63-1.84(7H, m), 1.20-1.29(3H, m).

[1435] MS 410(M+1).

Step 6: Production of methyl 12-cyclohexyl-3-hydroxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylate

[1436]

[1437] To a solution of methyl 3-cyclohexyl-2-(2,4-dihydroxyphenyl)-1-(2-hydroxyethyl)-1H-indole-6-carboxylate (10.3 g, 28.2 mmol) in tetrahydrofuran (500 ml) were added triphenylphosphine (7.3 g, 27.7 mmol) and diethyl azodicarboxylate (4.4 ml, 27.7 mmol) under ice-cooling, and the mixture was stirred for 4 hr. The reaction mixture was concentrated and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=3:2) to give methyl 12-cyclohexyl-3-hydroxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylate (6.5 g, yield 66%).

[1438] 1H-NMR(400 MHz, CDCl3): δ(ppm) 8.04(1H, s), 7.85(1H, d, J=8.4 Hz), 7.74(1H, dd, J=8.4, 1.2 Hz), 7.27(1H, d, J=8.4 Hz), 6.76(1H, dd, J=8.0, 2.4 Hz), 6.72(1H, d, J=2.4 Hz), 5.18(1H, s), 4.48(2H, t, J=5.6 Hz), 4.28(2H, t, J=5.6 Hz), 3.94(3H, s), 2.87-2.97(1H, m), 1.98-2.12(2H, m), 1.74-1.90(5H, m), 1.29-1.45(3H, m).

[1439] MS 392(M+1).

Example 2-2

Production of methyl 3-benzyloxy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylate

[1440]
To a solution of methyl 12-cyclohexyl-3-hydroxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylate (150 mg, 0.38 mmol) in N,N-dimethylformamide (2.0 ml) were added potassium carbonate (132 mg, 0.96 mmol) and benzyl bromide (0.07 ml, 0.61 mmol) and the mixture was stirred at 60°C for 3 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=3:1) to give methyl 3-benzylxoy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylate (173 mg, yield 94%).

Example 2-3

Production of 3-benzylxoy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid

[1443]

\[
\text{MeOOC} \quad \text{O} \quad \text{O} \quad \text{MeOOC}
\]

[1444] To a solution of methyl 3-benzylxoy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylate (173 mg, 0.38 mmol) in methanol (3.5 ml) and tetrahydrofuran (3.5 ml) was added 4N aqueous sodium hydroxide solution (1.7 ml), and the mixture was stirred for 13 hr. To the reaction mixture were added 2N hydrochloric acid (3.7 ml) and water, and the precipitated solid was collected by filtration and dried in vacuo. The obtained solid was purified by silica gel chromatography (hexane:ethyl acetate=1:1) to give 3-benzylxoy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid (81 mg, yield 48%).

[1445] \( \text{^1}H\)-NMR (300 MHz, DMSO-\(d_6\)) \( \delta \) ppm: 12.54 (1H, brs), 8.17 (1H, d, J=1.2 Hz), 7.86 (1H, d, J=8.4 Hz), 7.63 (1H, dd, J=8.4, 1.2 Hz), 7.32-7.53 (6H, m), 7.03 (1H, dd, J=9.0, 2.7 Hz), 6.92 (1H, d, J=2.4 Hz), 5.18 (2H, s), 4.41-4.49 (2H, m), 4.33-4.40 (2H, m), 2.79-2.93 (1H, m), 1.93-2.12 (2H, m), 1.68-1.87 (5H, m), 1.24-1.45 (3H, m).

[1446] MS 468(M+1).

[1447] The compounds of Examples 2-4 to 2-53 were produced by the same methods as in Examples 2-1 to 2-3 or other methods similar thereto, and where necessary, by employing other conventional methods. The chemical structural formulas are shown in Tables 101-111.

[1448] 12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid (Example 2-4).

[1449] 12-cyclohexyl-3-[2-(morpholin-4-yl)-5-(2-oxoptyridin-1-yl)benzoxyl]6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid monohydrochloride (Example 2-5).

[1450] 12-cyclohexyl-2-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid (Example 2-6).

[1451] 2-benzylxoy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid (Example 2-7).

[1452] 12-cyclohexyl-2-[2-(morpholin-4-yl)-5-(2-oxoptyridin-1-yl)benzoxyl]6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid monohydrochloride (Example 2-8).

[1453] 12-cyclohexyl-3-[2-(morpholin-4-yl)-4-(2-oxoptyridin-1-yl)benzoxyl]6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid monohydrochloride (Example 2-9).

[1454] 3-(1-tert-butoxycarbonylpiperidin-4-yl)oxy)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid (Example 2-10).

[1455] 3-(1-tert-butoxycarbonylpiperidin-3-yl)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid (Example 2-11).

[1456] 12-cyclohexyl-3-[5-methanesulfonyl-2-(morpholin-4-y]benzoxyl]6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid monohydrochloride (Example 2-12).

[1457] 12-cyclohexyl-3-[2-(4-methanesulfonylpiperazin-1-yl)-5-(2-oxoptyridin-1-yl)benzoxyl]6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid monohydrochloride (Example 2-13).

[1458] 12-cyclohexyl-3-[2-(morpholin-4-yl)benzoxyl]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid monohydrochloride (Example 2-14).

[1459] 3-[5-acetylamino-2-(morpholin-4-yl)benzoxyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid monohydrochloride (Example 2-15).
Example 3-1
Production of 6-ethyl 9-methyl 12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-6,9-dicarboxylate

Step 1: Production of methyl 3-cyclohexyl-2-(2-hydroxyphenyl)-1H-indole-6-carboxylate

To a suspension of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (2 g, 5.95 mmol) obtained in the same manner as in the method described in WO03/01040 and 2-hydroxyphenylboronic acid (1.23 g, 8.91 mmol) in 1,2-dimethoxyethane (20 ml) and water (10 ml) were added lithium chloride (504 mg, 11.9 mmol), sodium carbonate (1.9 g, 17.9 mmol) and tetrakis(triphenylphosphine)palladium (687 mg, 0.59 mmol), and the mixture was heated under reflux for 10 hr. The mixture was allowed to cool to room temperature, and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane:ethyl acetate=3:1-2:1) to give methyl 3-cyclohexyl-2-(2-hydroxyphenyl)-1H-indole-6-carboxylate (1.81 g, yield 87.7%).

1H-NMR (300 MHz, DMSO-d6, δ ppm) 11.24 (1H, brs), 9.71 (1H, brs), 7.98 (1H, d, J=1.5 Hz), 7.78 (1H, d, J=8.7 Hz), 7.58 (1H, dd, J=1.5, 8.4 Hz), 7.20-7.31 (2H, m), 7.00 (1H, d, J=7.5 Hz), 6.92 (1H, t, J=7.5 Hz), 3.85 (3H, s), 2.60-2.75 (1H, m), 1.62-1.98 (7H, m), 1.14-1.41 (3H, m).
Step 2: Production of 6-ethyl 9-methyl 12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-6,9-dicarboxylate

Example 3-2

Production of 12-cyclohexyl-9-methoxycarbonyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-6-carboxylic acid

[1479]

[1480] To a solution of methyl 3-cyclohexyl-2-(2-hydroxyphenyl)-1H-indole-6-carboxylate (300 mg, 0.85 mmol) in N,N-dimethylacetamide (15 ml) were added ethyl 2,3-dibromopropionate (0.14 ml, 0.96 mmol) and potassium carbonate (356 mg, 2.57 mmol), and the mixture was stirred at 80°C for 9 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=10:1-6:1) to give 6-ethyl 9-methyl 12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-6,9-dicarboxylate (186 mg, yield 48.6%).

[1481] 1H-NMR(400 MHz, DMSO-d6): δ(ppm) 8.18(1H, brs), 7.92(1H, d, J=8.4 Hz), 7.65(1H, dd, J=8.8, 1.6 Hz), 7.42-7.52(2H, m), 7.39(1H, td, J=7.6, 0.8 Hz), 7.33(1H, dd, J=8.0, 1.2 Hz), 5.33(1H, dd, J=5.6, 5.2 Hz), 4.57-4.85(2H, m), 4.07-4.21(2H, m), 3.88(3H, s), 2.84-2.94(1H, m), 1.95-2.09(2H, m), 1.69-1.88(5H, m), 1.31-1.44(3H, m), 1.23(3H, t, J=7.4 Hz).

[1482] MS 448(M+1).

[1483]

[1484] To a solution of 6-ethyl 9-methyl 12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-6,9-dicarboxylate (270 mg, 0.60 mmol) in tetrahydrofuran (1 ml), methanol (1 ml) and water (1 ml) was added lithium hydroxide monohydrate (30 mg, 0.71 mmol) under ice-cooling, and the mixture was stirred at room temperature for 20 hr. 1N Hydrochloric acid was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give 12-cyclohexyl-9-methoxycarbonyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-6-carboxylic acid as a crude product. The obtained crude product was used in Example 3-3 without further purification.
Example 3-3
Production of methyl 12-cyclocexyl-6-dimethylcarbamoyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate

[1485]

Example 3-4
Production of 12-cyclohexyl-6-dimethylcarbamoyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid

[1488]

[1486] To a solution of 12-cyclohexyl-9-methoxycarbonyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-6-carboxylic acid obtained as a crude product in Example 3-2 in N,N-dimethylformamide (5 ml) were added dimethylamine hydrochloride (246 mg, 3.01 mmol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide monohydrate (231 mg, 1.20 mmol), 1-hydroxybenzotriazole monohydrate (163 mg, 1.20 mmol) and triethylamine (0.42 ml, 3.01 mmol), and the mixture was stirred at room temperature for 16 hr. 1N Hydrochloric acid was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane:ethyl acetate=1:1) to give methyl 12-cyclohexyl-6-dimethylcarbamoyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (100 mg, yield 37.2%).

[1487] 1H-NMR(300 MHz, CDCl3): δ (ppm) 8.11 (1H, d, J=1.2 Hz), 7.90 (1H, d, J=9.0 Hz), 7.77 (1H, dd, J=8.4, 1.5 Hz), 7.44 (1H, d, J=6.6, 1.0 Hz), 7.38 (1H, dd, J=7.5, 1.8 Hz), 7.31 (1H, d, J=7.2, 0.6 Hz), 7.09 (1H, dd, J=7.8, 1.5 Hz), 5.27 (1H, d, J=8.4, 6.0 Hz), 4.49-4.56 (2H, m), 3.95 (3H, s), 3.25 (3H, s), 3.05 (3H, s), 2.92-3.03 (1H, m), 1.72-2.17 (7H, m), 1.22-1.49 (3H, m).

[1489] To a solution of methyl 12-cyclohexyl-6-dimethylcarbamoyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (100 mg, 0.22 mmol) in tetrahydrofuran (1 ml) and methanol (1 ml) was added 4N aqueous sodium hydroxide solution (1 ml), and the mixture was stirred at room temperature for 18 hr. 1N Hydrochloric acid was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (chloroform:methanol=30:1-20:1) to give 12-cyclohexyl-6-dimethylcarbamoyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (9 mg, yield 9.4%).

[1490] 1H-NMR(400 MHz, DMSO-d6): δ (ppm) 12.45 (1H, brs), 8.24 (1H, d, J=1.2 Hz), 7.87 (1H, d, J=8.8 Hz), 7.62 (1H, dd, J=8.4, 1.6 Hz), 7.34-7.48 (3H, m), 7.12 (1H, brd, J=8.0 Hz), 5.52 (1H, dd, J=8.8, 5.2 Hz), 4.52-4.65 (1H, m), 4.23-4.37 (1H, m), 3.21 (3H, s), 2.84-2.94 (1H, m), 2.92 (3H, s), 1.59-2.10 (7H, m), 1.17-1.46 (3H, m).

[1491] MS 433(M+1).
Example 4-1
Production of methyl 11-cyclohexyl-5-oxa-6a-azabeno[a]fluorene-8-carboxylate

[1492]

Example 4-2
Production of 11-cyclohexyl-5-oxa-6a-azabeno[a]fluorene-8-carboxylic acid

[1496]

[1497] To a solution of methyl 11-cyclohexyl-5-oxa-6a-azabeno[a]fluorene-8-carboxylate (40 mg, 0.11 mmol) in tetrahydrofuran (1 ml) and methanol (1 ml) was added 4N aqueous sodium hydroxide solution (1 ml), and the mixture was stirred at 60° C. for 3 hr. 1N Hydrochloric acid was added to the reaction mixture, and the precipitated solid was collected by filtration, washed with hexane and dried in vacuo to give 11-cyclohexyl-5-oxa-6a-azabeno[a]fluorene-8-carboxylic acid (26 mg, yield 68.4%).

[1498] ^1H-NMR (400 MHz, DMSO-d$_6$): (ppm) 12.65 (1H, brs), 8.19 (1H, d, J=1.2 Hz), 7.91 (1H, d, J=8.8 Hz), 7.82 (1H, dd, J=8.0, 1.6 Hz), 7.63 (1H, dd, J=8.8, 1.6 Hz), 7.37 (1H, td, J=8.4, 1.0 Hz), 7.27 (1H, td, J=7.6, 0.8 Hz), 7.21 (1H, d, J=8.0, 1.2 Hz), 6.07 (2H, s), 3.21-3.35 (1H, m), 1.99-2.13 (2H, m), 1.72-1.91 (5H, m), 1.37-1.55 (3H, m).

[1499] MS 348 (M+1).

Example 5-1
Production of methyl 13-cyclohexyl-6,7-dihydro-5H-benzo[3,4]azepino[1,2-a]indole-10-carboxylate

Step 1: Production of methyl 1-[3-(2-bromophenyl)propyl]-3-cyclohexyl-1H-indole-6-carboxylate

[1500]
To a solution of methyl 3-cyclohexyl-1H-indole-6-carboxylate (500 mg, 1.94 mmol) obtained in the same manner as in the method described in W003/010140 in N,N-dimethylformamide (2 ml) was added sodium hydride (93 mg, 2.33 mmol) under ice-cooling, and the mixture was stirred for 30 min. A solution of 1-bromo-2-(3-iodopropyl)benzene (695 mg, 2.14 mmol), obtained in the same manner as in the method described Tetrahedron Letter, Vol. 32, No. 28, pp. 3317-3320, 1991, in N,N-dimethylformamide (1.5 ml) was added and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane:ethyl acetate=8:1) to give methyl 1-[3-(2-bromophenyl)propyl]-3-cyclohexyl-1H-indole-6-carboxylate (770 mg, yield 79%).

1H-NMR(400 MHz, DMSO-d₆): (ppm) 8.03(1H, s), 7.65(1H, d, J=8.0 Hz), 7.60(1H, dd, J=8.0, 1.1 Hz), 7.54(1H, d, J=7.6 Hz), 7.40(1H, s), 7.27-7.33(2H, m), 7.11-7.15(1H, m), 4.27(2H, t, J=7.0 Hz), 3.85(3H, s), 2.75-2.83(1H, m), 2.67(2H, dd, J=8.4, 5.6 Hz), 1.92-2.10(4H, m), 1.69-1.84(3H, m), 1.37-1.50(4H, m), 1.21-1.32(1H, m).

Step 2: Production of methyl 13-cyclohexyl-6,7-dihydro-5H-benzo[3,4]azepino[1,2-a]indole-10-carboxylate

Example 5-2

Production of 13-cyclohexyl-6,7-dihydro-5H-benzo[3,4]azepino[1,2-a]indole-10-carboxylic acid
[1508] To a solution of methyl 13-cyclohexyl-6,7-dihydro-5H-benzo[3,4]azepino[1,2-a]indole-10-carboxylate (55 mg, 0.147 mmol) in tetrahydrofuran (2 ml) and methanol (2 ml) was added 4N aqueous sodium hydroxide solution (1 ml), and the mixture was stirred at 50° C, for 2 hr. The reaction mixture was allowed to cool to room temperature, and 2N hydrochloric acid (2.5 ml) and water were added to the reaction mixture. The precipitated solid was collected by filtration, washed with water and dried in vacuo to give 13-cyclohexyl-6,7-dihydro-5H-benzo[3,4]azepino[1,2-a]indole-10-carboxylic acid (44 mg, yield 83%).

[1509] 1H-NMR (400 MHz, DMSO-d6): δ (ppm) 12.54 (1H, brs), 8.10 (1H, s), 7.85 (1H, d, J=8.4 Hz), 7.60 (1H, d, J=8.4 Hz), 7.36-7.45 (4H, m), 4.53-4.62 (1H, m), 3.45-3.58 (1H, m), 2.77-2.88 (1H, m), 2.65-2.75 (1H, m), 2.27-2.42 (2H, m), 1.11-2.10 (10H, m).

[1510] MS 360(M+1).

[1511] The compound of Example 5-3 was produced by the same method as in Examples 5-1 to 5-2 or a method similar thereto, and where necessary, by employing other conventional methods. The chemical structural formulas are shown in Table 112.

[1512] 11-cyclohexyl-6H-isocarbodol[2,1-a]indole-3-carboxylic acid (Example 5-3).

Example 6-1

Production of methyl 13-cyclohexyl-6,7-dihydro-5H-pyrrol(2',1',3,4)azepino[1,2-a]indole-10-carboxylate

Step 1: Production of methyl 2-(1-tert-butoxycarbonyl-1H-pyrrol-2-yl)-3-cyclohexyl-1H-indole-6-carboxylate

[1513]

[1514] To a suspension of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (800 mg, 2.38 mmol) obtained in the same manner as in the method described in WO2003/010140 and N-tert-butoxycarbonyl[pyrro]le-2-boronic acid (1.00 g, 4.76 mmol) in dimethoxyethene (10 ml) and water (5 ml) were added sodium carbonate (757 mg, 7.14 mmol), lithium chloride (202 mg, 4.76 mmol) and tetrakis(triphenylphosphine)palladium (275 mg, 0.238 mmol), and the mixture was heated under reflux for 9 hr. The reaction mixture was allowed to cool to room temperature. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane:ethyl acetate=8:1-6:1) to give methyl 2-(1-tert-butoxycarbonyl-1H-pyrrol-2-yl)-3-cyclohexyl-1H-indole-6-carboxylate (642 mg, yield 64%).

[1515] 1H-NMR (400 MHz, DMSO-d6): δ (ppm) 11.41 (1H, s), 7.90 (1H, d, J=1.2 Hz), 7.75 (1H, d, J=8.4 Hz), 7.56 (1H, dd, J=8.0, 1.2 Hz), 7.48 (1H, t, J=2.6 Hz), 6.38 (2H, d, J=2.8 Hz), 3.84 (3H, s), 1.62-1.84 (7H, m), 1.21-1.32 (3H, m), 1.12 (9H, s).

Step 2: Production of methyl 2-(1-tert-butoxycarbonyl-1H-pyrrol-2-yl)-1-(3-chloropropyl)-3-cyclohexyl-1H-indole-6-carboxylate

[1516]
[1517] To a solution of methyl 2-(1-tert-butoxycarbonyl-1H-pyrrol-2-yl)-3-cyclohexyl-1H-indole-6-carboxylate (140 mg, 0.331 mmol) and 1-bromo-3-chloropropane (156 mg, 0.994 mmol) in N,N-dimethylformamide (4 ml) was added sodium hydride (17 mg, 0.430 mmol) under ice-cooling, and the mixture was stirred for 2 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane:ethyl acetate=5:1) to give methyl 2-(1-tert-butoxycarbonyl-1H-pyrrol-2-yl)-1-(3-chloropropyl)-3-cyclohexyl-1H-indole-6-carboxylate (167 mg, yield 100%).

[1518] 1H-NMR(400 MHz, DMSO-d6): δ (ppm) 11.39(1H, s), 7.88(1H, d, J=1.2 Hz), 7.73(1H, d, J=8.4 Hz), 7.54(1H, dd, J=8.4, 1.6 Hz), 7.46(1H, t, J=2.6 Hz), 6.36(2H, d, J=2.8 Hz), 3.82(3H, s), 2.62-2.72(1H, m), 1.60-1.82(7H, m), 1.19-1.30(3H, m), 1.10(9H, s).

Step 3: Production of methyl 1-(3-chloropropyl)-3-cyclohexyl-2-(1H-pyrrol-2-yl)-1H-indole-6-carboxylate

[1519]

[1520] To a solution of methyl 2-(1-tert-butoxycarbonyl-1H-pyrrol-2-yl)-1-(3-chloropropyl)-3-cyclohexyl-1H-indole-6-carboxylate (167 mg, 0.344 mmol) in chloroform (1.5 ml) was added trifluoroacetic acid (1 ml), and the mixture was stirred at room temperature for 8 hr. The reaction mixture was evaporated under reduced pressure. To the residue was added saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 1-(3-chloropropyl)-3-cyclohexyl-2-(1H-pyrrol-2-yl)-1H-indole-6-carboxylate (135 mg, yield 98%).

[1521] 1H-NMR(400 MHz, DMSO-d6): δ (ppm) 11.13(1H, brs), 8.13(1H, s), 7.82(1H, d, J=8.4 Hz), 7.64(1H, d, J=8.4 Hz), 6.97-7.02(1H, m), 6.20-6.26(2H, m), 4.21(2H, t, J=7.3 Hz), 3.87(3H, s), 3.48(2H, t, J=6.3 Hz), 2.63-2.76(1H, m), 1.63-1.97(9H, m), 1.18-1.33(3H, m).

Step 4: Production of methyl 13-cyclohexyl-6,7-dihydro-5H-pyrrolo[2′,1′:3,4][1,4]diazepino[1,2-a]indole-10-carboxylate

[1522]
[1523] To a solution of methyl 1-(3-chloropropyl)-3-cyclohexyl-2-(1H-pyrrol-2-yl)-1H-indole-6-carboxylate (130 mg, 0.326 mmol) in N,N-dimethylformamide (4 ml) was added sodium hydride (17 mg, 0.424 mmol) under ice-cooling, and the mixture was stirred for 1 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane:ethyl acetate= 4:1) to give methyl 13-cyclohexyl-6,7-dihydro-5H-pyrrolo[2,1',3,4][1,4]diazepino[1,2-al]indole-10-carboxylate (91 mg, yield 77%).

[1524] 1H-NMR(400 MHz, DMSO-d6): δ (ppm) 8.13 (1H, d, J=1.2 Hz), 7.82 (1H, d, J=8.8 Hz), 7.60 (1H, dd, J=8.4, 1.6 Hz), 7.04 (1H, dd, J=2.4, 1.6 Hz), 6.29 (1H, dd, J=3.6, 1.6 Hz), 6.18 (1H, dd, J=4.0, 2.8 Hz), 4.11 (2H, t, J=6.4 Hz), 3.98 (2H, t, J=6.4 Hz), 3.86 (3H, s), 2.91-3.01 (1H, m), 2.25-2.33 (2H, m), 1.91-2.03 (2H, m), 1.69-1.85 (5H, m), 1.26-1.43 (3H, m).

[1525] MS 363(M+1).

Example 6-2

Production of 13-cyclohexyl-6,7-dihydro-5H-pyrrolo[2,1',3,4][1,4]diazepino[1,2-al]indole-10-carboxylic acid

[1526]

[1527] To a solution of methyl 13-cyclohexyl-6,7-dihydro-5H-pyrrolo[2,1',3,4][1,4]diazepino[1,2-al]indole-10-carboxylate (88 mg, 0.17 mmol) in tetrahydrofuran (2 ml) and methanol (2 ml) was added 4N aqueous sodium hydroxide solution (1 ml) and the mixture was stirred at 50°C for 2 hr. The reaction mixture was allowed to cool to room temperature, and 2N hydrochloric acid (2.5 ml) and water were added to the reaction mixture. The precipitated solid was collected by filtration, washed with water and dried in vacuo to give 13-cyclohexyl-6,7-dihydro-5H-pyrrolo[2',1':3,4][1,4]diazepino[1,2-al]indole-10-carboxylic acid (74 mg, yield 85%).

[1528] 1H-NMR(400 MHz, DMSO-d6): δ (ppm) 12.54 (1H, brs), 8.09 (1H, d, J=1.6 Hz), 7.78 (1H, d, J=8.4 Hz), 7.58 (1H, dd, J=8.8, 1.6 Hz), 7.04 (1H, dd, J=2.4, 1.6 Hz), 6.28 (1H, dd, J=4.0, 1.6 Hz), 6.17 (1H, dd, J=3.2, 2.4 Hz), 4.09 (2H, t, J=6.0 Hz), 3.97 (2H, t, J=6.4 Hz), 3.32 (3H, s), 2.91-3.01 (1H, m), 2.25-2.32 (2H, m), 1.90-2.04 (2H, m), 1.69-1.85 (5H, m), 1.27-1.42 (3H, m).

[1529] MS 349(M+1).

Example 7-1

Production of ethyl 12-cyclohexyl-3-hydroxy-6,7-dihydro-5-oxo-7a,8-diaza[benzo[a,c]azulene-9-carboxylate

Step 1: Production of 3-cyclohexyl-1H-pyrrolo[2,3-b]pyridine-6-carbonitrile

[1530]
[1531] To a solution of 3-cyclohexyl-1H-pyrrolo[2,3-b]
pyridine-N-oxide (3.0 g, 13.7 mmol) obtained in the same
manner as in the method described in WO03/010140 in
acetonitrile (30 ml) were added triethylamine (5.8 ml, 41.2
mmol) and trimethylsilyl cyanide (8.3 ml, 61.8 mmol), and
the mixture was heated under reflux at 110°C for 10 hr. The
mixture was allowed to cool to room temperature, and
saturated aqueous sodium hydrogen carbonate solution was
added. The precipitated solid was collected by filtration and
the obtained solid was purified by silica gel chromatography
(hexane:ethyl acetate=2:1) to give 3-cyclohexyl-1H-pyrrolo
[2,3-b]pyridine-6-carbonitrile (1.60 g, yield 52%).

[1532] 1H-NMR(400 MHz, CDCl₃): δ(ppm) 9.48(1H,
bs), 8.03(1H, d, J=8.0 Hz), 7.44(1H, d, J=8.0 Hz), 7.32(1H,
d, J=2.4 Hz), 2.74-2.88(1H, m), 2.00-2.11(2H, m), 1.74-
1.92(3H, m), 1.39-1.53(4H, m), 1.24-1.36(1H, m).

[1533] MS 226(M+1).

Step 2: Production of ethyl 1-(2-benzylxoyethyl)-3-cyclo-
hexyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate

[1534]

[1535] To a solution of 3-cyclohexyl-1H-pyrrolo[2,3-b]
pyridine-6-carbonitrile (1.0 g, 13.7 mmol) in N,N-dimeth-
yllformamide (10 ml) was added sodium hydride (213 mg,
5.33 mmol) under ice-cooling, and the mixture was stirred
for 15 min. After stirring, benzyl 2-bromoethyl ether (0.77
ml, 4.88 mmol) was added and the mixture was stirred at 50°C
for 1 hr. The mixture was allowed to cool to room
temperature and water was added. The mixture was
extracted with ethyl acetate. The organic layer was washed
successively with water and saturated brine, and dried over
anhydrous magnesium sulfate. After filtration, the solvent
was evaporated under reduced pressure and the residue was
purified by silica gel chromatography (hexane:ethyl acetate=
4:1) to give 1-(2-benzylxoyethyl)-3-cyclohexyl-1H-pyrrolo
[2,3-b]pyridine-6-carbonitrile (1.44 g, yield 90%).

[1536] 1H-NMR(400 MHz, CDCl₃): δ(ppm) 7.95(1H, d,
J=8.0 Hz), 7.37(1H, d, J=8.0 Hz), 7.33(1H, s), 7.16-7.29(5H,
m), 4.48(2H, s), 4.46(2H, t, J=5.2 Hz), 3.81(2H, t, J=5.0 Hz),
2.73-2.83(1H, m), 2.00-2.07(2H, m), 1.74-2.00(3H, m),
1.37-1.52(4H, m), 1.26-1.35(1H, m).

MS 360(M+1).

Step 3: Production of ethyl 1-(2-benzylxoyethyl)-3-cyclo-
hexyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate

[1537]

[1538] To a solution of 1-(2-benzylxoyethyl)-3-cyclo-
hexyl-1H-pyrrolo[2,3-b]pyridine-6-carbonitrile (1.44 g,
4.00 mmol) in ethanol (30 ml) was added acetyl chloride
(8.5 ml, 120 mmol) under ice-cooling, and the mixture was
heated under reflux for 3 hr. The mixture was allowed to cool
to room temperature, and the solvent was evaporated under
reduced pressure. The residue was dissolved in ethyl acetate
and water was added. The mixture was extracted with ethyl
acetate, and the organic layer was washed successively with
water and saturated brine, and dried over anhydrous mag-
nesium sulfate. After filtration, the solvent was evaporated
under reduced pressure and the residue was purified by silica
gel chromatography (hexane:ethyl acetate=4:1) to give ethyl
1-(2-benzylxoyethyl)-3-cyclohexyl-1H-pyrrolo[2,3-b]pyri-
dine-6-carboxylate (1.14 g, yield 70%).

[1539] 1H-NMR(400 MHz, CDCl₃): δ(ppm) 7.96(1H, d,
J=8.0 Hz), 7.86(1H, d, J=8.0 Hz), 7.32(1H, s), 7.19-7.30(5H,
m), 4.55(2H, t, J=5.2 Hz), 4.49(2H, s), 4.44(2H, q,
J=7.2
Hz), 3.84(2H, t, J=5.0 Hz), 2.75-2.85(1H, m), 2.01-2.12(2H, m), 1.73-1.90(3H, m), 1.38-1.53(7H, m), 1.26-1.34(1H, m).

[1540] MS 407(M+1).

Step 4: Production of ethyl 1-(2-benzylxyethy1)-2-bromo-3-cyclohexyl-1H-pyrrol[2,3-b]pyridine-6-carboxylate

Step 5: Production of ethyl 1-(2-benzylxyethy1)-2-(2,4-bismethoxymethoxyphenyl)-3-cyclohexyl-1H-pyrrol[2,3-b]pyridine-6-carboxylate

[1546] To a suspension of ethyl 1-(2-benzylxyethy1)-2-bromo-3-cyclohexyl-1H-pyrrol[2,3-b]pyridine-6-carboxylate (592 mg, 1.22 mmol) and 2,4-bismethoxymethoxyphenyboronic acid (384 mg, 1.59 mmol) obtained in the same manner as in Example 2-1, Step 2 in 1,2-dimethoxyethane (12 ml) and water (6 ml) were added lithium chloride (155 mg, 3.66 mmol), sodium carbonate (388 mg, 3.66 mmol) and tetrakis(triphenylphosphine)palladium (141 mg, 0.12 mmol), and the mixture was stirred with heating at 110°C for 2.5 hr. The reaction mixture was allowed to cool to room temperature. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=6:1) to give ethyl 1-(2-benzylxyethy1)-2-bromo-3-cyclohexyl-1H-pyrrol[2,3-b]pyridine-6-carboxylate (592 mg, yield 56%).

[1543] 1H-NMR(400 MHz, CDCl3): (ppm) 8.03(1H, d, J=8.0 Hz), 7.84(1H, d, J=8.0 Hz), 7.15-7.25(5H, m), 4.66(2H, t, J=6.2 Hz), 4.55(2H, s), 4.43(2H, q, J=7.1 Hz), 3.88(2H, t, J=6.0 Hz), 2.80-2.93(1H, m), 1.76-1.92(6H, m), 1.23-1.49(7H, m).

[1544] MS 485(M+1).
7.09 (3H, m), 6.92 (1H, d, J=2.4 Hz), 6.74 (1H, dd, J=8.4, 2.4 Hz), 5.23 (2H, s), 4.97 (2H, dd, J=21.6, 6.8 Hz), 4.55-4.64 (1H, m), 4.33-4.49 (4H, m), 4.07-4.18 (1H, m), 3.66-3.75 (1H, m), 3.56-3.64 (1H, m), 3.54 (3H, s), 3.27 (3H, s), 2.43-2.54 (1H, m), 1.65-1.84 (7H, m), 1.43 (3H, t, J=7.0 Hz), 1.17-1.31 (3H, m).

[1548] MS 603(M+1).

Step 6: Production of ethyl 2-(2,4-bis-methoxymethoxyphenyl)-3-cyclohexyl-1-(2-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxylate

[1549]

[1550] To a solution of ethyl 1-(2-benzylxoyethyl)-2-(2,4-bis-methoxymethoxyphenyl)-3-cyclohexyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate (727 mg, 1.20 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL) was added 7.5% palladium on carbon (225 mg), and the mixture was stirred at atmospheric pressure and in a hydrogen atmosphere at room temperature for 24 hr. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give ethyl 2-(2,4-bis-methoxymethoxyphenyl)-3-cyclohexyl-1-(2-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxylate as a crude product. The obtained compound was used in Step 7 without further purification.

[1551] 1H-NMR (400 MHz, CDCl3): δ (ppm) 8.15 (1H, d, J=8.4 Hz), 7.91 (1H, d, J=8.4 Hz), 7.10 (1H, d, J=8.4 Hz), 6.97 (1H, d, J=2.0 Hz), 6.82 (1H, dd, J=8.4, 2.4 Hz), 5.24 (2H, s), 5.05 (2H, dd, J=22.0, 7.2 Hz), 4.45 (2H, q, J=7.2 Hz), 3.87-4.15 (4H, m), 3.55 (3H, s), 3.30 (3H, s), 2.44-2.56 (1H, m), 1.66-1.84 (7H, m), 1.45 (3H, t, J=7.0 Hz), 1.19-1.34 (3H, m).

[1552] MS 513(M+1).

Step 7: Production of ethyl 3-cyclohexyl-2-(2,4-dihydroxyphenyl)-1-(2-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxylate

[1553]

[1554] To a solution of ethyl 2-(2,4-bis-methoxymethoxyphenyl)-3-cyclohexyl-1-(2-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxylate obtained as a crude product in the previous step in tetrahydrofuran (10 mL) and methanol (10 mL) was added 6N hydrochloric acid (10 mL), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was ice-cooled. 4N Aqueous sodium hydroxide solution (15 mL) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give ethyl 3-cyclohexyl-2-(2,4-dihydroxyphenyl)-1-(2-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxylate as a crude product. The obtained compound was used in Step 8 without further purification.

[1555] 1H-NMR (400 MHz, CDCl3): δ (ppm) 8.15 (1H, d, J=8.4 Hz), 7.89 (1H, d, J=8.0 Hz), 6.98 (1H, d, J=8.4 Hz), 6.89 (1H, d, J=2.4 Hz), 6.52 (1H, dd, J=8.0, 2.0 Hz), 4.40-4.48 (2H, m), 4.08-4.15 (2H, m), 4.00-4.08 (1H, m), 3.92-3.99 (1H, m), 2.53-2.66 (1H, m), 1.64-1.89 (7H, m), 1.43 (3H, t, J=7.0 Hz), 1.33-1.33 (3H, m).

[1556] MS 425(M+1).
Step 8: Production of ethyl 12-cyclohexyl-3-hydroxy-6,7-dihydro-5-oxo-7a,8-diazadibenzo[a,e]azulene-9-carboxylate

Example 7-2
Production of ethyl 3-benzoxyl-12-cyclohexyl-6,7-dihydro-5-oxo-7a,8-diazadibenzo[a,e]azulene-9-carboxylate

To a solution of ethyl 3-cyclohexyl-2-(2,4-dihydroxyphenyl)-1-(2-hydroxyethyl)-1H-pyrol[2,3-b]pyridine-6-carboxylate in tetrahydrofuran (25 ml) obtained as a crude product in the previous step were added triphenylphosphine (463 mg, 1.77 mmol) and diisopropyl azodicarboxylate (0.35 ml, 1.77 mmol) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=3:2) to give ethyl 12-cyclohexyl-3-hydroxy-6,7-dihydro-5-oxo-7a,8-diazadibenzo[a,e]azulene-9-carboxylate (344 mg, yield 72%).

$^1$H-NMR(400 MHz, CDCl$_3$); (ppm) 8.15(1H, d, J=8.0 Hz), 7.88(1H, d, 7.8 Hz), 7.27(1H, d, J=8.0 Hz), 6.77(1H, d, J=8.4, 2.8 Hz), 6.72(1H, d, J=2.8 Hz), 5.85(1H, brs), 4.52-4.58(2H, m), 4.43-4.51(4H, m), 2.88-2.98(1H, m), 1.74-2.01(7H, m), 1.45(3H, t, J=7.2 Hz), 1.32-1.40(3H, m).

MS 407(M+1).

To a solution of ethyl 12-cyclohexyl-3-hydroxy-6,7-dihydro-5-oxo-7a,8-diazadibenzo[a,e]azulene-9-carboxylate (50 mg, 0.12 mmol) in N,N-dimethylformamide (1 ml) were added potassium carbonate (20 mg, 0.15 mmol) and benzyl bromide (0.02 ml, 0.14 mmol), and the mixture was stirred at 80°C for 3 hr. The reaction mixture was allowed to cool to room temperature. The reaction mixture was added saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=3:1) to give ethyl 3-benzoxyl-12-cyclohexyl-6,7-dihydro-5-oxo-7a,8-diazadibenzo[a,e]azulene-9-carboxylate (50 mg, yield 82%).

$^1$H-NMR(400 MHz, CDCl$_3$); (ppm) 8.15(1H, d, J=8.4 Hz), 7.88(1H, d, J=8.4 Hz), 7.31-7.48(6H, m), 6.90(1H, dd, J=8.4, 2.4 Hz), 6.86(1H, d, J=2.8 Hz), 5.11(2H, s), 4.51-4.61(4H, m), 4.47(2H, m), 1.72-2.00(7H, m), 1.45(3H, t, J=7.0 Hz), 1.32-1.41(3H, m).

MS 497(M+1).
Example 7-3

Production of 3-benzyloxy-12-cyclohexyl-6,7-dihydro-5-oxo-7a,8-diazadibenzo[a,e]azulene-9-carboxylic acid

[1565]

[1566] To a solution of ethyl 3-benzyloxy-12-cyclohexyl-6,7-dihydro-5-oxo-7a,8-diazadibenzo[a,e]azulene-9-carboxylate (50 mg, 0.10 mmol) in tetrahydrofuran (2 ml) and methanol (2 ml) was added 4N aqueous sodium hydroxide solution (1 ml), and the mixture was stirred for heating at 60°C for 1 hr. The reaction mixture was allowed to cool to room temperature. 2N Hydrochloric acid (2 ml) was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. Hexane was added to the residue, and the precipitated solid was collected by filtration and dried in vacuo to give 3-benzyloxy-12-cyclohexyl-6,7-dihydro-5-oxo-7a,8-diazadibenzo[a,e]azulene-9-carboxylic acid (21 mg, yield 41%).

[1567] 1H-NMR (400 MHz, DMSO-d6): δ (ppm) 12.75 (1H, brs), 8.30 (1H, d, J=8.4 Hz), 7.78 (1H, d, J=8.0 Hz), 7.45-7.49 (2H, m), 7.31-7.44 (4H, m), 7.02 (1H, dd, J=8.8, 2.8 Hz), 6.93 (1H, d, J=2.8 Hz), 5.17 (2H, s), 4.45 (4H, brs), 2.82-2.92 (1H, m), 1.88-2.01 (2H, m), 1.65-1.85 (4H, m), 1.19-1.46 (3H, m).

[1568] MS 469(M+1).

[1569] The compounds of Examples 7-4 to 7-8 were produced by the same methods as in Examples 7-1 to 7-3 or methods similar thereto, and where necessary, by employing other conventional methods. The chemical structural formulas are shown in Tables 113 and 114.

[1570] 12-cyclohexyl-3-[2-(morpholin-4-yl)-5-(2-oxopyrrolidin-1-yl)benzoyl]oxy]-6,7-dihydro-5-oxa-7a,8-diazadibenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 7-4),

[1571] 12-cyclohexyl-3-[5-methanesulfonyl-2-(morpholin-4-yl)benzoyl]oxy]-6,7-dihydro-5-oxa-7a,8-diazadibenzo[a,e]azulene-9-carboxylic acid monohydrochloride (Example 7-5),

[1572] 3-[5-(N-acetyl-N-methylamino)-2-(morpholin-4-yl)benzoyl]oxy]-12-cyclohexyl-6,7-dihydro-5-oxa-7a,8-diazadibenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 7-6),

[1573] 12-cyclohexyl-3-[2-(4-methanesulfonylpiperazin-1-yl)-5-(2-oxopyrrolidin-1-yl)benzoyl]oxy]-6,7-dihydro-5-oxa-7a,8-diazadibenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 7-7),

[1574] 3-benzyloxy-12-cyclohexyl-6,7-dihydro-5-oxa-7a,8-diazadibenzo[a,e]azulene-9-carboxylic acid (Example 7-8)

Example 8-1

Production of ethyl 12-cyclohexyl-6-oxo-5,6,7-dihydro-5H-5,7a,8-triazadibenzo[a,e]azulene-9-carboxylate

Step 1: Production of methyl (6-cyano-3-cyclohexylpyrrolo[2,3-b]pyridin-1-yl)acetate

[1575]

[1576] To a solution of 3-cyclohexyl-1H-pyrrolo[2,3-b]pyridine-6-carbonitrile (541 mg, 2.40 mmol) obtained in the same manner as in the method described in Example 7-1, Step 1 in N,N-dimethylformamide (5 ml) was added sodium hydride (115 mg, 2.88 mmol) under ice-cooling, and the mixture was stirred for 20 min. Methyl bromoacetate (0.27 ml, 2.88 mmol) was added and the mixture was stirred at room temperature for 1.5 hr. Water was added to the reaction mixture, and the precipitated solid was collected by filtration, washed with water and dried in vacuo to give methyl (6-cyano-3-cyclohexylpyrrolo[2,3-b]pyridin-1-yl)acetate (647 mg, yield 91%).

[1577] 1H-NMR (400 MHz, CDCl3): δ (ppm) 7.98 (1H, d, J=8.0 Hz), 7.41 (1H, d, J=8.0 Hz), 7.17 (1H, s), 5.03 (2H, s),
Step 2: Production of ethyl 3-cyclohexyl-1-ethoxycarbonylmethyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate

3.78 (3H, s), 2.72-2.85 (1H, m), 1.99-2.11 (2H, m), 1.73-1.92 (3H, m), 1.37-1.51 (4H, m), 1.20-1.34 (1H, m).

Step 3: Production of ethyl 2-bromo-3-cyclohexyl-1-ethoxycarbonylmethyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate

To a solution of ethyl 3-cyclohexyl-1-ethoxycarbonylmethyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate (463 mg, 1.34 mmol) in carbon tetrachloride (10 ml) was added N-bromosuccinimide (287 mg, 1.61 mmol), and the mixture was heated under reflux for 4 hr. The mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane:ethyl acetate=5:1) to give ethyl 2-bromo-3-cyclohexyl-1-ethoxycarbonylmethyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate (457 mg, yield 64%).

Step 4: Production of ethyl 12-cyclohexyl-6-oxo-6,7-dihydro-5H-5,7a,8-triazadibenzo[a,e]azulene-9-carboxylate

To a solution of methyl (6-cyano-3-cyclohexylpyrrolo[2,3-b]pyridin-1-yl)acetate (647 mg, 2.18 mmol) in ethanol (13 ml) was added acetyl chloride (4.7 ml, 65.4 mmol) under ice-cooling, and the mixture was heated under reflux for 3 hr. The mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane:ethyl acetate=4:1) to give ethyl 3-cyclohexyl-1-ethoxycarbonylmethyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate (563 mg, yield 75%).

1H-NMR (400 MHz, CDCl3): δ (ppm) 7.98 (1H, d, J=8.0 Hz), 7.89 (1H, d, J=8.4 Hz), 7.15 (1H, s), 5.11 (2H, s), 4.45 (2H, q, J=7.1 Hz), 4.22 (2H, q, J=7.1 Hz), 2.75-2.85 (1H, m), 2.02-2.14 (2H, m), 1.71-1.91 (3H, m), 1.37-1.53 (7H, m), 1.23-1.33 (4H, m).

MS 359 (M+1).
To a suspension of ethyl 2-bromo-3-cyclohexyl-1-ethoxy carbonylmethyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate (457 mg, 1.05 mmol) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine (275 mg, 1.25 mmol) obtained in the same manner as in the method described in Example 1-1, Step 1 in 1,2-dimethoxyethane (7.5 ml) and water (3.5 ml) were added sodium hydrogen carbonate (260 mg, 3.14 mmol) and tetrais(triphenylphosphine)palladium (60 mg, 0.05 mmol) and the mixture was stirred at 110° C. for 3.5 hr. The mixture was allowed to cool to room temperature and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=3:2) to give ethyl 12-cyclohexyl-6-oxo-6,7-dihydro-5H-5,7a,8-triazadibenzo[a,e]azulene-9-carboxylate (74 mg, yield 69%).

Example 8-3
Production of ethyl 12-cyclohexyl-5-[2-oxo-2-(morpholin-4-yl)ethyl]-6,7-dihydro-5H-5,7a,8-triazadibenzo[a,e]azulene-9-carboxylate

[1594]
[1595] To a solution of ethyl 12-cyclohexyl-6,7-dihydro-5H,5,7a,8-triazadibenzo[α,ε]azulene-9-carboxylate (74 mg, 0.19 mmol) in N,N-dimethylformamide (2 ml) and acetonitrile (2 ml) were added 4-(2-chloroacetyl)aniline (94 mg, 0.57 mmol), potassium iodide (64 mg, 0.38 mmol) and potassium carbonate (66 mg, 0.48 mmol), and the mixture was stirred with heating at 90°C for 12 hr. The reaction mixture was allowed to cool to room temperature, and water was added to the reaction mixture. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel chromatography (ethyl acetate) to give ethyl 12-cyclohexyl-5-[2-oxo-2-(morpholin-4-yl)ethyl]-6,7-dihydro-5H,5,7a,8-triazadibenzo[α,ε]azulene-9-carboxylate (62 mg, yield 63%).

[1596] MS 517(M+1).

Example 8-4

Production of 12-cyclohexyl-5-[2-oxo-2-(morpholin-4-yl)ethyl]-6,7-dihydro-5H,5,7a,8-triazadibenzo[α,ε]azulene-9-carboxylic acid dihydrochloride

[1597]

[1598] To a solution of ethyl 12-cyclohexyl-5-[2-oxo-2-(morpholin-4-yl)ethyl]-6,7-dihydro-5H,5,7a,8-triazadibenzo[α,ε]azulene-9-carboxylate (62 mg, 0.12 mmol) in tetrahydrofuran (3 ml) and methanol (3 ml) was added 4N aqueous sodium hydroxide solution (1.5 ml) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. 2N Hydrochloric acid (3 ml) was added to the reaction mixture to adjust to pH 7, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel chromatography (chloroform:methanol=8:1) and the solvent was evaporated under reduced pressure. To a solution of the residue in ethyl acetate (1 ml) was added 4N HCl-ethyl acetate solution (1 ml) and the solvent was evaporated under reduced pressure. Hexane was added to the residue, and the precipitated solid was collected by filtration, washed with hexane and dried in vacuo to give 12-cyclohexyl-5-[2-oxo-2-(morpholin-4-yl)ethyl]-6,7-dihydro-5H,5,7a,8-triazadibenzo[α,ε]azulene-9-carboxylic acid dihydrochloride (20 mg, yield 30%).

[1599] MS 562(M+1).

Example 8-7

Production of 3-chloro-14-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-6,7,8-tetrahydrobenzo[6,7][1,5]diazocino[8,1-a]indole-11-carboxylic acid dihydrochloride

Step 1: Production of methyl 2-bromo-3-cyclohexyl-1-(2-ethoxycarbonyl)tetrahydrobenzo[6,7][1,5]diazocino[8,1-a]indole-11-carboxylate

[1600]
[1601] To a solution of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (5.00 g, 14.9 mmol) obtained in the same manner as in the method described in WO03/010140 in N,N-dimethylformamide (30 ml) were added ethyl 3-bromoacetopropionate (3.84 ml, 30.1 mmol) and potassium carbonate (6.20 g, 44.6 mmol), and the mixture was stirred at 90° C. for 3.5 hr. The reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane:ethyl acetate=4:1) to give methyl 2-bromo-3-cyclohexyl-1-(2-ethoxycarbonyl)ethyl)-1H-indole-6-carboxylate (6.40 g, yield 98%).

[1602] 1H-NMR (400 MHz, CDCl3): δ (ppm) 8.04 (1H, s), 7.70-7.76 (2H, m), 4.53 (2H, t, J=5.8 Hz), 4.13 (2H, q, J=5.4 Hz), 3.93 (3H, s), 2.81-2.90 (1H, m), 2.75 (2H, t, J=5.7 Hz), 1.73-1.95 (7H, m), 1.29-1.48 (3H, m), 1.22 (3H, t, J=5.4 Hz).

Step 2: Production of methyl 2-(2-amino-4-chlorophenyl)-3-cyclohexyl-1-(2-ethoxycarbonyl)ethyl)-1H-indole-6-carboxylate

[1603]

[1604] To a suspension of methyl 2-bromo-3-cyclohexyl-1-(2-ethoxycarbonyl)ethyl)-1H-indole-6-carboxylate (1.00 g, 2.29 mmol) and 5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine (697 mg, 2.75 mmol) in 1,2-dimethoxyethane (12 ml) and water (6 ml) were added lithium chloride (291 mg, 6.87 mmol), sodium carbonate (729 mg, 6.87 mmol) and tetrais(triphenylphosphine)palladium (265 mg, 0.229 mmol), and the mixture was stirred at 90° C. for 3.5 hr. The mixture was allowed to cool to room temperature and saturated aqueous ammonium chloride solution and ethyl acetate were added. The mixture was filtered through celite, and the filtrate was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane:acetone=3:1) to give methyl 2-(2-amino-4-chlorophenyl)-3-cyclohexyl-1-(2-ethoxycarbonyl)ethyl)-1H-indole-6-carboxylate (1.10 g, yield 100%).

[1605] 1H-NMR (400 MHz, CDCl3): δ (ppm) 8.10 (1H, s), 7.78 (2H, s), 6.99 (1H, dd, J=6.0, 0.6 Hz), 6.79-6.83 (2H, m), 4.12-4.31 (2H, m), 4.01 (2H, q, J=5.4 Hz), 3.94 (3H, s), 3.76 (2H, brs), 2.45-2.64 (3H, m), 1.66-1.85 (7H, m), 1.21-1.31 (3H, m), 1.15 (3H, t, J=5.4 Hz).

Step 3: Production of methyl 2-(2-amino-4-chlorophenyl)-1-(2-carboxyethyl)-3-cyclohexyl-1H-indole-6-carboxylate

[1606]
To a suspension of methyl 2-(2-amino-4-chlorophenyl)-3-cyclohexyl-1-(2-ethoxycarbonylthethyl)-1H-indole-6-carboxylate (1.05 g, 2.17 mmol) in tetrahydrofuran (11 ml) and methanol (11 ml) was added 4N aqueous sodium hydroxide solution (1.08 ml, 4.34 mmol), and the mixture was stirred for 2 hr. 2N Hydrochloric acid (2.2 ml) and water were added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 2-(2-amino-4-chlorophenyl)-1-(2-carboxyethyl)-3-cyclohexyl-1H-indole-6-carboxylate (949 mg) as a crude product. The obtained crude product was used for Step 4 without further purification.

Step 4: Production of methyl 3-chloro-14-cyclohexyl-6-oxo-5,6,7,8-tetrahydrobenzo[6,7][1,5]diazocino[8,1-a]indole-11-carboxylate

To a solution of methyl 2-(2-amino-4-chlorophenyl)-1-(2-carboxyethyl)-3-cyclohexyl-1H-indole-6-carboxylate (949 mg) in N,N-dimethylformamide (33 ml) were added triethylamine (0.61 ml, 4.35 mmol) and benzotriazol-1-yloxytri(pyrrrolidino)phosphonium hexafluorophosphate (1.36 g, 2.61 mmol) under ice-cooling, and the mixture was stirred for 22.5 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane:ethyl acetate=2:3), and hexane: diisopropyl ether (3:2) mixture was added to the obtained residue. The precipitated solid was collected by filtration and washed with hexane: diisopropyl ether (3:2) mixture. The obtained solid was dried in vacuo to give methyl 3-chloro-14-cyclohexyl-6-oxo-5,6,7,8-tetrahydrobenzo[6,7][1,5]diazocino[8,1-a]indole-11-carboxylate (657 mg, yield 72%).

Step 5: Production of methyl 3-chloro-14-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-5,6,7,8-tetrahydrobenzo[6,7][1,5]diazocino[8,1-a]indole-11-carboxylate
[1613] A suspension of methyl 3-chloro-14-cyclohexyl-6-oxo-5,6,7,8-tetrahydrobenzo[6,7][1,5]diazocino[8,1-a]-indole-11-carboxylate (200 mg, 0.457 mmol), 1-chloro-acetyl)piperidine (85 mg, 0.526 mmol) and potassium carbonate (126 mg, 0.914 mmol) in N,N-dimethylformamide (4 ml) was stirred at 80°C for 4.5 hr. The mixture was allowed to cool to room temperature and water was added. The precipitate was collected by filtration, washed with water, and dried in vacuo to give methyl 3-chloro-14-cyclohexyl-6-oxo-5-[2-oxo-2-(piperdin-1-yl)ethy]-5,6,7,8-tetrahydrobenzo[6,7][1,5]diazocino[8,1-a]-indole-11-carboxylate (245 mg, yield 95%) as a crude product. The obtained crude product was used for Step 6 without further purification.

[1614] 1H-NMR(400 MHz, CDCl3): δ (ppm) 8.09(1H, s), 7.96(1H, d, J=1.8 Hz), 7.77(2H, s), 7.44(1H, dd, J=6.3, 1.5 Hz), 7.36(1H, d, J=6.0 Hz), 6.49-4.79(2H, m), 3.92(3H, s), 3.81-3.89(1H, m), 3.62-3.69(1H, m), 3.41-3.48(1H, m), 3.36(1H, d, J=12.0 Hz), 3.23-3.30(1H, m), 3.12-3.20(1H, m), 2.99-3.08(1H, m), 2.77-2.85(1H, m), 2.38-2.48(1H, m), 1.68-1.92(7H, m), 1.41-1.64(6H, m), 1.15-1.32(3H, m).

Step 6: Production of methyl 3-chloro-14-cyclohexyl-5-[2-(piperdin-1-yl)ethy]-5,6,7,8-tetrahydrobenzo[6,7][1,5]diazocino[8,1-a]-indole-11-carboxylate

[1616] To a solution of methyl 3-chloro-14-cyclohexyl-6-oxo-5-[2-oxo-2-(piperdin-1-yl)ethy]-5,6,7,8-tetrahydrobenzo[6,7][1,5]diazocino[8,1-a]-indole-11-carboxylate (245 mg, 0.456 mmol) in tetrahydrofuran (2 ml) was added a solution (3 ml) of 1.0M BH3·THF complex in tetrahydrofuran, and the mixture was stirred at room temperature for 17.5 hr. 4N Hydrochloric acid (3 ml) was added to the reaction mixture, and the mixture was stirred at 70°C for 7.5 hr. The reaction mixture was allowed to cool to room temperature, neutralized with 2N aqueous sodium hydroxide solution and saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (chloroform:methanol=50:1-20:1) to give methyl 3-chloro-14-cyclohexyl-5-[2-(piperdin-1-yl)ethy]-5,6,7,8-tetrahydrobenzo[6,7][1,5]diazocino[8,1-a]-indole-11-carboxylate (50 mg, yield 21%).

[1617] 1H-NMR(400 MHz, CDCl3): δ (ppm) 8.05(1H, s), 7.81(1H, d, J=6.3 Hz), 7.75(1H, dd, J=6.6, 1.2 Hz), 6.99(1H, d, J=6.3 Hz), 6.84(1H, s), 6.66-6.71(1H, m), 4.39-4.47(1H, m), 3.93(3H, s), 3.76-3.86(1H, m), 3.28-3.72(6H, m), 2.82-2.90(2H, m), 2.64-2.75(1H, m), 2.40-2.64(4H, m), 1.20-2.09(16H, m).

Step 7: Production of 3-chloro-14-cyclohexyl-5-[2-(piperdin-1-yl)ethy]-5,6,7,8-tetrahydrobenzo[6,7][1,5]diazocino[8,1-a]-indole-11-carboxylic acid dihydrochloride

[1618]
[1619] To a solution of methyl 3-chloro-14-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-5,6,7,8-tetrahydroseleno[6,7][1,5] diazocino[8,1-a]indole-11-carboxylate (50 mg, 0.094 mmol) in tetrahydrofuran (1 ml) and methanol (1 ml) was added 4N aqueous sodium hydroxide solution (0.5 ml), and the mixture was stirred at 60°C for 2 hr. 2N Hydrochloric acid (1.1 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran (2:1). The organic layer was washed saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the mixture in tetrahydrofuran (1 ml) was added 4N HCl-ethanol acetic solution (1 ml), and the solvent was evaporated under reduced pressure. Hexane:ethyl acetate (4:1) was added and the precipitated solid was collected by filtration, washed with hexane:ethyl acetate (4:1) and dried in vacuo to give 3-chloro-14-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-5,6,7,8-tetrahydroseleno[6,7][1,5]diazocino[8,1-a]indole-11-carboxylic acid dihydrochloride (26 mg, yield 47%).

[1620] 1H-NMR(300 MHz, DMSO-d6): δ (ppm) 12.57 (1H, s), 9.96 (1H, s), 8.12 (1H, s), 7.84 (1H, d, J=8.4 Hz), 7.65 (1H, d, J=8.4 Hz), 7.05-7.10 (2H, m), 6.88 (1H, d, J=8.1 Hz), 4.58-4.68 (1H, m), 3.56-3.78 (4H, m), 3.41-3.50 (2H, m), 3.11-3.29 (1H, m), 2.54-3.04 (7H, m), 1.21-2.04 (16H, m).

[1621] MS 520.2 (M+1).

[1622] The compounds of Examples 8-5 and 8-6 were produced by the same method as in Examples 8-1 to 8-4 and 8-7 or methods similar thereto, and where necessary, by employing other conventional methods. The chemical structural formulas are shown in Table 115.

[1623] 3-chloro-12-cyclohexyl-5-[2-piperidin-1-yl]ethyl]-6,7-dihydro-5H-5,7a,8-tetraazabenzof[a]azarulen-9-carboxylic acid trihydrochloride (Example 8-5)

[1624] 3-chloro-12-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)ethyl]-6,7-dihydro-5H-5,7a,8-tetraazabenzof[a]azarulen-9-carboxylic acid trihydrochloride (Example 8-6)

[1625] Example 9-1

Production of methyl 12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azarulen-9-carboxylate

Step 1: Production of methyl 2-[2-(2-chloroethoxy)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate

[1626] To a solution of methyl 3-cyclohexyl-2-(2-hydroxyphenyl)-1H-indole-6-carboxylate (500 mg, 1.43 mmol), obtained in the same manner as in the method described in Example 3-1, Step 1, in acetone (20 ml) were added 1-bromo-2-chloroethane (0.14 ml, 1.72 mmol) and potassium carbonate (237 mg, 1.72 mmol), and the mixture was stirred at 50°C for 2 hr. 1-Bromo-2-chloroethane (0.28 ml, 3.44 mmol) and potassium carbonate (474 mg, 3.44 mmol) were further added and the mixture was stirred at 50°C for 24 hr. The reaction mixture was allowed to cool to room temperature. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=3:1) to give methyl 2-[2-(2-chloroethoxy)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate (370 mg, yield 62.8%).

[1627] 1H-NMR(400 MHz, CDCl3): δ (ppm) 9.00 (1H, s), 8.06-8.07 (1H, m), 7.85 (1H, d, J=8.4 Hz), 7.74 (1H, ddd, J=10.0, 8.0, 1.2 Hz), 7.41 (1H, dd, J=7.6, 1.6 Hz), 7.37 (1H, td, J=7.8, 1.8 Hz), 7.12 (1H, t, J=7.6 Hz), 6.99 (1H, d, J=8.0 Hz), 4.28 (2H, t, J=5.2 Hz), 3.93 (3H, s), 3.81 (2H, t, J=5.2 Hz), 2.88-2.95 (1H, m), 1.99-2.10 (2H, m), 1.76-1.87 (5H, m), 1.32-1.41 (3H, m).
Step 2: Production of methyl 12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulene-9-carboxylate

Example 9-2
Production of 12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulene-9-carboxylic acid

[1629] To a solution of methyl 2-[2-(2-chloroethoxy)phen yl]-3-cyclohexyl-1H-indole-6-carboxylate (180 mg, 0.44 mmol) in N,N-dimethylformamide (6 ml) was added sodium hydride (20 mg, 0.49 mmol) under ice-cooling, and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and diisopropyl ether was added to the residue. The precipitated solid was collected by filtration, washed with diisopropyl ether and dried in vacuo to give methyl 12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulene-9-carboxylate (70 mg, yield 42.3%).

[1630] $^1$H-NMR(400 MHz, DMSO-d$_6$): δ(ppm) 8.20(1H, d, J=1.6 Hz), 7.89(1H, d, J=8.4 Hz), 7.62(1H, dd, J=8.4, 1.2 Hz), 7.40-7.47(2H, m), 7.33(1H, td, J=7.4, 1.2 Hz), 7.23(1H, dd, J=8.0, 1.2 Hz), 4.33-4.45(4H, m), 3.85(3H, s), 2.83-2.90(1H, m), 1.95-2.06(2H, m), 1.67-1.83(5H, m), 1.24-1.44(3H, m).

[1631] MS 376(M+1).

[1632] To a solution of methyl 12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulene-9-carboxylate (70 mg, 0.19 mmol) in tetrahydrofuran (2 ml) and methanol (1 ml) was added 4N aqueous sodium hydroxide solution (1 ml) and the mixture was stirred at room temperature for 24 hr. 1N Hydrochloric acid was added to the reaction mixture, and the precipitated solid was collected by filtration, washed with water and dried in vacuo to give 12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulene-9-carboxylic acid (59 mg, yield 85.2%).

[1634] $^1$H-NMR(400 MHz, DMSO-d$_6$): δ(ppm) 12.54(1H, brs), 8.17(1H, s), 7.86(1H, d, J=8.4 Hz), 7.60(1H, dd, J=8.8, 1.6 Hz), 7.40-7.47(2H, m), 7.33(1H, td, J=7.4, 0.8 Hz), 7.22(1H, d, J=8.0 Hz), 4.33-4.44(4H, m), 2.83-2.91(1H, m), 1.95-2.05(2H, m), 1.68-1.81(5H, m), 1.25-1.37(3H, m).

[1635] MS 362(M+1).

[1636] The compounds of Examples 9-3 and 9-4 were produced by the same methods as in Examples 9-1 and 9-2 or methods similar thereto, and where necessary, by employing other conventional methods. The chemical structural formulas are shown in Tables 116.

Example 10-2
Production of ethyl 3-chloro-12-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylate

Step 1: Production of methyl 4-chloro-2-(3-ethoxy-carbonylpropionylamino)benzoate

To a solution of methyl 2-amino-4-chlorobenzoate (18.60 g, 100 mmol) and pyridine (11.5 ml, 142 mmol) in toluene (138 ml), was added dropwise a solution of ethyl succinyl chloride (18.9 ml, 133 mmol) in toluene (19 ml) at a temperature between 0°C and 10°C. The mixture was stirred at 10°C for 1 hr, water was added and the mixture was extracted with ethyl acetate. The organic layer was successively washed with 0.1N hydrochloric acid and 10% aqueous sodium hydrogen carbonate solution and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 4-chloro-2-(3-ethoxy-carbonylpropionylamino)benzoate (27.90 g, yield 89%).

[1640] 1H-NMR(300 MHz, DMSO-d6): δ (ppm) 10.73 (1H, s), 8.40 (1H, d, J=2.3 Hz), 7.93 (1H, d, J=8.3 Hz), 7.26 (1H, d, J=12.8 Hz), 4.06 (2H, q, J=7.0 Hz), 3.87 (3H, s), 2.70-2.68 (2H, m), 2.63-2.61 (2H, m), 1.18 (3H, t, J=7.2 Hz).

Step 2: Production of a mixture of ethyl 8-chloro-5-hydroxy-2-oxo-2,3-dihydro-1H-benzo[b]azepine-4-carboxylate and methyl 8-chloro-5-hydroxy-2-oxo-2,3-dihydro-1H-benzo[b]azepine-4-carboxylate

[1641] 1H-NMR(300 MHz, DMSO-d6): δ (ppm) 12.51 (1H, brs), 10.48 (1H, s), 7.81 (1H, d, J=8.7 Hz), 7.33 (1H, dd, J=8.7, 2.3 Hz), 7.26 (1H, d, J=1.9 Hz), 4.30 (2H, q, J=7.2 Hz), 2.97 (2H, s), 1.30 (3H, t, J=7.0 Hz).

[1643] 1H-NMR(300 MHz, DMSO-d6): δ (ppm) 12.44 (1H, brs), 10.48 (1H, s), 7.81 (1H, d, J=8.7 Hz), 7.33 (1H, dd, J=8.7, 2.3 Hz), 7.26 (1H, d, J=1.9 Hz), 3.84 (3H, s), 2.97 (2H, s).
Step 3: Production of 8-chloro-3,4-dihydro-1H-benzof[b]azepine-2,5-dione

[1645]

A solution of ethyl 8-chloro-5-hydroxy-2-oxo-2,3-dihydro-1H-benzo[b]azepine-4-carboxylate (wet weight 21.3 g) obtained as a crude product in Step 2 in dimethyl sulfoxide (200 ml) and water (10 ml) was heated at 150°C. Under stirring, water was added 3 times in total by 10 ml every one hour. The mixture was allowed to cool to room temperature, water (400 ml) was added, and the precipitated solid was collected by filtration. The crude product was washed with water and dried in vacuo. A mixed solvent (200 ml) of hexane:ethyl acetate (10:1) was added to the obtained crude product to give a suspension. After filtration, the obtained solid was washed with a mixed solvent (50 ml) of hexane:ethyl acetate (10:1) and dried in vacuo to give 8-chloro-3,4-dihydro-1H-benzo[b]azepine-2,5-dione (12.60 g, yield 80%).

[1647] $^1$H-NMR (300 MHz, DMSO-d$_6$): δ (ppm) 10.18 (1H, s), 7.86-8.70 (1H, m), 7.25-7.18 (2H, m), 2.93-2.87 (2H, m), 2.71-2.64 (2H, m).

Step 4: Production of ethyl 4-cyclohexylaminobenzoate

[1648]

Step 5: Production of ethyl 4-(N-cyclohexylnitroso)benzoate

[1650] $^1$H-NMR (400 MHz, CDCl$_3$): δ (ppm) 7.85 (2H, d, J=8.8 Hz), 6.53 (2H, d, J=8.8 Hz), 4.32 (2H, q, J=7.1 Hz), 4.03 (1H, brs), 3.34 (1H, brs), 2.08-2.05 (2H, m), 1.80-1.78 (2H, m), 1.68-1.65 (2H, m), 1.44-1.43 (2H, m), 1.37 (3H, t, J=7.2 Hz), 1.26-1.19 (2H, m).

[1651]
To a solution of ethyl 4-cyclohexylaminobenzoate (24.00 g, 97.0 mmol) in acetic acid (120 ml) was added dropwise an aqueous solution (120 ml) of sodium nitrite (13.40 g, 194 mmol) over 15 min at room temperature, and the mixture was further stirred for 2 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give ethyl 4-(N-cyclohexyl-nitroso)benzoate (26.90 g). The obtained compound was used for Step 6 without purification.

To a suspension of zinc powder (18.50 g, 282 mmol) in water (130 ml) was added dropwise a solution of ethyl 4-(N-cyclohexyl-nitroso)benzoate (26.00 g, 94.1 mmol) in acetic acid (250 ml) over 15 min under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was filtered through celite, and the filtrate was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=10:1) to give ethyl 4-(N-cyclohexyl-hydrazino)benzoate (7.60 g, yield 31%).

A suspension of 8-chloro-3,4-dihydro-1H-benzo[b]azepine-2,3-dione (1.18 g, 5.65 mmol) and ethyl 4-(N-cyclohexyl-hydrazino)benzoate (1.14 g, 4.35 mmol) in acetic acid (11 ml) was stirred at 85°C for 1 hr. The reaction mixture was allowed to cool to room temperature, and conc. sulfuric acid (0.55 ml) was added to the reaction mixture. The mixture was stirred at 85°C for 3 hr. The mixture was allowed to cool, and the reaction mixture was poured into water (250 ml) and extracted with a mixed solvent of ethyl acetate (200 ml) and ethanol (30 ml). The organic layer was washed twice with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. Water (10 ml) and ethanol (10 ml) were added to the obtained crude product and the precipitated solid was collected by filtration. The obtained solid was washed with a mixed solvent (10 ml) of water:ethanol (1:1) and dried in vacuo to give ethyl 3-chloro-12-cyclohexyl-6-oxo-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylate (0.97 g, yield 39%).
J=14.3 Hz), 3.09 (1H, d, J=14.3 Hz), 2.48-2.17 (3H, m), 2.05-1.93 (1H, m), 1.79-1.60 (2H, m), 1.54-1.11 (4H, m), 1.37 (3H, t, J=7.0 Hz).

Step 8: Production of ethyl 3-chloro-12-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylate (Example 10-6)

[1660]

[1661] To a suspension of ethyl 3-chloro-12-cyclohexyl-6-oxo-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylate (772 mg, 1.77 mmol) in N,N-dimethylformamide (7.7 ml) were added a solution of 1-(2-chloroacetyl)piperidine (343 mg, 2.12 mmol) in N,N-dimethylformamide (2 ml) and potassium carbonate (488 mg, 3.53 mmol), and the mixture was stirred at 90°C for 1 hr. Furthermore, a solution of 1-(2-chloroacetyl)piperidine (171 mg, 1.06 mmol) in N,N-dimethylformamide (1 ml) and potassium carbonate (244 mg, 1.77 mmol) were added, and the mixture was stirred at 90°C for 1.5 hr. The mixture was allowed to cool to room temperature, water (10 ml) was added, and the precipitated solid was collected by filtration. The obtained solid was washed with water (10 ml) and dried in vacuo to give ethyl 3-chloro-12-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3] azepino[4,5-b]indole-9-carboxylate (911 mg, yield 92%).

[1662] 1H-NMR(300 MHz, DMSO-d6): δ(ppm) 8.37 (1H, s), 7.97-7.87 (1H, m), 7.82 (1H, d, J=8.7 Hz), 7.71 (1H, s), 7.52 (1H, d, J=8.3 Hz), 7.51 (1H, s), 4.74-4.55 (2H, m), 4.40-4.26 (1H, m), 4.35 (2H, q, J=7.0 Hz), 3.94 (1H, d, J=13.6 Hz), 3.44-3.18 (4H, m), 3.02 (1H, d, J=13.6 Hz), 2.47-2.12 (3H, m), 2.05-1.94 (1H, m), 1.83-1.10 (12H, m), 1.37 (3H, t, J=7.2 Hz).

[1663] Production of ethyl 3-chloro-12-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylate (Example 10-2)

[1664] To a solution of ethyl 3-chloro-12-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylate (886 mg, 1.57 mmol) in tetrahydrofuran (15 ml) was added dropwise a solution (8.2 ml) of 1M BH3·THF complex in tetrahydrofuran under ice-cooling, and the mixture was stirred under ice-cooling for 30 min, at room temperature for 3 hr, at 30°C for 2 hr, and further at 60-70°C for 1 hr. The reaction mixture was allowed to cool, a solution (4.1 ml) of 1M BH3·THF complex in tetrahydrofuran was added, and the mixture was allowed to stand overnight at room temperature. The reaction mixture was stirred at 70°C for 2 hr, 5M hydrochloric acid (8 ml) was added under ice-cooling, and the mixture was stirred at 70°C for 2 hr. The reaction mixture was neutralized with 1N aqueous sodium hydroxide solution under ice-cooling, saturated sodium hydrogen carbonate solution was added and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate) to give ethyl 3-chloro-12-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylate (512 mg, yield 61%).

[1665] 1H-NMR(300 MHz, DMSO-d6): δ(ppm) 8.22 (1H, s), 7.82 (1H, d, J=8.7 Hz), 7.73 (1H, dd, J=9.0, 1.9 Hz), 7.36 (1H, s), 7.23-7.16 (2H, m), 4.32 (2H, q, J=7.2 Hz), 4.27-4.14 (1H, m), 3.53-3.42 (2H, m), 3.29-3.20 (2H, m), 2.89-2.71 (2H, m), 2.40-2.15 (9H, m), 1.90-1.59 (5H, m), 1.40-1.19 (8H, m), 1.34 (3H, t, J=7.5 Hz).
Example 10-1

Production of 3-chloro-12-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3]azepino [4,5-b]indole-9-carboxylic acid

Example 10-3

Production of 3-chloro-12-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3]azepino [4,5-b]indole-9-carboxamide

[1666]  To a solution of ethyl 3-chloro-12-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylate (309 mg, 0.579 mmol) in tetrahydrofuran (4 ml) and methanol (4 ml) was added 1N aqueous sodium hydroxide solution (2 ml), and the mixture was stirred at 70°C for 2 hr. The mixture was allowed to cool to room temperature. 4N aqueous lithium hydroxide solution (2 ml) was added, and the mixture was stirred at 70°C for 2 hr. The mixture was allowed to cool to room temperature, water (100 ml) was added, and the mixture was extracted with ethyl acetate (20 ml) and other (10 ml). The aqueous layer was adjusted to pH 7 with 1N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water and dried in vacuo to give 3-chloro-12-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylic acid (212 mg, yield 72%).

[1668] ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 8.22 (1H, s), 7.80 (1H, d, J=8.7 Hz), 7.74 (1H, d, J=8.7 Hz), 7.37 (1H, s), 7.21 (2H, brs), 4.26-4.15 (1H, m), 3.55-3.45 (2H, m), 3.32-3.20 (2H, m), 2.89-2.75 (2H, m), 2.45-2.20 (8H, m), 1.90-1.60 (5H, m), 1.49-1.20 (9H, m).

[1669]  To a solution of 3-chloro-12-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylic acid (100 mg, 0.198 mmol) in N,N-dimethylformamide (3 ml) were added triethylamine (0.041 ml, 0.297 mmol), benzotriazol-1-ylxytripyrrolidinophosphonium hexafluorophosphate (155 mg, 0.297 mmol) and 28% aqueous ammonia (0.1 ml), and the mixture was stirred overnight at room temperature. Water (15 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (20 ml). The organic layer was washed with saturated brine (15 ml) and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give an oil (36 mg). Tetrahydrofuran (2 ml), methanol (2 ml) and water (2 ml) were added to the oil, and the precipitated solid was collected by filtration. The obtained solid was dried in vacuo to give 3-chloro-12-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxamide (32 mg, yield 32%).

[1670] ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 8.18 (1H, s), 7.84 (1H, brs), 7.74 (1H, d, J=8.7 Hz), 7.69 (1H, dd, J=8.7, 1.9 Hz), 7.36 (1H, d, J=1.9 Hz), 7.25-7.15 (2H, m), 7.10 (1H, brs), 4.26-4.10 (1H, m), 3.51-3.47 (2H, m), 3.40-3.29 (2H, m), 2.81 (2H, brs), 2.40-2.20 (8H, m), 1.90-1.55 (5H, m), 1.40-1.15 (9H, m).
[1672] The compound of Example 10-4 was produced by the same method as in Examples 10-1 and 10-2 or methods similar thereto, and where necessary, by employing other conventional methods. The chemical structural formula is shown in Table 118.

[1673] 12-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-5,6,7, 12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylic acid (Example 10-4)

Example 1-157

Production of 13-cyclohexyl-5-[2-(1-cyclopentylpiperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride

Step 1: Production of methyl 5-[2-(1-tert-butoxycarbonylpiperidin-4-yl)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-601)

[1674]

[1675] To a solution of methyl 13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (1.00 g, 2.67 mmol) obtained in Example 1-2 and 1-(tert-butoxycarbonyl)-4-(2-methanesulfonyloxyethyl)piperidine (2.46 g, 8.02 mmol) in N,N-dimethylformamide (10 mL) were added potassium carbonate (1.85 g, 13.4 mmol) and potassium iodide (2.00 g, 8.02 mmol), and the mixture was stirred at 90°C for 36 hr. The reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=4:1-2:1) to give methyl 5-[2-(1-tert-butoxycarbonylpiperidin-4-yl)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (1.16 g, yield 74%).

[1676] 1H-NMR(400 MHz, DMSO-d6), δ (ppm) 8.18 (1H, d, J=1.4 Hz), 7.87 (1H, d, J=8.3 Hz), 7.61 (1H, dd, J=8.3, 1.4 Hz), 7.44 (1H, td, J=7.6, 1.4 Hz), 7.31 (1H, dd, J=7.6, 1.4 Hz), 7.22 (1H, d, J=7.6 Hz), 7.18 (1H, t, J=7.6 Hz), 3.87 (3H, s), 3.65 (2H, brs), 3.44 (2H, brs), 3.10 (2H, brs), 2.83 (1H, brt, J=12.8 Hz), 2.33 (2H, brs), 2.07-1.92 (2H, m), 1.87-1.49 (4H, m), 1.41-1.10 (11H, m), 1.33 (9H, s), 0.85-0.67 (2H, m).

[1677] MS 586.2(M+1).

Step 2: Production of methyl 13-cyclohexyl-5-[2- (piperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-602)

[1678]

[1679] To a solution of methyl 5-[2-(1-tert-butoxycarbonylpiperidin-4-yl)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (1.06 g, 1.81 mmol) in chloroform (10 mL) was added trifluoroacetic acid (2 mL), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 13-cyclohexyl-5-[2-(piperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (859 mg, yield 98%).

[1680] 1H-NMR(400 MHz, DMSO-d6), δ (ppm) 8.17 (1H, d, J=1.4 Hz), 7.87 (1H, d, J=8.5 Hz), 7.61 (1H, dd, J=8.5, 1.4 Hz), 7.43 (1H, dd, J=7.7, 1.4 Hz), 7.30 (1H, dd, J=7.7, 1.6 Hz), 7.26-7.11 (3H, m), 6.16 (1H, brs), 4.68 (1H, brs), 3.87
Step 4: Production of 13-cyclohexyl-5-[2-(1-cyclopentylpiperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5, 6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-157)

To a solution of methyl 13-cyclohexyl-5-[2-(1-cyclopentylpiperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5, 6][1,4]diazepino[7,1-a]indole-10-carboxylate (124 mg, 0.224 mmol) in tetrahydrofuran (2 ml) and methanol (2 ml) was added 4N aqueous sodium hydroxide solution (1 ml), and the mixture was stirred at 70°C. for 2 hr. The reaction mixture was adjusted to pH 6.5 by adding 2N hydrochloric acid, and the mixture was extracted with chloroform. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the obtained residue in chloroform was added 4N HCl-ethyl acetate solution (10 ml), and the solvent was evaporated under reduced pressure. A mixed solvent (hexane:ethyl acetate=4:1) was added to the residue. The precipitated solid was collected by filtration to give 13-cyclohexyl-5-[2-(1-cyclopentylpiperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5, 6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (125 mg, yield 91%).

1H-NMR(400 MHz, DMSO-d6): δ(ppm) 8.17 (1H, s), 7.86 (1H, d, J=8.3 Hz), 7.60 (1H, d, J=8.3 Hz), 7.43 (1H, t, J=7.4 Hz), 7.30 (1H, d, J=7.4 Hz), 7.21 (1H, d, J=7.4 Hz), 7.16 (1H, t, J=7.4 Hz), 4.69 (2H, brs), 3.86 (3H, s), 3.11 (4H, brs), 2.87-2.75 (1H, m), 2.69-2.54 (1H, m), 2.31-2.13 (1H, m), 2.07-0.78 (28H, m).
Example 2-44

Production of 12-cyclohexyl-3-(1-methanesulfonylpiperidin-3-yl)oxo)-6,7-dihydro-5-oxa-7a-aza-dibenzo[a,e]jululene-9-carboxylic acid

Step 1: Production of tert-butyl 3-(toluene-4-sulfonyloxy)piperidine-1-carboxylate

[1689]

To a solution of tert-butyl 3-hydroxy piperidine-1-carboxylate (2.00 g, 9.94 mmol) in chloroform (20 ml) were successively added p-toluenesulfonyl chloride (2.27 g, 11.9 mmol) and triethylamine (1.66 ml, 11.9 mmol) at 0°C, and the mixture was stirred at 70°C for 9 hr. The reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture and the mixture was extracted with chloroform. The organic layer was successively washed with water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was concentrated under reduced pressure to give tert-butyl 3-(toluene-4-sulfonyloxy)piperidine-1-carboxylate (1.00 g, yield 28%).

[1691] 1H-NMR (300 MHz, DMSO-d6); δ(ppm) 7.81 (2H, d, J=9.0 Hz), 7.48 (2H, d, J=9.0 Hz), 4.54-4.56 (1H, m), 3.67-2.89 (4H, m), 2.42 (3H, s), 1.81-1.52 (3H, m), 1.47-1.21 (1H, m), 1.35 (9H, s).

Step 2: Production of methyl 3-(1-tert-butoxycarbonylpiperidin-3-yl)oxo)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-dibenzo[a,e]jululene-9-carboxylate (Example 2-501)

[1692]

To a solution of methyl 12-cyclohexyl-3-hydroxy-6,7-dihydro-5-oxa-7a-aza-dibenzo[a,e]jululene-9-carboxylate (0.80 g, 2.04 mmol) in N,N-dimethylformamide (8 ml) were successively added tert-butyl 3-(toluene-4-sulfonyloxy)piperidine-1-carboxylate (1.09 g, 3.07 mmol) and potassium carbonate (0.57 g, 4.08 mmol) at room temperature, and the mixture was stirred overnight at 60°C. The reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was concentrated under reduced pressure to give methyl 3-(1-tert-butoxycarbonylpiperidin-3-yl)oxo)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-dibenzo[a,e]jululene-9-carboxylate (0.68 g). The obtained compound was used for Step 3 without purification.

Step 3: Production of methyl 12-cyclohexyl-3-(piperidin-3-yl)oxo)-6,7-dihydro-5-oxa-7a-aza-dibenzo[a,e]jululene-9-carboxylate (Example 2-502)

[1694]

Methyl 3-(1-tert-butoxycarbonylpiperidin-3-yl)oxo)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-dibenzo[a,e]jululene-9-carboxylate (0.68 g) was dissolved in trifluoroacetic acid (20 ml), and the mixture was stirred at room temperature for 3 hr. Toluene was added to the reaction mixture and the solvent was evaporated under reduced pressure.
pressure. 4N HCl-ethyl acetate solution (2.0 ml) was added to the obtained residue and the mixture was stirred, and the solvent was evaporated under reduced pressure. The residue was neutralized with saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (chloroform-methanol=9:1) to give methyl 12-cyclohexyl-3-(piperidin-3-yloxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (0.16 g, yield 17%).

[1696] 1H-NMR(300 MHz, CDCl3): δ(ppm) 8.05(1H, s), 7.87(1H, d, J=8.3 Hz), 7.75(1H, d, J=8.7 Hz), 7.31(1H, d, J=8.3 Hz), 6.85(1H, dd, J=2.3, 8.3 Hz), 6.79(1H, d, J=2.3 Hz), 4.98(1H, t, J=5.5 Hz), 4.39-4.24(3H, m), 3.94(3H, s), 3.28-3.17(1H, m), 3.02-2.73(4H, m), 2.17-1.96(4H, m), 1.95-1.74(7H, m), 1.64-1.48(1H, m), 1.47-1.30(3H, m).

Step 4: Production of methyl 12-cyclohexyl-3-(1-methanesulfonyl)piperidin-3-yloxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-503)

[1697]

[1698] To a solution of methyl 12-cyclohexyl-3-(piperidin-3-ylxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (43 mg, 0.091 mmol) in pyridine (0.5 ml) was added dropwise methanesulfonyl chloride (8.5 μl, 0.11 mmol), and the mixture was stirred at 0° C. for 2 hr. Toluene was added to the reaction mixture and the solvent was evaporated under reduced pressure. Hexane and ethyl acetate were added to the obtained residue, and the precipitate was collected by filtration, washed with hexane, and dried in vacuo to give methyl 12-cyclohexyl-3-(1-methanesulfonylpiperidin-3-ylxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (47 mg, yield 94%).

[1699] 1H-NMR(300 MHz, DMSO-d6): δ(ppm) 8.20(1H, s), 7.89(1H, d, J=8.6 Hz), 7.63(1H, d, J=1.1, 8.3 Hz), 7.35(1H, d, J=8.3 Hz), 6.99(1H, dd, J=2.3, 8.3 Hz), 6.89(1H, d, J=2.6 Hz), 4.67-4.56(1H, m), 4.51-4.31(4H, m), 3.87(3H, s), 3.59-3.51(1H, m), 3.32-3.05(3H, m), 2.94(3H, s), 2.92-2.79(1H, m), 2.11-1.92(4H, m), 1.92-1.59(7H, m), 1.46-1.22(3H, m).

Step 5: Production of 12-cyclohexyln-3-(1-methanesulfonyl)piperidin-3-ylxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-44)

[1700]

[1701] To a solution of methyl 12-cyclohexyl-3-(1-methanesulfonyl)piperidin-3-ylxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (47 mg, 0.085 mmol) in tetrahydrofuran (1 ml) and methanol (1 ml) was added 4N aqueous sodium hydroxide solution (0.5 ml), and the mixture was stirred at 55° C. for 2 hr. The mixture was adjusted to pH 6.5 by adding 1N hydrochloric acid (2 ml), and extracted with a mixed solvent of ethyl acetate and tetrahydrofuran. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was concentrated under reduced pressure. Hexane and ethyl acetate were added to the obtained residue, and the precipitate was collected by filtration, washed with hexane and dried in vacuo to give 12-cyclohexyl-3-(1-methanesulfonylpiperidin-3-ylxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (25 mg, yield 56%).

[1702] 1H-NMR(300 MHz, DMSO-d6): δ(ppm) 12.55(1H, brs), 8.17(1H, s), 7.86(1H, d, J=8.7 Hz), 7.62(1H, d, J=7.9 Hz), 7.34(1H, d, J=7.9 Hz), 6.98(1H, d, J=7.9 Hz), 6.88(1H, s), 4.71-4.55(1H, m), 4.53-4.25(4H, m), 3.67-3.49(2H, m), 3.29-3.02(3H, m), 3.00-2.78(1H, m), 2.94(3H, s), 2.14-1.53(11H, m), 1.47-1.29(2H, m).

[1703] MS 539.2(M+1).
Example 2-53
Production of 12-cyclohexyl-4-[2-(piperidin-1-yl)ethoxy]-6,7-dihydro-5-oxa-7a-azabenzo[a,e]azulene-9-carboxylic acid hydrochloride

Step 1: Production of 2-[2-(benzylxyloxyphenoxy)ethoxy]tetrahydropyran

![Chemical structure]

[1704]

\[ \text{OH} \quad \text{Br} \quad \text{OTHP} \]

[1705] To a solution of 2-benzylxylophenol (3.00 g, 15.0 mmol) in N,N-dimethylformamide (15 ml) was added sodium hydride (60% in oil) (719 mg, 18.0 mmol) under ice-cooling, and the mixture was stirred at 30 min. 2-(2-Bromoethoxy)tetrahydropyran (2.72 ml, 18.0 mmol) was added to the reaction mixture and the mixture was stirred at 18 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give 2-[2-(benzylxyloxyphenoxy)ethoxy]tetrahydropyran (4.90 g). The obtained compound was used for Step 2 without purification.

[1706] \(^{1}H\)-NMR(400 MHz, CDCl\(_3\)): δ(ppm) 7.47–7.28 (5H, m), 6.99–6.85 (4H, m), 5.13 (2H, s), 4.73 (1H, t, J=3.5 Hz), 4.23 (2H, t, J=5.1 Hz), 3.92–3.85 (2H, m), 3.55–3.45 (2H, m), 1.87–1.77 (1H, m), 1.74–1.67 (1H, m), 1.64–1.46 (4H, m).

Step 2: Production of 2-(2-benzylxyloxyphenoxy)ethanol

![Chemical structure]

[1707]

[1708] To a solution of 2-[2-(benzylxyloxyphenoxy)ethoxy]tetrahydropyran (4.90 g) in tetrahydrofuran (25 ml) and methanol (25 ml) was added 6N hydrochloric acid (15 ml), and the mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=1:1) to give 2-(benzylxyloxyphenoxy)ethanol (3.07 g, yield 84%).

[1709] \(^{1}H\)-NMR(400 MHz, CDCl\(_3\)): δ(ppm) 7.47–7.31 (5H, m), 7.01–6.93 (4H, m), 5.13 (2H, t, J=4.4 Hz), 3.89 (2H, t, J=4.4 Hz), 2.48 (1H, brs).

Step 3: Production of 2-(2-benzylxyloxyphenoxy)ethyl methanesulfonate

![Chemical structure]

[1710]

[1711] To a solution of 2-(benzylxyloxyphenoxy)ethanol (3.07 g, 12.6 mmol) and triethylamine (2.63 ml, 18.8 mmol) in chloroform (30 ml) was added methanesulfonyl chloride (1.12 ml, 14.4 mmol) under ice-cooling, and the mixture was stirred for 2 hr. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. Hexane was added to the obtained residue and the precipitated solid was collected by filtration and washed with hexane. The obtained solid was dried in vacuo to give 2-(benzylxyloxyphenoxy)ethyl methanesulfonate (3.77 g, yield 93%).

[1712] \(^{1}H\)-NMR(400 MHz, CDCl\(_3\)): δ(ppm) 7.46–7.35 (5H, m), 7.00–6.91 (4H, m), 5.06 (2H, s), 4.59 (2H, t, J=4.4 Hz), 4.26 (2H, t, J=4.4 Hz), 2.88 (3H, s).

Step 4: Production of methyl 1-[2-(benzylxyloxyphenoxy)ethyl]-2-bromo-3-cyclohexyl-1H-indole-6-carboxylate

![Chemical structure]

[1713]
[1714] To a solution of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (1.50 g, 4.46 mmol) obtained in the same manner as in the method described in WO03/010140 and 2-(2-benzoxypylenoxy)ethyl methanesulfonate (1.73 g, 5.35 mmol) in N,N-dimethyformamide (15 ml) were added potassium iodide (740 mg, 4.46 mmol) and potassium carbonate (1.85 g, 13.4 mmol), and the mixture was stirred at 90° C. for 7 hr. The reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=6:1) to give methyl 1-{2-(2-benzoxypylenoxy)ethyl}-2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (2.61 g). The obtained compound was used as it was for Step 5.

[1715] 1H-NMR(400 MHz, CDCl₃): δ (ppm) 8.15 (1H, s), 7.76-7.75 (2H, m), 7.35-7.29 (5H, m), 6.89-6.81 (4H, m), 5.06 (2H, s), 4.68 (2H, t, J=6.3 Hz), 4.34 (2H, t, J=6.5 Hz), 3.88 (3H, s), 2.92-2.85 (1H, m), 1.98-1.78 (7H, m), 1.49-1.35 (3H, m).

Step 5: Production of methyl 4-benzoxypylenoxy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (Example 2-504)

[1716] [1717] To a solution of methyl 1-{2-(2-benzoxypylenoxy)ethyl}-2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (2.61 g) in N,N-dimethylacetamide (100 ml) were added potassium acetate (905 mg, 9.22 mmol) and tetrakis(triphenylphosphine)palladium (800 mg, 0.69 mmol), and the mixture was stirred at 130° C. for 41 hr. The mixture was allowed to cool to room temperature, and filtered through celite. Saturated aqueous ammonium chloride solution was added to the filtrate, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous ammonium chloride solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=6:1) to give methyl 4-benzoxypylenoxy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (745 mg, yield 34%).

[1718] 1H-NMR(400 MHz, CDCl₃): δ (ppm) 8.09 (1H, s), 7.90 (1H, d, J=8.8 Hz), 7.77 (1H, dd, J=8.3, 1.4 Hz), 7.48 (2H, d, J=7.0 Hz), 7.43-7.39 (2H, m), 7.36-7.33 (1H, m), 7.18 (1H, t, J=7.9 Hz), 7.08-7.03 (2H, m), 5.22 (2H, s), 4.53 (2H, t, J=5.8 Hz), 4.32-4.26 (2H, m), 3.96 (3H, s), 3.04-2.96 (1H, m), 2.12-2.02 (2H, m), 1.92-1.77 (5H, m), 1.43-1.34 (3H, m).

Step 6: Production of methyl 12-cyclohexyl-4-hydroxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (Example 2-505)

[1719]
[1720] To methyl 4-benzylxoy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (745 mg, 1.55 mmol) was added 25% hydrogen bromide-acetic acid solution (5 ml), and the mixture was stirred at room temperature for 30 min. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. Hexane: diisopropyl ether (3:1) solution was added to the obtained residue and the precipitated solid was collected by filtration. The solid was washed with hexane: diisopropyl ether (3:1) solution. The obtained solid was dried in vacuo to give methyl 12-cyclohexyl-4-hydroxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (470 mg, yield 78%).

[1721] \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 8.09 (1H, s), 7.91 (1H, d, \(J=8.3\) Hz), 7.78 (1H, dd, \(J=8.3, 1.4\) Hz), 7.17 (1H, t, \(J=7.9\) Hz), 7.08 (1H, dd, \(J=8.1, 1.6\) Hz), 6.97 (1H, dd, \(J=7.7, 1.6\) Hz), 5.88 (1H, s), 4.60 (2H, t, \(J=5.6\) Hz), 4.37 (2H, t, \(J=5.6\) Hz), 3.96 (3H, s), 3.04-2.96 (11H, m), 2.12-2.02 (2H, m), 1.91-1.78 (5H, m), 1.43-1.34 (3H, m).

Step 7: Production of methyl 12-cyclohexyl-4-[2-oxo-2-(pipеридин-1-ил)этил]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (Example 2-506)

[1722]

[1723] To a solution of methyl 12-cyclohexyl-4-hydroxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (200 mg, 0.51 mmol) and 1-chloroacetyl-piperidine (99 mg, 0.61 mmol) in N,N-Dimethylformamide (4 ml) was added potassium carbonate (106 mg, 0.77 mmol), and the mixture was stirred at room temperature for 13 hr. The mixture was heated to 80°C, and the mixture was stirred for 3 hr. The mixture was allowed to cool to room temperature and water was added. The precipitated solid was collected by filtration and washed with water, and the obtained solid was dried in vacuo to give methyl 12-cyclohexyl-4-[2-oxo-2-(pipеридин-1-ил)этил]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (240 mg, yield 97%).

[1724] \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 8.09 (1H, s), 7.91 (1H, d, \(J=8.3\) Hz), 7.77 (1H, d, \(J=8.8\) Hz), 7.25-7.22 (1H, m), 7.09 (2H, t, \(J=7.4\) Hz), 4.68 (2H, t, \(J=4.4\) Hz), 4.52 (2H, t, \(J=5.6\) Hz), 4.34-4.29 (2H, m), 3.96 (3H, s), 3.79-3.69 (2H, m), 3.44 (2H, t, \(J=4.2\) Hz), 3.02-2.84 (3H, m), 2.38-2.23 (2H, m), 2.12-2.00 (2H, m), 1.95-1.77 (5H, m), 1.69-1.33 (7H, m).

Step 8: Production of methyl 12-cyclohexyl-4-[2-(pipеридин-1-ил)этил]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (Example 2-507)

[1725]

[1726] To a solution of methyl 12-cyclohexyl-4-[2-oxo-2-(pipеридин-1-ил)этил]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (254 mg, 0.49 mmol) in tetrahydrofuran (1 ml) was added a solution (1 ml) of 1M BH\(_3\)-THF complex in tetrahydrofuran, and the mixture was stirred at room temperature for 3 hr. 2N Hydrochloric acid (2 ml) was added to the reaction mixture, and the mixture was stirred at 70°C for 4 hr. The reaction mixture was allowed to cool to room temperature, and the reaction mixture was neutralized by adding aqueous sodium hydroxide solution and saturated aqueous sodium hydroxide solution. Water was added, and the precipitated solid was collected by filtration and washed with water. The obtained solid was dried in vacuo to give methyl 12-cyclohexyl-4-[2-(pipеридин-1-ил)этил]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (240 mg, yield 97%).
Step 9: Production of 12-cyclohexyl-4-[2-(piperidin-1-yl)ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylic acid hydrochloride (Example 2-53)

Example 2-57

Production of (E)-3-[4-{[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carbonyl)amino]cyclobutanecarbonyl}amino]phenyl}acrylic acid

Step 1: Production of ethyl (E)-3-[4-{[(1-tert-butoxycarbonylaminocyclobutanecarbonyl)amino]phenyl}acrylate

[1729] To a solution of methyl 12-cyclohexyl-4-[2-(piperidin-1-yl)ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (240 mg, 0.48 mmol) in tetrahydrofuran (4 ml) and methanol (4 ml) was added 4N aqueous sodium hydroxide (2.5 ml), and the reaction mixture was stirred at 60°C for 2 hr. 2N Hydrochloric acid (5.1 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran (2:1). The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the obtained residue in tetrahydrofuran (1 ml) was added 4N HCl-ethyl acetate solution (2 ml). The solvent was evaporated under reduced pressure, and hexanecetyl acetate (4:1) solution was added to the obtained residue. The precipitated solid was collected by filtration and washed with hexanecetyl acetate (4:1) solution. The obtained solid was dried in vacuo to give 12-cyclohexyl-4-[2-(piperidin-1-yl)ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylic acid hydrochloride (160 mg, yield 64%).

[1730] 1H-NMR(400 MHz, DMSO-d6); δ(ppm) 12.59 (1H, brs), 10.26 (1H, brs), 8.20 (1H, s), 7.88 (1H, d, J=8.3 Hz), 7.63 (1H, d, J=8.3, 1.4 Hz), 7.32 (1H, t, J=7.9 Hz), 7.25 (1H, d, J=8.3 Hz), 7.07 (1H, dd, J=7.4, 1.4 Hz), 4.54-4.25 (2H, m), 3.63-3.46 (4H, m), 3.13-2.99 (2H, m), 2.93-2.85 (1H, m), 2.07-1.96 (2H, m), 1.86-1.65 (9H, m), 1.46-1.21 (5H, m).

[1731] MS 489.2 (M+1).

[1733] To a solution of ethyl 4-aminocinnamate (1.00 g, 5.23 mmol) and 1-tert-butoxycarbonylaminocyclobutanecarbonyl chloride (1.24 g, 5.75 mmol) in N,N-dimethylformamide (10 ml) were added 1-hydroxybenzotriazole monohydrate (1.44 g, 9.41 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.80 g, 9.41 mmol) under ice-cooling, and the mixture was stirred at room temperature for 21 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and hexane: diethyl ether (2:3) solution was added to the obtained residue. The precipitated solid was collected by filtration and washed with hexane: diethyl ether (2:3) solution. The obtained solid was dried in vacuo to give ethyl (E)-3-[4-{[(1-tert-butoxycarbonylaminocyclobutanecarbonyl)amino]phenyl}acrylate (943 mg, yield 46%).

[1734] 1H-NMR(400 MHz, CDCl3); δ(ppm) 9.43 (1H, s), 7.64 (1H, d, J=16.2 Hz), 7.58 (2H, d, J=8.8 Hz), 7.49 (2H, d, J=8.3 Hz), 6.36 (1H, d, J=15.8 Hz), 5.08 (1H, s), 4.26 (2H, q, J=7.3 Hz), 2.83-2.77 (2H, m), 2.21-1.93 (4H, m), 1.46 (9H, s), 1.33 (3H, t, J=7.7 Hz).

Step 2: Production of ethyl (E)-3-[4-{[1-aminocyclobutanecarbonyl]amino}phenyl]acrylate hydrochloride

[1735]
[1736] To a solution of ethyl (E)-3-[4-{(1-tert-butoxycarbonylaminocyclobutanecarbonyl)amino}[phenyl]acrylate (943 mg, 2.43 mmol) in chloroform (10 ml) was added 4N HCl-ethyl acetate solution (10 ml) under ice-cooling, and the mixture was stirred for 4 hr. The solvent was evaporated under reduced pressure and hexane: diethyl ether (1:1) solution was added to the obtained residue. The precipitated solid was collected by filtration and washed with hexane: diethyl ether (1:1) solution. The obtained solid was dried in vacuo to give ethyl (E)-3-[4-{(1-amino-cyclobutanecarbonyl)amino}[phenyl]acrylate hydrochloride (720 mg, yield 91%).

[1737] 1H-NMR(400 MHz, DMSO-d6): δ(ppm) 10.73 (1H, s), 8.94 (3H, s), 7.80 (2H, d, J=8.3 Hz), 7.72 (2H, d, J=8.8 Hz), 7.59 (1H, d, J=15.8 Hz), 6.55 (1H, d, J=15.8 Hz), 4.17 (2H, q, J=7.1 Hz), 2.80-2.73 (2H, m), 2.35-2.20 (3H, m), 2.01-1.91 (1H, m), 1.24 (3H, t, J=7.2 Hz).

Step 3: Production of ethyl (E)-3-[4-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carbonyl)amino]cyclobutanecarbonyl)amino[phenyl]acrylate (Example 2-508)

[1738]

[1739] To a solution of 12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (100 mg, 0.26 mmol) and ethyl (E)-3-[4-{(1-amino-cyclobutanecarbonyl)amino}[phenyl]acrylate hydrochloride (74 mg, 0.26 mmol) in N,N-dimethylformamide (2 ml) were added 1-hydroxybenzotriazole monohydrate (59 mg, 0.38 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (73 mg, 0.38 mmol) and triethylamine (78 μl, 0.56 mmol) under ice-cooling, and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel chromatography (hexane/ethyl acetate=2:1:1:2). Hexane: diethyl ether (1:1) solution was added to the obtained residue, and the precipitated solid was collected by filtration, and washed with hexane: diethyl ether (1:1) solution. The obtained solid was dried in vacuo to give ethyl (E)-3-[4-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carbonyl)amino]cyclobutanecarbonyl)amino[phenyl]acrylate (102 mg, yield 60%).

[1740] 1H-NMR(400 MHz, CDCl3): δ(ppm) 10.20 (1H, s), 7.94 (1H, s), 7.89 (1H, d, J=8.3 Hz), 7.65-7.61 (3H, m), 7.48 (2H, d, J=8.3 Hz), 7.35 (2H, t, J=9.0 Hz), 6.86 (1H, d, J=8.3 Hz), 6.80 (1H, s), 6.73 (1H, s), 6.35 (1H, d, J=15.8 Hz), 4.51 (2H, t, J=5.3 Hz), 4.34-4.28 (2H, m), 4.25 (2H, q, J=7.1 Hz), 3.88 (3H, s), 3.03-2.90 (3H, m), 2.45-2.36 (2H, m), 2.12-1.98 (4H, m), 1.91-1.76 (5H, m), 1.43-1.28 (6H, m).
Step 4: Production of (E)-3-4-[4-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carbonylamino)cyclobutanecarbonylamino)phenyl]acrylic acid

(Example 2-57)

[1741]

[1742] To a solution of ethyl (E)-3-4-{4-[1-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carbonylamino)cyclobutanecarbonylamino)phenyl]acrylate (102 mg, 0.154 mmol) in tetrahydrofuran (3 ml) and methanol (2 ml), was added 2N aqueous sodium hydroxide solution (1.2 ml), and the mixture was stirred at room temperature for 17 hr. 2N Hydrochloric acid (1.3 ml) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. Hexane: diethyl ether (1:1) solution was added to the obtained residue, and the precipitated solid was collected by filtration and washed with hexane: diethyl ether (1:1) solution. The obtained solid was dried in vacuo to give (E)-3-4-{4-[1-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carbonylamino)cyclobutanecarbonylamino)phenyl]acrylic acid (84 mg, yield 86%).

[1743] 1H-NMR(300 MHz, DMSO-d6): δ(ppm) 12.22 (1H, s), 9.67 (1H, s), 8.74 (1H, s), 8.21 (1H, s), 7.83 (1H, d, J=8.4 Hz), 7.68-7.58 (5H, m), 7.50 (1H, d, J=16.1 Hz), 7.35 (1H, d, J=8.4 Hz), 6.95 (1H, dd, J=8.6, 2.8 Hz), 6.83 (1H, d, J=2.6 Hz), 6.39 (1H, d, J=16.1 Hz), 4.50-4.43 (2H, m), 4.40-4.32 (2H, m), 3.83 (3H, s), 2.91-2.81 (1H, m), 2.80-2.69 (2H, m), 2.41-2.30 (2H, m), 2.08-1.69 (9H, m), 1.44-1.23 (3H, m).

[1744] MS 634.3(M+1).

[1745] Example 1-520

Production of N-acetyl-13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide dihydrochloride

Step 1: Production of 4-methyl-3-nitrobenzenesulfonyl chloride

[1746] To a mixed solution of fuming nitric acid (3.5 ml) and conc. sulfuric acid (5.4 ml) was added p-toluenesulfonyl chloride (5.00 g, 26.2 mmol) in several portions under ice-cooling, and the mixture was stirred under ice-cooling for 2 hr. To the reaction mixture was added ice, and the mixture was extracted with diethyl ether. The organic layer was successively washed with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure to give 4-methyl-3-nitrobenzenesulfonyl chloride (5.43 g, yield 88.0%).
ether and dried in vacuo to give N-tert-butyl-4-((E)-2-dimethylaminovinyl)-3-nitrobenzenesulfonyamide (5.41 g, yield 76.6%).

[1753] 1H-NMR(400 MHz, CDCl₃): δ(ppm) (1H, d, J=1.9 Hz), 8.74-7.71 (1H, m), 7.51 (1H, d, J=8.2 Hz), 7.16 (1H, d, J=10.7 Hz), 5.95 (1H, d, J=6.7 Hz), 4.56 (1H, s), 3.00 (6H, s), 1.26 (9H, s).

Step 4: Production of N-tert-butyl-1H-indole-6-sulfonyamide

[1754]

[1754] A suspension of N-tert-butyl-4-((E)-2-dimethylaminovinyl)-3-nitrobenzenesulfonyamide (5.41 g, 16.5 mmol) and 7.5% palladium/carbon (500 mg) in tetrahydrofuran (50 ml) and ethanol (50 ml) was stirred at room temperature for 3.5 hr under a hydrogen atmosphere of 3.5 atm. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. Ethyl acetate was added to the residue, and the mixture was successively washed with 1N hydrochloric acid and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure to give N-tert-butyl-1H-indole-6-sulfonamide (3.62 g, yield 87.1%).

[1756] MS 253.1(M+1).

Step 5: Production of N-tert-butyl-3-(cyclohex-1-enyl)-1H-indole-6-sulfonamide

[1757]
To a solution of N-tert-butyl-1H-indole-6-sulfonamide (3.60 g, 14.2 mmol) and cyclohexanone (4.50 ml, 43.4 mmol) in methanol (72 ml) was added 28% sodium methoxide in methanol solution (17 ml), and the mixture was stirred for 12 hr with heating under reflux. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. 2N Hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexanecyclohexane=3:1:1-2:1) to give N-tert-butyl-3-(cyclohex-1-enyl)-1H-indole-6-sulfonamide (2.82 g, yield 59.7%).

To a solution of N-tert-butyl-3-(cyclohex-1-enyl)-1H-indole-6-sulfonamide (2.82 g, 6.86 mmol) in chloroform (30 ml) was added pyridinium hydrobromide perbromide (2.40 g, 7.50 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 30 min. 1M aqueous sodium hydrogen sulfite solution was added to the reaction mixture and the mixture was extracted with chloroform. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. A mixed solvent of hexanoehexane (5:1) was added to the residue. The precipitated solid was collected by filtration and dried in vacuo to give N-tert-butyl-2-bromo-3-cyclohexyl-1H-indole-6-sulfonamide (2.19 g, yield 78.3%).
Step 8: Production of N-tert-butyl-2-(2-amino-4-methylphenyl)-3-cyclohexyl-1H-indole-6-sulfonamide

\[ \text{N-tert-butyl-2-(2-amino-4-methylphenyl)-3-cyclohexyl-1H-indole-6-sulfonamide} \]

[1766]

To a suspension of N-tert-butyl-2-bromo-3-cyclohexyl-1H-indole-6-sulfonamide (2.10 g, 5.08 mmol) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-methylphenylamine (1.86 g, 8.00 mmol) in 1,2-dimethoxyethane (20 ml) and water (10 ml) were added sodium hydrogen carbonate (1.60 g, 19.2 mmol) and tetrakis(triphenylphosphine)palladium (176 mg, 0.15 mmol), and the mixture was heated under reflux for 14 hr. The reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture and the mixture was extracted with toluene. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and diisopropyl ether was added to the residue. The precipitated solid was collected by filtration and dried in vacuo to give N-tert-butyl-2-(2-amino-4-methylphenyl)-3-cyclohexyl-1H-indole-6-sulfonamide (2.14 g, yield 96.3%).

[1768] \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) 8.23 (1H, s), 7.90 (1H, d, J=1.8 Hz), 7.86 (1H, d, J=8.4 Hz), 7.55 (1H, dd, J=8.4, 1.8 Hz), 7.07 (1H, d, J=7.7 Hz), 6.67 (1H, d, J=8.1 Hz), 6.64 (1H, s), 4.43 (1H, s), 3.72 (2H, s), 2.76-2.68 (1H, m), 2.34 (3H, s), 1.89-1.84 (7H, m), 1.30-1.23 (3H, m), 1.25 (9H, s).

Step 9: Production of N-tert-butyl-2-[2-(chloroacetylamino)-4-methylphenyl]-3-cyclohexyl-1H-indole-6-sulfonamide

[1769]

[1767] To a suspension of N-tert-butyl-2-bromo-3-cyclohexyl-1H-indole-6-sulfonamide (2.10 g, 5.08 mmol) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-methylphenylamine (1.86 g, 8.00 mmol) in 1,2-dimethoxyethane (20 ml) and water (10 ml) were added sodium hydrogen carbonate (1.60 g, 19.2 mmol) and tetrakis(triphenylphosphine)palladium (176 mg, 0.15 mmol), and the mixture was heated under reflux for 14 hr. The reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture and the mixture was extracted with toluene. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and diisopropyl ether was added to the residue. The precipitated solid was collected by filtration and dried in vacuo to give N-tert-butyl-2-[2-(chloroacetylamino)-4-methylphenyl]-3-cyclohexyl-1H-indole-6-sulfonamide (2.14 g, 4.86 mmol), sodium acetate (472 mg, 5.75 mmol) and acetic acid (0.33 ml, 5.76 mmol) in tetrahydrofuran (20 ml) was added dropwise chloroacetyl chloride (0.45 ml, 5.64 mmol) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and water was added to the residue. The precipitated solid was collected by filtration and dried in vacuo. A suspension of the obtained solid in diethyl ether was stirred at room temperature for 1 hr. The solid was collected by filtration and dried in vacuo to give N-tert-butyl-2-[2-(chloroacetylamino)-4-methylphenyl]-3-cyclohexyl-1H-indole-6-sulfonamide (2.22 g, yield 89.9%). The obtained crude product was used for Step 10 without further purification.

[1770]
Step 10: Production of N-tert-butyl-13-cyclohexyl-3-methyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-α]indole-10-sulfonamide (Example 1-604)

[1774] A suspension of N-tert-butyl-13-cyclohexyl-3-methyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-α]indole-10-sulfonamide (150 mg, 0.31 mmol), 1-(2-chloroacetyl)piperidine (55 mg, 0.34 mmol) and potassium carbonate (107 mg, 0.77 mmol) in N,N-dimethylformamide (2 ml) was stirred at 80°C for 2 hr. The reaction mixture was allowed to cool to room temperature, and 2N hydrochloric acid and water were added to the reaction mixture. The precipitated solid was collected by filtration and dried in vacuo to give N-tert-butyl-13-cyclohexyl-3-methyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-α]indole-10-sulfonamide (202 mg, 0.21 mmol, 69%).
yield 100%). The obtained crude product was used for Step 12 without further purification.

Step 12: Production of N-tert-butyl-13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (Example 1-606)

[1778] MS 577.1(M+1).

Step 13: Production of 13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (Example 1-607)

[1779] A solution of N-tert-butyl-13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (169 mg, 0.29 mmol) in trifluoroacetic acid (2 ml) was stirred at 60°C for 1 hr. The mixture was allowed to cool to room temperature and concentrated under reduced pressure. Saturated aqueous sodium carbonate solution was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give N-tert-butyl-13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (152 mg, yield 100%).

[1780] MS 521.2(M+1).
Step 14: Production of N-acetyl-13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide dihydrochloride (Example 1-520)

![Chemical structure image]

J=8.4 Hz), 7.48 (1H, dd, J=8.6, 1.7 Hz), 7.26 (1H, d, J=7.3 Hz), 7.19 (1H, s), 7.10 (1H, d, J=7.7 Hz), 3.62-3.58 (4H, m), 3.10-3.07 (4H, m), 2.85-2.82 (1H, m), 2.62-2.57 (2H, m), 2.42 (3H, s), 1.99-1.95 (2H, m), 1.91 (3H, s), 1.88-1.75 (4H, m), 1.79-1.70 (2H, m), 1.34-1.12 (6H, m).

Example 1-567

Production of 13-cyclohexyl-3,5,6-trimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid

Step 1: Production of methyl 2-bromo-3-cyclohexyl-1-(2-oxopropyl)-1H-indole-6-carboxylate

![Chemical structure image]

[1783] To a suspension of 13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (152 mg, 0.29 mmol) and potassium carbonate (88 mg, 0.63 mmol) in acetone (2 ml) was added acetyl chloride (0.02 ml, 0.30 mmol), and the mixture was stirred at room temperature for 12 hr. 2N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (chloroform:methanol=20:1-10:1) to give N-acetyl-13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide. To a solution of the obtained N-acetyl-13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide in ethyl acetate was added 4N HCl-ethyl acetate solution (2 ml), and the mixture was concentrated under reduced pressure. Hexane was added to the residue. The precipitated solid was collected by filtration and dried in vacuo to give N-acetyl-13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide dihydrochloride (74 mg, yield 40%).

[1784] 1H-NMR(300 MHz, DMSO-d6); δ(ppm) 11.91 (1H, s), 9.96 (1H, s), 8.12 (1H, d, J=2.4 Hz), 7.98 (1H, d, J=8.4 Hz), 7.48 (1H, dd, J=8.6, 1.7 Hz), 7.26 (1H, d, J=7.3 Hz), 7.19 (1H, s), 7.10 (1H, d, J=7.7 Hz), 3.62-3.58 (4H, m), 3.10-3.07 (4H, m), 2.85-2.82 (1H, m), 2.62-2.57 (2H, m), 2.42 (3H, s), 1.99-1.95 (2H, m), 1.91 (3H, s), 1.88-1.75 (4H, m), 1.79-1.70 (2H, m), 1.34-1.12 (6H, m).

[1787] To a solution of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (2.00 g, 5.95 mmol) obtained in the same manner as in the method described in WO03/010140 and bromoacetonitrile (0.55 ml, 6.55 mmol) in N,N-dimethylformamide (10 ml) was added sodium hydride (60% in oil) (262 mg, 6.55 mmol) under ice-cooling, and the mixture was stirred for 2 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane:ethyl acetate=4:1) to give methyl 2-bromo-3-cyclohexyl-1-(2-oxopropyl)-1H-indole-6-carboxylate (1.72 g, yield 74%).

[1788] 1H-NMR(400 MHz, CDCl3); δ(ppm) 7.83(1H, s), 7.79-7.71(2H, m), 4.92(2H, s), 3.91(3H, s), 2.93-2.83(1H, m), 2.08(3H, s), 1.98-1.74(7H, m), 1.49-1.31(3H, m).
Step 2: Production of methyl 2-(2-amino-4-methylphenyl)-3-cyclohexyl-1-(2-oxopropyl)-1H-indole-6-carboxylate

![Chemical structure 1]

Step 3: Production of methyl 13-cyclohexyl-3,6-dimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-608)

![Chemical structure 2]

[1789] To a suspension of methyl 2-bromo-3-cyclohexyl-1-(2-oxopropyl)-1H-indole-6-carboxylate (700 mg, 1.78 mmol) and 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine (456 mg, 1.96 mmol) in 1,2-dimethoxyethane (6 ml) and water (2 ml) were added sodium hydrogen carbonate (177 mg, 2.14 mmol) and tetrakis(triphenylphosphine)palladium (103 mg, 0.09 mmol), and the mixture was heated under reflux for 4 hr. The reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=2:1) to give methyl 2-(2-amino-4-methylphenyl)-3-cyclohexyl-1-(2-oxopropyl)-1H-indole-6-carboxylate (727 mg, yield 97%).

[1791] 1H-NMR (400 MHz, CDCl3): δ (ppm) 8.14 (1H, s), 7.88 (1H, d, J=8.8 Hz), 7.76 (1H, d, J=8.8 Hz), 7.40 (1H, d, J=8.0 Hz), 7.17 (1H, s), 7.12 (1H, d, J=8.0 Hz), 4.88 (1H, d, J=13.6 Hz), 4.15 (1H, d, J=13.6 Hz), 3.95 (3H, s), 3.00-2.91 (1H, m), 2.44 (3H, s), 2.32 (3H, s), 2.10-1.98 (3H, m), 1.81-1.72 (2H, m), 1.68-1.59 (1H, m), 1.50-1.29 (4H, m).

[1793] To a solution of methyl 2-(2-amino-4-methylphenyl)-3-cyclohexyl-1-(2-oxopropyl)-1H-indole-6-carboxylate (727 mg, 1.74 mmol) in tetrahydrofuran (10 ml) and acetic acid (3 ml) was added sodium triacetoxyborohydride (736 mg, 3.47 mmol) at room temperature, and the mixture was stirred for 1 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous sodium hydrogen carbonate and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=2:1) to give methyl 13-cyclohexyl-3,6-dimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (578 mg, yield 83%).

[1794] 1H-NMR (400 MHz, CDCl3): δ (ppm) 8.04 (1H, s), 7.85 (1H, d, J=8.4 Hz), 7.72 (1H, dd, J=8.4, 1.6 Hz), 7.24 (1H, d, J=7.6 Hz), 6.88 (1H, d, J=7.6 Hz), 6.71 (1H, s), 4.29-4.26 (1H, m), 3.93 (3H, s), 3.97-3.88 (2H, m), 2.97-2.88 (1H, m), 2.35 (3H, s), 2.12-1.99 (2H, m), 1.92-1.72 (5H, m), 1.66-1.53 (1H, m), 1.41-1.30 (3H, m), 1.21 (3H, d, J=6.4 Hz),
Step 4: Production of methyl 13-cyclohexyl-3,5,6-
trimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino
[7,1-a]indole-10-carboxylate (Example 1-609)

[1795]

Step 5: Production of 13-cyclohexyl-3,5,6-trimethyl-
6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-
a]indole-10-carboxylic acid (Example 1-567)

[1798]

[1796] To a solution of methyl 13-cyclohexyl-3,6-dimeth-
ethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]ind-
ole-10-carboxylate (150 mg, 0.373 mmol) in 37% aqueous
formalin solution (1.5 ml), chloroform (3 ml) and acetic
acid (0.3 ml) was added sodium triacetoxyborohydride (395
mg, 1.86 mmol) at room temperature, and the mixture was
stirred overnight. Water was added to the reaction mixture
and the mixture was extracted with ethyl acetate. The
organic layer was successively washed with saturated aq-
eous sodium hydrogen carbonate and saturated brine and
dried over anhydrous magnesium sulfate. After filtration,
the solvent was evaporated under reduced pressure to give
methyl 13-cyclohexyl-3,5,6-trimethyl-6,7-dihydro-5H-
benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (155
mg, yield 98%).

[1797] 1H-NMR (400 MHz, CDCl₃): δ (ppm) 8.05 (1H, s),
7.84 (1H, d, J=8.4 Hz), 7.71 (1H, d, J=8.4, 1.2 Hz), 7.23-
7.19 (1H, m), 6.98-6.90 (2H, m), 4.41-4.30 (1H, m), 3.93 (3H,
s), 3.87-3.78 (1H, m), 3.56-3.44 (1H, m), 2.95-2.85 (1H, m),
2.76 (3H, s), 2.41 (3H, s), 2.12-1.64 (7H, m), 1.45-1.30 (3H,
m), 1.09 (3H, d, J=6.0 Hz).

[1799] To a solution of methyl 13-cyclohexyl-3,5,6-trimeth-
ethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]ind-
ole-10-carboxylate (155 mg, 0.373 mmol) in tetrahydrofur-
r (3 ml) and methanol (1 ml) was added 4N aqueous
sodium hydroxide solution (2 ml), and the mixture was
stirred at 60°C for 1 hr. The mixture was adjusted to pH 7
by adding 2N hydrochloric acid (4 ml), and extracted with
chloroform. The organic layer was washed with saturated
brine and dried over anhydrous sodium sulfate. After filtration.
the solvent was evaporated under reduced pressure, and the
residue was purified by silica gel chromatography (chloro-
form:methanol=15:1) to give 13-cyclohexyl-3,5,6-trimeth-
ethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]ind-
ole-10-carboxylic acid (100 mg, yield 67%).

[1800] 1H-NMR (400 MHz, DMSO-d₆): δ (ppm) 12.46 (1H, brs),
8.15 (1H, s) 7.79 (1H, d, J=8.4 Hz), 7.56 (1H,
d, J=8.4, 1.2 Hz), 7.21-7.09 (1H, m), 7.01-7.69 (2H, m),
4.69 (1H, brm), 3.75 (1H, brm), 2.82-2.72 (1H, m), 2.67 (3H,
s), 2.34 (3H, s), 2.04-1.60 (7H, m), 1.52-1.28 (3H, m),
0.98 (1H, d, J=5.6 Hz).

[1801] MS 403.2(M+1).
Example 1-595

Production of 13-cyclohexyl-5-{2-(piperidin-1-yl-ethyl)}-3-(pyridin-2-ylmethoxy)-6,7-dihydro-3H-benzo[5,6][1,4]diazepino[7,1-α]nucleo-10-carboxylic acid trihydrochloride

Step 1: Production of 4-benzylxy-1-iodo-2-nitrobenzene

[1802]

\[
\begin{array}{c}
\text{Ph} \\
\text{Br} \\
\end{array}
\]

[1803] To a solution of 4-ido-3-nitrophenol (5.00 g, 18.9 mmol) in acetone (50 ml) were added potassium carbonate (3.39 g, 24.6 mmol) and benzyl bromide (2.92 ml, 24.6 mmol), and the mixture was stirred at 50°C for 6 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the residue in ethyl acetate (30 ml) was added 4N HCl-ethyl acetate solution (20 ml). The precipitated solid was collected by filtration, washed with ethyl acetate and dried in vacuo to give 5-benzylxy-2-iodophenylamine hydrochloride. The obtained crude product (5.70 g) was used for Step 3 without further purification.

Step 2: Production of 5-benzylxy-2-iodophenylamine hydrochloride

[1804]

[1805] To a solution of 4-benzylxy-1-iodo-2-nitrobenzene (6.20 g, 17.5 mmol) in methanol (31 ml) were added iron trichloride hexahydrate (142 mg, 0.53 mmol) and activated carbon (1.24 g), and the mixture was stirred at 60°C for 5 min. The mixture was heated to 70°C, a solution of hydrazine monohydrate (2.55 ml) in methanol (4.3 ml) was added dropwise, and the mixture was stirred for 3 hr. After filtration through celite, the filtrate was concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the residue in ethyl acetate (30 ml) was added 4N HCl-ethyl acetate solution (20 ml). The precipitated solid was collected by filtration, washed with ethyl acetate and dried in vacuo to give 5-benzylxy-2-iodophenylamine hydrochloride. The obtained crude product (5.70 g) was used for Step 3 without further purification.

Step 3: Production of 5-benzylxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine

[1806]

[1807] To a solution of 5-benzylxy-2-iodophenylamine hydrochloride (5.70 g, 15.8 mmol) in 1,4-dioxane (86 ml) were added triethylamine (11.0 ml, 79.0 mmol) and PdCl₂(dppe)CH₂Cl₂ (645 mg, 0.79 mmol) at room temperature. To the mixture was added dropwise pinacolborane (6.86 ml, 47.4 mmol) at room temperature, and the mixture was stirred at 100°C for 12 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate = 5:1) to give 5-benzylxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine (3.93 g, yield 76%).

[1808] 1H-NMR(400 MHz, DMSO-d₆): δ(ppm) 7.42-7.25 (6H, m), 6.20-6.15 (2H, m), 5.50 (2H, s), 5.02 (2H, s), 1.26 (12H, s).
Step 4: Production of methyl 2-(2-amino-4-benzylloxyphenyl)-3-cyclohexyl-1H-indole-6-carboxylate

To a suspension of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (3.38 g, 10.0 mmol) obtained in the same manner as in the method described in WO03/010140 and 5-benzylxoy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl-2-y)phenylamine (3.93 g, 12.1 mmol) in 1,2-dimethoxyethane (70 ml) and water (35 ml) were added sodium hydrogen carbonate (2.49 g, 30.0 mmol) and tetakis(triphenylphosphine)palladium (582 mg, 0.50 mmol), and the mixture was stirred at 90°C. for 3 hr. The reaction mixture was cooled to room temperature, saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The obtained crude product (6.20 g) was used for Step 5 without further purification.

Step 5: Production of methyl 2-[4-benzylxoy-2-(2-chloroacetamino)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate

To a suspension of methyl 2-(2-amino-4-benzylloxyphenyl)-3-cyclohexyl-1H-indole-6-carboxylate (6.17 g, 13.5 mmol), sodium acetate (1.22 g, 14.9 mmol) and acetic acid (0.86 ml, 14.9 mmol) in tetrahydrofuran (62 ml) was added dropwise chloroacetyl chloride (1.19 ml, 14.9 mmol), and the mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and methanol was added. The precipitated solid was collected by filtration, washed with methanol and dried in vacuo to give methyl 2-[4-benzylxoy-2-(2-chloroacetamino)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate (3.90 g, yield 54%).

1H-NMR (400 MHz, DMSO-d6): δ(ppm) 11.38 (1H, s), 9.32 (1H, s), 7.96 (1H, d, J=0.9 Hz), 7.80 (1H, d, J=8.8 Hz), 7.66 (1H, d, J=2.3 Hz), 7.59 (1H, dd, J=8.3, 1.4 Hz), 7.50 (2H, d, J=7.9 Hz), 7.45-7.40 (2H, m), 7.35 (1H, t, J=8.6 Hz), 7.27 (1H, d, J=8.8 Hz), 6.97 (1H, dd, J=8.6, 2.6 Hz), 5.17 (2H, s), 4.20 (2H, s), 3.84 (3H, s), 2.50-2.43 (1H, m), 1.85-1.71 (7H, m), 1.34-1.13 (31H, m).
Step 6: Production of methyl 3-benzyloxy-13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-610)

To a solution of methyl 2-[4-benzyloxy-2-(2-chloroacetamino)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate (3.90 g, 7.34 mmol) in N,N-dimethylformamide (98 ml) was added 60% sodium hydride (1.08 g, 16.1 mmol) under ice-cooling, and the mixture was stirred for 5 hr. Water was added to the reaction mixture, and the precipitated solid was collected by filtration and washed with water and hexane. The obtained solid was dried in vacuo to give methyl 3-benzyloxy-13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (3.60 g, yield 99%).

Step 7: Production of methyl 3-benzyloxy-13-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-611)
A suspension of methyl 3-benzyloxy-13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzof[5,6][1,4]diazepin[7,1-a]indole-10-carboxylate (1.00 g, 2.02 mmol), 1-chloroacetylpyperidine (425 mg, 2.63 mmol) and potassium carbonate (558 mg, 4.02 mmol) in N,N-dimethylformamide (20 ml) was stirred at 90°C for 4 hr. The reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The obtained crude product was suspended in a mixed solvent (hexane/ethyl acetate=5:1) and filtered. The solid was collected by filtration and dried in vacuo to give methyl 3-benzyloxy-13-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepin[7,1-a]indole-10-carboxylate (800 mg, yield 64%).

1H-NMR (400 MHz, DMSO-d6): δ (ppm) 8.26 (1H, d, J=1.4 Hz), 7.93 (1H, d, J=8.8 Hz), 7.67 (1H, d, J=8.3, 1.4 Hz), 7.52-7.35 (6H, m), 7.18 (1H, dd, J=8.8, 2.3 Hz), 7.12 (1H, d, J=2.3 Hz), 5.19 (2H, s), 5.17 (1H, d, J=14.8 Hz), 4.68 (1H, d, J=16.2 Hz), 4.49 (1H, d, J=14.8 Hz), 4.40 (1H, d, J=16.2 Hz), 3.89 (3H, s), 3.44-3.26 (4H, m), 2.91-2.81 (1H, m), 2.10-1.83 (4H, m), 1.79-1.66 (2H, m), 1.63-1.32 (9H, m), 1.27-1.12 (11H, m).

Step 8: Production of methyl 3-cyclohexyl-3-hydroxy-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepin[7,1-a]indole-10-carboxylate (Example 1-612)

To a solution of methyl 3-benzyloxy-13-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepin[7,1-a]indole-10-carboxylate (7.40 g, 11.9 mmol) in acetic acid (15 ml) was added 25% hydrogen bromide-acetic acid solution (15 ml) and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure. Toluene was added to the residue and the mixture was concentrated to dryness under reduced pressure. The obtained crystals were suspended in a mixed solvent (hexane/ethyl acetate=3:1) and filtered. The solid was collected by filtration and dried in vacuo to give methyl 13-cyclohexyl-3-hydroxy-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepin[7,1-a]indole-10-carboxylate (6.30 g, yield 100%).

1H-NMR (400 MHz, DMSO-d6): δ (ppm) 8.24 (1H, d, J=0.9 Hz), 7.91 (1H, d, J=8.8 Hz), 7.66 (1H, dd, J=8.3, 1.4 Hz), 7.33 (1H, d, J=7.9 Hz), 6.90-6.85 (2H, m), 5.15 (1H, d, J=14.4 Hz), 4.64 (1H, d, J=16.7 Hz), 4.47 (1H, d, J=14.4 Hz), 4.31 (1H, d, J=16.7 Hz), 3.88 (3H, s), 3.51-3.26 (5H, m), 2.91-2.79 (1H, m), 2.10-1.81 (4H, m), 1.80-1.66 (2H, m), 1.64-1.33 (9H, m), 1.29-1.12 (11H, m).

Step 9: Production of methyl 13-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-3-(pyridin-2-ylmethoxy)-6,7-dihydro-5H-benzof[5,6][1,4]diazepin[7,1-a]indole-10-carboxylate (Example 1-613)

A suspension of methyl 13-cyclohexyl-3-hydroxy-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepin[7,1-a]indole-10-carboxylate (400 mg, 0.76 mmol), 2-chloromethylpyridine hydrochloride (186 mg, 1.14 mmol), potassium carbonate (315 mg, 2.28 mmol) and potassium iodide (63.0 mg, 0.38 mmol) in N,N-dimethylformamide (8 ml) was stirred at 80°C for 3 hr. The reaction mixture was allowed to cool to room temperature and 1N aqueous hydrochloric acid solution was added to the reaction mixture. The precipitated solid was collected by filtration, washed with water and dried in vacuo. The obtained crude product (393 mg) was used for Step without further purification.
Step 10: Production of methyl 13-cyclohexyl-5\[2-(piperidin-1-yl)ethyl\]-3-(piperidin-2-ylmethoxy)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-614)

[1825]

Step 11: Production of 13-cyclohexyl-5\[2-(piperidin-1-yl)ethyl\]-3-(piperidin-2-ylmethoxy)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid trihydrochloride (Example 1-595)

[1827]

[1826] To a solution of methyl 13-cyclohexyl-6-oxo-5\[2-oxo-2-(piperidin-1-yl)ethyl\]-3-(pyridin-2-ylmethoxy)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (393 mg, 0.63 mmol) in tetrahydrofuran (1.2 ml) was added a solution (3.2 ml) of 1M BH₃ THF complex in tetrahydrofuran under ice-cooling, and the mixture was stirred at room temperature for 3 hr. 4N Aqueous hydrochloric acid solution (4.4 ml) was added to the reaction mixture, and the mixture was stirred at 60° C. for 12 hr. The reaction mixture was allowed to cool to room temperature. The reaction mixture was adjusted to pH 7 with 1N aqueous sodium hydroxide solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The obtained crude product (298 mg) was used for Step 11 without further purification.

[1828] To a solution of methyl 13-cyclohexyl-5\[2-(piperidin-1-yl)ethyl\]-3-(piperidin-2-ylmethoxy)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (298 mg, 0.50 mmol) in tetrahydrofuran (6 ml) and methanol (3 ml) was added 4N aqueous sodium hydroxide solution (3 ml), and the mixture was stirred at room temperature for 24 hr. The reaction solution was adjusted to pH 7 with 1N aqueous hydrochloric acid solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was concentrated under reduced pressure. Ethyl acetate (6 ml) and 4N HCl-ethyl acetate solution (3 ml) were added to the crude product at room temperature, and the mixture was concentrated under reduced pressure. The obtained solid was suspended in diethyl ether, collected by filtration and washed with diethyl ether. The solid was dried in vacuo to give 13-cyclohexyl-5\[2-(piperidin-1-yl)ethyl\]-3-(pyridin-2-ylmethoxy)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid trihydrochloride (242 mg, yield 70%).

[1829] ¹H-NMR(400 MHz, DMSO-d₆): δ(ppm) 10.08 (1H, br s), 8.71 (1H, d, J=4.6 Hz), 8.15 (1H, d, J=1.4 Hz), 8.09 (1H, t, J=7.2 Hz), 7.82 (1H, d, J=8.8 Hz), 7.78 (1H, d, J=7.4 Hz), 7.59 (1H, dd, J=8.6, 1.2 Hz), 7.56 (1H, d, J=5.6 Hz), 7.30 (1H, d, J=8.3 Hz), 7.01 (1H, d, J=2.3 Hz), 6.97 (1H, dd, J=8.3, 2.3 Hz), 5.38 (2H, s), 4.98-4.42 (1H, m), 3.94-3.36 (2H, m), 3.20-3.01 (4H, m), 2.81 (1H, t, J=12.1 Hz), 2.59-2.50 (2H, m), 2.05-1.96 (3H, m), 1.89-1.73 (6H, m), 1.48-1.28 (9H, m), 1.10-1.00 (1H, m).

[1830] MS 579.3(M+1).
Example 2-175

Production of methyl (S)-2-[[12-cyclohexyl-6,7-
dihydro-5-oxa-7-azadibenzo[a,e]azulene-9-carbonyl-amino]-3-(4-hydroxyphenyl)propionate

Step 1: Production of 12-cyclohexyl-6,7-dihydro-5-oxa-7-azadibenzo[a,e]azulene-9-carbonyl chloride

[1831]

Step 2: Production of methyl (S)-2-[[12-cyclohexyl-6,7-dihydro-5-oxa-7-azadibenzo[a,e]azulene-9-carbonyl-amino]-3-(4-hydroxyphenyl)propionate (Example 2-175)

[1834]

To a solution of 12-cyclohexyl-6,7-dihydro-5-oxa-7-azadibenzo[a,e]azulene-9-carbonyl chloride (100 mg, 0.26 mmol) in chloroform (2 ml) was added methyl (S)-2-amino-3-(4-hydroxyphenyl)propionate (154 mg, 0.78 mmol). The mixture was stirred at room temperature for 2 hr, 1N hydrochloric acid was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration and concentration, diethyl ether was added to the obtained residue, and the precipitated solid was collected by filtration. The solid was washed with diethyl ether to give methyl (S)-2-[[12-cyclohexyl-6,7-dihydro-5-oxa-7-azadibenzo[a,e]azulene-9-carbonyl amino]-3-(4-hydroxyphenyl)propionate (102 mg, yield 82%).

[1835]

1H-NMR (400 MHz, DMSO-d6): δ (ppm) 9.18 (1H, s), 8.58 (1H, d, J=7.4 Hz), 8.08 (1H, d, J=0.9 Hz), 7.85 (1H, d, J=8.3 Hz), 7.53-7.42 (3H, m), 7.35 (1H, dd, J=7.4, 0.9 Hz), 7.25 (1H, dd, J=8.1, 1.2 Hz), 7.09 (2H, d, J=8.3 Hz), 6.65 (2H, d, J=5.8 Hz), 4.64-4.59 (1H, m), 4.46 (2H, t, J=5.6 Hz), 4.32 (2H, s), 3.64 (3H, s), 3.08-2.98 (2H, m), 2.88 (1H, t, J=12.3 Hz), 2.05-1.94 (1H, m), 1.89-1.70 (6H, m), 1.43-1.23 (3H, m).

[1836]

MS 539.3(M+1).
Example 2-180
Production of (S)-2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azidobenzof[\(\alpha\),\(e\)]azulene-9-carbonylamino)-3-(4-hydroxyphenyl)propionic acid

[1838]

Example 2-298
Production of 12-cyclohexyl-4-(pyridin-3-yl)-6,7-dihydro-5-oxa-7a-azidobenzof[\(\alpha\),\(e\)]azulene-9-carboxylic acid hydrochloride

Step 1: Production of methyl 12-cyclohexyl-4-trifluoromethanesulfonyloxy-6,7-dihydro-5-oxa-7a-azidobenzof[\(\alpha\),\(e\)]azulene-9-carboxylate (Example 2-509)

[1842]

[1839] To a solution of methyl (S)-2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azidobenzof[\(\alpha\),\(e\)]azulene-9-carbonylamino)-3-(4-hydroxyphenyl)propionate (87 mg, 0.16 mmol) in tetrahydrofuran (2 ml) and methanol (1 ml) was added 4N aqueous sodium hydroxide solution (1 ml), and the mixture was stirred at room temperature for 12 hr. The mixture was adjusted to pH 6.5 with 1N hydrochloric acid (4 ml) and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration and concentration, diethyl ether was added to the obtained residue, and the precipitated solid was collected by filtration. The solid was washed with diethyl ether to give (S)-2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azidobenzof[\(\alpha\),\(e\)]azulene-9-carbonylamino)-3-(4-hydroxyphenyl)propionic acid (61 mg, yield 74%).

[1840] 1H-NMR(400 MHz, DMSO-d_6): \(\delta\) (ppm) 8.15-8.03 (2H, m), 7.83 (1H, d, \(J=8.3\) Hz), 7.43-7.36 (3H, m), 7.34 (1H, dd, \(J=15.3, 7.9, 6.5\) Hz), 7.24 (1H, dd, \(J=7.9, 1.4\) Hz), 7.02 (2H, d, \(J=8.3\) Hz), 6.58 (2H, d, \(J=8.8\) Hz), 4.45 (2H, t, \(J=5.3\) Hz), 4.25-4.40 (3H, m), 3.10 (1H, dd, \(J=4.6, 13.4\) Hz), 2.97 (1H, dd, \(J=7.9, 13.4\) Hz), 2.88 (1H, dd, \(J=13.2, 10.9\) Hz), 2.04-2.01 (2H, m), 1.82-1.76 (5H, m), 1.36-1.29 (3H, m).

[1841] MS 525.3(M+1).

[1843] To a solution of methyl 12-cyclohexyl-4-hydroxy-6,7-dihydro-5-oxa-7a-azidobenzof[\(\alpha\),\(e\)]azulene-9-carboxylate (1.00 g, 2.55 mmol) obtained in the same manner as in Step 6 of Example 2-53 and triethylamine (427 \(\mu\)l, 3.06 mmol) in chloroform (10 ml) was added dropwise trifluoromethanesulfonic anhydride (476 \(\mu\)l, 2.81 mmol) under ice-cooling, and the mixture was stirred for 3 hr. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 12-cyclohexyl-4-trifluoromethanesulfonyloxy-6,7-dihydro-5-oxa-7a-azidobenzof[\(\alpha\),\(e\)]azulene-9-carboxylate (1.30 g, yield 97%).

[1844] 1H-NMR(400 MHz, CDCl_3): \(\delta\) (ppm) 8.27 (1H, d, \(J=1.4\) Hz), 7.97 (1H, d, \(J=8.4\) Hz), 7.68 (1H, dd, \(J=8.4, 1.4\) Hz), 7.63 (1H, dd, \(J=7.9, 1.9\) Hz), 7.54 (1H, dd, \(J=7.9, 1.9\) Hz), 7.49 (1H, t, \(J=7.9\) Hz), 4.62 (2H, t, \(J=5.1\) Hz), 4.52 (1H, brs), 3.88 (3H, s), 2.87 (1H, brt, \(J=12.3\) Hz), 2.10-1.96 (2H, m), 1.86-1.68 (5H, m), 1.48-1.26 (3H, m).
Step 2: Production of methyl 12-cyclohexyl-4-(pyridin-3-yl)-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulene-9-carboxylate (Example 2-510)

[1845]

\[
\text{MeOOC} \quad \text{OTf} \quad \text{N}_{\text{SO}_{2}} \quad \text{MeOOC}
\]

Step 3: Production of 12-cyclohexyl-4-(pyridin-3-yl)-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulene-9-carboxylic acid hydrochloride (Example 2-298)

[1848]

\[
\text{MeOOC} \quad \text{N}_{\text{SO}_{2}} \quad \text{MeOOC} \quad \text{HOOC} 
\]

[1846] To a suspension of methyl 12-cyclohexyl-4-trifluoromethanesulfonyl-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulene-9-carboxylate (130 mg, 0.248 mmol), 3-(1,3,2-dioxaborinan-2-yl)pyridine (53 mg, 0.323 mmol) and sodium hydroxide carbonate (62 mg, 0.744 mmol) in 1,2-dimethoxyethane (2 ml) and water (0.75 ml) was added tetrakis(triphenyolphosphine) palladium (16 mg, 0.014 mmol), and the mixture was heated at 90°C for 3 hr. The reaction mixture was cooled to room temperature, saturated aqueous sodium hydroxide carbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated sodium hydroxide carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:2) to give methyl 12-cyclohexyl-4-(pyridin-3-yl)-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulene-9-carboxylate (92 mg, yield 82%).

[1847] \(^1\text{H-NMR}(400 \text{ MHz, DMSO-}d_6); \delta (\text{ppm}) 8.77 (1H, d, J=2.2 \text{ Hz}), 8.60 (1H, dd, J=6.3, 2.2 \text{ Hz}), 8.25 (1H, d, J=1.5 \text{ Hz}), 8.00 (1H, dt, J=8.0, 2.2 \text{ Hz}), 7.94 (1H, d, J=8.5 \text{ Hz}), 7.66 (1H, dd, J=8.5, 1.5 \text{ Hz}), 7.57 (1H, dd, J=6.3, 2.2 \text{ Hz}), 7.53-7.44 (3H, m), 4.46 (2H, brs), 4.34 (2H, brs), 3.87 (3H, s), 2.92 (1H, brt, J=11.6 \text{ Hz}), 2.12-1.97 (2H, m), 1.89-1.70 (5H, m), 1.48-1.27 (3H, m).

[1849] To a solution of methyl 12-cyclohexyl-4-(pyridin-3-yl)-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulene-9-carboxylate (130 mg, 0.203 mmol) in tetrahydrofuran (2 ml) and methanol (2 ml) was added 4N aqueous sodium hydroxide solution (1 ml), and the mixture was stirred at room temperature for 12 hr. The reaction mixture was adjusted to pH 6.5 with 2N hydrochloric acid, and extracted with chloroform. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To a solution of the residue in chloroform was added 4N HCl-ethyl acetate solution (0.5 ml), and the solvent was evaporated under reduced pressure. A mixed solvent (hexane:ethyl acetate=4:1) was added to the residue. The precipitated solid was collected by filtration to give 12-cyclohexyl-4-(pyridin-3-yl)-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulene-9-carboxylic acid hydrochloride (88 mg, yield 91%).

[1850] \(^1\text{H-NMR}(400 \text{ MHz, DMSO-}d_6); \delta (\text{ppm}) 9.01 (1H, s), 8.82 (1H, d, J=5.1 \text{ Hz}), 8.50 (1H, d, J=7.9 \text{ Hz}), 8.23 (1H, d, J=0.9 \text{ Hz}), 7.92 (2H, d, J=8.3 \text{ Hz}), 7.68-7.63 (2H, m), 7.58-7.50 (2H, m), 4.48 (2H, brs), 4.37 (2H, brs), 2.91 (1H, br t, J=11.8 \text{ Hz}), 2.12-1.98 (2H, m), 1.90-1.69 (5H, m), 1.49-1.22 (3H, m).

[1851] MS 439.2(M+1).
Example 2-332

Production of 2-{[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxylamino]-1-methylthyl}-3-[1-benzimidazole-5-carboxylic acid

Step 1: Production of methyl 2-{[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxylamino]-2-methylpropionate
(Example 2-511)

7.34(1H, d, J=8.3 Hz), 6.94(1H, dd, J=2.6, 8.7 Hz), 6.84(1H, d, J=2.6 Hz), 4.51-4.28 (4H, m), 3.83(3H, s), 3.59(3H, s), 2.93-2.79 (1H, m), 2.12-1.91 (2H, m), 1.88-1.61 (5H, m), 1.50(6H, s), 1.45-1.22 (3H, m).

Step 2: Production of 2-{[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxylamino]-2-methylpropionic acid (Example 2-512)

[1855]

[1853] To a solution of 12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxylic acid (2.40 g, 6.13 mmol) in N,N-dimethylformamide (20.0 ml) were successively added methyl 2-amino-2-methylpropionate hydrochloride (1.13 g, 7.36 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide monohydrochloride (1.41 g, 7.36 mmol), 1-hydroxybenzotriazole (0.99 g, 7.36 mmol) and diethylamine (1.00 ml, 7.36 mmol) at room temperature, and the mixture was stirred overnight. To the reaction mixture were added saturated aqueous sodium hydrogen carbonate solution, methanol and water. The precipitate was collected by filtration, washed with water, and dried in vacuo to give methyl 12-{[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxylamino]-2-methylpropionate (3.10 g). The obtained compound was used for Step 2 without purification.

[1854] H-NMR(300 MHz, DMSO-d6); δ(ppm) 8.40(1H, s), 8.12(1H, s), 7.81(1H, d, J=8.7 Hz), 7.56(1H, d, J=8.3 Hz), 7.44(1H, d, J=8.3 Hz), 6.94(1H, d, J=8.3 Hz), 6.83(1H, d, J=2.3 Hz), 4.52-4.28 (4H, m), 3.83(3H, s), 2.93-2.78 (1H, m), 2.12-1.91 (2H, m), 1.88-1.61 (5H, m), 1.50(6H, s), 1.44-1.21 (3H, m).

[1856] To a solution of methyl 2-{[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxylamino]-2-methylpropionate (3.00 g, 6.11 mmol) in tetrahydrofuran (20.0 ml) and methanol (20.0 ml) was added 2N aqueous sodium hydroxide solution (10.00 ml, 20.00 mmol) at room temperature, and the mixture was stirred overnight. To the reaction mixture were successively added 2N hydrochloric acid (11.00 ml, 22.00 mmol), water and methanol, and the mixture was stirred at room temperature for 30 min. The precipitate was collected by filtration, washed with water, and dried in vacuo to give methyl 12-{[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxylamino]-2-methylpropionic acid (2.60 g, yield 89%).

[1857] H-NMR(300 MHz, DMSO-d6); δ(ppm) 8.27(1H, s), 8.10(1H, s), 7.81(1H, d, J=8.3 Hz), 7.54(1H, d, J=9.0 Hz), 7.34(1H, d, J=8.3 Hz), 6.94(1H, d, J=8.3 Hz), 6.83(1H, d, J=2.3 Hz), 4.52-4.28 (4H, m), 3.83(3H, s), 2.93-2.78 (1H, m), 2.12-1.91 (2H, m), 1.88-1.64 (5H, m), 1.50(6H, s), 1.44-1.21 (3H, m).
Step 3: Production of methyl 4-amino-3-{2-{12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-aza-dibenzo[a,e]azulene-9-carbonyl}amino}-2-methylpropionylamino} benzoate (Example 2-513)

[1858]

[1859] To a solution of 2-{(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carbonyl}amino}-2-methylpropionic acid (0.60 g, 1.26 mmol) in chloroform (18.0 ml) was added a catalytic amount of N,N-dimethylformamide, and thionyl chloride (0.28 ml, 3.78 mmol) was added dropwise under ice-cooling. The mixture was stirred for 2 hr. Then, the reaction mixture was evaporated under reduced pressure to give a yellow solid. Further, the obtained solid was dissolved in chloroform (2.5 ml) and added dropwise to a solution of methyl 3,4-diaminobenzoate (0.29 g, 1.76 mmol) in pyridine (1.5 ml) under ice-cooling. After dropwise addition, the mixture was warmed to room temperature, and the mixture was stirred at overnight. To the reaction mixture were added saturated aqueous sodium hydrogen carbonate solution, methanol and water. The precipitate was collected by filtration, washed with water, and dried in vacuo to give methyl 4-amino-3-[2-{12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-aza-dibenzo[a,e]azulene-9-carbonyl}amino]-2-methylpropionylamino] benzoate (0.73 g, yield 93%).

[1860] ¹H-NMR (400 MHz, DMSO-d₆): (ppm) 9.14 (1H, s), 8.45 (1H, s), 8.17 (1H, s), 7.83 (1H, d, J=6.3 Hz), 7.60 (1H, d, J=6.4 Hz), 7.56 (1H, dd, J=6.2, 1.2 Hz), 7.49 (1H, d, J=1.1 Hz), 7.35 (1H, d, J=6.2 Hz), 6.94 (1H, dd, J=1.6, 6.2 Hz), 6.84 (1H, d, J=1.7 Hz), 6.67 (1H, d, J=6.2 Hz), 5.87 (2H, br), 4.51-4.30 (4H, m), 3.83 (3H, s), 3.74 (3H, s), 2.91-2.79 (1H, m), 2.10-1.94 (2H, m), 1.86-1.66 (5H, m), 1.57 (6H, s), 1.43-1.21 (3H, m).

Step 4: Production of methyl 2-{1-{(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carbonyl}amino}-1-methylthyl]-3H-benzimidazole-5-carboxylate (Example 2-514)

[1861]
Methyl 4-amino-3-{2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]jululene-9-carbonyl]amino}-2-methylpropionylamino} benzoate (0.73 g, 1.16 mmol) was dissolved in acetic acid (14.0 ml), and the mixture was stirred at 100°C for 2 hr. The mixture was allowed to cool to room temperature, toluene was added, and the solvent was evaporated under reduced pressure. To the obtained residue were added methanol and water. The precipitate was collected by filtration, washed with water, and dried in vacuo to give methyl 2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]jululene-9-carbonyl]amino]-1-methylthiethyl]-3H-benzimidazole-5-carboxylate (0.67 g, yield 95%).

[1863] ¹H-NMR(400 MHz, DMSO-d₆): δ/ppm 12.49-12.40 (1H, m), 8.49-8.43 (1H, m), 8.18-8.14 (1H, m), 8.04-8.01 (0.5H, m), 7.85-7.75 (2H, m), 7.65-7.60 (0.5H, m), 7.60-7.55 (1H, m), 7.50-7.47 (0.5H, m), 7.37-7.33 (1H, m), 7.27-7.22 (0.5H, m), 7.20-7.14 (0.5H, m), 6.97-6.92 (1H, m), 6.84 (1H, d, J=1.7 Hz), 4.50-4.31 (4H, m), 3.86 (3H, s), 2.91-2.80 (1H, m), 2.09-1.95 (2H, m), 1.82 (6H, s), 1.87-1.68 (5H, m), 1.43-1.25 (3H, m).

Step 5: Production of 2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]jululene-9-carbonyl]amino]-1-methylthiethyl]-3H-benzimidazole-5-carboxylic acid (Example 2-332)

[1866] ¹H-NMR(300 MHz, DMSO-d₆): δ/ppm 12.49 (1H, brs), 9.00 (1H, s), 8.26 (1H, d, J=12.4 Hz), 8.03 (1H, d, J=8.3 Hz), 7.88-7.74 (2H, m), 7.59 (1H, d, J=8.7 Hz), 7.35 (1H, d, J=8.3 Hz), 6.95 (1H, dd, J=2.6, 8.7 Hz), 6.84 (1H, d, J=2.6 Hz), 4.54-4.30 (4H, m), 3.83 (3H, s), 2.94-2.78 (1H, m), 2.12-1.95 (2H, m), 1.92 (6H, s), 1.87-1.65 (5H, m), 1.45-1.20 (3H, m).

[1867] MS 593.3(M+1).

To a mixed solution of methyl 2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]jululene-9-carbonyl]amino]-1-methylthiethyl]-3H-benzimidazole-5-carboxylate (0.66 g, 1.09 mmol) in tetrahydrofuran (10.0 ml) and methanol (10.0 ml) was added 4N aqueous lithium hydroxide solution (5.00 ml, 20.00 mmol) at room temperature, and the mixture was stirred at 70°C for 7 hr. The mixture was allowed to cool to room temperature, and 2N hydrochloric acid (11.00 ml, 22.00 mmol) and water were successively added. The mixture was stirred at room temperature for 30 min. Then, the precipitate was collected by filtration, washed with water, and dried in vacuo to give methyl 2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]jululene-9-carbonyl]amino]-1-methylthiethyl]-3H-benzimidazole-5-carboxylic acid (0.65 g, yield 100%).
Example 2-346

Production of N-[1-(6-dimethylcarbamoyl-1H-benzimidazol-2-yl)-1-methylthethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7H-azadirbenzo[a,e]jazu- lene-9-carboxamide

[1868]

[1869] To a solution of 2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7H-azadirbenzo[a,e]jazulene-9-carbonyl]amino]-1-methylthethyl]-1H-benzimidazole-5-carboxylic acid (0.07 g, 0.12 mmol) in N,N-dimethylformamide (1.0 ml) was successively added 2M dimethylamine-tetrahydrofuran solution (0.30 ml, 0.59 mmol), N-ethyl-N'-3-dimethylaminopropylcarbodiimide hydrochloride (0.03 g, 0.15 mmol) and 1-hydroxybenzotriazole monohydrate (0.02 g, 0.15 mmol) at room temperature, and the mixture was stirred overnight. Saturated aqueous sodium hydrogen carbonate solution, methanol and water were added to the reaction mixture. The precipitate was collected by filtration, washed with water, and dried in vacuo to give N-[1-(6-dimethylcarbamoyl-1H-benzimidazol-2-yl)-1-methylthethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7H-azadirbenzo[a,e]jazulene-9-carboxamide (0.05 g, yield 63%).

[1870] \(^1\)H-NMR (300 MHz, DMSO-d<sub>6</sub>): 8 (ppm) 12.67-11.54 (1H, m), 8.56 (1H, brs), 8.15 (1H, s), 7.83 (1H, d, J=8.7 Hz), 7.56 (1H, d, J=8.3 Hz), 7.49 (1H, s), 7.46 (1H, d, J=8.3 Hz), 7.35 (1H, d, J=8.6 Hz), 7.13 (1H, d, J=9.4 Hz), 6.95 (1H, dd, J=2.6, 8.7 Hz), 6.84 (1H, d, J=2.6 Hz), 4.51-4.28 (4H, m), 3.83 (3H, s), 2.98 (6H, s), 2.93-2.79 (1H, m), 2.13-1.93 (2H, m), 1.82 (6H, s), 1.80-1.66 (5H, m), 1.45-1.21 (3H, m)

[1871] MS 620.3 (M+1).

Example 2-349

Production of methyl 4-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7H-azadirbenzo[a,e]jazulene-9-carbonyl]amino]-2-methylpropionylamino]benzoate

[1872]
[1873] To a solution of 2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azabenzol[a,e]azulene-9-carbonyl)amino]-2-methylpropionic acid (200 mg, 0.42 mmol) in chloroform (4.0 ml) was added a catalytic amount of N,N-dimethylformamide solution, thionyl chloride (0.07 ml, 1.26 mmol) was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 3 hr. Then, the solvent was evaporated under reduced pressure to give a yellow solid. The obtained solid was dissolved in chloroform (1.5 ml), and added dropwise to a solution of methyl 4-aminobenzoate (95.2 mg, 0.63 mmol) in a mixture of chloroform (1.0 ml) and pyridine (1.0 ml) under ice-cooling. Then, methyl 4-aminobenzoate (52 mg, 0.21 mmol) and pyridine (2.0 ml) were added, and the mixture was stirred at room temperature for 24 hr. To the reaction mixture was added aqueous sodium hydrogen carbonate solution and the mixture was extracted with chloroform. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. Methanol and chloroform were added to the residue, and the mixture was stirred. The precipitate was collected by filtration to give methyl 4-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azabenzol[a,e]azulene-9-carbonyl)amino]-2-methylpropionylamino] benzoate (105 mg, yield 41%).

[1874] 1H-NMR (300 MHz, CDCl3): δ (ppm) 9.75 (1H, s), 8.21 (2H, d, J=15.0 Hz), 7.89-7.75 (5H, m), 7.61 (1H, d, J=9.0 Hz), 7.34 (1H, d, J=12.0 Hz), 6.96-6.91 (1H, m), 6.84 (1H, d, J=3.0 Hz), 4.49-4.43 (2H, m), 4.39-4.33 (2H, m), 3.83 (3H, s), 3.81 (3H, s), 2.91-2.80 (1H, m), 2.10-1.95 (2H, m), 1.87-1.69 (5H, m), 1.58 (6H, s), 1.44-1.25 (3H, m). 610.3 (M+1).

Example 2-350

Production of 4-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azabenzol[a,e]azulene-9-carbonyl)amino]-2-methylpropionylamino] benzoic acid

[1875]
To a solution of methyl 4-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxy]laminio]-2-methylpropionylamino]benzoate (81 mg, 0.13 mmol) in tetrahydrofuran (8.0 ml) and methanol (2.0 ml) was added 2N aqueous sodium hydroxide solution (1.0 ml, 2.0 mmol), and the mixture was stirred at room temperature for 64 hr. The solvent was evaporated under reduced pressure, 1N aqueous HCl solution (3.0 ml, 3.0 mmol) and methanol (1.0 ml) were added, and the mixture was stirred. The precipitate was collected by filtration to give 4-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxy]laminio]-2-methylpropionylamino]benzoic acid (73 mg, yield 92%).

\[ \text{H-NMR (300 MHz, CDCl}_3\text{): } \delta (\text{ppm}) 12.63 (1H, s), 9.72 (1H, s), 8.21 (2H, d, J=12.0 Hz), 7.86-7.72 (5H, m), 7.61 (1H, d, J=9.0 Hz), 7.35 (1H, d, J=9.0 Hz), 6.96-6.93 (1H, m), 6.84 (1H, d, J=5.0 Hz), 4.51-4.45 (2H, m), 4.39-4.34 (2H, m), 3.83 (3H, s), 2.92-2.79 (1H, m), 2.13-1.93 (2H, m), 1.87-1.69 (5H, m), 1.58 (6H, s), 1.46-1.27 (3H, m), 596.2 (M+1). \]

Example 2-369

Production of N—(S)-[2-(4-benzyloxyphenyl)-1-thiazol-2-yl]ethyl-1-carbamoylethyl]carbamate

Step 1: Production of tert-buty1 (S)-[2-(4-benzyloxyphenyl)-1-carbamoylethyl]carbamate

To a solution of (S)-3-(4-benzyloxyphenyl)-2-tert-butoxycarboxyaminopicramic acid (5.00 g, 13.5 mmol) and 1-hydroxybenzotriazole monohydrate (2.50 g, 16.1 mmol) in N,N-dimethylformamide (50 ml) were added 1-ethyl-3-[(dimethylaminopropyl)carbodiimide hydrochloride (3.10 g, 16.1 mmol) and 28% aqueous ammonia solution (5 ml) under ice-cooling, and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (chloroform:ethyl acetate=8:1-5:1). Disopropyl ether was added to the obtained residue. The precipitated solid was collected by filtration and washed with disopropyl ether. The obtained solid was dried in vacuo to give tert-buty1 (S)-[2-(4-benzyloxyphenyl)-1-thiazol-2-yl]ethyl]carbamate (540 mg, yield 34%).

\[ \text{H-NMR (400 MHz, CDCl}_3\text{): } \delta (\text{ppm}) 7.44-7.31 (6H, m), 7.21 (1H, brs), 7.17 (2H, d, J=8.8 Hz), 6.92 (2H, d, J=8.8 Hz), 5.29 (1H, brs), 5.04 (2H, s), 4.56 (1H, dd, J=7.3, 3.6 Hz), 3.18-3.03 (2H, m), 1.42 (9H, s). \]

Step 3: Production of tert-buty1 (S)-[2-(4-benzyloxyphenyl)-1-thiazol-2-yl]ethyl]carbamate

\[ \text{Step 2: Production of tert-buty1 (S)-[2-(4-benzyloxyphenyl)-1-thiocarbamoylethyl]carbamate} \]

\[ \text{H-NMR (400 MHz, CDCl}_3\text{): } \delta (\text{ppm}) 7.44-7.32 (5H, m), 7.15 (2H, d, J=8.8 Hz), 6.93 (2H, d, J=8.3 Hz), 5.79 (1H, brs), 5.48 (1H, brs), 5.07-5.00 (3H, m), 4.37-4.26 (1H, m), 3.09-2.95 (2H, m), 1.42 (9H, s). \]
[1885] To a solution of tert-butyl (S)-[2-(4-benzyloxyphenyl)-1-thiocarbamoyl]ethylcarbamate (250 mg, 0.647 mmol) in acetone (5 mL) was added bromoacetaldehyde diethyl acetal (149 μL, 0.970 mmol), and the mixture was stirred at 65°C for 14 hr. The mixture was further heated to 75°C and stirred for 5 hr. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=4:1) to give tert-butyl (S)-[2-(4-benzyloxyphenyl)-1-(thiazol-2-yl)ethyl] carbamate (112 mg, yield 42%)

[1886] 1H-NMR(400 MHz, CDCl3): δ (ppm) 7.76 (1H, d, J=3.2 Hz), 7.44-7.30 (5H, m), 7.22 (1H, d, J=3.2 Hz), 6.99 (2H, d, J=8.3 Hz), 6.87 (2H, d, J=8.3 Hz), 5.25 (2H, brs), 5.03 (2H, s), 3.27-3.19 (2H, m), 1.42 (9H, s).

Step 4: Production of (S)-2-(4-benzyloxyphenyl)-1-(thiazol-2-yl)ethylamine hydrochloride

[1887]

[1888] To a solution of tert-butyl (S)-[2-(4-benzyloxyphenyl)-1-(thiazol-2-yl)ethyl]carbamate (112 mg, 0.273 mmol) in ethyl acetate (1 mL) was added 4N HCl-ethyl acetate solution (1 mL), and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, and hexane: diethyl ether (3:1) solution was added to the obtained residue. The precipitated solid was collected by filtration and washed with hexane: diethyl ether (3:1) solution. The obtained solid was dried in vacuo to give (S)-2-(4-benzyloxyphenyl)-1-(thiazol-2-yl)ethylamine hydrochloride (66 mg, yield 70%).

[1889] 1H-NMR(400 MHz, DMSO-d6): δ (ppm) 8.81 (3H, brs), 7.87 (1H, d, J=3.2 Hz), 7.74 (1H, d, J=3.2 Hz), 7.43-7.29 (5H, m), 7.05 (2H, d, J=8.8 Hz), 6.90 (2H, d, J=8.3 Hz), 5.04 (2H, s), 5.03-4.94 (1H, m), 3.34 (1H, dd, J=13.7, 5.3 Hz), 3.10 (1H, dd, J=13.4, 9.7 Hz).

[1890] Step 5: Production of N—(S)-[2-(4-benzyloxyphenyl)-1-(thiazol-2-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxamide (Example 2-369)

[1891] To a solution of 12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylic acid (50 mg, 0.13 mmol) and (S)-2-(4-benzyloxyphenyl)-1-(thiazol-2-yl)ethylamine hydrochloride (49 mg, 0.14 mmol) in N,N-dimethylformamide (1 mL) were added 1-hydroxybenzotriazole monohydrate (24 mg, 0.15 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29 mg, 0.15 mmol) and triethylamine (43 μL, 0.31 mmol) under ice-cooling, and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. Hexane: diethyl ether (2:1) solution was added to the obtained residue. The precipitated solid was collected by filtration and washed with hexane: diethyl ether (2:1) solution. The obtained solid was dried in vacuo to give N—(S)-[2-(4-benzyloxyphenyl)-1-(thiazol-2-yl)ethyl]-12-cyclohexyl-3-
methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]azulene-9-carboxamide (68 mg, yield 77%).

[1892] ¹H-NMR(300 MHz, DMSO-d₆): δ(ppm) 8.95 (1H, d, J=8.8 Hz), 8.06 (1H, s), 7.82 (1H, d, J=8.8 Hz), 7.78 (1H, d, J=3.3 Hz), 7.63 (1H, d, J=3.3 Hz), 7.54 (1H, d, J=8.8 Hz), 7.54 (8H, m), 6.94 (1H, dd, J=8.4, 2.6 Hz), 6.89 (2H, d, J=8.8 Hz), 6.83 (1H, d, J=2.6 Hz), 5.62-5.53 (1H, m), 5.01 (2H, s), 4.49-4.42 (2H, m), 4.36-4.28 (2H, m), 3.83 (3H, s), 3.45 (1H, dd, J=13.9, 4.0 Hz), 3.27-3.20 (1H, m), 2.91-2.80 (1H, m), 2.08-1.94 (2H, m), 1.86-1.68 (5H, m), 1.41-1.25 (3H, m).

[1893] MS 684.2 (M+1).

Example 2-381

Production of N—[(S)-2-(4-hydroxyphenyl)-1-(thiazol-2-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]azulene-9-carboxamide

[1894]

[1895] To N—[(S)-2-(4-benzyloxyphenyl)-1-(thiazol-2-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]azulene-9-carboxamide (58 mg, 0.10 mmol) was added 25% hydrogen bromide-acetic acid solution (1 ml), and the mixture was stirred at room temperature for 30 min. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. To the obtained residue was added hexane: diethyl ether (2:1) solution, and the precipitated solid was collected by filtration and washed with hexane: diethyl ether (2:1) solution. The obtained solid was dried in vacuo to give N—[(S)-2-(4-hydroxyphenyl)-1-(thiazol-2-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]azulene-9-carboxamide (50 mg, yield 85%).

[1896] ¹H-NMR(300 MHz, DMSO-d₆): δ(ppm) 9.12 (1H, s), 8.91 (1H, d, J=8.8 Hz), 8.05 (1H, s), 7.82 (1H, d, J=8.4 Hz), 7.78 (1H, d, J=2.9 Hz), 7.62 (1H, d, J=3.3 Hz), 7.53 (1H, d, J=7.3 Hz), 7.33 (1H, d, J=8.4 Hz), 7.14 (2H, d, J=8.4 Hz), 6.94 (1H, dd, J=8.4, 2.6 Hz), 6.83 (1H, d, J=2.6 Hz), 6.63 (2H, d, J=8.4 Hz), 5.57-5.49 (1H, m), 4.49-4.42 (2H, m), 3.46-3.28 (2H, m), 3.83 (3H, s), 3.42 (1H, dd, J=13.9, 4.0 Hz), 3.27-3.20 (1H, m), 2.91-2.80 (1H, m), 2.08-1.94 (2H, m), 1.86-1.68 (5H, m), 1.41-1.25 (3H, m).

[1897] MS 594.2 (M+1).

Example 2-427

Production of N—[(S)-2-(4-hydroxyphenyl)-1-(N-methoxy-N-methylcarbamoyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]azulene-9-carboxamide

[1898]

[1899] To a solution of (S)-2-{12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]azulene-9-carboxamido]-3-(4-hydroxyphenyl)propionic acid (50.0 mg, 0.090 mmol) synthesized in the same manner as in Examples 2-175 and 2-180, N,N-dimethylhydroxylamine hydrochloride (10.5 mg, 0.180 mmol), 1-hydroxybenzotriazole monohydrate (15.2 mg, 0.38 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (20.7 mg, 0.180 mmol) in N,N-dimethylformamide (1 ml) was added triethylamine (25.1 µl, 0.180 mmol), and the mixture was stirred overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture. The precipitated solid was collected by filtration, further washed with water and dried in vacuo. The obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=1:4). To the obtained residue was added a mixed solvent of hexane:ethyl acetate (5:1), and the precipitated solid was collected by filtration and washed with a mixed solvent of hexane:ethyl acetate (5:1). The obtained solid was dried in vacuo to give N—[(S)-2-(4-hydroxyphenyl)-1-(N-methoxy-N-methylcarbamoyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]azulene-9-carboxamide (30.0 mg, yield 54.1%).
[1900] $^1$H-NMR (400 MHz, DMSO-d$_6$): $\delta$(ppm) 9.18 (1H, s), 8.46 (1H, d, $J$=8.6 Hz), 8.12 (1H, brs), 7.81 (1H, d, $J$=8.6 Hz), 7.53 (1H, dd, $J$=8.6, 1.4 Hz), 7.34 (1H, d, $J$=8.6 Hz), 7.13 (2H, d, $J$=8.6 Hz), 6.95 (1H, dd, $J$=8.6, 2.6 Hz), 6.84 (1H, d, $J$=2.6 Hz), 6.66 (2H, d, $J$=8.6 Hz), 5.18-5.04 (1H, m), 4.47 (2H, brt, $J$=5.6 Hz), 4.37-4.30 (2H, brs), 3.83 (1H, s), 3.80 (3H, brs), 3.14 (3H, s), 2.95-2.79 (3H, m), 2.08-1.95 (2H, m), 1.85-1.67 (5H, m), 1.48-1.21 (3H, m).

[1901] MS 598.2 (M+1).

Example 2.481

Production of 12-cyclohexyl-4-{N-[2-(piperidin-1-yl)ethyl]-N-propylamino}-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid dihydrochloride

Step 1: Production of methyl 3-cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-6-carboxylate

[1902]

[1903] To a solution of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (40.00 g, 119.0 mmol) obtained in the same manner as in the method described in WO03/010140 in 1,4-dioxane (400 ml) was added pinacolborane (51.8 ml, 357.0 mmol). Triethylamine (66.3 ml, 476.0 mmol) was added dropwise at room temperature and the mixture was stirred for 3 hr. (2-Biphenyl)dicyclohexylphosphine (5.01 g, 14.3 mmol) and palladium(II) acetate (802 mg, 3.57 mmol) were added and the reaction mixture was heated to 85$^\circ$C. for 1 hr. The reaction mixture was cooled to room temperature, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous ammonium chloride solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was subjected to azotropic evaporation with toluene and the precipitated solid was washed with a mixed solvent of hexane/ethyl acetate (20:1). The solid was collected by filtration to give methyl 3-cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-6-carboxylate (39.20 g, yield 86%).

[1904] $^1$H-NMR (400 MHz, DMSO-d$_6$): $\delta$(ppm) 11.28 (1H, s), 8.04 (1H, d, $J$=1.4 Hz), 7.82 (1H, d, $J$=8.6 Hz), 7.53 (1H, d, $J$=8.6, 1.4 Hz), 3.85 (3H, s), 2.53-2.48 (1H, m), 2.00-1.64 (7H, m), 1.45-1.27 (3H, m), 1.35 (12H, s).

Step 2: Production of methyl 3-cyclohexyl-2-[3-nitro-2-[2-(tetrahydropryan-2-yl)oxy]ethoxy]phenyl]-1H-indole-6-carboxylate

[1905]

[1906] To a solution of 2-(2-(2-bromo-6-nitrophenoxy)tetrahydropryan (12.30 g, 35.6 mmol) in 1,2-dimethoxyethane (150 ml) and water (75 ml) was added sodium hydrogen carbonate (9.74 g, 117.0 mmol) and triethylamine (4.52 g, 3.91 mmol) and the mixture was heated at 85$^\circ$C for 15 min. Methyl 3-cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-6-carboxylate (16.40 g, 35.6 mmol) was added in 6 divided portions to the reaction mixture at 30 min intervals, and the mixture was stirred at the same temperature for 1 hr. The reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=3:5:1) to give methyl 3-cyclohexyl-2-[3-nitro-2-[2-(tetrahydropryan-2-yl)oxy]ethoxy]phenyl]-1H-indole-6-carboxylate (14.40 g, yield 77%).

[1907] $^1$H-NMR (400 MHz, DMSO-d$_6$): $\delta$(ppm) 11.65 (1H, s), 8.62 (1H, d, $J$=1.4 Hz), 7.98 (1H, dd, $J$=8.8, 1.4 Hz), 7.87 (1H, d, $J$=8.8 Hz), 7.66 (1H, dd, $J$=8.1, 1.6 Hz), 7.62 (1H, dd, $J$=8.1, 1.6 Hz), 7.45 (1H, t, $J$=8.1 Hz), 4.27-4.24
(1H, m), 3.86 (3H, s), 3.73-3.63 (2H, m), 3.53-3.13 (4H, m), 2.64 (1H, brt, J=12.3 Hz), 2.01-1.62 (7H, m), 1.55-1.15 (9H, m).

Step 3: Production of methyl 3-cyclohexyl-2-[2-(2-hydroxyethoxy)-3-nitrophenyl]-1H-indole-6-carboxylate

[1908]

Step 4: Production of methyl 3-cyclohexyl-2-[2-(2-methanesulfonyloxyethoxy)-3-nitrophenyl]-1H-indole-6-carboxylate

[1911]

[1909] To a solution of methyl 3-cyclohexyl-2-[3-nitro-2-[2-(tetrahydrofuran-2-yl)oxy]phenyl]-1H-indole-6-carboxylate (6.48 g, 18.6 mmol) in tetrahydrofuran (30 ml) and methanol (90 ml) was added 6N hydrochloric acid (15 ml), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was neutralized with 4N aqueous sodium hydroxide solution (22.5 ml), saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=3:1:2:1) to give methyl 3-cyclohexyl-2-[2-(2-hydroxyethoxy)-3-nitrophenyl]-1H-indole-6-carboxylate (11.00 g, yield 91%).

[1910] $^1$H-NMR (400 MHz, DMSO-d$_6$): $\delta$(ppm) 11.63 (1H, s), 8.02 (1H, d, J=1.6 Hz), 7.97 (1H, dd, J=8.1, 1.6 Hz), 7.88 (1H, d, J=8.1 Hz), 7.65 (1H, dd, J=7.9, 1.4 Hz), 7.62 (1H, dd, J=7.9, 1.4 Hz), 7.44 (1H, t, J=7.9 Hz), 4.61 (1H, t, J=5.1 Hz), 3.87 (3H, s), 3.56 (2H, t, J=5.6 Hz), 3.55 (2H, t, J=5.6 Hz), 2.64 (1H, brt, J=12.1 Hz), 2.01-1.63 (7H, m), 1.43-1.17 (3H, m).

[1912] To a solution of methyl 3-cyclohexyl-2-[2-(2-hydroxyethoxy)-3-nitrophenyl]-1H-indole-6-carboxylate (11.00 g, 25.1 mmol) and triethylamine (5.25 ml, 37.7 mmol) in chloroform (77 ml) was added dropwise methanesulfonyl chloride (2.33 ml, 30.1 mmol) under ice-cooling, and the mixture was stirred for 30 min. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 3-cyclohexyl-2-[2-(2-methanesulfonyloxyethoxy)-3-nitrophenyl]-1H-indole-6-carboxylate (12.60 g, yield 97%).

[1913] $^1$H-NMR (400 MHz, DMSO-d$_6$): $\delta$(ppm) 11.66 (1H, s), 8.02 (1H, d, J=1.4 Hz), 8.02 (1H, dd, J=8.3, 1.4 Hz), 7.88 (1H, d, J=8.3 Hz), 7.68 (1H, dd, J=8.3, 1.4 Hz), 7.63 (1H, dd, J=8.3, 1.4 Hz), 7.49 (1H, t, J=8.3 Hz), 4.14-4.10 (2H, m), 3.86 (3H, s), 3.80-3.75 (2H, m), 2.94 (3H, s), 2.64 (1H, brt, J=12.1 Hz), 1.99-1.96 (7H, m), 1.42-1.40 (3H, m).
Step 5: Production of methyl 12-cyclohexyl-4-nitro-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (Example 2-515)

![Chemical Structure](image1)

Step 6: Production of methyl 4-amino-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (Example 2-516)

![Chemical Structure](image2)

[1915] To a solution of methyl 3-cyclohexyl-2-[2-(2-methanesulfonyloxyethoxy)-3-nitrophenyl]-1H-indole-6-carboxylate (12.60 g, 24.4 mmol) in N,N-dimethylformamide (190 ml) was added potassium carbonate (5.06 g, 36.6 mmol), and the mixture was stirred at 90°C for 1.5 hr. The reaction mixture was allowed to cool to room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was concentrated under reduced pressure to give methyl 12-cyclohexyl-4-nitro-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (9.96 g, yield 97%).

![Chemical Structure](image3)

[1916] ¹H-NMR(400 MHz, DMSO-d₆): δ(ppm) 8.29 (1H, d, J=1.4 Hz), 8.05 (1H, dd, J=8.5, 1.4 Hz), 7.97 (1H, d, J=8.5 Hz), 7.75 (1H, dd, J=8.0, 1.4 Hz), 7.67 (1H, dd, J=8.0, 1.4 Hz), 7.58 (1H, t, J=8.0 Hz), 4.68-4.61 (2H, m), 4.55 (2H, brs), 3.89 (3H, s), 2.84 (1H, brt, J=12.1 Hz), 2.10-1.95 (2H, m), 1.88-1.68 (5H, m), 1.48-1.26 (3H, m).

[1917] To a solution of methyl 12-cyclohexyl-4-nitro-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (9.94 g, 23.6 mmol) in tetrahydrofuran (85 ml), ethanol (170 ml) and water (42.5 ml) were added ammonium chloride (6.31 g, 118 mmol) and reduced iron (6.60 g, 118 mmol), and the mixture was stirred at 100°C for 2 hr. After filtration of the reaction solution, saturated aqueous sodium hydrogen carbonate solution was added to the filtrate, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was concentrated under reduced pressure to give a solid. The obtained solid was washed with a mixed solvent (hexane:ethyl acetate=20:1). The solid was collected by filtration to give methyl 4-amino-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jazulene-9-carboxylate (8.62 g, yield 93%).

[1918] ¹H-NMR(300 MHz, DMSO-d₆): δ(ppm) 8.20 (1H, d, J=1.4 Hz), 7.88 (1H, d, J=8.3 Hz), 7.63 (1H, dd, J=8.3, 1.4 Hz), 7.01 (1H, t, J=7.9 Hz), 6.82 (1H, dd, J=7.9, 1.4 Hz), 6.58 (1H, dd, J=7.9, 1.4 Hz), 5.15 (2H, s), 4.44-4.38 (2H, m), 4.33 (2H, brs), 2.95 (1H, brt, J=12.1 Hz), 2.07-1.93 (2H, m), 1.86-1.65 (5H, m), 1.46-1.21 (3H, m).
Step 7: Production of methyl 4-\{bis[2-oxo-2-(piperidin-1-yl)ethyl]amino]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-517) and methyl 12-cyclohexyl-4-\{2-oxo-2-(piperidin-1-yl)ethylamino\}-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-518)

\[\text{MeOOC} \xrightarrow{\text{Boc-N}} \text{NH}_2 \xrightarrow{\text{Boc-N}} \text{MeOOC}\]

methyl 4-\{bis[2-oxo-2-(piperidin-1-yl)ethyl]amino\}-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-517)

\[\text{MeOOC} \xrightarrow{\text{Boc-N}} \text{NH}_2 \xrightarrow{\text{Boc-N}} \text{MeOOC}\]

methyl 12-cyclohexyl-4-\{2-oxo-2-(piperidin-1-yl)ethylamino\}-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-518)

Step 8: Production of methyl 4-\{bis[2-(piperidin-1-yl)ethyl]amino\}-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-519)

\[\text{MeOOC} \xrightarrow{\text{Boc-N}} \text{NH}_2 \xrightarrow{\text{Boc-N}} \text{MeOOC}\]

To a solution of methyl 4-amino-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (3.50 g, 8.96 mmol) in N,N-dimethylformamide (35.0 ml) were added potassium carbonate (6.20 g, 44.8 mmol), sodium iodide (1.48 g, 8.91 mmol) and 1-(2-bromoacetyl)piperidine (3.60 g, 17.4 mmol), and the mixture was stirred at 90°C for 3 hr. The mixture was allowed to cool to room temperature and water was added, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and hexane and dried in vacuo. The residue was purified by silica gel chromatography (hexane:ethyl acetate=2:1-1:5) to give methyl 4-\{bis[2-oxo-2-(piperidin-1-yl)ethyl]amino\}-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (3.31 g, yield 58%) and methyl 12-cyclohexyl-4-\{2-oxo-2-(piperidin-1-yl)ethylamino\}-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (2.15 g, yield 47%).

To a solution of methyl 4-\{bis[2-oxo-2-(piperidin-1-yl)ethyl]amino\}-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (3.31 g, yield 58%) and methyl 12-cyclohexyl-4-\{2-oxo-2-(piperidin-1-yl)ethylamino\}-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (2.15 g, yield 47%).

[1921] To a solution of methyl 4-amino-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (3.50 g, 8.96 mmol) in N,N-dimethylformamide (35.0 ml) were added potassium carbonate (6.20 g, 44.8 mmol), sodium iodide (1.48 g, 8.91 mmol) and 1-(2-bromoacetyl)piperidine (3.60 g, 17.4 mmol), and the mixture was stirred at 90°C for 3 hr. The mixture was allowed to cool to room temperature and water was added, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and hexane and dried in vacuo. The residue was purified by silica gel chromatography (hexane:ethyl acetate=2:1-1:5) to give methyl 4-\{bis[2-oxo-2-(piperidin-1-yl)ethyl]amino\}-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (3.31 g, yield 58%) and methyl 12-cyclohexyl-4-\{2-oxo-2-(piperidin-1-yl)ethylamino\}-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (2.15 g, yield 47%).

[1922] \^H-NMR(300 MHz, CDCl₃): δ (ppm) 8.05 (1H, d, J=1.5 Hz), 7.87 (1H, d, J=8.4 Hz), 7.74 (1H, dd, J=8.4, 1.5 Hz), 7.10 (1H, t, J=7.9 Hz), 6.87 (1H, dd, J=7.7, 1.5 Hz), 6.82 (1H, d, J=8.1 Hz), 4.39 (2H, t, J=5.7 Hz), 4.30 (4H, brs), 4.25-4.12 (2H, m), 3.94 (3H, s), 3.58 (4H, t, J=5.1 Hz), 3.37 (4H, t, J=5.1 Hz), 2.95 (1H, brt, J=10.5 Hz), 2.12-1.95 (3H, m), 1.91-1.74 (3H, m), 1.69-1.47 (14H, m), 1.42-1.30 (2H, m).

[1923] \^H-NMR(300 MHz, CDCl₃): δ (ppm) 8.07 (1H, s), 7.88 (1H, d, J=8.4 Hz), 7.75 (1H, dd, J=8.4, 1.5 Hz), 7.13 (1H, t, J=7.9 Hz), 6.76 (1H, dd, J=7.7, 1.5 Hz), 6.64 (1H, dd, J=7.7, 1.5 Hz), 5.62 (1H, brs), 4.57 (2H, t, J=5.7 Hz), 4.30 (2H, t, J=5.1 Hz), 3.96-3.92 (2H, m), 3.94 (3H, s), 3.65-3.61 (2H, m), 3.43-3.40 (2H, m), 3.02 (1H, t, J=11.9 Hz), 2.07-2.00 (2H, m), 1.90-1.50 (12H, m), 1.36 (2H, s).

[1925] To a solution of methyl 4-\{bis[2-oxo-2-(piperidin-1-yl)ethyl]amino\}-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (3.31 g, yield 58%) and methyl 12-cyclohexyl-4-\{2-oxo-2-(piperidin-1-yl)ethylamino\}-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (2.15 g, yield 47%)...
azadibenzo[a,e]azulene-9-carboxylate (500 mg, 0.78 mmol) in tetrahydrofuran (2.0 ml) was added a solution (5.0 ml) of 1M BH$_3$ THF complex in tetrahydrofuran, and the mixture was stirred at room temperature for 14 hr. 2N Hydrochloric acid was added to the reaction mixture, and the mixture was stirred at 70°C for 4 hr. The reaction mixture was allowed to cool to room temperature, neutralized with 4N aqueous sodium hydroxide solution and saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (chloroform:methanol=10:1-5:1) to give methyl 4-[(bis[2-(piperidin-1-yl)ethyl]amino)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (401 mg, yield 84%).

[1926] ¹H-NMR(300 MHz, CDCl$_3$): δ (ppm) 8.06 (1H, s), 7.88 (1H, d, J=8.4 Hz), 7.75 (1H, d, J=8.4 Hz), 7.20-7.05 (2H, m), 6.97 (1H, d, J=6.6 Hz), 4.46 (2H, t, J=5.7 Hz), 4.23 (2H, brs), 3.95 (3H, s), 3.50-3.33 (4H, m), 3.02-2.95 (1H, m), 2.60-2.47 (4H, m), 2.46-2.36 (6H, m), 2.17-1.98 (2H, m), 1.95-1.75 (6H, m), 1.70-1.49 (9H, m), 1.47-1.33 (7H, m).

Step 9: Production of 4-[(bis[2-(piperidin-1-yl)ethyl]amino)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid trihydrochloride (Example 2-52b)

[1927]

[1928] To a solution of methyl 4-[(bis[2-(piperidin-1-yl)ethyl]amino)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (401 mg, 0.65 mmol) in tetrahydrofuran (4.0 ml) and methanol (4.0 ml) was added 4N aqueous sodium hydroxide solution (4.0 ml), and the mixture was stirred at room temperature for 12 hr. The reaction mixture was adjusted to pH 6 with 2N hydrochloric acid, and extracted with chloroform. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the mixture was concentrated under reduced pressure, and ethyl acetate was added to the residue. The precipitated solid was collected by filtration to give 4-[(bis[2-(piperidin-1-yl)ethyl]amino)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid. To a solution of the obtained 4-[(bis[2-(piperidin-1-yl)ethyl]amino)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid in chloroform was added 4N HCl-ethyl acetate solution (4.0 ml). The reaction mixture was concentrated under reduced pressure and ethyl acetate was added. The precipitated solid was collected by filtration and dried in vacuo to give 4-[(bis[2-(piperidin-1-yl)ethyl]amino)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid trihydrochloride (338 mg, yield 75%)

[1929] ¹H-NMR(400 MHz, DMSO-d$_6$): δ (ppm) 10.61 (2H, brs), 8.22 (1H, d, J=0.9 Hz), 7.89 (1H, d, J=8.3 Hz), 7.63 (1H, dd, J=8.3, 1.4 Hz), 7.41 (1H, t, J=4.6 Hz), 7.29 (1H, t, J=7.9 Hz), 7.09 (1H, dd, J=16.5, 7.2 Hz), 5.20 (1H, brs), 5.00 (2H, t, J=5.1 Hz), 4.45-4.21 (2H, m), 3.59 (4H, t, J=7.0 Hz), 3.45 (4H, d, J=11.6 Hz), 3.24 (4H, dd, J=11.6, 7.0 Hz), 2.97-2.77 (5H, m), 2.10-1.95 (2H, m), 1.90-1.67 (15H, m), 1.45-1.20 (5H, m).

[1930] MS 599.4(M+1).

Step 10: Production of methyl 12-cyclohexyl-4-[[N-[2-oxo-2-(piperidin-1-yl)ethyl]-N-propylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-521)

[1931]

[1932] To a solution of methyl 12-cyclohexyl-4-[[N-[2-oxo-2-(piperidin-1-yl)ethyl]-N-propylamino]-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]jululene-9-carboxylate (3.40 g, 6.59 mmol) obtained in Step 7 and propionialdehyde (4.76 ml, 65.9 mmol) in chloroform (20 ml), water (20 ml) and acetic acid (1 ml) was added to sodium triacetylborohydride (6.98 g, 33.0 mmol) under ice-cooling, and the mixture was stirred for 8 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous sodium hydrogen carbonate solution, water and saturated brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1-1.5:1) to give methyl 12-cyclohexyl-4-([N-[2-oxo-2-(piperidin-1-y)ethyl]-N-propylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylate (3.63 g, yield 99%).

[1933] 1H-NMR (400 MHz, CDCl3): δ (ppm) 8.20 (1H, d, J=1.4 Hz), 7.89 (1H, d, J=8.5 Hz), 7.63 (1H, dd, J=8.5, 1.4 Hz), 7.18 (1H, t, J=7.9 Hz), 7.07 (1H, dd, J=7.9, 1.4 Hz), 6.87 (1H, dd, J=7.9, 1.4 Hz), 4.37 (2H, brs), 4.12 (2H, brs), 3.87 (3H, s), 3.37 (4H, brs), 3.21 (2H, brs), 2.88 (1H, brt, J=12.1 Hz), 2.08-1.93 (2H, m), 1.86-1.66 (5H, m), 1.60-1.47 (4H, m), 1.46-1.22 (7H, m), 0.86 (3H, t, J=7.2 Hz).

Step 11: Production of methyl 12-cyclohexyl-4-([N-[2-oxo-2-(piperidin-1-y)ethyl]-N-propylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylate (Example 2-522)

[1934]

[1935] To a solution of methyl 12-cyclohexyl-4-([N-[2-oxo-2-(piperidin-1-y)ethyl]-N-propylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylate (3.63 g, 6.51 mmol) in tetrahydrofuran (7 ml) was added a solution (50 ml) of 1M BH₃·THF complex in tetrahydrofuran under ice-cooling, and the mixture was stirred at room temperature for 1 hr. 4N Hydrochloric acid was added to the reaction mixture under ice-cooling, and the mixture was stirred at 65°C for 3 hr. The reaction mixture was adjusted to pH 8 with 4N aqueous sodium hydroxide solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=35:1.15:1) to give methyl 12-cyclohexyl-4-([N-[2-(piperidin-1-y)ethyl]-N-propylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylate (3.25 g, yield 92%).

[1936] 1H-NMR (400 MHz, DMSO-d₆): δ (ppm) 8.21 (1H, d, J=1.4 Hz), 7.90 (1H, d, J=8.3 Hz), 7.64 (1H, dd, J=8.3, 1.4 Hz), 7.20 (1H, t, J=7.3 Hz), 7.12 (1H, d, J=7.3 Hz), 6.92 (1H, d, J=7.3 Hz), 4.40 (4H, brs), 3.87 (3H, s), 3.28 (2H, brs), 3.13 (2H, brs), 2.90 (1H, brt, J=12.1 Hz), 2.41 (2H, brs), 2.29 (2H, brs), 2.09-1.92 (2H, m), 1.87-1.65 (5H, m), 1.57-1.21 (14H, m), 0.86 (3H, t, J=7.4 Hz).

Step 12: Production of 12-cyclohexyl-4-([N-[2-(piperidin-1-y)ethyl]-N-propylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid dihydrochloride (Example 2-481)

[1937]
ml) was added to a solution of the residue in chloroform, and the solvent was evaporated under reduced pressure. A mixed solvent (hexane:ethyl acetate=4:1) was added to the residue and the precipitated solid was collected by filtration to give [12-cyclohexyl-4-{N-[2-(piperidin-1-yl)ethyl]-N-propylamino}-6,7-dihydro-5-oxa-azadibenzo[a,c]azulene-9-carboxylic acid dihydromchloride (3.41 g, yield 95%).

[1939] \(^1\)H-NMR(400 MHz, DMSO-d<sub>6</sub>): \(\delta\) (ppm) 10.53 (1H, brs), 8.21 (1H, d, \(J=1.4\) Hz), 7.89 (1H, d, \(J=8.6\) Hz), 7.64 (1H, dd, \(J=8.6, 1.4\) Hz), 7.29 (2H, brs), 7.09 (1H, brs), 4.48 (4H, brs), 3.62 (2H, brs), 3.45 (2H, brs), 3.17 (4H, brs), 2.99-2.80 (2H, m), 2.11-2.05 (2H, m), 1.87-1.61 (10H, m), 1.57-1.22 (6H, m), 0.87 (3H, t, \(J=7.2\) Hz).

[1940] MS 530.3(M+1).

Example 5-4
Production of 12-cyclohexyl-5,6-dihydroindol[2,1-a]squinoline-9-carboxylic acid

Step 1: Production of 2-[2-(2-bromophenyl)ethoxy]tetrahydropyran

[1941]

[1942] A solution of 2-(2-bromophenyl)ethanol (3.10 g, 15.4 mmol), 3,4-dihydro-2H-pyran (1.70 ml, 18.6 mmol) and p-toluenesulfonic acid monohydrate (10.0 mg, 5.35 mmol) in chloroform (30 ml) was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=3:1-10:1) to give 2-[2-(2-bromophenyl)ethoxy]tetrahydropyran (3.58 g, yield 81.7%).

[1943] \(^1\)H-NMR(400 MHz, CDCl<sub>3</sub>): \(\delta\) (ppm) 7.53 (1H, dd, \(J=8.1, 1.2\) Hz), 7.30 (1H, d, \(J=7.4, 1.9\) Hz), 7.23 (1H, td, \(J=7.4, 1.4\) Hz), 7.07 (1H, td, \(J=7.7, 1.7\) Hz), 4.61 (1H, t, \(J=3.7\) Hz), 3.95 (1H, dt, \(J=12.8, 4.9\) Hz), 3.79-3.73 (1H, m), 3.65 (1H, dt, \(J=12.8, 4.9\) Hz), 3.47-3.45 (1H, m), 3.07 (2H, t, \(J=7.2\) Hz), 1.82-1.80 (1H, m), 1.72-1.67 (1H, m), 1.57-1.53 (4H, m).

Step 2: Production of 2-[2-(tetrahydropyran-2-yloxy)ethyl]phenylboronic acid

[1944]

[1945] To a solution of 2-[2-(2-bromophenyl)ethoxy]tetrahydropyran (3.58 g, 12.5 mmol) and trisopropyl borate (3.70 ml, 16.1 mmol) in tetrahydrofuran (10.0 ml) was added a solution (10.0 ml) of 1.6M n-butyl lithium in hexane at \(-78^\circ\) C., and the mixture was stirred for 2 hr while gradually raising the temperature to 0° C. 1N HCl hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=3:1-2:1) to give 2-[2-(tetrahydropyran-2-yloxy)ethyl]phenylboronic acid (1.77 g, yield 56.6%).

[1946] \(^1\)H-NMR(400 MHz, CDCl<sub>3</sub>): \(\delta\) (ppm) 7.67 (1H, d, \(J=7.4\) Hz), 7.38 (1H, t, \(J=7.7\) Hz), 7.24-7.23 (2H, m), 6.42 (2H, brs), 4.60-4.58 (1H, m), 4.34-4.31 (1H, m), 3.71-3.66 (1H, m), 3.36-3.33 (2H, m), 3.05-3.01 (2H, m), 1.66-1.26 (4H, m), 0.95-0.90 (2H, m).

Step 3: Production of methyl 1-cyclohexyl-2-[2-(tetrahydropyran-2-yloxy)ethyl]phenyl-1H-indole-6-carboxylate

[1947]
[1948] To a suspension of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (2.10 g, 6.24 mmol) obtained in the same manner as in the method described in WO03/010140 and 2-[2-(tetrahydropryan-2-yloxy)ethyl]phenylboronic acid (1.77 g, 7.10 mmol) in 1.2-dimethoxyethane (20 ml) and water (10 ml) were added sodium hydroxide carbonate (2.00 g, 24.0 mmol) and tetakis(triphenylphosphine)palladium (360 mg, 0.31 mmol), and the mixture was heated under reflux for 7 hr. The reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=6:1-5:1) to give methyl 3-cyclohexyl-2-[2-(2-[2-(tetrahydropryan-2-yloxy)ethyl]phenyl]-1H-indole-6-carboxylate (2.21 g, yield 77.2%).

[1949] MS 462.0(M+1).

Step 4: Production of methyl 3-cyclohexyl-2-[2-(2-hydroxyethyl)phenyl]-1H-indole-6-carboxylate

[1950] A solution of methyl 3-cyclohexyl-2-[2-(2-tetrahydropryan-2-yloxy)ethyl]phenyl]-1H-indole-6-carboxylate (2.21 g, 4.80 mmol) in tetrahydrofuran (10 ml), methanol (10 ml) and 6N hydrochloric acid (20 ml) was stirred at room temperature for 2 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=5:1-2:1) to give methyl 3-cyclohexyl-2-[2-(2-hydroxyethyl)phenyl]1H-indole-6-carboxylate (1.20 g, yield 66.7%).

[1951] \(^1\)H-NMR(400 MHz, CDCl\(_3\)), \(\delta\) (ppm) 9.85 (1H, s), 8.10 (1H, s), 7.84 (1H, d, \(J=8.3\) Hz), 7.76 (1H, dd, \(J=8.3, 1.4\) Hz), 7.46-7.51 (4H, m), 4.01-3.97 (2H, m), 3.94 (3H, s), 2.72-2.69 (3H, m), 1.98-1.80 (7H, m), 1.50-1.26 (3H, m).

Step 5: Production of methyl 2-[2-(2-bromomethyl)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate

[1952]
[1954] To a solution of methyl 3-cyclohexyl-2-{2-(2-hydroxyethyl)phenyl]-1H-indole-6-carboxylate (600 mg, 1.58 mmol) in chloroform (6 ml) were added carbon tetrabromide (790 mg, 2.38 mmol) and triphenylphosphine (497 mg, 1.89 mmol), and the mixture was stirred at room temperature for 5 min. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=7:1-6:1) to give methyl 2-[2-(2-bromomethyl)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate (300 mg, yield 71.9%).

Step 6: Production of methyl 12-cyclohexyl-5,6-dihydroindol[2,1-a]isoquinoline-9-carboxylate (Example 5-5)

[1955]

Step 7: Production of 12-cyclohexyl-5,6-dihydroindol[2,1-a]isoquinoline-9-carboxylic acid (Example 5-4)

[1959]

[1960] To a solution of methyl 12-cyclohexyl-5,6-dihydroindol[2,1-a]isoquinoline-9-carboxylate (337 mg, 0.93 mmol) in tetrahydrofuran (3 ml) and methanol (3 ml) was added 4N aqueous sodium hydroxide solution (3.0 ml), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was acidified with 2N hydrochloric acid. The precipitated solid was collected by filtration and dried in vacuo to give 12-cyclohexyl-5,6-dihydroindol[2,1-a]isoquinoline-9-carboxylic acid (298 mg, yield 92.3%).

[1961] 1H-NMR(300 MHz, DMSO-d6); δ(ppm) 12.5 (1H, br s), 8.06 (1H, s), 7.88 (1H, d, J=8.4 Hz), 7.68 (1H, d, J=8.1 Hz), 7.59 (1H, d, J=8.4 Hz), 7.44-7.42 (1H, m), 7.33 (1H, t, J=7.5 Hz), 4.27 (2H, br s), 3.08 (2H, brs), 2.57-2.45 (1H, m), 2.08-2.04 (2H, m), 1.85-1.76 (5H, m), 1.46-1.42 (3H, m).

[1962] MS 346.2(M+1).

Example 11-1

Production of 14-cyclohexyl-6-methyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocino[8,1-a]indole-11-carboxylic acid monohydrochloride

Step 1: Production of N-(2-hydroxyethyl)-2-iodobenzamide

[1963]

[1956] To a solution of methyl 2-[2-(2-bromomethyl)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate (500 mg, 1.13 mmol) in N,N-dimethylformamide (10 ml) was added sodium hydride (60% in oil, 48 mg, 1.20 mmol) under ice-cooling, and the mixture was stirred for 30 min. 2N Hydrochloric acid was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=10:1-8:1) to give methyl 12-cyclohexyl-5,6-dihydroindol[2,1-a]isoquinoline-9-carboxylate (337 mg, yield 83.0%).

[1957] 1H-NMR(400 MHz, CDCl3); δ(ppm) 8.06 (1H, d, J=1.4 Hz), 7.88 (1H, d, J=8.3 Hz), 7.67 (1H, d, J=8.3 Hz), 7.40-7.25 (4H, m), 4.24 (2H, t, J=6.3 Hz), 3.94 (3H, s), 3.34 (1H, br t, J=12.3 Hz), 3.11 (2H, t, J=6.3 Hz), 2.14-2.11 (2H, m), 1.92-1.87 (5H, m), 1.50-1.45 (3H, m).

[1958] MS 360.1(M+1).
[1964] To a solution of 2-iodobenzoic acid (5.00 g, 20.1 mmol) in chloroform (50 ml) were added oxaly chloride (1.9 ml, 21.7 mmol) and N,N-dimethylformamide (5 drops with Pasteur pipette) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure and ethyl acetate (5 ml) was added to the residue to give a solution of 2-iodobenzoyl chloride in ethyl acetate.

[1965] To a solution of sodium hydrogen carbonate (3.30 g, 39.7 mmol) and 2-aminoethanol (1.80 ml, 29.8 mmol) in ethyl acetate (25 ml) and water (15 ml) was added dropwise the solution of 2-iodobenzoyl chloride in ethyl acetate prepared above under ice-cooling, and the mixture was stirred at room temperature for 12 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol= 30:1) to give methyl 3-cyclohexyl-2-{2-(2-hydroxyethylcarbamoyl)phenyl]-1H-indole-6-carboxylate (7.40 g, yield 100%).

[1969] 

[1966] \(^1\)H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) (ppm) 7.86 (1H, d, \(J=7.9\) Hz), 7.40-7.38 (2H, m), 7.11 (1H, ddd, \(J=8.6, 6.3, 1.6\) Hz), 6.29 (1H, brs), 3.86 (2H, dd, \(J=5.6, 4.6\) Hz), 3.62 (2H, dt, \(J=5.3, 4.9\) Hz), 2.22 (1H, brs).

Step 2: Production of methyl 3-cyclohexyl-2-{2-(2-hydroxyethylcarbamoyl)phenyl]-1H-indole-6-carboxylate

[1967]

[1968] To a suspension of N-(2-hydroxyethyl)-2-iodobenzamide (5.12 g, 17.5 mmol), sodium hydrogen carbonate (5.80 g, 69.8 mmol) and tetrais(triphenylphosphine)palladium (2.00 g, 1.73 mmol) in 1,2-dimethoxyethane (70 ml) and water (35 ml) was added methyl 3-cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-6-carboxylate (7.50 g, 19.5 mmol) in five divided portions at 90° C., and the mixture was stirred for 1 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol= 30:1) to give methyl 3-cyclohexyl-2-{2-(2-hydroxyethylcarbamoyl)phenyl]-1H-indole-6-carboxylate (7.40 g, yield 100%).

[1970]

[1971] To a solution of methyl 3-cyclohexyl-2-{2-(2-hydroxyethylcarbamoyl)phenyl]-1H-indole-6-carboxylate (2.00 g, 4.75 mmol) in tetrahydrofuran (5.0 ml) was added a solution (20.0 ml, 20.0 mmol) of 1M BH\textsubscript{4} THF complex in tetrahydrofuran under ice-cooling, and the mixture was stirred at room temperature for 17 hr. 2N Hydrochloric acid (20 ml) was added to the reaction mixture, and the mixture was stirred at 70° C. for 1.5 hr. The reaction mixture was allowed to cool to room temperature, the reaction mixture...
was neutralized with 4N aqueous sodium hydroxide solution and aqueous sodium hydrogen carbonate solution. To this mixture was added di-tert-butyl dicarbonate (1.60 g, 7.33 mmol), and the mixture was stirred at room temperature for 6 hr. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (chloroform:methanol=30:1 to 10:1) to give methyl 2-(2-[[N-tert-butoxycarbonyl-N-(2-hydroxyethyI)amino]methyl]phenyl)-3-cyclohexyl-1H-indole-6-carboxylate (524 mg, yield 22.1%).

[1972] $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$(ppm) 8.08 (1H, s), 7.82 (1H, d, J=8.3 Hz), 7.78 (1H, dd, J=8.3, 1.4 Hz), 7.46-7.39 (3H, m), 7.32 (1H, d, J=7.0 Hz), 4.37-4.35 (2H, m), 3.94 (3H, s), 3.41-3.39 (4H, m), 2.55 (1H, brs), 1.96-1.71 (7H, m), 1.40-1.09 (3H, m), 1.25 (9H, s).

[1973] MS 407.0(M+1).

Step 4: Production of methyl 2-(2-[[N-tert-butoxycarbonyl-N-(2-methanesulfonyloxyethyl)amino]methyl]phenyl)-3-cyclohexyl-1H-indole-6-carboxylate

[1974]

[1975] To a solution of methyl 2-(2-[[N-tert-butoxycarbonyl-N-(2-hydroxyethyI)amino]methyl]phenyl)-3-cyclohexyl-1H-indole-6-carboxylate (424 mg, 0.830 mmol) and triethylamine (0.14 ml, 1.0 mmol) in chloroform (5.0 ml) was added dropwise methanesulfonyl chloride (0.07 ml, 0.90 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 2-(2-[[N-tert-butoxycarbonyl-N-(2-methanesulfonyloxyethyl)amino]methyl]phenyl)-3-cyclohexyl-1H-indole-6-carboxylate as a crude product. The obtained crude product was used for Step 5 without purification.

Step 5: Production of methyl 6-tert-butoxycarbonyl-14-cyclohexyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocino[8,1-a]indole-11-carboxylate (Example 11-2)

[1976]

[1977] To a solution of methyl 2-(2-[[N-tert-butoxycarbonyl-N-(2-methanesulfonyloxyethyl)amino]methyl]phenyl)-3-cyclohexyl-1H-indole-6-carboxylate (crude product obtained in Step 4) in N,N-dimethylformamide (10 ml) was added sodium hydride (60% in oil, 36 mg, 0.90 mmol) under ice-cooling, and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=2:1-3:2) to give methyl 6-tert-butoxycarbonyl-14-cyclohexyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocino[8,1-a]indole-11-carboxylate (89 mg, yield 21.9%).

[1978] $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$(ppm) 8.08 (0.51, s), 8.07 (0.51, s), 7.90-7.78 (3.01, m), 7.53-7.34 (3.01, m),
4.98 (0.5H, d, J=14.8 Hz), 4.90 (0.5H, d, J=14.4 Hz), 4.66 (0.5H, dd, J=14.6, 4.9 Hz), 4.50 (1.0H, dd, J=19.5, 8.3 Hz), 4.31 (0.5H, d, J=14.4 Hz), 3.97 (3.0H, s), 3.75-3.67 (1.0H, m), 3.43 (0.5H, d, J=14.8 Hz), 3.29 (0.5H, d, J=14.8 Hz), 3.26 (0.5H, d, J=9.3 Hz), 3.03-2.97 (0.5H, m), 2.75-2.57 (1.0H, m), 2.03-1.72 (4.0H, m), 1.77-1.74 (2.0H, m), 1.60 (4.5H, s), 1.41 (4.5H, s), 1.35-1.18 (4.0H, m).

Step 6: Production of methyl 14-cyclohexyl-6-methyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinino[8,1-a]indole-11-carboxylate (Example 11-3)

[1979]

[1980] A solution of methyl 6-tert-butoxycarbonyl-14-cyclohexyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinino[8,1-a]indole-11-carboxylate (89 mg, 0.18 mmol) in 4N HCl-ethyl acetate was stirred at room temperature for 3 hr. The reaction mixture was concentrated under reduced pressure and chloroform (2.0 ml) was added to the residue. To this solution were successively added sodium acetate (30 mg, 0.36 mmol), acetic acid (0.01 ml, 0.20 mmol), 37% aqueous formaldehyde solution (2.0 ml) and sodium triacetoxborohydride (46 mg, 0.21 mmol), and the mixture was stirred for 13 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (chloroform:methanol=50:1-40:1) to give methyl 14-cyclohexyl-6-methyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinino[8,1-a]indole-11-carboxylate (73 mg, yield 100%).

[1981] 1H-NMR(300 MHz, CDCl3): δ (ppm) 8.06 (1H, s), 7.88 (1H, d, J=8.4 Hz), 7.81 (1H, t, J=4.2 Hz), 7.52-7.30 (4H, m), 4.31 (1H, dd, J=15.4, 5.5 Hz), 4.03-3.92 (1H, m).

[1982] Step 7: Production of 14-cyclohexyl-6-methyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinino[8,1-a]indole-11-carboxylic acid monohydrochloride (Example 11-1)

[1983] To a solution of methyl 14-cyclohexyl-6-methyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinino[8,1-a]indole-11-carboxylate (73 mg, 0.18 mmol) in tetrahydrofuran (1 ml) and methanol (1 ml) solution was added 4N aqueous sodium hydroxide solution (1 ml), and the mixture was stirred at room temperature for 3 hr. 2N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate and dried over anhydrous sodium carbonate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (chloroform:methanol=30:1-10:1) to give 14-cyclohexyl-6-methyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinino[8,1-a]indole-11-carboxylic acid. To a solution of the obtained 14-cyclohexyl-6-methyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinino[8,1-a]indole-11-carboxylic acid in ethyl acetate was added 4N HCl-ethyl acetate solution (2 ml), and the mixture was concentrated under reduced pressure. A mixed solvent of ethyl acetate:hexane (1:1) was added to the residue. The precipitated solid was collected by filtration and dried in vacuo to give 14-cyclohexyl-6-methyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinino[8,1-a]indole-11-carboxylic acid hydrochloride (25 mg, yield 52.9%).
[1984] \(^1\text{H-NMR}\) (400 MHz, DMSO-\(\text{d}_6\)): \(\delta\) (ppm) 12.69 (1H, brs), 10.68 (1H, brs), 8.21 (1H, s), 7.96-7.90 (2H, m), 7.93 (2H, d, \(J=8.8\) Hz), 7.73 (1H, dd, \(J=8.6, 1.2\) Hz), 7.67-7.60 (2H, m), 7.49-7.42 (1H, m), 4.79 (1H, d, \(J=13.0\) Hz), 4.40 (1H, d, \(J=13.0\) Hz), 3.73-3.62 (3H, m), 3.47-3.30 (1H, m), 2.98 (3H, s), 2.68-2.55 (1H, m), 2.01-1.75 (4H, m), 1.72-1.52 (3H, m), 1.40-1.05 (3H, m).

[1985] MS 389.2 (M+1).

Example 12-1

Production of 12-cyclohexyl-6,7-dihydro-5-thia-7a-
azadibenz(a,e)azulene-9-carboxylic acid

Step 1: Production of 2-(2-(bromophenyl)sulfanyl)ethoxy]tetrahydropyran

[1986]

[1987] To a solution of 2-bromobenzenethiol (3.0 ml, 24.9 mmol) in N,N-dimethylformamide (50 ml) was added sodium hydride (60% in oil, 1.10 g, 27.5 mmol) under ice-cooling, and the mixture was stirred for 1 hr. To this reaction mixture was added 2-(2-bromoethoxy)tetrahydropyran (4.5 ml, 29.7 mmol) under ice-cooling, and the mixture was stirred at room temperature for 3 hr. Aqueous sodium carbonate solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=10:1) to give 2-(2-(bromophenyl)sulfanyl)ethoxy]tetrahydropyran (7.91 g, yield 100%).

[1988] \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.55 (1H, dd, \(J=8.1, 1.2\) Hz), 7.36 (1H, dd, \(J=8.1, 1.6\) Hz), 7.29-7.25 (1H, m), 7.03 (1H, dt, \(J=1.4, 7.7\) Hz), 4.65 (1H, t, \(J=3.5\) Hz), 4.00-3.94 (1H, m), 3.91-3.85 (1H, m), 3.70 (1H, dt, \(J=12.8, 5.3\) Hz), 3.54-3.49 (1H, m), 3.20 (2H, dt, \(J=2.0, 6.8\) Hz), 1.83-1.69 (2H, m), 1.63-1.50 (4H, m).

[1989] Step 2: Production of methyl 3-cyclohexyl-2-[2-(tetrahydropyran-2-yloxy)ethylsulfanyl]phenyl]-1H-indole-6-carboxylate

[1990] To a suspension of 2-(2-(bromophenyl)sulfanyl)ethoxy]tetrahydropyran (1.00 g, 3.2 mmol), sodium hydrogen carbonate (1.10 g, 13.2 mmol) and tetrakis(triphenylphosphine)palladium (363 mg, 0.310 mmol) in 1,2-dimethoxyethane (10 ml) and water (5 ml) was added methyl 3-cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-6-carboxylate (1.45 g, 3.78 mmol) with heating under reflux and the mixture was heated under reflux for 2.5 hr. The reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=5:1-3:1) to give methyl
3-cyclohexyl-2-{2-[2-(tetrahydropropyran-2-yloxy)ethylsulfanyl]phenyl}-1H-indole-6-carboxylate (1.38 g, yield 74.5%).

[1991] 'H-NMR (300 MHz, CDCl₃): δ (ppm) 8.86 (1H, s), 8.11 (1H, d, J=0.7 Hz), 7.82 (1H, d, J=8.4 Hz), 7.76 (1H, dd, J=8.4, 0.7 Hz), 7.54 (1H, d, J=7.7 Hz), 7.41-7.25 (3H, m), 4.50 (1H, t, J=3.9 Hz), 4.12 (1H, q, J=7.1 Hz), 3.93 (3H, s), 3.84 (1H, t, J=11.6, 4.7 Hz), 3.61 (1H, dt, J=11.6, 5.3 Hz), 3.44 (1H, q, J=5.5 Hz), 3.05 (1H, dt, J=5.9, 5.8 Hz), 2.96 (1H, dt, J=6.1, 6.2 Hz), 2.69-2.59 (1H, m), 1.98-1.69 (7H, m), 1.68-1.40 (7H, m), 1.38-1.22 (2H, m).

Step 3: Production of methyl 3-cyclohexyl-2-[2-(2-hydroxyethylsulfanyl)phenyl]-1H-indole-6-carboxylate

[1992]

[1993] To a solution of methyl 3-cyclohexyl-2-[2-(tetrahydropropyran-2-yloxy)ethylsulfanyl]phenyl]-1H-indole-6-carboxylate (1.38 g, 2.81 mmol) in tetrahydrofuran (4 ml) and methanol (4 ml) was added 6N hydrochloric acid (4 ml), and the mixture was stirred at room temperature for 30 min. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=2:1-1:1) to give methyl 3-cyclohexyl-2-[2-(2-hydroxyethylsulfanyl)phenyl]-1H-indole-6-carboxylate (1.00 g, yield 87.5%).

Step 4: Production of methyl 3-cyclohexyl-2-[2-(2-methanesulfonyl)ethylsulfanyl]phenyl]-1H-indole-6-carboxylate

[1994]

[1995] To a solution of methyl 3-cyclohexyl-2-[2-(2-hydroxyethylsulfanyl)phenyl]-1H-indole-6-carboxylate (500 mg, 1.22 mmol) and triethylamine (0.19 ml, 1.4 mmol) in chloroform (5 ml) was added dropwise methanesulfonyl chloride (0.10 ml, 1.3 mmol) under ice-cooling, and the mixture was stirred for 30 min. Water was added to the reaction mixture and the mixture was extracted with chloroform. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 3-cyclohexyl-2-[2-(2-methanesulfonyl)ethylsulfanyl]phenyl]-1H-indole-6-carboxylate as a crude product. The obtained crude product was used for Step 5 without purification.
Step 5: Production of methyl 12-cyclohexyl-6,7-dihydro-5-thia-7a-azabenzof[a,e]azulene-9-carboxylate (Example 12-3)

[1996]

[2000]

Step 6: Production of 12-cyclohexyl-6,7-dihydro-5-thia-7a-azabenzof[a,e]azulene-9-carboxylate (Example 12-1)

[1997] To a solution of methyl 3-cyclohexyl-2-[2-(2-methanesulfonyloxyethyl)sulfinyl]phenyl]-1H-indole-6-carboxylate obtained as a crude product in Step 4 in N,N-dimethylformamide (10 ml) was added sodium hydride (60% in oil, 53 mg, 1.3 mmol) under ice-cooling, and the mixture was stirred for 30 min. 2N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=30:1-10:1) to give methyl 12-cyclohexyl-6,7-dihydro-5-thia-7a-azabenzof[a,e]azulene-9-carboxylate (186 mg, yield 39.0%).

[1998] 1H-NMR(300 MHz, CDCl3): δ(ppm) 8.08 (1H, d, J=1.1 Hz), 7.90 (1H, d, J=8.4 Hz), 7.77 (1H, dd, J=8.4, 1.5 Hz), 7.72 (1H, dd, J=7.3, 1.1 Hz), 7.52-7.37 (3H, m), 4.70 (1H, dd, J=15.0, 4.8 Hz), 3.95 (3H, s), 3.92-3.88 (1H, m), 3.47 (1H, dd, J=11.7, 3.3 Hz), 3.28 (1H, dt, J=5.5, 12.5 Hz), 2.89-2.80 (1H, m), 2.06-1.95 (4H, m), 1.75-1.71 (3H, m), 1.35-1.28 (3H, m).


[2001] To a solution of methyl 12-cyclohexyl-6,7-dihydro-5-thia-7a-azabenzof[a,e]azulene-9-carboxylate (186 mg, 0.470 mmol) in tetrahydrofuran (2 ml) and methanol (2 ml) was added 4N aqueous sodium hydroxide solution (2 ml), and the mixture was stirred at room temperature for 13 hr. 2N Hydrochloric acid and water were added to the reaction mixture. The precipitated solid was collected by filtration and dried in vacuo to give 12-cyclohexyl-6,7-dihydro-5-thia-7a-azabenzof[a,e]azulene-9-carboxylic acid (157 mg, yield 87.7%)

[2002] 1H-NMR(300 MHz, DMSO-d6): δ(ppm) 12.57 (1H, brs), 8.18 (1H, d, J=1.1 Hz), 7.89 (1H, d, J=8.4 Hz), 7.73-7.70 (1H, m), 7.65 (1H, dd, J=8.4, 1.5 Hz), 7.59 (1H, d, J=4.4 Hz), 7.49-7.47 (2H, m), 4.93 (1H, dd, J=15.0, 4.8 Hz), 3.80-3.70 (1H, m), 3.44 (1H, dd, J=12.1, 3.7 Hz), 3.36-3.28 (1H, m), 2.76-2.73 (1H, m), 1.99-1.89 (4H, m), 1.78-1.71 (2H, m), 1.49-1.24 (4H, m).


Example 12-2

Production of 11-cyclohexyl-5-thia-6a-azabenzof[a]fluorene-8-carboxylic acid

Step 1: Production of methyl 2-bromo-3-cyclohexyl-1-phenylsulfonylmethyl-1H-indole-6-carboxylate

[2004]
[2005] To a solution of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (1.00 g, 2.97 mmol) in N,N-dimethylformamide (10 ml) was added sodium hydride (60% in oil, 139 mg, 3.47 mmol) under ice-cooling, and the mixture was stirred for 1 hr. To this reaction mixture was added chloromethylsulfonylbenzene (0.38 ml, 2.94 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate=20:1-7:1) to give methyl 2-bromo-3-cyclohexyl-1-phenylsulfonylmethyl-1H-indole-6-carboxylate (1.10 g, yield 84.0%).

[2006] 1H-NMR(300 MHz, CDCl3): δ (ppm) 7.79 (1H, bs), 7.74 (1H, dd, J=8.4, 1.6 Hz), 7.69 (1H, brd, J=8.4 Hz), 7.23-7.29 (1H, m), 7.21-7.21 (2H, brd, J=6.8 Hz), 7.16-7.16 (2H, dd, J=8.4, 7.6 Hz), 5.52 (2H, s), 3.92 (3H, s), 2.75-2.85 (1H, m), 1.95-1.83 (4H, m), 1.82-1.71 (3H, m), 1.48-1.40 (3H, m).

Step 2: Production of methyl 11-cyclohexyl-5-thia-6a-azabenzo[a]fluorene-8-carboxylate (Example 12-4)

[2008] A suspension of methyl 2-bromo-3-cyclohexyl-1-phenylsulfonylmethyl-1H-indole-6-carboxylate (1.10 g, 2.41 mmol), potassium acetate (260 mg, 2.64 mmol) and tetrakis(triphenylphosphine)palladium (279 mg, 0.42 mmol) in N,N-dimethylacetamide (30 ml) was stirred at 100°C for 3 hr. The reaction mixture was allowed to cool to room temperature, 2N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate=20:1-7:1) to give methyl 11-cyclohexyl-5-thia-6a-azabenzo[a]fluorene-8-carboxylate (100 mg, yield 11.0%).

[2009] 1H-NMR(300 MHz, CDCl3): δ (ppm) 8.08 (1H, d, J=0.7 Hz), 7.91 (1H, d, J=8.4 Hz), 7.75 (1H, dd, J=8.8, 1.5 Hz), 7.65 (1H, dd, J=7.7, 1.5 Hz), 7.52 (1H, dd, J=7.5, 1.3 Hz), 7.37 (1H, dt, J=1.6, 7.6 Hz), 7.29 (1H, dt, J=1.6, 7.5 Hz), 5.22 (2H, s), 3.95 (3H, s), 3.19 (1H, t, J=12.3 Hz), 2.12-2.05 (2H, m), 1.90-1.85 (5H, m), 1.44-1.41 (3H, m).

Step 3: Production of 11-cyclohexyl-5-thia-6a-azabenzo[a]fluorene-8-carboxylic acid (Example 12-2)

[2010]

[2011] To a solution of methyl 11-cyclohexyl-5-thia-6a-azabenzo[a]fluorene-8-carboxylate (100 mg, 0.26 mmol) in
tetrahydrofuran (2 ml) and methanol (2 ml) was added 4N aqueous sodium hydroxide solution (2 ml), and the mixture was stirred at room temperature for 15 hr. 2N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=2:1-1.1) to give 11-cyclohexyl-5-dihydro-4H-azepine[4,5]diazocino[8,1-a]indole-11-carboxylic acid (32 mg, yield 33.3%).

**[2012]** $^1$H-NMR(300 MHz, DMSO-d$_6$): δ=12.62 (1H, brs), 8.23 (1H, d, J=8.4 Hz), 7.94 (1H, d, J=8.4 Hz), 7.64-7.51 (3H, m), 7.47 (1H, td, J=7.6, 1.2 Hz), 7.40-7.35 (1H, m), 5.53 (2H, s), 3.13 (1H, t, J=11.7 Hz), 2.12-2.08 (2H, m), 1.82-1.76 (5H, m), 1.42-1.38 (3H, m).

**[2013]** MS 364.0(M+1).

**Example 11-2 (2)**

**Production of methyl 6-tert-butoxy carbonyl-14-cyclohexyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocino[8,1-a]indole-11-carboxylate**

**Step 1: Production of methyl 2-bromo-3-cyclohexyl-1-[2-(tetrahydropryan-2-yloxy)ethyl]-1H-indole-6-carboxylate**

**[2014]**

To a solution of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (5.00 g, 14.8 mmol) in N,N-dimethylformamide (50 ml) was added sodium hydride (60% in oil, 715 mg, 17.8 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 1 hr. 2-(2-Bromoethoxy)tetrahydropryan (2.90 ml, 19.2 mmol) was added to the reaction mixture under ice-cooling, and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 2-bromo-3-cyclohexyl-1-[2-(tetrahydropryan-2-yloxy)ethyl]-1H-indole-6-carboxylate as a crude product. The obtained crude product was used for Step 2 without purification.

**Step 2: Production of methyl 2-bromo-3-cyclohexyl-1-(2-hydroxyethyl)-1H-indole-6-carboxylate**

**[2016]**

**[2017]** To a solution of methyl 2-bromo-3-cyclohexyl-1-[2-(tetrahydropryan-2-yloxy)ethyl]-1H-indole-6-carboxylate obtained as a crude product in Step 1 in tetrahydropryan (30 ml) and methanol (30 ml) was added 6N hydrochloric acid (30 ml), and the mixture was stirred at room temperature for 3 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:ethyl acetate=4:1-1:1) to give methyl 2-bromo-3-cyclohexyl-1-(2-hydroxyethyl)-1H-indole-6-carboxylate (3.43 g, yield 61%).

**[2018]** $^1$H-NMR(400 MHz, CDCl$_3$): δ=8.12 (1H, s), 7.79-7.71 (2H, m), 4.43 (2H, t, J=5.8 Hz), 3.99 (2H, t, J=5.6 Hz), 3.94 (3H, s), 2.95-2.84 (1H, m), 1.99-1.76 (7H, m), 1.51-1.33 (3H, m).
Step 3: Production of methyl 2-bromo-3-cyclohexyl-1-(2-methanesulfonyloxyethyl)-1H-indole-6-carboxylate

To a solution of methyl 2-bromo-3-cyclohexyl-1-(2-hydroxyethyl)-1H-indole-6-carboxylate (3.43 g, 9.01 mmol) in chloroform (30 ml) were added triethylamine (1.40 ml, 10.0 mmol) and methanesulfonyl chloride (0.77 ml, 9.90 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 30 min. Water was added to the reaction mixture and the mixture was extracted with chloroform. The organic layer was successively washed with 1N hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 2-bromo-3-cyclohexyl-1-(2-methanesulfonyloxyethyl)-1H-indole-6-carboxylate as a crude product. The obtained crude product was used for Step 4 without purification.

Step 4: Production of methyl 2-bromo-3-cyclohexyl-1-[2-(1,3-dioxo-1,3-dihydroisindol-2-yl)ethyl]-1H-indole-6-carboxylate

To a solution of methyl 2-bromo-3-cyclohexyl-1-(2-methanesulfonyloxyethyl)-1H-indole-6-carboxylate obtained as a crude product in Step 3 in N,N-dimethylformamide (40 ml) were added potassium phthalimide (2.50 g, 13.4 mmol) and potassium carbonate (2.50 g, 18.0 mmol), and the mixture was stirred at 80°C for 7 hr. Water was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration and dried in vacuo to give methyl 2-bromo-3-cyclohexyl-1-[2-(1,3-dioxo-1,3-dihydroisindol-2-yl)ethyl]-1H-indole-6-carboxylate (3.96 g, yield 86%).

1H-NMR (400 MHz, CDCl3): δ (ppm) 8.02 (1H, s), 7.75 (1H, d, J=2.8 Hz), 7.74 (1H, d, J=2.8 Hz), 7.68-7.65 (4H, m), 4.54 (2H, t, J=6.0 Hz), 4.04 (2H, t, J=6.0 Hz), 3.91 (5H, s), 2.82 (1H, brt, J=12.1 Hz), 1.95-1.72 (7H, m), 1.46-1.30 (3H, m).

Step 5: Production of methyl 1-(2-aminooethyl)-2-bromo-3-cyclohexyl-1H-indole-6-carboxylate
[2025] To a suspension of methyl 2-bromo-3-cyclohexyl-1-[2-(1,3-dioxo-1,3-dihydroisindol)-2-yl]ethyl]-1H-indole-6-carboxylate (3.96 g, 7.78 mmol) in methanol (50 ml) and tetrahydrofuran (30 ml) was added hydrazine monohydrate (1.88 ml, 38.7 mmol), and the mixture was stirred at room temperature for 14 hr. The reaction mixture was filtered with celite and washed with ethyl acetate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=30:1-15:1) to give methyl 1-(2-aminoethyl)-2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (2.95 g, yield 100%).

[2026] 1H-NMR (400 MHz, CDCl3): δ (ppm) 8.07 (1H, brs), 7.77-7.73 (2H, m), 4.50 (2H, t, J=6.5 Hz), 3.94 (3H, s), 3.10 (2H, t, J=6.7 Hz), 2.83 (1H, brt, J=12.3 Hz), 2.00-1.75 (7H, m), 1.50-1.30 (4H, m).

Step 6: Production of methyl 2-bromo-1-(2-tert-butoxycarbonylaminooethyl)-3-cyclohexyl-1H-indole-6-carboxylate

[2027]

[2028] To a solution of methyl 1-(2-aminoethyl)-2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (2.95 g, 7.78 mmol) in ethyl acetate (30 ml) and saturated aqueous sodium hydrogen carbonate solution (10 ml) was added di-tert-butyl dicarbonate (2.10 g, 9.62 mmol), and the mixture was stirred at room temperature for 3 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=8:1-3:1) to give methyl 2-bromo-1-(2-tert-butoxycarbonylaminoethyl)-3-cyclohexyl-1H-indole-6-carboxylate (2.78 g, yield 74%).

[2029] 1H-NMR (400 MHz, CDCl3): δ (ppm) 8.04 (1H, s), 7.76 (2H, brs), 4.58 (1H, brs), 4.39 (2H, t, J=6.0 Hz), 3.93 (3H, s), 3.51 (2H, q, J=6.0 Hz), 2.92-2.86 (1H, m), 2.00-1.76 (7H, m), 1.50-1.32 (3H, m), 1.42 (9H, s).

Step 7: Production of methyl 1-(2-tert-butoxycarbonylaminoethyl)-3-cyclohexyl-2-(2-formylphenyl)-1H-indole-6-carboxylate

[2030]

[2031] To a suspension of methyl 2-bromo-1-(2-tert-butoxycarbonylaminoethyl)-3-cyclohexyl-1H-indole-6-car-
boxylate (500 mg, 1.04 mmol), 2-formylphenylboronic acid (187 mg, 1.24 mmol) and sodium hydrogen carbonate (345 mg, 4.15 mmol) in 1,2-dimethoxyethane (5 mL) and water (2.5 mL) was added tetrakis(triphenylphosphine)palladium (60.0 mg, 0.05 mmol), and the mixture was stirred at 90°C for 2 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane-ethyl acetate=5:1-3:1) to give methyl 1-(2-tert-butoxycarbonylaminomethyl)-3-cyclohexyl-2-(2-formylphenyl)-1H-indole-6-carboxylate (450 mg, yield 85%).

[2032] 1H-NMR(400 MHz, CDCl3): δ(ppm) 9.79 (1H, brs), 8.15 (1H, brs), 8.11 (1H, d, J=7.7, 1.2 Hz), 7.84 (2H, brs), 7.75 (1H, t, J=7.2 Hz), 7.67 (1H, t, J=7.4 Hz), 7.46 (1H, d, J=7.4 Hz), 4.38 (1H, brs), 4.16-4.10 (2H, m), 3.96 (3H, s), 3.27 (2H, t, J=5.8 Hz), 2.49-2.36 (1H, m), 1.85-1.60 (7H, m), 1.31 (9H, s), 1.26-1.10 (3H, m).

Step 8: Production of methyl 1-(2-tert-butoxycarboxylic acid)-3-cyclohexyl-2-(2-hydroxymethyl)-1H-indole-6-carboxylate

[2033]
and methanesulfonyl chloride (0.02 ml, 0.25 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 10 min. Water was added to the reaction mixture and the mixture was extracted with chloroform. The organic layer was successively washed with 1N hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution and saturated brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure to give methyl 1-(2-tert-butoxycarbonylaminomethyl)-3-cyclohexyl-2-(2-methanesulfonyloxyethylphenyl)-1H-indole-6-carboxylate as a crude product. The obtained crude product was used for Step 10 without purification.

Step 10: Production of methyl 6-tert-butoxycarbonyl-14-cyclohexyl-5,6,7,8-tetrahydrobenzo[6,7][1,4] diazocino[8,1-a]indole-11-carboxylate (Example 11-2)

[2039] To a solution of methyl 1-(2-tert-butoxycarbonylaminomethyl)-3-cyclohexyl-2-(2-methanesulfonyloxyethylphenyl)-1H-indole-6-carboxylate obtained as a crude product in Step 9 in N,N-dimethylformamide (5 ml) was added sodium hydride (60% in oil, 12 mg, 0.30 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1.5 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration and dried in vacuo to give methyl 6-tert-butoxycarbonyl-14-cyclohexyl-5,6,7,8-tetrahydrobenzo[6,7][1,4] diazocino[8,1-a]indole-11-carboxylate (92 mg, yield 100%)

[2040] ^1H-NMR(400 MHz, CDCl_3); δ(ppm) 8.08 (0.5H, s), 8.07 (0.5H, s), 7.90-7.78 (3H, m), 7.53-7.34 (3H, m), 4.98 (0.5H, d, J=14.3 Hz), 4.90 (0.5H, d, J=14.4 Hz), 4.66 (0.5H, dd, J=14.6, 4.9 Hz), 4.50 (1H, dd, J=19.5, 8.3 Hz), 4.31 (0.5H, d, J=14.4 Hz), 3.97 (3H, s), 3.75-3.67 (1H, m), 3.43 (0.5H, d, J=14.8 Hz), 3.29 (0.5H, d, J=14.8 Hz), 3.26 (0.5H, d, J=9.3 Hz), 3.03-2.97 (0.5H, m), 2.75-2.57 (1H, m), 2.03-1.72 (4H, m), 1.77-1.74 (2H, m), 1.60 (4.5H, s), 1.41 (4.5H, s), 1.35-1.18 (4H, m).

[2041] MS 489.0(M+1).

[2042] The compounds of Examples 1-446 to 1-472 and Examples 2-54 to 2-150 were produced by the same methods as in the above-mentioned Examples, particularly, Examples 2-57, 2-175, 2-180, 2-332, 2-346, 2-349, 2-350, 2-369 and 2-381 or methods similar thereto, and where necessary, by employing other conventional methods. The chemical structural formulas are shown in Tables 119-144.

[2043] The compounds of Examples 1-473 to 1-623, Examples 2-151 to 2-556, Examples 5-6 and 5-7, Examples 7-9 and 7-10, Examples 8-8 and 8-9 and Examples 11-4 to 11-8 were produced by the same methods as in the above-mentioned Examples or methods similar thereto, and where necessary, by employing other conventional methods. The chemical structural forms are shown in Tables 145-268.

[2044] 2-[13-cyclohexyl-10-(2H-tetrazol-5-yl)-6,7-dihydrobenzo[5,6][1,4] diazepino[7,1-a]indole-5-yl]-1-(4-ethylpiperazin-1-yl)ethanone (Example 1-96)

[2045] 13-cyclohexyl-5-[2-(4-ethoxybenzyloxy)piperazin-1-yl]ethyl]-6,7-dihydro-5H-benzo[5,6][1,4] diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-97)

[2046] 5-[2-(4-acetylpiperazin-1-yl)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4] diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-98)


[2048] 13-cyclohexyl-3-[2-(morpholin-4-yl)-benzoxyl]-6,7-dihydro-5H-benzo[5,6][1,4] diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-100)

[2049] 13-cyclohexyl-3-[5-methanesulfonyl-2-(morpholin-4-yl)benzoxyl]-6,7-dihydro-5H-benzo[5,6][1,4] diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-101)

[2050] N-acetyl]-13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4] diazepino[7,1-a]indole-10-carboxamide (Example 1-102)

[2051] 13-cyclohexyl-3-[5-methanesulfonyl-2-(morpholin-4-yl)benzoxyl]-5-methyl-6,7-dihydro-5H-benzo[5,6][1,4] diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-103)

[2052] 13-cyclohexyl-5-[2-(4-methoxybenzyloxy)piperazin-1-yl]ethyl]-6,7-dihydro-5H-benzo[5,6][1,4] diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-104)

[2053] 13-cyclohexyl-5-[3-(tetrahydropyran-2-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4] diazepino[7,1-a]indole-10-carboxylic acid (Example 1-105)
[2054] 13-cyclohexyl-5-[2-(3-hydroxypiperidin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-106)

[2055] 13-cyclohexyl-3-fluoro-5-[2-(morpholin-4-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-107)

[2056] 13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-108)

[2057] 13-cyclohexyl-3-fluoro-5-[2-(morpholin-4-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-109)

[2058] 13-cyclohexyl-5-[2-(4-ethylpiperazine-1-yl)-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-110)

[2059] 13-cyclohexyl-5-[3-(piperidin-1-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-111)

[2060] 13-cyclohexyl-5-(3-hydroxypropyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-112)

[2061] 13-cyclohexyl-5-[2-(3-hydroxypiperidin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-113)

[2062] 13-cyclohexyl-3-fluoro-5-[2-oxo-2-(piperidin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-114)

[2063] 13-cyclohexyl-3-methyl-5-[2-oxo-2-(piperidin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-115)

[2064] 13-cyclohexyl-3-fluoro-5-[2-(piperidin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-116)

[2065] 13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-117)

[2066] 5-[1-acetylpiperidin-4-ylmethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-118)

[2067] 13-cyclohexyl-5-[2-(1-isopropylpiperidin-4-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-119)

[2068] 13-cyclohexyl-5-(tetrahydropryan-4-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-120)

[2069] 13-cyclohexyl-2-fluoro-5-[2-(piperidin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-121)

[2070] 13-cyclohexyl-5-[2-(3-methylpiperidin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-122)

[2071] 13-cyclohexyl-5-[2-(1-ethylpiperidin-4-ylidene)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-123)

[2072] 13-cyclohexyl-5-[2-(4-isopropylpiperidin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-124)

[2073] 13-cyclohexyl-5-[2-(3-methoxypiperidin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-125)

[2074] 13-cyclohexyl-5-(pyridin-2-ylmethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-126)

[2075] 3-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-127)

[2076] methyl 3-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-128)

[2077] N-[13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carbonyl]propane-1-sulfonamide dihydrochloride (Example 1-129)

[2078] 13-cyclohexyl-5-(1-ethylpiperidin-4-ylmethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-130)

[2079] 5-[2-(azocan-1-yl)-2-oxoethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-131)

[2080] 5-[2-(azonan-1-yl)-2-oxoethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-132)

[2081] 13-cyclohexyl-5-(1-ethylpiperidin-4-ylmethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-133)

[2082] 13-cyclohexyl-5-(pyridin-4-ylmethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-134)

[2083] 13-cyclohexyl-5-(pyridin-3-ylmethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-135)

[2084] 13-cyclohexyl-5-[2-(6,6-dihydro-2H-pyrindin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-136)

[2085] 13-cyclohexyl-5-[2-(2-methylpiperidin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-137)
[2086] 13-cyclohexyl-5-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-138)

[2087] 13-cyclohexyl-5-[2-(octahydroquinolin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-139)

[2088] 13-cyclohexyl-5-[2-(1,3-dihydroisindol-2-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-140)

[2089] 13-cyclohexyl-5-[2-(octahydroisquinolin-2-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-141)

[2090] 13-cyclohexyl-5-[2-(3,4-dihydro-1H-isoquinolin-2-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-142)

[2091] 13-cyclohexyl-5-[2-(3-methylpipеридин-1-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-143)

[2092] 13-cyclohexyl-5-[2-(octahydroquinolin-1-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-144)

[2093] 13-cyclohexyl-5-[2-(1,3-dihydroisindol-2-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-145)

[2094] 13-cyclohexyl-5-[2-(octahydroisquinolin-2-yl)-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-146)

[2095] 3-chloro-13-cyclohexyl-5-[2-(пиперидин-1-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-147)

[2096] 13-cyclohexyl-5-(3-dimethylaminopropyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-148)

[2097] 13-cyclohexyl-4-fluoro-5-[2-(пиперидин-1-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-149)

[2098] 13-cyclohexyl-5-[2-(4-isopropylпиперидин-1-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-150)

[2099] 13-cyclohexyl-5-[2-(3-methoxyпиперидин-1-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-151)

[2100] 5-[1-tert-butoxyкарбонилпиперидин-3-илмethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-152)

[2101] 13-cyclohexyl-5-[1-этилпиперидин-3-илметил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-153)

[2102] 5-[2-(азокан-1-ил)этил]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-154)

[2103] 5-[2-(азокан-1-ил)этил]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-155)

[2104] 13-cyclohexyl-5-[2-(2-метилпиперидин-1-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-156)

[2105] 13-cyclohexyl-5-[2-(1-циклопентилпиперидин-4-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-157)

[2106] 13-cyclohexyl-5-[2-оксо-2-(4-трифлуорометилпиперидин-1-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-158)

[2107] 13-cyclohexyl-5-[2-(пиперидин-1-ил)этил]-3-трифлуорометил-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-159)

[2108] 13-cyclohexyl-5-[2-(4-этилпиперазин-1-ил)этил]-3-трифлуорометил-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid trihydrochloride (Example 1-160)

[2109] 5-[2-(1-терти-бутоксикарбонилпиперидин-2-ил)этил]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-161)

[2110] 13-cyclohexyl-5-[2-(4-этилпиперазин-1-ил)-2-оксоэтан-3-ил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-162)

[2111] 13-cyclohexyl-5-[2-(пирдин-2-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-163)

[2112] 13-cyclohexyl-5-[2-(метоксипиперидин-2-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-164)

[2113] 13-cyclohexyl-5-[2-(пиперидин-3-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-165)

[2114] 13-cyclohexyl-5-[2-(1-этилпиперидин-3-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-166)

[2115] 5-[2-(1-терти-бутоксикарбонилпиперидин-3-ил)этил]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-167)

[2116] 13-cyclohexyl-3-метил-5-[2-(1,4-окзазепан-4-ил)этил]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-168)
[2117] 3-chloro-13-cyclohexyl-5-[2-(1,4-oxazepan-4-yl-ethyl)]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid monohydrochloride (Example 1-169)

[2118] 13-cyclohexyl-3-fluoro-5-[2-(1,4-oxazepan-4-yl-ethyl)]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-170)

[2119] 13-cyclohexyl-5-[2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-171)

[2120] 13-cyclohexyl-5-[2-(4-trifluoromethylpiperidin-1-yl)-ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-172)

[2121] 13-cyclohexyl-5-[2-(1-propylpiperidin-4-yl-ethyl)]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-173)

[2122] 13-cyclohexyl-5-[2-(4,4-difluoropiperidin-1-yl-ethyl)]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-174)

[2123] 13-cyclohexyl-5-[2-(1-ethylpiperidin-4-ylidene)-2-fluoromethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-175)

[2124] 2-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl-ethyl)]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-176)

[2125] 13-cyclohexyl-5-[2-(piperidin-2-yl)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-177)

[2126] 13-cyclohexyl-5-[2-(1-ethylpiperidin-2-yl)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-178)

[2127] 13-cyclohexyl-3-methylsulfanyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-179)

[2128] 3-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl-ethyl)]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxamide dihydrochloride (Example 1-180)

[2129] 13-cyclohexyl-5-[2-(pyridin-3-yl)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-181)

[2130] 13-cyclohexyl-5-[2-(pyridin-4-yl)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-182)

[2131] 13-cyclohexyl-5-[-(3aS,7aR)-2-(octahydroisindol-2-yl)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-183)

[2132] 5-[2-(8-azaspiro[4.5]decan-8-yl)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-184)

[2133] 13-cyclohexyl-5-[2-(diethylaminomethyl)-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-185)

[2134] 13-cyclohexyl-5-[2-(diisopropylaminomethyl)-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-186)

[2135] 13-cyclohexyl-5-[2-(3,5-dimethylpiperidin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid monohydrochloride (Example 1-187)

[2136] 13-cyclohexyl-5-[2-(3-ethylpiperidin-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid monohydrochloride (Example 1-188)

[2137] 13-cyclohexyl-5-[2-(3,5-dimethylpiperidin-1-yl-ethyl)]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-189)

[2138] 13-cyclohexyl-5-[2-(3-ethylpiperidin-1-yl)-ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-190)

[2139] 13-cyclohexyl-2-methyl-5-[2-(piperidin-1-yl-jethyl)]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-191)

[2140] 13-cyclohexyl-5-[2-(4-propylpiperidin-1-yl-jethyl)]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-192)

[2141] 13-cyclohexyl-5-[2-(28,6R)-2,6-dimethylpiperidin-1-yl)ethyl)]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-193)

[2142] 5-[3-(azepan-1-yl)propyl]-13-cyclohexyl-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-194)

[2143] 5-[adamantan-1-ylcarbamoylmethyl]-13-cyclohexyl-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid monohydrochloride (Example 1-195)

[2144] 5-[2-(adamantan-1-yl)aminoethyl]-13-cyclohexyl-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-196)

[2145] 13-cyclohexyl-5-[2-(4-methoxyethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-197)

[2146] 13-cyclohexyl-5-[2-(N-methyl-N-propylamino)ethyl]-6,7-dihydro-5H-benzof[5,6][1,4]diazepino[7,1-a] indole-10-carboxylic acid dihydrochloride (Example 1-198)
[2147] 13-cyclohexyl-5-[2-(4,4-dimethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-199)

[2148] 13-cyclohexyl-5-[2-(3-methoxyethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-200)

[2149] 13-cyclohexyl-5-[2-(1-methylpiperidin-3-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-201)

[2150] 13-cyclohexyl-5-[2-(4-isopropylpiperidin-3-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-202)

[2151] 13-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-203)

[2152] 13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-6-oxo-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-204)

[2153] 13-cyclohexyl-5-[2-(3,6-dihydro-2H-pyridin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-205)

[2154] 13-cyclohexyl-4-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-206)

[2155] 13-cyclohexyl-5-[2-((S)-2-methoxyethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-207)

[2156] 13-cyclohexyl-5-[2-(2-methylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-208)

[2157] 13-cyclohexyl-5-[2-(N-isopentyl-N-methylamino)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-209)

[2158] 13-cyclohexyl-5-[2-(morpholin-4-yl)-2-oxoethyl]-6-oxo-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-210)

[2159] 3-benzyloxy-13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-211)

[2160] 13-cyclohexyl-5-[2-(N-isopropyl-N-methylamino)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-212)

[2161] 3-chloro-13-cyclohexyl-5-[2-(2-methylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-213)

[2162] 3-chloro-13-cyclohexyl-5-[2-(3-methylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-214)

[2163] 3-chloro-13-cyclohexyl-5-[2-(4-methylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-215)

[2164] 3-chloro-13-cyclohexyl-5-[2-(pyrrolidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-216)

[2165] 5-[2-azepan-1-yl)ethyl]-3-chloro-13-cyclohexyl-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-217)

[2166] 5-[2-azepan-1-yl)ethyl]-3-chloro-13-cyclohexyl-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-218)

[2167] 3-chloro-13-cyclohexyl-5-[2-(piperidin-3-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-219)

[2168] 13-cyclohexyl-5-[2-(3-methylmorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-220)

[2169] 3-chloro-13-cyclohexyl-5-[2-(1-methylpiperidin-3-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-221)


[2172] 13-cyclohexyl-5-[2-(4-ethanesulfonylpiperazin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-224)

[2173] 13-cyclohexyl-5-[2-(4-propionylpiperazin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-225)

[2174] 13-cyclohexyl-5-[2-(4-isopropoxy carbonylpiperazin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-226)

[2175] 13-cyclohexyl-3-isopropoxy-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-227)

[2176] 3-benzyloxy-13-cyclohexyl-5-[2-(dimethylamino)ethyl]-6,7-dihydro-5H-benzof[5,6]1,4-diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-228)
[2177] 3-chloro-13-cyclohexyl-5-[2-(1-isopropylpiperidin-3-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-229)

[2178] 3-chloro-13-cyclohexyl-5-[2-(1-propylpiperidin-3-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-230)

[2179] 13-cyclohexyl-5-[2-(N-cyclohexyl-N-methylamino)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-231)

[2180] 13-cyclohexyl-5-[2-(4-methanesulfonyl-1,4-diazepan-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-232)

[2181] 13-cyclohexyl-5-[2-(4-methoxyxycarbonyl-1,4-diazepan-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-233)

[2182] 5-[2-(6-oxo-7,6-dihydro-5H-indole-5-carboxylic acid monohydrochloride (Example 1-234)

[2183] 13-cyclohexyl-6-oxo-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-235)

[2184] 13-cyclohexyl-5-[2-[N-[2-(N-methoxyxycarbonyl-N-methyllamino)ethyl]-N-methyllamino)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-236)

[2185] 13-cyclohexyl-5-[2-(3-methylpyrrolidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-237)

[2186] 13-cyclohexyl-5-[2-(3-methylpyrrolidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-238)

[2187] 13-cyclohexyl-5-[2-(4-ethyl-1,4-diazepan-1-yl)-2-oxoethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-239)

[2188] 3-chloro-13-cyclohexyl-5-[2-(1-isopropylpiperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-240)

[2189] 13-cyclohexyl-1-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-241)

[2190] 3-chloro-13-cyclohexyl-5-[3-(piperidin-1-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-242)

[2191] 3-chloro-13-cyclohexyl-5-[2-(1-ethylpiperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-243)

[2192] 3-chloro-13-cyclohexyl-5-[2-(piperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-244)

[2193] 5-[3-(azepan-1-yl)propyl]-3-chloro-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-245)

[2194] 3-chloro-13-cyclohexyl-5-[2-(1-methylpiperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-246)

[2195] 3-chloro-13-cyclohexyl-5-[3-dimethylaminopropyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-247)

[2196] 13-cyclohexyl-2,3-dihydro-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-248)

[2197] 5-[2-(N-[1-acetylpyrrolidin-3-yl]-N-methylamino)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-250)

[2198] 13-cyclohexyl-5-[2-[N-[2-(N-methoxyxycarbonyl-N-methyllamino)ethyl]-N-methyllamino)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-251)

[2200] 13-cyclohexyl-5-[2-[N-[1-methanesulfonylpyrrolidin-3-yl]-N-methylamino)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-252)

[2201] 13-cyclohexyl-3-methyl-5-[2-(3-methylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-253)

[2202] 13-cyclohexyl-3-fluoro-5-[2-(3-methylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-254)

[2203] 13-cyclohexyl-5-[2-(2-methylmorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-255)

[2204] 13-cyclohexyl-5-[2-(2-ethylmorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-256)

[2205] 13-cyclohexyl-5-[2-(3-ethylmorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-257)

[2206] 13-cyclohexyl-3-methyl-5-[2-(2-methylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-258)
[2207] 13-cyclohexyl-3-methyl-5-[2-(4-methylpyridin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-259)

[2208] 13-cyclohexyl-3-methyl-5-[2-(pyrrolidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-260)

[2209] 3-chloro-13-cyclohexyl-5-[2-(1-ethylpiperidin-3-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-261)

[2210] 3-chloro-13-cyclohexyl-5-[2-(1-methylpiperidin-4-yl)oxyethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-262)

[2211] 3-chloro-13-cyclohexyl-5-[2-(1-isobutylpiperidin-3-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-263)

[2212] 3-chloro-13-cyclohexyl-5-[2-(1-cyclopentylpiperidin-3-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-264)

[2213] 3-chloro-13-cyclohexyl-5-[2-(3-methoxy-piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-265)

[2214] 13-cyclohexyl-5-[2-(3-methoxy-piperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-266)

[2215] 3-chloro-13-cyclohexyl-5-[2-(3-propylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-267)

[2216] 13-cyclohexyl-3-methyl-5-[2-(3-propylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-268)

[2217] 3-chloro-13-cyclohexyl-5-[3-(pyrrolidin-1-yl)pro-pyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-269)

[2218] 3-chloro-13-cyclohexyl-5-[3-(1,4-oxazepan-4-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-270)

[2219] 13-cyclohexyl-5-[2-(2-methoxymethyl-piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-271)

[2220] 13-cyclohexyl-5-[2-(3-ethylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-272)

[2221] 13-cyclohexyl-5-[2-(1-ethylpiperidin-3-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-273)

[2222] 13-cyclohexyl-3-methyl-5-[2-(1-methylpiperidin-3-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-274)

[2223] 13-cyclohexyl-5-[2-(1-isopropylpiperidin-3-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-275)

[2224] 13-cyclohexyl-3-ethoxy-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-276)

[2225] 5-[2-(azocan-1-yl)ethyl]-3-chloro-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-277)

[2226] 5-[2-(azocan-1-yl)ethyl]-13-cyclohexyl-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-278)

[2227] 5-[2-N-(1-acetyl-piperidin-4-yl)-N-methylaminio]ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid mono-hydrochloride (Example 1-279)

[2228] 13-cyclohexyl-5-[2-N-(1-methanesulfonylpiperidin-4-yl)-N-methylaminio]ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid mono-hydrochloride (Example 1-280)


[2230] 13-cyclohexyl-5-[2-N-(methyl-N-(1-methylpyridin-4-yl)aminio)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-282)

[2231] 13-cyclohexyl-5-[2-N-(methyl-N-(tetrahydro-pyran-4-yl)aminio)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-283)

[2232] 13-cyclohexyl-5-[2-N-(methyl-N-(1-methylpyridin-3-yl)aminio)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-284)

[2233] 13-cyclohexyl-5-[2-N-(methyl-N-(pyrrolidin-3-yl)aminio)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-285)

[2234] 13-cyclohexyl-5-[2-(4-ethyl-1,4-diazepan-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid trihydrochloride (Example 1-286)

[2235] 13-cyclohexyl-3-methyl-5-[2-(1-methyl-piperidin-2-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-287)
[2236] 13-cyclohexyl-5-[2-(1-ethyl)piperidin-2-yl)ethyl]-3-methyl-6,7 dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-288)

[2237] 5-[2-(azepan-1-yl)ethyl]-13-cyclohexyl-3-methylsulfanyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-289)

[2238] 3-chloro-13-cyclohexyl-5-[2-(2-ethylmorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-290)

[2239] 19-cyclohexyl-5-[2-(2-ethylmorpholin-4-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-291)

[2240] 13-cyclohexyl-5-[2-(3-ethylmorpholin-4-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-292)

[2241] 3-chloro-13-cyclohexyl-5-[2-(3-methoxymethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-293)

[2242] 13-cyclohexyl-5-[2-(3-methoxymethylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-294)

[2243] 13-cyclohexyl-3-ethyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-295)

[2244] 13-cyclohexyl-3-isopropyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-296)

[2245] 13-cyclohexyl-3-methylsulfanyl-5-[3-(piperidin-1-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-297)

[2246] 13-cyclohexyl-3-methyl-5-[3-(piperidin-1-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-298)

[2247] 13-cyclohexyl-3-methyl-5-[3-(p-pyridin-1-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-299)

[2248] 5-[3-(azepan-1-yl)propyl]-13-cyclohexyl-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-300)

[2249] 13-cyclohexyl-5-[3-(dimethylaminopropyl)-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-301)

[2250] 3-chloro-13-cyclohexyl-5-[3-diethylaminopropyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-302)

[2251] 13-cyclohexyl-3-methylsulfanyl-5-[2-(pyrrolidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-303)

[2252] 3-chloro-13-cyclohexyl-5-[2-(2-methoxymethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-304)

[2253] 13-cyclohexyl-5-[2-(2-methoxymethylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-305)

[2254] 13-cyclohexyl-5-[2-[3-(2-methoxethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-306)

[2255] 3-chloro-13-cyclohexyl-5-[2-[3-(2-methoxethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-307)

[2256] 13-cyclohexyl-5-[2-[3-(2-methoxyethyl)piperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-308)

[2257] 13-cyclohexyl-5-(2-dimethylaminomethyl)-3-[5-methanesulfonfyl-2-(morpholin-4-yl)benzoxoxy]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid trihydrochloride (Example 1-509)

[2258] 13-cyclohexyl-5-(2-dimethylaminomethyl)-3-methoxybenzoxoxy-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-310)

[2259] 13-cyclohexyl-5-(2-dimethylaminomethyl)-3-phenoxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-311)

[2260] 3-chloro-13-cyclohexyl-5-[2-(1-methylpiperidin-2-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-312)

[2261] 3-chloro-13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-313)

[2262] 3-chloro-13-cyclohexyl-5-[2-[4-(methoxymethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-314)

[2263] 13-cyclohexyl-5-[2-[4-(methoxymethyl)piperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-315)

[2264] 13-cyclohexyl-5-[2-[3-(2-methoxymethyl)pyrroldin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-316)

[2265] 3-chloro-13-cyclohexyl-5-[2-(1-ethylpiperidin-4-yloxy)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-317)
[2266] 3-chloro-13-cyclohexyl-5[2-(1-isopropylpiperidin-4-yl)oxyethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-318)


[2268] 3-chloro-13-cyclohexyl-5[3-(3-methylpiperidin-1-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin[7,1-a]indole-10-carboxylic acid (Example 1-320)


[2270] 3-chloro-13-cyclohexyl-5[3-(2-methylpiperidin-1-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepin[7,1-a]indole-10-carboxylic acid (Example 1-322)


[2273] 13-cyclohexyl-5[2-(3-ethoxy-piperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepine[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-325)


[2275] 3-chloro-13-cyclohexyl-5[2-(3-ethylmorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-327)

[2276] 3-chloro-13-cyclohexyl-5[2-(2-methylmorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-328)

[2277] 13-cyclohexyl-3-methyl-5[2-(2-methylmorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-329)


[2281] 13-cyclohexyl-5[2-(2-ethylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-333)


[2285] 5[2-(azepan-1-yl)ethyl]-13-cyclohexyl-3-isopropyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-337)

[2286] 5[2-(azepan-1-yl)ethyl]-13-cyclohexyl-3-ethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-338)

[2287] 13-cyclohexyl-3-ethyl-5[2-(3-methylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-339)


[2289] 13-cyclohexyl-5[2-(3-ethylpiperidin-1-yl)ethyl]-3-isopropyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-341)


[2291] 13-cyclohexyl-5[2-(piperidin-1-yl)ethyl]-3-propyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-343)

[2292] N-[2-{10-carboxy-13-cyclohexyl-3-(5-methylisoxazol-3-ylmethyl)oxy}-6,7-dihydro-benzo[5,6][1,4]diazepine[7,1-a]indole-5-yl]ethyl]-NN-dimethyl-N-(5-methylisoxazol-3-ylmethyl)ammonium chloride monohydrochloride (Example 1-344)

[2293] 13-cyclohexyl-3-ethyl-5[2-(3-methylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-345)

[2294] 13-cyclohexyl-5[2-(3-methoxymethylpiperidin-1-yl)ethyl]-3-propyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepine[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-346)
[2295] 13-cyclohexyl-3-ethoxy-5-{2-(3-ethylpiperidin-1-yl)ethyl}-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-347)

[2296] 3-benzyloxy-13-cyclohexyl-5-{2-(3-ethylpiperidin-1-yl)ethyl}-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-348)

[2297] 13-cyclohexyl-3-ethoxy-5-{2-(1-isopropylpiperidin-3-yl)ethyl}-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-349)

[2298] 13-cyclohexyl-3-ethyl-5-{2-(3-ethylpiperidin-1-yl)ethyl}-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-350)

[2299] 3-chloro-13-cyclohexyl-5-{2-(3-isopropylpiperidin-1-yl)ethyl}-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-351)

[2300] 3-chloro-13-cyclohexyl-5-[3-(3-methoxymethylpiperidin-1-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-352)

[2301] 3-chloro-13-cyclohexyl-5-{3-(2-ethylpiperidin-1-yl)propyl}-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-353)

[2302] 13-cyclohexyl-5-[2-(1-isopropylpiperidin-3-yl)ethyl]-3-propyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-354)

[2303] 3-chloro-13-cyclohexyl-5-[3-(2-methoxymethylpiperidin-1-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-355)

[2304] 13-cyclohexyl-5-{2-(3-methylpiperidin-1-yl)ethyl]-3-propyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-356)

[2305] 13-cyclohexyl-5-{2-(3-ethylpiperidin-1-yl)ethyl]-3-propyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-357)

[2306] 3-benzyloxy-13-cyclohexyl-5-[2-(3-methoxymethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-358)

[2307] 13-cyclohexyl-3-isopropyl-5-[2-(pyrrolidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-359)

[2308] 13-cyclohexyl-3-ethyl-5-[2-(pyrrolidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-360)

[2309] 3-benzyloxy-13-cyclohexyl-5-[2-(3-methylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-361)

[2310] 3-benzyloxy-13-cyclohexyl-5-[2-(1-isopropylpiperidin-3-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-362)

[2311] 13-cyclohexyl-3-(5-methylisoxazol-3-ylmethylene)-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-363)

[2312] 13-cyclohexyl-5-[2-(3-isopropylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-364)

[2313] 13-cyclohexyl-5-[2-(3-isopropylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-365)

[2314] 13-cyclohexyl-3-ethyl-5-[2-(3-methoxymethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-366)

[2315] 13-cyclohexyl-3-isopropyl-5-[2-(3-methoxymethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-367)

[2316] 3-chloro-13-cyclohexyl-5-[3-(2-methylpyrrolidin-1-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-368)

[2317] 13-cyclohexyl-3-ethyl-5-[2-(1-isopropylpiperidin-3-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-369)

[2318] 13-cyclohexyl-3-ethoxy-5-[2-(3-methoxymethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-370)

[2319] 3-chloro-13-cyclohexyl-5-[2-(1-isopropylpiperidin-3-yl)oxy]ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-371)

[2320] 3-chloro-13-cyclohexyl-5-[3-(3-ethylpiperidin-1-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-372)

[2321] 13-cyclohexyl-3-isobutoxy-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-373)

[2322] 13-cyclohexyl-5-(2-dimethylaminoethyl)-3-(5-methylisoxazol-3-ylmethylene)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-374)

[2323] 13-cyclohexyl-3-isobutoxy-5-[2-(3-methylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-375)
(Example 1-376)

(Example 1-377)

(Example 1-378)

(Example 1-379)

(Example 1-380)

(Example 1-381)

(Example 1-382)

(Example 1-383)

(Example 1-384)

(Example 1-385)

(Example 1-386)

(Example 1-387)

(Example 1-388)

(Example 1-389)

(Example 1-390)

(Example 1-391)

(Example 1-392)

(Example 1-393)

(Example 1-394)

(Example 1-395)

(Example 1-396)

(Example 1-397)

(Example 1-398)

(Example 1-399)

(Example 1-400)

(Example 1-401)

(Example 1-402)

(Example 1-403)

(Example 1-404)

(Example 1-405)
[2354] 3-chloro-13-cyclohexyl-5-[2-(3-isopropoxymethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-406)

[2355] 13-cyclohexyl-5-[2-(3-isopropoxymethylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-407)

[2356] 3-chloro-13-cyclohexyl-5-[2-[(R)-1-cyclopentylpiperidin-3-yl]ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-408)

[2357] 13-cyclohexyl-5-[[2-[(R)-3-(2-methoxyethyl)piperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-409)

[2358] 13-cyclohexyl-3-methyl-5-[[2-[1-propylpiperidin-3-yl]ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-410)

[2359] 3-chloro-13-cyclohexyl-5-(3-[1-ethylpiperidin-3-yl]propyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-411)

[2360] 3-chloro-13-cyclohexyl-5-[3-(1-cyclopentylpiperidin-3-yl)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-412)

[2361] 13-cyclohexyl-5-[[2-[(S)-3-(2-methoxethyl)piperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-413)

[2362] 13-cyclohexyl-5-[[2-[1-isopropylpiperidin-3-yl]ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-414)

[2363] 3-chloro-13-cyclohexyl-5-[4-(piperidin-1-yl)butyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid (Example 1-415)

[2364] 13-cyclohexyl-5-[2-[[2(R)-3-methoxymethylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-416)

[2365] 13-cyclohexyl-5-[2-[[2(S)-3-methoxymethylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-417)

[2366] 13-cyclohexyl-3-[3-methanesulfonylbenzoyloxy]-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-418)

[2367] 3-chloro-13-cyclohexyl-5-[2-[[2(R)-3-ethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid (Example 1-419)

[2368] 13-cyclohexyl-5-[2-[[2(R)-3-ethylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-420)

[2369] 3-chloro-13-cyclohexyl-5-[2-[[2(S)-3-ethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid (Example 1-421)

[2370] 13-cyclohexyl-5-[2-[[2(S)-3-ethylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-422)

[2371] 5-[[2-(azocan-1-yl)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-423)

[2372] 3-chloro-13-cyclohexyl-5-[4-(diethylaminobutyl)-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid (Example 1-424)

[2373] 13-cyclohexyl-3-methyl-5-[4-(piperidin-1-yl)butyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-425)

[2374] 3-chloro-13-cyclohexyl-5-[2-[(1-methylpyrrolidin-2-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-426)

[2375] 13-cyclohexyl-3-ethoxy-5-[[2-[[2(S)-3-(2-methoxyethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-427)

[2376] 3-chloro-13-cyclohexyl-5-[3-(N-ethyl-N-propylamino)propyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-428)

[2377] 3-chloro-13-cyclohexyl-5-[3-diisopropylamino-propyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-429)

[2378] 13-cyclohexyl-3-ethyl-5-[[2-[[2(S)-3-(2-methoxethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-430)


[2382] 13-cyclohexyl-3-fluoro-5-[[2-[[2(S)-3-(2-methoxyethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-434)

[2383] 13-cyclohexyl-5-[[2-(3-hydroxymethyl)piperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]dizepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-435)
[2384] 3-chloro-13-cyclohexyl-5-(3-diethylamino-2,2-dimethylpropyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 2-436)

[2385] 13-cyclohexyl-5-methyl-3-[2-(piperidin-1-yl)ethoxy]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-437)

[2386] 13-cyclohexyl-5-methyl-3-[2-(piperidin-4-yl)ethoxy]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-438)

[2387] 13-cyclohexyl-5-methyl-3-[2-(1-methylpiperidin-4-yl)ethoxy]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-439)

[2388] 13-cyclohexyl-5-[2-(3,3-dimethylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-440)

[2389] 3-chloro-13-cyclohexyl-5-(3-diethylamino-2-methoxypropyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-441)


[2391] 13-cyclohexyl-5-[2-(4-hydroxymethylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-443)

[2392] 13-cyclohexyl-5-[2-[(S)-3-(2-phenoxyethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-444)

[2393] 13-cyclohexyl-3-methoxy-5-[2-[(S)-3-(2-methoxyethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-445)

[2394] 12-cyclohexyl-3-(5-methylisoxazol-3-ylmethoxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-32)

[2395] 3-[2-(tert-butoxycarbonylamino)ethoxy]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-33)

[2396] 12-cyclohexyl-3-(2-methylthiazol-4-ylmethoxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-34)

[2397] 3-[1-(tert-butoxycarbonyl)pyrrolidin-2-ylmethoxy]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-35)

[2398] 12-cyclohexyl-3-[2-(methoxycarbonylamino)ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-36)

[2399] 3-chloro-13-cyclohexyl-5-(3-diethylamino-2-methoxypropyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 2-37)

[2400] 12-cyclohexyl-3-[2-(2-oxooxazolidin-3-yl)ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-38)

[2401] 4-benzylxoy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-39)

[2402] 3-[(S)-1-(tert-butoxycarbonyl)pyrrolidin-3-yl]oxy]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-40)

[2403] 3-[(S)-2-butoxycarbonylamino-3-phenylpropoxy]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-41)

[2404] 3-[(S)-2-butoxycarbonylamino-3-methylbutoxy]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid monohydrochloride (Example 2-42)

[2405] 3-[(S)-2-butoxycarbonylamino-3-methylbutoxy]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid monohydrochloride (Example 2-43)

[2406] 12-cyclohexyl-3-(1-methanesulfonfylpiperidin-5-yl)xy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-44)

[2407] 12-cyclohexyl-3-(1-methylpiperidin-2-ylmethoxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-45)

[2408] 12-cyclohexyl-3-(piperidin-3-yl)oxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid monohydrochloride (Example 2-46)

[2409] 12-cyclohexyl-3-[2-(morpholin-4-yl)-5-(2-oxopyrrolidin-1-yl)benzoyloxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide monohydrochloride (Example 2-47)

[2410] 12-cyclohexyl-3-[5-methanesulfonfyl-2-(morpholin-4-yl)benzoyloxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide monohydrochloride (Example 2-48)

[2411] 12-cyclohexyl-3-(5-methoxycarbonylamino-3-phenylpropoxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-49)

[2412] 12-cyclohexyl-3-(5-methoxycarbonylpyrrolidin-3-yl)oxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-50)

[2413] 12-cyclohexyl-3-[5-(5-methoxycarbonylpyrrolidin-3-yl)oxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-51)

[2414] 12-cyclohexyl-3-[2-(5-methoxycarbonylamino)phenoxo]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-52)

[2415] 12-cyclohexyl-4-[2-(piperidin-1-yl)ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid monohydrochloride (Example 2-53)

[2416] 3-benzylxox-12-cyclohexyl-6,7-dihydro-5-oxa-7a,8-diazadibenzo[a,e]azulene-9-carboxylic acid (Example 7-8)
[2417] 3-chloro-12-cyclohexyl-5-[2-(piperidin-1-yl-ethyl)-1,6,7-dihydro-5H-1,5a,8-triazadibenzo[a,e]julene-9-carboxylic acid trihydrochloride (Example 1-85)

[2418] 3-chloro-12-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-ethyl]-6,7-dihydro-5H-1,5a,8-triazadibenzo[a,e]julene-9-carboxylic acid trihydrochloride (Example 1-86)

[2419] 3-chloro-12-cyclohexyl-5-[2-(piperidin-1-yl-ethyl)]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylic acid (Example 10-1)

[2420] ethyl 3-chloro-12-cyclohexyl-5-[2-(piperidin-1-yl-ethyl)]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylate (Example 10-2)

[2421] 3-chloro-12-cyclohexyl-5-[2-(piperidin-1-yl-ethyl)]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylic acid (Example 10-3)

[2422] 12-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-b]indole-9-carboxylic acid (Example 10-4)

[2423] 13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxo-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indol-5-yl)ethyipiperidine-1-carboxylate (Example 1-446)

[2424] N-methyl-13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxo-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxamide (Example 1-446)

[2425] N-(2-hydroxyethyl)-13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxo-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxamide (Example 1-448)

[2426] N-(2-hydroxy-1,1-dimethylethyl)-13-cyclohexyl-5-[2-(4-ethylpiperazin-1-yl)-2-oxo-ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxamide (Example 1-449)

[2427] (E)-3-[4-[[1-(13-cyclohexyl-5-methyl-3-methylsulfonyl-1,6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylo]-amino)cyclobutane-carbonyl]amino]phenyl]acrylic acid (Example 1-450)

[2428] 9-chloro-13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-452)

[2429] 9-chloro-13-cyclohexyl-3,5-dimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-452)

[2430] (S)-6-amino-2-[[13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-carbonyl]amino]hexanoic acid dihydrochloride (Example 1-453)

[2431] benzyl 4-[[13-cyclohexyl-3-methyl-10-methylcarbamoyl-6,7-dihydrobenzo[5,6][1,4]diazepino[7,1-a]indol-5-yl)piperidine-1-carboxylate (Example 1-454)


[2433] N-methyl-5-(1-acetylprop-1-yl)-13-cyclohexyl-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxamide (Example 1-456)

[2434] N-methyl-13-cyclohexyl-5-[2-(1S)-3-(2-methoxy-ethyl)piperidin-1-yl)-2-oxoethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxamide (Example 1-457)

[2435] N-methyl-13-cyclohexyl-5-[2-(4-methoxy-piperidin-1-yl)-2-oxoethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxamide (Example 1-458)


[2438] N-methyl-13-cyclohexyl-5-[2-(4-fluorophenyl-ethyl)]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxamide (Example 1-461)


[2444] (E)-3-[[1-(13-cyclohexyl-3-methyl-5-[2-(1,4-oxazepan-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carbonyl]amino]cyclobutane-carbonyl]amino]phenyl]acrylic acid (Example 1-467)


[2464] 2-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino)-3-methoxypropionic acid (Example 2-68)

[2465] 2-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino)-3-methylsulfanylpropionic acid (Example 2-69)

[2466] 2-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino)-3-dimethylaminopropionic acid (Example 2-70)

[2467] (E)-3-(4-2-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino)acrylamide (Example 2-71)

[2468] 1-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino)cyclopentane-
carboxylic acid (Example 2-72)

[2469] 2-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino)-2-methylpropionic acid (Example 2-73)

[2470] 2-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino)-2-phenylacetic acid (Example 2-74)

[2471] 2-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino)-3-phenylpropionic acid (Example 2-75)

[2472] 2-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino]methyl benzoic acid (Example 2-76)

[2473] 4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino]methyl benzoic acid (Example 2-77)

[2474] ethyl (E)-3-4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino]piperidine-1-carboxylate (Example 2-78)

[2475] (E)-3-4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-

[2476] 4-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]piperazine-2,6-dione (Example 2-80)

[2477] 3-4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino]cyclobutanecarboxylate (Example 2-81)

[2478] cis-4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino]cyclohexanecarboxylic acid (Example 2-82)

[2479] 6-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino]hexanoic acid (Example 2-83)

[2480] 1-6-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-aza-
dibenzo[a,e]azulen-9-carbonyl]amino]hexanoic acid (Example 2-84)
[2481] trans-4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino]cyclohexanecarboxylic acid (Example 2-85)

[2482] N-tert-butoxy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbamamide (Example 2-86)

[2483] 4-[[6-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino]hexanoylamino][phenyl]acetic acid (Example 2-87)

[2484] 4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][phenyl]acetic acid (Example 2-88)

[2485] (E)-3-4-[[2-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][2-methylpropionylamino][phenyl]acrylic acid (Example 2-89)

[2486] (E)-3-4-[[2-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][3-phenylpropionylamino][phenyl]acrylic acid (Example 2-90)

[2487] 4-2-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][2-methylpropionylamino][benzoyl acetic acid (Example 2-91)

[2488] 3-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][methyl]benzoic acid (Example 2-92)

[2489] 1-2-4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][phenyl]acetylamino)cyclopentancarboxylic acid (Example 2-93)

[2490] (E)-3-4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][cyclopropanecarboxylic acid (Example 2-94)

[2491] (E)-3-4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][cyclohexanecarboxylic acid (Example 2-95)

[2492] 1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][cyclohexanecarboxylic acid (Example 2-96)

[2493] 1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][cyclohexanecarboxylic acid (Example 2-97)

[2494] 1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][4,4-dimethylcyclohexanecarboxylic acid (Example 2-98)

[2495] 2-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][2-ethylbutyric acid (Example 2-99)

[2496] 4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][cyclohexanecarboxylic acid (Example 2-100)

[2497] (E)-3-4-[[1-N-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]-N-methylalanine][cyclohexanecarboxylic acid (Example 2-101)

[2498] 4-[4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][phenyl]acetic acid (Example 2-102)

[2499] N-1-phenylmecarbamoylcyclobutyl)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbamamide (Example 2-103)

[2500] 4-[[1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino]cyclobutanecarboxylic acid (Example 2-104)

[2501] (E)-3-[[cis-4-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino]cyclohexanecarboxylic acid (Example 2-105)

[2502] 6-[[1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino]cyclohexanecarboxylic acid (Example 2-106)

[2503] 4-[[1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino]cyclohexanecarboxylic acid (Example 2-107)

[2504] (N-1-phenylbenzamidomethyl)cyclobutyl)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbamamide (Example 2-108)

[2505] (E)-3-4-[[1-N-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]-N-(2-methoxyethyl)-alanine][acetic acid (Example 2-109)

[2506] 3-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][3-methylbutyric acid (Example 2-110)

[2507] (E)-3-4-[[1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino]-4-methylpentanoylamine][phenyl]acrylic acid (Example 2-111)

[2508] 1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino]cyclopropanecarboxylic acid (Example 2-112)

[2509] 1-[[1-N-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]-N-methylalanine][cyclohexanecarboxylic acid (Example 2-113)

[2510] 4-[[1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino]cyclohexanecarboxylic acid (Example 2-114)

[2511] 1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][cyclopropanecarboxylic acid (Example 2-115)

[2512] (E)-3-4-[[1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino]cyclohexanecarboxylic acid (Example 2-116)

[2513] (E)-3-4-[[1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azaazadibenzo[a,e]jululene-9-carbonyl]amino][phenyl]acrylic acid (Example 2-117)
(E)-3-[4-{1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}cyclohexanecarbonyl}amino]phenyl]acrylic acid (Example 2-118)

(E)-3-[4-{1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}[piperidine-1-carbonyl]amino]phenyl]acrylic acid (Example 2-119)

N-1-{4-[3-hydroxypropyl]phenyl]carbamoyl}cyclobutyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carboxamide (Example 2-120)

{4-[1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}cyclobutanecarbonyl]amino}phenoxy acetic acid (Example 2-121)

(E)-3-[4-[1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-122)

(E)-3-[4-{2-{12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}2-ethylbutylamino]phenyl]acrylic acid (Example 2-123)

(E)-3-[4-{1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-124)

3-4-1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)sulfamoyl}phenyl]propionic acid (Example 2-125)

(E)-3-[4-3-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}3-methylbutryl]amino]phenyl]acrylic acid (Example 2-126)

N-[1-(4-acetylphenyl]carbamoyl)cyclobutyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carboxamide (Example 2-127)

2-[1-{1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}cyclobutanecarbonyl]amino]benzoic acid (Example 2-128)

4-N-[1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}N-methyl]benzoic acid (Example 2-129)

3-4-1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}cyclobutanecarbonyl]amino]benzoic acid (Example 2-130)

2-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carboxamide]-2,4-dimethylpentanoic acid (Example 2-131)

(E)-3-[4-[1-{(3-chloro-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-132)

4-[1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino]1-methyl)ethyl]benzoic acid (Example 2-133)

(E)-3-[4-1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino]phenyl]acrylic acid (Example 2-134)

(E)-3-[4-[2-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}phenyl]acrylic acid (Example 2-135)

3-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino]cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-136)

(E)-3-[4-[1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-137)


(E)-3-[4-1-{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino}cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-139)

2-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino]3-methyl-3-methylsulfanylbutyric acid (Example 2-140)

(E)-3-[4-{1-{12-cyclohexyl-2,3-dihydro-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl]amino}cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-141)

(E)-3-[4-{1R,2R)-2-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino]cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-142)

2-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino]-3,3-dimethylbutyric acid (Example 2-143)

(E)-3-[4-{2-{12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carbonyl)amino]3,3-dimethylbutyrylamino]phenyl]acrylic acid (Example 2-144)


N-[1-(2-hydroxyethyl]carbamoyl)cyclobutyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carboxamide (Example 2-146)

N-[1-(2-methoxyethyl]carbamoyl)cyclobutyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carboxamide (Example 2-147)

12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carboxamide (Example 2-148)

N-[1R,2R)-2-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]zulene-9-carboxamide (Example 2-149).
[2546] (E)-3-[3-[[1-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carbonyl)amino]cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-150)

[2547] methyl (S)-2-([13-cyclohexyl-3,5-dimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxyl]amino)-3-(4-hydroxyphenyl)propionate (Example 1-473)

[2548] 13-cyclohexyl-5-ethyl-3-methoxy-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-474)

[2549] 13-cyclohexyl-5-isopropyl-3-methoxy-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid monohydrochloride (Example 1-475)

[2550] sodium salt of 13-cyclohexyl-5-methyl-5-(2-(1,4-oxazepan-4-yl)-2-oxoethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-476)


[2553] 13-cyclohexyl-3-methoxy-5-(2-methoxyethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-479)

[2554] 13-cyclohexyl-5-(2-isopropoxyethyl)-3-methoxy-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-480)


[2557] 13-cyclohexyl-5-isobutyl-3-methoxy-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-483)


[2559] 1-[[{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carbonyl)amino}cyclobutanecarbonyl]amino]cycolobutanecarbonylic acid (Example 2-151)

[2560] methyl 2-[[{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carbonyl)amino}cyclobutanecarbonyl]amino]cycolobutanecarbonylic acid (Example 2-152)


[2562] 2-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carbonyl]amino]-3-methoxy-2-methylpropionic acid (Example 2-154)


[2564] 4-{{(E)-2-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carbonyl]amino}methylpropoxy}benzoic acid (Example 2-156)

[2565] N-[2-(4-cyanophenony)-1,1-dimethylthethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxamide (Example 2-157)

[2566] N-[2-(4-cyanophenony)-1,1-dimethylthethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxamide (Example 2-158)

[2567] N-(2-hydroxy-1,1-dimethylthethyl)-12-cyclohexyl-6,1-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxamide (Example 2-159)

[2568] 2-1-[[{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carbonyl]amino}cyclobutyl]-3H-benzimidazole-5-carboxylic acid (Example 2-160)

[2569] 12-cyclohexyl-4-[[N-isopropyl-N-{2-(piperidin-1-yl)ethy]lamino}-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 2-161)

[2570] 12-cyclohexyl-4-[[N-(2-dimethylaminoethyl)N-methy]lamino]-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 2-162)

[2571] (E)-3-{{2-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carbonyl]amino}-3-methoxy-2-methylpropionylamino}phenyl]acrylic acid (Example 2-163)

[2572] N-[2-(2-hydroxyethoxy)ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxamide (Example 2-164)

[2573] N-tert-butyl-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxamide (Example 2-165)

[2574] N-(trans-4-hydroxy(cyclohexyl)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxamide (Example 2-166)

[2575] 2-1-[[{(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carbonyl]amino}1-methylethyl]thiazole-4-carboxylic acid (Example 2-167)

[2576] 12-cyclohexyl-4-[[N-ethyl-N-[2-(1,4-oxazepan-4-yl)ethy]lamino]-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 2-168)

[2577] 12-cyclohexyl-4-[[N-ethyl-N-[3-(piperidin-1-yl)propyl]lamino]-6,7-dihydro-5-oxa-7a-azadinbenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 2-169)
[2578] 12-cyclohexyl-4-[(N-ethyl-N-(2-morpholin-4-yl)-ethyl)amino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 2-170)

[2579] N-[1((4-hydroxymethylphenyl)-1-methylethyl)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-171)

[2580] ethyl 2-[[1(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 2-172)

[2581] N-methyl-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-173)

[2582] 3(4-[4-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 2-174)

[2583] N-[1-trans-4-hydroxycyclohexylcarboxamoyl)-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-177)

[2584] N-[1(4-hydroxymethylcarboxamoyl)methylethylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-176)

[2585] N-[1(4-hydroxycyclohexylcarboxamoyl)-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-178)

[2586] 12-cyclohexyl-4-[(N-ethyl-N[(2-piperidin-1-yl)acetylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid monohydrochloride (Example 2-178)

[2587] N-[1-(4-benzylxophenyl)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-179)

[2588] N-[1(4-hydroxymethylphenyl)-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-198)

[2589] 4-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-181)

[2590] 4-[4-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 2-182)

[2591] 2-[4(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylamino)-2-methylpropionylamino]benzoic acid (Example 2-183)

[2592] N-[2(4-carboxamidophenylamino)-1,1-dimethylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-184)

[2593] tert-butyl 2-[1(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylamino)-2-methylpropyl]carbamate (Example 2-185)

[2594] N-[2-amino-1,1-dimethylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide monohydrochloride (Example 2-186)

[2595] N-[2(4-hydroximino)ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-187)

[2596] N-[1,1-dimethyl-2-(4-nitrophenoxo)ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-188)

[2597] 2-[1(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylamino)-3-methylaminol-2-methylpropionic acid (Example 2-189)

[2598] N-[2(4-hydroxyperidin-1-yl)-1,1-dimethyl-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-190)

[2599] N-[2-benzyl-N(2-piperidin-1-yl)ethylamino]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 2-191)

[2600] N-[4-hydroxyphenyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-192)

[2601] N-[4-carbamoylphenylcarbamoyl)-1-methyl-ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-193)

[2602] N-[4-dimethylcarbamoylphenylcarbamoyl)-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-194)

[2603] N-[1(4-hydroxymethylphenylcarbamoyl)-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-195)

[2604] N-[1(4-hydroxymethylphenylcarbamoyl)-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-196)

[2605] N-[1(4-benzylxophenyl)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-197)

[2606] N-[1(1H-benzimidazol-2-yl)-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-198)

[2607] N-[1(4-chloro-1H-benzimidazol-2-yl)-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-199)

[2608] 5-[1(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylamino)-2-methylpropionylamino]-2-methylbenzoic acid (Example 2-200)

[2609] N-[1(4-hydroxyphenylcarbamoyl)-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-201)

[2610] N-[1(4-hydroxyphenylcarbamoyl)-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-202)

[2611] N-[1(4-hydroxyphenyl)ethylcarbamoyl)-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-203)

[2612] N-[1(4-fluorophenyl)carbamoyl)-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-204)

[2613] N-[2(4-hydroxyphenyl)ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-205)
[2614] N-(1-hydroxycyclohexyl)methyl-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-206)

[2615] N-[(S)-1-carbamoyl-2-(4-hydroxyphenoxy)ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-207)

[2616] 4-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)1-methylthyl]cyclohexanecarboxylic acid (Example 2-208)

[2617] methyl 2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)1-methylthyl]5-methyl-3H-imidazole-4-carboxylate (Example 2-209)

[2618] methyl 2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)3-(5-hydroxy-1H-indol-2-y1)propanoate (Example 2-210)

[2619] N-2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)2-methylpropyl]terephthalamic acid (Example 2-211)

[2620] methyl N-2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)2-methylpropyl]terephthalame (Example 2-212)

[2621] N-1-[4(dimethylaminomethylphenylcarbamoyl)1-methylthethyl]12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-213)

[2622] 2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)1-methylthethyl]-1H-benzimidazole-5-carboxylic acid (Example 2-214)

[2623] methyl 4-2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)2-methylpropyl]benzoate (Example 2-215)

[2624] 4-2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)2-methylpropyl]benzoic acid (Example 2-216)

[2625] N-[(S)-1-hydroxymethyl-2-(4-hydroxyphenyl)ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-217)

[2626] methyl (S)-2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)3-(4-methoxyphenyl)propanoate (Example 2-218)

[2627] N-2-(4-methoxyphenyl)-1,1-dimethylthethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-219)

[2628] N-2-(4-hydroxyphenyl)-1,1-dimethylthethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-220)

[2629] 12-cyclohexyl-4-[N-phenethyl-N-2-(piperidin-1-yl)ethyl]julaminio]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid (Example 2-221)

[2630] (E)-3-4-{(1-acetyl-4-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)1-methylthyl]piperidin-4-carboxamido)aminophenyl}acrylic acid (Example 2-222)

[2631] (E)-3-4-{(4-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)1-methylthyl]piperidine-4-carboxylamino)phenyl}acrylic acid (Example 2-223)

[2632] N-2-(4-aminocephoxy)-1,1-dimethylthethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-224)

[2633] N-1-[6(carbamoyl)-1H-benzimidazol-2-y1]-1-methylthethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-225)

[2634] N-1,1-dimethyl-2-4-[2-(oxoxyzolidin-1-yl)phenoxylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-226)

[2635] 2-1-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)1-methylthethyl]-5-methyl-3H-imidazole-4-carboxylic acid (Example 2-227)

[2636] N-1-(4-benzoxyphenyl)-1-methylthethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-228)

[2637] 1-carboxymethyl-4-[2-(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)1-methylthyl]piperidine-4-carboxylic acid monohydrochloride (Example 2-229)

[2638] N-1-[4-hydroxyphenyl]-1-methylthethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-230)

[2639] 4-2-[azepan-1-y1]-ethyl]-N-ethylamino]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid dihydrochloride (Example 2-231)

[2640] 4-2-[1-acetyl]piperidin-4-yl]ethyl]N-ethylamino]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid (Example 2-232)

[2641] 4-N-acetyl-N-2-(1-acetyl]piperidin-4-yl]ethyl]amino)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid (Example 2-233)

[2642] N-2-(4-hydroxyperidin-1-yl)-1,1-dimethylthethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-234)

[2643] methyl 2-1-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)1-methylthethyl]-5-methyloxazole-4-carboxylate (Example 2-235)

[2644] 2-1-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)1-methylthethyl]-5-methyloxazole-4-carboxylic acid (Example 2-236)

[2645] (S)-2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)3-(4-methoxyphenyl)propanoic acid (Example 2-237)

[2646] methyl (R)-2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamido)1-methylthethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-238)

[2647] N-2-(trans-4-hydroxycyclohexylamino)-1,1-dimethylthethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-239)
[2648] N-(2-(3-hydroxyperidin-1-yl)-1,1-dimethyl-2-oxoethyl)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-240)

[2649] 4-[1-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]-1-methylthyl]phenoxyacetic acid (Example 2-241)

[2650] N-[2-(4-hydroxymethylperidin-1-yl)-1,1-dimethyl-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-242)

[2651] 12-cyclohexyl-4-(N-ethyl-N-[2-(1-ethylperidin-4-yl)ethyl]amino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid dihydrochloride (Example 2-243)

[2652] N-[2-(4-hydroxymethylperidin-1-yl)-1,1-dimethylthyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-244)

[2653] 5-[2-(4-hydroxyphenyl)-1-methylcarbamoyl]-ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-245)

[2654] (R)-2-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]-3-(4-hydroxyphenyl)propionic acid (Example 2-246)

[2655] 4-(1H-benzimidazol-2-yl)-4-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]piperidin-1-yl)acetate monohydrochloride (Example 2-247)

[2656] methyl (4-(1H-benzimidazol-2-yl)-4-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]piperidin-1-yl)acetate (Example 2-247)

[2657] N-(1H-benzimidazol-2-yl)methyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-249)

[2658] 2-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]-3(4-hydroxy-1H-indol-2-yl)proionic acid (Example 2-250)

[2659] methyl [2-[[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]-3(4-hydroxy-1H-indol-2-yl)proionic acid (Example 2-250)

[2660] N-(1H-benzimidazol-2-yl)methyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-252)

[2661] 2-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]-3(5-hydroxy-1H-indol-2-yl)proionic acid (Example 2-253)

[2662] (E)-3-[[2-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]-2-methylpropanoylamino]acrylic acid (Example 2-254)


[2664] 4-[N-(2-benzoyloxethyl)-N-[2-(piperidin-1-yl)ethyl]amino]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid dihydrochloride (Example 2-256)

[2665] 12-cyclohexyl-4-(N-(2-isopropoxyethyl)-N-[2-(piperidin-1-yl)ethyl]amino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid dihydrochloride (Example 2-257)

[2666] N-[1-(4,5-dimethyl-1H-imidazol-2-yl)-1-methyl-ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-258)

[2667] N-[1-methyl-1-(1,4,5-trimethyl-1H-imidazol-2-yl)ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-259)

[2668] N-[1-(3-hydroxyphenylcarbamoyl)-1-methyl-ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-260)

[2669] 12-cyclohexyl-4-[N-(2-hydroxyethyl)-N-[2-(piperidin-1-yl)ethyl]amino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-261)

[2670] N-[1-[(S)-1-dimethylcarbamoyl]-2-(4-hydroxyphenyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-262)

[2671] N-[1-[(S)-2-(4-hydroxyphenyl)]-1-(methylcarbamoyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-263)

[2672] methyl (2-[1-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]-1-methylthyl]4,5-dimethylimidazol-1-yl)acetate (Example 2-264)

[2673] 2-[1-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]-1-methylthyl]-4,5-dimethylimidazol-1-yl)acetate (Example 2-265)

[2674] methyl (2-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]-3(1H-benzimidazol-5-carboxylate (Example 2-266)

[2675] N-(1H-benzimidazol-2-yl)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-267)

[2676] 2-[12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]-3(1H-benzimidazol-5-carboxylic acid (Example 2-268)

[2677] N-[1-(6-cyano-1H-benzimidazol-2-yl)-1-methyl-ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-269)

[2678] methyl (S)-2-[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]-2-(4-hydroxyphenyl)acetate (Example 2-270)

[2679] methyl (R)-2-[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]l]amino]-2-(4-hydroxyphenyl)acetate (Example 2-271)

[2680] 12-cyclohexyl-4-[N-ethyl-N-[2-(4-methoxyperidin-1-yl)ethyl]amino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid dihydrochloride (Example 2-272)

[2681] 12-cyclohexyl-4-phenyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid (Example 2-273)
[2682] 12-cyclohexyl-4-\{N-ethyl-N\{2-(3-methoxymethyl)piperidin-1-yl)ethyl\}amino\}-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid dihydrochloride (Example 2-274)

[2683] 12-cyclohexyl-4-\{N-ethyl-N\{2-(4-methoxymethyl)piperidin-1-yl)ethyl\}amino\}-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid dihydrochloride (Example 2-275)

[2684] 2-[\{12-cyclohexyl-4-\{N-2-(piperidin-1-yl)ethyl\}N-propylamino\}-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxyl]amino\}2-methylpropionic acid (Example 2-276)

[2685] 4-\{bis[2-oxo-2-(piperidin-1-yl)ethyl]amino\}-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid (Example 2-277)

[2686] 4-\{bis[2-(piperidin-1-yl)ethyl]amino\}-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid dihydrochloride (Example 2-278)

[2687] methyl (S)-2-[\{12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]amino\}-3-(4-fluorophenyl)propionate (Example 2-279)

[2688] methyl (S)-2-[\{12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]amino\}-3-(1H-imidazol-4-yl)propionate (Example 2-280)

[2689] methyl (S)-2-[\{12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]amino\}-7-hydroxy-1,2,3,4-tetrahydropyridinoline-3-carboxylate (Example 2-281)

[2690] methyl 2-\{1-[\{12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]amino\}-1-methyl-ethyl\}-6-methyl-3H-benimidazole-5-carboxylate (Example 2-282)

[2691] 2-\{1-[\{12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]amino\}-1-methyl-ethyl\}-6-methyl-3H-benimidazole-5-carboxylic acid (Example 2-283)

[2692] methyl 2-\{1-[\{12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]amino\}-1-methyl-ethyl\}-benzimidazol-2-ylacetate (Example 2-284)

[2693] N-[1-methyl-1-(1-methyl-1H-benimidazol-2-yl)ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenz[a,e,julene-9-carboxamid (Example 2-285)

[2694] N-(1-methyl-1H-benimidazol-2-yl)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-286)

[2695] 4-[\{12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxy]amino\}-4-hydroxymethylpiperidin-1-yl]acetic acid monohydrochloride (Example 2-287)

[2696] N-[1-(2-hydroxyethyl)-1H-benimidazol-2-yl]ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-288)

[2697] N-[1,1-dimethyl-2-(morpholin-4-yl)-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-289)

[2698] N-[1,1-dimethyl-2-(4-methyppiperazin-1-yl)-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-290)

[2699] N-[1,1-dimethyl-2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-291)

[2700] N-[1-(2-hydroxyethyl)-4,5-dimethyl-1H-imidazol-2-yl]-1-methylpiperazin]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-292)

[2701] N-[1-(dimethylcarbamoylmethyl)-4,5-dimethyl-1H-imidazol-2-yl]-1-methylpiperazin]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-293)

[2702] N-[2-(4-methoxypiperazin-1-yl)-1,1-dimethyl-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-294)

[2703] N-[\{S\}-2-(4-hydroxyphenyl)-1-[N-(2-methoxyethyl)-N-methylcarbamoyl]ethyl\}-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-295)

[2704] N-[\{S\}-2-(4-hydroxyphenyl)-1-(2-methoxycarbamoyl)ethyl\}-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-296)

[2705] N-[\{S\}-1-(4-hydroxybenzyl)-2-(4-methoxypiperazin-1-yl)-2-oxoethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-297)

[2706] 12-cyclohexyl-4-(pyridin-3-yl)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid monohydrochloride (Example 2-298)

[2707] 12-cyclohexyl-4-(pyridin-4-yl)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid monohydrochloride (Example 2-299)

[2708] 12-cyclohexyl-4-[\{2-(piperidin-1-yl)ethyl\}-N-propylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-300)

[2709] 12-cyclohexyl-4-[\{N-ethyl-N\{2-(4-ethylpiperazin-1-yl)-2-oxoethyl\}amino\}-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid dihydrochloride (Example 2-301)

[2710] 12-cyclohexyl-4-(3-hydroxymethylphenyl)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxylic acid (Example 2-302)

[2711] N-[2-(4-acetyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-303)

[2712] N-[2-(4-hydroxyethyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-304)

[2713] N-[2-(4-methoxethyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-305)

[2714] N-[1,1-dimethyl-2-(morpholin-4-yl)-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]julene-9-carboxamide (Example 2-306)
[2715] N-[1-{5-(4-methoxyphenyl)-1H-imidazol-2-yl}-1-methyllethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid (Example 2-307)

[2716] N-[1-{(S)-2-dimethylamino-1-{4-hydroxybenzyl}ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid (Example 2-308)

[2717] methyl (S)-6-tert-butoxycarbonylmino-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]hexanoate (Example 2-309)

[2718] (S)-2-[(12-cyclohexyl-1-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-3-(1H-imidazol-4-yl)propionic acid (Example 2-310)

[2719] N-[1-methyl-1-[5-(1H-tetrazol-5-yl)-1H-benimidazol-2-yl]ethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid (Example 2-311)

[2720] (2-1'[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-1-methyllethyl)benzimidazole-1-ylic acid (Example 2-312)

[2721] methyl 2-4-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-1-methylpiperidin-4-yl)-3H-benzimidazole-5-carboxylate (Example 2-313)

[2722] N-[1-(4-hydroxybenzyl)-2-methoxethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid (Example 2-314)

[2723] methyl 2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-3-(3-fluoro-4-hydroxyphenyl)propionate (Example 2-315)

[2724] methyl (S)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-3-(5-hydroxy-1H-indol-3-yl)propionate (Example 2-316)

[2725] methyl (S)-3-(4-benzoylcarboxyaminophenyl)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]propionate (Example 2-317)

[2726] (S)-3-(4-benzoylcarboxyaminophenyl)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]propionate (Example 2-318)

[2727] methyl (S)-3-(4-aminophenyl)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]propionate (Example 2-319)

[2728] (S)-3-(4-aminophenyl)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]propionate (Example 2-320)

[2729] tert-butyl (1-2-[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-2-methylpropionyl)piperidin-4-yl)carbamate (Example 2-321)

[2730] N-[2-(3-hydroxyprorolinid-1-yl)-1,1-dimethyl-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid (Example 2-322)

[2731] 12-cyclohexyl-4-{3-methoxymethylenylphenyl)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid (Example 2-323)

[2732] 12-cyclohexyl-4-phenylamino-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid (Example 2-324)

[2733] 12-cyclohexyl-4-(2-hydroxymethylphenyl)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid (Example 2-325)

[2734] N-[2-cyclohexyl-9-{1H-tetrazol-5-yl}-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-4-yl]-N-[2-(piperidin-1-yl)ethyl]propylamine (Example 2-326)

[2735] 12-cyclohexyl-4-(2-methoxymethylphenyl)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid (Example 2-327)

[2736] 12-cyclohexyl-4-(3-dimethylaminophenyl)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid monohydrochloride (Example 2-328)

[2737] ethyl 2-1'[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-1-methyllethyl]-1-methyl-1H-benimidazole-5-carboxylate (Example 2-329)

[2738] 2-1'[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-1-methyllethyl]-1-methyl-1H-benimidazole-5-carboxylic acid (Example 2-330)

[2739] methyl 2-1'[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-1-methyllethyl]-6-methoxy-1H-benimidazole-5-carboxylate (Example 2-331)

[2740] 2-1'[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-1-methyllethyl]-1H-benimidazole-5-carboxylic acid (Example 2-332)

[2741] N-[1-N-ethyl-N-4-methoxybutylcarbamoyl]-1-methyllethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid (Example 2-333)

[2742] N-[2-(4-acetylamino)peridin-1-yl]-1,1-dimethyl-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid (Example 2-334)

[2743] N-[2-(4-methanesulfonylamino)peridin-1-yl]-1,1-dimethyl-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxylic acid (Example 2-335)

[2744] methyl 2-1'[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-1-methyllethyl]-3-methyl-1H-benimidazole-5-carboxylate (Example 2-336)

[2745] 2-1'[(12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-1-methyllethyl]-3-methyl-1H-benimidazole-5-carboxylic acid (Example 2-337)

[2746] methyl (S)-3-(4-acetylamino)phenyl)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]propionate (Example 2-338)

[2747] methyl (S)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululene-9-carboxy)amino]-3-(4-methanesulfonylaminophenyl)propionate (Example 2-339)
[2748] (S)-3-(4-acetylamino-phenyl)-2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid) propionic acid (Example 2-340)

[2749] (S)-2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid) propionic acid (Example 2-341)

[2750] 12-cyclohexyl-4-[N-(3-methoxypropyl)-N-[2-(pipеридин-1-yl)ethyl]амино]-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid (Example 2-342)

[2751] 12-cyclohexyl-4-(2-dimethylaminomethylphenyl)-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid (Example 2-343)

[2752] 12-cyclohexyl-4-(2-oxoepipiperidin-1-yl)-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid (Example 2-344)

[2753] 12-cyclohexyl-4-(piperidin-1-yl)-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid (Example 2-345)

[2754] N-[1-(5-dimethylcarbamoyl-1H-benimidazol-2-yl)-1-methylethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxamide (Example 2-346)

[2755] 2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxamide)-1-methylethyl]-6-methoxy-1H-benzimidazole-5-carboxylic acid (Example 2-347)

[2756] N-[1-(benzoxazol-2-yl)-1-methylethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxamide (Example 2-348)

[2757] methyl 4-[2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid)-2-methylpropioylamino] benzolate (Example 2-349)

[2758] 4-[2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid)-2-methylpropioylamino] benzoic acid (Example 2-350)

[2759] N-[1-(2-hydroxyethyl)-1H-benzimidazol-2-yl]-1-methylethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxamide (Example 2-351)

[2760] methyl (S)-2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid)-3-(3-trifluoromethyl)phenylpropionate (Example 2-352)

[2761] methyl 2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid)-3-(3-hydroxypropyl)propionate (Example 2-353)

[2762] (S)-2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid)-3-(3-trifluoromethyl)phenylpropionate (Example 2-354)

[2763] 2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid)-3-(3-hydroxypropyl)propionic acid (Example 2-355)

[2764] methyl (S)-2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid)-3-(pyridin-4-yl)propionate (Example 2-356)

[2765] 4-(bis[2-(1,4-oxazepan-4-yl)-2-oxoethyl]amino)-12-cyclohexyl-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid (Example 2-357)

[2766] N-2-[4-(4-fluorophenyl)-4-hydroxyperidin-1-yl]-1,1-dimethyl-2-oxoethyl]-12-cyclohexyl-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxamide (Example 2-358)

[2767] 4-(bis-[2-morpholin-4-yl]ethy]amino)-12-cyclohexyl-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid trihydrochloride (Example 2-359)

[2768] 4-(bis[2-(1,4-oxazepan-4-yl)]ethy]amino)-12-cyclohexyl-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid (Example 2-360)

[2769] 4-[bis-[2-(morpholin-4-yl)]ethy]amino]-12-cyclohexyl-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid trihydrochloride (Example 2-361)

[2770] methyl (S)-2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid)-3-(methylcarbonylaminopropyl)propionate (Example 2-362)

[2771] methyl (S)-3-(3-chloro-4-hydroxyphenyl)-2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid)-3-(methylcarbonylaminopropyl)propionate (Example 2-363)

[2772] (S)-2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid)-3-(4-methylcarbonylaminophenyl)propionic acid (Example 2-364)

[2773] (S)-3-(3-chloro-4-hydroxyphenyl)-2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid)-3-(4-methylcarbonylaminophenyl)propionic acid (Example 2-365)

[2774] methyl (S)-2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylic acid)-3-(4-hydroxyphenyl)butyrate (Example 2-366)

[2775] N-[1-(5-dimethylamino-1H-benimidazol-2-yl)-1-methylethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxamide (Example 2-367)

[2776] N-[2-(4-hydroxyperidin-1-yl)-1-methoxymethyl-2-oxoethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxamide (Example 2-368)

[2777] N—([S]-2-(4-benzoxyphenyl)-1-(thiazol-2-yl)-ethyl)-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxamide (Example 2-369)

[2778] N-[1-(methylyl)-1-[5-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-benimidazol-2-yl]ethy]]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxamide (Example 2-370)

[2779] tert-butyl (S)-4-carbamoyl-2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylamino)butyrate (Example 2-371)

[2780] (S)-4-carbamoyl-2-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7-azaazidobenz[e]azulene-9-carboxylamino)butyric acid (Example 2-372)
[2781] methyl (S)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-3(4-hydroxyphenyl)propionate (Example 2-373)

[2782] methyl 2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-3(4-trifluoromethyl)phenylpropionate (Example 2-374)

[2783] (S)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-3(4-hydroxyphenyl)propionic acid (Example 2-375)

[2784] (S)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-4(4-hydroxyphenyl)butyric acid (Example 2-376)

[2785] methyl (S)-3-[4-(tert-butoxycarbonylmethoxycarbonyl)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]propanoic acid (Example 2-377)

[2786] methyl (S)-3-[4-(carboxymethyl)phenyl]-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulen-9-carbonyl)amino]-3(4-hydroxyphenyl)propionic acid monohydrochloride (Example 2-379)

[2787] methyl 2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-3(4-hydroxyphenyl)propionic acid (Example 2-380)

[2788] N-(1-(5-fluoro-1H-benzo[d][1,2,3]triazol-2-yl))-1-methyl ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulen-9-carboxamide (Example 2-381)

[2789] N-[(S)-2-(4-hydroxyphenyl)-1-(thiazol-2-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carboxamide (Example 2-382)

[2790] methyl (S)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-3(4-methylcarbamoylmethoxy)phenylpropionate (Example 2-383)

[2791] methyl (S)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-3(4-dimethylcarbamoylmethoxy)phenylpropionate (Example 2-384)

[2792] methyl (4-1(S)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-2-(methylcarbamoyl)ethyl)phenyl)carbamate (Example 2-384) (S)-2-(5-hydroxy-1H-indol-3-yl)-1-[(2-methylthiazol-4-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carboxamide (Example 2-385)

[2793] N-[1-(5-[4-(hydroxy)phenylidene)carbonyl]-1H-benzoimidazol-2-yl]-1-methyl ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carboxamide (Example 2-386)

[2794] N-[(S)-1-(2-hydroxyethylcarbamoyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carboxamide (Example 2-387)

[2795] N-[(S)-2-(4-hydroxyphenyl)-1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carboxamide (Example 2-388)

[2796] N-[(S)-1-(2-dimethylaminoethyl)carbamoyl]-2-(4-hydroxyphenyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carboxamide (Example 2-389)

[2797] N-[1-(5-[2-(hydroxyethyl)carbamoyl]-1H-benzimidazol-2-yl)]-1-methyl ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carboxamide (Example 2-390)

[2798] methyl (S)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-3(4,3,3-dimethylureido)phenylpropionate (Example 2-391)

[2799] methyl (S)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-3(4-[3-hydroxypropoxy)phenyl]propionate (Example 2-392)

[2800] methyl 2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-3(4-hydroxyethyl)phenylpropionate (Example 2-393)

[2801] N-[1-(3H-imidazol-4,5-b)[1,2,3]triazin-2-yl)-1-methyl ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carboxamide (Example 2-394)

[2802] 2,1-[1-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-1-methyl ethyl]-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazol-5-carboxylic acid (Example 2-395)

[2803] N-[1-methyl-1-(5-methylcarbamoyl-1H-benzimidazol-2-yl)]ethy]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carboxamide (Example 2-396)

[2804] 4-[4-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-1-methyl piperidine-4-carbonyle]amino]benzoic acid (Example 2-397)

[2805] ethyl 4-2,1-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-1-methyl ethyl]-1-3H-imidazol-4-yl]benzoate (Example 2-398)

[2806] 4,2,1-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-1-methyl ethyl]-1-3H-imidazol-4-yl]benzoic acid (Example 2-399)

[2807] 4,[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]tetrahydro pyran-4-carboxylic acid (Example 2-400)

[2808] (E)-3,4-4-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]tetrahydropyran-4-carboxylate (Example 2-401)

[2809] 4-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]tetrahydropyran-4-carboxylate (Example 2-402)

[2810] 2,1-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadi benzo[a,e]azulen-9-carbonyl)amino]-1-methyl ethyl]-4-[3,4-dihydroquinazoline-7-carboxylic (Example 2-403)
[2811] 2-{1-[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methyllethyl]-1-methylamino}-4-dimethylaminooxazolino-7-carboxylic acid (Example 2-404)

[2812] N-[1-[5-hydroxymethyl-1H-benimidazol-2-yl]-1-methyllethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-405)

[2813] 2-{4-{1-[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]cyclobutanecarbonyl[1-amino]phenyl}-2-methylpropionic acid (Example 2-406)

[2814] methyl [4-([S]-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]phenyl]carbamate (Example 2-407)

[2815] N-[1-[1H-benimidazol-2-yl]-1-methyllethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-408)

[2816] 2-{4-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]tetrahydropryan-4-yl]31-henimidazolato-5-carboxylic acid (Example 2-409)

[2817] benzyll (4-([S]-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]-2-(2-methylthiazol-4-yl)ethyl]phenyl)carbamate (Example 2-410)

[2818] (E)-3-{2-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methyllethyl]-1H-benimidazol-5-yl]acrylic acid (Example 2-411)

[2819] 3-[2-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methyllethyl]-1H-benimidazol-5-yl]propionic acid (Example 2-412)

[2820] N-[1-[5-hydroxymethyl-6-methoxy-1H-benimidazol-2-yl]cyclobutyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-413)

[2821] N-[[S]-2-(4-aminophenyl)-1-(2-methylthiazol-4-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-414)

[2822] methyl [4-([S]-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]-2-(2-methylthiazol-4-yl)ethyl]phenyl]carbamate (Example 2-415)

[2823] 2-[[S]-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]-3-(4-hydroxyphenyl)propionylamino]-2-methylpropionic acid (Example 2-416)

[2824] methyl [3-[[S]-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]-2-(2-methylthiazol-4-yl)ethyl]-1H-indol-5-yloxylacetate (Example 2-417)

[2825] N-[1-methyl-1-[6-(4-methylpiperazine-1-carboxyl)-1H-benimidazol-2-yl]ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-418)

[2826] N-[1-methyl-1-[6-(morpholine-4-carboxyl)-1H-benimidazol-2-yl]ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-419)

[2827] N-[1-(6-benzoxyl-1H-benimidazol-2-yl)cyclobuthyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-420)

[2828] N-[[S]-2-[(5-(2-hydroxyethoxy)-1H-indol-3-yl)-1-(2-methylthiazol-4-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-421)

[2829] (E)-3-[[4-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]-1-methyllethyl]phenyl]acyric acid (Example 2-422)

[2830] 3-(4-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]-1-methyllethyl]phenyl)propionic acid (Example 2-423)

[2831] methyl (S)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]-4-[[3-methoxypropoxy]phenyl]propionate (Example 2-424)

[2832] (S)-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]-3-[4-(3,3-dimethylureido)phenyl]propionic acid (Example 2-425)

[2833] N-[[S]-2-((4-hydroxyphenyl)-1-(methoxycarbamoyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-426)

[2834] N-[[S]-2-(4-hydroxyphenyl)-1-(N-methoxy-N-methylcarbamoyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-427)

[2835] N-[[S]-2-(4-benzoxylphenyl)-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-428)

[2836] N-[[S]-2-(4-hydroxyphenyl)-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-429)

[2837] 4-[[S]-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]-2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)ethyl]phenyl acetate (Example 2-430)

[2838] 4-[[S]-2-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxylato][1-methylamino]-2-(4,4-dimethyl-5-oxo-4,5-dihydrooxazol-2-yl)ethyl]phenyl acetate (Example 2-431)

[2839] N-[1-methyl-1-[2-(morpholin-4-yl)ethyl]-1H-benimidazol-2-yl]ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenz[a,e]julene-9-carboxamide (Example 2-432)
N-[1-(2-hydroxyethyl)-1H-benzimidazol-2-yl]-1-methyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carboxamide (Example 2-433)

N-[1-(2-methoxyethyl)-1H-benzimidazol-2-yl]-1-methyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carboxamide (Example 2-434)

Ethyl (S)-2-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carbonyl]amino]-3-(4-hydroxyphenyl)propionate (Example 2-435)

N-[1-(4-hydroxybenzyl)-2-methylpropyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carboxamide (Example 2-436)

2-[1-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carbonyl]cyclobutyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carboxamide (Example 2-438)

N-[1-(5-hydroxymethyl)-6-(2-methoxyethoxy)-1H-benzimidazol-2-yl]cyclobutyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carboxamide (Example 2-437)

N-[1-(6-hydroxy-1H-benzimidazol-2-yl)cyclobutyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carboxamide (Example 2-438)

N-[1-(S)-cyano-(4-hydroxybenzyl)-methyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carboxamide (Example 2-441)

Methyl 2-amino-3-(4-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carbonyl]amino]-1-methyl ethyl)phenyl)propionate mono hydrochloride (Example 2-442)

2-acetylamino-3-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carbonyl]amino]-1-methyl ethyl)phenyl)propionic acid (Example 2-443)

2-amino-3-[4-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carbonyl]amino]-1-methyl ethyl)phenyl)propionic acid (Example 2-444)

2-[1-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carbonyl]cyclobutyl]-31H-benzimidazol-5-yl]2-methyl propionic acid (Example 2-445)

(E)-3-[4-[[12-cyclohexyl-3-ethoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carbonyl]amino]cyclobutane carbonyl]amino] phenyl]acrylic acid (Example 2-446)

N-[1-(5-hydroxy-1-methyl ethyl)-6-methoxy-1H-benzimidazol-2-yl]cyclobutyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carboxamide (Example 2-447)

N-[1-(3H-benzimidazol-5-ylcarbamoyl)cyclobutyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carboxamide (Example 2-448)

2-[4-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carbonyl]amino]-1-methyl piperidin-4-yl]-3H-benzimidazol-5-ylcarboxylic acid (Example 2-449)

N-[1-1-(4,5-dihydro-1H-imidazol-2-yl)-2-[(4-hydroxyphenyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carboxamide (Example 2-450)


tert-butyl (S)-2-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carbonyl]amino]-3-(4-hydroxyphenyl)propionate (Example 2-452)

N-[1-(2-[(4-hydroxyphenyl)oxy]-1H-tetrazol-5-yl)]ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carboxamide (Example 2-453)

N-[1-(2-[(4-hydroxyphenyl)oxy]-1H-tetrazol-5-yl)]ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carboxamide (Example 2-454)

2-[4-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]jululen-9-carbonyl]amino]cyclobutyl]-1H-benzimidazol-5-yl]oxy]acetic acid (Example 2-455)

13-cyclohexyl-5-[2-[(S)-3-phenoxymethyl-piperidin-1-yl)]ethyl]-6,7-dihydro-5H-benz[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-485)

3-chloro-13-cycloheptyl-5-[2-[(piperidin-1-yl)]ethyl]-6,7-dihydro-5H-benz[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-486)

5-[2-[(7-benzyl-7-azabicyclo[2.2.1]hept-1-yl)]ethyl]-13-cyclohexyl-3-methyl-6,7-dihydro-5H-benz[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-487)

5-[2-[(7-azabicyclo[2.2.1]hept-1-yl)]ethyl]-13-cyclohexyl-3-methyl-6,7-dihydro-5H-benz[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid mono hydrochloride (Example 1-488)

5-[2-[(7-azabicyclo[2.2.1]hept-1-yl)]ethyl]-13-cyclohexyl-3-methyl-6,7-dihydro-5H-benz[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-489)

3-cyano-13-cyclohexyl-5-[2-[(piperidin-1-yl)]ethyl]-6,7-dihydro-5H-benz[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid mono hydrochloride (Example 1-490)

3-carbamoyl-13-cyclohexyl-5-[2-[(piperidin-1-yl)]ethyl]-6,7-dihydro-5H-benz[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid mono hydrochloride (Example 1-491)
[2870] 13-cyclohexyl-5-(2-cyclohexyloxyethyl)-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-492)

[2871] 13-cyclohexyl-5-(4-diethyloaminoethyl)-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-493)

[2872] 13-cyclohexyl-5-[2-[(S)-3-(2-hydroxyethyl)piperidin-1-yl]ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-494)

[2873] 13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-495)

[2874] 13-cyclohexyl-5-methyl-3-[3-(piperidin-1-yl)propoxy]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-496)

[2875] 13-cyclohexyl-5-[2-((R)-3-phenoxymethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-497)

[2876] 5-[2-(azocan-1-yl)ethyl]-13-cyclohexyl-3-ethoxy-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-498)

[2877] 13-cyclohexyl-3-ethoxy-5-[2-((R)-3-methoxymethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-499)

[2878] 13-cyclohexyl-3-ethoxy-5-[2-(1,4-oxazepan-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-500)

[2879] 13-cyclohexyl-3-ethoxy-5-[2-[4-(2-methoxymethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-501)

[2880] 13-cyclohexyl-5-[2-[4-(2-methoxymethylpiperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-502)

[2881] 13-cyclohexyl-5-(3-diethyloamino-2-hydroxypropyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-503)

[2882] 5-[2-(4-acetyl-1,4-diazepan-1-yl)ethyl]-13-cyclohexyl-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-504)

[2883] N-tert-butyl-13-cyclohexyl-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (Example 1-505)

[2884] 13-cyclohexyl-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (Example 1-506)

[2885] 13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide dihydrochloride (Example 1-507)

[2886] 13-cyclohexyl-3-methoxy-5-[2-((R)-3-methoxymethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-508)

[2887] 13-cyclohexyl-3-fluoro-5-[2-((R)-3-methoxymethylpiperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-509)

[2888] 13-cyclohexyl-3-methoxy-5-[2-(1,4-oxazepan-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-510)


[2892] 13-cyclohexyl-5-[2-[(S)-3-(2-ethoxyethyl)piperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-514)

[2893] 13-cyclohexyl-3-ethoxy-5-[2-[(S)-3-(2-ethoxyethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-515)

[2894] N-tert-butyl-13-cyclohexyl-3,5-dimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (Example 1-516)

[2895] 13-cyclohexyl-3,5-dimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (Example 1-517)

[2896] 13-cyclohexyl-5-[2-(4-methoxybenzyl-1,4-diazepan-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-518)

[2897] 13-cyclohexyl-5-[2-[5-oxo-1,4-diazepan-1-yl]ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-519)

[2898] N-tert-butyl-13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide dihydrochloride (Example 1-520)

[2899] 13-cyclohexyl-5-[3-(3-diisopropylamino)propyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-521)

[2900] 13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-3-trifluoromethoxy-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-522)
[2901] 13-cyclohexyl-5-[2-{(S)-3-(2-methoxyethyl)piperidin-1-yl}ethyl]-3-trifluoromethoxy-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-523)

[2902] 13-cyclohexyl-5-[3-(N-ethyl-N-isopropylamino)propyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-524)

[2903] 13-cyclohexyl-5-[2-(4-methoxyazepan-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-525)

[2904] 13-cyclohexyl-5-methyl-5-[2-(4-methyl-5-oxo-1,4-diazepan-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-526)

[2905] 13-cyclohexyl-5-[2{(S)-3-(dimethylcarbamoylmethyl)piperidin-1-yl}ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-527)

[2906] 13-cyclohexyl-5-[2{(R)-3-(2-methoxyethylmethyl)piperidin-1-yl}ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-528)

[2907] 13-cyclohexyl-5-[2{(S)-3-(2-hydroxy-2-methylpropyl)piperidin-1-yi}ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-529)

[2908] 13-cyclohexyl-2,3-difluoro-5-[2-(7(R)-3-methoxyethylmethyl)piperidin-1-yl]ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-530)

[2909] 13-cyclohexyl-5-[2{(N-ethyl-N-(3-methoxypropylamino)ethyl)piperidin-1-yl}ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-531)

[2910] 13-cyclohexyl-3-methyl-5-[2-(6-methyl-1,4-oxazepan-4-yi)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-532)

[2911] 13-cyclohexyl-5-[2{(R)-3-(1-hydroxy-1-methylethyl)piperidin-1-yl}ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-533)

[2912] 3-chloro-13-cyclohexyl-5-[2-{1-(2-methoxyethyl)piperidin-3-yi}ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-534)

[2913] 13-cyclohexyl-5-[2(dimethylaminoethyl)-3-{3,5-dimethylisoxazol-4-ylmethyl}-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-535)

[2914] 13-cyclohexyl-3-(methyl-5-[2-(4-oxazepan-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-536)

[2915] 13-cyclohexyl-5-[2{(S)-3-(2-dimethylcarbamoyl-ethyl)piperidin-1-yl}ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-537)

[2916] 13-cyclohexyl-5-[2-(4-hydroxyazepan-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-538)

[2917] 13-cyclohexyl-5-[2{(N-ethyl-N-(4-methoxybutylamino)ethyl)piperidin-1-yl}ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-539)

[2918] 13-cyclohexyl-5-[2{(S)-3-(methoxypropyl)piperidin-1-yl}ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-540)

[2919] 13-cyclohexyl-5-[2{(R)-3-(1-methoxy-1-methylethyl)piperidin-1-yl}ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-541)

[2920] 13-cyclohexyl-5-[2{(2-methoxyethyl)piperidin-1-yl}ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-542)


[2922] 13-cyclohexyl-2,3-difluoro-5-[2{(S)-3-(2-methoxyethyl)piperidin-1-yl}ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-544)

[2923] 13-cyclohexyl-5-[2{(3-dimethylcarbamoylpiperidin-1-yl)ethyl}-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-545)

[2924] 13-cyclohexyl-3-(2-methoxyethoxy)-5-[2{piperidin-1-yl}ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-546)

[2925] 13-cyclohexyl-5-[2{(R)-3-(2-methoxyethoxy)piperidin-1-yl}ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-547)

[2926] 13-cyclohexyl-5-[2(dimethylaminoethyl)-3-(2-phenoxyethoxy)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-548)


[2928] 13-cyclohexyl-2,3-difluoro-5-[2-(1,4-oxazepan-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-550)

[2929] 13-cyclohexyl-5-[2{(3-methoxymethylazepan-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-551)
[2930] 13-cyclohexyl-5-methyl-4-[2-(piperidin-1-yl)ethoxy]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-552)

[2931] 5-(2-[(S)-3-((N-acetyl-N-methylamino)ethyl)piperidin-1-yl)ethyl]-13-cyclohexyl-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-553)

[2932] 13-cyclohexyl-3,9-dimethyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-554)

[2933] 13-cyclohexyl-5-[2-[(S)-3-((2-dimethylaminoethyl)piperidin-1-yl)ethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-555)

[2934] 5-[(S)-3-((S)-3-carboxymethylpiperidin-1-yl)ethyl]-13-cyclohexyl-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-556)

[2935] 5-(1-benzyloxy carbonylpiperidin-4-yl)-13-cyclohexyl-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-558)

[2937] 13-cyclohexyl-3-methyl-5-2-[(S)-3-((trimethylureido)ethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-559)

[2938] 3-(5-chlorothiophen-2-ylmethoxy)-13-cyclohexyl-5-(2-dimethylaminoethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-560)

[2939] 13-cyclohexyl-3-methyl-5-2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-561)

[2940] 13-cyclohexyl-3-methyl-5-(piperidin-4-yl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-562)

[2941] 5-(1-acetlypiperidin-4-yl)-13-cyclohexyl-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-563)

[2942] 13-cyclohexyl-3-methyl-5-(1-methylpiperidin-4-yl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-564)

[2943] 13-cyclohexyl-5-(2-dimethylaminoethyl)-3-(pyridin-4-ylmethoxy)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid trihydrochloride (Example 1-565)

[2944] 13-cyclohexyl-3-methyl-5-[2-[(S)-3-((2-oxopyrrolidin-1-yl)ethyl)piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-566)

[2945] 13-cyclohexyl-3,5,6-trimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-567)

[2946] 13-cyclohexyl-3-methoxy-5-[2-(thiomorpholin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-568)

[2947] 13-cyclohexyl-3,5,9-trimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-569)

[2948] 13-cyclohexyl-5-[2-[(S)-3-((2-methoxyethyl)piperidin-1-yl)-2-oxoethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-570)

[2949] 13-cyclohexyl-5-[2-(4-methanesulfonylpiperazin-1-yl)-2-oxoethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-571)

[2950] 13-cyclohexyl-5-[2-(4-methoxy piperidin-1-yl)-2-oxoethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-572)

[2951] N-methyl-13-cyclohexyl-5-[2-(4-methanesulfonylpiperazin-1-yl)-2-oxoethyl]-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxamide (Example 1-573)

[2952] 13-cyclohexyl-3,5-dimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-574)

[2953] 13-cyclohexyl-5-(2-dimethylaminoethyl)-3-[2-(2-oxooxazolidin-3-yl)ethoxy]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-575)


[2955] 13-cyclohexyl-5-(2-dimethylaminoethyl)-3-(3-methoxybenzoxo)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-577)

[2956] 3-(3-aminobenzoxyloxy)-13-cyclohexyl-5-(2-dimethylaminoethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid trihydrochloride (Example 1-578)

[2957] 13-cyclohexyl-5-(2-dimethylaminoethyl)-3-(3-nitrobenzyloxy)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-579)

[2958] 3-chloro-13-cyclohexyl-5-[2-(1-methoxy carbonylpiperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-580)

[2959] 13-cyclohexyl-5-(2-(4-fluorophenyl)ethyl)-3-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-581)
[2960] 3-(3-acetylamino benzyl)oxy)-13-cyclohexyl-5-(2-dimethylaminomethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-582)

[2961] methyl 3-(3-carboxybenzyl)oxy)-13-cyclohexyl-5-(2-dimethylaminomethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate dihydrochloride (Example 1-583)

[2962] 13-cyclohexyl-5-(2-dimethylaminomethyl)-3-[3-(pi peridin-1-yl)propoxy]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid trihydrochloride (Example 1-584)


[2964] 3-(3-carboxybenzyl)oxy)-13-cyclohexyl-5-(2-dimethylaminomethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-586)

[2965] 13-cyclohexyl-5-(2-dimethylaminomethyl)-3-(3-dimethylcarbamoyl benzyl)oxy]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-587)

[2966] 13-cyclohexyl-3-methyl-5-[2-(4-methylthiazol-2-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-588)

[2967] 13-cyclohexyl-5-(2-dimethylaminomethyl)-3-(6-methylpyridin-2-ylmethoxy)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-589)

[2968] 13-cyclohexyl-5-(2-dimethylaminomethyl)-3-(3-methylcarbamoyl benzyl)oxy]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-590)

[2969] 13-cyclohexyl-3-(3-dimethylaminobenzyl)oxy)-5-(2-dimethylaminomethyl)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid dihydrochloride (Example 1-591)

[2970] 13-cyclohexyl-3-ethoxy-5-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-592)

[2971] 3-benzoxyloxy-13-cyclohexyl-5-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-593)

[2972] 13-cyclohexyl-3-methoxy-5-methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid (Example 1-594)

[2973] 13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-3-(pyridin-2-ylmethoxy)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylic acid trihydrochloride (Example 1-595)

[2974] methyl 5-(2-[(1-tert-butoxycarbonylpiperidin-4-yl)ethyl]-13-cyclohexyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-601)

[2975] methyl 13-cyclohexyl-5-[2-(piperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-602)

[2976] methyl 13-cyclohexyl-5-[2-(1-cyclopentylpiperidin-4-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-603)

[2977] N-tet-butyl-13-cyclohexyl-3-methyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (Example 1-604)

[2978] N-tet-butyl-13-cyclohexyl-3-methyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (Example 1-605)

[2979] N-tet-butyl-13-cyclohexyl-3-methyl-6-oxo-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (Example 1-606)

[2980] 13-cyclohexyl-3-methyl-5-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-sulfonamide (Example 1-607)

[2981] methyl 13-cyclohexyl-3,6-dimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-608)

[2982] methyl 13-cyclohexyl-3,5,6-trimethyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-609)

[2983] methyl 3-benzoxyloxy-13-cyclohexyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-610)

[2984] methyl 3-benzoxyloxy-13-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-611)

[2985] methyl 13-cyclohexyl-3-hydroxy-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-612)

[2986] methyl 13-cyclohexyl-6-oxo-5-[2-oxo-2-(piperidin-1-yl)ethyl]-3-(pyridin-2-ylmethoxy)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-613)

[2987] methyl 13-cyclohexyl-5-[2-(piperidin-1-yl)ethyl]-3-(pyridin-2-ylmethoxy)-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-10-carboxylate (Example 1-614)

[2988] 12-cyclohexyl-4-[2-(4-ethylpiperazin-1-yl)ethoxy]-6,7-dihydro-5-oxa-7-aza dibenzofuro[3,2-e]joueline-9-carboxylic acid dihydrochloride (Example 2-456)

[2989] 4-[2-(1-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-12-cyclohexyl-6,7-dihydro-5-oxa-7-aza dibenzofuro[3,2-e]joueline-9-carboxylic acid (Example 2-457)

[2990] 12-cyclohexyl-4-[2-(piperidin-4-yl)ethoxy]-6,7-dihydro-5-oxa-7-aza dibenzofuro[3,2-e]joueline-9-carboxylic acid monohydrochloride (Example 2-458)

[2991] 12-cyclohexyl-4-[2-(1-methylpiperidin-4-yl)ethoxy]-6,7-dihydro-5-oxa-7-aza dibenzofuro[3,2-e]joueline-9-carboxylic acid monohydrochloride (Example 2-459)
[2992] 12-cyclohexyl-4-[3-(piperidin-1-yl)propoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid monohydrochloride (Example 2-469)

[2993] 12-cyclohexyl-4-[2-oxo-2-(piperidin-1-yl)ethyl]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-461)

[2994] 12-cyclohexyl-4-[2-(morpholin-4-yl)ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid monohydrochloride (Example 2-462)

[2995] 12-cyclohexyl-4-(2-dimethylaminoethoxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid monohydrochloride (Example 2-463)

[2996] 12-cyclohexyl-4-[2-(piperidin-1-yl)ethyl]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid monohydrochloride (Example 2-464)

[2997] 4-[2-(1-tert-butoxy carbonyl piperidin-4-yloxy)ethoxy]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-465)

[2998] 12-cyclohexyl-4-[2-(piperidin-4-yloxy)ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid monohydrochloride (Example 2-466)

[2999] 12-cyclohexyl-4-[2-(1-methyl piperidin-4-yloxy)ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid monohydrochloride (Example 2-467)

[3000] 12-cyclohexyl-4-[2-(1-cyclopentyl piperidin-4-yloxy)ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid monohydrochloride (Example 2-468)

[3001] 12-cyclohexyl-4-(1-methyl piperidin-3-yloxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid monohydrochloride (Example 2-469)

[3002] 12-cyclohexyl-4-[1-(2-methoxyethyl) piperidin-3-yloxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid monohydrochloride (Example 2-470)

[3003] 12-cyclohexyl-4-[2-(morpholin-4-yl)-5-(2-oxopyrrolidin-1-yl)benzoxoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid monohydrochloride (Example 2-471)

[3004] 12-cyclohexyl-4-[2-(N-methyl-N-(1-methyl piperidin-4-yl) amino) ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid trihydrochloride (Example 2-472)

[3005] methyl 4-carboxymethoxy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-473)

[3006] 12-cyclohexyl-4-(N-methyl-N-[2-(piperidin-1-yl)ethyl] amino)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid dihydrochloride (Example 2-474)

[3007] 12-cyclohexyl-4-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-475)

[3008] 4-amino-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-476)

[3009] 12-cyclohexyl-4-nitro-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-477)

[3010] 12-cyclohexyl-4-[2-(piperidin-1-yl)ethylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid dihydrochloride (Example 2-478)

[3011] 12-cyclohexyl-3-methyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-479)

[3012] 12-cyclohexyl-4-[N-ethyl-N-[2-(piperidin-1-yl)ethyl] amino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid dihydrochloride (Example 2-480)

[3013] 12-cyclohexyl-4-[N-[2-(piperidin-1-yl)ethyl] N-propylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid dihydrochloride (Example 2-481)

[3014] 12-cyclohexyl-4-[N-[2-methoxyethyl] N-[2-(piperidin-1-yl)ethyl] amino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid dihydrochloride (Example 2-482)

[3015] 12-cyclohexyl-4-dimethylamino-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-483)

[3016] 12-cyclohexyl-1-fluoro-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-484)

[3017] 4-[N-acetyl-N-[2-(piperidin-1-yl)ethyl] amino]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-485)

[3018] 12-cyclohexyl-4-[N-[2-methyl-N-[2-oxo-2-(piperidin-1-yl)ethyl] amino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-486)

[3019] methyl 3-(1-tert-butoxy carbonyl piperidin-3-yloxy)-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-501)

[3020] methyl 12-cyclohexyl-3-(piperidin-3-yloxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-502)

[3021] methyl 12-cyclohexyl-3-(1-methanesulfonyl piperidin-3-yloxy)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-503)

[3022] methyl 4-benzyloxy-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-504)

[3023] methyl 12-cyclohexyl-4-hydroxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-505)

[3024] methyl 12-cyclohexyl-4-[2-oxo-2-(piperidin-1-yl)ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-506)

[3025] methyl 12-cyclohexyl-4-[2-(piperidin-1-yl)ethoxy]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-507)

[3026] ethyl (E)-3-[4-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid ethyl)amino]cyclobutanecarboxyl] amino phenyl) acrylate (Example 2-508)

[3027] methyl 12-cyclohexyl-4-trifluoromethanesulfonyl oxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]juzulene-9-carboxylic acid (Example 2-509)
[3028] methyl 12-cyclohexyl-4-(pyridin-3-yl)-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-510)

[3029] methyl 2-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carbonyl]amino]-2-methylpropionate (Example 2-512)

[3030] 2-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carbonyl]amino]-2-methylpropionic acid (Example 2-512)

[3031] methyl 4-amino-3-[[2-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carbonyl]amino]-2-methylpropionyl]amino] benzotate (Example 2-513)

[3032] methyl 2-[[1-[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carbonyl]amino]-1-methylhexyl]-3H-benimidazole-5-carboxylate (Example 2-514)

[3033] methyl 12-cyclohexyl-4-nitro-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-515)

[3034] methyl 4-amino-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-516)

[3035] methyl 4-[[bis[2-oxo-2-[piperidin-1-yl]ethyl]amino]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-517)


[3037] methyl 4-[[bis[2-[piperidin-1-yl]ethyl]amino]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-519)

[3038] 4-[[bis[2-[piperidin-1-yl]ethyl]amino]-12-cyclohexyl-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid trihydrochloride (Example 2-520)

[3039] methyl 12-cyclohexyl-4-[[N-[2-oxo-2-[piperidin-1-yl]ethyl]-N-propylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-521)

[3040] methyl 12-cyclohexyl-4-[[N-[2-[piperidin-1-yl]ethyl]-N-propylamino]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 2-522)

[3041] 12-cyclohexyl-5,6-dihydropindololo[2,1-a]isoquinoline-9-carboxylic acid (Example 5-4)

[3042] methyl 12-cyclohexyl-5,6-dihydropindololo[2,1-a]isoquinoline-9-carboxylate (Example 5-5)

[3043] 11-cyclohexyl-6-hydroxy-6H-isoindolo[2,1-a]indole-3-carboxylic acid (Example 5-6)

[3044] 11-cyclohexyl-6-methoxy-6H-isoindolo[2,1-a]indole-3-carboxylic acid (Example 5-7)

[3045] 12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a,8-diazadibenzo[a,e]azulene-9-carboxylic acid (Example 7-9)

[3046] (E)-3-[4-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a,8-diazadibenzo[a,e]azulene-9-carbonyl]amino]cyclobutane-carbonyl]amino]phenyl]acrylic acid (Example 7-10)

[3047] 12-cyclohexyl-3,5-dimethyl-6,7-dihydro-5H-5,7a,8-triazadibenzo[a,e]azulene-9-carboxylic acid (Example 8-8)


[3049] 14-cyclohexyl-6-methyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinof[8,1-a]indole-11-carboxylic acid monohydrochloride (Example 11-1)

[3050] methyl 6-tert-butoxy-carbonyl-14-cyclohexyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinof[8,1-a]indole-11-carboxylate (Example 11-2)

[3051] methyl 14-cyclohexyl-6-methyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinof[8,1-a]indole-11-carboxylate (Example 11-3)

[3052] 6-tert-butoxy-carbonyl-14-cyclohexyl-3-methoxy-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinof[8,1-a]indole-11-carboxylic acid (Example 11-4)

[3053] 14-cyclohexyl-3-methoxy-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinof[8,1-a]indole-11-carboxylic acid monohydrochloride (Example 11-5)

[3054] 14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinof[8,1-a]indole-11-carboxylic acid monohydrochloride (Example 11-6)

[3055] 14-cyclohexyl-3-methoxy-6-[(2-methoxyacetyl)-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocinof[8,1-a]indole-11-carboxylic acid (Example 11-7)


[3057] 12-cyclohexyl-6,7-dihydro-5-thia-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 12-1)

[3058] 11-cyclohexyl-5-thia-6a-azabenzof[a]luorene-8-carboxylic acid (Example 12-2)

[3059] methyl 12-cyclohexyl-6,7-dihydro-5-thia-7a-azadibenzo[a,e]azulene-9-carboxylate (Example 12-3)

[3060] methyl 11-cyclohexyl-5-thia-6a-azabenzof[a]luorene-8-carboxylate (Example 12-4)


[3064] (E)-3-[2-chloro-5-[[13-cyclohexyl-3-ethoxy-5-methyl-6,7-dihydro-5H-1-benzo[5,6][1,4]diazepinof[7,1-


[3071] N-[[1-(4,4-dimethyl-5-oxo-4,5-dihydroxazol-2-yl)ethyl]-2-(4-hydroxyphenyl)ethy1]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxamide (Example 2-524)

[3072] N-[[1-(4-benzyloxyphenyl)-1-[(5-methyl-1H-1,2,4-triazol-3-yl)ethy1]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxamide (Example 2-525)

[3073] N-[[1-(4-hydroxyphenyl)-1-[(5-methyl-1H-1,2,4-triazol-3-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxamide (Example 2-526)

[3074] N-[[5-methylcarbomoylmethoxy-1H-benzimidazol-2-yl)cyclobutyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxamide (Example 2-527)


[3077] (E)-3-[3-(2-benzoxoyethoxy)-4-[1-[[1-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carbonyl]amino]cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-530)

[3078] (E)-3-[4-{1-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carbonyl]amino]cyclobutanecarbonyl]amino}-2-methoxyphenyl]acrylic acid (Example 2-531)

[3079] (S)-2-[[1-(4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-(4-hydroxyphenyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxamide (Example 2-532)

[3080] N-[[1-(4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-(4-hydroxyphenyl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxamide (Example 2-533)

[3081] 12-cyclohexyl-4-[[2-[[E]-3-oxo-3-(piperidin-1-yl)propenyl]phenyl]-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxylic acid (Example 2-534)

[3082] 12-cyclohexyl-4-[[2-[[3-oxo-3-(piperidin-1-yl)propenyl]phenyl]-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxylic acid (Example 2-535)

[3083] 12-cyclohexyl-4-[[2-3-(piperidin-1-yl)propenyl]phenyl]-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxylic acid monohydrochloride (Example 2-536)

[3084] (E)-3-[4-[[2-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carbonyl]amino]-3-methoxy-2-methylpropionylamino]phenyl]acrylic acid (Example 2-537)

[3085] N-[[1-(2-[(4-benzyloxyphenyl)-1-(1,3-dioxolane-2-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxamide (Example 2-538)

[3086] N-4-[[2-[[12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carbonyl]amino]-2-methoxycarbonyl]ethyl]-N,N,N-triethylammonium chloride (Example 2-539)

[3087] 4-2-[[1-[(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carbonyl]amino]-1-methylthethyl]-3H-imidazol-4-yl)benzoic acid monohydrochloride (Example 2-540)

[3088] N-[[12-oxo-2H-6-carbomamoyl]cyclobutyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxamide (Example 2-541)

[3089] N-[[2-([4-(benzyloxyphenyl)-1-[(5-methyl-1,2,4-oxadiazol-3-yl)ethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxamide (Example 2-542)


[3092] N-[[5-(4-hydroxymethylphenyl)-1H-imidazol-2-yl]-1-methylthethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[f,e]azulene-9-carboxamide (Example 2-545)
<table>
<thead>
<tr>
<th>Page 344</th>
<th>Mar. 1, 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>[3093] N-{5-(4-carbamoylphenyl)-1H-imidazol-2-yl}-1-methylethyl]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-546)</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>[3094] N-{1-methyl-1-[5-(4-methylcarbamoylphenyl)-1H-imidazol-2-yl}ethy]-12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxamide (Example 2-547)</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>(E)-3-{4-2-[1-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-548)</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>[3096] 12-cyclohexyl-4-[2-(2-piperidin-1-yl)acetylamino]phenyl]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid (Example 2-549)</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>(E)-3-{3-3{1-(12-cyclohexyl-3-methoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylamino]cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-550)</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>[3097] (E)-3-{3-3{1-(12-cyclohexyl-3-ethoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylamino]cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-551)</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>[3098] (E)-3-{3-3{1-(12-cyclohexyl-3-ethoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylamino]cyclobutanecarbonyl]amino]phenyl]acrylic acid (Example 2-552)</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>[3099] (E)-3-{4-2-[2-(2-piperidin-1-yl)ethyl]phenyl]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid monohydrate (Example 2-553)</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>[3100] 12-cyclohexyl-4-[2-(2-piperidin-1-yl)ethyl]phenyl]-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 2-554)</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>[3101] 12-cyclohexyl-3-isopropoxy-6,7-dihydro-5-oxa-7a-azadibenzo[a,e]azulene-9-carboxylic acid dihydrochloride (Example 2-555)</td>
<td>Lengthy table referenced here</td>
</tr>
</tbody>
</table>
Lengthy table referenced here
US20070049593A1-20070301-T00010
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00011
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00012
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00013
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00014
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00015
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00016
Please refer to the end of the specification for access instructions.
Lengthy table referenced here
US20070049593A1-20070301-T00024
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00025
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00026
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00027
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00028
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00029
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00030
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00031
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00032
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00033
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00034
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00035
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00036
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00037
Please refer to the end of the specification for access instructions.
Lengthy table referenced here
US2007049593A1-20070331-T00038
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US2007049593A1-20070331-T00039
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US2007049593A1-20070331-T00040
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US2007049593A1-20070331-T00041
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US2007049593A1-20070331-T00042
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US2007049593A1-20070331-T00043
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US2007049593A1-20070331-T00044
Please refer to the end of the specification for access instructions.
<table>
<thead>
<tr>
<th>Lengthy table referenced here</th>
<th>Lengthy table referenced here</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
</tbody>
</table>
Lengthy table referenced here
US20070049593A1-20070301-T00080
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00081
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00082
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00083
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00084
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00085
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00086
Please refer to the end of the specification for access instructions.
<table>
<thead>
<tr>
<th>Lengthy table referenced here</th>
<th>Lengthy table referenced here</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lengthy table referenced here</th>
<th>Lengthy table referenced here</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lengthy table referenced here</th>
<th>Lengthy table referenced here</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lengthy table referenced here</th>
<th>Lengthy table referenced here</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lengthy table referenced here</th>
<th>Lengthy table referenced here</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lengthy table referenced here</th>
<th>Lengthy table referenced here</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lengthy table referenced here</th>
<th>Lengthy table referenced here</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
</tbody>
</table>
Lengthy table referenced here
US20070049593A1-20070301-T00108
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00109
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00110
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00111
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00112
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00113
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00114
Please refer to the end of the specification for access instructions.
Lengthy table referenced here
US20070049593A1-20070301-T00150
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00151
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00152
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00153
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00154
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00155
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00156
Please refer to the end of the specification for access instructions.
Lengthy table referenced here
US2007049593A1-20070301-T00164
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US2007049593A1-20070301-T00165
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US2007049593A1-20070301-T00166
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US2007049593A1-20070301-T00167
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US2007049593A1-20070301-T00168
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US2007049593A1-20070301-T00169
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US2007049593A1-20070301-T00170
Please refer to the end of the specification for access instructions.
Lengthy table referenced here
US20070049593A1-20070301-T00178
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00180
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00181
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00182
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00183
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00184
Please refer to the end of the specification for access instructions.
Lengthy table referenced here
US20070049593A1-20070301-T00192
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00193
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00194
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00195
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00196
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00197
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00198
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00199
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00200
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00201
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00202
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00203
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00204
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00205
Please refer to the end of the specification for access instructions.
<table>
<thead>
<tr>
<th>Lengthy table referenced here</th>
<th>Lengthy table referenced here</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
</tbody>
</table>
Lengthy table referenced here
US20070049593A1-20070301-T00220
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00221
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00222
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00223
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00224
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00225
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00226
Please refer to the end of the specification for access instructions.
<table>
<thead>
<tr>
<th>Lengthy table referenced here</th>
<th>Lengthy table referenced here</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Lengthy table referenced here</td>
<td>Lengthy table referenced here</td>
</tr>
<tr>
<td>Please refer to the end of the specification for access instructions.</td>
<td>Please refer to the end of the specification for access instructions.</td>
</tr>
</tbody>
</table>
Lengthy table referenced here
US20070049593A1-20070301-T00262
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00263
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00264
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00265
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00266
Please refer to the end of the specification for access instructions.

Lengthy table referenced here
US20070049593A1-20070301-T00267
Please refer to the end of the specification for access instructions.

[3104] The evaluation of the HCV polymerase inhibitory activity of the compound of the present invention is explained in the following. This polymerase is an enzyme coded for by the non-structural protein region called NS5B on the genome RNA of HCV (EMBO J., 15:12-22, 1996).

Experimental Example [1]

i) Preparation of Enzyme (HCV Polymerase)

[3105] Using, as a template, a cDNA clone corresponding to the full length genome RNA of HCV BK strain obtained from the blood of a patient with hepatitis C, a region encoding NS5B (J Virol 1991 March, 65(3), 1105-13, 544 amino acids after deletion of 47 amino acids on the C-terminal) was amplified by PCR. The objective gene was prepared by adding a 6 His tag [base pair encoding 6 continuous histidine (His)] to the 3’ end thereof and transformed to Escherichia coli. The Escherichia coli capable of producing the objective protein was cultured. The obtained cells were suspended in a buffer solution and crushed in a microfluidizer. The supernatant was obtained by centrifugation and applied to various column chromatographies [mono-S, Sephacyrl S-200 (Pharmacia)], inclusive of metal chelate chromatography, to give a standard enzyme product.

ii) Synthesis of Substrate RNA

[3106] Using a synthetic primer designed based on the sequence of HCV genome 3’ untranslated region, a DNA fragment (148 bp) containing polyU and 3’X sequence was entirely synthesized and cloned into plasmid pBluescript SK II(+) (Stratagene). The cDNA encoding full length NS5B, which was prepared in i) above, was digested with restriction enzyme KpnI to give a cDNA fragment containing the nucleotide sequence of the restriction enzyme cleavage site to the termination codon. This cDNA fragment was inserted into the upstream of 3’ untranslated region of the DNA in pBluescript SK II(+) and ligated. The about 450 bp inserted DNA sequence was used as a template in the preparation of substrate RNA. This plasmid was cleaved immediately after the 3’X sequence, linearized and purified by phenol-chloroform treatment and ethanol precipitation to give DNA.

[3107] RNA was synthesized (37°C, 3 hr) by run-off method using this purified DNA as a template, a promoter of pBluescript SK II(+), MEGAscript RNA synthesis kit (Ambion) and T7 RNA polymerase. DNase I was added and the mixture was incubated for 1 hr. The template DNA was removed by decomposition to give a crude RNA product. This crude product was treated with phenol-chloroform and purified by ethanol precipitation to give the objective substrate RNA.

[3108] This RNA was applied to formaldehyde denaturation agarose gel electrophoresis to confirm the quality thereof and preserved at ~80°C.

iii) Assay of Enzyme (HCV Polymerase) Inhibitory Activity

[3109] A test substance (compound of the present invention) and a reaction mixture (30 µl) having the following composition were reacted at 25°C for 90 min.

[3110] 10% Trichloroacetic acid at 4°C, and 1% sodium pyrophosphate solution (150 µl) were added to this reaction mixture to stop the reaction. The reaction mixture was left standing in ice for 15 min to insolubilize RNA. This RNA was trapped on a glass filter (Whatman GF/C and the like) upon filtration by suction. This filter was washed with a solution containing 1% trichloroacetic acid and 0.1% sodium pyrophosphate, washed with 90% ethanol and dried. A liquid scintillation cocktail (Packard) was added and the radioactivity of RNA synthesized by the enzyme reaction was measured on a liquid scintillation counter.

[3111] The HCV polymerase inhibitory activity (IC50) of the compound of the present invention was calculated from the values of radioactivity of the enzyme reaction with and without the test substance.

[3112] The results are shown in Tables 269-293.

[3113] As the compound of the present invention, preferred is a compound showing less than 1 µM of HCV
polymerase inhibitory activity ($IC_{50}$), more preferred is a compound showing less than 0.1 µM of HCV polymerase inhibitory activity ($IC_{50}$), and still more preferred is a compound showing less than 0.01 µM of HCV polymerase inhibitory activity ($IC_{50}$).

[3114] Reaction mixture: HCV polymerase (0.5 µg/ml) obtained in i), substrate RNA (5 µg/ml) obtained in ii), ATP (50 µM), GTP (50 µM), CTP (50 µM), UTP (2 µM), [5,6-3H]UTP (46 Ci/mmol (Amersham), 1 µCi) 20 mM Tris-HCl (pH 7.5), EDTA (1 mM), MgCl₂ (5 mM), NaCl (50 mM), DTT (1 mM), BSA (0.01%)

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>B</td>
<td>1-7</td>
<td>B</td>
</tr>
<tr>
<td>1-9</td>
<td>B</td>
<td>1-14</td>
<td>B</td>
</tr>
<tr>
<td>1-18</td>
<td>B</td>
<td>1-19</td>
<td>A</td>
</tr>
<tr>
<td>1-20</td>
<td>B</td>
<td>1-21</td>
<td>B</td>
</tr>
<tr>
<td>1-22</td>
<td>B</td>
<td>1-23</td>
<td>B</td>
</tr>
<tr>
<td>1-24</td>
<td>B</td>
<td>1-25</td>
<td>B</td>
</tr>
<tr>
<td>1-26</td>
<td>B</td>
<td>1-27</td>
<td>B</td>
</tr>
<tr>
<td>1-28</td>
<td>B</td>
<td>1-29</td>
<td>B</td>
</tr>
<tr>
<td>1-30</td>
<td>B</td>
<td>1-31</td>
<td>A</td>
</tr>
<tr>
<td>1-32</td>
<td>B</td>
<td>1-33</td>
<td>B</td>
</tr>
<tr>
<td>1-34</td>
<td>B</td>
<td>1-35</td>
<td>B</td>
</tr>
<tr>
<td>1-36</td>
<td>B</td>
<td>1-37</td>
<td>B</td>
</tr>
<tr>
<td>1-38</td>
<td>B</td>
<td>1-39</td>
<td>B</td>
</tr>
<tr>
<td>1-40</td>
<td>B</td>
<td>1-41</td>
<td>B</td>
</tr>
<tr>
<td>1-42</td>
<td>B</td>
<td>1-43</td>
<td>B</td>
</tr>
<tr>
<td>1-44</td>
<td>B</td>
<td>1-45</td>
<td>B</td>
</tr>
<tr>
<td>1-46</td>
<td>B</td>
<td>1-47</td>
<td>B</td>
</tr>
<tr>
<td>1-48</td>
<td>B</td>
<td>1-49</td>
<td>B</td>
</tr>
<tr>
<td>1-50</td>
<td>B</td>
<td>1-51</td>
<td>B</td>
</tr>
<tr>
<td>1-52</td>
<td>B</td>
<td>1-53</td>
<td>B</td>
</tr>
<tr>
<td>1-54</td>
<td>B</td>
<td>1-55</td>
<td>B</td>
</tr>
</tbody>
</table>

[3117] TABLE 271

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-9</td>
<td>B</td>
<td>2-10</td>
<td>B</td>
</tr>
<tr>
<td>2-11</td>
<td>B</td>
<td>2-12</td>
<td>B</td>
</tr>
<tr>
<td>2-13</td>
<td>B</td>
<td>2-14</td>
<td>B</td>
</tr>
<tr>
<td>2-15</td>
<td>B</td>
<td>2-16</td>
<td>B</td>
</tr>
<tr>
<td>2-17</td>
<td>B</td>
<td>2-18</td>
<td>B</td>
</tr>
<tr>
<td>2-19</td>
<td>B</td>
<td>2-20</td>
<td>B</td>
</tr>
<tr>
<td>2-21</td>
<td>B</td>
<td>2-22</td>
<td>B</td>
</tr>
<tr>
<td>2-23</td>
<td>B</td>
<td>2-24</td>
<td>B</td>
</tr>
<tr>
<td>2-25</td>
<td>B</td>
<td>2-26</td>
<td>B</td>
</tr>
<tr>
<td>2-27</td>
<td>B</td>
<td>2-28</td>
<td>B</td>
</tr>
<tr>
<td>2-29</td>
<td>B</td>
<td>2-30</td>
<td>B</td>
</tr>
<tr>
<td>2-31</td>
<td>B</td>
<td>3-4</td>
<td>B</td>
</tr>
<tr>
<td>4-2</td>
<td>A</td>
<td>4-3</td>
<td>B</td>
</tr>
<tr>
<td>5-3</td>
<td>A</td>
<td>5-3</td>
<td>B</td>
</tr>
<tr>
<td>7-4</td>
<td>B</td>
<td>7-5</td>
<td>B</td>
</tr>
<tr>
<td>7-6</td>
<td>B</td>
<td>7-7</td>
<td>B</td>
</tr>
<tr>
<td>8-4</td>
<td>B</td>
<td>9-2</td>
<td>B</td>
</tr>
<tr>
<td>9-3</td>
<td>B</td>
<td>9-4</td>
<td>B</td>
</tr>
</tbody>
</table>

[3115] TABLE 270

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-56</td>
<td>B</td>
<td>1-57</td>
<td>B</td>
</tr>
<tr>
<td>1-60</td>
<td>B</td>
<td>1-61</td>
<td>B</td>
</tr>
<tr>
<td>1-62</td>
<td>B</td>
<td>1-63</td>
<td>B</td>
</tr>
<tr>
<td>1-64</td>
<td>B</td>
<td>1-65</td>
<td>B</td>
</tr>
<tr>
<td>1-66</td>
<td>B</td>
<td>1-67</td>
<td>B</td>
</tr>
<tr>
<td>1-68</td>
<td>B</td>
<td>1-69</td>
<td>B</td>
</tr>
<tr>
<td>1-70</td>
<td>B</td>
<td>1-71</td>
<td>B</td>
</tr>
<tr>
<td>1-72</td>
<td>B</td>
<td>1-73</td>
<td>B</td>
</tr>
<tr>
<td>1-74</td>
<td>B</td>
<td>1-75</td>
<td>B</td>
</tr>
<tr>
<td>1-76</td>
<td>B</td>
<td>1-77</td>
<td>B</td>
</tr>
<tr>
<td>1-78</td>
<td>B</td>
<td>1-79</td>
<td>B</td>
</tr>
<tr>
<td>1-80</td>
<td>B</td>
<td>1-81</td>
<td>B</td>
</tr>
<tr>
<td>1-82</td>
<td>B</td>
<td>1-83</td>
<td>B</td>
</tr>
<tr>
<td>1-84</td>
<td>B</td>
<td>1-85</td>
<td>B</td>
</tr>
<tr>
<td>1-86</td>
<td>A</td>
<td>1-87</td>
<td>B</td>
</tr>
<tr>
<td>1-88</td>
<td>B</td>
<td>1-89</td>
<td>B</td>
</tr>
<tr>
<td>1-90</td>
<td>B</td>
<td>1-91</td>
<td>B</td>
</tr>
<tr>
<td>1-92</td>
<td>B</td>
<td>1-93</td>
<td>B</td>
</tr>
<tr>
<td>1-94</td>
<td>B</td>
<td>1-95</td>
<td>B</td>
</tr>
<tr>
<td>2-3</td>
<td>B</td>
<td>2-4</td>
<td>B</td>
</tr>
<tr>
<td>2-5</td>
<td>B</td>
<td>2-6</td>
<td>A</td>
</tr>
</tbody>
</table>

[3118] TABLE 273

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-140</td>
<td>B</td>
<td>1-141</td>
<td>B</td>
</tr>
<tr>
<td>1-142</td>
<td>B</td>
<td>1-143</td>
<td>B</td>
</tr>
<tr>
<td>1-144</td>
<td>B</td>
<td>1-145</td>
<td>B</td>
</tr>
<tr>
<td>1-146</td>
<td>B</td>
<td>1-147</td>
<td>B</td>
</tr>
<tr>
<td>1-148</td>
<td>B</td>
<td>1-149</td>
<td>B</td>
</tr>
<tr>
<td>1-150</td>
<td>B</td>
<td>1-151</td>
<td>B</td>
</tr>
<tr>
<td>1-152</td>
<td>B</td>
<td>1-153</td>
<td>B</td>
</tr>
<tr>
<td>1-154</td>
<td>B</td>
<td>1-155</td>
<td>B</td>
</tr>
<tr>
<td>1-156</td>
<td>B</td>
<td>1-157</td>
<td>B</td>
</tr>
</tbody>
</table>
### TABLE 273-continued

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC₅₀</th>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-158</td>
<td>B</td>
<td>1-159</td>
<td>B</td>
</tr>
<tr>
<td>1-160</td>
<td>B</td>
<td>1-161</td>
<td>B</td>
</tr>
<tr>
<td>1-162</td>
<td>B</td>
<td>1-163</td>
<td>B</td>
</tr>
<tr>
<td>1-164</td>
<td>B</td>
<td>1-165</td>
<td>B</td>
</tr>
<tr>
<td>1-166</td>
<td>B</td>
<td>1-167</td>
<td>A</td>
</tr>
<tr>
<td>1-168</td>
<td>B</td>
<td>1-169</td>
<td>B</td>
</tr>
<tr>
<td>1-170</td>
<td>B</td>
<td>1-171</td>
<td>B</td>
</tr>
<tr>
<td>1-172</td>
<td>B</td>
<td>1-173</td>
<td>B</td>
</tr>
<tr>
<td>1-174</td>
<td>B</td>
<td>1-175</td>
<td>B</td>
</tr>
<tr>
<td>1-176</td>
<td>B</td>
<td>1-177</td>
<td>B</td>
</tr>
<tr>
<td>1-178</td>
<td>B</td>
<td>1-179</td>
<td>B</td>
</tr>
<tr>
<td>1-180</td>
<td>B</td>
<td>1-181</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 275-continued

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC₅₀</th>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-256</td>
<td>B</td>
<td>1-257</td>
<td>B</td>
</tr>
<tr>
<td>1-258</td>
<td>B</td>
<td>1-259</td>
<td>B</td>
</tr>
<tr>
<td>1-260</td>
<td>B</td>
<td>1-261</td>
<td>B</td>
</tr>
<tr>
<td>1-262</td>
<td>B</td>
<td>1-263</td>
<td>B</td>
</tr>
<tr>
<td>1-264</td>
<td>B</td>
<td>1-265</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 276

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC₅₀</th>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-266</td>
<td>B</td>
<td>1-267</td>
<td>B</td>
</tr>
<tr>
<td>1-268</td>
<td>B</td>
<td>1-269</td>
<td>B</td>
</tr>
<tr>
<td>1-270</td>
<td>B</td>
<td>1-271</td>
<td>B</td>
</tr>
<tr>
<td>1-272</td>
<td>B</td>
<td>1-273</td>
<td>B</td>
</tr>
<tr>
<td>1-274</td>
<td>B</td>
<td>1-275</td>
<td>B</td>
</tr>
<tr>
<td>1-276</td>
<td>B</td>
<td>1-277</td>
<td>B</td>
</tr>
<tr>
<td>1-278</td>
<td>B</td>
<td>1-279</td>
<td>B</td>
</tr>
<tr>
<td>1-280</td>
<td>B</td>
<td>1-281</td>
<td>B</td>
</tr>
<tr>
<td>1-282</td>
<td>B</td>
<td>1-283</td>
<td>B</td>
</tr>
<tr>
<td>1-284</td>
<td>B</td>
<td>1-285</td>
<td>B</td>
</tr>
<tr>
<td>1-286</td>
<td>B</td>
<td>1-287</td>
<td>B</td>
</tr>
<tr>
<td>1-288</td>
<td>B</td>
<td>1-289</td>
<td>B</td>
</tr>
<tr>
<td>1-290</td>
<td>B</td>
<td>1-291</td>
<td>B</td>
</tr>
<tr>
<td>1-292</td>
<td>B</td>
<td>1-293</td>
<td>B</td>
</tr>
<tr>
<td>1-294</td>
<td>B</td>
<td>1-295</td>
<td>B</td>
</tr>
<tr>
<td>1-296</td>
<td>B</td>
<td>1-297</td>
<td>B</td>
</tr>
<tr>
<td>1-298</td>
<td>B</td>
<td>1-299</td>
<td>B</td>
</tr>
<tr>
<td>1-300</td>
<td>B</td>
<td>1-301</td>
<td>B</td>
</tr>
<tr>
<td>1-302</td>
<td>B</td>
<td>1-303</td>
<td>B</td>
</tr>
<tr>
<td>1-304</td>
<td>B</td>
<td>1-305</td>
<td>B</td>
</tr>
<tr>
<td>1-306</td>
<td>B</td>
<td>1-307</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 277

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC₅₀</th>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-308</td>
<td>B</td>
<td>1-309</td>
<td>B</td>
</tr>
<tr>
<td>1-310</td>
<td>B</td>
<td>1-311</td>
<td>B</td>
</tr>
<tr>
<td>1-312</td>
<td>B</td>
<td>1-314</td>
<td>B</td>
</tr>
<tr>
<td>1-315</td>
<td>B</td>
<td>1-316</td>
<td>B</td>
</tr>
<tr>
<td>1-317</td>
<td>B</td>
<td>1-318</td>
<td>B</td>
</tr>
<tr>
<td>1-319</td>
<td>B</td>
<td>1-320</td>
<td>D</td>
</tr>
<tr>
<td>1-321</td>
<td>B</td>
<td>1-322</td>
<td>B</td>
</tr>
<tr>
<td>1-323</td>
<td>B</td>
<td>1-324</td>
<td>B</td>
</tr>
<tr>
<td>1-325</td>
<td>B</td>
<td>1-326</td>
<td>B</td>
</tr>
<tr>
<td>1-327</td>
<td>D</td>
<td>1-328</td>
<td>B</td>
</tr>
<tr>
<td>1-329</td>
<td>B</td>
<td>1-330</td>
<td>B</td>
</tr>
<tr>
<td>1-331</td>
<td>B</td>
<td>1-332</td>
<td>B</td>
</tr>
<tr>
<td>1-333</td>
<td>B</td>
<td>1-334</td>
<td>B</td>
</tr>
<tr>
<td>1-335</td>
<td>B</td>
<td>1-336</td>
<td>B</td>
</tr>
<tr>
<td>1-337</td>
<td>B</td>
<td>1-338</td>
<td>B</td>
</tr>
<tr>
<td>1-339</td>
<td>B</td>
<td>1-340</td>
<td>B</td>
</tr>
<tr>
<td>1-341</td>
<td>B</td>
<td>1-342</td>
<td>B</td>
</tr>
<tr>
<td>1-343</td>
<td>B</td>
<td>1-344</td>
<td>B</td>
</tr>
<tr>
<td>1-345</td>
<td>B</td>
<td>1-346</td>
<td>B</td>
</tr>
<tr>
<td>1-347</td>
<td>B</td>
<td>1-348</td>
<td>B</td>
</tr>
<tr>
<td>1-349</td>
<td>B</td>
<td>1-350</td>
<td>B</td>
</tr>
</tbody>
</table>
### TABLE 278

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC_{50}</th>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-351</td>
<td>B</td>
<td>1-352</td>
<td>B</td>
</tr>
<tr>
<td>1-353</td>
<td>B</td>
<td>1-354</td>
<td>B</td>
</tr>
<tr>
<td>1-355</td>
<td>B</td>
<td>1-356</td>
<td>B</td>
</tr>
<tr>
<td>1-357</td>
<td>B</td>
<td>1-358</td>
<td>B</td>
</tr>
<tr>
<td>1-359</td>
<td>B</td>
<td>1-360</td>
<td>B</td>
</tr>
<tr>
<td>1-361</td>
<td>B</td>
<td>1-362</td>
<td>B</td>
</tr>
<tr>
<td>1-363</td>
<td>B</td>
<td>1-364</td>
<td>B</td>
</tr>
<tr>
<td>1-365</td>
<td>B</td>
<td>1-366</td>
<td>B</td>
</tr>
<tr>
<td>1-367</td>
<td>B</td>
<td>1-368</td>
<td>B</td>
</tr>
<tr>
<td>1-369</td>
<td>B</td>
<td>1-370</td>
<td>B</td>
</tr>
<tr>
<td>1-371</td>
<td>B</td>
<td>1-372</td>
<td>B</td>
</tr>
<tr>
<td>1-373</td>
<td>B</td>
<td>1-374</td>
<td>B</td>
</tr>
<tr>
<td>1-375</td>
<td>B</td>
<td>1-376</td>
<td>B</td>
</tr>
<tr>
<td>1-377</td>
<td>B</td>
<td>1-378</td>
<td>B</td>
</tr>
<tr>
<td>1-379</td>
<td>B</td>
<td>1-380</td>
<td>B</td>
</tr>
<tr>
<td>1-381</td>
<td>B</td>
<td>1-382</td>
<td>B</td>
</tr>
<tr>
<td>1-383</td>
<td>B</td>
<td>1-384</td>
<td>B</td>
</tr>
<tr>
<td>1-385</td>
<td>B</td>
<td>1-386</td>
<td>B</td>
</tr>
<tr>
<td>1-387</td>
<td>B</td>
<td>1-388</td>
<td>B</td>
</tr>
<tr>
<td>1-389</td>
<td>B</td>
<td>1-390</td>
<td>B</td>
</tr>
<tr>
<td>1-391</td>
<td>B</td>
<td>1-392</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 280-continued

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC_{50}</th>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-443</td>
<td>B</td>
<td>1-444</td>
<td>B</td>
</tr>
<tr>
<td>1-445</td>
<td>B</td>
<td>2-32</td>
<td>B</td>
</tr>
<tr>
<td>2-34</td>
<td>B</td>
<td>2-35</td>
<td>B</td>
</tr>
<tr>
<td>2-36</td>
<td>B</td>
<td>2-37</td>
<td>B</td>
</tr>
<tr>
<td>2-38</td>
<td>B</td>
<td>2-39</td>
<td>B</td>
</tr>
<tr>
<td>2-40</td>
<td>B</td>
<td>2-41</td>
<td>B</td>
</tr>
<tr>
<td>2-42</td>
<td>B</td>
<td>2-43</td>
<td>B</td>
</tr>
<tr>
<td>2-44</td>
<td>B</td>
<td>2-45</td>
<td>B</td>
</tr>
<tr>
<td>2-46</td>
<td>B</td>
<td>2-47</td>
<td>B</td>
</tr>
<tr>
<td>2-48</td>
<td>B</td>
<td>2-49</td>
<td>B</td>
</tr>
<tr>
<td>2-50</td>
<td>B</td>
<td>2-51</td>
<td>B</td>
</tr>
<tr>
<td>2-52</td>
<td>B</td>
<td>2-53</td>
<td>B</td>
</tr>
<tr>
<td>7-8</td>
<td>B</td>
<td>8-5</td>
<td>B</td>
</tr>
<tr>
<td>8-6</td>
<td>B</td>
<td>8-7</td>
<td>B</td>
</tr>
<tr>
<td>10-1</td>
<td>B</td>
<td>10-2</td>
<td>A</td>
</tr>
<tr>
<td>10-3</td>
<td>B</td>
<td>10-4</td>
<td>A</td>
</tr>
</tbody>
</table>

### TABLE 279

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC_{50}</th>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-393</td>
<td>B</td>
<td>1-394</td>
<td>B</td>
</tr>
<tr>
<td>1-395</td>
<td>B</td>
<td>1-396</td>
<td>B</td>
</tr>
<tr>
<td>1-397</td>
<td>B</td>
<td>1-398</td>
<td>B</td>
</tr>
<tr>
<td>1-399</td>
<td>B</td>
<td>1-400</td>
<td>B</td>
</tr>
<tr>
<td>1-401</td>
<td>B</td>
<td>1-402</td>
<td>B</td>
</tr>
<tr>
<td>1-403</td>
<td>B</td>
<td>1-404</td>
<td>B</td>
</tr>
<tr>
<td>1-405</td>
<td>B</td>
<td>1-406</td>
<td>B</td>
</tr>
<tr>
<td>1-407</td>
<td>B</td>
<td>1-408</td>
<td>B</td>
</tr>
<tr>
<td>1-409</td>
<td>B</td>
<td>1-410</td>
<td>B</td>
</tr>
<tr>
<td>1-411</td>
<td>B</td>
<td>1-412</td>
<td>B</td>
</tr>
<tr>
<td>1-413</td>
<td>B</td>
<td>1-414</td>
<td>B</td>
</tr>
<tr>
<td>1-415</td>
<td>B</td>
<td>1-416</td>
<td>B</td>
</tr>
<tr>
<td>1-417</td>
<td>B</td>
<td>1-418</td>
<td>B</td>
</tr>
<tr>
<td>1-419</td>
<td>B</td>
<td>1-420</td>
<td>B</td>
</tr>
<tr>
<td>1-421</td>
<td>B</td>
<td>1-422</td>
<td>B</td>
</tr>
<tr>
<td>1-423</td>
<td>B</td>
<td>1-424</td>
<td>B</td>
</tr>
<tr>
<td>1-425</td>
<td>B</td>
<td>1-426</td>
<td>B</td>
</tr>
<tr>
<td>1-427</td>
<td>B</td>
<td>1-428</td>
<td>B</td>
</tr>
<tr>
<td>1-429</td>
<td>B</td>
<td>1-430</td>
<td>B</td>
</tr>
<tr>
<td>1-431</td>
<td>B</td>
<td>1-432</td>
<td>B</td>
</tr>
<tr>
<td>1-433</td>
<td>B</td>
<td>1-434</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 281

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-450</td>
<td>B</td>
</tr>
<tr>
<td>1-451</td>
<td>B</td>
</tr>
<tr>
<td>1-452</td>
<td>B</td>
</tr>
<tr>
<td>1-473</td>
<td>B</td>
</tr>
<tr>
<td>1-474</td>
<td>B</td>
</tr>
<tr>
<td>1-475</td>
<td>B</td>
</tr>
<tr>
<td>1-476</td>
<td>B</td>
</tr>
<tr>
<td>1-477</td>
<td>B</td>
</tr>
<tr>
<td>1-478</td>
<td>B</td>
</tr>
<tr>
<td>1-479</td>
<td>B</td>
</tr>
<tr>
<td>1-480</td>
<td>B</td>
</tr>
<tr>
<td>1-481</td>
<td>B</td>
</tr>
<tr>
<td>1-482</td>
<td>B</td>
</tr>
<tr>
<td>1-483</td>
<td>B</td>
</tr>
<tr>
<td>1-484</td>
<td>B</td>
</tr>
<tr>
<td>2-54</td>
<td>B</td>
</tr>
<tr>
<td>2-55</td>
<td>B</td>
</tr>
<tr>
<td>2-151</td>
<td>B</td>
</tr>
<tr>
<td>2-152</td>
<td>B</td>
</tr>
<tr>
<td>2-153</td>
<td>B</td>
</tr>
<tr>
<td>2-154</td>
<td>A</td>
</tr>
<tr>
<td>2-155</td>
<td>B</td>
</tr>
<tr>
<td>2-156</td>
<td>B</td>
</tr>
<tr>
<td>2-157</td>
<td>A</td>
</tr>
<tr>
<td>2-158</td>
<td>B</td>
</tr>
<tr>
<td>2-159</td>
<td>A</td>
</tr>
<tr>
<td>2-160</td>
<td>B</td>
</tr>
<tr>
<td>2-161</td>
<td>B</td>
</tr>
<tr>
<td>2-162</td>
<td>B</td>
</tr>
<tr>
<td>2-163</td>
<td>B</td>
</tr>
<tr>
<td>2-164</td>
<td>A</td>
</tr>
<tr>
<td>2-165</td>
<td>A</td>
</tr>
<tr>
<td>2-166</td>
<td>B</td>
</tr>
<tr>
<td>2-167</td>
<td>B</td>
</tr>
<tr>
<td>2-168</td>
<td>B</td>
</tr>
<tr>
<td>2-169</td>
<td>B</td>
</tr>
<tr>
<td>2-170</td>
<td>B</td>
</tr>
<tr>
<td>2-171</td>
<td>B</td>
</tr>
<tr>
<td>2-172</td>
<td>B</td>
</tr>
<tr>
<td>2-173</td>
<td>B</td>
</tr>
<tr>
<td>2-174</td>
<td>B</td>
</tr>
<tr>
<td>2-175</td>
<td>B</td>
</tr>
</tbody>
</table>
### TABLE 282

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-176</td>
<td>B</td>
</tr>
<tr>
<td>2-177</td>
<td>B</td>
</tr>
<tr>
<td>2-178</td>
<td>B</td>
</tr>
<tr>
<td>2-179</td>
<td>A</td>
</tr>
<tr>
<td>2-180</td>
<td>B</td>
</tr>
<tr>
<td>2-181</td>
<td>B</td>
</tr>
<tr>
<td>2-182</td>
<td>B</td>
</tr>
<tr>
<td>2-183</td>
<td>B</td>
</tr>
<tr>
<td>2-184</td>
<td>B</td>
</tr>
<tr>
<td>2-185</td>
<td>A</td>
</tr>
<tr>
<td>2-186</td>
<td>A</td>
</tr>
<tr>
<td>2-187</td>
<td>A</td>
</tr>
<tr>
<td>2-188</td>
<td>A</td>
</tr>
<tr>
<td>2-189</td>
<td>A</td>
</tr>
<tr>
<td>2-190</td>
<td>B</td>
</tr>
<tr>
<td>2-191</td>
<td>B</td>
</tr>
<tr>
<td>2-192</td>
<td>B</td>
</tr>
<tr>
<td>2-193</td>
<td>B</td>
</tr>
<tr>
<td>2-194</td>
<td>B</td>
</tr>
<tr>
<td>2-195</td>
<td>B</td>
</tr>
<tr>
<td>2-196</td>
<td>B</td>
</tr>
<tr>
<td>2-197</td>
<td>B</td>
</tr>
<tr>
<td>2-198</td>
<td>B</td>
</tr>
<tr>
<td>2-199</td>
<td>B</td>
</tr>
<tr>
<td>2-200</td>
<td>B</td>
</tr>
<tr>
<td>2-201</td>
<td>B</td>
</tr>
<tr>
<td>2-202</td>
<td>B</td>
</tr>
<tr>
<td>2-203</td>
<td>B</td>
</tr>
<tr>
<td>2-204</td>
<td>B</td>
</tr>
<tr>
<td>2-205</td>
<td>B</td>
</tr>
<tr>
<td>2-206</td>
<td>A</td>
</tr>
<tr>
<td>2-207</td>
<td>B</td>
</tr>
<tr>
<td>2-208</td>
<td>A</td>
</tr>
<tr>
<td>2-209</td>
<td>B</td>
</tr>
<tr>
<td>2-210</td>
<td>B</td>
</tr>
<tr>
<td>2-211</td>
<td>A</td>
</tr>
<tr>
<td>2-212</td>
<td>A</td>
</tr>
<tr>
<td>2-213</td>
<td>B</td>
</tr>
<tr>
<td>2-214</td>
<td>B</td>
</tr>
<tr>
<td>2-215</td>
<td>A</td>
</tr>
<tr>
<td>2-216</td>
<td>B</td>
</tr>
<tr>
<td>2-217</td>
<td>B</td>
</tr>
<tr>
<td>2-218</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 284

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-221</td>
<td>A</td>
</tr>
<tr>
<td>2-222</td>
<td>B</td>
</tr>
<tr>
<td>2-223</td>
<td>B</td>
</tr>
<tr>
<td>2-224</td>
<td>B</td>
</tr>
<tr>
<td>2-225</td>
<td>B</td>
</tr>
<tr>
<td>2-226</td>
<td>B</td>
</tr>
<tr>
<td>2-227</td>
<td>B</td>
</tr>
<tr>
<td>2-228</td>
<td>B</td>
</tr>
<tr>
<td>2-229</td>
<td>B</td>
</tr>
<tr>
<td>2-230</td>
<td>B</td>
</tr>
<tr>
<td>2-231</td>
<td>B</td>
</tr>
<tr>
<td>2-232</td>
<td>B</td>
</tr>
<tr>
<td>2-233</td>
<td>B</td>
</tr>
<tr>
<td>2-234</td>
<td>A</td>
</tr>
<tr>
<td>2-235</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 283-continued

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-236</td>
<td>B</td>
</tr>
<tr>
<td>2-237</td>
<td>B</td>
</tr>
<tr>
<td>2-238</td>
<td>B</td>
</tr>
<tr>
<td>2-239</td>
<td>A</td>
</tr>
<tr>
<td>2-240</td>
<td>B</td>
</tr>
<tr>
<td>2-241</td>
<td>B</td>
</tr>
<tr>
<td>2-242</td>
<td>B</td>
</tr>
<tr>
<td>2-243</td>
<td>B</td>
</tr>
<tr>
<td>2-244</td>
<td>A</td>
</tr>
<tr>
<td>2-245</td>
<td>B</td>
</tr>
<tr>
<td>2-246</td>
<td>B</td>
</tr>
<tr>
<td>2-247</td>
<td>B</td>
</tr>
<tr>
<td>2-248</td>
<td>B</td>
</tr>
<tr>
<td>2-249</td>
<td>B</td>
</tr>
<tr>
<td>2-250</td>
<td>B</td>
</tr>
<tr>
<td>2-251</td>
<td>B</td>
</tr>
<tr>
<td>2-252</td>
<td>B</td>
</tr>
<tr>
<td>2-253</td>
<td>B</td>
</tr>
<tr>
<td>2-254</td>
<td>A</td>
</tr>
<tr>
<td>2-255</td>
<td>B</td>
</tr>
<tr>
<td>2-256</td>
<td>B</td>
</tr>
<tr>
<td>2-257</td>
<td>H</td>
</tr>
<tr>
<td>2-258</td>
<td>B</td>
</tr>
<tr>
<td>2-259</td>
<td>B</td>
</tr>
<tr>
<td>2-260</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 284

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-261</td>
<td>B</td>
</tr>
<tr>
<td>2-262</td>
<td>B</td>
</tr>
<tr>
<td>2-263</td>
<td>B</td>
</tr>
<tr>
<td>2-264</td>
<td>B</td>
</tr>
<tr>
<td>2-265</td>
<td>A</td>
</tr>
<tr>
<td>2-266</td>
<td>A</td>
</tr>
<tr>
<td>2-267</td>
<td>A</td>
</tr>
<tr>
<td>2-268</td>
<td>A</td>
</tr>
<tr>
<td>2-269</td>
<td>B</td>
</tr>
<tr>
<td>2-270</td>
<td>B</td>
</tr>
<tr>
<td>2-271</td>
<td>B</td>
</tr>
<tr>
<td>2-272</td>
<td>B</td>
</tr>
<tr>
<td>2-273</td>
<td>B</td>
</tr>
<tr>
<td>2-274</td>
<td>B</td>
</tr>
<tr>
<td>2-275</td>
<td>B</td>
</tr>
<tr>
<td>2-276</td>
<td>B</td>
</tr>
<tr>
<td>2-277</td>
<td>B</td>
</tr>
<tr>
<td>2-278</td>
<td>B</td>
</tr>
<tr>
<td>2-279</td>
<td>B</td>
</tr>
<tr>
<td>2-280</td>
<td>B</td>
</tr>
<tr>
<td>2-281</td>
<td>A</td>
</tr>
<tr>
<td>2-282</td>
<td>B</td>
</tr>
<tr>
<td>2-283</td>
<td>B</td>
</tr>
<tr>
<td>2-284</td>
<td>B</td>
</tr>
<tr>
<td>2-285</td>
<td>B</td>
</tr>
<tr>
<td>2-286</td>
<td>A</td>
</tr>
<tr>
<td>2-287</td>
<td>A</td>
</tr>
<tr>
<td>2-288</td>
<td>B</td>
</tr>
<tr>
<td>2-289</td>
<td>B</td>
</tr>
<tr>
<td>2-290</td>
<td>A</td>
</tr>
<tr>
<td>2-291</td>
<td>B</td>
</tr>
<tr>
<td>2-292</td>
<td>A</td>
</tr>
<tr>
<td>2-293</td>
<td>A</td>
</tr>
<tr>
<td>2-294</td>
<td>B</td>
</tr>
<tr>
<td>2-295</td>
<td>B</td>
</tr>
</tbody>
</table>
### TABLE 284-continued

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity</th>
<th>IC_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-296</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-297</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-298</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-299</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-300</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-301</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-302</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 285

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity</th>
<th>IC_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-303</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-304</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-305</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-306</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-307</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-308</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-309</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>2-310</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-311</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-312</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-313</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-314</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-315</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-316</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-317</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-318</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-319</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-320</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-321</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-322</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-323</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-324</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-325</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-326</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-327</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-328</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-329</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-330</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-331</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-332</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-333</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-334</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-335</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-336</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-337</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-338</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-339</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-340</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-341</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-342</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-343</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-344</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 286

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity</th>
<th>IC_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-345</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-346</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-347</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-348</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-349</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-350</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-351</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-352</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-353</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-354</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-355</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-356</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-357</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-358</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-359</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-360</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-361</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-362</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-363</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-364</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-365</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-366</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-367</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-368</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-369</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-370</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-371</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-372</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-373</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-374</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-375</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-376</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-377</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-378</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-379</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>2-380</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-381</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-382</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-383</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-384</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-385</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-386</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 287

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity</th>
<th>IC_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-387</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-388</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-389</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-390</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-391</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-392</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-393</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-394</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-395</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-396</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-397</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-398</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-399</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-400</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-401</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-402</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2-403</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 288

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-429</td>
<td>B</td>
</tr>
<tr>
<td>2-430</td>
<td>B</td>
</tr>
<tr>
<td>2-431</td>
<td>B</td>
</tr>
<tr>
<td>2-432</td>
<td>B</td>
</tr>
<tr>
<td>2-433</td>
<td>B</td>
</tr>
<tr>
<td>2-434</td>
<td>B</td>
</tr>
<tr>
<td>2-435</td>
<td>B</td>
</tr>
<tr>
<td>2-436</td>
<td>B</td>
</tr>
<tr>
<td>2-437</td>
<td>B</td>
</tr>
<tr>
<td>2-438</td>
<td>B</td>
</tr>
<tr>
<td>2-439</td>
<td>B</td>
</tr>
<tr>
<td>2-440</td>
<td>B</td>
</tr>
<tr>
<td>2-441</td>
<td>B</td>
</tr>
<tr>
<td>2-442</td>
<td>B</td>
</tr>
<tr>
<td>2-443</td>
<td>B</td>
</tr>
<tr>
<td>2-444</td>
<td>B</td>
</tr>
<tr>
<td>2-445</td>
<td>B</td>
</tr>
<tr>
<td>2-446</td>
<td>B</td>
</tr>
<tr>
<td>2-447</td>
<td>B</td>
</tr>
<tr>
<td>2-448</td>
<td>B</td>
</tr>
<tr>
<td>2-449</td>
<td>B</td>
</tr>
<tr>
<td>2-450</td>
<td>B</td>
</tr>
<tr>
<td>2-451</td>
<td>B</td>
</tr>
<tr>
<td>2-452</td>
<td>B</td>
</tr>
<tr>
<td>2-453</td>
<td>B</td>
</tr>
<tr>
<td>2-454</td>
<td>B</td>
</tr>
<tr>
<td>2-455</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 289

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-485</td>
<td>B</td>
</tr>
<tr>
<td>1-486</td>
<td>B</td>
</tr>
<tr>
<td>1-487</td>
<td>B</td>
</tr>
<tr>
<td>1-488</td>
<td>B</td>
</tr>
<tr>
<td>1-489</td>
<td>B</td>
</tr>
<tr>
<td>1-490</td>
<td>B</td>
</tr>
<tr>
<td>1-491</td>
<td>B</td>
</tr>
<tr>
<td>1-492</td>
<td>B</td>
</tr>
<tr>
<td>1-493</td>
<td>B</td>
</tr>
<tr>
<td>1-494</td>
<td>B</td>
</tr>
<tr>
<td>1-495</td>
<td>B</td>
</tr>
<tr>
<td>1-496</td>
<td>B</td>
</tr>
<tr>
<td>1-497</td>
<td>B</td>
</tr>
<tr>
<td>1-498</td>
<td>B</td>
</tr>
<tr>
<td>1-499</td>
<td>B</td>
</tr>
<tr>
<td>1-500</td>
<td>B</td>
</tr>
<tr>
<td>1-501</td>
<td>B</td>
</tr>
<tr>
<td>1-502</td>
<td>B</td>
</tr>
<tr>
<td>1-503</td>
<td>B</td>
</tr>
<tr>
<td>1-504</td>
<td>B</td>
</tr>
<tr>
<td>1-505</td>
<td>A</td>
</tr>
<tr>
<td>1-506</td>
<td>A</td>
</tr>
<tr>
<td>1-507</td>
<td>A</td>
</tr>
<tr>
<td>1-508</td>
<td>B</td>
</tr>
<tr>
<td>1-509</td>
<td>B</td>
</tr>
<tr>
<td>1-510</td>
<td>B</td>
</tr>
<tr>
<td>1-511</td>
<td>B</td>
</tr>
<tr>
<td>1-512</td>
<td>B</td>
</tr>
<tr>
<td>1-513</td>
<td>B</td>
</tr>
<tr>
<td>1-514</td>
<td>B</td>
</tr>
<tr>
<td>1-515</td>
<td>B</td>
</tr>
<tr>
<td>1-516</td>
<td>A</td>
</tr>
<tr>
<td>1-517</td>
<td>A</td>
</tr>
<tr>
<td>1-518</td>
<td>B</td>
</tr>
<tr>
<td>1-519</td>
<td>B</td>
</tr>
<tr>
<td>1-520</td>
<td>B</td>
</tr>
<tr>
<td>1-521</td>
<td>B</td>
</tr>
<tr>
<td>1-522</td>
<td>B</td>
</tr>
<tr>
<td>1-523</td>
<td>B</td>
</tr>
<tr>
<td>1-524</td>
<td>B</td>
</tr>
<tr>
<td>1-525</td>
<td>B</td>
</tr>
<tr>
<td>1-526</td>
<td>B</td>
</tr>
<tr>
<td>1-527</td>
<td>B</td>
</tr>
<tr>
<td>1-528</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 287-continued

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-404</td>
<td>B</td>
</tr>
<tr>
<td>2-405</td>
<td>B</td>
</tr>
<tr>
<td>2-406</td>
<td>B</td>
</tr>
<tr>
<td>2-407</td>
<td>B</td>
</tr>
<tr>
<td>2-408</td>
<td>B</td>
</tr>
<tr>
<td>2-409</td>
<td>B</td>
</tr>
<tr>
<td>2-410</td>
<td>B</td>
</tr>
<tr>
<td>2-411</td>
<td>B</td>
</tr>
<tr>
<td>2-412</td>
<td>B</td>
</tr>
<tr>
<td>2-413</td>
<td>B</td>
</tr>
<tr>
<td>2-414</td>
<td>B</td>
</tr>
<tr>
<td>2-415</td>
<td>B</td>
</tr>
<tr>
<td>2-416</td>
<td>B</td>
</tr>
<tr>
<td>2-417</td>
<td>B</td>
</tr>
<tr>
<td>2-418</td>
<td>B</td>
</tr>
<tr>
<td>2-419</td>
<td>B</td>
</tr>
<tr>
<td>2-420</td>
<td>B</td>
</tr>
<tr>
<td>2-421</td>
<td>B</td>
</tr>
<tr>
<td>2-422</td>
<td>B</td>
</tr>
<tr>
<td>2-423</td>
<td>B</td>
</tr>
<tr>
<td>2-424</td>
<td>B</td>
</tr>
<tr>
<td>2-425</td>
<td>B</td>
</tr>
<tr>
<td>2-426</td>
<td>B</td>
</tr>
<tr>
<td>2-427</td>
<td>B</td>
</tr>
<tr>
<td>2-428</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 287

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-404</td>
<td>B</td>
</tr>
<tr>
<td>2-405</td>
<td>B</td>
</tr>
<tr>
<td>2-406</td>
<td>B</td>
</tr>
<tr>
<td>2-407</td>
<td>B</td>
</tr>
<tr>
<td>2-408</td>
<td>B</td>
</tr>
<tr>
<td>2-409</td>
<td>B</td>
</tr>
<tr>
<td>2-410</td>
<td>B</td>
</tr>
<tr>
<td>2-411</td>
<td>B</td>
</tr>
<tr>
<td>2-412</td>
<td>B</td>
</tr>
<tr>
<td>2-413</td>
<td>B</td>
</tr>
<tr>
<td>2-414</td>
<td>B</td>
</tr>
<tr>
<td>2-415</td>
<td>B</td>
</tr>
<tr>
<td>2-416</td>
<td>B</td>
</tr>
<tr>
<td>2-417</td>
<td>B</td>
</tr>
<tr>
<td>2-418</td>
<td>B</td>
</tr>
<tr>
<td>2-419</td>
<td>B</td>
</tr>
<tr>
<td>2-420</td>
<td>B</td>
</tr>
<tr>
<td>2-421</td>
<td>B</td>
</tr>
<tr>
<td>2-422</td>
<td>B</td>
</tr>
<tr>
<td>2-423</td>
<td>B</td>
</tr>
<tr>
<td>2-424</td>
<td>B</td>
</tr>
<tr>
<td>2-425</td>
<td>B</td>
</tr>
<tr>
<td>2-426</td>
<td>B</td>
</tr>
<tr>
<td>2-427</td>
<td>B</td>
</tr>
<tr>
<td>2-428</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 288

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity $IC_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-429</td>
<td>B</td>
</tr>
<tr>
<td>2-430</td>
<td>B</td>
</tr>
<tr>
<td>2-431</td>
<td>B</td>
</tr>
<tr>
<td>2-432</td>
<td>B</td>
</tr>
<tr>
<td>2-433</td>
<td>B</td>
</tr>
<tr>
<td>2-434</td>
<td>B</td>
</tr>
<tr>
<td>2-435</td>
<td>B</td>
</tr>
<tr>
<td>2-436</td>
<td>B</td>
</tr>
<tr>
<td>2-437</td>
<td>B</td>
</tr>
<tr>
<td>2-438</td>
<td>B</td>
</tr>
<tr>
<td>2-439</td>
<td>B</td>
</tr>
<tr>
<td>2-440</td>
<td>B</td>
</tr>
<tr>
<td>2-441</td>
<td>B</td>
</tr>
<tr>
<td>2-442</td>
<td>B</td>
</tr>
<tr>
<td>2-443</td>
<td>B</td>
</tr>
<tr>
<td>2-444</td>
<td>B</td>
</tr>
<tr>
<td>2-445</td>
<td>B</td>
</tr>
<tr>
<td>2-446</td>
<td>B</td>
</tr>
<tr>
<td>2-447</td>
<td>B</td>
</tr>
<tr>
<td>2-448</td>
<td>B</td>
</tr>
<tr>
<td>2-449</td>
<td>B</td>
</tr>
<tr>
<td>2-450</td>
<td>B</td>
</tr>
<tr>
<td>2-451</td>
<td>B</td>
</tr>
<tr>
<td>2-452</td>
<td>B</td>
</tr>
<tr>
<td>2-453</td>
<td>B</td>
</tr>
<tr>
<td>2-454</td>
<td>B</td>
</tr>
<tr>
<td>2-455</td>
<td>B</td>
</tr>
</tbody>
</table>
### TABLE 290-continued

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC&lt;sub&gt;50&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-546</td>
<td>B</td>
</tr>
<tr>
<td>1-547</td>
<td>B</td>
</tr>
<tr>
<td>1-548</td>
<td>B</td>
</tr>
<tr>
<td>1-549</td>
<td>B</td>
</tr>
<tr>
<td>1-550</td>
<td>B</td>
</tr>
<tr>
<td>1-551</td>
<td>B</td>
</tr>
<tr>
<td>1-552</td>
<td>B</td>
</tr>
<tr>
<td>1-553</td>
<td>B</td>
</tr>
<tr>
<td>1-554</td>
<td>B</td>
</tr>
<tr>
<td>1-555</td>
<td>B</td>
</tr>
<tr>
<td>1-556</td>
<td>B</td>
</tr>
<tr>
<td>1-557</td>
<td>B</td>
</tr>
<tr>
<td>1-558</td>
<td>A</td>
</tr>
<tr>
<td>1-559</td>
<td>B</td>
</tr>
<tr>
<td>1-560</td>
<td>B</td>
</tr>
<tr>
<td>1-561</td>
<td>B</td>
</tr>
<tr>
<td>1-562</td>
<td>B</td>
</tr>
<tr>
<td>1-563</td>
<td>B</td>
</tr>
<tr>
<td>1-564</td>
<td>B</td>
</tr>
<tr>
<td>1-565</td>
<td>B</td>
</tr>
<tr>
<td>1-566</td>
<td>B</td>
</tr>
<tr>
<td>1-567</td>
<td>B</td>
</tr>
<tr>
<td>1-568</td>
<td>B</td>
</tr>
<tr>
<td>1-569</td>
<td>A</td>
</tr>
<tr>
<td>1-570</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 291-continued

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-466</td>
<td>B</td>
</tr>
<tr>
<td>2-467</td>
<td>B</td>
</tr>
<tr>
<td>2-468</td>
<td>B</td>
</tr>
<tr>
<td>2-469</td>
<td>B</td>
</tr>
<tr>
<td>2-470</td>
<td>B</td>
</tr>
<tr>
<td>2-471</td>
<td>B</td>
</tr>
<tr>
<td>2-472</td>
<td>B</td>
</tr>
</tbody>
</table>

### TABLE 292

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity IC&lt;sub&gt;50&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-473</td>
<td>A</td>
</tr>
<tr>
<td>2-474</td>
<td>B</td>
</tr>
<tr>
<td>2-475</td>
<td>B</td>
</tr>
<tr>
<td>2-476</td>
<td>B</td>
</tr>
<tr>
<td>2-477</td>
<td>B</td>
</tr>
<tr>
<td>2-478</td>
<td>B</td>
</tr>
<tr>
<td>2-479</td>
<td>B</td>
</tr>
<tr>
<td>2-480</td>
<td>B</td>
</tr>
<tr>
<td>2-481</td>
<td>B</td>
</tr>
<tr>
<td>2-482</td>
<td>B</td>
</tr>
<tr>
<td>2-483</td>
<td>B</td>
</tr>
<tr>
<td>2-484</td>
<td>B</td>
</tr>
<tr>
<td>2-485</td>
<td>B</td>
</tr>
<tr>
<td>2-486</td>
<td>B</td>
</tr>
<tr>
<td>5-4</td>
<td>A</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
</tr>
<tr>
<td>7-10</td>
<td>B</td>
</tr>
<tr>
<td>8-8</td>
<td>A</td>
</tr>
<tr>
<td>8-9</td>
<td>B</td>
</tr>
<tr>
<td>11-1</td>
<td>B</td>
</tr>
<tr>
<td>12-1</td>
<td>B</td>
</tr>
<tr>
<td>12-2</td>
<td>A</td>
</tr>
<tr>
<td>1-615</td>
<td>B</td>
</tr>
<tr>
<td>1-616</td>
<td>B</td>
</tr>
<tr>
<td>1-617</td>
<td>B</td>
</tr>
<tr>
<td>1-618</td>
<td>B</td>
</tr>
<tr>
<td>1-619</td>
<td>B</td>
</tr>
<tr>
<td>1-620</td>
<td>B</td>
</tr>
<tr>
<td>1-621</td>
<td>B</td>
</tr>
<tr>
<td>1-622</td>
<td>B</td>
</tr>
<tr>
<td>1-623</td>
<td>B</td>
</tr>
<tr>
<td>2-523</td>
<td>B</td>
</tr>
<tr>
<td>2-524</td>
<td>B</td>
</tr>
<tr>
<td>2-525</td>
<td>B</td>
</tr>
<tr>
<td>2-526</td>
<td>B</td>
</tr>
<tr>
<td>2-527</td>
<td>B</td>
</tr>
<tr>
<td>2-528</td>
<td>B</td>
</tr>
<tr>
<td>2-529</td>
<td>B</td>
</tr>
<tr>
<td>2-530</td>
<td>B</td>
</tr>
<tr>
<td>2-531</td>
<td>B</td>
</tr>
<tr>
<td>2-532</td>
<td>B</td>
</tr>
<tr>
<td>2-533</td>
<td>B</td>
</tr>
</tbody>
</table>
### TABLE 293

<table>
<thead>
<tr>
<th>Example No.</th>
<th>HCV polymerase inhibitory activity EC₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-534</td>
<td>B</td>
</tr>
<tr>
<td>2-535</td>
<td>B</td>
</tr>
<tr>
<td>2-536</td>
<td>B</td>
</tr>
<tr>
<td>2-537</td>
<td>B</td>
</tr>
<tr>
<td>2-538</td>
<td>B</td>
</tr>
<tr>
<td>2-539</td>
<td>B</td>
</tr>
<tr>
<td>2-540</td>
<td>B</td>
</tr>
<tr>
<td>2-541</td>
<td>B</td>
</tr>
<tr>
<td>2-542</td>
<td>B</td>
</tr>
<tr>
<td>2-543</td>
<td>B</td>
</tr>
<tr>
<td>2-544</td>
<td>B</td>
</tr>
<tr>
<td>2-545</td>
<td>B</td>
</tr>
<tr>
<td>2-546</td>
<td>B</td>
</tr>
<tr>
<td>2-547</td>
<td>B</td>
</tr>
<tr>
<td>2-548</td>
<td>B</td>
</tr>
<tr>
<td>2-549</td>
<td>B</td>
</tr>
<tr>
<td>2-550</td>
<td>B</td>
</tr>
<tr>
<td>2-551</td>
<td>B</td>
</tr>
<tr>
<td>2-552</td>
<td>B</td>
</tr>
<tr>
<td>2-553</td>
<td>B</td>
</tr>
<tr>
<td>2-554</td>
<td>B</td>
</tr>
<tr>
<td>2-555</td>
<td>B</td>
</tr>
<tr>
<td>2-556</td>
<td>B</td>
</tr>
<tr>
<td>5-6</td>
<td>A</td>
</tr>
<tr>
<td>11-4</td>
<td>B</td>
</tr>
<tr>
<td>11-5</td>
<td>B</td>
</tr>
<tr>
<td>11-6</td>
<td>B</td>
</tr>
<tr>
<td>11-7</td>
<td>B</td>
</tr>
<tr>
<td>11-8</td>
<td>B</td>
</tr>
</tbody>
</table>

K₅₀:
- A not less than 0.1 μM, less than 1 μM
- B less than 0.1 μM

**Experimental Example [1]**

**[3139]** The test compound was dissolved in DMSO (dimethyl sulfoxide; final concentration 0.5%), and adjusted to a 10-fold concentration of the final concentration with a medium.

**[3140]** Replicon cells (Huh-7-2: manufactured by ReBi-Likon GmbH) were inoculated on a medium at 5×10⁷/90 μl/well in a 96-well plate.

**[3141]** The medium was changed to a 4% HSA (human serum albumin)-containing medium (90 μl) the next day, and 10 μl of the above-mentioned adjusted product at each concentration was added.

**[3142]** At 48 hr later, luciferase activity was measured with Steady-Glo (manufactured by PROMEGA). The inhibitory rate relative to the control group (0.5% DMSO addition group) was calculated and EC₅₀ value was determined by proportional calculation, based on the data of two points across 50%, with the concentration of the compound taken as logarithm. Composition of medium: Dulbecco’s modified Eagle’s medium (DMEM), 10% fetal bovine serum (FBS), 2 mM L-glutamine, 0.1 mM MEM non-essential amino acid, 100 U/ml penicillin, 0.1 mg/ml streptomycin.

**[3143]** As in the test, one showing high replication inhibitory, or HCV polymerase inhibitory activity in the presence of a protein is one of the preferable embodiments.

**[3144]** As is evident from the above-mentioned results, the compound of the present invention shows a high inhibitory activity against HCV polymerase.

**[3145]** Therefore, the compound of the present invention can provide a pharmaceutical agent effective for the prophylaxis or treatment of hepatitis C, based on the anti-HCV effect afforded by the HCV polymerase inhibitory activity. When used concurrently with a different anti-HCV agent, such as interferon, and/or an anti-inflammatory agent and the like, it can provide a pharmaceutical agent more effective for the prophylaxis or treatment of hepatitis C. Its high inhibitory activity specific to HCV polymerase suggests the possibility of the compound being a pharmaceutical agent with slight side effects, which can be used safely for humans.

**[3146]** Formulation Example is given in the following. This example is merely for the purpose of exemplification and does not limit the invention.

**Formulation Example**

**[3147]**

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) compound of Example 1-9</td>
<td>10 g</td>
</tr>
<tr>
<td>(b) lactose</td>
<td>50 g</td>
</tr>
<tr>
<td>(c) corn starch</td>
<td>15 g</td>
</tr>
<tr>
<td>(d) sodium carboxymethyl cellulose</td>
<td>44 g</td>
</tr>
<tr>
<td>(e) magnesium stearate</td>
<td>1 g</td>
</tr>
</tbody>
</table>

**[3148]** The entire amounts of (a), (b) and (c) and 30 g of (d) are kneaded with water, dried in vacuo and granulated. The obtained granules are mixed with 14 g of (d) and 1 g of (e) and processed into tablets with a tableting machine to give 1000 tablets each containing 10 mg of (a).

**[3149]** This application is based on a patent application Nos. 2004-48815, 2004-169190 and 2004-296390 filed in Japan, the contents of which are hereby incorporated by reference.

**LENGTHY TABLE**

The patent application contains a lengthy table section. A copy of the table is available in electronic form from the USPTO website (http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US20070419593A1). An electronic copy of the table will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).
A compound represented by the following formula [1] or a pharmaceutically acceptable salt thereof:

R1
R2
R3
R4
R5
R6
R7
R8
R9
R10

wherein

G1
G2
G3
G4
G5

C2
C3
C4
C5
C6
C7

Q is
(1) —O—,
(2) —NH—,
(3) —S—,
(4) —OCO—,
(5) —OCONH—,
(6) —CO—,
(7) —SO—,
(8) —SO₂—,
(9) —NHCO—,
(10) —NH₂—,
(11) —NHCOO—,
(12) —COO—,
(13) —CONH—,
(14) —SO₂NH—,
(15) —NHCONH—,
(16) —NH₂SO₂—,
(17) —CH==CH—,
(18) —CH==N— or
(19) —N==CH—,
ring A is
(1) benzene,
(2) cyclopentane or cyclohexane,
(3) cyclopentene or cyclohexene or
(4) a 5- or 6-membered heterocycle comprising 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom,

R3 is
(1) a carboxyl group,
(2) a carboxylic acid equivalent,
(3) —CONR¹²R¹³

(wherein R¹¹ and R¹² are each independently
(1) a hydrogen atom,
(2) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the following group E,
(3) a C₂₋₆ alkenyl group optionally substituted by 1 to 3 substituents selected from the following group E,
(4) a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from the following group E,
(5) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group E,

(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),

(6) a C₁₋₁₀ cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group E,
(7) —NR¹³¹R¹³²
(8) —NHCOOR¹³³,
(9) —NHCR¹³₄

(wherein R¹³¹, R¹³², R¹³³ and R¹³₄ are each independently a hydrogen atom or a group selected from the following group E),

(10) —CR¹³⁶R¹³⁵L¹₀₀²R¹³⁷,
(11') —CR¹³⁵R¹³⁶L¹₀₀²CONR¹⁴⁰—R¹³⁷,

(12')
(13')
(14')

(wherein R¹³⁵, R¹³⁶, R¹³⁷ and R¹³₈ are each independently
(1') a hydrogen atom or
(2') a group selected from the following group G,
group G:

(1") a cyano group,
(2") —COOR\^1\^2
(wherein R\^1\^2 is a hydrogen atom or a group selected from the following group F)
(3") —CONR\^1\^3R\^1\^4
(wherein R\^1\^3 and R\^1\^4 are each independently a hydrogen atom, a C\_1\_6 alkoxy group or a group selected from the following group F)

(4") a C\_1\_6 alkyl group optionally substituted by 1 to 3 substituents selected from the following group A,
(5") a C\_2\_6 alkenyl group optionally substituted by 1 to 3 substituents selected from the following group A,
(6") a C\_6\_1\_4 aryl group optionally substituted by 1 to 5 substituents selected from the following group B,
(7") a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group B
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),

(8") a C\_3\_1\_0 cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group B,
(9") a C\_5\_1\_4 aryl C\_1\_6 alkyl group optionally substituted by 1 to 5 substituents selected from the following group B,
(10") a heterocycle C\_1\_6 alkyl group optionally substituted by 1 to 5 substituents selected from the following group B

(11") a C\_3\_1\_0 cycloalkyl C\_1\_6 alkyl group optionally substituted by 1 to 5 substituents selected from the following group B; or
R\^1\^5 and R\^1\^6, or, R\^1\^8 and R\^1\^9 are bonded to each other, and optionally form, together with the carbon atom bonded thereto,

(1") a C\_3\_1\_0 cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group B or
(2") a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group B
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),
R\^1\^7 is

(1") a hydrogen atom,
(2") a carboxyl group,
(3") a C\_1\_6 alkyl group optionally substituted by 1 to 3 substituents selected from the following group E,
(4") a C\_2\_6 alkenyl group optionally substituted by 1 to 3 substituents selected from the following group E,
(5") a C\_6\_1\_4 aryl group optionally substituted by 1 to 5 substituents selected from the following group E,
(6") a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group E
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom or
(7") a C\_3\_1\_0 cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group E,
R\^1\^3\_40 and R\^1\^3\_41 are each independently
(1") a hydrogen atom or
(2") a C\_1\_6 alkyl group,
L\^1\^00 is

(1") a bond,
(2") —CO—,
(3") —CH\_2\_O—,
(4") —CH\_2\_NH—,
(5") —CH\_2\_NCO—,
(6") a C\_1\_6 alkyne optionally substituted by hydroxyl group or
(7") a C\_2\_6 alkenylene,
L\^1\^01 and L\^1\^02 are each independently

(1") a bond,
(2") —CO—,
(3") a C\_1\_6 alkyl group optionally substituted by hydroxyl group or
(4") a C\_2\_6 alkenylene,
L\^1\^03 is

(1") a bond or
(2") a C\_1\_6 alkylene,
L\^1\^04 is a C\_1\_6 alkyne,
L\^1\^05 is

(1") a bond or
(2") a C\_1\_6 alkylene,
L\^1\^06 is

(1") a bond,
(2") a C\_1\_6 alkyne,
(3") —NH—,
(4") —NH—CH\_2— or
(5") —CH\_2—CONH—,
ring D\_1, ring D\_2 and ring D\_3 are each independently

(1") a C\_5\_1\_4 aryl group optionally substituted by 1 to 5 substituents selected from the following group E,
(2") a C\_3\_1\_0 cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group E or
(3") a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group E
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom)),
(4) \(-\text{COOR}^{103}\)

(wherein \(R^{103}\) is a group selected from the following group C or a glucuronic acid residue),

\[
\begin{align*}
\text{CO} & \quad \text{D}^9 \\
\text{or} \\
\text{CO} & \quad \text{D}^9 \quad \text{O} \quad \text{D}^9
\end{align*}
\]

(wherein ring \(D^9\) is a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group E)

(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),

ring \(D^7\) is a \(C_{6-14}\) aryl group optionally substituted by 1 to 5 substituents selected from the following group E),

\(R^2\) may substitute at a substitutable position on carbon atom or nitrogen atom constituting Q and is

(1) a hydrogen atom,

(2) a group selected from the following group E,

(3) a \(C_{1-6}\) alkyl group optionally substituted by 1 to 3 substituents selected from the following group E,

(4) a \(C_{2-6}\) alkenyl group optionally substituted by 1 to 3 substituents selected from the following group E,

\[
\begin{align*}
\text{L}^2 & \quad \text{D}^9 \quad \text{L}^1 \quad \text{D}^9 \\
\text{or} \\
\text{L}^1 & \quad \text{D}^9 \\
\text{or} \\
\text{L}^2 & \quad \text{CH}_2 \quad \text{L}^1 \quad \text{D}^9 \\
\text{or} \\
\text{L}^1 & \quad \text{CH}_2 \quad \text{D}^9 \\
\text{or} \\
\text{L}^1 & \quad \text{CH}_3 \quad \text{L}^2 \quad \text{CH}_2 \quad \text{D}^9
\end{align*}
\]

{wherein \(L^1\) and \(L^2\) are each independently

\(1')\) a bond,

\(2')\) \(C_{1-6}\) alkylene,

\(3')\) \(C_{2-6}\) alkenylene,

\(4')\) \(\text{-(CH}_2\text{)}_{u1}-\text{O-}(\text{CH}_2\text{)}_{v1}-\),

\(5')\) \(\text{-(CH}_2\text{)}_{u1}-\text{S-}(\text{CH}_2\text{)}_{v1}-\),

\(6')\) \(\text{-(CH}_2\text{)}_{u1}-\text{NR}^{1.1}-\text{(CH}_2\text{)}_{v1}-\),

\(7')\) \(\text{-(CH}_2\text{)}_{u1}-\text{CO-}(\text{CH}_2\text{)}_{v1}-\),

\(8')\) \(\text{-(CH}_2\text{)}_{u1}-\text{CONR}^{1.2}-\text{(CH}_2\text{)}_{v1}-\),

\(9')\) \(\text{-(CH}_2\text{)}_{u1}-\text{NR}^{1.2}\text{CO}_2-\text{(CH}_2\text{)}_{v1}-\),

\(10')\) \(\text{-(CH}_2\text{)}_{u1}-\text{NR}^{1.2}\text{CONR}^{1.2}-\text{(CH}_2\text{)}_{v1}-\),

\(11')\) \(\text{-(CH}_2\text{)}_{u1}-\text{NR}^{1.2}\text{CO}-\text{(CH}_2\text{)}_{v1}-\),

\(12')\) \(\text{-(CH}_2\text{)}_{u1}-\text{NR}^{1.2}\text{SO}_2-\text{(CH}_2\text{)}_{v1}-\),

\(13')\) \(\text{-(CH}_2\text{)}_{u1}-\text{SO}_2-\text{(CH}_2\text{)}_{v1}-\),

\(14')\) \(\text{-(CH}_2\text{)}_{u1}-\text{SO}_2\text{NR}^{1.2}-\text{(CH}_2\text{)}_{v1}-\), or

\(15')\) \(\text{-(CH}_2\text{)}_{u1}-\text{N}^\text{R}^{1.2}\text{R}^{1.2}-\text{(CH}_2\text{)}_{v1}-\),

wherein \(u, v, u1\) and \(v1\) are each independently 0 or an integer of 1 to 6,

\(R^{1.1}\) is

\(1'^n\) a hydrogen atom,

\(2'^n\) a group selected from the following group C,

\(3'^n\) \(-\text{COR}^{1.1}\),

\(4'^n\) \(-\text{CONR}^{1.1}\text{R}^{1.1}\),

\(5'^n\) \(-\text{COOR}^{1.1}\) or

\(6'^n\) \(-\text{SO}_2\text{R}^{1.1}\)

(wherein \(R^{1.1}\) and \(R^{1.2}\) are each independently a hydrogen atom or a group selected from the following group C, and \(R^{1.2}\) is a group selected from the following group C).}

\(R^{1.2}\), \(R^{1.2}\) and \(R^{1.3}\) are each independently

\(1'^n\) a hydrogen atom,

\(2'^n\) a group selected from the following group C,

\(3'^n\) \(-\text{COR}^{1.1}\) or

\(4'^n\) \(-\text{SO}_2\text{R}^{1.1}\)

(wherein \(R^{1.1}\) and \(R^{1.3}\) are as defined above),

\(L^3\) is

\(1'^o\) \(-\text{CHR}^{1.1}\text{R}^{1.4}\) or

\(2'^o\) \(-\text{NR}^{1.1}\text{R}^{1.4}\)

(wherein \(R^{1.1}\) is a group selected from the following group F),

ring \(D^1\) and ring \(D^2\) are each independently

\(1')\) a \(C_{6-14}\) aryl group optionally substituted by 1 to 5 substituents selected from the following group E,

\(2')\) a \(C_{2-10}\) cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group E or

\(3')\) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group E

(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom)],

\(R^3\) is

\(1\) a hydrogen atom,

\(2\) a halogen atom,
(3) a C_{1-6} alkanoyl group,  
(4) a carboxyl group, 
(5) a cyano group, 
(6) a nitro group, 
(7) a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from the following group A, 
(8) —OR\textsuperscript{101}  
(wherein R\textsuperscript{101} is a hydrogen atom or a group selected from the following group C), 
(9) —NR\textsuperscript{102}R\textsuperscript{119}  
(wherein R\textsuperscript{102} and R\textsuperscript{119} are each independently a hydrogen atom, a C\textsubscript{1-6} alkanoyl group or a C\textsubscript{1-6} alkylsulfonyl group),  
(10) —COOR\textsuperscript{103}  
(wherein R\textsuperscript{103} is a group selected from the following group C or a glucuronic acid residue),  
(11) —CONR\textsuperscript{104}R\textsuperscript{105}  
(wherein R\textsuperscript{104} and R\textsuperscript{105} are each independently a hydrogen atom, a hydroxyl group, a cyano group, a C\textsubscript{1-6} alkoxy group or a C\textsubscript{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from the following group A),  
(12) —SO\textsubscript{2}R\textsuperscript{106}  
(wherein R\textsuperscript{106} is a hydroxyl group, an amino group, a C\textsubscript{1-6} alkyl group or a C\textsubscript{1-6} alkyamino group),  
(13) —NHCOR\textsuperscript{107}  
(wherein R\textsuperscript{107} is an amino group or a C\textsubscript{1-6} alkyamino group),  
(14) —C(═NR\textsuperscript{108})—NH\textsubscript{2}  
(wherein R\textsuperscript{108} is a hydrogen atom, a C\textsubscript{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from the following group A, a hydroxyl group or a C\textsubscript{1-6} alkoxy group),  
(15) —P(═O)(OR\textsuperscript{109})\textsubscript{2}  
(wherein R\textsuperscript{109} are each independently a hydrogen atom or a group selected from the following group C),  
(16) —P(═O)(OR\textsuperscript{110})NR\textsuperscript{111}R\textsuperscript{112}  
(wherein R\textsuperscript{110}, R\textsuperscript{111} and R\textsuperscript{112} are each independently a hydrogen atom or a group selected from the following group C), 
(17) —CONHCO—R\textsuperscript{113}  
(wherein R\textsuperscript{113} is a group selected from the following group C),  
(18) —CONHSO\textsubscript{2}—R\textsuperscript{114}  
(wherein R\textsuperscript{114} is a group selected from the following group C),  
(19) —SO\textsubscript{2}NHCO—R\textsuperscript{115}  
(wherein R\textsuperscript{115} is a group selected from the following group C) or
(20) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group B  
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom), 
R\textsuperscript{7} may substitute at a substitutable position on carbon atom or nitrogen atom constituting Q and each is independently 
(1) a halogen atom,  
(2) a C\textsubscript{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from the following group A,  
(3) —OR\textsuperscript{116}  
(wherein R\textsuperscript{116} is a hydrogen atom or a group selected from the following group C), 
(4) —NR\textsuperscript{117}R\textsuperscript{118}  
(wherein R\textsuperscript{117} and R\textsuperscript{118} are each independently a hydrogen atom, a C\textsubscript{1-6} alkanoyl group or a group selected from the following group C),  
(5) a C\textsubscript{6-14} aryl group optionally substituted by 1 to 5 substituents selected from the following group B or  
(6) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group B  
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom), 

a is 0, 1 or 2,  
R\textsuperscript{7} and R\textsuperscript{8} are each independently  
(1) a hydrogen atom,  
(2) a halogen atom,  
(3) a C\textsubscript{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from the following group A,  
(4) —OR\textsuperscript{120}  
(wherein R\textsuperscript{120} is a hydrogen atom or a group selected from the following group C) or  
(5) —NR\textsuperscript{121}R\textsuperscript{122}  
(wherein R\textsuperscript{121} and R\textsuperscript{122} are each independently a hydrogen atom, a C\textsubscript{1-6} alkanoyl group or a group selected from the following group C), 

ring Cy is  
(1) a C\textsubscript{3-10} cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group B,  
(2) a C\textsubscript{3-10} cycloalkenyl group optionally substituted by 1 to 5 substituents selected from the following group B or  
(3) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group B  
(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),
X is

(1) a group selected from the following group D,
(2) a C₂₋₆ alkenyl group optionally substituted by 1 to 3 substituents selected from the following group A or

\[ Y \rightarrow B \rightarrow (Z)_w \]  

(3)

wherein ring B is

(1') a C₆₋₁₄ aryl group,
(2') a C₃₋₆ cycloalkyl group or
(3') a heterocyclic group comprising 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom,

each Z is independently

(1') a group selected from the following group D,
(2') a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from the following group D,
(3') a C₃₋₆ cycloalkyl group optionally substituted by 1 to 5 substituents selected from the following group D,
(4') a C₆₋₁₄ aryl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from the following group D,
(5') a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group D

(wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom) or

(6') a heterocyclic C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from the following group D

(wherein said heterocyclic C₁₋₆ alkyl group is a C₁₋₆ alkyl group substituted by “a heterocyclic group optionally substituted by 1 to 5 substituents selected from group D” as defined above),

w is an integer of 1 to 3,

Y is

(a) C₁₋₆ alkylene,
(b) C₂₋₆ alkylene or
(c) \(-Y^1-(CH₂)_m-Y^2-(CH₂)_n-\)

(wherein m and n are each independently 0 or an integer of 1 to 6,

Y¹ and Y² are each independently

(1') a bond,
(2') –O–,
(3') –NR³¹–,
(4') –S–,
(5') –CO–,
(6') –SO–,
(7') –SO₂–,
(8') –CO₂–,
(9') –OCO–,
(10') –CONR²¹–,
(11') –NR⁵¹CO–,
(12') –SO₃NR²¹–,
(13') –NR⁵¹SO₂–,
(14') –NR⁵¹CO₂–,
(15') –OCONR²¹–,
(16') –NR⁵¹CONR⁵¹–,
(17') –CR²ⁿR⁵ⁿ– or
(18') –CH═CH–

(wherein R⁹¹ is

(1') a hydrogen atom,
(2') a group selected from the following group C,
(3') –(CH₂)ₜ–COOR⁷¹₁₁,
(4') –(CH₂)ₜ–CONR⁷¹₁₁R⁷¹₁₂,
(5') –(CH₂)ₜ–COR⁷¹₁¹ or
(6') –(CH₂)ₜ–SO₂R⁷¹₁₃

(wherein s is 0 or an integer of 1 to 6, R⁷¹₁₁ and R⁷¹₁₂ are each independently a hydrogen atom or a group selected from the following group C, R⁷¹₁₃ is a group selected from the following group C),

R⁷¹₂ and R⁷¹₃ are each independently

(1') a hydrogen atom,
(2') a group selected from the following group C,
(3') –COR⁷¹₁¹ or
(4') –SO₂R⁷¹₁₃ (wherein R⁷¹₁¹ and R⁷¹₁₃ are as defined above),

R⁷¹⁴ and R⁷¹⁵ are each independently

(1') a hydrogen atom,
(2') a carboxyl group,
(3') a group selected from group F,
(4') –OR⁷¹₁⁴ or
(5') –NHR⁷¹₁⁵

(wherein R⁷¹₁⁴ is a group selected from the following group C, R⁷¹₁₅ is a hydrogen atom, a C₁₋₆ alkyl group, a C₁₋₆ alkanoyl group, a C₆₋₁₄ aryl C₁₋₆ alkylalkoxy carbonyl group or a C₁₋₆ alkylalkoxycarbonyl group))

group A:

(1) a halogen atom,
(2) a C₁₋₆ alkoxy C₁₋₆ alkoxy group,
(3) a cyano group,
(4) –OR⁷¹₁,
(5) –SR⁷¹₁.
(6) —NR²¹R²²,
(7) —COOR²¹,
(8) —CONR≡²¹R²²,
(9) —SO₂J¹,
(10) —SO₂N⁺R²¹R²²,
(11) —NHCO₂¹,
(12) —NHSO₃R²³,
(13) —NHC₀₂R²⁴,
(14) —COR²¹ and 
(15) —N⁺R²¹R²²R²³
(wherein R²¹ and R²² are each a hydrogen atom, a C₁₋₆ alkyl group or a benzyl group, R²³ is a C₁₋₆ alkyl group and R²⁴ is a C₁₋₆ alkyl group)

Group B:
(1) a halogen atom,
(2) a cyano group,
(3) a nitro group,
(4) a C₁₋₆ alkyl group,
(5) a C₁₋₆ alkynyl group optionally substituted by carboxyl group,
(6) a halogenated C₁₋₆ alkyl group,
(7) —(CH₂)₅—OR²¹,
(8) —(CH₂)₆—SR²¹,
(9) —(CH₂)₇—NR²¹R²²,
(10) —(CH₂)₈—COOR²¹,
(11) —(CH₂)₉—CONR²¹R²²,
(12) —(CH₂)₁₀—COR²¹,
(13) —(CH₂)₁₁—NR²¹—COR²²,
(14) —(CH₂)₁₂—NR²¹—SO₂R²³,
(15) —(CH₂)₁₃—SO₂R²₅,
(16) —(CH₂)₁₄—SO₂NR²¹R²²,
(17) —(CH₂)₁₅—CONR²¹—SO₂R²₃,
(18) —(CH₂)₁₆—SO₂NR²¹—COR²²,
(19) —(CH₂)₁₇—NR²¹—COOR²₅,
(20) —(CH₂)₁₈—NR²¹—CONR²¹R²⁴,
(21) —O—(CH₂)₉—COOR²¹ and
(22) —O—(CH₂)₁₀—R²⁵
(wherein R²¹, R²² and R²³ are each independently a hydrogen atom or a C₁₋₆ alkyl group, R²³ is a C₁₋₆ alkyl group, R²⁵ is a heterocyclic group and r is 0 or an integer of 1 to 6)

Group C:
(1) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
(2) a C₆₋₁₄ aryl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B, (3) a C₆₋₁₄ aryl C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,
(4) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the aforementioned group B and
(5) a heterocyclic C₁₋₆ alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B

Group D:
(a) a hydrogen atom,
(b) a halogen atom,
(c) a cyano group,
(d) a nitro group,
(e) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
(f) —(CH₂)₅—OR²¹,
(1) a hydrogen atom,
(2) a group selected from the following group F,
(3) a C₂₋₅ alkynyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A or
(4) a C₂₋₅ alkynyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
hereinafter each t is independently 0 or an integer of 1 to 6,
(g) —(CH₂)₅—S(O)₆—R²²,
(1) a hydrogen atom or
(2) a group selected from the following group F,
q is 0, 1, 2 or 3,
(h) —(CH₂)₅—NR²³R²₄,
(1) a hydrogen atom or
(2) a group selected from the following group F,
(i) —(CH₂)₅—COOR²⁵,
(1) a hydrogen atom or
(2) a group selected from the following group F,
(j) —(CH₂)₅—CONR²⁶R²⁷,
(1) a hydrogen atom,
(2) a hydroxyl group,
(3) a group selected from the following group F or
(4) a C₁₋₆ alkoxy group,
(k) —(CH₂)ₙ—CORₖ⁺,
wherein Rₖ⁺ is
(1) a hydrogen atom or
(2) a group selected from the following group F,
   (1) —(CH₂)ₙ—NRₖ⁻CO—Rₖ⁻
   wherein Rₖ⁻ is
   (1) a hydrogen atom,
   (2) a C₁₋₅ alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A
   or
   (3) a C₁₋₅ alkanoyl group, Rₖ⁻¹ is
       (1) an amino group,
       (2) a C₁₋₅ alkylamino group or
       (3) a group selected from the following group F,
   (m) —(CH₂)ₙ—NRₖ⁻¹SO₂—Rₖ⁻²,
   wherein Rₖ⁻¹ is
   (1) a hydrogen atom,
   (2) a C₁₋₅ alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A
   or
   (3) a C₁₋₅ alkanoyl group, Rₖ⁻² is
       (1) a hydrogen atom or
       (2) a group selected from the following group F,
   (n) —(CH₂)ₙ—SO₂—NRₖ⁻¹Rₖ⁻⁴,
   wherein Rₖ⁻³ and Rₖ⁻⁴ are each independently
   (1) a hydrogen atom or
   (2) a group selected from the following group F,
   (o) —(CH₂)ₙ—CONRₖ⁻¹SOₖ⁻¹Rₖ⁻⁶,
   wherein Rₖ⁻⁵ and Rₖ⁻⁶ are each independently
   (1) a hydrogen atom or
   (2) a group selected from the following group F,
   (p) —(CH₂)ₙ—SOₖ⁺NRₖ⁻¹—CORₖ⁺,
   wherein Rₖ⁻¹ is
   (1) a hydrogen atom or
   (2) a group selected from the following group F,
   Rₖ⁺ is a group selected from the following group F,
   (q) —(CH₂)ₙ—NRₖ⁻¹COORₖ⁺,
   wherein Rₖ⁻¹ and Rₖ⁺ are each independently
   (1) a hydrogen atom or
   (2) a group selected from the following group F,
   (r) —(CH₂)ₙ—NRₖ⁻²¹—CONRₖ⁻²⁺Rₖ⁻²²,
   wherein Rₖ⁻²¹, Rₖ⁻²², and Rₖ⁻²³ are each independently
   (1) a hydrogen atom or
   (2) a group selected from the following group F,
   (s) —(CH₂)ₙ—C(═NRₖ⁻²⁴)NH₂,
   wherein Rₖ⁻²⁴ is
   (1) a hydrogen atom,
   (2) a hydroxyl group,
   (3) a C₁₋₅ alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A
   or
   (4) a C₁₋₅ alkoxy group,
   (t) —(CH₂)ₙ—O—(CH₂)ₘ—CORₖ⁺,
   wherein Rₖ⁺ is
   (1) an amino group,
   (2) a C₁₋₅ alkylamino group or
   (3) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,
   p is 0 or an integer of 1 to 6,
   (u) —(CH₂)ₙ—O—(CH₂)ₘ—NRₖ⁻²⁹Rₖ⁻³⁰,
   wherein Rₖ⁻²⁹ and Rₖ⁻³⁰ are each independently
   (1) a hydrogen atom or
   (2) a C₁₋₅ alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,
   p is 0 or an integer of 1 to 6,
   (v) —(CH₂)ₙ—O—COORₖ⁺,
   wherein Rₖ⁺ is
   (1) a hydrogen atom or
   (2) a group selected from the following group F, and
   (w) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the aforementioned group B
   (wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom)

group E:
   (a) a halogen atom,
   (b) a cyano group,
   (c) a nitro group,
   (d) an azido group,
   (e) —OP(═O)(OH)₂,
   (f) —ORₖ⁺,
   wherein Rₖ⁺ is
   (1) a hydrogen atom,
   (2) a group selected from the following group F,
(3) a C₂₋₆ alkynyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A or
(4) a C₂₋₆ alkynyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,

(g) —S(O)₉₄—R²
wherein R² is
(1) a hydrogen atom or
(2) a group selected from the following group F,
q is 0, 1, 2 or 3,
(h) NR³R⁴
wherein R³ and R⁴ are each independently
(1) a hydrogen atom,
(2) a cyan group or
(3) a group selected from the following group F,
(i) —COR⁵,
wherein R⁵ is
(1) a hydrogen atom or
(2) a group selected from the following group F,
(j) —CONR⁶R⁷,
wherein R⁶ and R⁷ are each independently
(1) a hydrogen atom,
(2) a hydroxyl group,
(3) a group selected from the following group F or
(4) a C₁₋₆ alkoxy group,
(k) —COR⁸,
wherein R⁸ is a group selected from the following group F,
(1) —NR⁹CO—R¹⁰,
wherein R⁹ is
(1) a hydrogen atom,
(2) a C₁₋₆ alkyl group or
(3) a C₁₋₆ alkoxy group,
R¹⁰ is
(1) a hydrogen atom,
(2) an amino group,
(3) a C₁₋₆ alkylaminogroup,
(4) a C₂₋₆ alkynyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A or
(5) a group selected from the following group F,
(m) —NR¹¹SO₂—R¹²,
wherein R¹¹ is
(1) a hydrogen atom,
(2) a C₁₋₆ alkyl group or
(3) a C₁₋₆ alkanoyl group,
R¹² is
(1) a hydrogen atom or
(2) a group selected from the following group F,
(n) —SO₂—NR¹³R¹⁴,
wherein R¹³ and R¹⁴ are each independently
(1) a hydrogen atom or
(2) a group selected from the following group F,
(o) —CONR¹⁵—SO₂R¹⁶,
wherein R¹⁵ and R¹⁶ are each independently
(1) a hydrogen atom or
(2) a group selected from the following group F,
(p) —SO₂NR¹⁷—COR¹⁸,
wherein R¹⁷ is
(1) a hydrogen atom or
(2) a group selected from the following group F,
R¹⁸ is a group selected from the following group F,
(q) NR²⁰—COOR²¹,
wherein R²⁰ and R²¹ are each independently
(1) a hydrogen atom or
(2) a group selected from the following group F,
(r) —NR²²—CONR²³R²³
wherein R²², R²² and R²³ are each independently
(1) a hydrogen atom or
(2) a group selected from the following group F,
(s) —NHCO—COOR²⁴
wherein R²⁴ is
(1) a hydrogen atom or
(2) a group selected from the following group F,
(t) —NHCO—CONR²⁵R²⁶
wherein R²⁵ and R²⁶ are each independently
(1) a hydrogen atom,
(2) a hydroxyl group or
(3) a group selected from the following group F,
(u) —CONH—COOH,
(w) a \( C_{5-14} \) aryl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,

(x) a \( C_{5-10} \) cycloalkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,

(y) a heterocyclylidene group optionally substituted by 1 to 5 substituents selected from the aforementioned group B

(z) a \( C_{5-10} \) cycloalkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B

(aa) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the aforementioned group B (wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom),

(bb) a \( C_{5-10} \) cycloalkylidene group optionally substituted by 1 to 5 substituents selected from the aforementioned group B, and

(cc) a heterocyclic group optionally substituted by 1 to 5 substituents selected from the aforementioned group B (wherein said heterocyclic group comprises 1 to 4 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom).

when group E is a substituent on a \( C_{5-14} \) aryl group, a \( C_{3-10} \) cycloalkyl group or a heterocyclic group, it may be

(dd) a \( C_{1-6} \) alkyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,

(ee) a \( C_{5-10} \) alkenyl group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,

(ff) a \( C_{2-6} \) alkyne group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,

(gg) \( C_{1-6} \) alkylidene group optionally substituted by 1 to 3 substituents selected from the aforementioned group A,

(hh) a \( C_{5-14} \) aryl \( C_{1-6} \) alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B,

(ii) a \( C_{3-10} \) cycloalkyl \( C_{1-6} \) alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B, or

(jj) a heterocycle \( C_{1-6} \) alkyl group optionally substituted by 1 to 5 substituents selected from the aforementioned group B

when \( G^2 \) is \( N\)–\( C \)=\( C \), or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein, in the formula [I],

\[ G^2 \] is \( N\)–\( C \)=\( C \), or a pharmaceutically acceptable salt thereof.

The moiety

\[ \text{moiety} \]
is a fused ring selected from the group consisting of

-continued
or a pharmaceutically acceptable salt thereof.

40. (canceled)

41. The compound of claim 1, wherein ring Cy is a C₃₋₁₀ cycloalkyl group or a C₅₋₁₀ cycloalkenyl group, or a pharmaceutically acceptable salt thereof.

42. (canceled)

43. The compound of claim 1, wherein X is a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A, —(CH₂)ₓ—OR⁻¹, —(CH₂)ₓ—S(O)ₓR⁻¹, or —(CH⁻¹)—NRₓ⁻¹R⁻³ or

\[ \text{Y} - B - (Z)_{\text{w}} \]

wherein each symbol is as defined in claim 1, or a pharmaceutically acceptable salt thereof.

44.-49. (canceled)

50. The compound of claim 1, which is represented by the following formula [I-A], or a pharmaceutically acceptable salt thereof:

\[ \text{[I-A]} \]

wherein X' is a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from group A or —OR⁻¹, and other symbols are as defined in claim 1.

51. The compound of claim 1, which is represented by the following formula [I-B], or a pharmaceutically acceptable salt thereof:

\[ \text{[I-B]} \]

wherein Q₂ is —O— or —NH—, and other symbols are as defined in claim 1.
52. The compound of claim 1, which is represented by the following formula [I-C], or a pharmaceutically acceptable salt thereof:

```
R1RN
O

Q^3
```

wherein Q^3 is —O— or —NR^2—, X' is a hydrogen atom, a halogen atom, a C\textsubscript{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from group A or —OR^1, and other symbols are as defined in claim 1.

53. A composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

54-64. (canceled)

65. A method for treating hepatitis C, which comprises administering an effective amount of a compound of claim 1 to a mammal.

66. The method of claim 65, further comprising administering an effective amount of at least one pharmaceutical agent selected from the group consisting of a different antiviral agent, an antiinflammatory agent and an immunostimulant to the mammal.

67. The method of claim 65, further comprising administering an effective amount of interferon to the mammal.

68. A method for inhibiting hepatitis C virus polymerase, which comprises administering an effective amount of a compound of claim 1 to a mammal.

69. The method of claim 68, further comprising administering an effective amount of at least one pharmaceutical agent selected from the group consisting of a different antiviral agent, an antiinflammatory agent and an immunostimulant to the mammal.

70. The method of claim 68, further comprising administering an effective amount of interferon to the mammal.